Amplitude Modulation Frequency and Duty Cycle Processing in the Auditory System: An fMRI Investigation

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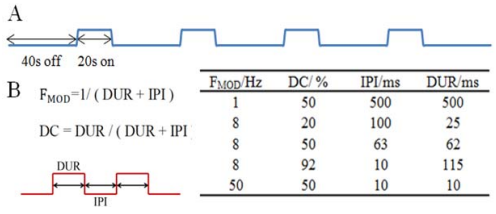
INTRODUCTION: Amplitude modulations (AMs) are essential cues for recognizing and categorizing behaviorally relevant sound and the coding of AM parameters has been studied using electrophysiological techniques[1-3]. Compared to electrophysiology, blood oxygenation level-dependent (BOLD) fMRI is non-invasive and offers large field of view and high spatial resolution and thus, is suitable for studying the coding of auditory AMs. Human fMRI studies have examined auditory pathway processing of modulation frequency [4, 5]. The inferior colliculus (IC) is a center of convergence of various auditory inputs. Compared to humans, rats have a larger IC and are thus are suitable for fMRI studies of this important subcortical structure. In this study, we compare the BOLD responses to three modulation frequencies (F_{MOD}s) and three duty cycles (DCs) to study the effects of AMs in the IC.

MATERIALS AND METHODS: Animal preparation: Adult male SD rats (n=5, 200-250g) were anesthetized using isoflurane (3% for induction and 1.5% for maintenance) and kept warm with a water pad. Respiration rate, heart rate, SpO2, and rectal temperature were monitored. Animals were scanned in a Bruker 7T scanner with a surface coil. **Auditory stimuli:** The stimuli were bursts of bandlimited noise produced by a closed-field electrostatic loudspeaker (TDT EC1) driven by an amplifier (TDT ED1), and delivered to the rat left ear canal via a custom-made tube. The sound pressure level at the tip of the tube was 85dB. A standard block-design paradigm with a 40s off period followed by four blocks of 20s on and 40s off was used (Fig. 1A). During 'on' periods, the noise was modulated at one of the following combinations of modulation frequencies (F_{MOD}) and duty cycles (DC, in units of %): 1Hz (50%), 8Hz (50%), 50 Hz (50%), 8Hz (20%), and 8Hz (92%) (Fig. 1B). The paradigm was repeated a equal number of sessions (two or three) for each combination. Rats rested for several minutes between sessions. fMRI images were acquired using a previously employed SE-EPI sequence (TR/TE=1000/28ms, FOV=32x32mm^2, data matrix=64x64) [5]. **Data analysis:** Data in the first 30s of each session were discarded. The remaining images were realigned and spatially low-pass filtered. Sessions corresponding to the same F_{mod}/DC combination were averaged. A functionally defined ROI covering the right IC was drawn by averaging the images of all five combinations and performing period cross correlation with Stimulate6. The average time-series of all voxels within the ROI were transformed to BOLD percentage changes (units of BOLD%) by normalizing to the baseline signal (mean of first 10 time points). BOLD changes were averaged across all blocks and animals. Statistical comparisons between different F_{MOD}s and DCs were performed using one-way, repeated measures ANOVA with Tukey's test.



F_{MOD}/Hz	DC/ %	IPI/ms	DUR/ms
1	50	500	500
8	20	100	25
8	50	63	62
8	92	10	115
50	50	10	10

Fig. 1: A. Stimulation paradigm. 40s off followed by 4 blocks of 20s on and 40s off. B. Illustration of modulation parameters in a pulse train during 'on' period and a table of the five stimulus conditions.

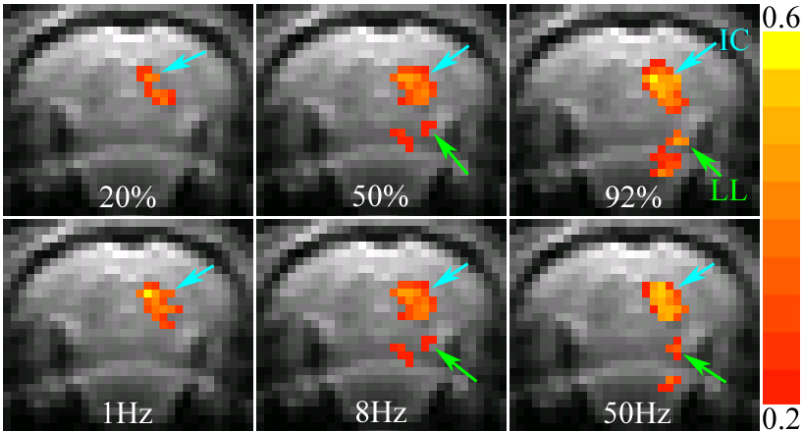


Fig. 2: Activation map of a representative animal responding to 8Hz (20%), 8Hz (50%), 8Hz (92%) (upper row) and 1Hz (50%), 8Hz (50%), 50 Hz (50%) (lower row) stimulation. Slice Location: Bregma -8.3mm.

