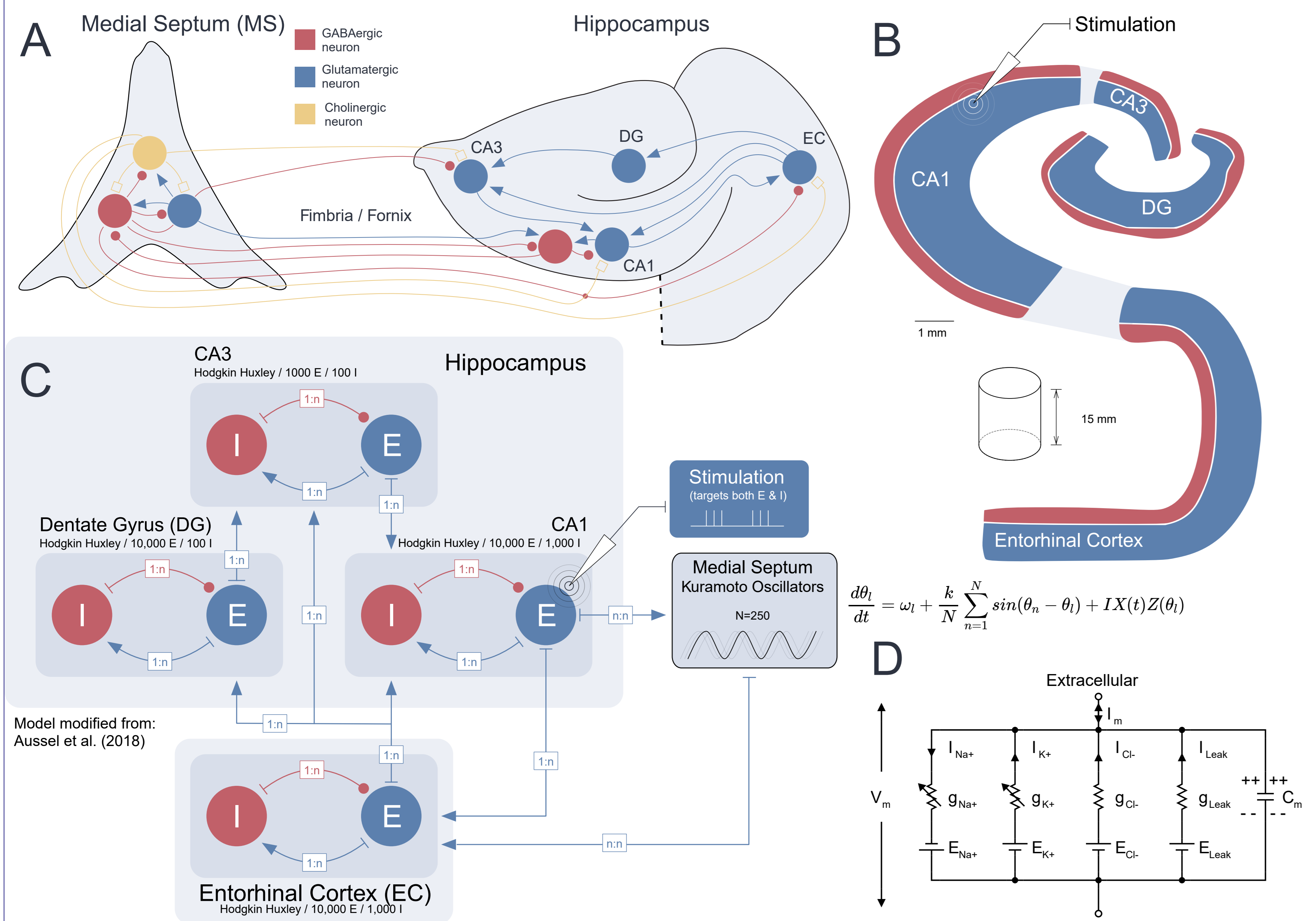


I. INTRODUCTION

Theta and gamma oscillations in the hippocampus play a crucial role in memory processes and are disrupted in several neurological disorders. Recently, **electrical stimulation of the hippocampal formation has been shown to enhance memory encoding in humans**, but the underlying mechanisms need to be investigated.

We aimed to validate the hypothesis that neurostimulation entrains theta-nested gamma oscillations and is capable of inducing phase reset of theta oscillations. We have developed a novel hybrid computational model that replicates both physiological hippocampal oscillations and **stimulation-induced theta phase reset**.

