Multivariate Granger Causality Analysis of Brain Networks

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Introduction

This paper describes an approach combining multivariate Ganger causality analysis, temporal down-sampling of fMRI time series and graph theory to investigate causal brain networks. Multivariate granger causality utilizes the directed transfer function (DTF) which is better suited for modeling networks [1] than bivariate granger causal methods [2]. In addition to permitting the investigation of slowly varying processes such as fatigue, the coarse temporal scale of analysis removes the effect of the spatial variability of the hemodynamic response as a confounding factor. Finally, graph theoretic concepts [3] provide a vehicle for characterizing the resulting network topology for effective interpretation of the results.

Materials and Methods

EPI data were acquired from ten healthy volunteers while they performed repetitive right-hand grips at 50% maximal voluntary contraction in a 3T Siemens Trio scanner. Each contraction lasted for 3.5 s, followed by a 6.5 s inter-trial interval. The task lasted 20 mins and visual feedback was provided to guide the performance. Scan parameters were: TR= 2 s, TE= 30 ms, FA= 90°, voxel size = 3.44×3.44×4 mm^3. Activated voxels were identified by cross-correlating a reference waveform derived from the activation paradigm. Mean voxel time series from primary motor (M1), SMA, primary sensory (S1), pre-motor (PM), cerebellum (C) and parietal (P) areas were detrended. A summary measure time series was derived by calculating the area under each epoch, to permit the investigation of epoch-to-epoch variations. The Granger analysis was carried out in three non-overlapping temporal windows. A multivariate autoregressive model (MVAR) was fit using the summary time series from the six ROIs in each window as given below, subsequent to which the non-normalized direct DTF (dDTF) [1] was computed.

$$X(t) = \sum_{i=1}^{p} A(i)X(t-i) + E(t) \qquad dDTF_{ij} = \sum_{f} H_{ij}(f)\eta_{ij}(f)$$

Table 1 Clustering coefficients for different ROIs

Window		M1	SMA	PM	S1	C	P
1	C_{in}	19	15	7	9	16	11
	C_{out}	8	13	7	25	10	13
2	C_{in}	15	21	15	9	16	8
	C_{out}	8	14	11	23	18	10
3	C_{in}	11	13	9	9	15	8
	C_{out}	7	8	9	18	14	9

where p is the model order, $X(t) = (x_1(t), x_2(t)\dots x_k(t))$ is the data matrix with x_k representing an ROI summary time series and $E(t)$ is the prediction error. $H(f)$ is the frequency domain representation of $A^{-1}(i)$ and η_{ij} is the partial coherence [1] between ROIs i and j. In addition to giving the magnitude and direction of the causal influence, dDTF de-emphasizes mediated influences [1]. The statistical significance of the influences was ascertained using surrogate data technique [1,4] subsequent to which the consensus-inference concept [5] was used to find a single group significance threshold for all the subjects. Once the network was determined, we used the concepts of clustering coefficient and eccentricity from graph theory [3] to characterize it. Cluster-in (C_{in}) and cluster-out (C_{out}) coefficients were calculated as the total inflow and outflow (as measured by dDTF) at a particular node, respectively. C_{in} and C_{out} indicate whether an ROI is predominantly driven or driving. Eccentricity of an ROI is defined as the maximal sum of causal influence of the ROI along the path involving maximal causal strength and is indicative of the impact of that particular ROI on network performance [3]. The ROI with maximum eccentricity was defined as the major node in each window.

Results and Discussion

There was a significant decrease ($p<0.002$) in hand grip force measured after the task, indicating that fatigue had occurred. The change in connection patterns during the task are illustrated in Fig. 1. In the first window, S1 is the major node and, as seen from the Table 1, is the prominent driver while M1 is predominantly driven. In the second window, S1 and C are the strong drivers. Also, C is the major node and the cluster coefficients of SMA and PM are elevated. The strengthening and paring of connections in the second window are most likely related to a learning effect because in this window the dependence on raw tactile feedback was likely decreased and the orchestration of movement timing probably gained importance. Though the final window retains a hint of the middle window organization, no significant bidirectional feedback connections are seen (the network is cyclic in the first two windows and becomes acyclic in the final window), and the magnitude of the cluster coefficients decreases. This is consistent with the disconnectivity effects of fatigue as shown previously [6].

Conclusions

In this work we have demonstrated the utility of an integrated approach involving multivariate Granger causality, coarse temporal scale analysis and graph theory to investigate causal brain networks. Our results support the hypothesis that muscle fatigue leads to disconnectivity in the cortical network involved.

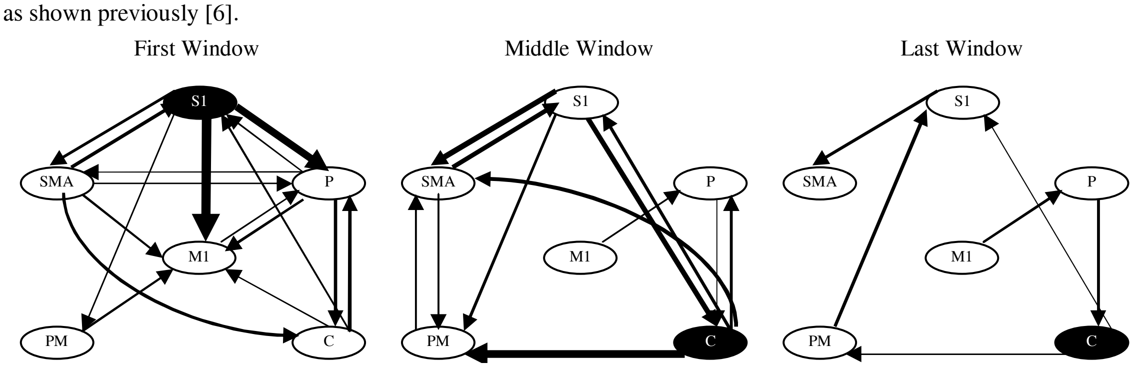

Figure 1 Temporal dynamics of networks. The significant links are represented as solid arrows and the p-value of the connections are indicated by the width of the arrows. The major node in each window is also indicated as dark ovals

References

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