Vasoconstriction Increases the Linearity of the BOLD Response

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Introduction

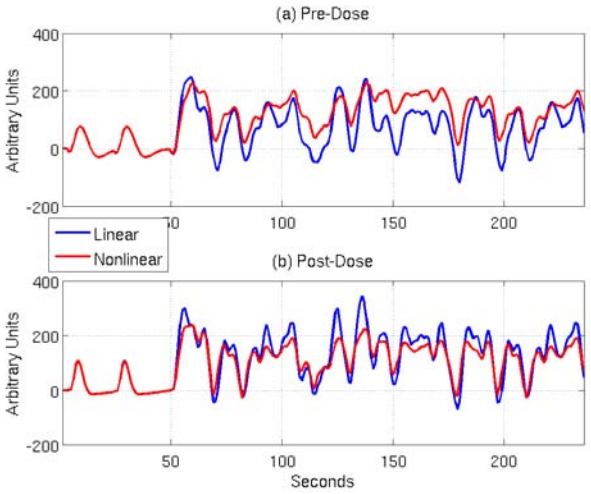
There is growing evidence that the amplitude and shape of the BOLD response depends on the baseline vascular state and can thus be modulated by a host of factors such as vasoactive medications, age, and disease [1-3]. A recent theoretical model indicates that these effects reflect the relative linearity of the vascular system, with vasoconstriction leading to an increase in linearity [4]. As the system becomes more linear, the vessels become more responsive to neural stimulus, resulting in a quickening of the BOLD response. In this abstract, we test the theoretical framework by experimentally assessing the linearity of the BOLD response both before and after the application of a vasoconstrictive agent.

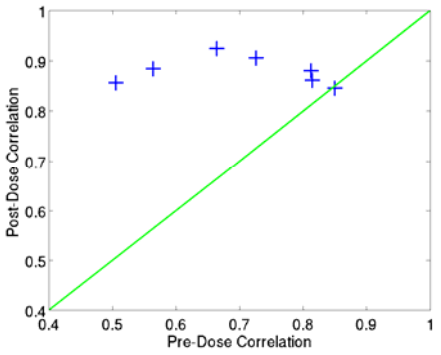
Methods

Seven subjects participated after giving informed consent. Experiments consisted of two imaging sessions (pre-dose and post-dose). Between sessions, subjects ingested a vasoconstrictive agent (200 mg caffeine pill) and waited outside for 30 minutes. During each session the subjects viewed two repeats of a mixed design stimulus consisting of a 12-s initial off period, two cycles of 1-s on and 20-s off, and a randomized design consisting of 96 one second long events randomly distributed on a 1 second grid over a 192 second long interval, where each event consisted of 1 second of a 8 Hz flickering radial checkerboard. BOLD-weighted images were acquired with a single-shot spiral acquisition (TR = 0.5s; TE = 25 ms; Flip 45 degrees; FOV 24; 64x64 matrix; 3 8mm slices through calcarine sulcus). High-resolution anatomical images were used to register the post-dose images to the pre-dose images. A common region of interest (ROI) consisting of voxels with BOLD responses that were significantly correlated ($p<0.05$) with the stimulus in both the pre-dose and post-dose conditions was defined. Using this ROI, average pre-dose and post-dose responses were calculated for each subject. To assess the linearity of the responses we performed a second order Volterra analysis [5] in which the first order kernel represents the linear part of the response and the second order kernel captures the nonlinear dynamics. We used the first order kernel to construct a **linear** response for each subject and condition (pre-dose and post-dose) and the first and second order kernels to construct a **nonlinear** response for each subject. To assess the linearity of the system we correlated the linear response with the nonlinear response. As the system becomes more linear, the correlation between the linear and nonlinear responses should increase.

Results

The upper figure to the right shows linear (blue) and nonlinear (red) responses (averaged over all subjects) in the pre-dose (top) and post-dose (bottom) conditions. During the first 50 seconds of the task, the linear and nonlinear responses are identical because of the wide spacing of the stimuli. During the remainder of the task, the two responses diverge due to the closer spacing of the stimuli and the presence of nonlinear interactions. The linear and nonlinear responses are more similar in the post-dose (vasoconstricted) condition. The lower figure shows a scatter plot of the per-subject post-dose versus pre-dose correlations between linear and nonlinear responses. The application of the vasoconstrictive agent significantly ($p=0.017$) increases the correlation between the linear and nonlinear responses.





Discussion

Our results indicate that vasoconstriction increases the linearity of the BOLD response. These findings are consistent with the theoretical model presented in [4]. In that model, the dynamic nonlinearities due to the relatively stiff passive components (collagen and basement membrane) of the arteriolar wall decrease with vasoconstriction as the vascular smooth muscle contracts and takes up more of the wall stress. Finally, since nonlinearities can play a significant role in the analysis of rapid event-related fMRI designs [6], the impact of vasoconstrictive agents, such as caffeine, should be considered in these analyses.

References. [1] D'esposito M et al., *Nat. Rev Neurosci* 4:863-72, 2003 [2] Cohen et al. JCBFM 22:1024;2002. [3] Mulderink et al. NIMG 15:37; 2002. [4] Behzadi et al, NIMG 25:1100; 2005. [5] Friston, K.J. et al., *MRM* 39:41-52, 1998 [6] Wager et al, NIMG 25:206, 2005.