Oscillatory Mechanisms for Hippocampal Memory Encoding Tested in Humans

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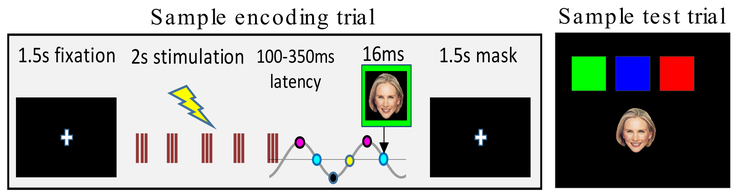
Introduction

- Rhythmic activity of the hippocampus and hippocampal-cortical network in the theta-frequency band (~3-8Hz) is thought to support episodic memory.[1]
- The phase of the hippocampal theta oscillation may orchestrate the transition between hippocampal connectivity states supporting memory formation vs. retrieval[2,3], but this has not been conclusively demonstrated in humans.
- Noninvasive transcranial magnetic stimulation (TMS) can produce phase-entrainment in a targeted brain region when delivered at a rhythm endogenously produced by that region[4].
- To investigate the theta phase dependence of memory processing in humans, we delivered theta-frequency stimulation to the hippocampal-cortical network to produce phase-entrainment, then measured performance on a specialized memory task timed relative to the entraining stimulation.

Methods

- We applied theta-burst TMS in an attempt to manipulate hippocampal theta phase via entrainment.
- Subjects received **5Hz theta-burst stimulation of a cortical location in the hippocampal network**, as in other recent work from our laboratory[5,6].
- Target location was identified from resting-state fMRI for each subject based on hippocampal connectivity, restricted to left parietal (angular gyrus, inferior parietal lobule), TMS-accessible sites.
- To control for sensory entrainment effects of TMS, we also performed trials where we delivered the same stimulation to a vertex control site.
- **Following each 2s TMS train, subjects performed a memory encoding task** where a brief (<17ms) visual stimulus was shown at a known latency relative to the last TMS burst.
- Encoding success was determined based on performance on a subsequent test of associative recall.

Design



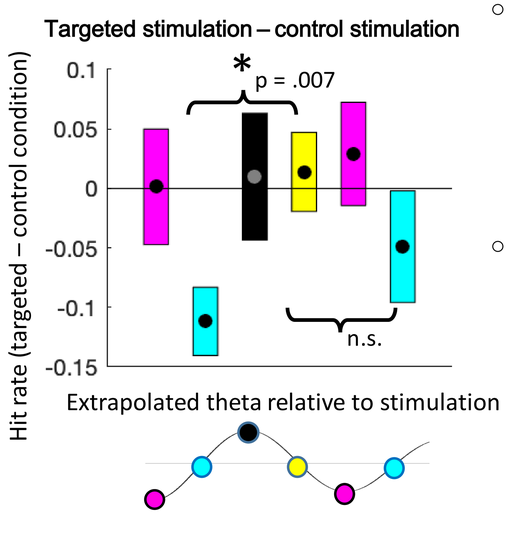
- Subjects performed blocks of TMS-entrained stimulus encoding (9 trials/block), distractor task, and memory testing with simultaneous EEG recording. Each block was randomly assigned to targeted or vertex control stimulation. (24 total blocks)
- Stimuli were presented at one of 6 phases, corresponding to π/2 intervals along the entrained theta oscillation.
- Performance on the memory test is compared across entrained theta phase values. If we successfully entrained hippocampal theta and if there is a phase dependence of encoding success, **memory performance vary periodically with entrained theta phase.**

Research aims

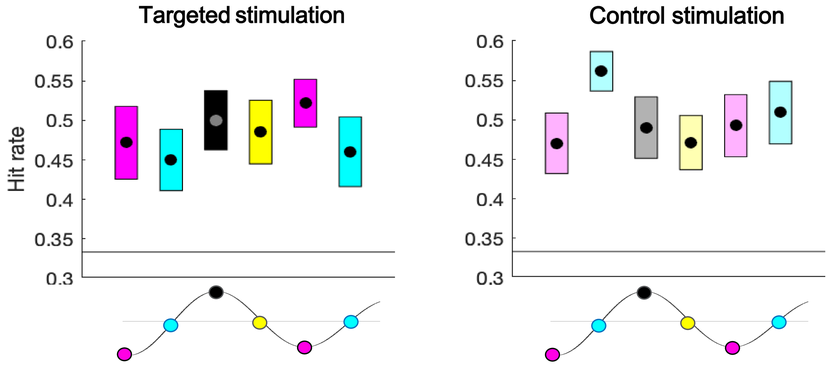
Aim 1: Investigate the relationship between exogenously entrained hippocampal theta phase and memory encoding ability.
Aim 2: Identify neural correlates of optimal encoding due to theta phase synchrony with memoranda.

Results

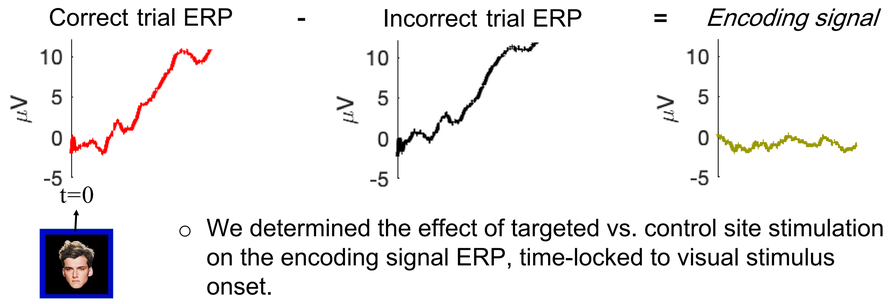
Encoding ability is theta-periodically influenced by targeted stimulation



