Graph analysis of resting-state ASL data reveals nonlinear correlations among CBF and network metrics

Xiaoyun Liang[1], Alan Connelly[1,2], and Fernando Calamante[1,2]

[1]*Brain Research Institute, Florey Institute of Neuroscience and Mental Health, Heidelberg, VIC, Australia,* [2]*Department of Medicine, Austin Health and Northern Health, University of Melbourne, Melbourne, VIC, Australia*

Introduction: Human connectome mapping provides opportunities to identify neural pathways that underlie human brain function, and to further our understanding of the physiological basis for information and mental representation. This is important to understand both normal brain function and disease-related dysfunction [1]. Since the 1990s, analysis of complex networks based on graph theory has lead to the rapid rise of studies of brain connectivity. Both structural and functional systems of the brain possess features of complex networks, such as small world properties [2]. It has been shown that pharmacological or psychological therapies can remediate sub-optimal network organization in patients [1]. Measures of network metrics are, therefore, of great importance for understanding the pathogenesis and treatment of brain disorders at network level. Mapping functional connectivity using BOLD fMRI, so far, has been the most popular method. However, given that BOLD signal changes reflect blood oxygenation, cerebral blood volume, cerebral blood flow (CBF), and metabolic rate of oxygen consumption [3], their interpretation can be complex, and may also include a large contribution from draining veins [4]. Arterial spin labeling (ASL) is an MRI technique to measure CBF directly and noninvasively. This typically comes at the expense of a reduced spatial and temporal resolution. However, previous results have demonstrated that ASL can successfully extract equivalent networks to BOLD data, yet with better sensitivity in brain regions with high-gradient susceptibility differences [5]**.** ASL studies of the small-world properties of the resting-state networks would allow us to investigate the intrinsic relationships between CBF and network metrics (such as degrees, characteristic path-lengths, etc.) more directly and interpretably. In this study, we investigate the connectome using ASL, which allows us for the first time to measure the network metrics of human brain during resting state based on ASL data, as well as to investigate the relationship between CBF and certain network metrics.

Materials and Methods: Ten subjects were scanned on a 3T Siemens Trio scanner with a whole-brain 3D-GRASE pCASL sequence [5]. Two ASL datasets (60 pairs each) were collected with two different post-labeling delays (PLD): short PLD (higher SNR and more suitable for the connectome) and long PLD (better for CBF quantification). *Short PLD:* TR/TE =3750/56ms, resolution=4x4x6mm^3, 20 slices, matrix size =64x51, PLD=600ms, with labeling duration = 1284ms. Background suppression (BS) was achieved using inversion-times of 1913ms and 523ms. *Long PLD:* Labeling duration= 1584ms, PLD=1540ms, BS inversion-times: 1800 and 520ms, otherwise identical to the parameters of short PLD. In addition, anatomical and calibration (M_0) images were acquired for registration and CBF quantification. ***Image analysis:*** ASL perfusion images with short PLD were pre-processed as follows: realignment followed by coregistration, normalization (MNI template, 61×73×61), de-trending and band-pass filtering. To remove intravascular contributions, independent component analysis was performed using the FSL MELODIC software. The pre-processed ASL perfusion images were employed as inputs to obtain adjacency matrix at individual level (the AAL template [6] was used to define the nodes). The region-wise mean time-courses were extracted to estimate connections among regions based on Pearson's correlation coefficients. A group-level adjacency matrix was obtained by averaging 10 individual-level matrices, which was then employed for small-world network analyses. For ASL data with long PLD, region-wise CBF were estimated for each subject. A sigmoid function was employed to estimate the relationships between network metrics, such as degrees (*Ki*), characteristic path length (*Lpi*), vulnerability (*Vi*) and eigencentrality (*ECi*), and region-wise mean CBF estimates by nonlinear fitting.

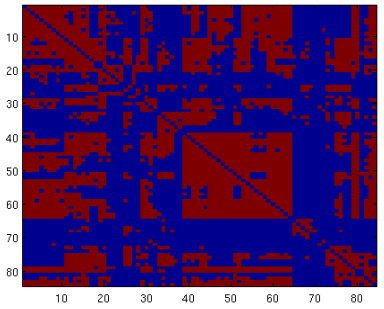

Fig.1 Group-level adjacency matrix (n=10); threshold R=0.6.

