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Nonlinear effects in the bold response for short stimulus duration heterogeneity of hemodynamic response

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Functional magnetic resonance imaging using the BOLD effect is a well established technique to investigate non-invasively brain function. Most functional magnetic resonance imaging studies use linear models to predict the observed BOLD response by convolving the stimulus profile with a haemodynamic response function. For very short stimulus durations (<2s) deviations from the linear model have been found in response area and amplitude. In this study we investigated the nonlinearities in the BOLD response in the human primary visual cortex for four very short stimulus durations (200, 400, 800 and 1000ms) and for a half visual field stimulation paradigm. The nonlinear behaviour of the BOLD signal was observed for all stimulus durations and was more pronounced for the shortest stimulus duration (200ms) both in response area and amplitude. No correlation in the BOLD response was found when comparing the elicited signal change in the left primary visual cortex to the one in the right primary visual cortex suggesting that even for functionally equivalent areas of the brain the hemodynamic response might be different at different points in time.

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1. Introduction

Most functional magnetic resonance imaging (fMRI) studies use linear models to predict the measured BOLD response to a stimulus. These models are based on convolving the stimulus profile with a haemodynamic response function (HRF) and generating statistical parametric maps (SPM) of the activated regions of the cerebral cortex during stimulation. Although experimental evidence for the presence of a linear relationship between the stimulus and the BOLD response has been reported (Boynton et al., 1996), systematic deviations from the linear model were found by several groups (Savoy et al., 1995; Vazquez and Noll, 1998; Glover, 1999; Friston et al., 2000; Kershaw et al., 2001). Correlation of BOLD data with measurements of neural activity via different types of evoked potentials (Ogawa et al., 2000; Janz et al., 2001; Logothetis et al., 2001) from simultaneous electrophysiological recordings provided insights into the link between brain activity and the BOLD response. These studies reported linear relationships between BOLD data and electrical potentials measured. However, Ogawa et al., (2000) observed that the characteristics of the linear relationship change with stimulus separation. Sources of nonlinear relationships were found between stimulus and neuronal response, neuronal activation and blood flow response, and blood flow and the BOLD response (Ances et al., 2000; Yang et al., 2000; Mechelli et al., 2001; Miller et al., 2001).

The goal of this study was to investigate BOLD nonlinearities in the human primary visual cortex for very short stimuli with stimulus durations at and less than 1000 ms. We also compared the elicited BOLD response between the left and right primary visual cortices and observed that the response nonlinearity is different in functionally identical parts of the brain when applying the stimuli with the same characteristics. The term nonlinearity has been defined as any deviation of the BOLD response from a linear model, where a linear model predicts that in absence of a stimulus the BOLD response is equal to zero.

2. Materials and methods

Data acquisition

Blood oxygen level dependent (BOLD) contrast functional images were acquired with a SIEMENS MAGNETOM VISION scanner at 1.5 T by means of T2*-weighted echo planar imaging (EPI) free induction decay (FID) sequences with the following parameters: TR = 2000 ms, TE = 60 ms, matrix size 64 × 64, FOV 256 mm, in-plane voxel size 4 mm × 4 mm, flip angle 90°, slice thickness 6 mm and no gap. Eight sagital single-shot images covering the primary visual cortices were acquired and the slices were oriented perpendicular to the occipital fissure. A high resolution structural volume was also acquired at the end of the session via a 3D MPRAGE sequence with the following features: sagital slices covering the entire brain, matrix 256 × 256, FOV 256 mm, slice thickness 1 mm, no gap, in-plane voxel size 1 mm × 1 mm, flip angle 12°, TR = 9.7 ms, TE = 4 ms.

