BOLD Temporal Dynamics of Superior Colliculus and Lateral Geniculate Nucleus during Monocular Visual Stimulation

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Introduction - In the mammalian visual system, light received by the eyes is transmitted through the optic nerves. Some of the nerve fibers go to the superior colliculus (SC), which mediates visual reflexes. The majority of other fibers go to the lateral geniculate nucleus (LGN) en route to the primary visual cortex (V1), which is responsible for visual perception[1]. The different parts of the visual system (SC, LGN, V1) interact to permit processing of visual information and responses to stimuli. Interaction between regions can be studied by measuring temporal differences of neural activations in different parts of the visual system. For example, Molotchnikoff *et al.* used electrical recordings to observe that LGN cells had reduced activation if SC cells were active in the preceding 250ms. This provided evidence that the SC interacts with the LGN to generate saccadic eye movements[2]. The majority of time-resolved studies to date use invasive and local measurements such as electrical recordings. Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI), which measures local changes in blood oxygenation induced by neuronal activation following a stimulus, is a non-invasive technique that can simultaneously examine a large FOV with high spatial resolution[3]. Recent advancements have shown that BOLD can be used to measure neuronal activity with sub-second temporal precision[4-5]. In this study, we apply BOLD fMRI with repetition time (TR) of 0.2s on rats to measure the difference in response temporal dynamics between the SC and the LGN to monocular visual stimuli, which has not been measured conclusively nor with high temporal resolution[6-7].

Methods - *Animal preparation*: Sprague-Dawley rats (N = 7) between two and three months of age were used in this study. Each animal was anesthetized with 3% isofluorane for induction and 1 – 1.5% for maintenance. Once sedated, animals were placed in a 7T MRI scanner (Bruker PharmaScan) with a brain surface receiver coil (Bruker BioSpin). Respiration rate was monitored with a pressure sensor (SA Instruments) and heart rate and blood oxygen level were monitored with a pulse oximeter (SA Instruments). *MRI protocol*: Scout images were acquired to determine the sagittal plane. Three 0.8mm thick slices (spaced 0.1mm apart) were positioned such that the middle slice covered both the SC and the LGN. An anatomical scan (3.2cm x 3.2cm, 256 x 256 voxels, TR = 4.2s, TE = 12.9ms) was acquired on the 3 slices. For BOLD experiments, animals were stimulated with a previously employed paradigm of four 40s rest periods with three 20s stimulation periods in between[8]. Stimulation was provided by a 1mm diameter, 0.22 numerical aperture optical fiber placed 1cm from the left eye. The fiber was illuminated by a 40 lux green LED flashed at 1 Hz with a duty cycle of 0.005. Throughout the 220s experiment, 1100 gradient-echo EPI scans (3.2cm x 3.2cm, 64 x 64 voxels, TR = 0.2s, TE = 18ms, α = 30°) were acquired. The experiment was repeated 5 times for each animal with 10 minute rest periods in between. *Data analysis*: The 1100 images from each experiment were registered using AIR5.2.5[9]. The time series from each pixel was cross correlated with the stimulus paradigm using Simulate6[10] and pixels with correlation coefficient (cc) greater than 0.15 were considered activated by the stimulus. ROIs were drawn over the contralateral SC and the LGN using the anatomical image and average time series were computed from activated pixels in each ROI. Each average time series was cross correlated with the stimulus paradigm and the time shift (TS) from onset of the first stimulus needed to obtain the maximum cc was recorded. The average value of the maximum amplitude (MA) during each of the three stimulation periods was also computed from each average time series. TS and MA from all experiments on an animal are averaged to obtain one pair of TS and MA for the SC and another for the LGN. Statistically significant differences ($p < 0.05$) between SC and LGN were identified with a signed-rank test.