- Change in subsequent memory performance (top left) due to stimulation targeting the hippocampus (bottom left) versus a control location (bottom right), organized by phase angle of memoranda presentation relative to the theta-burst stimulation. n=15
- **Stimulation targeting the hippocampus periodically influenced encoding relative to vertex stimulation, reducing encoding ability during the rising phase of both cycles compared to the falling phase.** (First cycle following stimulation: p=0.007, robust after multiple comparisons.. Second cycle: trend-level)



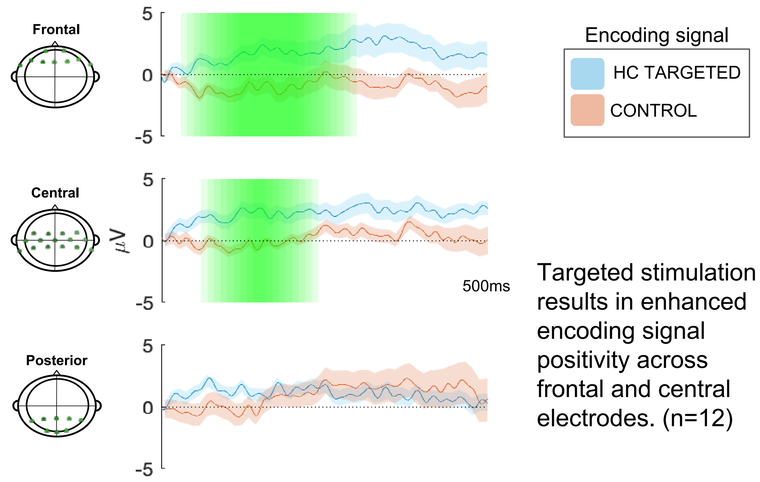
Calculating ERP correlates of successful encoding



- We determined the effect of targeted vs. control site stimulation on the encoding signal ERP, time-locked to visual stimulus onset.
- The goal of this analysis was to **determine how extrapolated stimulatory phase angle at the time of memoranda onset influenced memory processing.**

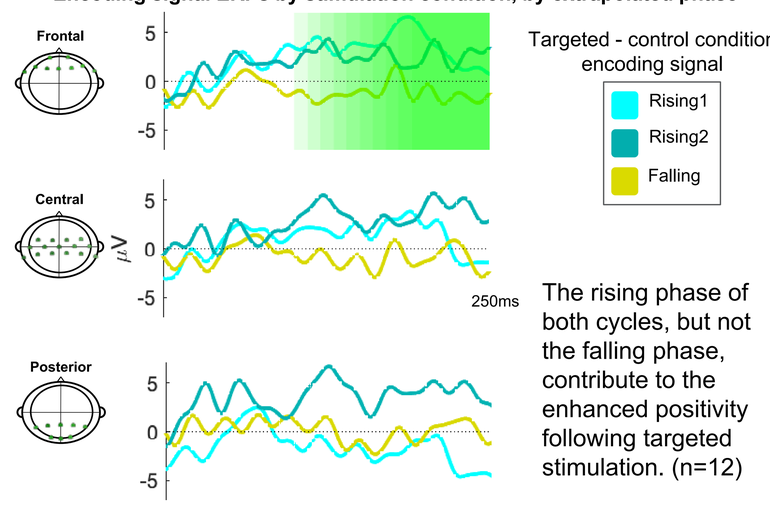
Calculating ERP correlates of successful encoding

Encoding signal ERPs by stimulation condition, across all extrapolated phases



Targeted stimulation results in enhanced encoding signal positivity across frontal and central electrodes. (n=12)

Encoding signal ERPs by stimulation condition, by extrapolated phase



The rising phase of both cycles, but not the falling phase, contribute to the enhanced positivity following targeted stimulation. (n=12)

Summary

- Parietal stimulation periodically influenced encoding relative to vertex, affecting rising phases of both cycles compared to falling phase.
- ERP encoding signals were also modulated by phase of stimulus onset, with rising phases of both cycles generating the maximal encoding signal for parietal stimulation versus vertex.
- These findings suggest an influence of stimulation on encoding-related theta signals and support the role of theta phase in encoding.

Acknowledgements

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References

1. Herweg, N. A., Solomon, E. A., & Kahana, M. J. (2020). Theta Oscillations in Human Memory. *Trends in Cognitive Sciences*, *24*(3), 208–227. https://doi.org/10.1016/j.tics.2019.12.006
2. Hasselmo, M. E., Bodelón, C., & Wyble, B. P. (2002). A Proposed Function for Hippocampal Theta Rhythm: Separate Phases of Encoding and Retrieval Enhance Reversal of Prior Learning. *Neural Computation*, *14*(4), 793–817. https://doi.org/10.1162/089976602317318965
3. Siegle, J. H., & Wilson, M. A. (2014). Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. *ELife*, *3*, e03061. https://doi.org/10.7554/eLife.03061
4. Thut, G., Veniero, D., Romei, V., Miniussi, C., Schyns, P., & Gross, J. (2011). Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures. *Current Biology*, *21*(14), 1176–1185. https://doi.org/10.1016/j.cub.2011.05.049
5. Wang, J. X., Rogers, L. M., Gross, E. Z., Ryals, A. J., Dokucu, M. E., Brandstatt, K. L., Hermiller, M. S., & Voss, J. L. (2014). Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science*, *345*(6200), 1054–1057. https://doi.org/10.1126/science.1252900
6. Hermiller, M. S., Karp, E., Nilakantan, A. S., & Voss, J. L. (2019). Episodic memory improvements due to noninvasive stimulation targeting the cortical–hippocampal network: A replication and extension experiment. *Brain and Behavior*, *9*(12), e01393. https://doi.org/10.1002/brb3.1393