Method for functional MRI mapping of non-linear neuronal response

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Synopsis

Non-linear systems analysis combining BOLD fMRI and m-sequence stimulation paradigms are proposed as a new method for exploring neuronal responses and interactions. Despite the confounding effect of the seconds long hemodynamic response, it is demonstrated that BOLD fMRI can be used to probe neuronal interactions on a time scale of 10's of ms. Visual activation experiments were performed with various stimuli, and amplitude maps of first and second order kernels were generated using correlation analysis. By including a reference experiment with slightly modified stimulus presentation, distinction could be made between (fast) neuronal non-linearities and (slow) hemodynamic effects. The results indicate that BOLD fMRI can probe fast neuronal non-linearities.

Introduction

Several research groups have investigated linearity of the fMRI BOLD response [1-6]. The principle of linear superposition has been tested [2,4] by varying the stimulus duration and amplitude, and deviations from linearity were observed. The cause of the non-linear fMRI response has been hypothesized [5] to be due to blood flow and BOLD effect based on a balloon model. In order to characterize nonlinear systems, Volterra-Wiener functional expansions may be used to model the system by analyzing the system response to appropriate input stimuli. Friston, et al. characterized the BOLD response [5] using a Volterra kernel model, and estimated first and second order kernels of a truncated 2nd order model using a basis fitting approach. Basis fitting enforces a model that may result in an incorrect kernel estimate. The approach taken here using correlation analysis does not employ basis fitting. Non-linear systems analysis using m-sequence probe stimuli [7] offers practical benefits of ease of implementation as well as reduced statistical fluctuation as compared to white Gaussian noise probes. Application of m-sequence probing has been described for measuring the second order nonlinear neuronal response of the visual system using electrode recordings [7,8]. Here, we propose the application of the m-sequence probing method to produce fMRI maps of the 1st and 2nd order responses for several visual stimuli.

Methods

A binary m-sequence (length 255 bits) was used to select between visual stimuli for the various experimental paradigms, including bullseye reversals, bullseye-gray, and uniform disk reversals. The m-sequence was extended to 300 bits to enable discarding the transient response. The inverse repeat method was used to separate even and odd order responses, which yielded a scan duration with the inverse repeat of 600 bits (10 min at 1 bps). For specific experiments, a small (variable) gap (e.g., 200ms) was introduced between bits during which the visual stimulus. The gap served to decorrelate the measured 2nd order response (i.e., correlation with transitions). A uniform gray stimulus with zero contrast was presented during the gap. Block paradigms, alternating between 30s each of bullseye reversals in a central disk and annular ring, were used to produce t-score maps of the fovea and periphery regions. T-score maps were thresholded to define foveal and peripheral regions used for measuring mean correlation scores of the 1st and 2nd order responses for various paradigms using m-sequence probes.

Imaging was performed on a GE 3T LX scanner, using a single shot EPI sequence with the following parameters: TE=40ms, TR= 1s, and 8 slices acquired each TR. The acquisition matrix was 64x48 with typically 24x18 cm^2 FOV producing a nominal resolution of 3.75 x3.75 and 4 mm slice thickness. The image plane orientation was parallel to the calcarine fissure, with the volume containing the V1 cortical region. The initial image in each scan provided a low resolution T2*-weighted anatomical reference. All individuals (n=9) in this study were normal, healthy volunteers giving informed consent in accordance with an NIH approved protocol.

