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Spatial Heterogeneity of the Nonlinear Dynamics in the FMRI BOLD Response

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Recent studies of blood oxygenation level dependent (BOLD) signal responses averaged over a region of interest have demonstrated that the response is nonlinear with respect to stimulus duration. Specifically, shorter duration stimuli produce signal changes larger than expected from a linear system. The focus of this study is to characterize the spatial heterogeneity of this nonlinear effect. A series of MR images of the visual and motor cortexes were acquired during visual stimulation and finger tapping, respectively, at five different stimulus durations (SD). The nonlinearity was assessed by fitting ideal linear responses to the responses at each SD. This amplitude, which is constant for different SD in a linear system, was normalized by the amplitude of the response to a blocked design, thus describing the amount by which the stimulus is larger than predicted from a linear extrapolation of the response to the long duration stimulus. The amplitude of the BOLD response showed a nonlinear behavior that varied considerably and consistently over space, ranging from almost linear to 10 times larger than a linear prediction at short SD. In the motor cortex different nonlinear behavior was found in the primary and supplementary motor cortexes.

Key Words: **BOLD fMRI; linearity; stimulus duration; visual; motor.**

INTRODUCTION

A primary goal in functional MRI (FMRI) is the accurate characterization of underlying neuronal activity from the measured signal changes. The most widely used technique for FMRI is gradient-echo imaging involving the use of blood oxygenation level dependent (BOLD) contrast to measure the hemodynamic changes accompanying neural activation. An increase in neuronal activity leads to a localized increase in blood flow and blood volume. As a result, oxygen delivery to the activated region is increased, causing changes in the local concentration of deoxyhemoglobin, to which the magnetic resonance signal is sensitive. The spatial mapping and measurement of the dynamic activity of neurons in the brain therefore requires a thorough understanding of the hemodynamic changes that relate the neuronal activity to the measured BOLD signal.

An important step in characterizing the relationship between the neuronal firing and measured FMRI signal is to assess the linearity of the measured BOLD signal in response to neural stimulation. Linearity is presumed in many analysis procedures and the determination of any deviation from this linearity is crucial in a more precise quantitation of neuronal activity. A linear time-invariant system needs to obey two basic principles—scaling and superposition. Scaling dictates that inputs that are scaled versions of one another produce responses related by the same scaling factor. Superposition dictates that the response to a sum of inputs is equal to the sum of the responses to each individual input. In particular, the response to a longer duration stimulus must be equal to the sum of responses to several shorter duration stimuli. Several recent studies have shown that the BOLD response does not obey superposition for certain stimuli (Boynton *et al.*, 1996; Friston *et al.*, 1998; Vazquez *et al.*, 1998). More precisely, studies have shown that while longer duration stimuli behave in an approximately linear fashion, short duration stimuli produce responses larger than predicted from a linear model. In a study of the visual system, Boynton *et al.* found that responses to a flashing checkerboard presented for 12 and 24 s was predicted from the linear combination of the response to 6-s checkerboard presentation. However, using the response of 3-s duration stimuli overestimated the response to the longer stimulus duration (Boynton *et al.*, 1996). This effect was directly investigated by Vazquez and Noll, who modeled the nonlinearity as the result of two cascaded filters—one to represent the linear time invariant properties of the BOLD response, and the second to absorb any varia-

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tions in amplitude, width, and delay for different duration stimuli (Vazquez *et al.*, 1998). In a similar study, Friston *et al.* modeled the nonlinearity using Volterra series, a more generalized form of the convolution to describe some of the nonlinear features of the BOLD signal (Friston *et al.*, 1998). Both of these studies found the response of short duration stimuli to be slightly narrower and larger in magnitude than predicted from a linear model. These studies were followed by others investigating the effect at higher field strengths (Ances *et al.*, 2000), higher resolution (Pfeuffer *et al.*, 2000), and higher order visual processing centers, such as the lateral occipital cortex (Kushnir *et al.*, 1999). All of these studies detected and analyzed this effect by averaging the BOLD response over large regions of interest, such as all activated voxels. The purpose of this study is to examine the spatial variation of this nonlinear effect.

The observed FMRI response to a stimulus is the resultant of two cascaded responses. The stimulus first triggers a neural response, which in turn triggers a hemodynamic response that is monitored by FMRI. Thus, the nonlinearity of the BOLD signal could arise from either a nonlinearity in the neuronal response, a nonlinearity in the hemodynamics, or both. Studies have shown that in certain cases the neuronal response is not linearly related to the stimulus duration. Visual stimuli presented with a step function time course, for example, cause neurons to fire rapidly with the onset of the stimulus followed by a lower firing rate. This lower firing rate is still higher than that observed during rest. Albrecht *et al.* reported that the neuronal response of the cat striate cortex during sustained high contrast stimuli decayed from a peak response to a sustained plateau response (Albrecht *et al.*, 1984). The exponential fit of the decay had a time constant between 0.5 and 2.0 s. Bonds *et al.* found that neuronal response gain adjustment occurs with longer time constants, typically 5–7 s but as brief as 3 s (Bonds, 1991). Maddess *et al.* estimated a ratio of 3:1 for the change in the firing rate between the stimulus onset and 6 s poststimulus onset (Maddess *et al.*, 1988). Due to functional specialization of different brain areas, different regions of the brain could behave quite differently to a stimulus, with varying degrees of this nonlinear dependence on the stimulus duration. Recent evidence suggests that the nonlinearity may also arise from the complex hemodynamics involved in producing the BOLD signal. Miller and coworkers, for example, found that in certain brain areas, the blood flow, as measured by arterial spin labeling MRI techniques, was linear whereas the BOLD response was nonlinear (Miller *et al.*, 1999). This suggests that the nonlinearities in the BOLD signal are due to the additional hemodynamic factors linking blood flow changes to the BOLD response, such as blood volume, oxygen extraction, and metabolism. Vazquez *et al.* suggested that these nonlinearities may be caused by dynamic changes in blood volume (Vazquez *et al.*, 1998), since these changes have been shown to have different temporal dynamics (Buxton *et al.*, 1998; Mandeville *et al.*, 1999). These hemodynamic nonlinearities would add to any neuronal nonlinearities present in the system, making the determination of variations in neuronal activity difficult. The potential of spatial variation in these hemodynamic factors and the neuronal response motivates the study of spatial variations in the nonlinearity of the BOLD signal. In this paper we quantified the spatial heterogeneity of the BOLD signal nonlinearity and analyzed the correlation between the nonlinearity and commonly used indicators of voxel vascular architecture.

