Comparison of Methodologies for Detecting Small Temporal Differences in BOLD Responses Using fMRI

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INTRODUCTION

Functional MRI (fMRI) has been able to infer neural onset differences of the order of hundreds of milliseconds, even though it measures a blood oxygenation level-dependent (BOLD) response that is delayed and dispersed on the order of seconds. This capability may contribute to our understanding of communication within the brain by helping to evaluate the temporal sequence of brain processes (mental chronometry), possibly giving insights into inter-regional influences (effective connectivity). The practical limit of fMRI for detecting small differences in the onsets of brain activity is not known. We aim to detect fine differences in BOLD response onsets, modeled as temporal shifts in hemodynamic responses, using Granger causality in order to infer minimum resolvable neural timing difference from fMRI data. For high sensitivity, we use high-resolution fMRI data from primary visual cortex (V1) acquired at high-field (7 Tesla). We select voxels responding to the task with self-organizing map (SOM), an artificial neural network trained by unsupervised learning for data-driven fMRI analysis [Liao]. We also select voxels using independent component analysis (ICA), a commonly used data-driven method, statistical parametric mapping (SPM) that uses general linear model (GLM) based multiple regressions and a separate localizer scan in conjunction with SPM. Additionally, we fit curves to the average signals by modeling the hemodynamic response with inverse logit (IL) functions and estimate differences in time-to-peak (dt) to compare temporal differences in the signals [Lindquist]. ROC curves are drawn to compare the performance of Granger causality and IL fits on average signals from voxels obtained from SOM, ICA, SPM and localizer scan with SPM.

METHODS

Visual stimuli were generated by a two-second flashing of two radial checkerboards (separated by a fixation cross) at a contrast reversal rate of 8Hz followed by a 16-second rest for a total 17 trials and 306 seconds total run time. The onset difference between the left and right hemifield stimuli ranged from 0 to 112 ms in steps of 28 ms (twice the refresh time of the projector). 2D gradient EPI (TR=250ms, TE=25ms, FOV=128x128 and voxel size=1x1x2mm^3) images were acquired on a Philips Achieva 7T MR scanner. Task-related voxels were selected for each session from one coronal slice via SOM, ICA and SPM. Voxels were also selected using SPM on the localizer scan. About the same number of voxels were chosen for each method. A bi-variate AR model was fit to the average time series, $\boldsymbol{x}$ and $\boldsymbol{y}$, from right and left hemispheres of V1 respectively. Granger causality was calculated as the overall ability of $\boldsymbol{x}$ to predict $\boldsymbol{y}$ using the Granger causality difference (GCD), $F_{x\to y} - F_{y\to x}$ [Roebroeck]. In the absence of any overall temporal precedence, the GCD should be zero. A positive value of the GCD implies precedence of $\boldsymbol{x}$ over $\boldsymbol{y}$ and a negative value means the opposite. It should be noted that Granger causality was used in this work to detect temporal shifts in the signals and not to quantify any direct neuronal influences. To compare results from Granger causality, difference in time-to-peak (dt) between $\boldsymbol{x}$ and $\boldsymbol{y}$ was also estimated from the curves fitted on the average responses using inverse logit functions following [Lindquist].

