# Standardized and Automatic Framework for Functional Connectivity Analysis: Functional Correlation Matrix and Sorted Index Curve

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## Introduction:

Functional connectivity refers to the spatially coherent patterns of low frequency (< 0.1 Hz) and spontaneous fluctuations in the fMRI signal [1]. These patterns, which are evident at a resting state, appear to represent the internal dynamics of the same brain systems that are engaged by various tasks (e.g. sensorimotor, language, emotion, memory among others) [1]. In contrast to the conventional fMRI studies that rely on task-evoked BOLD signals, the resting-state functional connectivity studies do not require the subjects to perform any task, and are thus particularly well-suited for patients who cannot readily perform the various required tasks. This advantage may help resting-state connectivity investigations to find broad applications in translational medicine. Indeed, recent studies showed that the resting-state functional connectivity provides the information reflecting the neurological disease progression, the treatment efficacy, and even the visual cortex functional plasticity in the early blind [2].

Several post-processing approaches (such as correlation analysis and independent component analysis (ICA)) are currently available for functional connectivity analysis. Since these existing methods were originally designed to map the functionally connected brain regions, they are limited in several ways in identifying brain regions of very low connectivity (i.e. functionally independent or functional deficient due to neurological diseases). For example, in correlation analysis, the cross correlation coefficients between a pre-defined seed and other voxels are calculated, and the whole-brain connectivity to the pre-defined seed region is then constructed. This approach, however, requires a prior knowledge or assumption for selecting the seed region. In ICA, the lowpass-filtered time course profiles from all voxels can be simultaneously examined without a prior assumption, and multiple connectivity components may be identified. However, the ICA method cannot quantify the low-connectivity regions that are not part of the identified connectivity components.

To address the limitations in existing connectivity analysis methods, we design an automatic post-processing pipeline that can reliably identify functionally correlated regions in resting-state fMRI data, without a prior assumption. Experimental results show that the proposed method provides a consistent and reliable assessment of the functional connectivity, and may potentially be applicable for an early detection of functionally deficient regions in an individual.

## Methods

The developed post-processing method consists of the following procedures. First, similar to other resting-state connectivity analysis methods, the acquired fMRI data are re-aligned for motion correction, and the re-aligned time course profiles are lowpass-filtered (<0.1Hz) to remove high-frequency components of the spontaneous fluctuations. In addition, the time-course signals are detrended. Second, the pre-processed fMRI data are normalized to a pre-segmented anatomic template. In our studies, the data were normalized to the AAL template [3] with 116 pre-segmented regions (e.g. Figure 1). Third, similar to the approach used by Liu et al. [2], the time course profiles within each pre-segmented anatomic region are averaged, and the cross correlation coefficients between time-course profiles from different anatomic regions are calculated. In our studies, the calculated coefficients are stored in a 116 x 116 *functional correlation matrix (FC-matrix)* (e.g. Figure 2, in which the upper and lower triangles are mirrored through the diagonal line). Fourth, the coefficients in each column of the FC-matrix are averaged to generate an index reflecting the connectivity level from an anatomic region to the remaining 115 regions. The generated index array (with 116 components) represents the functional connectivity level of all pre-segmented regions. Fifth, the 116-component index array is re-ordered, according to the connectivity level for each region (e.g. Figure 4: see Experiments and Results section for details). The sorted index array, termed *SI-curve*, provides a comprehensive view of the brain connectivity, facilitating the identification of the low connectivity regions (i.e. functionally independent or deficient regions).

Figure 1

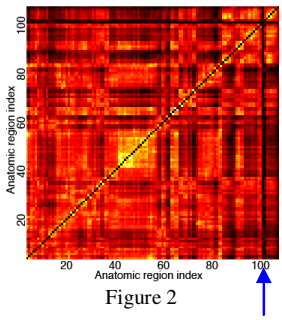


Figure 2

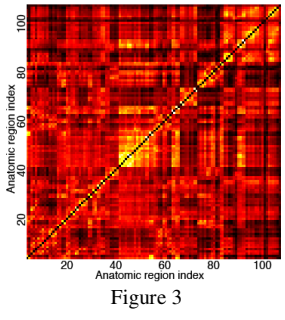


Figure 3

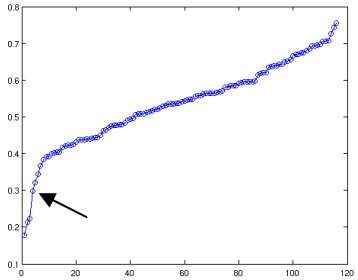

Figure 4

Figure 5

## Experiments and Results

The developed methods have been evaluated in multiple fMRI data sets (17 healthy subjects at 3 T; and 10 longitudinal scan sessions from a healthy subject at 1.5 T). The FC-matrix (representing the cross-correlation between every pairs of 116 anatomic regions) calculated from a single scan session from 1.5 T is shown in Figure 2, and the mean FC-matrix of all 10 scan sessions from the same subject is shown in Figure 3. It can be seen that the pattern of the FC-matrix is consistent across sessions for an individual subject. While it is possible to identify a few brain regions with low connectivity to others (such as the black stripes indicated by an arrow in Figure 2), it is not straightforward to obtain a complete assessment of functionally independent or deficient regions from a FC-matrix. By reducing a FC-matrix to an SI-curve (Figure 4), as described in the Methods section, brain regions with relatively lower connectivity can be identified more easily. For example, it can be seen in Figure 4 that there are 7 anatomic regions with significantly lower connectivity to other regions (indicated by an arrow). Since the spatial information is retained in the FC-matrix and SI-curve, the identified low-connectivity regions can be mapped back to the original anatomic template. For example, Figure 5 shows one of the functionally independent brain region identified in the SI-curve – the vermis. SI-curve analysis of our multi-subject data from 3T confirms that the vermis has generally lower connectivity to the cortex, in comparison to other brain regions. We have also been assessing the difference in the FC-matrix and SI-curves between younger and aged groups. Our preliminary study shows that the connectivity between the amygdala and other regions is significantly different between young and aged groups, in agreement with the previous findings [4].

## Discussion

In comparison to existing functional connectivity analysis methods that are optimized for detecting functionally connecting brain regions (such as the ICA), our new approach provides a comprehensive view of the functional connectivity across the whole brain (e.g. the occipital lobe is readily visible as the yellow squares near the centers of Figures 2 and 3), and is also well suited for identifying brain regions with low connectivity, all without a prior assumption. For example, we have identified several brain regions (including the vermis) that are functioning more independently from other cortical regions. Furthermore, we expect that the developed SI-curve analysis can reliably identify brain regions that are functionally deficient due to neurological diseases.

**References:** [1] Fox MD and Raichle ME. Nat Rev Neurosci 2007, 8(9): 700-711. [2] Liu Y et al., Brain 2007, 130(8): 2085-2096. [3] Tzourio-Mazoyer N et al. Neuroimage 2002, 15(1): 273-289. [4] Jacques P et al. Neurobiology in Aging 2008, E-Print. **Acknowledgments**: NIH research grant R01 AG011622.