Mapping the sonication parameter space to characterise neuromodulation by ultrasound stimulation in the hippocampus

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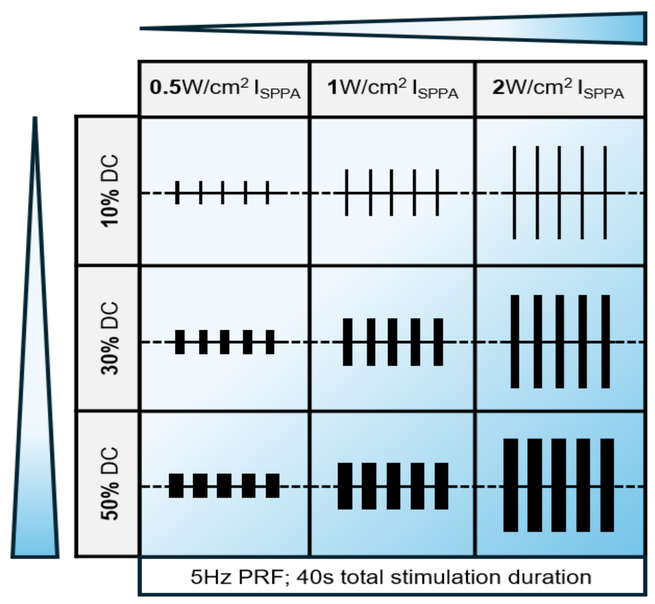
Background

Transcranial focused ultrasound (tFUS) is a promising tool for non-invasive neuromodulation, capable of targeting neural activity with high spatial precision [1]. However, the influence of acoustic parameters on neural excitability and circuit-level function remains poorly defined, making it difficult to select protocols that maximise desired effects given the growing evidence of parameter-dependent outcomes [2].

We investigated how variations in duty cycle (DC) and spatial peak pulse average intensity (ISPPA) shape network responses. This approach allows us to identify parameter combinations that differentially affect circuit function and to guide the design of ultrasound paradigms for future applications.

We recently reported that stimulation with 5 Hz, 50% DC, ~140 kPa ultrasound enhances offline circuit function in the hippocampus [3], and here we extend this by systematically testing nine ultrasound conditions combining three DCs (10, 30, and 50%) and three intensities (0.5, 1, and 2 W/cm²).



Aim

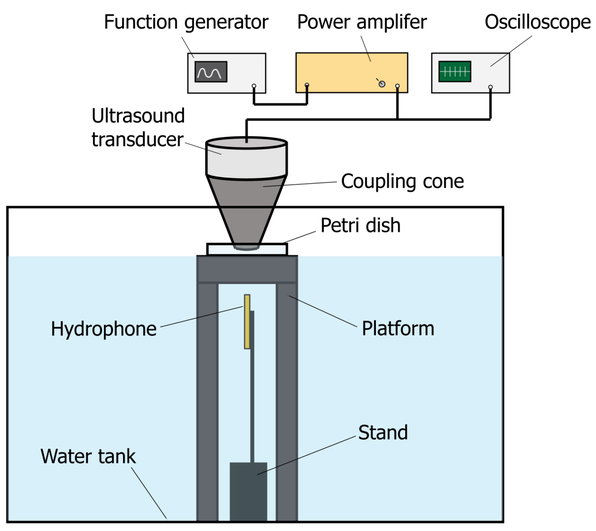
To determine how different stimulation parameters interact to drive specific neuromodulation effects in the hippocampus.

Methods

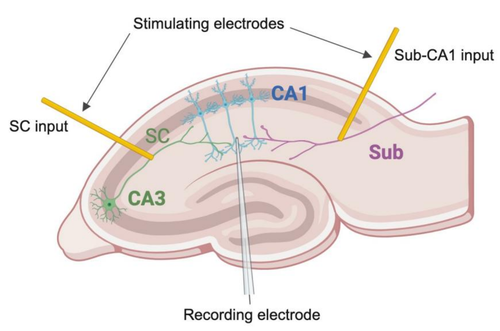
Animals: Male and female Han Wistar 3-4-week-old juvenile rats (51-75g). All experiments were approved by the U.K. Home Office as defined by the Animals (Scientific Procedures) Act 1986.

Acute hippocampal slice preparation: Rats were sacrificed via Schedule 1 cervical dislocation and promptly decapitated to remove the brain into ice-cold artificial cerebrospinal fluid (aCSF). Hippocampi were isolated and sliced into 400 µm transverse slices.

Ultrasound stimulation: A 1MHz transducer powered by a signal generator amplified by a radio frequency amplifier, was used to deliver pulses of theta-burst ultrasound (5 Hz pulse repetition frequency) over a 40 s sonication duration. We tested nine ultrasound conditions combining three DCs (10, 30, and 50%) and three intensities (0.5, 1, and 2 W/cm²). For sham stimulation, the transducer was disconnected, but all other conditions remained the same.



Field electrophysiology: A recording electrode was placed in the CA1 *stratum radiatum* of the hippocampal slice and CA3-CA1 field responses were evoked by 0.1 ms voltage pulses to the Schaffer collateral (SC) pathway at increasing stimulation strength (0-20V in 1V increments)



Results

Ultrasound-induced offline neuromodulation effects are sensitive to duty cycle/intensity interactions.

