Experimental validation of dynamic Granger causality for inferring sub-100ms neuronal timing differences from fMRI without the confounding effect of hemodynamic variability

Yunzhi Wang[1], Santosh Katwal[2,3], Baxter Rogers[2,4], John Gore[2,4], and Gopikrishna Deshpande[1,5]

[1]AU MRI Research Center, Department of Electrical and Computer Engineering, Auburn University, Auburn, AL, United States, [2]Vanderbilt University Institute of Imaging Science (VUIIS), Nashville, TN, United States, [3]Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, United States, [4]Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States, [5]Department of Psychology, Auburn University, Auburn, AL, United States

Introduction

It has been previously shown that functional MRI (fMRI) can indirectly infer timing differences of the order of hundreds of milliseconds from activations in the human brain, even though its temporal resolution is poor [1,2]. Recently, Katwal et al [3] attempted to directly detect small timing differences by introducing known timing differences between left and right visual cortex. They showed that Granger Causality (GC) works well for detecting temporal precedence in BOLD responses in visual cortex. However, regular GC cannot mitigate the effects of hemodynamic response function (HRF) variability [4]. The goal of our study is to propose a method which can not only infer timing differences, but also does not suffer from problems with HRF variability.

Methods

Gradient-echo EPI data (TR=250 ms, TE=25 ms, flip angle=30°, FOV=128 mm×128 mm and voxel size=1 mm×1 mm×2 mm) were acquired from a 7T Philips Achieva scanner from 5 healthy subjects in two coronal slices (with no slice gap) around the calcarine fissure. An event-related visual hemifield paradigm with known stimulus timing differences between the hemifields was used as described in [3]. The fMRI data used in the current analysis consisted of time series from two activated visual cortical regions (denoted as X and Y for right and left hemisphere, respectively) from a single slice selected through self-organizing map (please refer to [3] for experimental details and activation analysis). For each subject, there were 5 time series corresponding to 5 delays (0, 28, 56, 84 and 112 ms) between the right and left hemifield stimuli. For each delay, there were 17 trials. Dynamic Granger causality model [5,6] was used to get X→Y and Y→X connectivity time series for all subjects and delays. Then, dynamic Granger causality difference (dGCD) time series were calculated from abs(X→Y) – abs(Y→X). An experimental paradigm was generated by the convolution of stimulus boxcar function with the canonical HRF in SPM8 and a GLM was fit between the paradigm and dGCD time series to get a t-value. For each delay, there were 5 t-values, and a one-side z-test was performed to examine whether they were significantly larger than zero.

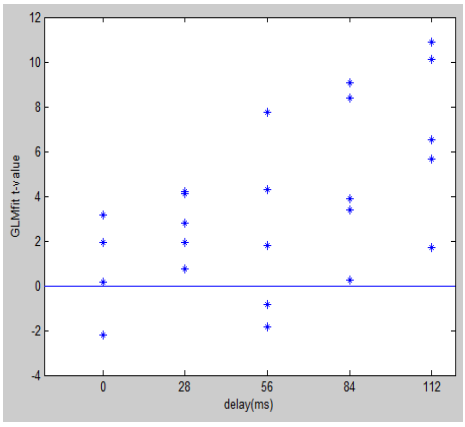

Fig.1 *GLM fit t-value versus delay times*

Results

Fig.1 shows the t-values of the GLM fit between the experimental paradigm and dGCD time series. Table 1 shows the p-values of a one-sided z-test used to test whether the t-value sample was significantly greater than zero. It is notable that no causality was detected for a delay of zero, while dGCD significantly covaried with the paradigm for all other delays. Also, the significance of causality generally increased with increasing delay. Fig.2 illustrates the covariance of dGCD with the paradigm (black) for delays 0 (blue) and 112 ms (red), averaged over all the 17 trial blocks for one of the subjects. For delay=112 ms, we see external stimulus driven increase in causality, which is not discernible for delay=0 ms. Also, the high causality near the start of stimulation for delay=112 ms may be driven by the initial dip of the HRF. This aspect needs further investigation.

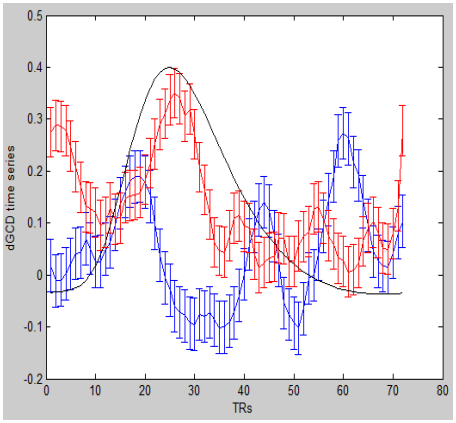

Fig.2 *Mean dGCD curves for delays 0 (blue) and 112 ms (red) for a subject*

Table 1 *z-test p-values*

Delay (ms)	p-value
0	0.1120
28	0.0034
56	0.0141
84	5.18×10^{-07}
112	3.81×10^{-12}

Discussion

In this study, dynamic Granger causality analysis was performed to detect sub-100ms timing differences in BOLD responses from the visual cortex. While Katwal et al [3] demonstrated this possibility using traditional Granger causality, our proposed metric of dGCD relies on experimental modulation of causality with time. Consequently, non-neuronal sources of HRF variability [7], which are structural and hence remain constant with time, cannot confound the results of dGCD as previously demonstrated by simulations [8]. In summary, our experimental validation of dynamic Granger causality to detect sub-100ms (as small as 28 ms) neuronal timing differences provides a reliable data-driven method for effective connectivity analysis or studies of timing from fMRI data.

References

[1] Menon *et al*, *PNAS* 95, 10902-10907, 1998. **[2]** Menon *et al*, Trends Cogn. Sci. 3, 207-216, 1999. **[3]** Katwal *et al*, NeuroImage, 2012, in press. **[4]** Deshpande *et al*, NeuroImage, 52, 884-896, 2010. **[5]** Lacey *et al*, NeuroImage, 55:420–433, 2011. **[6]** Sato et al, NeuroImage, 31:187–196, 2006. **[7]** Ollinger *et al*, NeuroImage, 21, 1639-1651, 2004. **[8]** Deshpande *et al*, Brain Connectivity, 2(5), 235-245, 2012