METHODS

Model

In this study, two measures of nonlinearity are considered. In the first measure, the degree of nonlinearity is assessed by computing the ratio of the area under the BOLD response (the "output") to the area of the input stimulus. In a linear system, this value is constant for different stimulus durations. In the second model, the nonlinearity is assessed by comparing the amplitude of the measured response to the amplitude expected from a linear system. In this case, the nonlinearity of the BOLD signal, $s_x(t)$, is modeled as an additional multiplicative factor, $f_x(SD)$, varying with the stimulus duration but constant across time, affecting the amplitude, α, of the ideal linear response, $r(t)$,

$$s_x(t) = [\alpha_x \cdot f_x(SD)]r(t) + \text{baseline} + \text{noise} \quad (1)$$

The goal of a typical FMRI experiment is to determine the activation amplitude, α_x, across the brain. Because of the nonlinearity, the measured activation amplitude is scaled by an additional factor that depends on the stimulus duration. By assuming a linear response, one underestimates the activation amplitude to brief stimuli. From previous studies it is expected that this factor is equal to one for large stimulus durations, and increases for shorter stimulus durations. These factors were estimated from signals averaged over regions of interest containing multiple activated voxels. However, this scaling factor may vary across space, depending on variations in the neuronal response, the vascular structure, neurovascular coupling, or all three. In terms of the above model, the goal in this study is to map this additional scaling factor across space.

Experimental Design

The linearity of the response with respect to stimulus duration (the "ON" period) was assessed in two

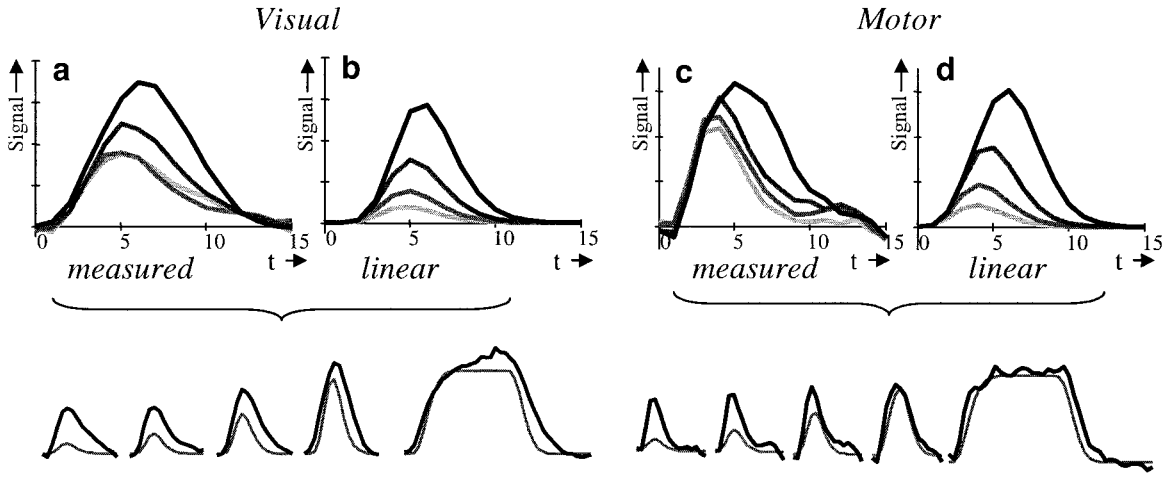

FIG. 1. Left: Measured (a) and ideal linear (b) BOLD responses after visual stimulation of 250 ms, 500 ms, 1000 ms, 2000 ms, and 20 s duration. Right: Measured (c) and ideal linear (d) responses after finger tapping of 500 ms, 1000 ms, 2000 ms, 4000 ms, and 20 s duration. Measured and ideal linear responses are also shown superimposed. Short duration stimuli are larger than predicted from a linear system.

tasks—a motor task consisting of bilateral finger tapping and a visual task where the subject passively viewed an 8 Hz contrast reversing checkerboard, fixating on its center during the "ON" period and fixating on a fixation cross presented during the "OFF," or rest, period. In the motor task, the subject performed finger tapping during the presentation of a visual cue, consisting of either a contrast reversing checkerboard or light from an incandescent lamp turned on for the duration of the task period. Subjects were instructed to maintain a constant rate of finger tapping within each run and between runs and were paced by an external auditory cue present during both ON and OFF periods. Even though the motor task contained a visual component, slices were acquired only through the motor cortex, and therefore contained primarily activity resulting from the finger tapping. Both tasks were performed at four different stimulus durations. The visual stimuli were presented at durations of 250, 500, 1000, and 2000 ms; and the finger tapping was performed at durations of 500, 1000, 2000, and 4000 ms. During each scan run, twenty repetitions of each stimulus

