Temporal BOLD Characteristics and Non-Linearity

Douglas C. Noll, Alberto Vazquez
Dept. of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

Introduction

While many early neuroimaging studies using fMRI relied on blocked designs, the rapid acquisition rate of single-shot MRI techniques, like echo-planar and spiral imaging, opened the prospect of imaging short neuronal events in what has become known as event-related fMRI or single-trial fMRI. With most blocked designs experimental paradigms, the temporal shape of the blood oxygenation (BOLD) response was not of paramount importance. The questions being asked usually focused on questions of "where" and "is it significant." Variations in the shape had only a minor effect, if any, on these questions. Event-related paradigms, on the other hand, depend heavily on the shape of the BOLD response. Furthermore, as events, tasks or subtasks are placed closer together, one must now consider if there are interactions between overlapping responses or if preceding events will influence the response size and shape. These latter issues relate to questions of the linearity of the BOLD response. In this document, we will discuss the general characteristics of the BOLD response, define linearity and its consequences, summarize the experimental evidence for and hypotheses regarding the sources of non-linearity, and describe implications for experimental design and data interpretation in fMRI.

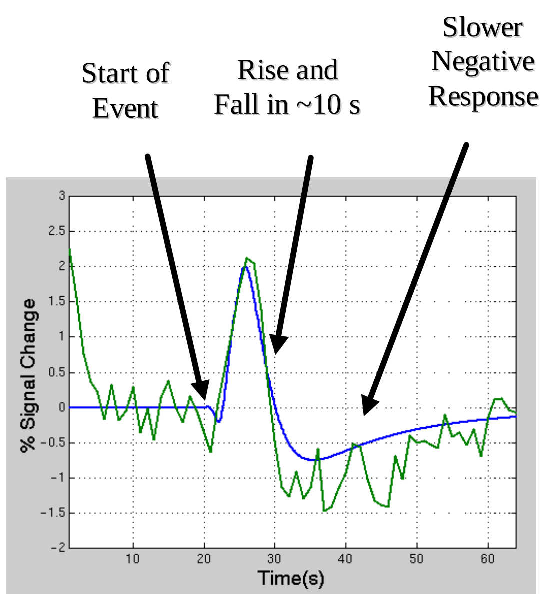

Figure 1 Typical BOLD response to a brief stimulus.

General Shape of the BOLD Response

While MRI technology will allow acquisition of images at a rate of many frames per second, the response of blood flow and oxygenation signals is typically much slower. The responses are typically much slower and longer than the underlying neuronal events and for many paradigms, show no response at all for 2-3 seconds – often after the neuronal activity has ended. Figure 1 demonstrates general shape the BOLD response – also known as the hemodynamic response function (HRF). In this figure, which was found by averaging the response in the visual system to a series of brief (1s) flashing checkerboard stimuli, the smooth line represents a model that was fit to the shape of the response curve. Various models for the hemodynamic response function have been proposed. For example, the use a gamma variate function (1) and Volterra kernels (2) have been proposed as model-free approaches, and the balloon model (3), as well as other windkessel-based models (4), have been proposed as more mechanistic approaches. Models of the HRF commonly have a subset of these characteristics:

1. An initial low amplitude negative response during 0.5 to 2 seconds following stimulation (the "pre-undershoot"),
2. A smooth rise to peak typically over the interval 2 to 5 seconds with a slower fall to baseline from 5 to 10 seconds, and
3. An even slower negative response that may last an additional 10 seconds or longer (the "post-undershoot").

The negative responses are not always seen, though the post-undershoot is both commonly modeled and observed. The pre-undershoot has been seen only in carefully controlled circumstances. While the HRF is slow, it is possible to achieve higher temporal resolution than the 5 seconds implied by the shape of the HRF. If the shape is reproducible, very small temporal shifts can be detected (5-7).

Longer periods of stimulation result in responses similar to the cartoon in Figure 2. Here we see again that there is a post-undershoot, but usually there is no overshoot in the initial rise to the peak level. The apparent asymmetry (the approach to the "on" steady state response is different from the approach to the "off" steady state response) has some implications related the question of linearity, described below.

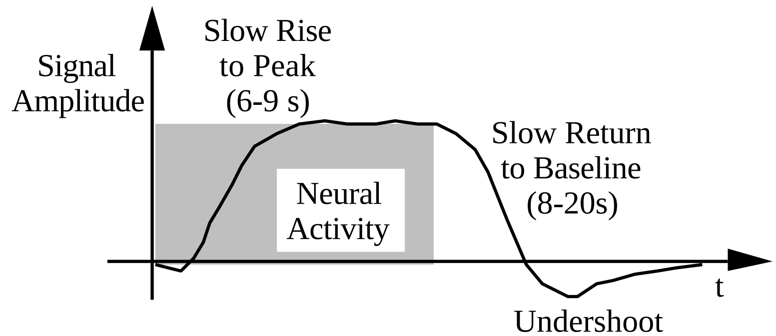

Figure 2. BOLD response to longer periods of stimulation.

