Increase in Refractoriness of the BOLD Response Along a Functionally Connected Neural Pathway

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Introduction

Nonlinear relation between the stimulus pattern and the BOLD response has been observed at short inter-stimulus intervals (ISIs ~3 sec) in primary visual [1], auditory [2] and motor cortices [3]. BOLD responses of higher cognitive systems, specifically the language areas of the medial frontal cortex, have been shown to exhibit refractory behavior even at slightly larger ISIs (~5 sec) [4]. Qualitative evidence of increase in non-linearity of the BOLD response along a functionally connected neural pathway, the input (auditory) and output (motor) cortices of the receptive and expressive language processing network [5], has been reported [6]. In this study, the refractoriness of the hemodynamic response function (HRF) in the primary auditory cortex Broadmann area (BA) 41, temporoparietal cortex BA 40, and the precentral gyrus, three sequential parts of the receptive and expressive language-processing network, was examined. Our results indicate a distinct increase in the nonlinearity of the BOLD response along this functionally connected neural pathway.

Methods

Five normal control subjects (2 female and 3 male), ages 19-35 years were scanned on a 3T GE LX scanner. Scanning parameters: 1-shot spiral gradient echo sequence [7]; 10 5-6 mm coronal slices covering the motor, auditory and the temporoparietal cortex, TR/TE/FA= 500ms/18ms/50°, 3mm x 3mm in-plane resolution. High-resolution anatomic images were obtained using a *T1*-weighted spoiled GRASS sequence (TR/TE/FA= 23ms/6ms/25°; 124 1.3mm slices; 0.9mm x 0.9mm in-plane resolution). Foam padding was provided to restrain subject head motion. Written informed consent was obtained for all the subjects. The subjects performed 3 tasks in which they were asked to overtly repeat the nonsense word cues presented as soon as they heard them. The first task was a 1-word event-related paradigm in which the ISIs were varied among 13.5 sec, 14.5 sec and 16 sec in a pseudo-random manner. There were two such runs of 491 images each. In the second task the subjects were presented a series of 2-word stimuli with intra-pair-interval (IPI = 1sec) for 2 runs of 521 images each. In the third task the subjects were presented a series of 2-word stimuli with IPI= 3 sec for 2 runs of 641 images each. The inter block intervals between the 2-word cues were the same as the ISIs of the 1-word task.

Data Analysis

For each of the three different tasks, the functional runs were registered, detrended of low-frequency drifts and concatenated. For each voxel, the observed voxel FMRI intensity time-series was modeled as the convolution of the experimental auditory cue stimulus vector and the best-fit fifty-lag impulse response. The co-efficient of determination, R^2 and F-statistic were used to assess brain activation. The high-resolution images were Talairached and voxel hemodynamic responses (HRFs) for each of the 3 tasks, above the activation threshold (R^2 p-value < 10^{-7}) were extracted and averaged for primary auditory cortex BA 41, temporoparietal cortex, BA 40, and precentral gyrus. The averaged HRFs were fitted to a regularized generic hemodynamic response form [8] with a non-linear large-scale least-squares optimization method. Analysis was done with *AFNI* and *Matlab*^{TM}.

Results and Discussion

All the subjects exhibited increase in non-linearity of the amplitude of the HRF along the receptive and expressive language-processing network, from primary auditory cortex (BA 41) through temporoparietal cortex (BA 40) and precentral gyrus. Fig 1 shows the single event amplitude of the HRF for the 1-word task, the 2-word (IPI 3 sec) task, and the 2-word (IPI 1 sec) task normalized to that of the 1-word task for the auditory cortex (blue), the temporoparietal cortex (green) and the pre-motor area (red). The amplitude has been averaged across all the subjects. The error-bars represent the standard deviation (σ) of the normalized amplitude across 5 subjects for the corresponding condition. The results indicate a distinct increase in refractoriness of the HRF to the second word in a 2-word task along the functionally connected neural pathway. This method may provide new information to quantitatively assess functionally connected neural pathways with FMRI.

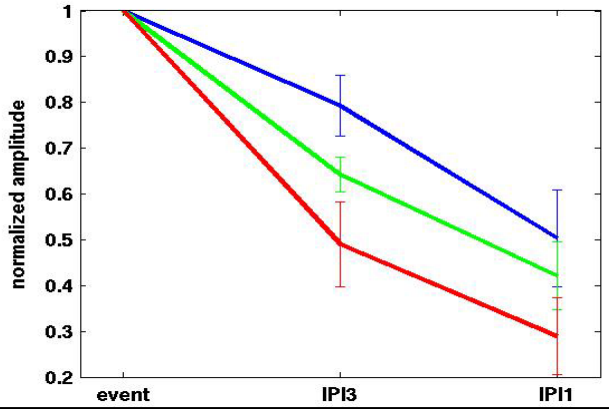

Fig.1 Single event amplitude of the HRF for the 3 different tasks, 1-word, 2-word IPI-3 sec and 2-word IPI-1sec, normalized to the amplitude of the 1-word task for auditory cortex BA 41 (blue), temporoparietal cortex BA 40 (green) and the motor cortex precentral gyrus (red). The error-bars indicate ± σ.

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