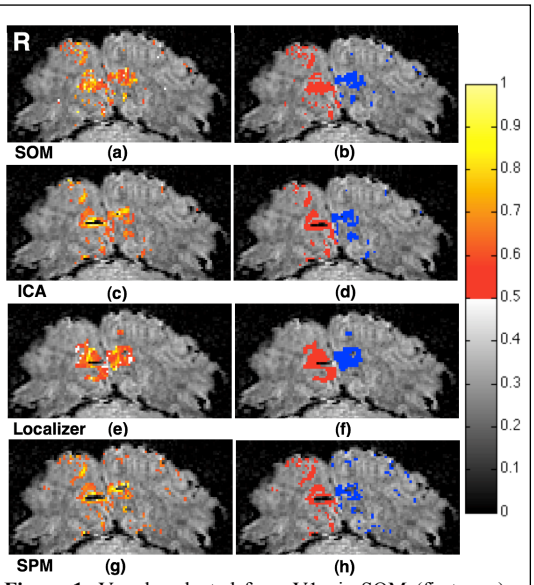

Figure 1: Voxels selected from V1 via SOM (first row), ICA (second row), localizer (third row) and SPM (fourth row). In the first column **(a, c, e, g)**, the colormap is based upon trial-to-trial reproducibility of the signals from the selected voxels. Second column **(b, d, f, h)** shows the same voxels after manual division into right hemisphere (red) and left hemisphere (blue) categories.

RESULTS

Figure 1 shows functional images with voxels selected by four methods. Figure 2 (Left) shows the GCD measures at various onset differences in five subjects with voxels selected via SOM. For statistical inference, 95% confidence interval (CI) was calculated from 1000 bootstrap samples drawn randomly with replacement from the set of trial time series. The GCDs were close to zero at zero onset difference and differences down to 28 ms were resolved in all subjects. However, GCDs did not seem to increase with increase in onset difference which may be due to motion across sessions. To plot receiver operating characteristic (ROC) curves, we drew thresholds passing through each measure for all subjects to calculate true and false positive rates at each threshold. If the measure for zero onset difference was more than the threshold, it resulted in a false positive. Likewise, if the measure for non-zero onset difference was more than the threshold, it would be a true positive. Fig 2 (Middle) shows a ROC curve from GCD measures where SOM outperformed others with 100% detectability. Fig 2 (Right) shows a ROC curve from differences in time-to-peak (dt) where SOM and ICA outperformed SPM.

CONCLUSIONS

SOM is a multivariate data-driven approach without any assumptions while SPM follows a univariate hypothesis-driven approach with assumed hemodynamic response shape based on gamma variate functions. ICA is also data-driven but is limited by a strong independence assumption. This possibly explains the lower detectability of ICA and SPM compared to SOM. However, ICA performed better with difference in time-to-peak measures. In summary, data-driven approach for voxel selection seems to work better for detecting temporal differences. The combination of SOM and Granger causality performed the best by detecting differences as small as 28 ms in this work with a controlled experiment and high signal-to-noise data.

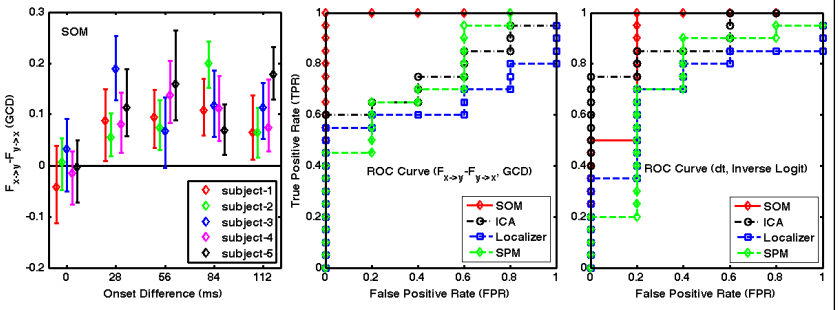

Figure 2: (Left) Granger causality difference (GCD) with 95% bootstrap CI for onset differences with voxels selected via SOM. Differences down to 28 ms were resolved in all five subjects. **(Middle)** ROC curve from GCD measures. Area-under-the-curve for: SOM = 1, ICA = 0.76, SPM = 0.75 and Localizer = 0.65. **(Right)** ROC curve from difference in time-to-peak (dt) measures with inverse logit curve fit. Area-under-the-curve for: SOM = 0.9, ICA = 0.89, SPM = 0.73 and Localizer = 0.71.

REFERENCES

Liao W et al. *IEEE TMI* 27:1472-83 (2008), **Roebroeck** A et al. *NeuroImage* 25:230-42 (2005), **Lindquist** M et al. *NeuroImage*, 45:S187-98 (2009).