Subjects and paradigm

The experimental paradigm consisted of stimulation of the left or the right visual hemi-fields and the BOLD signal was measured in the primary visual cortices. The stimulus used was a black and white checkerboard with a reversing rate of 5 Hz projected on a screen at the back of the MRI scanner. During stimulus presentation and in the rest periods in between the volunteers were asked to look at a red cross in the centre of the screen and not to

move their eyes when the stimulus appeared on the screen. All this was done to ensure that the BOLD response occurs only in the left or right primary visual cortex. The durations of the stimuli used were 200, 400, 800 and 1000 milliseconds. Because of the short duration of the stimuli, the time of presentation and the duration of each stimulus were rigorously controlled by using the dedicated software package Presentation (Neurobehavioral Systems, S.U.A.). For one stimulus duration 40 trials were presented and the total duration of each trial was 14 seconds. As the duration of the longest stimulus was 1000 milliseconds this ensured an intertrial interval of at least 13 seconds that was deemed enough for the BOLD response to completely recover to the baseline (Pfeuffer et al, 2003).

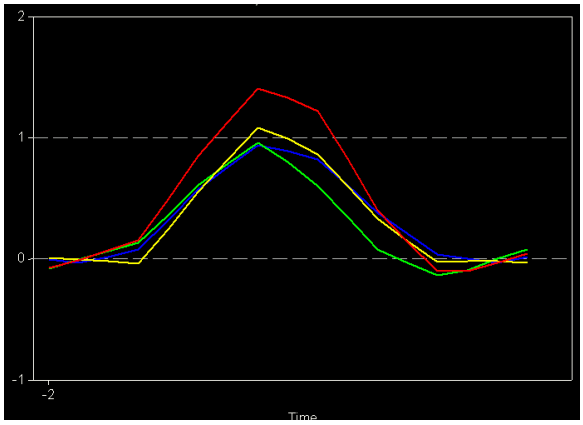

Fig. 1a. Typical BOLD response for a visual stimulation paradigm. The colour-coded curves represent the BOLD response to the four stimulus durations as follows: blue – 200ms; green – 400ms; yellow – 800 ms; red – 1000ms. The X axis represents time in seconds and the Y axis percent signal change (compared to the baseline).

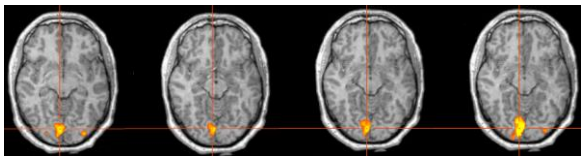

Fig. 1b. GLM maps in the right primary visual cortex for left visual field stimulation. From left to right: BOLD activation for 200, 400, 800 and 1000ms stimulus duration, respectively.

A total of 10 healthy volunteers were enrolled in our study. The study had ethical approval and all volunteers provided written consent. All 10 volunteers underwent the left visual field stimulation protocol but, when recalled for a second scan, only 8 agreed to take part in the right visual stimulation protocol. Each stimulation session (left or right) was performed on separate days and the scanning sessions were spaced in time several weeks apart.

Data analysis

Data were analyzed by means of the Brain Voyager 4.9 software (Brain Innovation, The Netherlands). Due to the T1 saturation effects, the first 5 scans of each run were discarded from the analysis. Pre-processing of functional scans included motion correction and removal of linear trends from voxel time series. The motion correction was performed by means of a three-dimensional rigid body transformation to match each functional volume to the reference volume (the sixth volume). The estimated translation and rotation parameters for each volume in the time course were inspected to check that the movement was not larger than approximately half a voxel for each functional run and that no stimulus-correlated movement had occurred (Friston et al., 1996 and Hajnal et al., 1994). Pre-processed functional volumes of a subject were co-registered th the corresponding structural data set. Since the 2D functional and 3D structural measurements were acquired in the same session, the co-registration transformation was determined using the Siemens slice position parameters of the functional images and the position parameters of the structural volume. Structural and functional volumes were transformed into Talairach space (Talairach and Tournoux, 1988) using a piecewise affine and continuous transformation. Functional volumes were re-sampled at a voxel size of 3 mm × 3 mm × 3 mm.

