Hemodynamics and nonlinearities of BOLD response to ultrashort visual stimulation (5ms - 1s)

K. Uludag[1], B. Yesilyurt[1], K. Ugurbil[1,2]

[1]MR Center, Max-Planck-Institute for biological Cybernetics, Tübingen, Germany, [2]Radiology, Center for Magnetic Resonance Research, Minnesota, Minneapolis, United States

Introduction

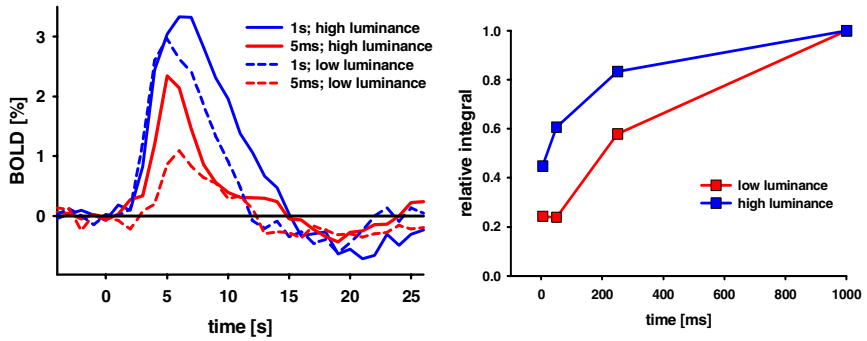
Blood oxygenation level dependent (BOLD) signal is used to detect changes in blood oxygenation and cerebral blood flow accompanying neural activity [1]. It has generally been suggested that one cannot temporally resolve alterations in neural activity in the range of milliseconds using BOLD signal since hemodynamic response evolves in seconds. However, using two-pulse stimulation with different interstimulus intervals up to 100 ms, Ogawa et al. [2] showed in rats that neuronal interactions are reflected by the amplitude of the BOLD signal. This experiment showed that although the hemodynamic response evolves in seconds, the magnitude of the hemodynamic response could encode events and interactions on a millisecond time scale. In addition, non-linearities of neural as well as vascular origin in the BOLD signal for different stimulus durations have been reported and are used to probe neuronal activity [3-6]. Furthermore, vascular non-linearities are minimized using ultrashort stimulations [2,4]. In this study, we have explored the BOLD non-linearities using stimulus durations that are shorter than those employed in any previous study (5 milliseconds to 1 second); in addition, we have examined the dependence of stimulus characteristics (i.e. luminance) on these non-linearities for the first time. We were able to show that 1) a BOLD response to stimulus durations as short as 5ms is detectable in humans; b) BOLD responses to different stimulus durations are highly non-linear and c) non-linearities depend not only on stimulus duration but also on intensity.

Methods

Imaging in normal volunteers was performed on a 3T Siemens/Trio whole body scanner. We used T2* -weighted gradient-echo EPI sequence [TE = 40ms; TR = 1s; voxel size =3.5x3.5x3mm^3; 12 slices; 310 repetitions]. For visual stimulation white light emitting diode (LED) goggles were used. 4 different stimulus durations (5, 50, 250, 1000ms) with 3 different light intensities (high, medium, low) were presented. In each run following 45s onset baseline period 8 visual stimuli were presented about every 30s. To avoid coherent summation of vascular oscillations, interstimulus interval was randomized between 28 to 32s. Data were motion corrected and statistical maps were generated cross correlating each voxel's time series with a standard gamma variate function using FSL Software [7]. No detrending or spatial smoothing were applied. 50 most activated voxels in the visual cortex based on the statistical map of each experiment were selected. In addition, alternatively in order not to bias our results a template mask for all experiments based on the statistical map of the experiment utilizing 1s stimulus duration was also generated. The time series of the activated voxels were averaged and normalized to the mean of the baseline period. Integral of the responses was determined in the interval from 0s to 15s after stimulus beginning and normalized to the value determined from 1s stimulation experiment at each stimulus intensity.

Results

In the left figure, exemplary average cycle time courses of the BOLD signal for high and low luminance for 5ms and 1s are shown. For high luminance, the amplitude of the BOLD response for 5ms stimulation is only 25% smaller than for 1s stimulation although the stimulus duration is 200 times longer. Interestingly, the integral for high luminance seems to saturate. For low luminance, the discrepancy between the responses is more pronounced: the amplitude for 5ms stimulation is 60% smaller than for 1s stimulation. Note that the amplitude of the BOLD responses for 5ms are ~2.2% for high resp. 1% for low luminance. A small post-stimulus undershoot of ~20% of the magnitude of the positive response is present for all stimulations possibly due to post-stimulus inhibition of neural activity. In the right figure, the integral of the responses are plotted. As can be seen, for both luminances the integral of the BOLD responses are highly non-linear being more pronounced for high luminance. The 1s responses would be overpredicted from the 5ms stimulus by a factor of ~90 for high luminance and by a factor of ~50 for low luminance.



Using the mask created from the 1s stimulation experiment does not change the results qualitatively (data not shown).

Discussion

For the first time, in humans we could show that BOLD responses to a stimulus duration as short as 5ms can be detected. As already pointed out by Ogawa et al. [2] using stimuli of 10ms duration, this opens the possibility to probe neuronal activity and interactions despite the slowness of the BOLD response. In addition, we could show that non-linearities depend not only on stimulus duration but also on stimulus characteristics like luminance. Previous results on non-linearities would suffer from this confound which was not accounted for. Thus, non-linearities in BOLD response must be characterized as a function of stimulus characteristics and take into account the spatial dependence [8]. The minimal response seen in the right figure was already shown with local field potentials changes during activation where the intercept was also non-zero [3]. Future experiments using even shorter stimulus durations have to show if there is indeed a threshold-like behaviour of the hemodynamic response and if this is vascular or neuronal origin.

References

[1] Ogawa et al., PNAS (1990), [2] Ogawa et al., PNAS (2000), [3] Logothetis et al., Nature (2001), [4] Buxton et al., MRM (1998), [5] Cannestra et al., J.Neurophysiol. (1998), [6] Kellman et al., NeuroImage (2003) [7] Smith et al., NeuroImage (2004) [8] Pfeuffer et al., NeuroImage (2003).