# Using Exploratory Structural Equation Modeling to Estimate the Functional Connectivity Networks from CBF and BOLD Signals Simultaneously Measured by ASL MRI

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**Introduction**   Recently, more attention of neuroscientists has been paid to functional connectivity between cortical areas detected from resting-state fMRI data. ASL (arterial spin labeling) MRI technique has provided more direct observation of cerebral blood flow (CBF) fluctuations than regular BOLD-based fMRI. Therefore the perfusion MRI may reveal further information about the underlying mechanism of functional connectivity. However, there are few existing reports on  detecting functional connectivity or elucidating the cause of connection networks based on perfusion MRI [1]. On the other hand, conventional correlation analysis across multiple spatial regions cannot reveal causal directions and the connection network between more than two regions. The Structural Equation Modeling (SEM) is an effective method to ascertain path directions and coefficients from the covariance structure in fMRI data [2]. Here we present an approach to estimate the functional connectivity networks from BOLD and CBF signals simultaneously measured by ASL MRI using an exploratory SEM analysis.

**Materials and Methods**   The ASL scans were performed on three healthy and right-handed subjects. They were scanned on a Siemens 3T Trio/Tim system using a PASL sequence. Acquisition parameters were field of view (FOV) = 224 mm, matrix = 64 × 64, repetition time (TR) = 4 sec, echo time (TE) = 52 ms, delay time (TI) = 1750 ms, and flip angle = 90°. Nineteen axial slices (5 mm thick without gap) were acquired from inferior to superior in a sequential order. Each PASL scan with 75 acquisitions took about 5 minutes. The subjects were instructed to close eyes but stay awake, and not to perform any mental task. The perfusion-weighted were realigned to correct head motion and coregistered to the anatomical image of individual subject. The pair-wise subtraction between labeled and control images was performed to obtain CBF weighted images. Thereafter, the data were high-pass filtered at 0.08 Hz to isolate the CBF signal. The labeled and control images of the low-pass filtered (<0.07 Hz) PASL data were summed together to generate BOLD signal [1]. In SEM analysis, the left and right primary motor areas (L/R M1) were chosen as two ROIs for the detection of sensory-motor network, and the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC) were selected as two ROIs for the detection of default-mode network. The signal of each voxel within the brain was regarded as the third observation in the two structural equation models. Each model consists of two connections start from the unknown region to the two predefined ROIs (Fig. 1). For every voxel, the models were estimated by statistical indices such as Adjusted Goodness-of-Fit Index (AGFI) with a significant t-value (>1.96) on each path [2]. The AGFI at each voxel was saved and displayed in the final connectivity map. The model fit indices were compared between connectivity maps obtained from CBF and BOLD signals.

**Results and Discussion**   The representative connectivity maps resulted from SEM are illustrated in the Figure 1. The connectivity maps were found to be reproducible across subjects, and were similar between CBF and BOLD results. It indicates that the supplementary motor area (SMA) has significant connections to both LM1 and RM1 in the sensory-motor network, and the bilateral inferior parietal lobules (IPL) link significantly with PCC and MPFC in the default-mode network, which is consistent with the neuroanatomical evidence and existing results from functional connectivity researches using BOLD-based fMRI. Parts of predefined ROIs shown in the connectivity map can be interpreted as direct interactions between the two ROIs, which is also often found in the fMRI studies of functional connectivity. The largest standardized residual (the latent variable) obtained from SEM fitting at CBF signal is much larger than that obtained at BOLD signal (Table 1), which implies BOLD signal is more directly linked to the neuronal cause of functional connectivity. The present approach of SEM analysis on the perfusion MRI data allows us to search the possible functional connections at each brain region directly from CBF signals. When several areas are involved in a functional connection network, which is often the case, such connections become too complicated to be ascertained simply via correlation analysis. SEM produced maps and estimations circumvent this difficulty, and can be used to further examine complicate network models and possible physiological mechanisms underlying functional connectivity results based on BOLD or perfusion MRI.

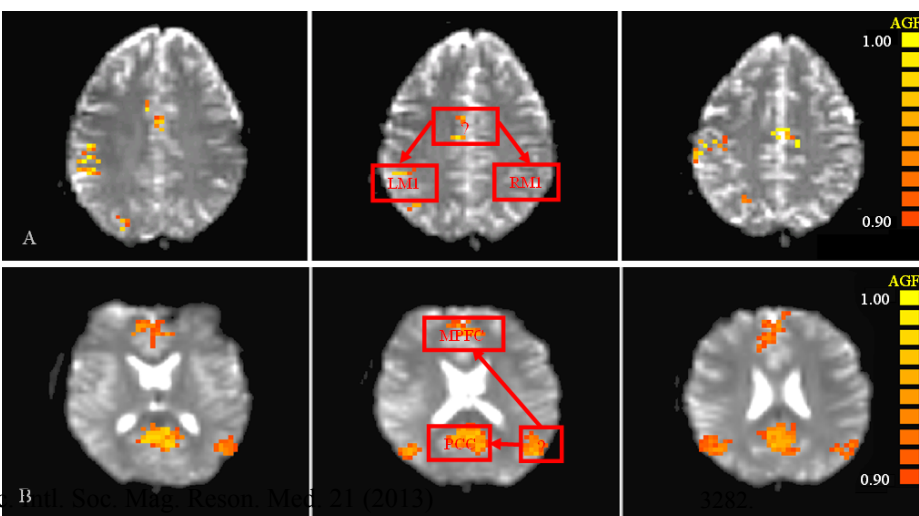**Reference**   [1] Chuang, et al, *Neuroimage* 40: 1595, 2008. [2] Zhuang, et al., *Neuroimage* 25: 462, 2005.



**Table 1.** Largest standardized residual averaged (and its standard deviation) from SEM fittings at each network and each signal.

|  | CBF | BOLD |
|---|---|---|
| **Sensory-motor Network** | 0.0417 (0.0133) | 0.0176 (0.0091) |
| **Default-mode Network** | 0.0923 (0.0165) | 0.0285 (0.0102) |

**Figure 1.**  The structural equation models (middle in red) and resulting connectivity maps in the sensory-motor network (**A**) and default-mode network (**B**) from CBF signals.