Target audience – Researchers and clinicians in the areas of functional magnetic resonance imaging (fMRI), hearing, sleep medicine, and altitude sickness.

Purpose – The brain depends on an adequate oxygen supply. Hypoxia occurs when the supply is inadequate. Chronic hypoxia is a significant feature of multiple health conditions and occupations. These include obstructive sleep apnea (OSA) and working/living at high altitude. OSA and high altitude work/residence are associated with an increased likelihood of hearing loss1,2. OSA can also result in an elevated minimum obstructive sleep apnea (OSA) and working/living at high altitude. OSA and high altitude work/residence are chronic hypoxia is a significant feature of multiple health conditions and occupations. These include obstructive sleep apnea (OSA) and working/living at high altitude. OSA and high altitude work/residence are associated with an increased likelihood of hearing loss1,2. OSA can also result in an elevated minimum sound intensity3. However, the increases in likelihood of hearing loss and minimum detectable sound intensity are small. Auditory processing deficits have been observed in OSA subjects6. Further, auditory event related potential studies of OSA subjects have recorded abnormal responses5. Both observations suggest central auditory system disorders. At present, relatively little is understood about which auditory brain structures are affected and in what way.

Methods – This pilot study employs BOLD fMRI to investigate the effects of chronic hypoxia on central auditory physiology. This research team is experienced with auditory investigations using fMRI and animal models6,9. The team is also experienced at developing animal models of chronic hypoxia10. The research team is experienced with auditory investigations using fMRI and animal models6,9. The team is also experienced at developing animal models of chronic hypoxia10. The research team is experienced with auditory investigations using fMRI and animal models6,9. The team is also experienced at developing animal models of chronic hypoxia10.

Animals: Sixty days old male Sprague-Dawley rats (N = 8) were employed. Four chronic hypoxia treatment subjects and four matched control subjects were treated with controlled oxygen levels for seven days (see below). After treatment, subjects were prepared for fMRI. Subjects were lightly anesthetized with isoflurane (3% induction/1% maintenance) and mechanical ventilation (Kent Scientific) was performed. The subject was placed on a holder and a custom sound transmission tube9 was inserted into the left ear canal. The right ear canal was blocked. A receive-only quadrature surface coil (Bruker Biospin) was placed over the head. This configuration reduced the MRI acoustic noise reaching the ear canals.

Chronic hypoxia treatment: The treatment procedure employed in this study modeled the intermittent hypoxia component of severe OSA10. The controlled oxygen level chambers that housed the subjects from 9am - 5pm had regulated levels of O2 and N2. This was performed by two oxygen purifiers (Reming Bioinstruments), one for each chamber. Each chamber measured 46x20x22cm3. In the treatment chamber, the O2 level was cycled between 5 and 17% with one minute period. In the control chamber, the O2 level was held at 21%. From 5pm to 9am, the subjects were housed together in a standard cage with room air.

Acoustic stimulation: Sound was transmitted from the high frequency speaker (Tucker-Davis Technologies) to the left ear canal through the sound tube. The tube permitted the speakers to be placed outside of the high magnetic field environment. The stimulus was noise pulses repeated at 10Hz with 50% duty cycle. The sound pressure level of each pulse was 89dB and the power spectrum was flat up to 40kHz (measured at tip of tube that entered the ear canal).

Image acquisition: fMRI was performed at 7T (Bruker Biospin). The fMRI acquisition sequence was: Gradient-Echo EPI, TR/TE = 10000/20ms, flip angle = 56°, slice dimensions = 32.0x32.0x1.4mm3, 64x64 voxels, interslice gap = 0.2mm, seven slices, 300 repetitions. The acoustic stimulation paradigm had 40s speaker OFF followed by four repetitions of 20s speaker ON and 40s speaker OFF. During ON periods, the speaker was pulsed as described above. During OFF periods, the speaker was silent. Each fMRI scan lasted 300s and 16 scans were performed per subject.

Data analysis: EPI images acquired from each subject were realigned and normalized to a template image using SPMS (Wellcome Trust Centre). The 16 scans per subject were averaged. Activated voxels were determined from the averaged images. The hemodynamic response to each ON period was modeled as a 20s long boxcar as in our earlier studies6,8,11,12. The p-value threshold for activation was 0.001. ROIs were drawn around activated central auditory system structures with guidance from the rat brain atlas. The atlas was used to delineate the boundaries of each structure and only activated voxels within each structure’s boundary were included in the ROI. ROIs were drawn for the contralateral lateral lemniscus, inferior colliculus, medial geniculate body, and both hemispheres of the auditory cortex. For ROI definition purposes only, activated voxels were determined by averaging the treatment and control images.

Results and Discussion – Fig. 1 shows more activated voxels and higher t-values in both auditory cortex hemispheres of treatment subjects. Table 1 shows considerably higher fMRI signal amplitudes in both auditory cortex hemispheres of treatment subjects. These results are likely related to the increased P2 amplitude seen in auditory evoked potential studies of OSA subjects, suggesting an abnormal stimulus classification response. Increased P2 amplitude has been correlated with increased fMRI signal amplitude11. Note that some fMRI features of transient hypoxia, such as CBF changes, are not expected to be present following chronic hypoxia6. Also, blood oxygenation level and blood pressure are not significantly different between treatments and controls based on earlier vital signs measurements performed on similar animal models10. Future fMRI studies can examine changes in auditory physiology in human OSA and high altitude subjects.