Spin-Echo BOLD Temporal Dynamics in the Rat Superior Colliculus and Lateral Geniculate Nucleus

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Introduction - The superior colliculus (SC) and lateral geniculate nucleus (LGN) are important subcortical components of the visual system[1]. The majority of fMRI studies to date focus on higher visual processing centers in the cortex. fMRI studies in rats have examined visual responses in the subcortex using long stimulus duration block-design paradigms[2-4]. These studies focused on locating responsive regions and measuring differences in BOLD responses for different stimulation frequencies. Relatively little attention has been given to BOLD temporal dynamics in the rat subcortex. In this study, we apply spin-echo BOLD fMRI to measure hemodynamic response temporal dynamics in the rat SC and LGN following short duration (1s) visual stimulation.

Methods - *Animal preparation*: Sprague-Dawley rats (N = 8) were used in this study. Each animal was inducted with 3% isofluorane and maintained at 1%. Animals were 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*: Four 1.0mm thick slices (spaced 0.2mm apart) were positioned to cover the SC and LGN (Fig. 1). A BOLD experiment consisted of 10s rest followed by 10 sets of 1s stimulation and 25s rest. Stimulation was provided by an optical fiber placed 1cm from the eye (5 left, 3 right) with the other eye blocked. The fiber was illuminated by a LED flashed at 10 Hz with a duty cycle of 0.5. Throughout the experiment, 270 spin-echo EPI scans (0.5 x 0.5mm^2 voxels, TR = 1.0s, TE = 43ms) were acquired. The experiment was repeated 15 times per animal with > 2 minutes rest in between. RARE and FLASH anatomical images were also acquired from one rat (template). The FLASH image was acquired after injecting 15mg Fe/Kg MION through the femoral vein. *Data analysis*: The 270 images from each experiment were corrected for slice timing differences using SPM5 and registered to the mean image of the first experiment using AIR5.2.5[5]. All 15 experiments from an animal were averaged to form one data set. Images from each data set were normalized to the mean image of the template rat also using AIR. Voxels from right eye stimulated rats were matched with the corresponding voxel from left eye stimulated rats by flipping images of the former about the midline of the brain. The data sets from all animals were averaged and the time series from each voxel was analyzed using Analysis of Variance[6]. Voxels with p = 0 (beyond computer precision) were considered activated by the stimulus. ROIs were drawn around active voxels in the contralateral (right) SC and LGN based on the rat brain atlas and the average time series from enclosed voxels computed[7]. Time series were transformed into BOLD signals (units of % BOLD) by averaging the responses from 5s before to 20s after the start of each of the ten stimuli and dividing by the amplitude from 5s before to onset of stimulation. Maximum signal amplitude (PEAK) and time to 25%, 50%, and 100% of PEAK (t25, t50, t100) after onset of stimulation were computed from the BOLD signals. t25 and t50 were computed using linear interpolation. The area under normalized BOLD signal (AUC) was computed by integrating the BOLD signals (normalized to maximum amplitude of 1) from t100 to 20s after onset of stimulation. Larger AUC indicates more area under the BOLD signal during the return to baseline. Statistically significant differences between SC and LGN were determined using a paired, two-tailed t-test.

Results - Figure 2 shows active voxels are concentrated in the contralateral SC and LGN. The highest amplitude SC responses are in the superficial 1mm (two voxels) and medial half. Less extensive responses are observed in the ipsilateral SC and contralateral ventral cortex. We caution that susceptibility artifacts are more significant near the bottom of the EPI images. The FLASH image shows the SC contains numerous dark lines, which are likely penetrating blood vessels as iron oxide particles enlarge susceptibility differences between vessels and surrounding tissue[8]. The majority of responsive LGN regions appear to be closer to the large surface vessels than that of responsive SC regions. Figure 3 shows the SC response rises slightly faster and decays considerably slower than the LGN response. Table 1 shows t25 is shorter (0.2 ± 0.2s, $p < 0.05$) and AUC is larger (3.2 ± 1.4 % BOLD, $p < 0.01$) in SC compared to LGN.