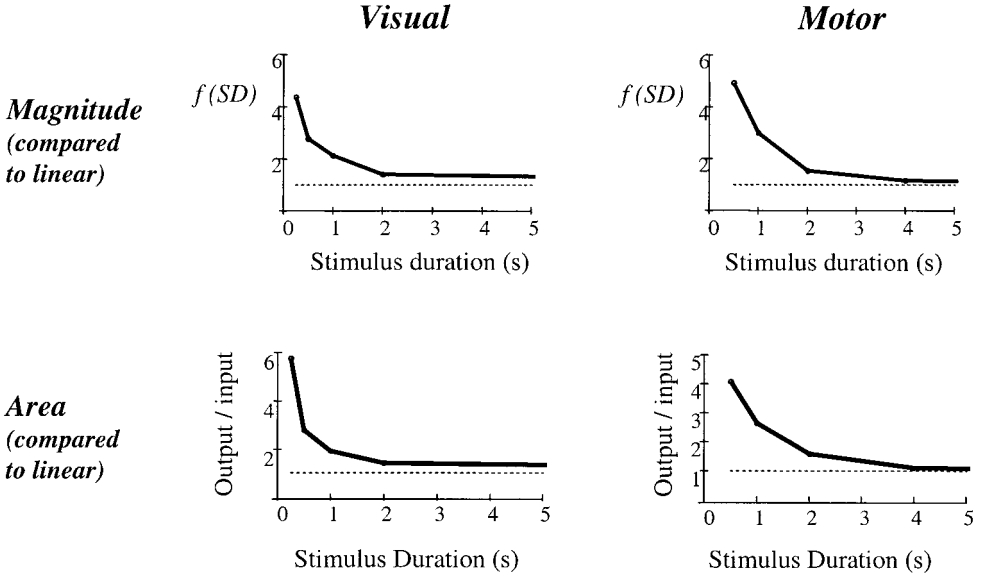

FIG. 2. The amount by which the amplitude (top) and the area (bottom) of the responses are larger at each stimulus duration than the response from a linear system, determined by a linear extrapolation of the responses at the blocked design. In this figure, the nonlinearity curves are averaged over all activated voxels. Left: Nonlinearity in the visual cortex; Right: Nonlinearity in the motor cortex.

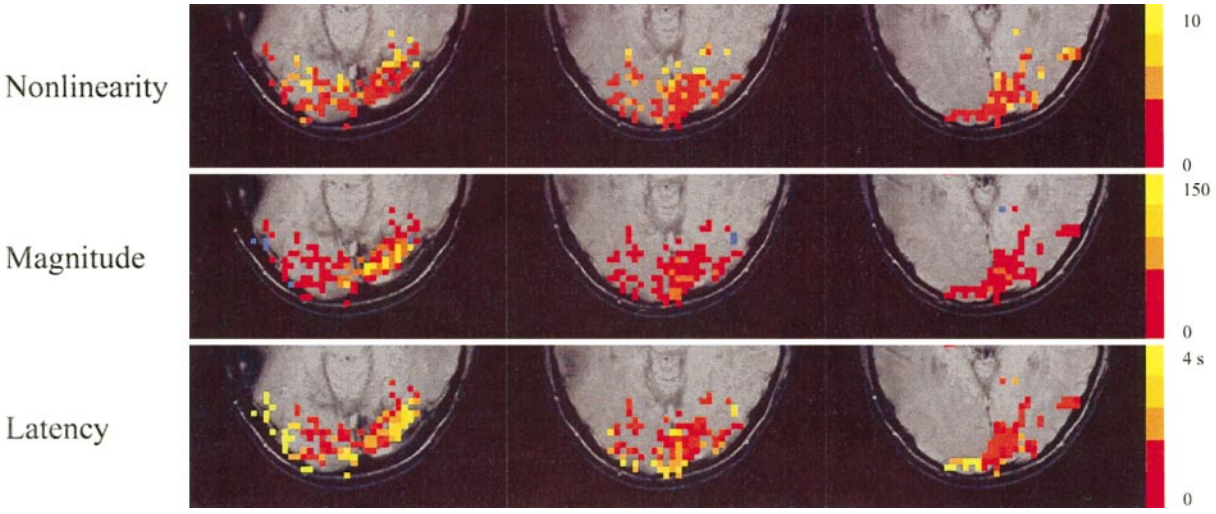

FIG. 3. The nonlinearity (top), activation amplitude (middle), and latency (bottom) for three slices in the visual cortex assessed with a contrast reversing checkerboard stimulus. Nonlinearity was assessed from the activation amplitude relative to a linear prediction. Spatial variation in the nonlinearity is evident, but does not appear to be correlated with either magnitude or latency.

were presented once every 16 s. Images were also acquired in a blocked trial paradigm, alternating eight 20-s periods of stimulation with eight 20-s periods of rest for a total duration of 320 s. Three subjects were studied for each task using an approved protocol.

During these tasks, a series of 320 echo-planar images (EPI) were acquired on a 3T GE Signa (Waukesha, WI) magnet, equipped with a local birdcage RF coil (Medical Advances, Milwaukee, WI). Eight axial slices with a 24-cm field of view and 5-mm slice thickness were used to cover the visual cortex during the visual task and the motor cortex during the finger tapping task. (TR: 1000 ms, TE: 30 ms, matrix size: 64 × 64). The entire experiment, consisting of five 320-second runs, was performed twice in one scanning session to assess the repeatability of the nonlinearity measure. For localization, a set of higher resolution T2*-weighted gradient echo images were also acquired. These T2*-weighted images allow visualization of small veins which appear black due to their very short T2* relative to the surrounding tissue at 3T.

