The Effect of Phase-Specific Optogenetic Stimulation on Memory Recall in Mice

Benjamin Lahner[1] and Melanie H. Quick[1], Bahar Rahsepar[1], Jad Noueihed[1], and John A. White[1]
[1]Boston University Department of Biomedical Engineering, Boston, MA
Contact: melquick@bu.edu

Introduction

Memory and its driving mechanisms are relevant to a wide variety of clinical and physiological applications. Better understanding of memory could lead to treatments of debilitating neural disorders or clinical techniques to improve memory. Theta waves (4 to 12 Hertz slow sinusoidal oscillations) are hallmarks of memory encoding and retrieval in the mammalian hippocampus. Disruptions of theta wave propagation limits the creation of new memories and retrieval of old. A prominent theoretical model proposes the phase of theta separates the state of encoding new information from recalling stored memories [1]. Despite physiological data supporting this model, *in vivo* testing of this hypothesis remains challenging. By adopting real-time phase specific stimulation of memory neurons in the brain circuitry underlying memory processes, this hypothesis can be tested in living animals. Furthermore, the provided platform will increase the specificity by which theta waves and other memory processes can be explored.

Methods

Peak & Trough Detection

The algorithm was tested causally using sample LFP data collected from freely moving mice using a tetrode.

Selection Criteria:

- First and second derivative testing
- Threshold latency
    - Peak-to-peak or trough-to-trough: 81 ms
    - Peak-to-trough or trough-to-peak: 41 ms
- Threshold amplitude set at 0.15 µV calculated around a moving average

Real-Time Implementation

The algorithm was implemented as a C++ Real Time eXperimental Interface (RTXI) module [2].

