Quantitative characterization of vascular non-linearities in BOLD fMRI

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Introduction

Establishment 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. Event-related studies have reported a non-linear relationship between stimuli and the BOLD response that can be partly attributed to neuronal effects 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.

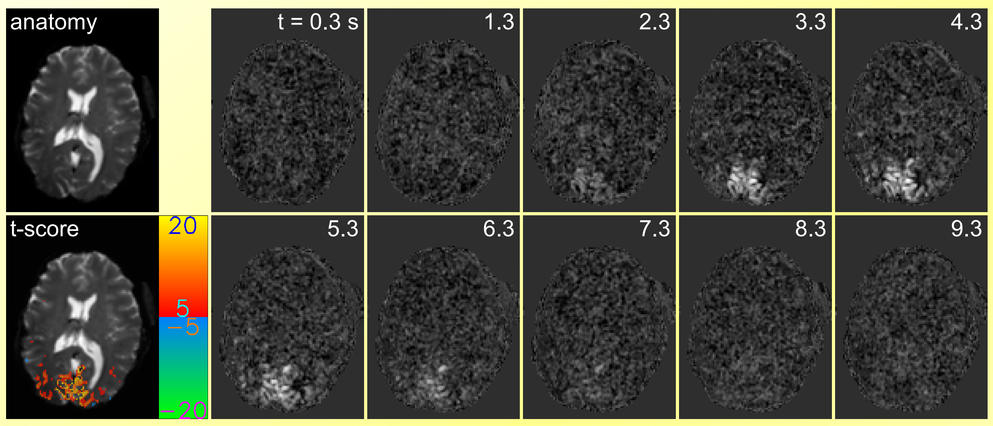

Figure 1: Example of the response observed in a representative slice in one of the volunteers during a full-contrast experiment with 200 ms gap. Anatomical data, from the first volume of the EPI time series, are shown in the top-left. The lower-left image shows a t-score overlay derived from the block paradigm experiment. The first 10 seconds of the response are shown in the remaining 10 images. Time in seconds relative to stimulus onset is indicated in the top-right corner of each image. Since this specific slice was number 7 out of 10 its acquisition timing was delayed 0.3 sec relative to stimulus onset.

Materials and Methods

Twenty-four subjects underwent visual fMRI 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, with inverse-repeat [3], which 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 (labeled '200' and '400'). The gap serves to reduce contribution of neuronal non-linearities. During gap and 'off' trials a uniform grey field was shown. A 3rd paradigm used 50%-reduced stimulus contrast and 200 ms gap (labeled '200lc'). 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 1st and 2nd order kernels at various lags were used to characterize the effect of preceding stimuli on the BOLD impulse response (IR).

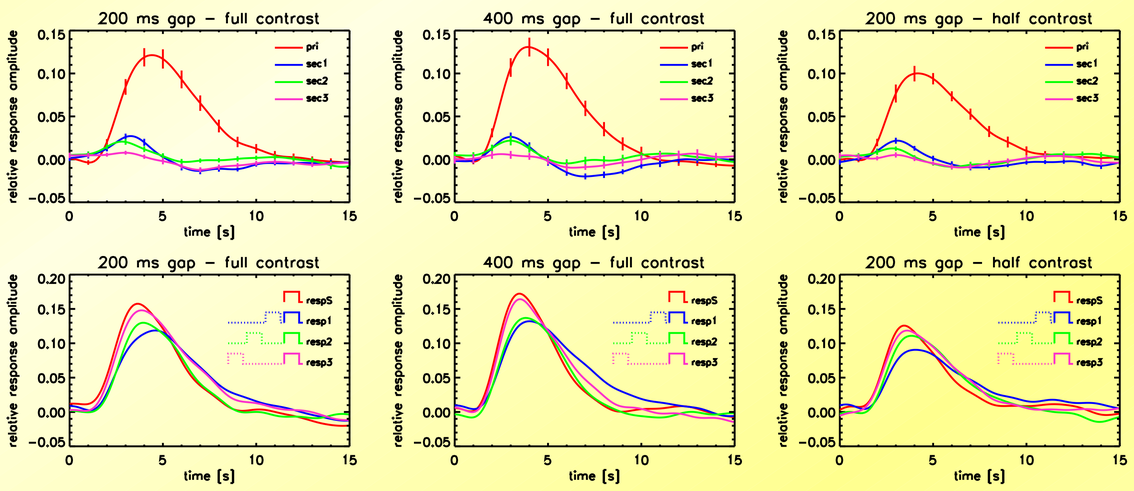

Figure 2: The results for the three different experiments (columns). The mean first order kernel (red) and the first three second order kernels (respectively blue, green and pink) are shown (top row), averaged over volunteers, where the error bars indicate inter-subject standard error. These kernels were used to compute the hemodynamic response a single stimulus (respS, bottom row), as well as the response that occurred when the current stimulus was directly preceded by another, identical stimulus (resp1, bottom row), or 2 respectively 3 bins before the current (resp2 and resp3, bottom row).