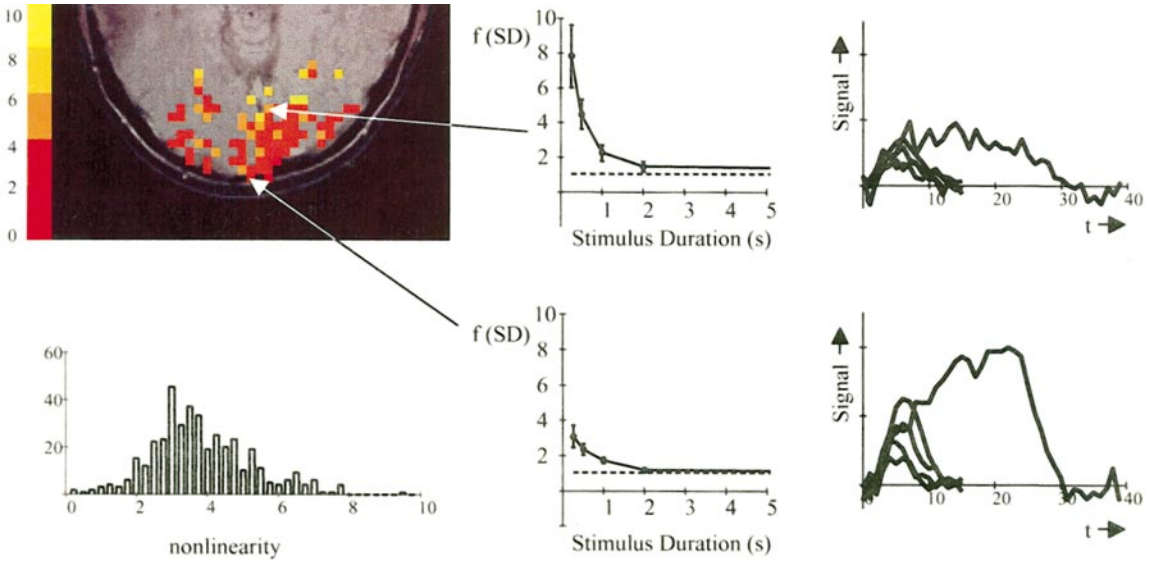

FIG. 4. Nonlinearity of the BOLD response in one slice of the visual cortex in response to a contrast reversing checkerboard presented for different durations. The amount by which the response is greater than a linear model at each stimulus duration is shown as a curve for two voxels. Responses are larger at shorter stimulus durations than predicted from a linear system. Averaged responses to the brief stimuli for the corresponding voxels are shown on the right. A histogram of computed nonlinearities is shown on the bottom. A considerable variation in the nonlinearity is observed across space.

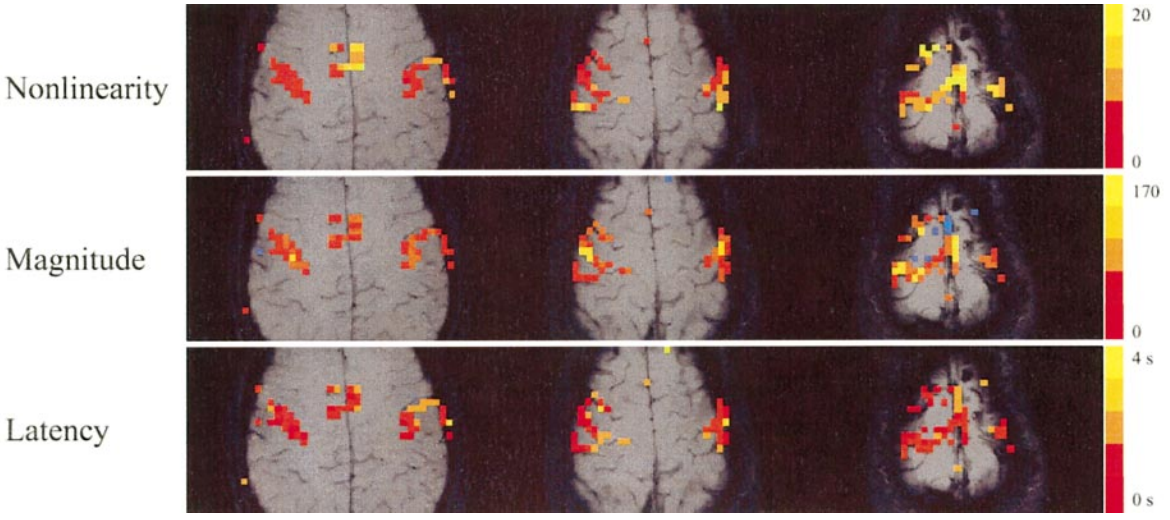

FIG. 5. The nonlinearity (top), activation amplitude (middle), and latency (bottom) for three axial slices in the motor cortex assessed with a bilateral finger tapping task. Nonlinearity was assessed from the activation amplitude relative to a linear prediction. Spatial variation in the nonlinearity is evident, but does not appear to be correlated with either magnitude or latency.

An ISI of 16 s was chosen for the event-related paradigm in order to increase the number of stimuli presented and thereby improve the estimate of the activation amplitude. A concern with this design, however, is that the poststimulus undershoot may not fully recover in 16 s, thereby confounding the amplitude measure from successive stimulation. A spatial variation in the linearity may therefore be influenced by spatial variations in the poststimulus undershoot. To address this issue, finger tapping and visual stimulation were repeated in three subjects with an ISI of 30 s (TR: 1000 ms, TE: 30 ms, 330 repetitions). Several studies indicate that the BOLD response has recovered sufficiently in this time (Friston *et al.*, 1998; Glover, 1999; Vazquez *et al.*, 1998). The estimated activation amplitudes and computed nonlinearities with the longer 30 s ISI were compared to the results obtained with a 16-s ISI.

