Functional network connectivity with temporal derivatives of sICA time-courses in schizophrenia patients vs healthy controls

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Introduction

There has been a growing interest in analyzing functional connectivity among brain networks. Functional network connectivity (FNC) can be assessed by measuring correlations between time-courses of different brain networks, which, for example, can be estimated with spatial independent component analysis (sICA). Spatially independent components (ICs), or brain networks, have associated time-courses which are not necessarily temporally uncorrelated, and studying dependencies among those time-courses can reveal functional connectivity. An approach that uses maximal lagged-correlation of ICs in this context has been recently developed and was applied to assess functional connectivity in schizophrenia patients [1]. In this work, a new approach that considers the derivatives of the time-courses for measuring the correlations among different IC time-courses was developed.

Given two time-series vectors $x(t)$ and $y(t)$, the existing maximal-lagged correlation method estimates the correlation between the two vectors as [1] c_{max}=<$x(t)$,$y(t-\Delta_{max})$>, where "<.>" denotes correlation coefficient operator and Δ_{max} is the delay value that results in the maximal correlation coefficient. This is also equivalent to finding the maximum r-value (goodness-of-fit) over shifted linear regression of $x(t)$ and $y(t)$. In order to search for the maximum, time-series need to be shifted incrementally and an exhaustive search within a delay set is performed. We propose a more efficient approach including 1st and 2nd temporal derivatives of time-series in regression, that is, estimating $y(t)=\beta_0+\beta_1 y(t)+\beta_2 y'(t)+\beta_3 y''(t)+e$. Then, the delay can be estimated by β_2/β_1 [3] and the r-value can be used as a measure of dependency between the two vectors, hence, connectivity. Delay estimation based on SPM5's canonical HRF that is convolved with a block design, regressed with shifted version of itself, was simulated and is shown in Fig. 1. Polynomial fitting can be used for further approximating the delay. In this study, we have used this approach to assess functional connectivity in networks.

Materials and Methods

The study was approved by the local Human Research Review Committee and Institutional Review Board. *Participants:* In this study, participants consisted of 27 chronic schizophrenia patients (SP) and 27 matched healthy controls (HC). Healthy controls were screened to rule out any psychiatric or neurological illnesses. *Task:* For the fMRI study, an auditory sensory-motor task with 16s on / 16s off block paradigm with TR=2s was used. During the "on" block, the participants were presented with 200msec-length sounds of different tones and were instructed to press a button with the right thumb after hearing each different tone. The tones first increased and then symmetrically decreased for every block. The total duration of the fMRI experiment was 240s. Prior to the scan, the participants were tested of their capability of performing the task correctly via a computer console or mock scanner session. Participants who were not able to perform the task were excluded from the study. *Scan parameters:* During the fMRI study, the participants were imaged on a 1.5T Siemens Sonata whole body MR system. The following scan parameters were used for the BOLD fMRI sequence: PACE-enabled, single-shot, single-echo EPI, oblique axial scan plane, AC-PC, copy T2 in-plane prescription, FOV=22cm, 64x64 matrix, 27 slices, thickness=4mm with 1mm gap, TR/TE of 2000ms/40ms, flip angle 90°, BW=±100kHz=3126kHz/Px. *Preprocessing:* Preprocessing was done by SPM5. Images were motion-corrected by using INRIalign, spatially normalized to MNI space and subsampled to 3x3x3mm, resulting in 53x63x46 voxels. They were subsequently smoothed by using a Gaussian kernel of fwhm=10x10x10mm. *ICA analysis:* The Group ICA of fMRI Toolbox (GIFT) [2] was used for the spatial ICA analysis. After preprocessing, in order to make group ICA analysis computationally tractable, each participant's time-series data were compressed by using PCA, then they were temporally concatenated, and further compressed by PCA. The number of ICs in group ICA was estimated to be 20 by using the modified minimum description length criteria [3]. Group ICA was then performed on data, and the independent components were estimated. The infomax algorithm was used for the ICA [4]. The 20 components were then spatially reconstructed and visually inspected to determine whether they were artifacts or noise. Six components were identified and selected for connectivity study: A) left lateral fronto-parietal (LFP) network, B) anterior default mode (DM) n/w C) primary motor (M) n/w D) posterior DM n/w, E) temporal (T) n/w, F) right LFP n/w, G) stimulus paradigm. *FNC Analysis:* For each subject, time-series associated with the selected six components and the stimulus time-series were taken. Time-series were then paired and 21 combinations were obtained. Time-series were band-pass filtered between 0.04-0.4Hz. Maximal lagged-correlation approach required time-series to be upsampled (12 times) for reasonably accurate lag estimation. The correlation and lag values were calculated by using both approaches, for each subject. Significance of correlation values and lag values were calculated for each group. Significance for the group difference of the two values was also calculated. For the maximal lagged-correlation approach, the lags between ±4s were searched. For the derivative-correlation approach, first, simulations of delay were done based on SPM5's HRF and its first two temporal derivatives, and a polynomial fitting based on the simulations was used to further approximate the delays (example shown in Fig. 1). This idea is similar to derivative-boost method used in modeling the HRF [5].

