Sonication of thalamic circuits changes brain oscillations during non-stimulus conditions in a way analogous to changes in anesthetic level

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Introduction

Transcranial Ultrasound Stimulation (TUS) can be focused through the intact skull to target deep regions of the brain. It has been shown that the level of arousal in anesthetized animals can be changed through TUS stimulation of the thalamus (Yoo et al., 2011). To investigate the effect of sonication and brain anesthetic level in a large animal model, we analyzed the spontaneous EEG activity of the frontal cortex during interleaved non-stimulus conditions during the TUS of lateral geniculate nucleus (LGN) and Non-LGN control sonication.

Methods

Male sheep (N=4) were anesthetized with tiletamine and zolazepam at 4 mg/kg, intramuscularly. The anesthesia was maintained with a combination of isoflurane (less than 1%) delivered continuously by endo-tracheal intubation and telazol delivered by intravenous infusion. Platinum monopolar 30-gauge subdermal 10-mm long needle electrodes were implanted subdermally on the head positioned to overlie the frontal and occipital cortices. Animals were positioned in a 3T MRI scanner with an MR-compatible ultrasound transducer (ExAblate 2100, Insightec Ltd) coupled to the skin. The LGN on one side was identified with T2-weighted MRI. MR acoustic radiation force imaging (MR-ARFI) was used to confirm focal sonication (in a position away from the experimental target).

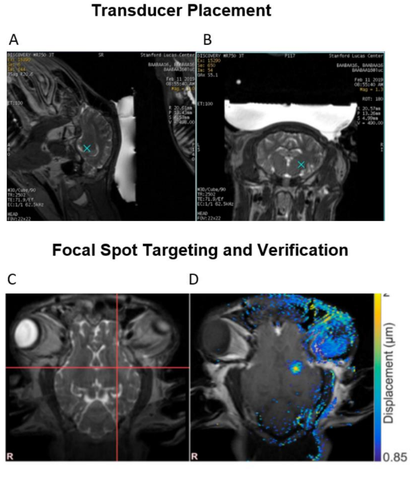


Figure 1. Sagittal (A) and frontal (B) MR image showing the TUS focal spot at non-LGN control location. A T2-weighted axial targeting MRI image (C) indicates the desired focal spot at a control location, and the MR-ARFI image (D) verified that the focal spot at control was at the desired location

Stimulation Paradigm

TUS pulses (PW 300 ms pulse duration, 50% duty cycle, 550kHz center frequency) were applied to LGN for 40 min, followed by 60 min sonication to a location approximately 10 mm anterior to the LGN and including a portion of the medial putamen and immediately adjacent internal capsule. In situ estimated ISPTA values between 1 and 10 W/cm2 were obtained based on ex vivo fiberoptic hydrophone (Precision Acoustics, Dorset, UK) measurements of pressure transmitted through each skull cap. Trials of TUS were interleaved with flashing light conditions in this order: No-stimulus, Light Only, TUS only and Light+TUS.

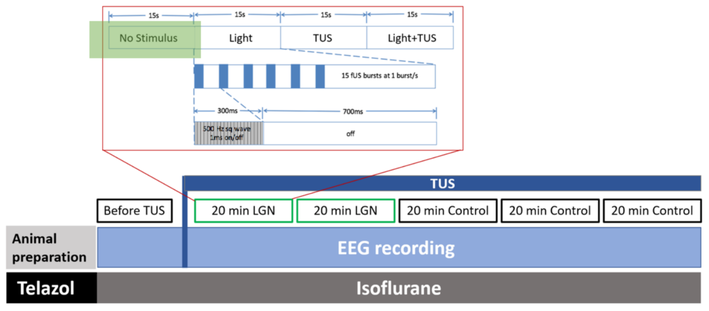
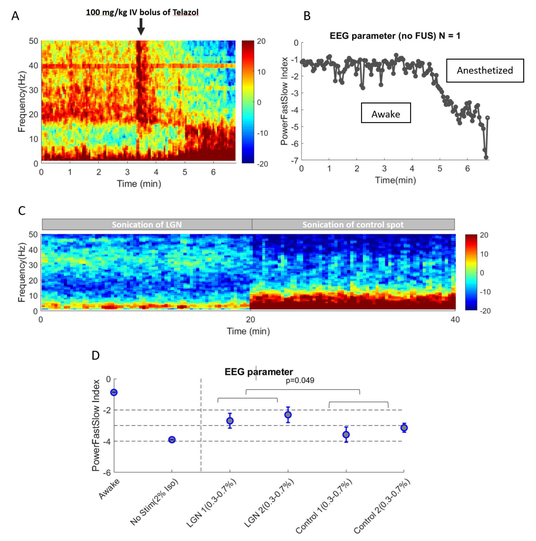


Figure 2. Experimental paradigm. Each 20-minute block (F) was split into 20 sections, each with four 15s conditions consisting of 1) no stimulus, no TUS, 2) light stimulus only, 3) TUS-only, and 4) light stimulus-plus-TUS. Only non-stimulus condition (green highlighted) was analyzed for the results.

Multi-taper spectrograms were computed using 10 s periods of spontaneous activity within each 20 minute block of sonication recorded from the frontal midline electrode. The trials from each block were then concatenated into a single 200-second epoch data for time-frequency decomposition. To quantify the power shift in the spectrum, a power spectrum-based parameter (PFS) was derived to compare the logarithmic ratio of high-frequency components (40 to 47 Hz) with the total (1 to 47 Hz) band. This method has been compared to the Bispectral (BIS) index, a quantified EEG index to monitor the level of anesthesia in the operating room, and showed similar performance (Miller et al., 2004).

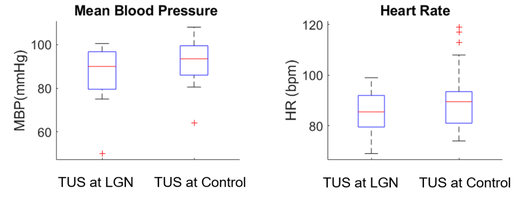
Results



The results from quantifying spectral analysis of EEG suggest that sonicating visual thalamus causes a shift in spontaneous EEG power analogous to the one from awakening from anesthesia, without any changes in vital sign measurements (MBP, HR).

Figure 3. Analysis of ongoing EEG activity prior to and after anesthesia during sonication of LGN and a non-LGN control location. A typical spectrogram computed from an awake animal before and after IV injection of Telazol (A). Changes in the PFS index in the awake state and during induction of anesthesia calculated from spectrogram in A (B). Representative spectrogram computed from concatenating the non-stimulus conditions during first LGN and non-LGN control spot sonication (C). Note that the first 20-minutes of LGN sonication is not immediately followed by the control sonication but here the spectra are placed next to each other for visualization. (D) Two timepoints in the absence of FUS are plotted on the left, while four timepoints are plotted in the presence of FUS on the right. Sonication to the LGN (a higher PFS index) demonstrate the animal is in a more "awake" state, compared to the sonication control.

Figure 4. Mean blood pressure (MBP) and heart rate (HR) recorded from 4 animals during LGN and control spot sonication. This figure demonstrates that there is no significance difference between the two conditions.



Conclusion

These results suggest that TUS can be non-invasively delivered to the thalamic circuits of the deep structures in the brain and causes a shift in the EEG power spectra that analogous to that observed during arousal from general anesthesia. This suggests that TUS of thalamus can affect brain anesthetics level corroborating the result reported in (Yoo et.,al 2011)

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