Quantitative Characterization of Vascular Non-Linearities in BOLD fMRI

J. A. de Zwart[1], P. van Gelderen[1], J. M. Jansma[1], J. H. Duyn[1]
[1]Advanced MRI, LFMI, NINDS, National Institutes of Health, Bethesda, MD, United States

Introduction: The linearity of the relationship between neuronal activity and the hemodynamic response is important for the interpretation of BOLD fMRI and has been subject of investigation in several studies. However, some of the reported non-linearities can be attributed to neuronal effects that are introduced by the stimulus design or that are inherent to the brain region under study. Studies that minimize these effects do report a small but significant remaining non-linearity [1,2]. In order to investigate the origin and mechanism of this non-linearity, we performed BOLD fMRI studies of the visual system at high temporal resolution.

Materials and Methods: Twenty subjects underwent fMRI of the visual system on a GE 3 T with 16-channel head coil array. Scan parameters: gradient-echo EPI, 10 slices, nominal resolution 1.6×1.6×2.0 mm^3, 44 ms TE, 1000 ms TR, 70° flip angle.
The stimulation paradigm was based on the m-sequence probe method using 255 bins (trials) of 1 s each, using an inverse-repeat [3]. This method allows system identification with high efficiency and temporal resolution [4]. 'On' trials (stimuli) consisted of either an 800- or 600-ms duration full field checkerboard, contrast reversing every 62 ms (7.5 Hz), followed by a gap of respectively 200 or 400 ms. The gap serves to reduce contribution of neuronal non-linearities. During the gap and the 'off' trials a uniform grey field was shown. A third paradigm used a m-sequence with 200 ms gap but at 50%-reduced stimulus contrast. For each volunteer 2 out of 3 paradigms were randomly picked and followed by a 5-min block paradigm, used to select a functional ROI (threshold: t=5.0) for response analysis and normalization of m-sequence correlograms. Correlograms of first and second order kernels at various lags were used to characterize the effect of preceding stimuli on the BOLD impulse response (IR).

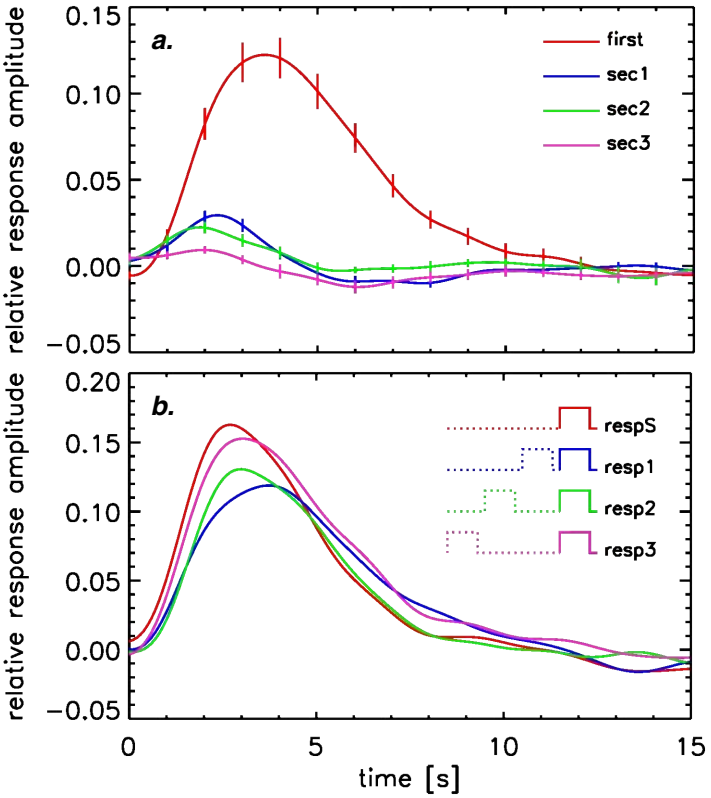

Figure 1: a. *Correlograms of first and second order kernels at various lags for the 200 ms gap experiments, averaged over volunteers.* ***b.*** *BOLD responses, computed from these kernels, show the response to an isolated stimulus (respS), as well as the responses to a stimulus that follows 1, 2 or 3 s after another, identical, stimulus (labeled respectively resp1, resp2 and resp3).*

Results and Discussion: Second order kernels at lag 1, 2 and 3 ('sec1', 'sec2' and 'sec3') were small compared to the first order ('first') and diminished with increasing lag (Figure 1a). Reconstruction of the BOLD IR (Figure 1b) shows that preceding stimuli have a dispersive (time-stretch) effect that decreases when center-to-center separation (lag) increases from 1 to 3 s. Similar results were found in response to 400-ms-gap and low-contrast stimuli. On average, a significant decrease in BOLD IR amplitude was found, whereas the latency (TTP) and width (FWHM) of the IR increased (see Table 1). No significant trend was found in the surface area of IR. Both response amplitude and surface area decreased with reduced stimulus duration or contrast. Similarities in the 2nd order responses for the 3 paradigms suggest minimal neuronal non-linear contributions. The small dispersive non-linearity found is suggestive of a vascular origin, and is consistent with the balloon model [5,6]. A blood volume effect that trails the flow response, as is suggested in this model, would slow the transit of oxyhemoglobin through the vasculature, thereby slowing the BOLD IR if preceded by earlier activity. Lag-dependence of the amplitude of the second order kernels suggests that this effect lasts at least 2-3 seconds.

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References: [1] Buckner, Proc. Natl. Acad. Sci. 1996, 93:14878; [2] Boynton, J. Neuroscience 1996, 16:4207; [3] Kellman, Neuroimage 2003, 19:190; [4] Buccaras, Neuroimage 2002, 16:801; [5] Buxton, Magn. Reson. Med. 1998, 39:855; [6] Friston, Magn. Reson. Med. 1998, 39:41

	amplitude			TTP [s]			FWHM [s]			surface area		
	200	400	200lc	200	400	200lc	200	400	200lc	200	400	200lc
respS	0.16	0.13	0.11	2.7	2.6	2.6	3.9	3.5	3.4	1.00	0.76	0.61
resp3	0.15	0.13	0.11	3.0	2.6	2.7	4.6	3.7	4.3	1.07	0.73	0.66
resp2	0.13	0.11	0.10	3.0	3.0	2.9	4.2	3.9	4.0	0.82	0.67	0.63
resp1	0.12	0.09	0.08	3.7	3.0	3.2	5.0	4.8	4.8	0.89	0.72	0.59

Table 1: *Parameters of the computed BOLD responses. The surface area is computed over the range 0-10 s and normalized to respS in the 200-ms-gap experiment.*