Linearity

Linearity is a term that has slightly different meanings in different contexts. In describing the BOLD response (HRF), we use the term linearity in the systems theory sense to describe a linear system. Systems theory characterizes input-output relationships. Though technically different, we will commonly lump another property – time-invariance – together with the linearity property. Thus, we are interested in knowing if the BOLD responses to stimuli or behavioral events can be characterized by a linear, time-invariant system. One possible representation of this system is described in Figure 3.

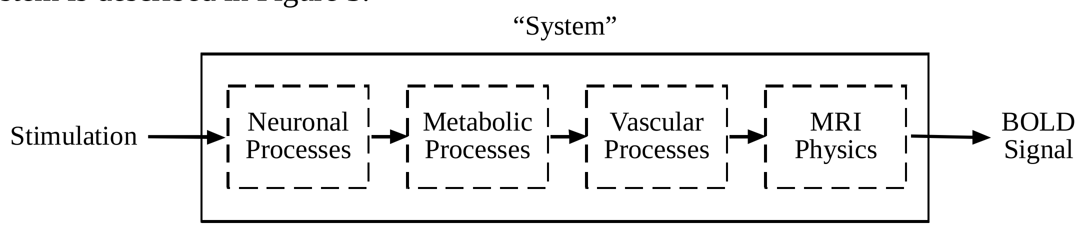

Figure 3. One description of a system that links the "input" stimulation to the "output" BOLD response.

Linearity (and time-invariance) are characterized by several well describe properties:

1. Scaling – this property states that if one scales the input by a factor α (e.g. makes the amount of stimulation α times as much or makes the subject work α times as hard), then the BOLD response will be scaled by exactly α. No other changes (e.g. in the shape of the response, etc.) are allowed. This must also be true for any arbitrary α.
2. Superposition – this property states that if one determines the responses to two different stimuli individually, then the response of both stimuli applied together will be sum of the individual responses. This must be true for any two arbitrary stimuli.
3. Time-invariance – this property states that if a stimulus is shifted by an time τ, then the response must also be shifted by exactly τ. Again, no other changes in the response are allowed and this must be true for any arbitrary τ.

When these three properties exist, a powerful collection of tools becomes available for designing experiments and interpreting data. For example, the response to a short period of stimulation (e.g. Figure 1) will define the "impulse response function" or HRF. The predicted BOLD response to a complicated sequence of stimuli of potentially varying amplitudes can then be written as the convolution of the stimuli with the HRF. This is demonstrated in Figure 4.

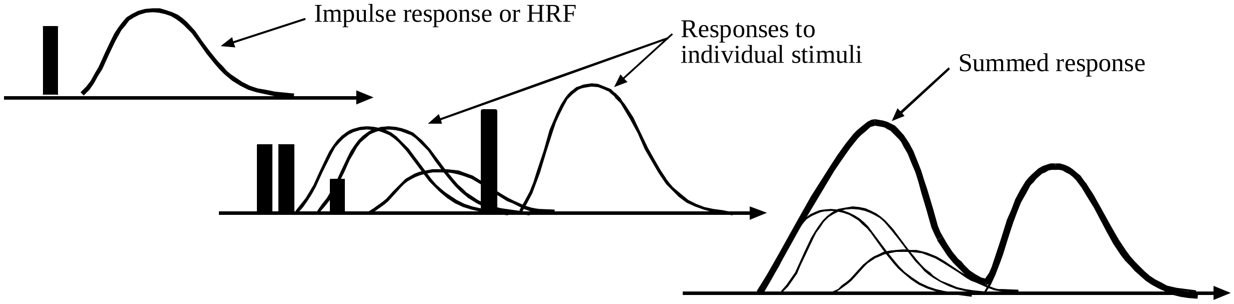

Figure 4. Demonstration convolution of stimuli and HRF to yield a summed response.

