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Effective connectivity estimation for evaluating encoding memory network

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Abstract— **Any defect in brain function and behavior may be attributed by a structural or functional deficiency. Effective connectivity is a potential approach for investigating the mechanisms of neural and psychological behaviors. In recent years, connectivity analysis has become increasingly significant in the field of computational neuroscience. Among Several neuroimaging modalities, fMRI has prominence for being non-invasive and having high spatial resolution.**

Memory networks have critical role in retrieval and encoding events, and they have been investigated in healthy subjects as well as patients such as those with temporal lobe epilepsy. In this work, we tried to use fMRI to extract the brain network among regions involved in memory encoding. We applied conditional granger causality method (GCM) to experimental fMRI time series data from a memory task.

For evaluating the accuracy of our analysis method we first tested the algorithm applied it on simulated data with known connections. Then the method was applied on real data from normal subjects for investigation the connectivity of hippocampal–neocortical regions.

The results from simulated data showed that GCM is able to reveal the connections in small number of ROIs (i.e. 7-8 regions). With increasing ROIs false negatives and false positives are increased. In the current work, seven ROIs of memory network introduced by C. McCormick (2010) were used and their connectivity and directionality were obtained. We found that activity of the left hippocampus causes the activity of the left inferior parietal cortex and also the right hippocampus positively influence the right retrospenial cortex.

I. Introduction

Whereas any region of brain controls specific behavior, doing or movements, any defect in these can return to lesion of structure or function. One of the important cognitive methods is survey of connection among these regions.

Connectivity includes structural and neuronal connections, functional connectivity and in the end causality and effective connectivity that has become increasingly significant in the field of computational neuroscience and treatment of illnesses in recent years.

Functional connectivity has been defined as "the temporal correlations between a seed region and other remote neurophysiological events" and effective connectivity as "the influence of one neural system exerts over another"[1, 2]. The effective connectivity definition is indeed a statement about causal relations between systems.

Several neuroimaging modalities such as EEG, PET, MEG and fMRI are used for studying of causality. Among these, imaging by fMRI has prominence for many reasons such as being noninvasive and its high spatial resolution.

There are many methods to evaluate causality in fMRI data set[3]. Structural equation modeling (SEM) among other methods is a well known one and has a longer history. After then it is worthwhile to mention dynamic causal modeling (DCM). Causality in DCM resulted from a non probabilistic and deterministic doing of dynamic system and assumes that this dynamic is reached to equilibrium state. In SEM model unlike DCM calculation is done on hemodynamic level and not on neural level [4-7]. DCM is completely diverse with two levels of hemodynamic and neural states. Hence in DCM changes emerge of neural level. So it is preferred to fmri data. But we should notice this point that DCM needs shorter TR[8, 9]. Memory networks modeling have a critical role in determining function of memory encoding and treatment of patients such as temporal lobe epilepsy (TLE). In 2001, Maguire[10] evaluated changes of connection of relative regions among two groups of healthy people and patients with bilateral hippocampus pathology and showed that, causality between hippocampus and parahippocampal cortex in control group during retrieval of memorabilia was increased while this wasn't so obvious in patients. In 2003 Simons perform a review on interactions between prefrontal cortex and the medial temporal lobe for processes of encoding memory[11]. In 2007, Rose Addis[11, 12] evaluate the role of hippocampus in changing of autobiographical memory networks in temporal lobe epilepsy patients by using of SEM method. Also, in other work, she presented positive and negative images to two groups of young and elderly people in evaluating of encoding memory networks[13]. In 2009, for better realization and treatment of TLE patients, was used from in vivo methods. First granger causality was applied on EEG data and then used structural techniques and diffusion tensor imaging(DTI) for evaluating structural changes of patients brain in animal models [14]. Recently McCormick compares existent changes of fMRI data between two networks memory: encoding and retrieval. He uses from Seed partial least squares (PLS) analysis first for determining activate hippocampal–neocortical regions candidate for connectivity analysis in two tasks. Then was applied SEM to compare two encoding and retrieval memory networks[15].

