Explicitly Nonlinear Connectivity-Matrix Independent Component Analysis in Resting fMRI Data

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Abstract

Connectivity-matrix independent component analysis (cmICA) is a data-driven method to calculate brain voxel maps of functional connectivity. It is a powerful approach, but one limitation is that it can only capture linear relationships. In this work, we focus on measuring the explicitly nonlinear relationships between the voxel connectivity to identify brain spatial map in which demonstrate explicitly nonlinear dependencies. We expand cmICA using normalized mutual information (NMI) after removing the linear relationships and find highly structured resting networks which would be completely missed by existing functional connectivity approaches.

1 INTRODUCTION

During the past few decades, functional magnetic resonance imaging (fMRI) has become one of the most widespread approaches to understanding brain function. In this area, functional (network) connectivity has been widely used to analyze the relationship among distinct brain regions. Studies on network models of fMRI data suggest linear correlation provides a powerful tool to identify the relation between fMRI time courses [1]. It is also easy to calculate and interpret positive and negative correlations in the field (e.g., the default mode network tends to be anti-correlated to other networks). However, some research has suggested that brain activity exhibits nonlinear dynamic behavior [2]. Other studies discuss the nonlinear effects of hemodynamic responses in fMRI data [3, 4], which can also vary with time (and location) and changes from subject to subject. Considering even just these few examples of nonlinear effects, it is likely, even expected, that distinct brain areas might be nonlinearly related in a way that would be missed by conventional linear analysis. In the current study, we were interested in evaluating the degree to which explicitly nonlinear relationships (i.e., after removing the linear relationships) exist among brain regions in a functional connectivity context. We proposed a new statistical tool, explicitly nonlinear ICA (EN-cmICA), to measure explicitly nonlinear dependencies in spatiotemporal fMRI data. To do this, we combine two previously distinct lines of work, connectivity matrix ICA (cmICA), which extracts resting fMRI networks from a linear connectivity matrix, and normalized mutual information (NMI), which is an information-theoretic approach that has the advantage of being capable of measuring both linear and nonlinear dependencies.

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2 MATERIALS AND METHODS

2.1 Participants and Preprocessing

In this work, we applied our method on one subject fBIRN dataset. This data set is part of a larger data set that has been analyzed previously in [5]. Eyes-closed resting-state fMRI data is collected in the United States. Informed consent was obtained before scanning in accordance with the internal review boards of corresponding institutions. Resting-state fMRI scans were acquired using a standard gradient-echo echo-planar imaging paradigm: FOV of 220 × 220 mm (64 × 64 matrices), TR = 2 s, TE = 30 ms, FA = 770, 162 volumes, 32 sequential ascending axial slices of 4 mm thickness and 1 mm skip. Data were preprocessed by using several toolboxes such as AFNI, SPM, GIFT. Rigid body motion correction using the INRIAlign [6] toolbox in SPM was applied to correct for head motion. To remove the outliers, the AFNI3s 3dDespike algorithm was performed. Then fMRI data were resampled to 3 mm3 isotropic voxels. Then data were smoothed to 6 mm full width at half maximum (FWHM) using AFNI3s BlurToFWHM algorithm and each voxel time course was variance normalized. Subjects with larger movement were excluded from the analysis to mitigate motion effects during the curation process. The preprocessing resulted in a 3D by time matrix for each subject witch of size (53×63×52)×157. For more details, please see [5].

2.2 Mutual Information Approach

The correlation coefficient mainly measures the linear dependence between two distributions. However, nonlinear dependence is not captured in the value of the correlation coefficient. Recent statistical approaches have been proposed to measure the correlation without underestimating the nonlinear dependency. One of these methods, mutual information (MI), measures both linear and nonlinear dependencies. However, MI units are not standardized, making it hard to compare across subjects and datasets. Some of normalizing factors for MI are: 1) min(H(x), H(y)), 2) H(x)+ H(y), and 3) max(H(x), H(y)). In this work we used the latter as [7] proved that it is a (normalized) similarity metric. The normalized MI (NMI) formula is

$$NMI(x, y) = (H(x) + H(y) - H(x, y))/(max[H(x), H(y)]).$$

In this work, our goal is to calculate only the nonlinear component of dependence. To do so, we measure the data's mutual information dependencies after removing the linear dependency. For a given vector *x* and *y*, fitting a linear model $y' = \alpha x + \beta$ gives the linear correlation between *x* and *y*. Here y' is the best linear estimation of *y* when *x* is given, the slope is denoted by , and is the y-intercept. Next, we cancel the linear effect by calculating z = *y* - y'. The nonlinear dependency of *x* and *z* is the same as *x* and *y*. Next, we can use NMI(x, z) to evaluate the nonlinear dependency of *x* and *y*. To assure symmetricity i.e., NMI(x, y)=NMI(y, x), we took the average of the results when switching *x* and *y*.