Results and Discussion

Both approaches found significant group difference in correlation (HC minus SP, $p<0.02$, with no lag value constraint) in functional connection of 1) stimulus with temporal n/w, 2) left LFP with right LFP (shown in Fig. 2), which is consistent with previous findings that task-related activations in SP are less focused. In addition, the derivative-correlation approach and maximal lagged-correlation approach each found significant group difference in connection of stimulus with left LFP n/w, and right LFP with anterior DM n/w, respectively. Thresholding at different p values has shown that two methods mostly agree in terms of significant FNC within groups, as well as significantly different group differences in FNC. The derivative-correlation approach was more computationally efficient than the maximal-lag correlation approach (approximately 5 times faster). Also, upsampling requirement that is present for maximal lagged-correlation is not as stringent for the derivative-correlation approach. In future work, the derivative-correlation approach also might be useful in constructing an analytical framework for ICA that incorporates expected FNC patterns as prior information.

References [1] Jafri *et al.* NeuroImg. **39**:1666-81(2008) [2] http://icatb.sourceforge.net [3] Li *et al.* HBM **28**(11): 1251-66(2007) [4] Bell *et al.* Neur. Comp. **7**(6):1129-59 (1995) [5] Henson *et al.* NeuroImg. **15**:83-97(2002).

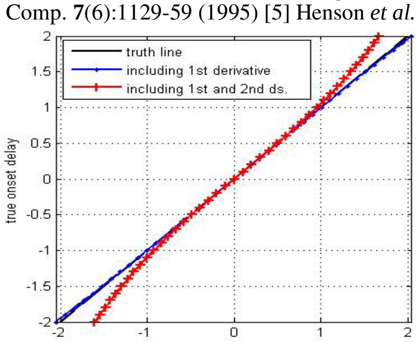

Figure 1 Simulation of delay estimation using SPM's canonical HRF convolved with the on/off block design and its temporal derivatives. Axes units are in seconds.

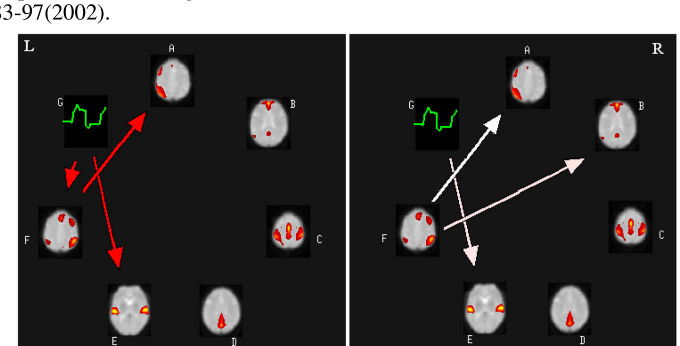

Figure 2 Functional network connectivity with **(L)** the derivative-correlation method **(R)** maximal lagged-correlation method. An arrow from A to B indicates that Component B's time-series lags A's time-series, and that they are significantly correlated if the lag was not present.