In addition to prediction of the responses to a single stimulus type, linearity (and time-invariance) implies that different behavioral task types can be mixed together and that the responses will be additive. This idea has lead to the powerful analysis technique of multiple linear regression or as it is commonly known in the neuroimaging field, the general linear model (GLM) (8). With this model, a predicted response is generated for each task type in a manner similar to that of Figure 4. The weighted sum of these predicted responses that best fits the data is determined, and the weights then represent the amount of activation of each task type. Here one can see that the superposition property of linearity implies that there is no interaction when determining the responses for different task types. One other important consequence of linearity is that signal intensity now has a quantitative interpretation. A doubling of the response would imply that that stimulation of task effort must have doubled. Assumptions of linearity has made possible experimental designs with multiple mixed trial types in rapid succession and allowed the use of the powerful event related experimental designs for fMRI.

Evidence for Non-linearity

To our knowledge the first study that examined the linearity of the fMRI response was that of Boynton, et al. (9). They varied the duration of a visual stimulus from 3s to 24s and found that the superposition of the 6s response could predict the responses to longer stimuli. However, they also found that the response from a 3s stimulus could not predict well the responses to longer stimuli, suggesting that the fMRI response behaves linearly for stimuli 6s or longer and non-linearly for shorter stimuli. This behavior was also observed in a study by our group (10, 11), where responses to stimuli 4s in duration and longer behaved linearly and responses to stimuli less than 4s in duration behaved non-linearly. When predicting the responses to long stimuli from responses to short stimuli, this non-linearity is manifest as responses that lower amplitude and broader width than suggested by linearity. This is demonstrated in Figure 5(a,b). In addition, reductions in the stimulus amplitude (reduction in contrast for visual stimulation) showed some changes in response shape (narrower) in violation of the scaling property associated with linearity, described above. Various other studies have found very similar linear and non-linear behavior not only in the visual cortex but also in sensory-motor and auditory cortices (12-15). Although fMRI responses are often averaged over a region of interest (ROI), it has been shown that these non-linearities are consistent within visual and motor ROIs (16).

The possible interaction between adjacent responses has also been studied (as opposed to either long continuous periods of stimualtion or long gaps between short stimuli). Departures from linearity and time-invariance of varying degrees have been reported for visual stimuli 1-2s in duration with short inter-stimulus separations of 2-10s (17-19). Often, subsequent stimuli are reduced in amplitude and delayed relative to the first stimulus, as demonstrated in Figure 5(c). While accounting for these interactions is necessary for accurate quantification, these changes are often subtle enough that detection of short individual stimuli closely separated is possible under assumptions of linearity.

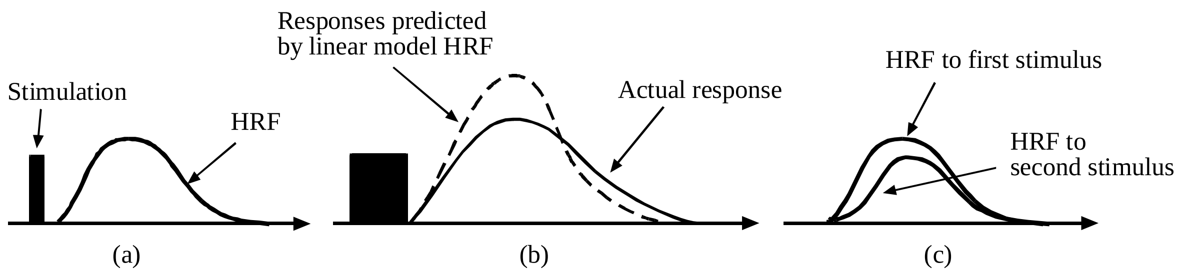

Figure 5. (a) A typical hemodynamic response function (HRF) with (b) a cartoon of nonlinearities seen by varying stimulus duration (lower and broader than predicted by a linear model) and (c) a cartoon of change in the HRF between the first and second stimulus when preceded by a substantial rest period.

The sources of these non-linearities are related to the underlying mechanisms involved in the generation of the observed fMRI response, for example, the processes depicted in Figure 3. Potentially, non-linearity can result from any of these processes. The two presumed dominant sources of non-linearity are the vascular and neuronal processes, though hypotheses of nonlinearities of metabolic origin also exist.

The vascular nature of the fMRI signal implies that the properties of the regional vascular compartment contribute to the dynamics of the fMRI signal. For instance, the early response may be due to a fast onset in oxygen demand (increasing the local amount of deoxy-Hb) before the evolution of the blood flow and blood volume responses. The main positive response is produced from the large increase in blood flow that follows the onset of neuronal activity (presumably to satisfy the oxygen demand) and results in an increase in the oxygenation of the venous side of the vasculature (so a decrease in the amount of deoxy-Hb). The post-stimulation undershoot may then be the result of a slow return to baseline of the blood volume response due to the compliant nature of the venous vasculature. These dynamics have been captured in various models of BOLD dynamics, for example, the Balloon model (3). In fact, the balloon model is able to explain some of the non-linearities observed, namely the decrease in response width and increase in amplitude with shorter stimuli and the decrease in response width with smaller amplitude stimulations. There are other non-linear aspects of the fMRI response that are of vascular origin and may need to be considered. For example, the dependence of the fMRI response dynamics on the baseline state of the vascular system (20). It has been shown that increases in the global blood flow (via hypercapnia) produce earlier, higher amplitude and narrower width responses compared to normocapnia fMRI responses. The opposite behavior is observed during hypocapnia responses.