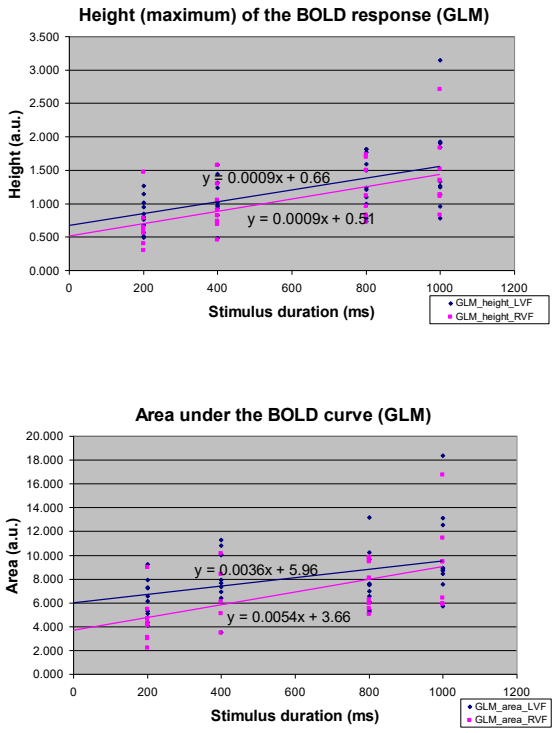

Fig. 2. Response amplitude and area vs. stimulus duration for the BOLD response for left visual field (blue) and right visual field stimulation (purple).

Statistical maps were generated from the fMRI time series based on an event-related analysis using the time information for stimulus presentation available from the stimulation protocol and two statistical methods: the general linear model (GLM) and the student t-test.

Before statistical analysis each image series was averaged over the 40 trials to increase the signal-to-noise ratio. For the GLM method the BOLD response to each visual stimulus was modelled by convolving the stimulus duration with the haemodynamic response function (Boyton et al, 1996). To determine the spatially averaged time courses for different series, a threshold ($p<0.01$ significance on the statistical maps) was used to determine the activated voxels. The signal was averaged over these voxels, which was done for all the series with different stimulus durations.

We also used a student t-test to find the activated voxels in the primary visual cortex by comparing a functional volume acquired during the baseline period to a functional volume acquired during the peak of the BOLD response. The level of significance used to threshold the t-test maps was the same as for the GLM method ($p<0.01$). This approach doesn't require the use of a haemodynamic response function and hence the BOLD response could be derived directly from the functional data without the use of a haemodynamic model. After selecting the whole activated area in the primary visual cortex, the response amplitude and area under the BOLD curve were derived and compared to the corresponding values obtained from the GLM analysis maps. A comparison between the BOLD response from the left and right visual cortices was performed to investigate the relationship between the nonlinearities from functionally equivalent brain areas (the primary visual cortices). The positive response area was determined by integration of the positive response and the response amplitude was calculated from the peak of the positive response.