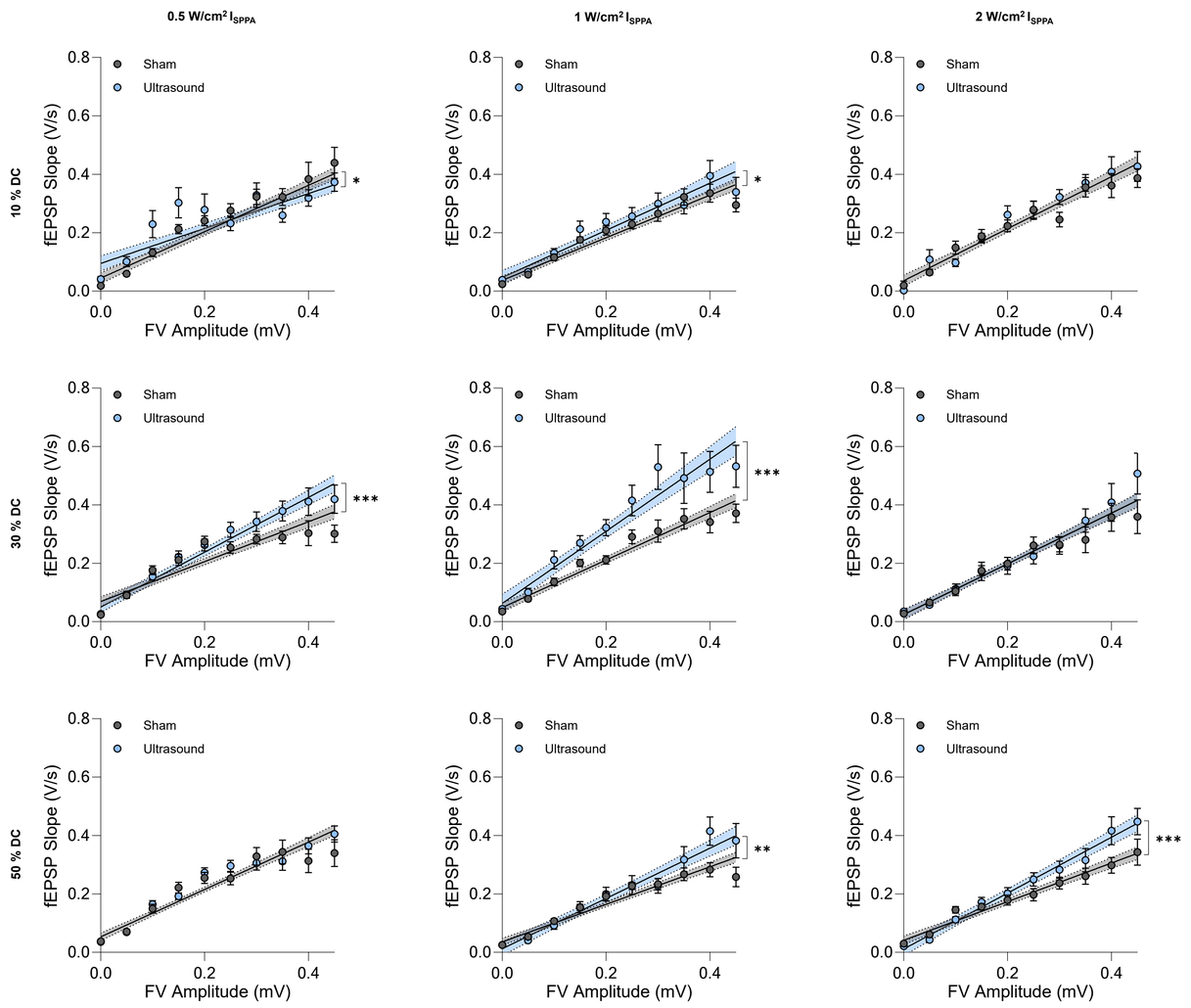


Fig. 1. Hippocampal basal synaptic function modified by ultrasound stimulation. Comparison of FV amplitude and fEPSP slope in corresponding field recordings in sham (Grey) and US (Blue) treated slices. fEPSP responses are binned by presynaptic fibre volley (FV) amplitude into 0.05 mV bins. Fit with a linear regression model (shaded area is 95 % CI). Difference between model fits is analysed by Extra Sum of Squares F-test. Data . *n = 20 (sham) vs 20 (US). *p < 0.05, **p < 0.01, ***p < 0.001.* Data is mean ± S.E.M.

Conclusion

These results suggest that offline neuromodulatory effects are sensitive to interactions between duty cycle and intensity. We propose that neuromodulatory outcome is shaped by the interaction of stimulation parameters and the targeted circuit. Differences in pulsing schemes may alter membrane mechanics, influence voltage-dependent excitability, and determine a minimum pressure or duration needed to elicit a response. Such protocol-dependent effects could bias activation toward excitatory or inhibitory cell populations.

Whilst the present range of intensity and duty cycle values was not broad enough to fully define these relationships and did not incorporate PRF or sonication duration dependent effects, the results nonetheless inform the selection of ultrasound paradigms for future systematic mapping.

Expanding the parameter space will be essential to establish links between protocol design and the magnitude of neuromodulation, paving the way for more scalable and consistent applications.

References

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