Results: Fig. 1 shows the adjacency matrix at group-level. For illustrative purposes, nonlinear fitting outcomes of 4 network metrics vs. CBF of 4 subjects (randomly selected) are shown in Fig. 2; all network metrics vs. region-wise CBF estimates show nonlinear patterns for the 10 subjects. However, the nonlinear pattern of *Lpi* (negative) is different from three other metrics (positive). The mean R-squares across the 10 subjects are 0.26, 0.31, 0.29 and 0.29 for nonlinear fitting outcomes of 4 network metrics, *Vi*, *Lpi*, *Ki and ECi*, vs. CBF, respectively.

Discussion: In this study, investigations on small-world network properties of ASL perfusion data have been conducted. The small-world network properties (*Ki*, *Lpi*, etc.) of ASL data are consistent with previous findings from BOLD data [6]. Interestingly, the outcomes on the relationships between 4 specific network metrics and region-wise CBF demonstrate that consistent nonlinear patterns exist across 10 normal subjects. In contrast to the positive nonlinear pattern of other network metrics (*Vi*, *Lpi*, *Ki* and *ECi*), *Lpi* shows a negative nonlinear pattern. This finding is well in line with the previous finding that 'hub' regions tend to have higher values for degree, vulnerability and centrality, but lower values for characteristic path length [6, 7], along with higher metabolic energy consumption (and CBF) [8]. While the sigmoid model is not ideal for *Ki* and *ECi*, and further work is required to identify an optimal model, it is clear from the data that such a model will be non-linear. To our knowledge, this is the first study that unravels the intrinsic relationships between specific network metrics and CBF estimates. This should provide useful information to further our understanding of the metabolic energy consumptions with which the brain can maintain normal cognition with the lowest cost. It should also have applications for clinical studies on brain disorders.

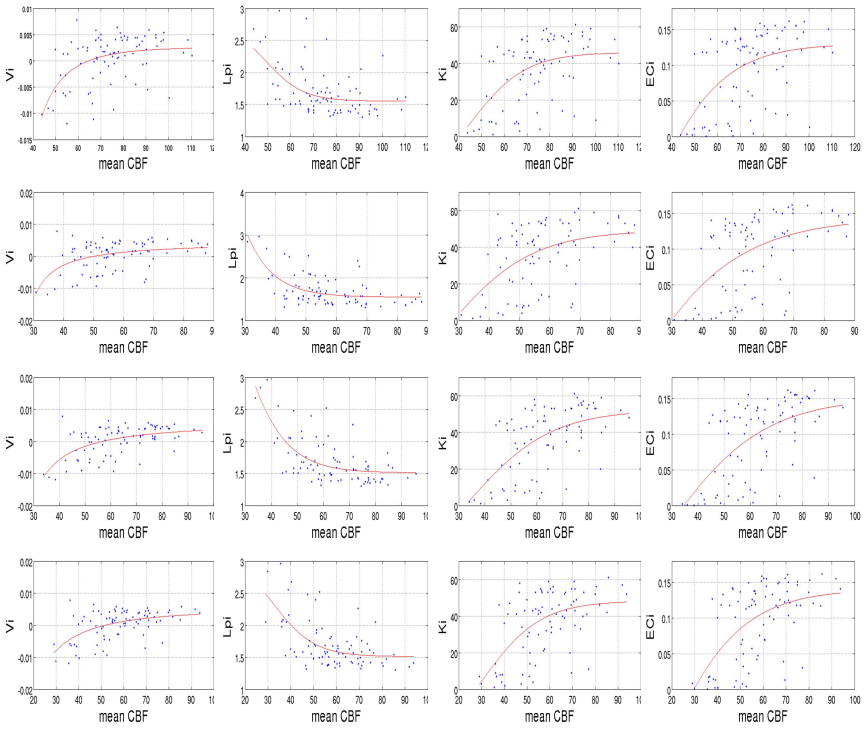

Fig. 2 Nonlinear fitting of 4 network metrics (*Vi*, *Lpi*, *Ki* and *ECi*) vs. CBF in 4 random subjects. Each row represents data from a single subject.

References:[1] Bullmore E et al., Nature Rev. Neuros. 2009; 10: 186-198; [2] Watts DJ et al., Nature 1998; 393: 440-2; [3] Buxton RB et al., NeuroImage 23 suppl 1 (2004): 220-33; [4] Boxerman JL et al., MRM 1995; 34: 4-10; [5] Liang X. et al., Int J of Imag and Syst Tech 2012; 22: 37-43; [6] Achard S et al., J. Neuroscience 2006; 26: 63-72; [7] Gong G. et al., Cerebral Cortex 2009; 19: 524-536; [8] Raichle ME et al., PNAS 2001; 676-682.