Maximal Accuracy and Precision of HRF Measurements in Rapid-Presentation ER-fMRI Experimental Designs

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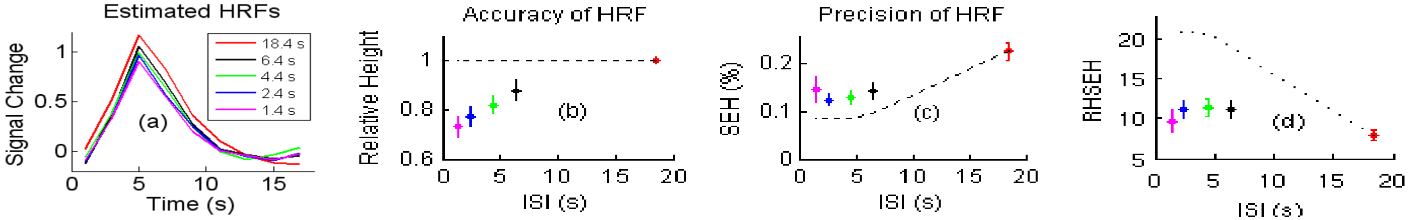
Introduction: In an event-related (ER) fMRI study of visual masking in humans [1], the measured V1 hemodynamic response functions (HRFs) to briefly displayed visual stimuli were found to be correlated with electrophysiological responses to similar stimuli in the monkey primary visual cortex [2]. This suggests a possible quantitative relationship between the HRFs and the corresponding neuronal firings. Determining this quantitative relationship requires an accurate and precise measurement of HRF. This type of measurement may be achieved by increasing the total number of stimuli in a periodic ER-fMRI experimental design with an adequate interstimulus interval (ISI) which ensures no overlap of the HRF between consecutive stimuli. However, due to the limited MRI scanning time and possible subjects' attention decline in a lengthy fMRI session, such a design constrains the total number of repeated stimuli which results in a low precision. The low precision could be improved with a rapid presentation (RP) ER-fMRI design utilizing the approximate linearity of the HRF [3]. For a given length of MRI scanning time and a selected ISI value, the estimator variance of the HRF could be minimized, therefore maximizing the precision via an appropriate design matrix selection. This results in a maximized estimator efficiency [4,5]. The estimator efficiency increases with decreasing ISI and could be ten times greater than that which can be achieved by periodic ER-fMRI designs [3]. Nevertheless, hemodynamic response is non-linear and its corresponding effect on the estimated HRF increases with decreasing ISI, rendering the estimated HRF inaccurate for small ISI values. A 17-25% reduction in the amplitude of HRF was observed for the ISI of 5 s compared to that for the ISI of 20 s [6]. Accordingly, an optimal ER-fMRI design should maximize both accuracy and precision of HRF measurements. In this preliminary study we investigated optimizing the accuracy and precision of HRF measurements in RP ER-fMRI experimental designs.

Methods and Materials: Six subjects (age from 19 to 58 years) participated in the study. Functional brain images covering the whole occipital cortex were acquired with a gradient echo EPI sequence (TR = 2 s). The visual stimuli were black and white stripes with a spatial frequency of 2 cycles per degree and with 4 orientations: 0°, 45°, 90°, and 135°. Each pattern was presented for 1.6 s and flipped between black and white at a rate of 2.5 Hz. The stripe orientation varied randomly across trials to minimize neural adaptation. The control condition was a blank screen with the mean luminance of the stripe. Each subject had ten functional scans and each scan acquired 124 volume images for one ISI value. One fixed ISI of 18.4 s and four mean ISI values (1.4 s, 2.4 s, 4.4 s, and 6.4 s) were used, and each ISI value was repeated twice. For the fixed ISI of 18.4 s, the stimulation temporal pattern was a periodic ER-fMRI design. For each of the other four ISI values, its temporal pattern was chosen as the one with the maximum efficiency among 1000 randomly generated patterns at that ISI value using an in-house developed Matlab-based software algorithm. In addition, a standard retinotopic mapping protocol was performed for delineating visual areas. The subjects were instructed to fixate at a mark displayed at the center of the visual field during all functional scans.

For each ISI value, the functional images were analyzed with a voxel-by-voxel least square time series fitting using the 3dREMLfit function in afni [7]. The 3dREMLfit accounts for temporal correlation of noise and estimates it using the ARMA(1,1) model [7]. The HRF is assumed to have 9 time points (18s) and to be time-invariant from trial to trial without a prior assumption of a specific form. A second order polynomial was included in the model to account for the baseline shift [8]. Activated voxels were defined as those with the estimated HRF significantly different from the baseline (F-value > 3.24 with an uncorrected $p < 0.001$). A region-of-interest (ROI) was then defined to include all activated voxels in V1 for the ISI of 4.4 s. For each subject, the estimated HRF was averaged over all the voxels in the ROI for each ISI value. For each estimated HRF, the peak height and the standard error of the height (SEH) were computed to estimate the accuracy and precision of the estimated HRF.

Results and Discussion:



The V1 activation maps for the five ISI values were very similar across all subjects. Figure (a) displays the group-averaged HRFs at the five ISI values. Before averaging, in order to minimize inter-subject variations, the HRFs for each subject were normalized with each curve being divided by the peak height of the HRF at the ISI of 18.4s. The figure shows the estimated HRF diminished with a decrease of ISI, indicating an increased nonlinear effect of hemodynamic response when the stimuli were presented closer in time. (A linear hemodynamic response would produce a similar HRF, independent of ISI.) Although the estimator efficiency increased with decreasing ISI, the diminished HRF demonstrates a decreased accuracy of the HRF measurements with a decrease of ISI. Figure (b) shows the group-averaged peak height of HRF versus ISI. In contrast to the linear model (dash-line), the monotonically decreasing peak height of HRF further demonstrates the decreasing accuracy of HRF measurements with decreasing ISI. Figure (c) shows the group-averaged estimated SEH at different ISI values in comparison to the linear model (dash-line). The general decreasing trend of SEH with a decrease of ISI reflects the reducing estimator variance of HRF in the RP ER-fMRI designs, resulting in an increased precision of HRF measurements. For each subject the ratio of the height and the SEH (RHSEH) was computed for each ISI value, and the group-averaged RHSEH for the five ISI values were plotted in Figure (d). The dash-line represents the theoretical RHSEH of the linear model. Figure (d) provides an overall measure for choosing accuracy and precision of HRF measurements in an RP ER-fMRI experimental design. Comparing the RHSEH among the four small ISI values, the design with the ISI of 6.4 s produced the most accurate HRF measurement with a moderately increased precision compared to the periodic ER-fMRI design. In conclusion, the diminishing HRF with decreasing ISI should be taken into account in choosing the optimal design in RP ER-fMRI experiments for producing maximal accurate and precise HRF measurements in a quantitative ER-fMRI study.

References: 1. J Huang, *et al*, NeuroImage **31**:1693-1699, 2006. 2. SL Macknik & MS Livingstone, Nat. Neurosci. **1**:144-149, 1998. 3. AM Dale, Human Brain Mapping **8**:109-114, 1999. 4. RM Birn, *et al*, NeuroImage **15**:252-264, 2002. 5. TT Liu, *et al*, NeuroImage **13**:759-773, 2001. 6. FM Miezin, *et al*, NeuroImage **11**:735-759, 2000. 7. http://afni.nimh.nih.gov/pub/dist/doc/misc/3dREMLfit/. 8. KN Kay, *et al*, Human Brain Mapping **29**:142-156, 2008.