A. Autoregressive modeling and granger causality

In this work we used autoregressive equations and granger models to evaluate connections among regions. The

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basic idea of this can be say presented by Wiener [16, 17]. He explained that, one time seri is Granger causal for other if the first helps predict the second at some stage in the future. Granger later formalized the prediction idea in the form of linear regression equations. Specifically, if the variance of the autoregressive prediction error of the first time series at the present time is reduced by inclusion of past measurements from the second time series, then the second time series is said to have a causal influence on the first one[17].

Granger causal modeling (GCM) doesn't need prior anatomical and structural information about network so we prefer it to other methods that are hypothesis driven . DTI tractography can provide a more data-driven way of forming these prior data [18].

GCM has a simple concept. It has ability of surveying in both time and frequency domain. Granger can be used as a pairwise method without regarding influence of other regions on connections and also as conditional ones with regarding influence of all of regions in our network. So we used from conditional granger causality in our work [16, 19-22].

If we assume 3 signals x,y,z and a particular autoregressive lag length p, can estimate the following restricted equation by ordinary least squares (OLS):

$$\begin{aligned} Xt &= \sum_{j=1}^{p} a_{3j} X_{t-j} + \sum_{j=1}^{p} b_{3j} Z_{t-j} + \varepsilon_{3t} \\ Zt &= \sum_{j=1}^{p} c_{3j} X_{t-j} + \sum_{j=1}^{p} d_{3j} Z_{t-j} + \gamma_{3t} \end{aligned} \quad (1)$$

Covariance noise matrix is:

$$\Sigma_4 = \begin{pmatrix} \Sigma_3 & \gamma_3 \\ \gamma_3 & \Gamma_3 \end{pmatrix} \quad (2)$$

So for an F-test of the null hypothesis we estimate the following unrestricted equation:

$$\begin{aligned} Xt &= \sum_{j=1}^{p} a_{4j} X_{t-j} + \sum_{j=1}^{p} b_{4j} Y_{t-j} + \sum_{j=1}^{p} c_{4j} Z_{t-j} + \varepsilon_{4t} \\ Yt &= \sum_{j=1}^{p} d_{4j} X_{t-j} + \sum_{j=1}^{p} e_{4j} Y_{t-j} + \sum_{j=1}^{p} g_{4j} Z_{t-j} + \eta_{4t} \\ Zt &= \sum_{j=1}^{p} u_{4j} X_{t-j} + \sum_{j=1}^{p} v_{4j} Y_{t-j} + \sum_{j=1}^{p} w_{4j} Z_{t-j} + \gamma_{4t} \end{aligned} \quad (3)$$

So covariance noise matrix is:

$$\Sigma_4 = \begin{pmatrix} \Sigma_{xx} \Sigma_{xy} \Sigma_{xy} \\ \Sigma_{yx} \Sigma_{yy} \Sigma_{yz} \\ \Sigma_{zx} \Sigma_{zy} \Sigma_{zz} \end{pmatrix} \quad (4)$$

From these two equations we can define granger cause of X on Y in the form of:

$$F_{Y \to X|Z} = \ln \frac{\Sigma_3}{\Sigma_{xx}} \quad (5)$$

So can said that when connection of Y to X is mediated by Z, b_{4j} will be zero and $\sum_{xx} = \sum_3$. But if this connection is related directly with regarding of influence of Z, Y the value of $F_{Y \to X|Z}$ will be positive and we'll have $\sum_{xx} < \sum_3$.

II. MATERIALS AND METHODES

A. Simulated data

We haven't any complete maps from function or effective connectivity. For evaluating accuracy of this method we first test algorithm on simulation data with known connections and then we applied to real data. All simulations were done on MATLAB 7.11.0 software. First we convolve the square signal as a task representation with a hemodynamic response for every node in our simulation. So we design my network with auto regression models from BOLD signals with 3 lags in five node network and 8 lags in ten node network. After that data was downsampled and added Gaussian noise to it. This simulation was done with five and ten nodes. We tried to design our signals similar to real fMRI data with 160 volumes and TR=3. So we calculated the accuracy of our algorithm[14, 18].

