Further Evidence of Initial BOLD Dip across Cortico-thalamic Visual Network during Visual Stimulation

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Introduction The initial decrease in the BOLD signal following stimulus onset (i.e. initial dip) has attracted much attention in the research field of brain imaging. It is an important phenomenon because initial dip is thought to have better spatial specificity to activated brain region compared to delayed positive BOLD response. Moreover, initial dip may be evidence of dynamic decoupling between cerebral blood flow and oxygen metabolic rate changes induced by local neuronal activation. Although initial dip has been reported in a number studies using different neuroimaging techniques[1-3], its existence and/or generality is still a controversial topic. In this study, we attempted to provide new evidence supporting the existence of initial dip by using a paired-stimulus paradigm which is composed to a pair of brief (10 ms duration) visual stimuli separated by an inter-stimulus interval (ISI). We first identified all activated pixels showing initial dip in response to the first of paired stimuli in the cat visual system. We found that for these pixels they also showed a second dip in response to the second stimulus and the delay between the two dips is tightly correlated to the ISI selected. In addition, we studied the initial dip in sub-cortical areas such as lateral geniculate nucleus (LGN) inside the cortico-thalamic visual network.

Method Cats were anesthetized with 0.9-1.2 isoflurane in a 70%N_2O/30%O_2 gas mixture. The fovea area of the cat retina was located with the aid of a fundus camera (Zeiss, Germany) ensuring that the cat eyes were focused on the visual stimulus. The head position of cat was fixed by a homebuilt head-holder with a mouth-bar and ear-bar system. Visual stimulation presented as short flashing light (10 ms duration per flash) was generated by a red LED checkerboard. All the fMRI studies were performed on a 9.4T horizontal magnet (Magnex Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA). The multi-slice T_1-weighted anatomical images were acquired first to ensure appropriate choice of slices located at the cat LGN and V1. Then, multi-slice gradient echo planar images (TR/TE = 252/14 ms, FOV = 5×5 cm^2, 780μm×780μm in-plane resolution, 1 mm slice thickness, 1 mm gap, 5 adjacent axial slices covering both LGN and V1) were applied for fMRI studies using an event-related paradigm design. Visual stimuli were displayed in the full visual field either singly or in pair separated by an ISI ranging from 1000 ms to 4000ms. Successive trials of single or paired stimuli were separated by an inter-trial interval (ITI) of 20 seconds to allow the hemodynamic response to return to baseline. During the baseline condition, cats were in uniform darkness. All stimuli were time locked to the onset of TR. For each single or paired task, 15 trials were repeated in one run. A total of 7 fMRI runs corresponding to 7 tasks (1 single and 6 paired tasks) were acquired in a pseudo-randomized order for each experiment. For each paired-stimulus task, pixels that show both positive BOLD response and initial dip after the onset of the first stimulus were identified. The BOLD time course for that task was then created by averaging the BOLD responses from all these pixels. The BOLD response to the second stimulus was individuated by subtracting the BOLD time course at the single-stimulus condition created similarly from that of paired-stimulus response.

Results Figure 1 compares the fMRI map of positive BOLD signal (left) to the map created based on activated pixels showing both positive BOLD signal and initial dip (right). Clearly, pixels characterized with initial dip are nicely localized at parenchyma area, consistent with the notion that initial dip has better spatial specificity to local neuronal activation. In addition, the majority of activated pixels in LGN also show initial dip. Figure 2 shows the BOLD time courses in response to the single stimulus averaged from all activated pixels showing initial dips in all 7 cats. Initial dip can be clearly observed in both V1 and LGN. The absolute amplitude of initial dip in V1 (-0.16%) is almost identical to that in LGN (-0.17%), albeit the ratio between the amplitudes of initial dip and positive BOLD signal is much higher in V1 (0.27) relative to LGN (0.11). Figure 3a shows the BOLD time courses in response to the single stimulus and that to paired stimuli at ISI = 4000 ms in V1. Figure 3b compares the BOLD responses to the first (or single) and second stimuli in the same paired-stimulus condition. Interestingly, the pixels showing initial dip to the first stimulus also show a prominent initial dip to the second stimulus. The delay between the two dips (inter-dip delay) is consistent with the delay of two stimuli (i.e. ISI). This situation is true for all paired-stimulus conditions at all ISIs in both LGN and V1. Figure 4 shows the correlation between inter-dip delay and ISI in both LGN and V1. A very high correlation was observed indicating that the second initial dip was indeed induced by the second of paired stimuli.

