BOLD Response Dependence on the Stimulation Light Intensity in the Rat Superior Colliculus

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Introduction - The contralateral superior colliculus (SC) is the primary target of axons projecting from the rat retina and is an important component of the visual system[1-2]. Functional imaging has been used to study the SC's light contrast dependence[3], but not its intensity dependence. This may be due to the fact relatively few fMRI studies have been conducted on the human SC because of technical challenges such as its small size[4-5]. The rat SC occupies a significantly larger portion of the brain and receives a greater fraction of retinal projections. Thus, the rat is a more suitable model for studying SC function. In this study, we apply BOLD fMRI on rats to measure the SC's hemodynamic response during five different visual stimulation intensities.

Methods - *Animal preparation*: Sprague-Dawley rats (N = 5) were used in this study. Each animal was anesthetized with 3% isofluorane for induction and 1% for maintenance and scanned in a 7T Bruker scanner with a surface receiver coil. Respiration rate was monitored with a pressure sensor, heart rate and blood oxygen level with a pulse oximeter, and rectal temperature with a temperature probe. *MRI protocol*: Three 1.0mm thick slices (spaced 0.2mm apart) were positioned to cover the SC (Fig. 1). For BOLD experiments, animals were stimulated with a block-design paradigm of 10s lights off then five blocks of 20s on and 40s off. Stimulation was provided by a 1mm diameter, 0.22 numerical aperture optical fiber placed 1cm from the left eye (right eye blocked). The fiber was illuminated by a variable power LED flashed at 1 Hz with a duty cycle of 0.05. Each on period was at one of five intensity settings (measured at the cornea): $4.2x10^{-3}$, $7.6x10^{-2}$, 0.23, 0.53, and 0.74W/m^2. The intensity was randomly chosen with the constraint each setting appeared once during the experiment. During the experiment, 310 gradient-echo EPI scans (0.5 x 0.5mm^2 voxels, TR = 1.0s, TE = 18ms, $\alpha = 56^\circ$) were acquired. The experiment was repeated 15 times per animal with > 2 minutes rest in between. *Data analysis*: The 310 images from each experiment were registered to the mean image of the first experiment using AIR5.2.5[6]. The images from an experiment were split into five sets, each covering 5s before to 60s after the onset of each stimulus, for a total of 75 sets per animal. Sets corresponding to the same stimulus intensity were averaged, resulting in five 65 images long BOLD data sets per animal, one for each intensity. Stimulate6 was used to correlate the stimulation paradigm with a data set and identify responsive brain regions. A ROI was drawn around the contralateral (right) SC according to the rat brain atlas[7]. Time series from all voxels within the ROI were averaged and transformed into BOLD signals (units of % BOLD) by averaging the responses from 5s before to 60s after the start of each stimulus and dividing by the amplitude from 5s before to onset of stimulation. The response amplitude, defined as the average BOLD signal from 5 to 15s after onset of stimulation, and the number of responsive voxels, those with correlation coefficient (cc) > than a threshold, were computed from the BOLD signals. Statistically significant differences between intensities were determined using one-way, repeat measures ANOVA with Tukey's HSD test.

Results - Figure 2 shows responsive voxels (cc > 0.41) are concentrated in the contralateral SC, lateral geniculate nucleus (LGN), visual cortex (VC), and ipsilateral SC. The contralateral SC responds to all intensities, but relatively fewer voxels respond at $4.2x10^{-3}$W/m^2. Extensive portions of the contralateral LGN also respond at all intensities. A small fraction of the VC responds at all intensities and an extensive ipsilateral SC response is observed at higher intensities. Figure 3 shows the SC hemodynamic response appears to have smallest amplitude at $4.2x10^{-3}$W/m^2. Differences between the four higher intensities are smaller. All responses have post-stimulus undershoots. Figure 4 shows the response amplitude at $4.2x10^{-3}$W/m^2 is significantly lower than at $7.6x10^{-2}$ and 0.23W/m^2 ($p < 0.05$). The responsive voxels number is lower at $4.2x10^{-3}$W/m^2 than at higher intensities ($p < 0.05$ and 0.01). These findings are largely independent of cc threshold.