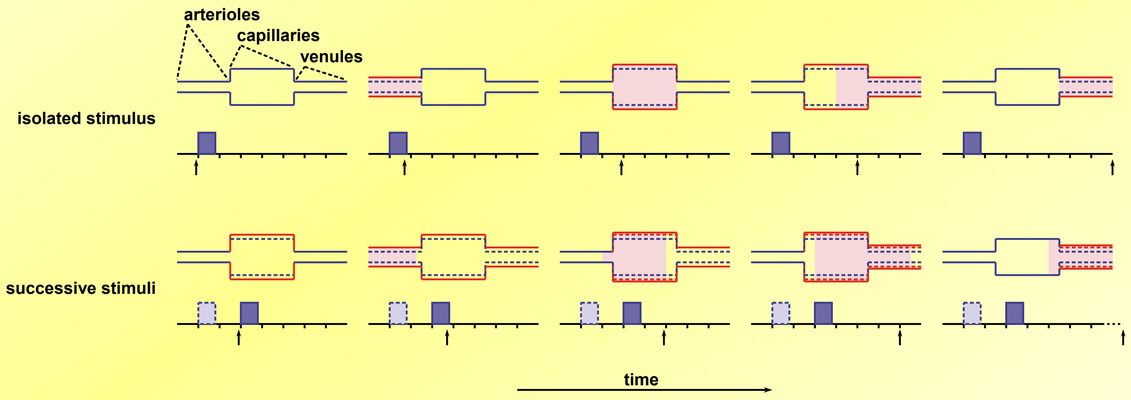

Figure 3: Schematic representation of the delayed vascular compliance model. The top row shows the vascular response to a single, isolated stimulus in three vascular domains: arterioles, capillaries and venules. The bottom row shows the response to a stimulus, equal to the one in the top row, however it is closely preceded by an identical stimulus. Solid red vessel outlines indicate dilation of vessels resulting from the most recent stimulus. The broken red lines in the bottom row indicate additional dilation as a result of the preceding stimulus. The BOLD bolus is represented by pink shading inside the vessels.

Comparison with data from a previous study with a different m-sequence was used to demonstrate that the observed effects are not a methodological artifact. These data referred to as '200old'.

Results and Discussion

Second order kernels at lag 1, 2 and 3 ('sec1', 'sec2' and 'sec3') were small compared to the first order ('pri'). They were found to diminish with increasing lag (Figure 2, top row). Reconstruction of the BOLD IR (Figure 2, bottom row) from these kernels 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 for all three stimuli and the data from the previous study. On average, a significant decrease in BOLD IR amplitude was found, whereas the latency (TTP) and width (FWHM) of the IR increased (Tables 1 and 2). 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 (Figure 3). Lag-dependence of the amplitude of the second order kernels suggests that this effect lasts at least 2-3 seconds.

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

	time to peak [s]				full width at half max. [s]				relative amplitude				relative surface area			
	200	400	200lc	200old	200	400	200lc	200old	200	400	200lc	200old	200	400	200lc	200old
respS	3.7 (0.1)	3.5 (0.1)	3.6 (0.1)	3.8 (0.1)	3.7 (0.1)	3.6 (0.3)	3.5 (0.2)	3.6 (0.2)	1.00 (0.10)	1.00 (0.09)	1.00 (0.11)	1.00 (0.07)	1.00 (0.11)	1.00 (0.15)	1.00 (0.10)	1.00 (0.09)
resp3	3.9 (0.1)	3.6 (0.1)	4.0 (0.2)	4.1 (0.1)	4.1 (0.2)	3.9 (0.3)	4.1 (0.3)	3.9 (0.2)	0.95 (0.10)	0.95 (0.10)	0.97 (0.10)	0.92 (0.07)	1.06 (0.13)	1.06 (0.15)	1.07 (0.12)	0.92 (0.10)
resp2	4.0 (0.1)	3.9 (0.2)	4.1 (0.2)	4.1 (0.2)	4.0 (0.2)	4.3 (0.4)	4.3 (0.3)	4.1 (0.3)	0.83 (0.07)	0.82 (0.07)	0.91 (0.10)	0.85 (0.05)	0.82 (0.09)	0.84 (0.08)	0.99 (0.12)	0.91 (0.10)
resp1	4.6 (0.1)	4.2 (0.3)	4.3 (0.2)	4.3 (0.2)	4.9 (0.3)	4.4 (0.3)	5.0 (0.5)	5.1 (0.2)	0.75 (0.07)	0.78 (0.07)	0.72 (0.07)	0.76 (0.05)	0.94 (0.10)	1.07 (0.12)	0.95 (0.11)	1.01 (0.07)

Table 1: Parameters derived from the average hemodynamic response curves per volunteer for the three experiments (200, 400 and 200lc), as well as for the data from a previous study (200old). Amplitude and surface area values are relative to the respective response to an isolated stimulus (respS). The surface area was computed over the first 10 seconds of the response. The standard error over volunteers is shown in parenthesis.

	stretch factor			amplitude factor			residual fraction [%]		
	200	400	200lc	200	400	200lc	200	400	200lc
resp3	1.04 (0.02)	1.06 (0.02)	1.06 (0.03)	0.91 (0.05)	0.84 (0.05)	0.94 (0.06)	1.13(0.24)	1.70 (0.48)	1.44 (0.24)
resp2	1.10 (0.04)	1.06 (0.02)	1.11 (0.02)	0.80 (0.03)	0.79 (0.04)	0.86 (0.03)	1.53 (0.25)	1.64 (0.47)	1.51 (0.24)
resp1	1.16 (0.03)	1.15 (0.03)	1.15 (0.04)	0.75 (0.03)	0.77 (0.06)	0.78 (0.03)	1.65 (0.32)	1.85 (0.53)	1.40 (0.17)

Table 2: The results of fitting resp1, resp2 and resp3 with a stretched and scaled version of respS. The stretch factor and amplitude factor resulting in the minimal RSS residual are shown, as well as the residual as a fraction of the maximum amplitude of respS. The standard error over volunteers is shown in parenthesis following each value.

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