Evaluation of Nonlinear Functional Connectivity Using Phase-space Embedding

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Introduction

Baseline functional connectivity in the human brain has been studied extensively using linear methods [1,2,3]. However, an inherent deficiency of these methods is that they do not account for nonlinear correlations. A recent study reported the utility of nonlinear methods for the analysis of functional connectivity [4]. In this study, we applied nonlinear dynamic analysis to baseline fMRI data in this work. Specifically, bivariate embedding, a technique that allows us to examine the evolution of an image voxel and a seed voxel in a bivariate state space, is used to quantify nonlinear couplings between them. We validate this method by showing that it captures nonlinear synchronizations in a simulated coupled oscillator, which are not identified by linear methods. We then apply the above technique to resting fMRI data to quantify the nonlinear functional connectivity and compare it with linear results obtained from cross correlation.

Materials and Methods

Two runs of EPI data were acquired on five human subjects, one in resting state and one in block design finger tapping paradigm, on a 3T Siemens Trio (TR=750 ms, TE=34 ms, Flip Angle=50 deg and FOV=22cm, with 5 axial slices, 5mm slice thickness, 1120 images and 64 phase and frequency encoding steps). A physiological monitoring unit consisting of a pulse-oximeter and nasal respiratory cannula was used during data acquisition to record cardiac and respiratory signals, respectively. These physiological fluctuations were corrected in the functional data retrospectively [5].

Activation maps were generated from the finger-tapping data set, and the voxel in the motor cortex with maximum activation was chosen as the reference location. Cross-correlation maps with the chosen reference were obtained and five regions of interests (ROI)- Motor (M), Contralateral Motor (CM), Frontal (F), Parietal (P) and Supplementary Motor (SMA) -were identified. A mean voxel time series was calculated for each of the regions and the one for motor area was chosen as the seed voxel for embedding analysis. Bivariate embedding of this seed voxel time series in the motor area with each of the mean voxel time series of other four regions (candidate voxels) was accomplished using a special case of the generalized multivariate embedding formulation [6]. A bivariate nonlinear connectivity index (BNC) was defined as

$$BNC=(|dsc-ds|+|dsc-dc|)/(ds+dc)$$

where *dsc* is the bivariate embedding dimension of the seed and candidate voxels, and *ds* and *dc* are the univariate dimensions of the seed and candidate voxels, respectively. When the seed and candidate voxels are fully connected, the bivariate dimension does not provide any extra information than the univariate dimension and *dsc=ds=dc* and hence *BNC=0*. Therefore, the smaller the value of BNC, the higher the connectivity. Since this method makes no assumption of linearity, both linear and nonlinear couplings are accounted for. To validate the method, we used a simulated nonlinear coupled oscillator [7] given by the pair of equations

$$x(t)= 0.9*x(t-1)+a*y(t-1) \text{ if } x(t-1)\geq 0.1 \text{ and zero elsewhere}$$

$$y(t)= 0.8*y(t-1)+a*x(t-1) \text{ if } x(t-1)\geq 0.08 \text{ and zero elsewhere}$$

The coupling strength was varied by varying the parameter 'a', which gave rise to different nonlinear frequency synchronizations between the two oscillators. The synchronization ratio signifies the period relation between fundamental periods of the two oscillators.

Results and Discussion

Table.1 shows the results of application of BNC and Linear Correlation (LC), which was obtained by taking the cross-correlation between the two time series, to evaluate the connectivity. It can be seen that LC fails to capture the nonlinear couplings. On the other hand, BNC captures linear/nonlinear and weak /strong synchronizations. This validated the utility of BNC in evaluating nonlinear connectivity. Moreover, BNC tends to be more robust and consistent in the presence of additive noise. Table.2 shows the results of application of BNC and LC to resting fMRI data. It can be seen that M↔P exhibits highest connectivity and M↔F, the lowest. Also, M↔CM and M↔SMA exhibit strong connectivity, in agreement with results reported earlier [1]. The emergence of M↔P as the strongest connection, contrary to M↔CM obtained by LC, may be attributed to nonlinear couplings in this connection. Also, BNC rankings of these connections are more consistent across subjects than LC.

Conclusions

We have developed and demonstrated an approach for quantifying nonlinear functional connectivity in baseline fMRI. In addition to connectivity of M with CM and SMA commonly reported by linear methods, parietal and frontal areas also exhibited connectivity with motor areas in resting state owing to nonlinear couplings. The fact that the proposed method is more robust to noise, gives more consistent results and accounts for nonlinear correlations also, demonstrates its superiority.

a	*Synchronization*	*BNC*		*Linear Correlation*	
		No Noise	*10 dB Noise*	*No Noise*	*10 dB Noise*
0.0001	*Uncoupled*	*1.06*	*0.80*	*0.002*	*0.012*
0.005	*1:2*	*0.20*	*0.26*	*0.018*	*0.100*
0.028	*2:5*	*0.70*	*0.75*	*-0.250*	*0*
0.03	*1:3*	*0.67*	*0.74*	*0.086*	*0.014*
0.08	*1:1*	*0.14*	*0.29*	*0.055*	*0.044*

Table.1 Linear and nonlinear connectivity indices using a simulated nonlinear coupled oscillator

	Network	*Linear Correlation*		*BNC*
		LC	*Significance*	
Subject-1	*M↔P*	*-.07*	*-2.5*	*0.46*
	M↔SMA	*0.18*	*6.2*	*0.55*
	M↔CM	*0.52*	*20.2*	*0.56*
	M↔F	*0.44*	*16.5*	*1.05*
Subject-2	*M↔P*	*0.65*	*28.2*	*0.34*
	M↔SMA	*0.67*	*30.0*	*0.36*
	M↔CM	*0.71*	*33.4*	*0.38*
	M↔F	*0.47*	*17.7*	*0.45*

Table.2 Linear and nonlinear connectivity indices for baseline fMRI data for two representative subjects

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