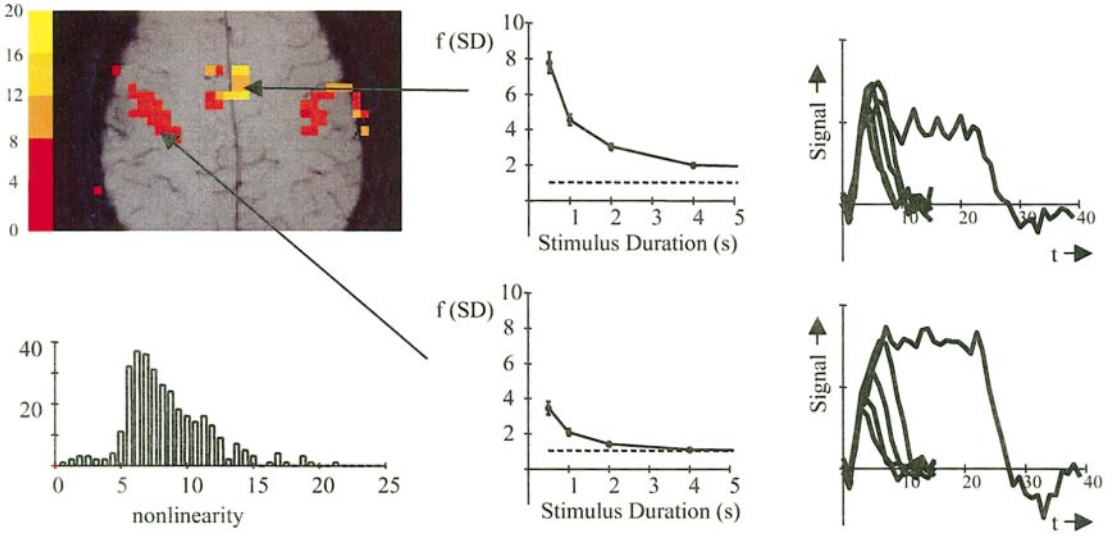

FIG. 6. Nonlinearity of the BOLD response in one slice of the motor cortex in response to various durations of bilateral finger tapping. The amount by which the response is greater than a linear model at each stimulus duration is shown as a curve for two voxels—one in the primary and one in the supplementary motor area. Responses are larger at shorter stimulus durations than predicted from a linear system. Averaged responses to the brief stimuli for the corresponding voxels are shown on the right. A histogram of computed nonlinearities is shown on the bottom. A considerable variation in the nonlinearity is observed across space. Note the difference in the nonlinearity between the primary and supplementary motor areas.

Processing

After reconstruction, images were registered to correct for movement artifacts. First, the series of slice images within each run were registered to the fifth acquired slice image. This reduced motion artifacts during one scan run. However, since the signal changes are compared across runs, an additional registration was performed across runs. To do so, each 3-dimensional volume, consisting of all the different slices, was registered to the fifth volume of the first run. To obtain the first measure of nonlinearity, the area of the BOLD response was obtained by computing the area under the FMRI response averaged over all stimulation epochs. This average response was computed by deconvolving the signal using the stimulus timing. This process of deconvolution also estimates the baseline. The deviation from this baseline is used to compute the area under the FMRI response. The area of the input (the stimulus) is directly proportional to the stimulus duration. Therefore, the area of the averaged response was divided by the stimulus duration to produce a measure of linearity—the output of the system for a given level of input. To obtain the second measure of nonlinearity, the activation amplitude in each voxel was determined by correlating the signal response with an ideal reference function. This function was obtained by convolving a gamma-variate function (with parameters according to Cohen *et al.* (1997)) with the stimulus timing, and hence represents the ideal *linear* response at a particular stimulus duration. To determine both the magnitude and the latency of the response, multiple reference functions with varying delays were generated. For each voxel, the response latency and magnitude was obtained from the reference function that resulted in the best fit.

For each voxel, the area or the amplitude of the response as function of stimulus duration was determined, and normalized by the area or amplitude of the FMRI response to a blocked-design, respectively. The normalized measures indicates how much larger the measured response is compared to that of a linear system. Without this normalization, differences in the curve representing the nonlinearity would simply reflect differences in the amplitude of activation in different brain regions. To map the nonlinearity across space, these curves were reduced to one number. This was accomplished by computing the area under the nonlinearity curve. Additionally, spatial variations in the nonlinearity can be observed by looking at the normalized activation amplitudes or areas at each of the stimulus durations.

The measure of nonlinearity in voxels with significant activation was correlated with the activation amplitude and latency computed from the blocked trial design. Only voxels that were significantly activated in the blocked design, with a correlation coefficient of 0.5 corresponding to a Bonferroni corrected P value of 1×10^{-15}, were used in the correlation. The same mask was applied to the functional maps from all stimulus durations.

The accuracy of the nonlinearity measure, shown as the error bars in Figs. 4 and 6, was evaluated by computing the standard error of the magnitude estimate at each stimulus duration. This standard error is obtained by dividing the fit amplitude by the t statistic, and scaling the result by the number of standard deviations corresponding to a P value of 0.05. This is equivalent to computing the covariance matrix of the regressor, and scaling the result by the standard deviation of the residual. Additionally, the reliability and repeatability of the nonlinearity measure was assessed by comparing the values obtained for the two successive runs. Only those voxels showing significant activation in the blocked design of both runs were compared.