Results

Fig.1 shows example images using the bullseye-gray experimental paradigm. Fig. 1(a) is an intensity image for anatomical reference, and Fig. 1(b) is the *t*-score for the block design using the fovea-periphery paradigm. The foveal and peripheral regions correspond to negative (black) and positive (white) *t*-scores, respectively. Correlation maps for the 1st (linear) and 2nd (non-linear) order responses are shown in Fig. 1(c)&(d), respectively, using no gap between m-sequence stimuli, and with a 200ms gap in Fig. 1(e)&(f), respectively. The 1st order response is stronger in the foveal than peripheral region, while the 2nd order response is stronger in the peripheral region. The 2nd order response is greatly diminished using a gap of 200ms (shown in Fig. 1(f)) as compared to no gap (shown in Fig. 1(d)). The 2nd order response is displayed inverted, i.e., negative is bright. Example plots of the raw correlation waveforms from a single pixel are shown in Fig. 2 to further illustrate the method. The top plots are the superimposed raw correlation waveforms from a pixel in the foveal region for normal and inverted polarity m-sequence stimulus to illustrate the inverse repeat method. The difference (center) and sum (bottom) correspond to odd and even order responses, respectively (scaled by ½). The kernel maps showed significant differences ($p<0.005$, $n=9$) between 2nd order non-linearities of foveal and peripheral vision.

Discussion

The measured fMRI BOLD response to the visual stimulus is the result of a cascade of neuronal responses from the retina, lateral geniculate nucleus (LGN), and cortex, as well as the hemodynamic and BOLD effect. It will be shown that, by including a reference experiment with a slightly modified stimulus presentation, the method allows distinction between (fast) neuronal non-linearities and effects on the time scale of the seconds-long BOLD response. The observed 2nd order response disappeared by introducing a de-correlating delay between m-sequence stimuli which was larger in duration than presumed neuronal response (10's ms) but smaller than the BOLD effect (several seconds). Based on the assumption that the temporal dynamics of the neuronal system are much faster than the hemodynamic effects, these tests indicate that the 2nd order response was predominately neuronal related corresponding to transitions in the stimulus sequence. These results are consistent with simulations (not shown) of a non-linear cascade model based on a linear dynamic system with memory and a memoryless non-linearity.

Mapping of nonlinear response using fMRI provides a new method with potential for exploring neuronal responses and interactions.

References

[1] Ogawa S, et al. *Proc. Natl. Acad. Sci.* 2000, **97**, 11026-31.
[2] Boynton GM, et al. *J. Neurosci.* 1996, **16**, 4207–4221.
[3] Glover GH, *NeuroImage* 1999, **9**, 416–429.
[4] Vazquez ML & Noll DC *NeuroImage* 1998, **7**, 108–118.
[5] Friston KJ, et al., *Magn. Reson. Med.* 1998, **39,** 41–52.
[6] Birn RM, et al., *NeuroImage* 2001, **14**, 817-26.
[7] Sutter EE, *Vision Res.* 2001, **41**, 1241-55.
[8] Benardete EA, & Victor JD, in *Adv Methods of Phys Syst Mod, III*, 1994, 87-110.

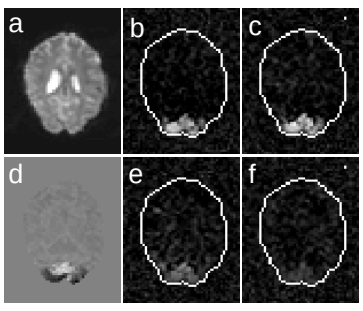

Figure 1. Example fMRI images (a) T1-weighted signal intensity, (d) foveal-periphery *t*-score map, (b),(e) 1st and 2nd order response maps for bullseye-gray paradigm without gap, respectively, and (c),(f) 1st and 2nd order response maps for bullseye-gray paradigm with 200 ms gap, respectively.

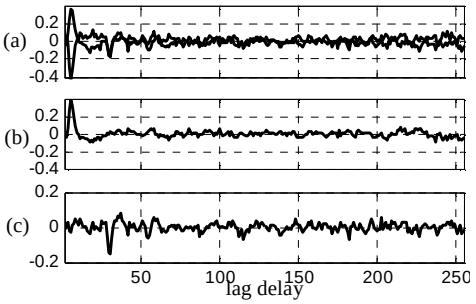

Figure 2. Example correlation plots for pixel in foveal region using bullseye-gray paradigm (a) raw correlation for inverse repeat, (b) odd order response (difference), (c) even order response (sum).