Discussion – The lower response amplitude and number of responsive voxels for $4.2x10^{-3}$W/m^2 stimulation intensity support the conclusion the SC BOLD response is weaker under dim light. Further, the relatively small differences from $7.6x10^{-2}$ to 0.74W/m^2 suggest the SC response saturates at higher intensities. However, these findings do not rule out the possibility of non-monotonic dependence. Previous BOLD studies have observed contrast dependence in the superior colliculus while maintaining constant stimulation intensity[3]. The authors found lower contrast resulted in lower response amplitude, but the slope of the dependence was shallow. We note that in our study, contrast was kept constant for different intensities. The brain regions observed to respond to light stimulation (SC, LGN, VC) agree with those in previous rat visual fMRI studies[8-9]. The ipsilateral SC response observed at higher intensities (Fig. 2) may be due to light leaking into the right eye. Electrical recording studies have observed evoked amplitude increased with light intensity[10]. Valjakka concluded that intensity information received by the retina was mediated to the SC. These findings suggest that the response amplitude and number of responsive voxel dependences observed in this fMRI study reflect retinal responses.

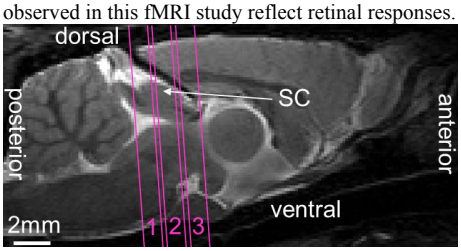

Figure 1: fMRI scan geometry. The scan slices were oriented orthogonal to the sagittal plane. The location of the SC and the anterior, posterior, dorsal, and ventral sides of the brain are indicated.

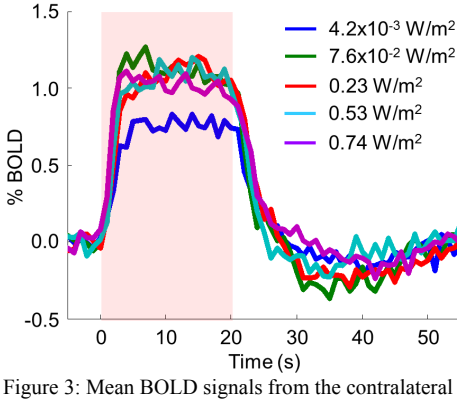

Figure 3: Mean BOLD signals from the contralateral SC of all animals for each stimulation intensity. Only voxels with cc > 0.41 are included. The shaded area indicates the 20s stimulation period.

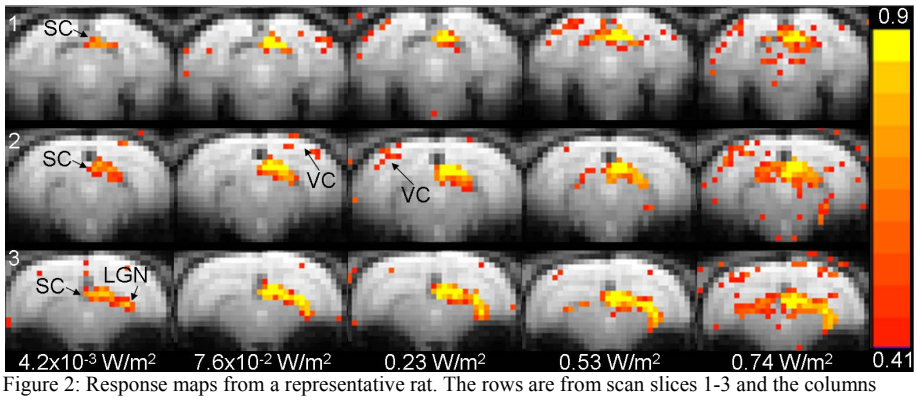

Figure 2: Response maps from a representative rat. The rows are from scan slices 1-3 and the columns correspond to the five stimulation intensities. The SC, VC, and LGN are labeled.

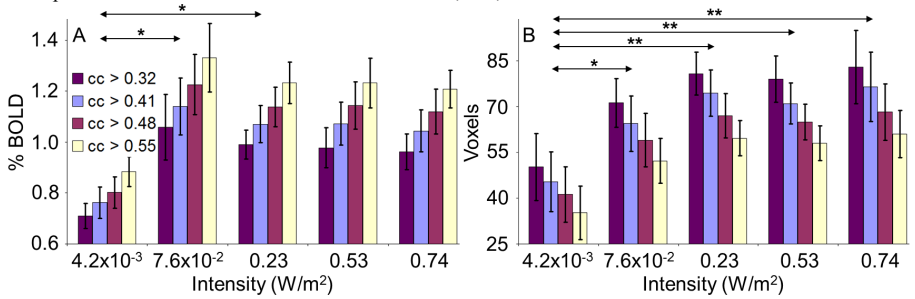

Figure 4: Mean and standard error (across all animals) of response amplitude (A) and number of responsive voxels (B) in the contralateral SC for different intensities. Plots are presented for different cc thresholds. * and ** indicate statistical significance at $p < 0.05$ and 0.01 computed using cc > 0.41.

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