Methods

Accuracy Analysis

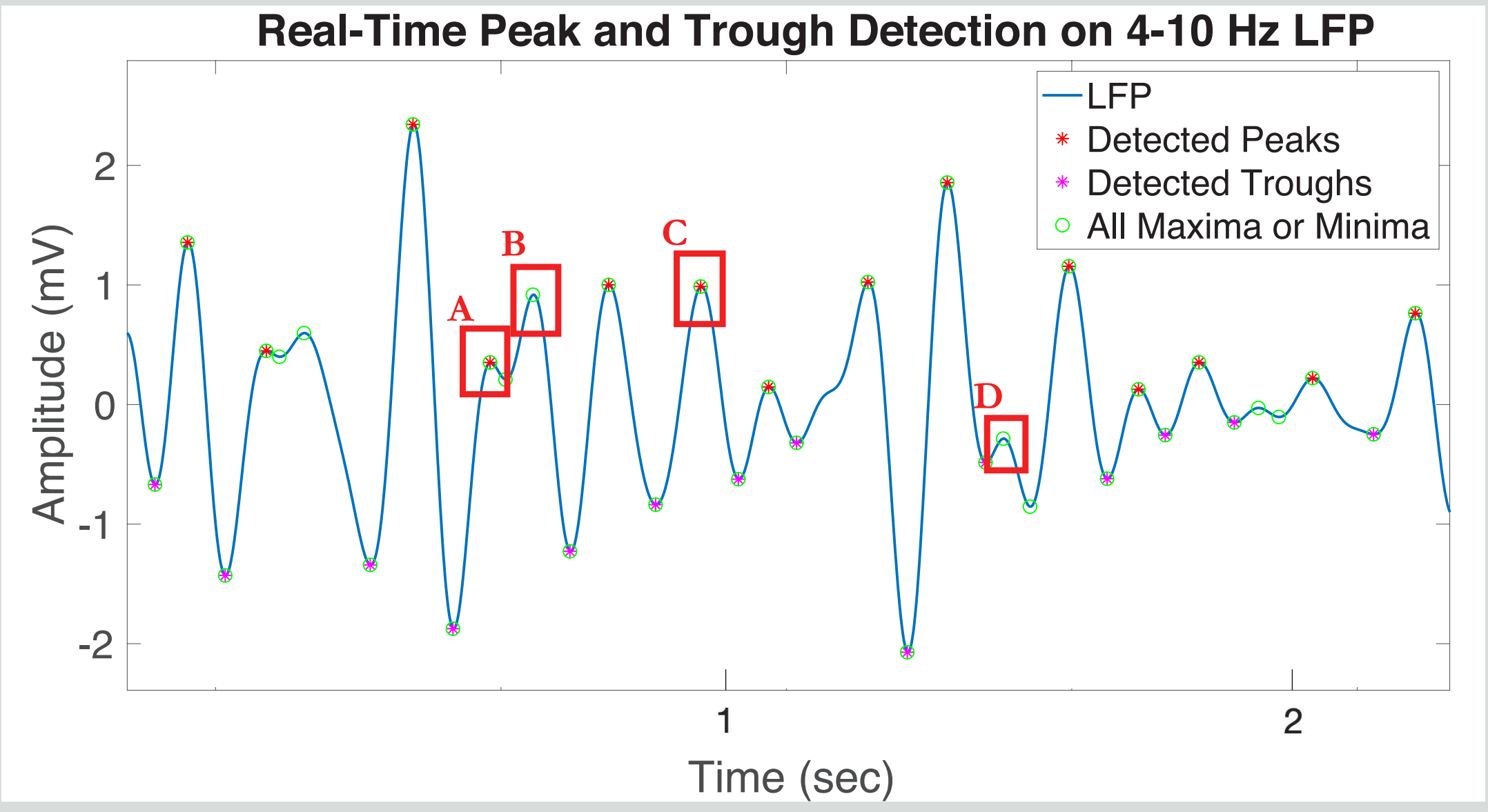

Figure I: **Representative section of analyzed LFP showing A) a local peak identified as a global peak (false positive), B) a missed global peak (false negative), C) a correctly identified global peak (true positive), and D) a local peak not identified as a global peak (true negative).**

In Vivo Experimentation

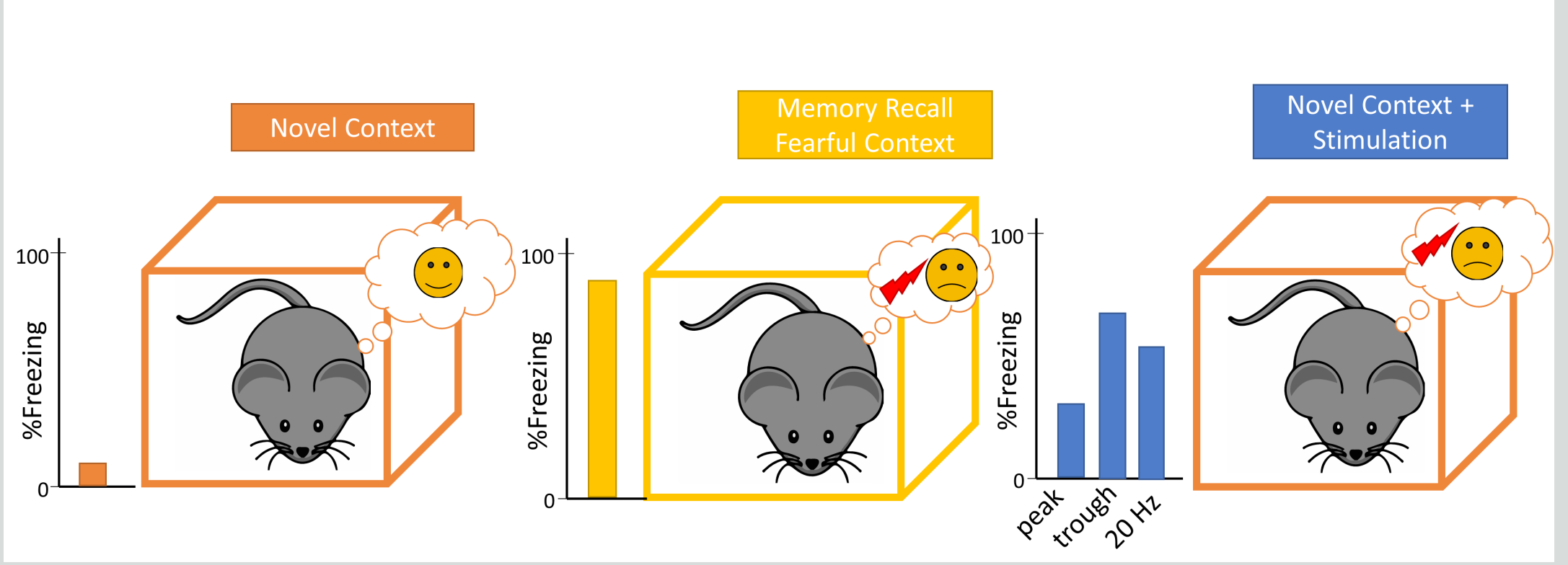

Figure II: **From left to right: minimal expected freezing (%) without stimulation or fear stimulus, maximum expected freezing (%) with fear stimulus, and variable expected freezing (%) with peak, trough, and 20 Hz stimulation. Near-maximum freezing is expected with trough stimulation. Near-minimum freezing is expected with peak stimulation. Mid-range freezing is expected with 20 Hz stimulation.**

Materials:

- Recording amplifier (MultiClamp 700B)
- Data acquisition bus (PCI 6221)
- Two fiber optic cables and one probe
- Real Time eXperimental Interface (RTXI) [2]

Results

Offline

From the 50 seconds of data analyzed, 396 maxima and 395 minima were measured.