Discussion - Pawela et al. observed the most significant SC responses in the medial half of the contralateral hemisphere along with responses in the LGN, pretectum, ipsilateral SC, and visual cortex[3]. Note Fig. 2c may contain pretectal responses and the ipsilateral SC responses may be partly due to light leaking into the contralateral eye. The absence of significant cortical responses in our study may be due to the shim volume, which was set to cover the SC and LGN to optimize fMRI signals from the subcortex. Wall et al. observed the SC t100 was 1 to 2s shorter than that of the LGN[9]. Their study was conducted in humans with a 3s stimulus, which may account for the larger temporal differences. The findings of our study appear to be in agreement with an earlier study using block-design fMRI[10]. The t25 and AUC differences are likely of vascular origin. Tian et al. recently observed BOLD responses from deep cortical layers rise faster and decay slower than those from superficial layers[11], although the apparent decay differences may not be statistically significant. They compared BOLD data to optical functional images and concluded the timing differences were due to vessel dilation rate differences amongst the cortical layers. Relating to our study, active LGN regions are closer to surface vessels (more superficial) and respond slower while active SC regions are relatively deeper and respond faster. This is supported by the vasculature patterns observed in the FLASH images. Note the large surface vessels dorsal of the SC contribute little BOLD signal (Fig. 2) due to the spin-echo sequence employed. To the best of our knowledge, the findings of this study represent the first spatiotemporal measurements of rodent subcortical hemodynamic responses following short duration monocular stimulation.

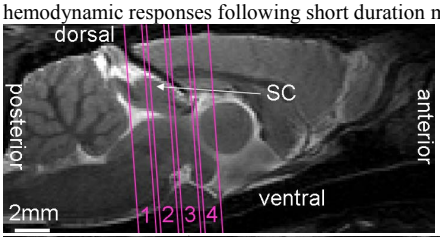

Figure 1: fMRI scan geometry. The scan slices were oriented orthogonal to the sagittal plane. The SC and anterior, posterior, dorsal, and ventral sides of the brain are indicated.

	PEAK (% BOLD)	t100 (s)	t50 (s)	t25* (s)	AUC**
SC	0.9 ± 0.1	3.3 ± 0.5	2.3 ± 0.2	1.8 ± 0.3	5.4 ± 0.9
LGN	0.8 ± 0.2	3.4 ± 0.5	2.4 ± 0.2	2.0 ± 0.3	2.2 ± 1.3

Table 1: Mean and standard deviation (across all animals) of PEAK, t25, t50, t100, and AUC from ROIs in Fig. 2. * and ** indicate statistical significance at $p < 0.05$ and $p < 0.01$.

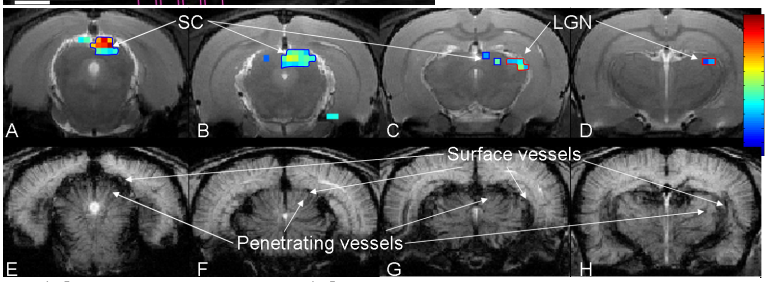

Figure 2: (A) – (D) Activation maps overlaid on the RARE image (w/o MION). Only active voxels are color coded. The color indicates PEAK (% BOLD). The SC and LGN are labeled. The blue and red ROIs cover active voxels in the contralateral SC and LGN. (E) – (H) FLASH image (w MION). The locations of surface and penetrating blood vessels are indicated.

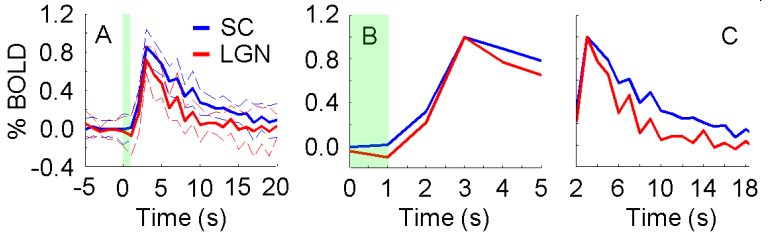

Figure 3: (A) Mean (solid lines) ± standard deviation (dashed lines), computed across all animals, of BOLD signals from the ROIs in Fig. 2. (B) and (C) Solid lines in (A) normalized to maximum amplitude of 1. The green bars indicate the 1s stimulation period.

References – [1] Sefton, The Rat Nervous System, 2004; [2] Chan, NeuroImage, 2010; [3] Pawela, NeuroImage, 2008; [4] Van Camp, J. Neurophysiol., 2006; [5] Woods, J. Comput. Assist. Tomogr., 1998; [6] Clare, MRM, 1999; [7] Watson, The Rat Brain in Stereotaxic Coord., 2005; [8] Van Camp, JMRI, 2005; [9] Wall, NeuroImage, 2009; [10] Lau, ISMRM, 2010; [11] Tian, PNAS, 2010.