RESULTS

In agreement with previous studies, the BOLD response is found to be nonlinear, with activation amplitudes larger than predicted from a linear model at shorter stimulus durations. This is illustrated in Fig. 1, which shows for each stimulus duration, the BOLD response averaged over all stimulation epochs and activated voxels and the responses predicted from a linear system. Note that the response to the 250 ms visual stimulus is approximately the same amplitude as the response to the 500 ms stimulus. This violates the additive property for linear systems. The amount by which the area and the magnitude of the responses at each stimulus duration is larger than expected from a linear model is shown in Fig. 2 for both the visual and motor tasks.

Next, the degree to which nonlinear behavior varied over space is examined. Figures 3 and 5 show the degree of nonlinearity, as measured by the area under the amplitude of the responses versus the stimulus duration, for both the visual and motor cortexes, respectively. For comparison, spatial maps of the magnitude and latency of the signal changes are shown. Note how the nonlinearity varies considerably over space for both visual (Fig. 3) and motor tasks (Fig. 5). Figure 4 shows how in some brain regions the response to a 250-ms visual stimulus is eight times larger than predicted by a linear model (obtained on a per-voxel basis from the blocked design), whereas in other areas it is only twice as large (see Fig. 4). Similarly, the nonlinearities in response to the motor task show a large range of variance (Fig. 6). However, there appears to be distinct differences between the degree of nonlinearity in the primary and supplementary motor areas. Figure

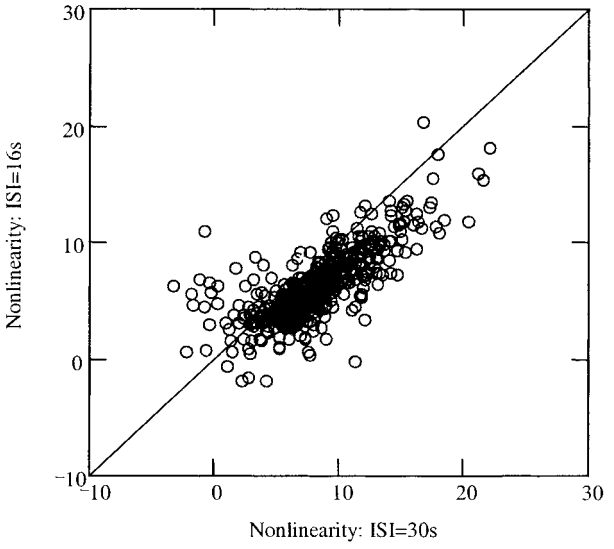

FIG. 7. Nonlinearity for multiple voxels computed from an experiment with a 16-s interstimulus interval (ISI) compared to the nonlinearity computed from an experiment with a 30-s ISI. Similar measures of nonlinearity are obtained in both studies (correlation coefficient = 0.759).

6 shows the averaged responses to each stimulus duration from voxels in SMA and voxels in Primary Motor cortex. Note that while responses in both areas are nonlinear, the manifestations of the nonlinearity are different. The responses in the supplementary motor cortex are almost the same amplitude regardless of the stimulus duration. Similar measured activation amplitudes and computed nonlinearities were obtained by using an ISI of 30 s instead of 16 s. Figure 7 shows a high correlation between the two nonlinearity measures obtained with different ISI (correlation coefficient = 0.759).

The correlation between the response nonlinearity and the underlying vascular architecture was considered by examining the nonlinearity measures as a function of response latency and response amplitude. Response latency and percent signal change have been surmised to discriminate between signals from large veins (with large percentage signal change and long latency) and small vessels (with small percent signal change and short latency) (Lee *et al.*, 1995). Figure 8 shows the measure of nonlinearity (computed from the area under the amplitude vs stimulus duration curve) versus the amplitude of the response (top) and the latency of the response (bottom) for both the visual and motor tasks. The nonlinearity is not significantly correlated with either response amplitude or latency at a P value of 0.01. The variability of the nonlinearity measure is larger at smaller activation amplitudes,

