Correction of hemodynamic latency based on breath holding improves Granger causality obtained from fMRI data

Zhihao Li[1], Behnaz Yousefi[1], Gopikrishna Deshpande[2,3], and Xiaoping Hu[1]

[1]*Biomedical Engineering, Emory University & Georgia Institute of Technology, Atlanta, GA, United States,* [2]*Electrical and Computer Engineering, Auburn University, Auburn, AL, United States,* [3]*Psychology, Auburn University, Auburn, AL, United States*

INTRODUCTION Granger causality analysis (GCA) has been widely used in fMRI studies for assessing effective brain connectivity. Yet its accuracy and sensitivity are confounded by the spatial variability of the hemodynamic response (HR) [1,2]. One possible solution to this problem is to use breath holding (BH) as a hypercapnic challenge to assess regional vascular reactivity [3]. To examine the efficacy of this approach, BH was used in the present study to elicit BOLD responses unassociated with neural activation, and the voxel-wise HR latency values were derived from these responses and used to time-adjust the fMRI time series before passing them through GCA. We applied this approach in assessing effective connectivity in the ventral visual pathway of primary visual cortex (V1) to fusiform face area (FFA). Our results demonstrate the utility of BH based HR latency correction for improving the GCA of fMRI data.

METHODS Two healthy adults (1F1M, 30 and 35 y.o.) participated in this study and each completed 3 fMRI scan runs (3T Siemens, TE=30 ms, Matrix=64x64, voxel size=3.4x3.4x3.4 mm^3, flip angle=60^o). The 1st scan (TR=2 s) was acquired while the participants performed 16 repetitions of 11 sec BH [3]. In the 2nd and 3rd runs, each lasting 6 minutes, a sequence of 90 different human faces was presented with random inter-stimulus intervals and the participants were asked to memorize the faces. These two scans of visual perception used a TR of 2 s and 1 s, respectively, to examine the effect of fMRI sampling rate. Due to different TRs, the 3 fMRI scans had different number of imaging slices; but they shared a common prescription of 17 axial slices covering the occipital/temporal lobe for examining ventral visual pathway.

In processing the BH data, cortical voxels sensitive to BH modulation were identified by GLM analysis. For each of these cortical voxels, the BOLD signal time series was up-sampled to TR=0.1 s and the mean time series of these up-sampled signal was calculated. This mean time series was then temporally shifted within the time range of -4 s to 4 s with a step size of 0.1s. Each of these shifted versions of the mean time series were subsequently correlated with the up-sampled signal at each voxel and the version with the best correlation was identified. The voxel-wise phase difference between the best-correlated version and the non-shifted mean time series was therefore determined as the HR latency to be corrected.

In processing the visual perception data, two regions of interest (ROI), V1 and FFA, were defined for each of the participants based on their activation maps (Fig.1). The fMRI time courses of these ROIs were then up-sampled into TR=0.1 s, temporally shifted according to the latency determined by BH data (only for voxels with a HR latency < 2s [4]), and down-sampled back into the original temporal resolution. In calculating the effective connectivity from V1 to FFA, both the shifted and non-shifted fMRI signal of these 2 ROIs were fed into an analysis of "correlation purged Granger causality (CPGC)" [5]. The outputs of this CPGC analysis were connectivity coefficients indicating how much the FFA signal changes given unit signal change in the V1. The significance of the resultant connectivity was assessed with a surrogate data approach [5]. According to the well known neurophysiology of this ventral visual pathway, we expected positive signal influence from V1 to FFA, and the correction of HR latency should improve the detection of this positive influence.

RESULTS As we expected, positive directional influences were detected from V1 to FFA and the latency correction generally increased this positive influence. The connectivity coefficients are shown in the Table 1. The latency correction increased the phase difference between the ROI signals, improving the derived connectivity in both subjects. This turned out to be particularly beneficial for the subject 2, whose data were somewhat compromised due to drowsiness; in this subject, the p-value of the connectivity improved from below significance to above significance with TR=1 s. It is also shown in the present data that a higher fMRI sampling rate is generally beneficial for GCA as suggested by previous simulation [2].

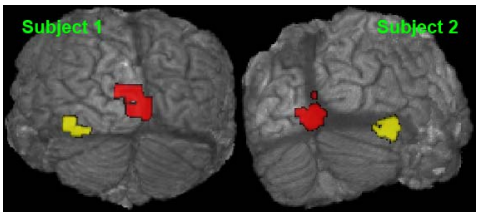

Fig.1 The ROIs of V1 (red) and FFA (yellow)

Table.1 Connectivity coefficient derived from CPGC

Subject	*Latency correction*	*TR=1s*	*TR=2s*
Sbj.1	*uncorrected*	$0.61(p<0.001)$	$0.40(p<0.001)$
	V1 / FFA: -0.07 s / 0.92 s	$0.72(p<0.001)$	$0.56(p<0.001)$
Sbj.2	*uncorrected*	$0.10\ (p=0.27)$	$0.03\ (p=0.50)$
	V1 / FFA: -0.92 s / -0.65 s	$0.32\ (p=0.03)$	$0.06\ (p=0.40)$

DISCUSSION The present study provides data supporting the feasibility of using the BH approach to correct the HR latency in analysis of brain effective connectivity with GCA. Further validations of this approach require a larger sample size as well as electrophysiological recordings such as EEG.

REFERENCES [1] David et al. PLoS Biol. 2008, 6:2686. [2] Deshpande et al. Neuroimage. 2010, 52:884. [3] Chang et al. Neuroimage. 2008, 43:90. [4] Handwerker et al. Neuroimage. 2004, 21:1639. [5] Deshpande et al. 2010, IEEE Trans. Biomed. Eng. 57:1446.

This work was supported by: GA Research Alliance, NIH grant RO1 DA17795 and RO1 EB00200