2.3 Explicitly nonlinear mutual Information of cmICA

We use connectivity matrix (cmICA) method, introduced in [8], to be applied on the brain connectivity to drive spatial map components. Brain connectivity is a voxel-by-voxel matrix whose element (i, j) value shows the similarity of voxel i and voxel j over time. In this work we used two measures, Pearson correlation and explicitly nonlinear mutual information (ENMI), to evaluate linear and explicitly nonlinear components of dependencies between voxels. Note that Pearson correlation is between -1 and 1 while NMI is 0 to 1. The cmICA is a novel method that can be used for dual parcellation of the brain connectivity. The dual parcellation consists of a set of spatially independent maps sk and a corresponding dual set of spatial maps rk such that rk defines the brain regions connected to sk. Our focus here is on driving spatially independent maps sk from the brain connectivity. To identify spatial map and explicitly nonlinear spatial map, we took these steps for an individual: The rsfMRI data is a 3D by time matrix (in total 4D). We first convert it to a vector by time, such that voxels get a long one dimension for each time pint. To reduce the calculation, we restricted to a 2D slice in this work. The subject data set is a 53 by 63 by 52 by 157 matrix, which is x, y, z, and time. We used the middle z = 26 slice, giving a 2D by time matrix. Next, we cancel voxels that don't have information about the brain and vectorize the rest voxels. After that, we calculate the Pearson correlation and ENMI of the brain voxels, which are the brain connectivity and ENMI brain connectivity (Fig. 1). These matrices

are the cmICA approach's input. In this work we let the number of components be five. This results in five linear and EN spatial maps. Fig. 2 demonstrates an example of each spatial maps.

3 RESULT AND FUTURE WORK

We implemented cmICA and EN-cmICA on one subject rsfMRI data set to drive five spatial maps from each approach. An example of each is displayed in Fig. 2. Note that the two methods, rather than being comparable, are complementary of each other. The cmICA reveals a set of statistically independent regions where in each region, the voxels showing a high level of linear correlation. Each region is considered as one spatial map. The EN-cmICA uncovers a set of statistically independent regions where in each region, the voxels show a high level of explicitly nonlinear relationship and considering them as one EN spatial map.

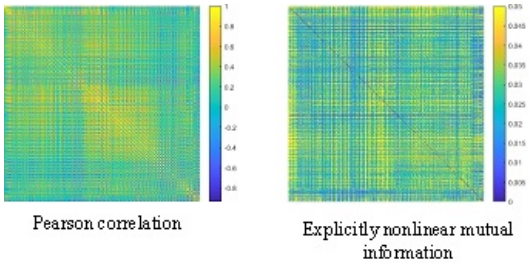

Figure 1: ENMI and linear connectivity of voxels. The left panel is the correlation between voxels over time. The right panel is the normalized mutual information after canceling the linear relationship between voxels over time. Pearson correlation is between -1 to 1, and NMI is between 0 to 1.

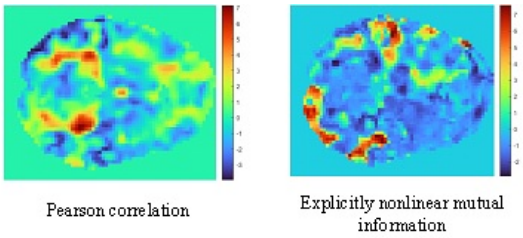

Figure 2: The EN and linear spatial component. Passing the connectivity and ENMI connectivity matrices to cmICA approach resulted in linear and explicitly nonlinear spatial maps. The left plot is one of the linear spatial maps, and the right is one of the EN spatial maps.

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