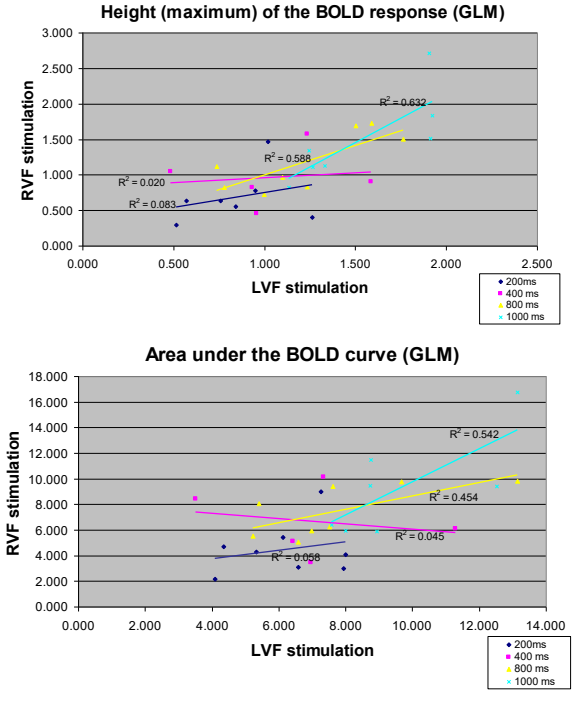

Fig. 3. Comparison in response amplitude and area of the BOLD response between the left and right visual cortices for right and left visual stimulation calculated using the General Linear Model. LVF –left visual field stimulation; RVF – right visual field stimulation.

3. Results

Typical BOLD responses to short visual stimuli from one volunteer at 1.5 Tesla are shown in Fig. 1a. The amplitude and area of the response decrease with stimulus duration. Figure 1b shows calculated GLM statistical maps for the BOLD response in the right primary visual cortex for all stimulus durations in one volunteer. In agreement with the anatomical visual pathways the BOLD signal was elicited in the right primary visual cortex for left visual field stimulation and in the left primary visual cortex for stimuli presented in the right visual field. The activation pattern was localised in the grey matter.

The results for the response area and response amplitude for the GLM analysis plotted vs. stimulus duration are presented in figure 2. For these two parameters used to characterise the BOLD response the expectation from a linear model would be straight line through zero. Clearly, there is a significant deviation from a linear model and this deviation was present both when using the GLM or t-test methods to calculate the activation maps.

When comparing the nonlinearities in the BOLD response in the same visual cortex, the two methods used to calculate the activation maps (GLM and t-test) showed good correlation between them both for the response area and maximum response for all stimulus durations. The correlation coefficients are presented in Table 1.

Table 1. Correlation coefficients for nonlinearities in the BOLD response between the two methods used to calculate activation maps (GLM and t-test).

	Left visual stimulation	Right visual stimulation
Height	0.770	0.868
Area	0.821	0.838

However, when we compared the BOLD response elicited for the same stimulation protocol in the left and right visual cortex of our volunteers we found that there was no correlation in response area and maximum response (Fig. 3). The correlation coefficients for both the GLM and t-test analysis are presented in table 2.

4. Discussion

Nonlinearities of the BOLD response to short visual stimuli were found in the response area and amplitude, being consistent with a sharper BOLD response at shorter stimulus durations. The two parameters used to investigate the behaviour of the BOLD response for short stimulus durations (area under the curve and maximum height) yielded similar results when comparing the statistical maps calculated either using the General Linear Model or the Student's t-test. This indicates that both methods are reliable in detecting the

nonlinear behaviour of the BOLD response for short stimulus durations.

Table 2. Correlation coefficients for height and area under the curve when comparing the BOLD response in the left and right primary visual cortices for the same stimulation protocol.

Stimulus duration (ms)	Height		Area under curve	
	GLM	t-test	GLM	t-test
200	0.083	0.072	0.058	0.051
400	0.020	0.027	0.045	0.049
800	0.588	0.561	0.454	0.460
1000	0.632	0.598	0.542	0.533

Because the nonlinearities were present in the t-test parametric maps which don't make any assumptions about the hemodynamic response function this might indicate that brain haemodynamics behave in a threshold-like manner, with a greater hemodynamic response than might be necessary being elicited for short stimuli.

No correlations in BOLD signal behaviour for short stimulus durations between the left and right primary visual cortices have been found. This might indicate that for very short stimuli the haemodynamic response to the same kind of stimulation varies in time and the haemodynamic response at one point in time could be different from the haemodynamic response at another point in time, even in the same brain.

5. Conclusions

Nonlinearities in the BOLD response for very short stimulus durations have been found. The hemodynamic response seems to behave in a threshold-like manner for short stimuli, with a greater hemodynamic response being elicited for these kinds of stimuli than expected from a linear model. The haemodynamic response seems also to vary in time, even in the same brain and for simple stimulation paradigms.

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