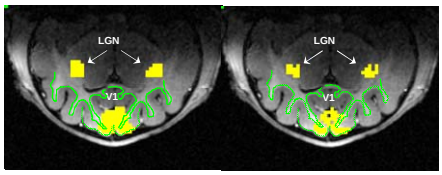

Fig. 1 Comparing the BOLD activation map of significant positive signal (left) to the map created based on activated pixels showing both positive signal and initial dip (right).

Conclusion In this study we individuated two BOLD time courses in response to a pair of visual stimulus in the cat visual system. We observed that for the activated pixels that showed initial dip to the first stimulus, they also showed obvious initial dip to the second stimulus. The delay between the two dips well correlates with the delay between the paired stimuli. Since the initial dip in response to the second stimulus is devoid of any data processing bias, the data clearly suggested that initial dip is a reliable phenomenon. Moreover, our study for the first time demonstrates that initial dip also exists in sub-cortical brain areas such as thalamus, and suggests the possibility to apply the initial dip BOLD signals for functional mapping of the entire cortico-thalamic visual network with improved specificity.

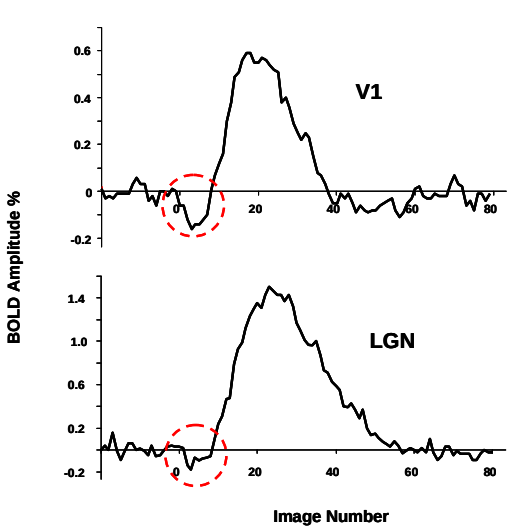

Fig. 2 BOLD time courses in V1 and LGN in response to the single stimulus averaged from all activated pixels showing initial dips in all 7 cats.

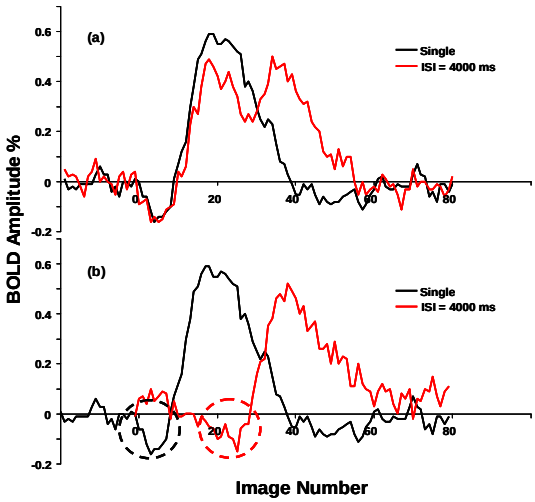

Fig. 3 (a) BOLD time courses in response to the single stimulus and paired stimuli at ISI = 4000 ms in V1. Subtracting the BOLD response at the single-stimulus condition from that at the paired-stimulus condition can individuate the BOLD response to the second stimulus shown as the red curve in (b).

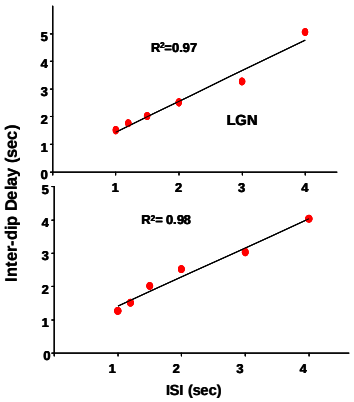

Fig. 4 Correlation between the inter-dip delay and ISI in both LGN and V1.

Acknowledgements NIH grants: NS41262, EB00329, EB00513, P41 RR08079 and P30NS057091; the Keck foundation.

References: *1.Malonek et al Science 1996. 2. Menon et al. MRM 1995. 3. Yacoub et al. NMR Biomed 2001.*