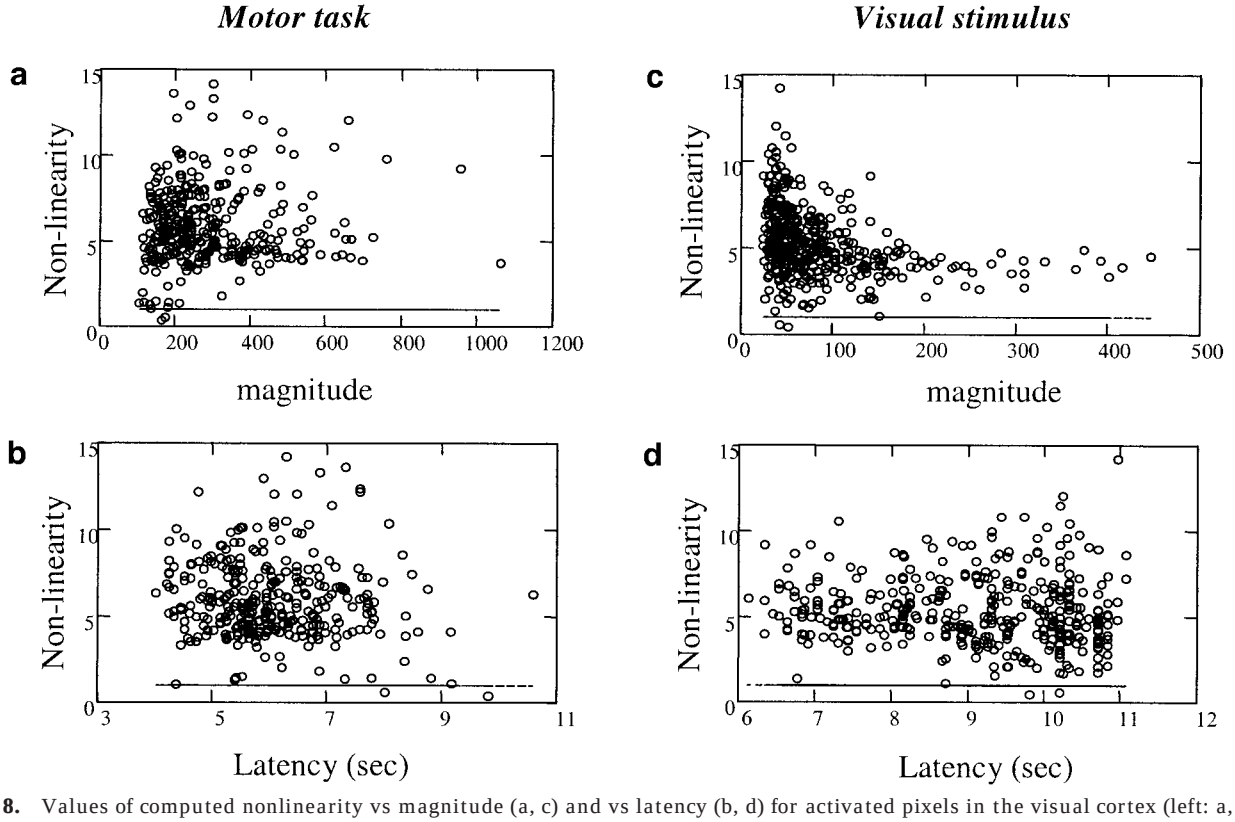

FIG. 8. Values of computed nonlinearity vs magnitude (a, c) and vs latency (b, d) for activated pixels in the visual cortex (left: a, b) and the motor cortex (right: c, d). The nonlinearity measure used here is the area under the activation amplitude (relative to a linear response) vs the stimulus duration curve. No significant correlation between nonlinearity and latency or magnitude is seen (at a P value of 0.01).

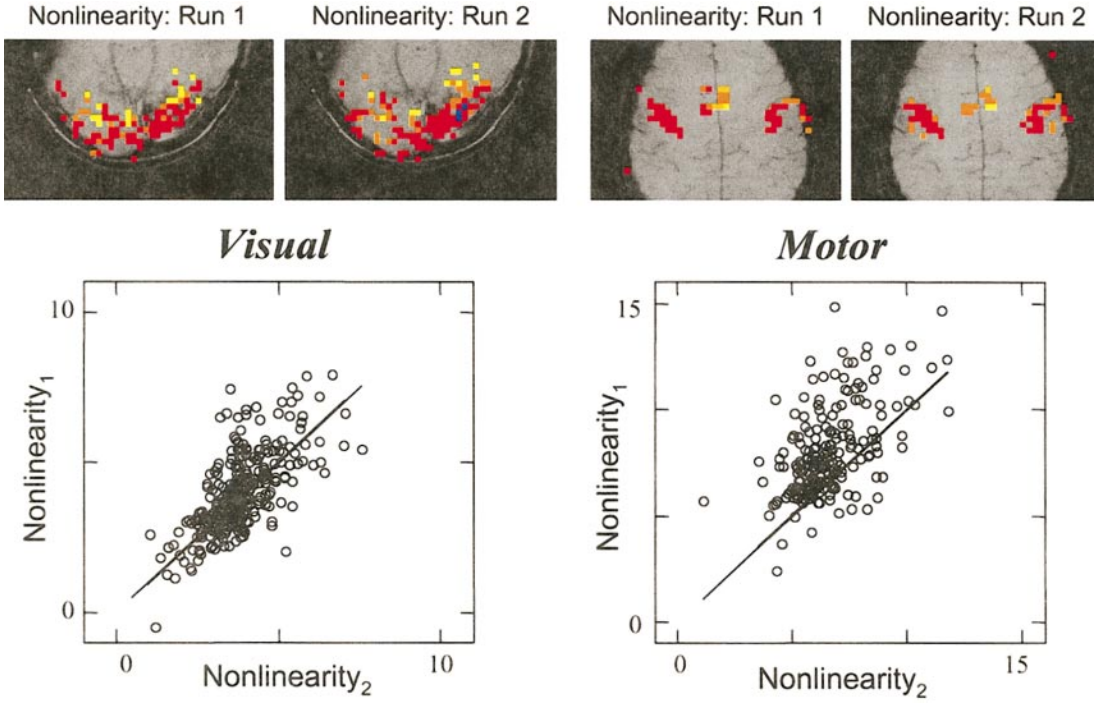

FIG. 9. Computed nonlinearity (as measured by the amplitude of the response compared to a linear model) in two separate runs in the same subject for the visual stimulation experiment (left) and the motor task (right). The line indicates the ideal case of identical nonlinearity values for both runs. The measure of nonlinearity is consistent and reproducible for both tasks. Using the area of the average response instead of the magnitude was equally reproducible.

which is to be expected since the measure of nonlinearity is normalized by the activation amplitude in the blocked-trial design. In addition, we found no distinct correlation between the regions of higher and lower nonlinearity and the location of veins detected in the T2*-weighted anatomical scan.