Results - Figure 1 shows brain regions in a representative rat activated by the stimulus. Notice the activated pixels in the contralateral SC and LGN. Figure 2 shows time series from the SC and the LGN along with the stimulus paradigm. The boxplots in figure 3 show the distributions of TS observed in the SC and LGN. The SC response is shifted less than that of the LGN ($p = 0.016$) by 0.8 ± 0.3s. Figure 4 shows the distributions of MA. The SC response has larger amplitude than that of the LGN ($p = 0.016$) by 0.4 ± 0.1 % BOLD.

Discussion and Conclusions - The primary finding of this study is that there is an approximately 0.8s difference between the BOLD responses of the rat contralateral SC and LGN to the visual stimuli. In addition, the amplitude of the SC response is larger than that of the LGN. These non-invasive measurements were simultaneously conducted over a large FOV and with high spatial and temporal resolution. In comparison, Pawela *et al.* observed SC amplitude was larger than that of the LGN, but did not report any differences in temporal dynamics[6]. Wall *et al.* observed in humans that SC reached peak amplitude 1 – 2s before the LGN, but the latter had larger amplitude[7]. However, the authors used significantly shorter stimulus duration and interstimulus time, possibly coupling the BOLD responses from multiple stimuli. One explanation of our results is that SC neurons respond faster and more frequently to the stimulus compared with LGN neurons. A second possibility involves the fact active SC neurons are known to reduce LGN activation in the proceeding 0.25s[2]. This would cause LGN neurons to be suppressed shortly after the onset of stimulation, leading to its reduced and delayed BOLD response. This effect would be less apparent using shorter stimuli. However, it is important to note that this study used spontaneous SC neuronal firing as the stimulus, which is different from our study where neuronal firing is caused by an external source. Alternatively, there are regional differences in physiological properties (blood volume, blood flow, etc.), which link neuronal activity to the BOLD response[11], between the SC and LGN that are not due to neuronal activity. For example, the SC may have slightly higher blood flow at rest compared to the LGN[12]. There may also be regional differences in vessel dilation rate, which have been observed in the somatosensory cortex and can affect BOLD responses[13]. To isolate the origin of the time shift difference, multimodality studies should be conducted with functional imaging and electrical recording techniques to help separate the hemodynamic and neuronal contributions to the BOLD signals.

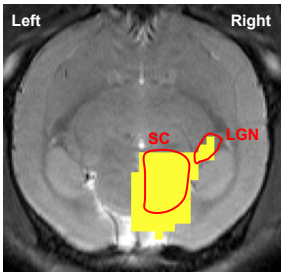

Figure 1: Activated pixels (yellow) overlaid on an anatomical scan covering the SC and LGN. ROIs delineating the SC and LGN are shown.

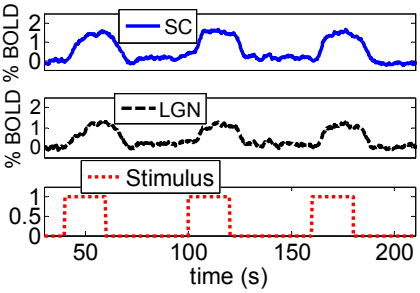

Figure 2: Time series from SC and LGN averaged across 7 rats and low-pass filtered. Only activated pixels in each ROI (see Fig. 1) are included. The stimulus paradigm is shown.

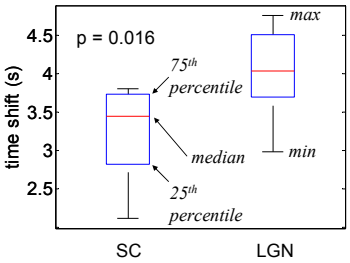

Figure 3: Median, interquartile range, and extent of time shift (TS) of BOLD responses measured from the SC and LGN in 7 rats.

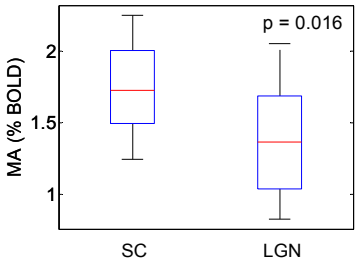

Figure 4: Maximum amplitude (MA) of BOLD responses measured from the SC and LGN in 7 rats. Refer to Fig. 3 for more details.

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