RESULTS: Fig. 2 shows the activation map at Bregma -8.3mm including IC and dorsal lateral lemniscus (DLL). Fig. 3 shows BOLD percentage changes increase with F_{MOD} and DC. The time-series of 8Hz (92%), 8Hz (50%), and 50Hz (50%) increased throughout the 20s 'on' period. Fig. 4 shows that BOLD% increase with F_{MOD} and DC. At 8Hz modulation frequency, BOLD change is 3.02± 0.30BOLD% (92% DC), 1.75± 0.32BOLD% ($p<0.001$) and 0.94±0.16BOLD% ($p>0.05$) larger than 20% and 50% DC, respectively. At 50% DC, BOLD change is 2.83± 0.13BOLD% (50Hz), 1.19±0.30BOLD% ($p<0.05$) and 0.75±0.24BOLD% ($p>0.05$) larger than 1Hz and 8Hz, respectively.

DISCUSSIONS AND CONCLUSIONS: This study observes the IC hemodynamic response increases with modulation frequencies up to 50Hz and with duty cycles between 20 and 92%. The frequency dependence agrees with electrophysiology studies that most IC neurons' firing rates increase with modulation frequency up to 100Hz [2, 3]. Higher F_{MOD} results in higher firing rates within the 'on' period and is likely responsible for higher BOLD%. Our results also agreed with previous human fMRI studies that show the IC's hemodynamic response increased from 2Hz to 35Hz [5]. The relationship between duty cycle and BOLD change is expected from earlier studies investigating hemodynamic and neuronal mechanisms underlying BOLD responses to different stimulus durations [6]. These results advance our understanding of AM processing in the inferior colliculus and provide data for optimizing BOLD signal change in future rat auditory fMRI studies.

REFERENCES: [1] Joris PX., et al. Physiol Rev 2004; 84:541-577; [2] Rees A., et al. Hearing Rev 1983; 10: 301-330; [3] Rees A., et al. Hearing Rev 1987; 27:129-143; [4] Giraud AL., et al. J Neurophysiol 2000; 84:1588-1598; [5] Harms MP., et al. J Neurophysiol 2002; 88:1433-1450; [6]Friston KJ., et al. Neuroimage 2000; 12:466-477;

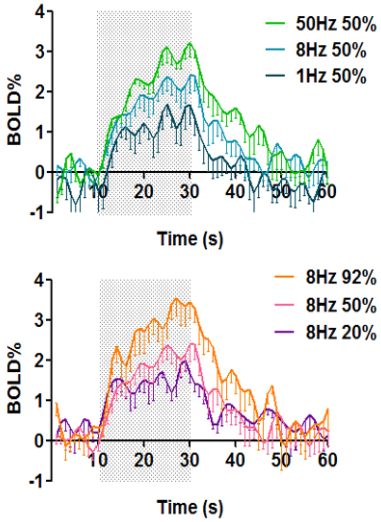


Fig. 3: Time-series averaged across all blocks and animals (n=5), presented as mean - standard error of mean (SEM). Shaded region indicates the applied stimulus.

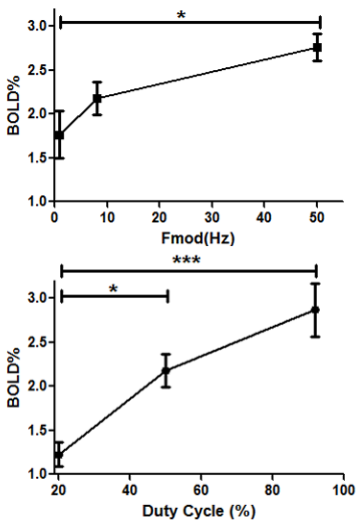


Fig. 4: BOLD percentage changes of the last 10s of 'on' period averaged over all blocks and animals (n=5), presented as mean ± SEM. (*p<0.05, ***p<0.0 01)