To assess whether the observed spatial variance in nonlinearity was an artifact of the spatial variance of FMRI noise, we compared the nonlinearity measures across two scan repetitions. Figure 9 shows scatter plots of the nonlinearity measures for each voxel in the first scan versus the corresponding voxel in the second scan. Note the high correlation between repeated measurements (significant at a P value of 0.001), which indicates that the variability of the nonlinearity is not an artifact of noise. Using the area under the averaged responses instead of the amplitude at each stimulus duration was equally reproducible.

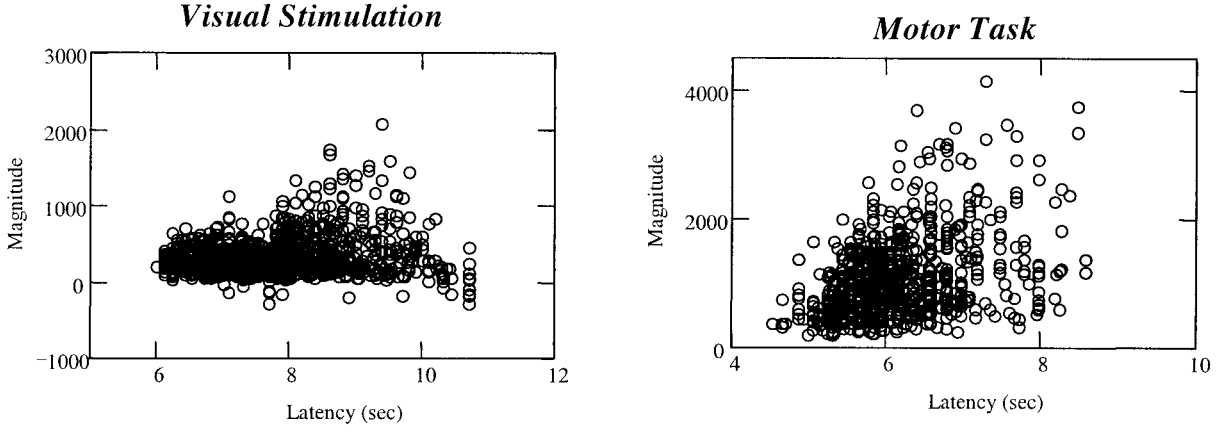

FIG. 10. Response magnitude versus the latency for activated voxels in the visual cortex (left) and the motor cortex (right). Note that there is no clear correlation between the latency and the magnitude of the response.

DISCUSSION

The nonlinearity of the FMRI BOLD response to varying stimulus durations has previously been studied and characterized only over large regions of interest (ROI). This study demonstrates that this nonlinearity varies substantially and consistently over the ROI. At a visual stimulation of 500 ms, the response magnitude varied from being close to what is predicted from a linear extrapolation of the response to longer duration stimuli to being over 10 times as large. A similar range of spatial variability in the nonlinearity was observed in the motor cortex.

The difference between the linearity of the BOLD response in the primary motor area and the supplementary motor area is particularly interesting, since it likely reflects the functional difference between the two areas. The supplementary motor area is generally responsible for planning of motor tasks, whereas the primary motor area is responsible for the execution of the task (Rao *et al.*, 1993; Roland *et al.*, 1980; Samuel *et al.*, 1998). For different duration stimuli, these data suggest that the execution of the movement is different, but that the planning for this movement is quite similar. In another recent study, Nakai *et al.* also found different responses in the supplementary and primary motor areas following finger tapping, but for much longer stimulus durations of 10-, 20-, and 30-s durations (Nakai *et al.*, 1999). In our study, however, one cannot rule out that potential differences in the vasculature may account for such a finding.

The nonlinearity of the response in the visual cortex is not as distinctly clustered as the nonlinearity observed in the motor regions. An initial concern was that the observed variations were dominated by noise in the estimation of the activation amplitude or the area of the response. However, the spatial patterns of nonlinearity distributions were repeatable indicating that these distributions are not an artifact of FMRI noise.

Since the subject was simply cued by visual stimulus to perform the motor task, and since the actual duration of the finger tapping was not recorded, it is likely that the duration of the finger tapping is not precisely equal to the cued duration. While this affects the computed nonlinearity of the response, it does not affect the measure of the *spatial variation* of this nonlinearity. The nonlinearity would be erroneously scaled by the same factor everywhere in space.

No correlation between the measures of nonlinearity and indicators of vascular architecture were found. This seems to suggest that the nonlinearities are not of vascular origins. However, it is possible that the vascular indicators are not very specific at separating large from small blood vessels. In fact, Fig. 10 shows no clear trend or correlation between response latency and response amplitude. Given existing models, the hemodynamics can explain the presence of these nonlinearities (Buxton *et al.*, 1998; Friston *et al.*, 2000; Mandeville *et al.*, 1999). Direct measurement of hemodynamic factors, such as blood flow and blood volume, in conjunction with the BOLD signal will corroborate this model and illuminate to what extent the interaction of hemodynamic factors play a role in producing this nonlinearity and its variation across space.

CONCLUSION

This study expanded on several recent studies on the nonlinearity of the BOLD signal at short stimulus durations by examining the spatial variation of this effect. The nonlinearity was found to vary substantially but consistently across voxels. The measures of nonlinearity were not correlated with the vascular architecture as classified by the magnitude and the latency of the BOLD response. In the motor task, the nature of the nonlinearity differed between SMA and Primary motor cortex, suggesting possible a neuronal contribution to the nonlinearity of the BOLD response. Future studies will delve further into determining the origin of the nonlinearity and the source of its variation over space by acquiring measures of blood flow and blood volume, fitting the responses to models of hemodynamics, and studying the FMRI BOLD response to stimuli where the neural response is well understood.

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