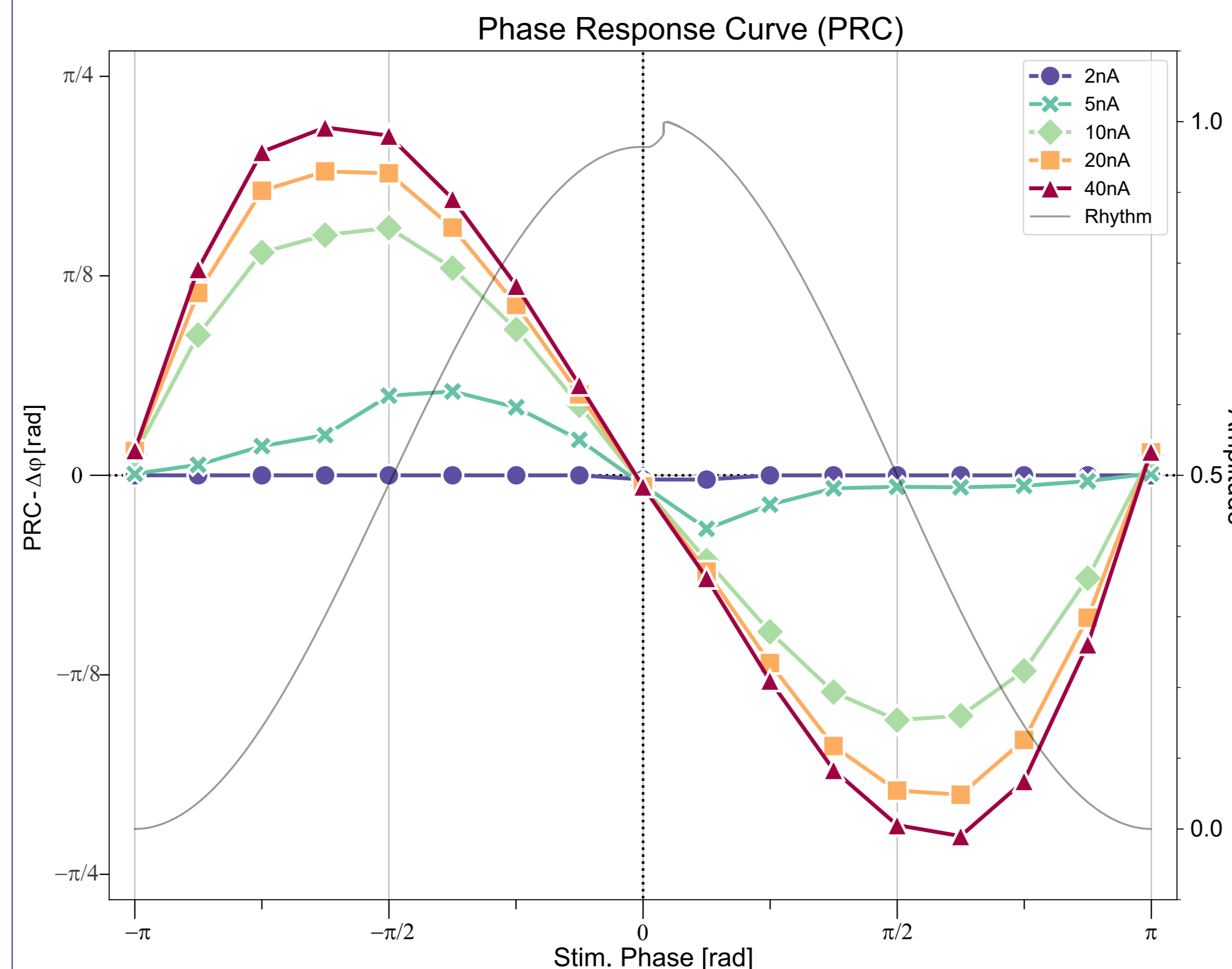