Peak Detection

- Accuracy : 92.2%
- Misclassification Rate: 7.8%

Trough Detection

- Accuracy: 93.4%
- Misclassification Rate: 6.6%

	Predicted (0)	Predicted (1)
Actual (0)	TNR = 80.4%	FPR = 19.6%
Actual (1)	FNR = 6.3%	TPR = 93.7%

Table I: **Confusion matrix of peak detector (n = 396 peaks). The algorithm was tuned to the following parameters: 0.15E-3 mV amplitude threshold, 83 milliseconds full cycle latency, and 41 milliseconds half cycle latency. 0 = local peak, 1 = true peak.**

	Predicted (0)	Predicted (1)
Actual (0)	TNR = 87.0%	FPR = 13.0%
Actual (1)	FNR = 5.7%	TPR = 94.3%

Table II: **Confusion matrix of trough detector (n = 395 troughs). The algorithm was tuned to the following parameters: 0.15E-3 mV amplitude threshold, 83 milliseconds full cycle latency, and 41 milliseconds half cycle latency. 0 = local trough, 1 = true trough.**

The latency of four infinite impulse response (IIR) filters were averaged over 100 peaks and troughs. The Chebyshev Type II IIR filter was identified with the lowest latency and time delay.

- Latency: 14.2 ms
- Sampling Rate: 1 kHz
- 4 to 10 Hz bandpass
- 40 dB stopband attenuation

Results

Real-Time

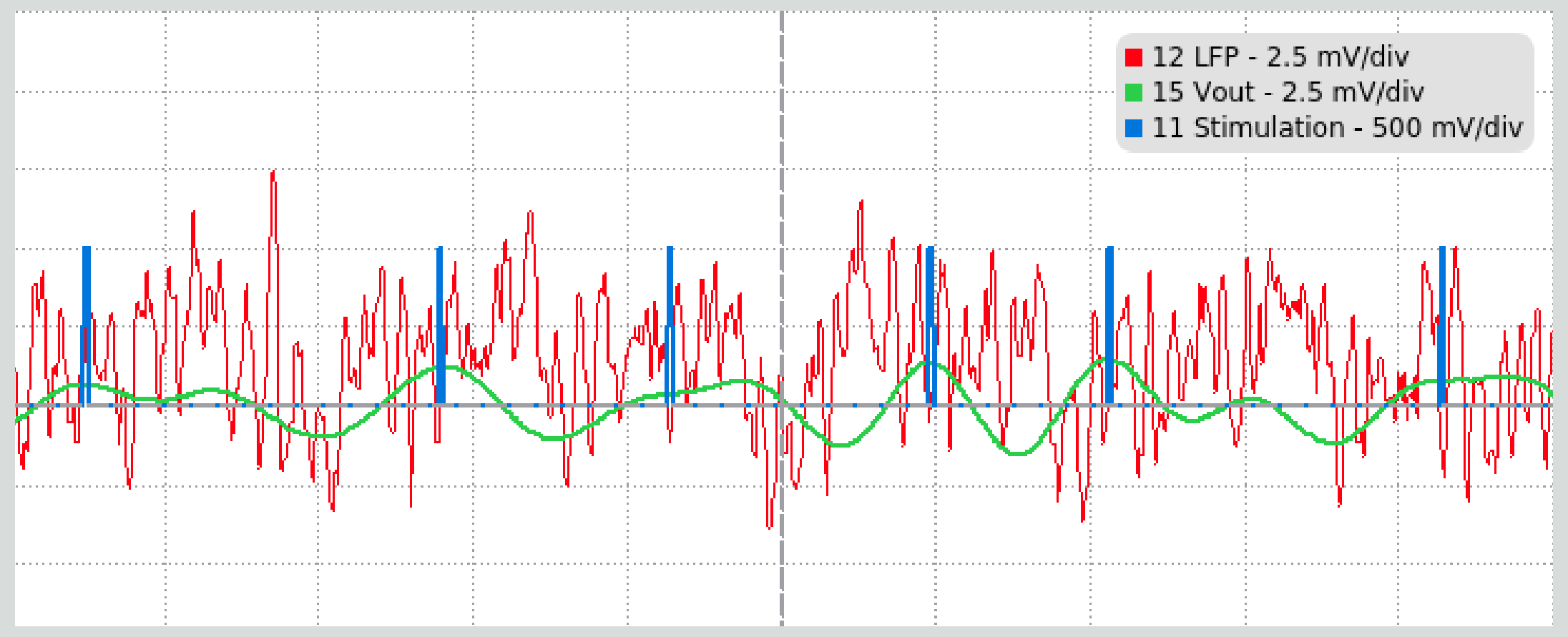

Figure III: **Sample peak stimulation in RTXI. 100 ms (x-axis) and 2.5 mV (y-axis) per division.**

