Detecting direct and indirect functional connections using Granger causality

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Introduction

In the past decade, fMRI using the blood oxygen level dependent effect has been successful in identifying functional brain circuits underlying neural computations. Nowadays, most interest in system neuroscience has been switched from mapping sites of activation towards identifying the interconnectivity that weaves them together into dynamic systems. Recently, a Granger causality mapping (GCM) method based on vector autoregressive modeling of fMRI time series was used to analyze effective connectivity in the human brain [1, 2]. Unfortunately, current methods may not distinguish direct connectivity and indirect connectivity among brain regions, and incur a large computational cost by processing independently the signals from thousands of voxels within selected regions of interest rather than averaging them [3]. In this abstract, we develop a conditional Granger causality mapping method based on principal component analysis (PCA) to deal with this situation. For an immediate application of our new method, fMRI data from humans performing an emotional task were analyzed to clarify real causalities in the brain network.

Materials and Methods

Twelve right-handed volunteers (6 females; mean [S.D.]: 29.42±12.44) with normal vision, consisting of comparable ages were recruited as approved by the University of Florida Institutional Review Board. Three conditions were used in the face matching task [4]: (1) *emotion*, participants were asked to match the faces by their expressed emotion from a target face to two probe faces below; (2) *identity*, participants were asked to match neutral faces by identity; (3) *control*, participants were asked to match pixilated patterns derived from neutral face pictures. The task was ordered in blocks of six 3-s trials of the same condition, preceded by a 3-s instruction screen. The entire run consisted of twelve 21-s tasks blocks interspersed with thirteen 9-s rest blocks and lasted 189s. During rest, a fixation cross was displayed. The experiment was performed on a Siemens Allegra 3.0 Tesla MR scanner with a dome-shaped standard head coil. Structure images were acquired using a T1 MPRAGE sequence in the sagittal plane at 1.0 mm^3 resolution, TR = 1780 ms, TE = 4.38ms, flip angle = 8º. Functional images were acquired T2* weighted echo planar imaging BOLD sequence in the axial orientation (parallel to the AC–PC line), covering the whole brain with 36 slices, 3.8mm thick with no gap using TR = 3000 ms, TE = 30 ms, flip angle = 90º, a 240 mm^2 FOV and a 64×64 voxels matrix, giving 3.75 mm in-plane resolution. Total 125 volumes were scanned during the matching task experiment and the first two volumes were discarded before analysis to allow for T1 equilibration. PCA was used for dimensionality reduction within the large number of voxels activated in each ROI by performing a covariance analysis between factors and was based on the hypotheses that most of the information and energy within the ROIs is included in a few principal components (PCs). In our study, ROIs included pregenual cingulate gyrus (pACC), subgenual cingulate gyrus (sACC), inferior frontal sulcus and right amygdala, which were represented by 180, 120, 208, and 510 cubic voxel values, respectively with 123 volumes (time points) for each subject. Subsequently, each region's BOLD data were transformed into a vector consisting of 5 PCs and 123 functional for subsequent Granger causality analysis. Suppose that $\mathbf{W_t}$ was has been decomposed into three vectors $\mathbf{X_t}$, $\mathbf{Y_t}$, and $\mathbf{Z_t}$ with dimensions *a*, *b*, and *c*, stands for aim ROI, reference ROI and all the other ROIs in the brain, respectively: $\mathbf{W_t} = (\mathbf{X_t}^T, \mathbf{Y_t}^T, \mathbf{Z_t}^T)^T$, where $a + b + c = n$. Here $\mathbf{X_t}$ and $\mathbf{Y_t}$ are two sets of time series without overlap, and $\mathbf{Z_t}$ represents all time series indices other $\mathbf{X_t}$ and $\mathbf{Y_t}$ in the network. The measure for the linear dependence of $\mathbf{X_t}$ on $\mathbf{Y_t}$, conditional on $\mathbf{Z_t}$, in the temporal domain is:

$$f_{Y\to X|Z} = \ln \frac{\mathrm{var}(x_t \mid \mathbf{X_{t-1}}, \mathbf{Z_{t-1}})}{\mathrm{var}(x_t \mid \mathbf{X_{t-1}}, \mathbf{Y_{t-1}}, \mathbf{Z_{t-1}})}$$

Results and Conclusion

The selected activated brain ROIs include sACC, pACC, amygdala and inferior frontal sulcus. The GCM analysis indicates that both sACC and pACC have a strong directional influence upon the right amygdala during the emotion task, but not upon the inferior frontal sulcus. Inferior frontal sulcus has an indirect influence upon the right amygdala via the sACC, and receives feedback from the right amygdala. Coupling Granger causality for directional intrinsic connectivity was shown in temporal domain in Tab.1, and was also shown in Fig.1. The only significant instantaneous interactions were among a triangular network consisting of the amygdala, sACC, and pACC. These results are consistent with previous human brain studies and animal studies of medial prefrontal-amygdalar interactions [5, 6].

References

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Table 1: Granger causality values*

ROIs	IFS	Amygdala	pACC	sACC
IFS	_	**0.254**	0.181	**0.331**
Amygdala	0.200	_	0.174	0.125
pACC	0.212	**0.346**	_	**0.208**
sACC	0.134	**0.256**	0.206	_

*Direction of influence is from the activated region at the left to the region at the top. in bold are shown the significant Granger causality between two brain regions.

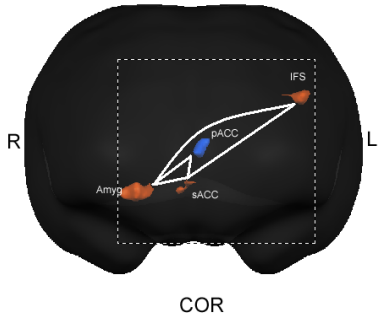

Figure 1: Granger causality graph in a local brain network.