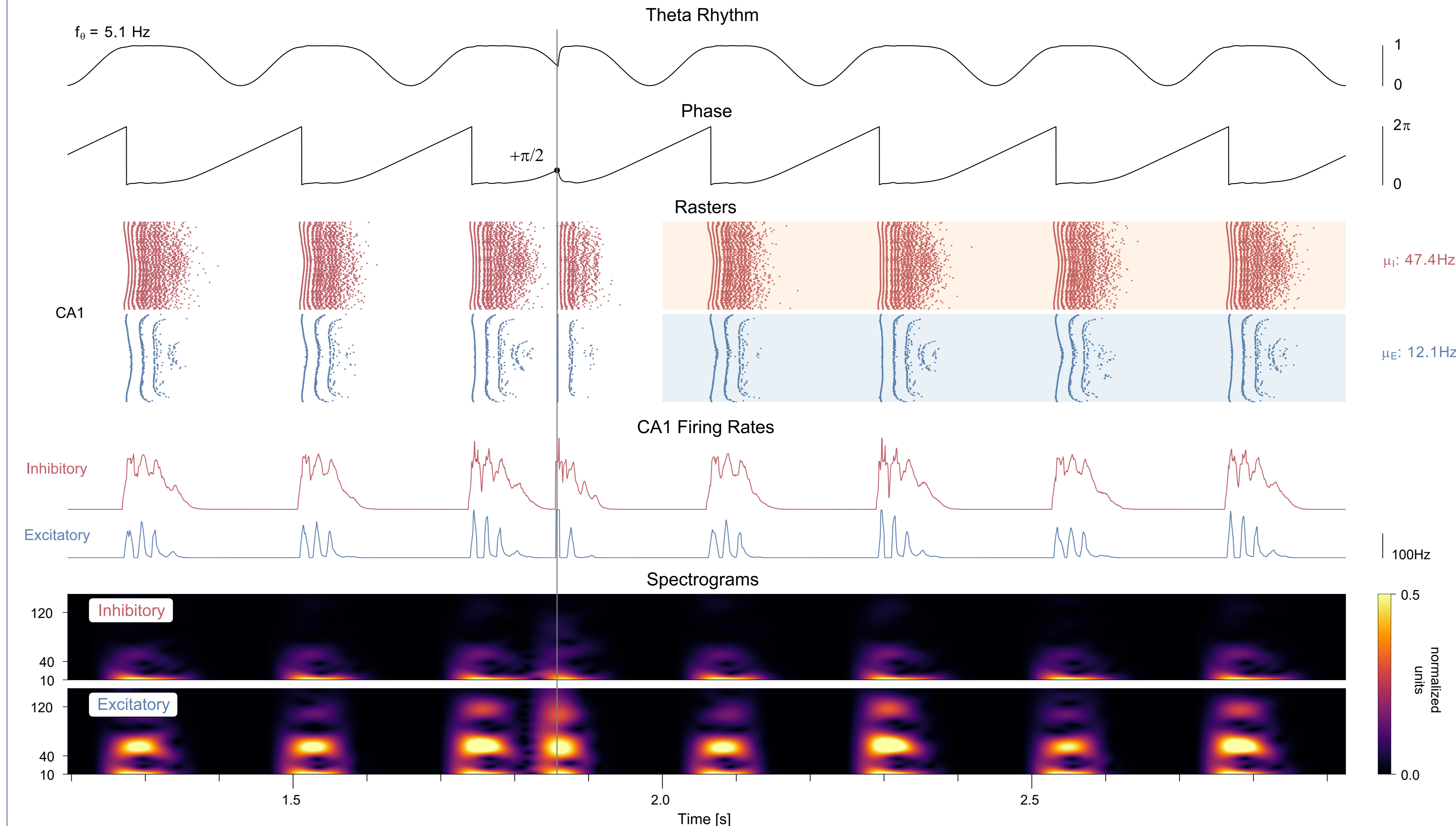
II. MODEL DESCRIPTION