B. subjects

Eighteen right-handed adults (12 female; mean age=25 years with age range of 20 to 30 years) participated in this study. They reported no psychiatric and neurologic illness and none of them were taking psychotropic medicine.

C. Experimental paradigm

The nonverbal memory encoding task, including 60 unfamiliar human faces was employed in this study. During scanning, subjects presented with 10 blocks which each block was consist of six faces. Before scanning, subjects were instructed to remember the faces for a later test. Approximately 20 minutes after scanning, subjects performed a recognition test outside the scanner. The subjects were shown the pictures and were asked if they were new pictures or identical to the ones previously shown. For 60 target faces, two states were assumed; a subject can recall faces (R response-FR) or not (F response-FF). Responses to recognition test were used in image analysis.

D. fMRI acquisition

Images were acquired on a Siemens 3 T Trio scanner with 12 channel head coil. Functional T2* weighted images were collected with blood oxygen level dependent contrast (BOLD), TR = 3,000ms, TE = 30ms, flip angle = 90 degree, FOV =192mm^2, matrix=64×64, voxel size=3×3×3 mm^3, Slice thickness=3mm, slice gap=0mm. Prior to the functional scan a T1-Weighted anatomical volume was acquired using a gradient echo pulse sequence, TR =1800ms, TE =3.44ms, flip angle =7 degree, voxel size=1×1×1 mm^3, fov=256 mm^2, matrix=256×256, slice thickness=1mm, slice gap=0mm.

F. fMRI data analysis

following pre-statistics processing were applied: motion correction, slice-timing correction, spatial smoothing using a Gaussian kernel of 6.0mm full width half maximum; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=60.0s. Time-series statistical analysis was carried out using FILM with local autocorrelation correction. As a result, for each subject, one contrast image obtains corresponding to the subsequent memory effect (FR-minus-FF). Functional data was registered to high resolution structural and/or standard space images. This entire image was used for the second-level analysis. In the next stage Higher-level analysis was carried out to obtain mean activation across the normal groups (one-sample t-test).

III. RESULTS

We made two simulated fMRI data for two permanent networks with five and ten nodes. Structure of each network and time series of each node are illustrated in figure 1 and 2. In these figures red lines indicate a bilateral connection between two nodes. First we checked covariance stationary matrix of time series using KPSS and ADF (Dickey-Fuller) test. Before making regression equations, was calculated the best model order. Either the Akaike information criterion (AIC) or the Bayesian/Schwartz information criterion (BIC) was used. Table 1 compares false negatives and false positives of resulted connections between two model orders after 20 repetition of our algorithm. The maximum false positive and false negative for 5 nodes network is 15 and 5. For 10 nodes network is 75 and 15. So we evaluated the portion of the correlation structure in data that is accounted for by an MVAR predicted model. Model consistency was higher than 80%. So we calculated significant Granger causalities with FDR (false discovery rate). P-value threshold was set to 0.01.