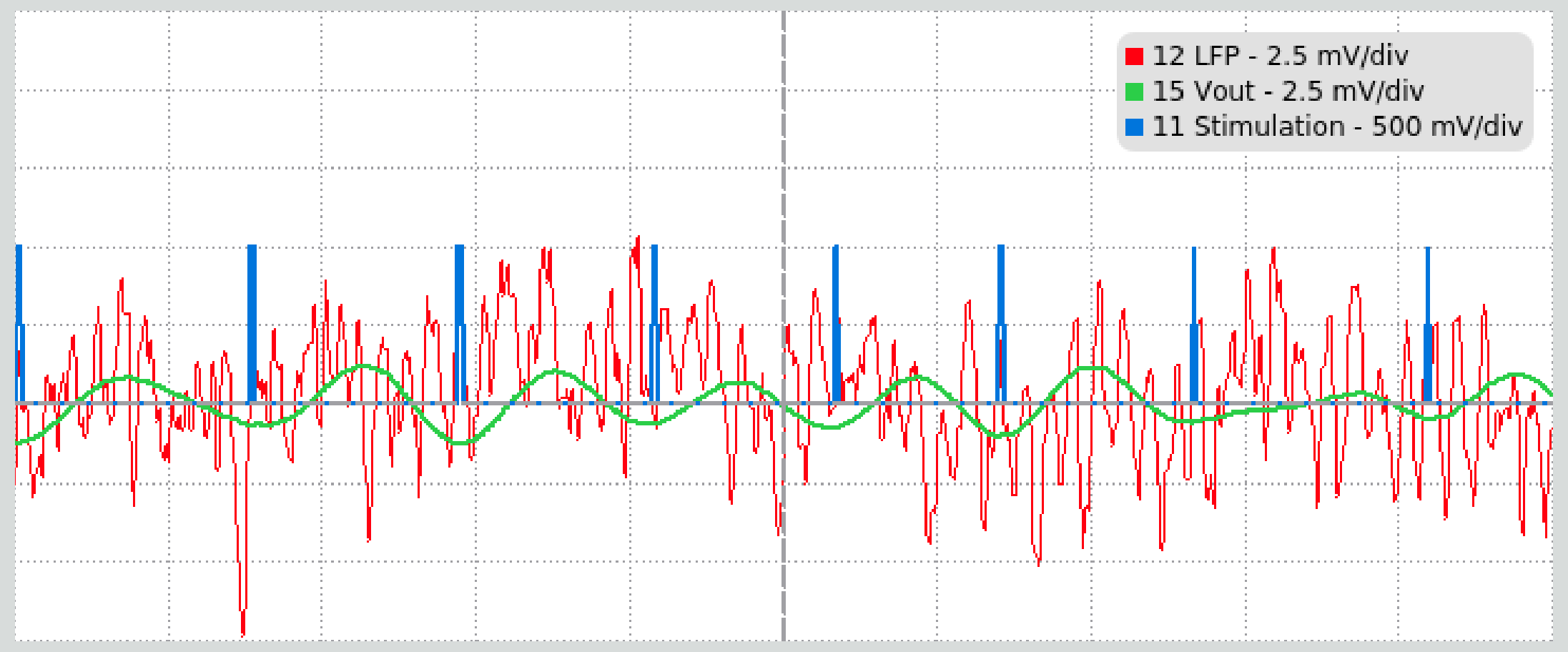

Figure IV: **Sample trough stimulation in RTXI. 100 ms (x-axis) and 2.5 mV (y-axis) per division.**

Conclusions

In integrating real-time manipulations of memory neurons with behavioral observations, the algorithm will help inform understanding of theta phase with the state of memory encoding versus retrieval. The neurophysiology of phase-specific stimulation on memory recall can be studied with increased specificity. The experimental paradigm created through this project will enable more detailed dissection of the physiology behind memory processing and offer useful methods to study and modify theta waves in real-time.

References

1. Hyman JM. et al. J Neurosci. 2003;23:11725-11731.
2. Patel YA. et al. PLoS Comput Biol. 2017;13:e1005656.