Schematic description of the hybrid model

A. Schematic of the connections between the Medial Septum (MS) and the Hippocampal formation. **B.** Hippocampal slice, including the stimulation electrode. **C.** Block diagram of the connections between populations and areas. Theta input to the Entorhinal Cortex (EC) from the MS is modeled using phase-coupled oscillators. Stimulation is applied to the CA1 subfield. **Excitatory populations (E); Inhibitory populations (I).** **D.** Generalized Hodgkin-Huxley model of a single cell. The evolution of the membrane voltage V_m is described by the set of differential equations characterizing the electrical circuit.

III. STIMULATION-INDUCED THETA PHASE RESET



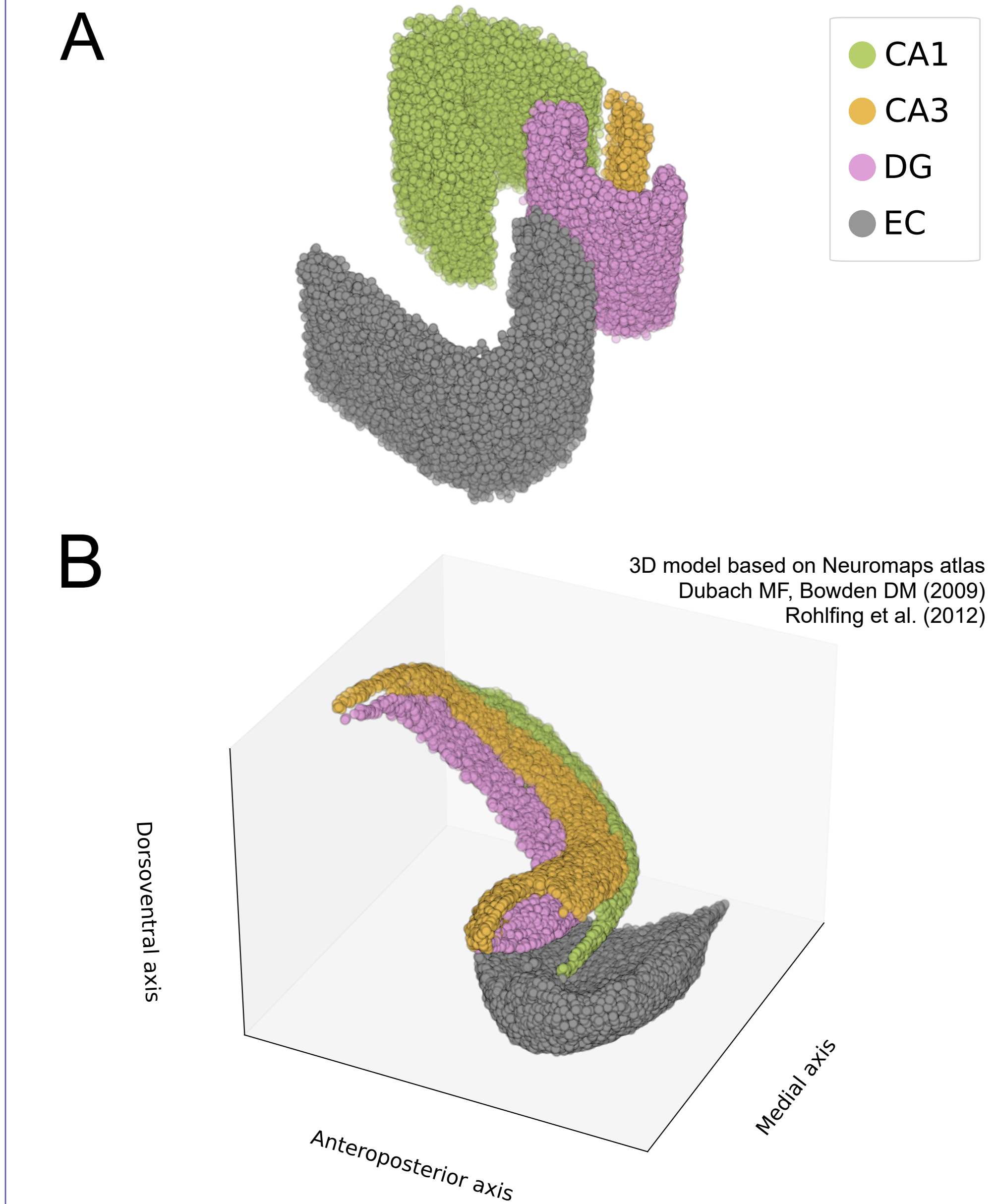
Single-pulse stimulation induces robust phase reset.

A single pulse of electrical stimulation is applied at the CA1 at phase $+\pi/2$. The synchronized depolarization of the cells produces a spike of the population's firing rate. The stimulation produces a robust theta phase reset, delaying the next peak of the theta rhythm (top panel).

Evaluation of phase reset

Single-pulse stimulation is applied at the CA1 region at different phases of the theta rhythm. The instantaneous phase difference $\Delta\phi$ is calculated based on the phase offset at the time right after the stimulation pulse is applied. Zero crossings indicate no phase change. Positive values indicate a phase advancement; negative values indicate a phase delay.

IV. MRI-BASED MODEL



Anatomical model of the hippocampus

A. Coronal slice of the hippocampal formation as used in the model. **B.** The anatomy of the hippocampal formation was extracted from the Macaque NeuroMaps atlas and populated with neurons. This approach can be used to generate subject-specific models in the future.

V. CONCLUSIONS

Novel biologically-realistic hybrid model of the hippocampal formation

The model is capable of producing theta-nested gamma oscillations and stimulation-induced theta phase reset. The model's predictions will be used to guide neurostimulation of different areas in the HPC during experimental procedures and will assist in the development of a closed-loop neurostimulation platform.