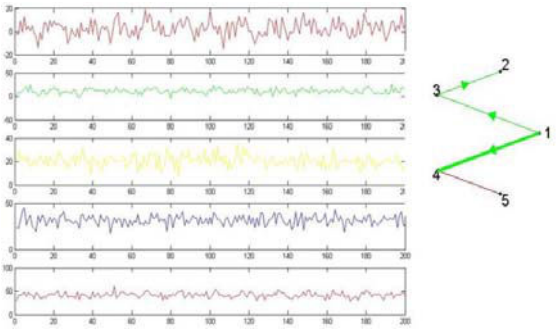

Fig1.five nodes network and timeseries of each nodes

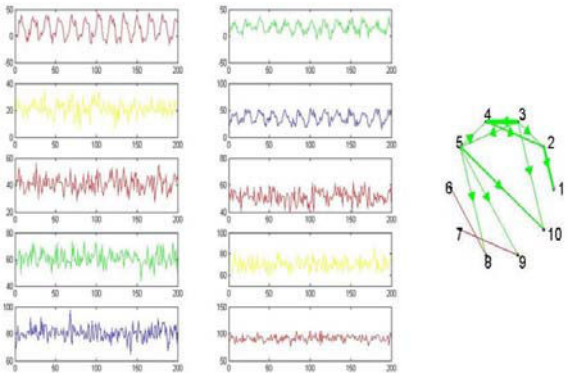

Fig2.ten nodes network and timeseries of each nodes

Table I. Errors in two networks with two model order estimation

Network	**Five Nodes**		**Ten Nodes**	
Model order / **Errors**	***AIC* = *7***	***BIC* = *3***	***AIC* = *10***	***BIC* = *3***
FP	0.5	0.9	1.6	3.03
FN	0.47	0.25	4.85	3.16
Total Errors	0.97	1.15	6.45	6.19

In next step, we determine interested active regions. Five of these are illustrated in figure 3.

So we select seven interest regions and averaging all of voxel's time series in each region. Our selection of regions for the GCM analysis was based on C. McCormick (2010) paper region selections. These regions are: bilateral hippocampi (LHC =−18, −32, −6; RHC= 14, −32, −10), bilateral inferior frontal cortices (LIFG =−34, 28, 4; RIFG = 36, −56, 40), left inferior parietal cortex (LIPC =−36, −56, 40), right parahippocampal gyrus (RPHG = 26, −28, −18) and right retrosplenial cortex (RRSC = 6, −44, 20). So we applied GCM in our regions. Selected best order with AIC and checked for uncorrelated residuals using Durbin-Watson test. For finding significant Granger causality interactions we set p-value to 0.01 and theresholded multiple testing with FDR. Results are illustrated in figure 4.

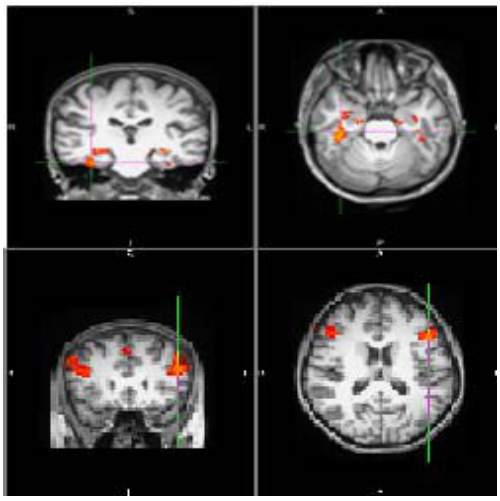

Fig3. Upper: bilateral hippocampi & right parahippcamal gyrus, bottom: bilateral inferior frontal gyrus regions that activated from encoding memory task

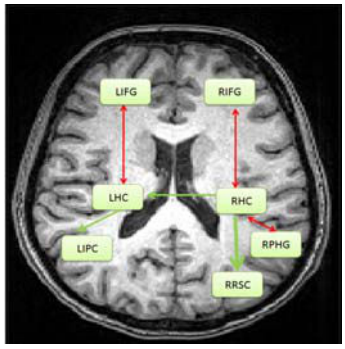

Fig4. Connections among seven hippocampal-neocortical regions

IV. Conclusion

In this study we examined conditional granger causality on two simulated and real data presented with encoding task. We estimated errors including false positive and false negative in simulated data .With various simulated data we showed that conditional GCM has more ability for recognition of small networks than greater networks with more nodes. So, definition of fewer regions in our memory encoding network helped us to achieve reliable results. In calculating best order of regression model, AIC method gives the values near the real values compared with BIC.

We found that activation of the left hippocampus causes the activation of the left inferior parietal cortex and also the right hippocampus positively influences the right retrospenial cortex.

We can use from other granger methods such as partial granger and nonlinear ones to achieve more accurate results.

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