A Method for Accurate Measurement of Timing Differences in the BOLD Response Demonstrated in a Simple Paced, Self-Paced Experiment

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Introduction: The introduction of fast imaging techniques such as Echo Planar Imaging [(1)] (EPI) have enabled the rapid collection of MR images. In turn, this allows a high temporal resolution to be achieved in fMRI. However, this high temporal resolution is blurred by the intrinsic latency of the haemodynamic response [(2,3)], which varies with position across the brain due to variations in local vasculature. In this study we show that cortical timing differences exist between a paced and a self-paced task [(4)], and that such timings can be measured using linear regression [(2,5)]. Voxel by voxel comparisons overcome the problems associated with spatial variation of haemodynamic latency and rigorous statistical analysis enables statistical parametric maps (SPM's) to be created showing timing differences across the brain.

Methods: In the paced task, the subject is visually cued to perform 15 single button presses presented with a pseudo-random inter-stimulus interval (ISI). The mean ISI was 12 s with a standard deviation of 1.83s. In the self-paced task, the subject is asked to repeat the 15 button presses with a similar timing, but without the visual cue. As the self-paced task will inherently involve a random ISI, the paced task was also presented with a pseudo-random ISI to avoid biasing the results. Experiments were performed on a whole body 3 T scanner equipped with a short head gradient coil and a whole head RF coil. MBEST EPI images ($TE = 40ms$, $TR_{slice} = 80ms$) were acquired continuously from 16 sagittal slices with a voxel size of $3\times3\times9mm^3$. Initially data covering the whole brain with an image matrix of 64x128 was recorded and the two tasks were analyzed separately using standard techniques in Spm99 [(5)]. This initial processing represents a first level of analysis assessing areas of activation in both the paced and self-paced experiments.

Timing differences were analyzed using a method based on that of Menon *et. al.* [(2)]. For each voxel in the functional image, the Jittered MR data were reordered with respect to the button presses to create a single epoch response for both the paced and self-paced tasks. The resulting HRF's were then overlaid and Savitzky-Golay Filtering applied in order to temporally smooth the data without loss of shape (fig1A). The haemodynamic rise, assumed to be linear [(2)], was then extracted from the two HRF's and modeled using two straight-line equations (fig1B). These straight lines were used to create a linear regression model and the timing difference between the two HRF onsets (δt) were calculated directly along with the associated error (fig1C). These methods were tested and shown to be accurate for simulated data.

The measurement of the timing difference with its associated error allows for calculation of a T-statistic for each voxel. By calculation of the number of degrees of freedom in the data over the range of the model [(5)], a p-value assessing the significance of the measured timing difference was obtained. Thus, a second level of statistical analysis was applied whereby overlapping areas of activation in the paced and self-paced tasks were assessed for significant timing differences. Such areas were then plotted in a volumetric statistical parametric map and overlaid on original EPI images to create a functional map of timing differences.

The paced self-paced experiments were performed on 6 normal volunteers, and the spatial distribution of timing differences between the two tasks were assessed using the methods described above.

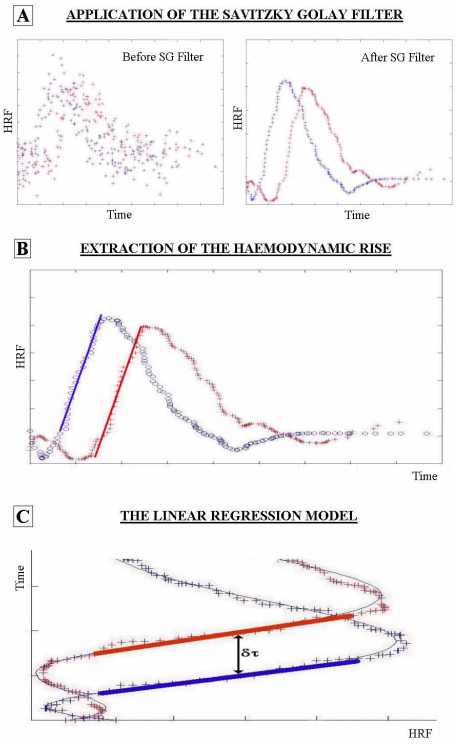

Figure 1:- Processing techniques applied to simulated data.

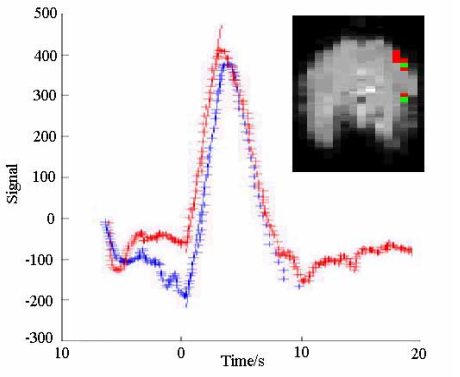

Figure 2:- Timecourses for voxel of interest in pre-motor cortex. $\delta t = 0.8(\pm 0.2)s$ *. Inset:- SPM of timing differences overlaid on an EPI image.*

Results and Discussion: Rigorous and consistent timing differences were detected in all six subjects in cortical areas known to be involved in motor tasks: primary motor cortex, pre-motor cortex and the supplementary motor area. The actual timing differences vary across areas in single subjects and show inter-subject variability. Figure 2 shows the model fitted to experimental data from a region of interest in premotor cortex for a single subject. Figure 2 (inset) shows a statistical parametric map of timing difference in pre-motor cortex in the same subject. Overlapping areas of activation (corrected p-value of 0.05) for both the paced and self-paced experiments defined by the first level statistics, and having significant ($p<0.001$) timing differences according to the second level of statistics are shown in red. Those areas defined as active (corrected p-value of 0.05) but with no significant timing difference ($p>0.001$) are shown in green.

Methods to obtain temporal information in fMRI data have been previously reported [(7)] However, Menon et. al. show that the rising edge provides the most accurate measure of onset timing of the haemodynamic response and this is exploited in our method.

Our results are in agreement with previously reported electrophysiological measurements [(6)] implying that the paced self-paced paradigm may be used in multi-modality temporal comparisons. In particular this may be applied to direct electrical measurement techniques such as EEG or MEG. Such experiments would help validate joint EEG or MEG / fMRI studies that exploit the high spatial resolution of fMRI and the high temporal resolution of EEG/MEG.

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