Dynamic windowing reveals task-modulation of functional connectivity in schizophrenia patients vs healthy controls

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Introduction

Studying functional connectivity (correlations among voxels) among brain networks helps reveal important information about brain function in healthy and diseased brain. Being a major psychotic disorder, schizophrenia, is known to disrupt cognitive and motor functions and it has been shown to disrupt task-related functional networks during performance of certain tasks. Functional network connectivity (FNC) is a more recent approach which 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 independent brain networks, have associated time-courses which are not necessarily temporally uncorrelated, and studying dependencies among those time-courses provides a measure of FNC. An approach that uses maximal lagged-correlation of ICs in this context has been recently developed and was applied to assess FNC in schizophrenia patients [1]. In this work, the maximal lagged-correlation approach was modified so that time-windowed data was used, FNC was estimated and was updated dynamically as the time-window was updated. The new approach allowed us to dynamically observe FNC changes under task/no-task transitions.

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: 1) left lateral fronto-parietal (LFP) network, 2) anterior default mode (DM) n/w 3) primary motor (M) n/w 4) posterior DM n/w, 5) temporal (T) n/w, 6) right LFP n/w. *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, upsampled (12 times) for reasonably accurate lag estimation, normalized to zero mean unit variance. Then, time window with length of 16s was taken (win. #1). The correlation values and lag values were calculated by using the maximal lagged-correlation approach for each group [1]. Significance for the group difference of the two values was also calculated. For the maximal lagged-correlation approach, the lags between ±4s were searched. Then, the window was shifted 4s in time, and the measurements were repeated until the window reached the end of overlap with the first HRF block (win. #8). This was repeated for the 7 task blocks. Mean and stds. of correlations over subjects in each group were computed, and then averaged over blocks.

Results and Discussion

We examined modulation of functional connectivity among certain networks in an auditory sensory-motor task in healthy controls (HC) within a short time-window (Fig. 1). For example, in HC, average correlation of temporal lobe (C#5) with all other components decreases 7-10% from win. #4 to #6 (in 8s) and recovers back at win. #8. In contrast, the SP group showed much less modulation with the task. Also, for each win. #, average correlation stds. of HC group were almost half of average stds. of the SP group, making the task-modulated FNC in HC group relatively more reliable and robust than the SP group. This result suggests a generalized cognitive deficit and is consistent with previous findings that schizophrenia disrupts focality of task-related components.

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).

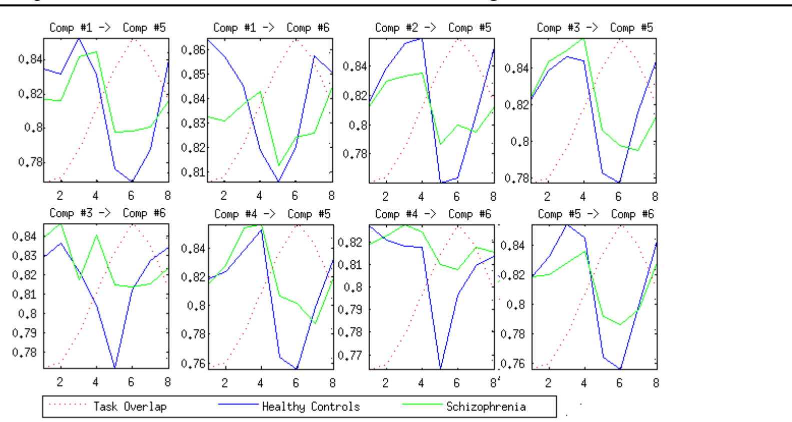

Figure 1 HC and SP correlations versus 8 window #s, averaged over 7 task blocks, for selected component pairs. Task overlap, i.e., relative area of the windowed time-frame with the "on" task block, is depicted with the task-overlap function. Index=6: max. task overlap. Index=1: min. task overlap. Notice the decrease in correlation of C#5 in HC, when maximum task is engaged.

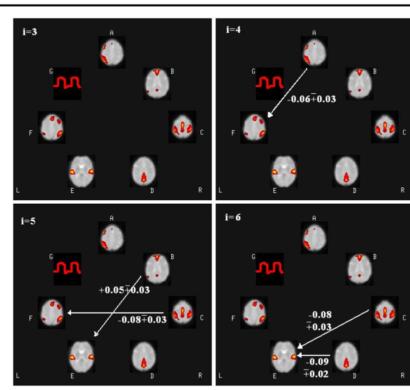

Figure 2 Significant connectivity difference (HC group minus SP group) for windows i=3 through i=6, in epoch #2 (task block #2). Connectivity is measured by maximal lagged-correlation of the components, averaged over subjects in each group. Group difference of average correlation and **s**td. of correlation values are displayed.