Effect of hemodynamic spatial variability on Granger-based long term causality

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Introduction

Causal relationships between different cortical regions can be inferred from fMRI using Granger causality (GC) analysis. However, GC may be affected by the spatial variability of hemodynamic response (HRF) [1]. In this work, we examine the effect of HRF variability on the derivation of causal influence exhibited by the evolution of the neural network that is slower than the HRF variability and the TR. Simulations showed that the HRF variability leads to erroneous results. Furthermore, we show that the true causality could be recovered by using summary measures derived from the BOLD data instead of the raw fMRI time series. These findings are illustrated using data obtained from a fatigue motor task.

Materials and Methods

The purpose of the simulations was to show that hemodynamic confounds can overwhelm long term effects if the raw time series is used, leading to erroneous results and this effect can be eliminated by analyzing summary time series derived from raw BOLD data. Two time series, R_1 and R_2, were simulated by assuming an event-related paradigm consisting of 120 trials with epoch duration of 20 seconds. Each event was assumed to lead to a HRF defined by two Gamma functions (as in SPM2) with the following parameters: sampling interval=2 s, dispersion of response=1 s, dispersion of undershoot=1 s, delay of response (relative to onset) =6 s, delay of undershoot (relative to onset) =10 s, ratio of response to undershoot=6, length of kernel=20 s. The HRF for R_1 was assumed to be 1 s behind that of R_2. To mimic slow evolution of the two ROIs, the peak amplitudes for the trials in R_1 and R_2 were modulated by slowly varying sinusoids, denoted by A_1 and A_2, with A_1 leading A_2 by one epoch (Fig.1). Hence R_1 leads R_2 by an epoch even though its HRF is behind that of R_2. Gaussian noise (SNR=0, 5, 10 and 100, 500 realizations each) was added to the simulated signals to test the effect of random noise. Granger causality analysis was applied to both raw time series, R_1 and R_2, and the summary time series obtained by integrating each epoch, C_1 and C_2.

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. Summary measure time series were derived by calculating the area under each epoch, to permit the investigation of epoch-to-epoch signal evolution. Multivariate Granger analysis [2] was carried out in three non-overlapping temporal windows using both summary time series and raw time series.

Results and Discussion

Simulation results in Table 1 show that long term influences in the system were correctly inferred using summary time series but not the raw time series. The networks obtained from fatigue data (Fig.2) shows that summary time series was able to capture the epoch-to-epoch changes due to fatigue. Specifically, the reduction of connectivity in the last window is in agreement with the notion that fatigue reduces cortical connectivity [3]. In contrast, networks obtained from raw fMRI time series did not change with fatigue. This suggests that raw time series reflects the motor execution network and HRF relationships between the ROIs, neither of which are likely to change.

Connection	Raw Time Series			
	SNR=0	SNR=5	SNR=10	SNR=100
$R_1 \rightarrow R_2$	0.03±0.04	0.08±0.09	0.7±0.2	3.7±0.1
$R_2 \rightarrow R_1$	0.05±0.08	6.2±1.0	8.5±1.1	13.9±0.5
	Summary Time Series			
$C_1 \rightarrow C_2$	0.4±0.6	20±3.4	28.1±2.9	38±0.8
$C_2 \rightarrow C_1$	0.4±0.4	0.6±0.5	2.1±0.9	6.8±0.3

Table 1 Granger connectivity obtained from the simulated system

Conclusions

Spatial variability of the hemodynamic response is likely to hamper our ability to recover causal influences evolving slower than the sampling rate. We have demonstrated the above fact using both simulations and experimental data.

References

1. Handwerker et al, 2004. NeuroImage 21: 1639-51. **2**. Stilla et al, 2007. J.NSci 27:11091-102. **3**. Peltier et al, 2005. Brain Research 1057: 10-16.

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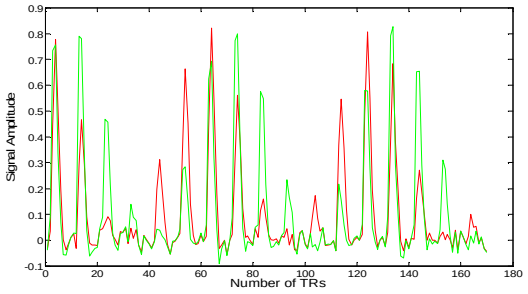

Figure 1 R_1 (red) and R_2 (green) modulated by slower sinusoids

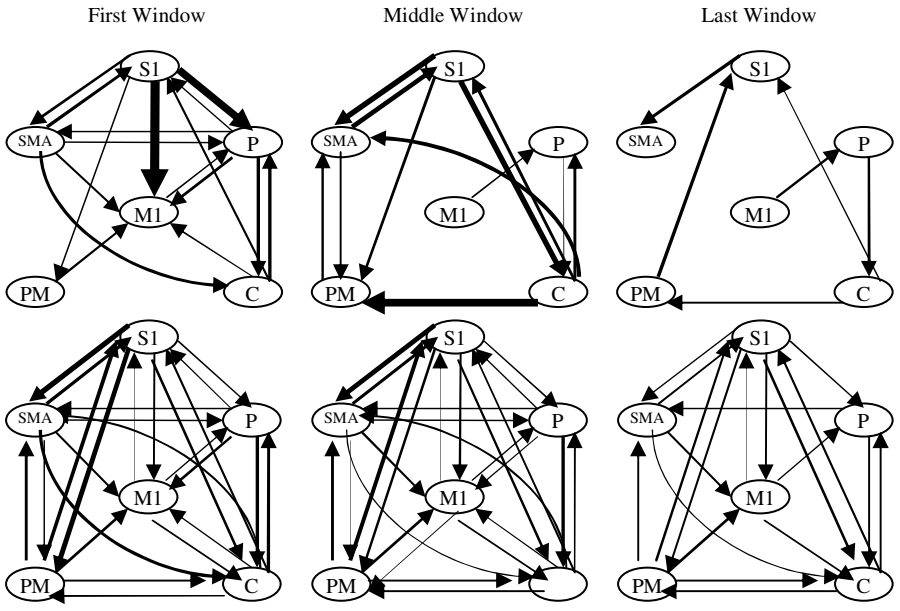

Figure 2 Top: Networks obtained from summary time series. Bottom: Networks obtained from raw fMRI time series. The significant links ($p<0.05$) are represented as solid arrows and the p-value of the connection are indicated by the width of the arrows.