It has also been suggested that neuronal response non-linearities may contribute to fMRI signal non-linearities. There exists a strong non-linear relation between the stimulus pattern and the observed fMRI response (21), implying that the non-linearities may be of neuronal origin (and possibly not vascular). Logothetis showed that a spatially localized increase in the BOLD fMRI signal directly (and monotonically) reflects an increase in neural activity and that local field potentials (LFPs) are dominated by stimulus-induced and stimulus-locked neuronal activity. Further, they studied the linearity of the fMRI response to variations in the stimulus contrast using LFP signals as the neuronal input and concluded that there is a linear relationship between neuronal activity and BOLD. In another study, Miller, et al., studied the linearity of the blood flow response and observed the CBF response to be, in general, non-linearly related to stimulus duration, similar to BOLD fMRI behavior (22). They also determined that non-linearities are consistent with a model of a non-linear step from stimulus duration to neuronal activity, a linear step from neuronal activity to CBF changes, and a non-linear step from CBF changes to the BOLD signal changes. Figure 6, describes a stimulus to neuronal non-linearity (consistent with a habituation effect) that can explain some observed non-linear effects with visual/sensory stimulation.

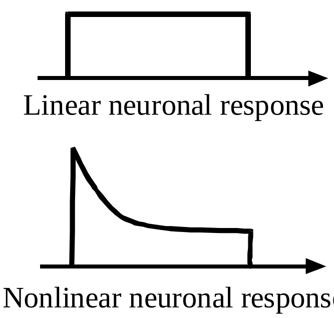

Figure 6. Demonstration of a linear and nonlinear neuronal response to constant stimulation.

Implications for Experimental Design and Data Analysis and Interpretation

There are a number of implications for non-linearities seen in fMRI related to experimental design, data analysis and data interpretation. First, we point out that the goal of most neuroimaging studies is to depict the neuronal activity associated with the performance of a particular task and thus, if the neuronal activity behaves non-linearly that is potentially not an artifact, but rather a piece of information that we wish to know. Other non-linearities (e.g. metabolic or vascular) may serve to obscure or bias our measurements of the desired (neuronal) information. One approach to dealing with non-linear effects in fMRI is the minimize them. First, the non-linear effects appear to be less prevalent in blocked design studies, which are somewhat immune to changes in the shape of the HRF. One can also avoid non-linearities by avoiding circumstances where non-linearities have been discovered – for example, paradigms with non-constant length blocks. In event related studies, one should avoid using combinations of long (> 30s) and short (< 10s) intertrial intervals (ITI's) in the same study. Event related designs that use rapid, random stimuli seem to behave in a nearly linear manner. Next, one should take care in asking questions that could be confounded by non-linearities. For example, if one is looking for effects of habituation in repeated trials, one may need to consider that the HRF might change in shape from trial to trial(18, 19)/

While some non-linearities can be avoided, there many fMRI studies for which it may be difficult to avoid non-linearities in the data. If non-linearities are possibly present the data, it may appropriate to model these effects in the data analysis. Failure to do so may reduce the statistical significance or introduce potentially biased or incorrect results. A number of approaches to account for the non-linearities in the data analysis have been suggested. Model-free approaches include using Volterra kernels (2) and estimating shape and amplitude deviations in the HRF indexed by number of preceding stimuli (23). One can also model the vasculature response using, for example, the balloon model (3) or other vascular models (4, 24). How to address non-linear effects in fMRI data is presently an active area of research and there net yet a standardized way of dealing with this issue.

Conclusions

The BOLD response in fMRI is primarily a vascular response, which accounts for its relatively slow (several seconds) response. If this response function (the HRF) can be considered to be linear, they data analysis and interpretation are significantly eased and allow the use of the popular general linear model approach for data analysis. There is, however, substantial evidence of non-linear effects, particularly with respect the neuronal processes and the vascular responses.

Appropriate experimental designs can often avoid non-linear effects or at least, avoid confounds to experimental questions. If non-linear effects are unavoidable, then an analysis that incorporates estimation of non-linear effects may be appropriate.

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