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The ventral midline thalamus consolidates fear memory during sleep

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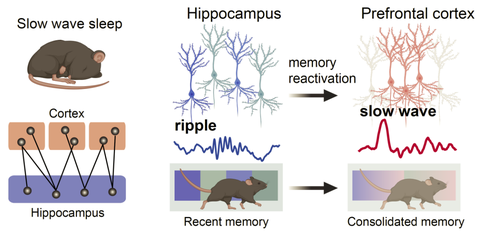
INTRODUCTION

Sleep is an essential step in memory consolidation. Memories of recent experience are encoded in the hippocampus during waking and transferred to the neocortex during sleep[1].

A key process in memory consolidation is the generation of ***ripples*** in the hippocampus during slow wave sleep - characterized as high-frequency oscillations between 100-300Hz[2].

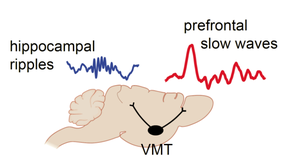


During ripples, hippocampal neurons that were recently active are reactivated. These replayed memories propagate to the cortex during the slow oscillation, characterized by alternating phases of neuronal activity and silence, called UP and DOWN states, respectively[1,2,3].

The precise timing between hippocampal ripples and cortical slow waves during slow wave sleep is crucial for memory consolidation.[4]

HYPOTHESES

The thalamus mediates ripple-slow wave coupling



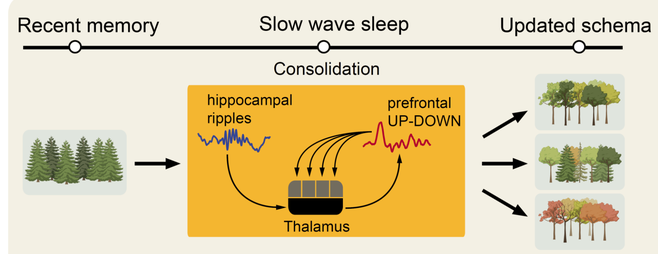
The ***ventral midline thalamus (VMT)*** links the hippocampus and the medial prefrontal cortex (mPFC) via bidirectional connections.

Contextual memory is consolidated by the thalamus during ripples

The reactivation of place cells during hippocampal ripples is closely linked to contextual memory.

The VMT is implicated in the contextual aspects of fear memory, likely due to its hippocampal connectivity.[5]

CONCLUSIONS



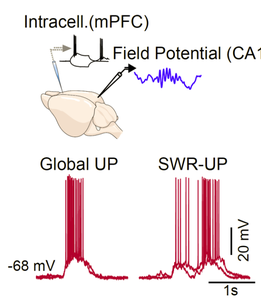
Hippocampal neurons replay recent experience during ripples in slow wave sleep.

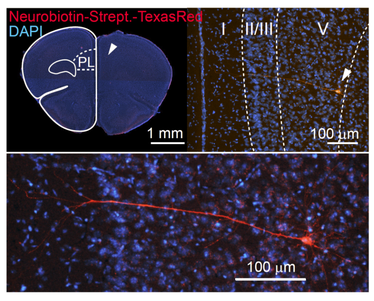
- Ripples trigger local UP-DOWN sequences in the mPFC via midline thalamic nuclei.
- In turn, prefrontal UP states drive multiple thalamic targets, exerting top-down influence over wide regions of the brain.

The cascading activation of thalamocortical loops updates existing schemas encoded at the network level with recent experience replayed in ripples.

RESULTS

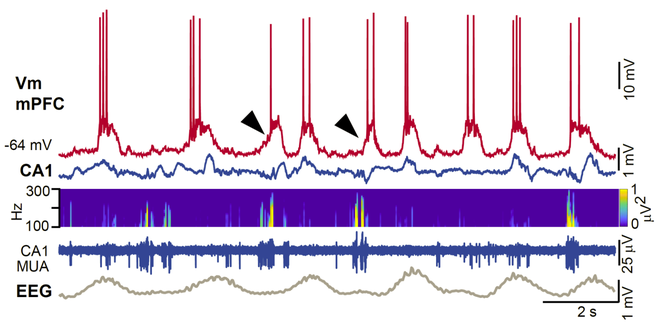
in vivo intracellular electrophysiology

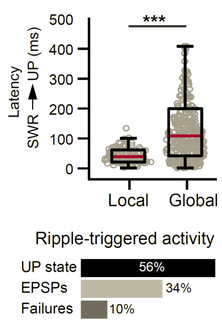




In vivo intracellular recordings of the mPFC. Pulled glass capillaries filled with neurobiotin and potassium acetate were used to record and label mPFC neurons in anesthetized mic together with field potential recordings of the hippocampus.

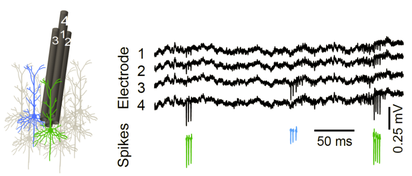
hippocampal ripples elicit prefrontal UP states

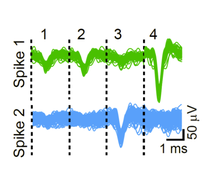




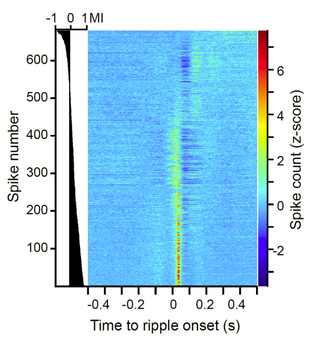
During hippocampal ripples, the membrane potential of mPFC neuron depolarized and transitioned to UP states, independently of the global slow oscillation, measured by the contralateral somatosensory EEG. Most ripples elicited UP states with a minority generating subthreshold EPSPs in mPFC neurons.

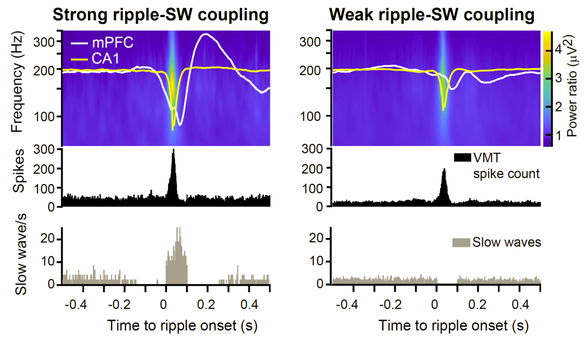
increased thalamic firing during ripple-slow waves





Neuronal spikes were recorded from sleeping mice, using twisted-wire tetrodes, implanted in the VMT. Single-units were detected from tetrode recordings using clustering algorithms.





Hippocampal ripples drive firing in the majority of recorded neurons from the VMT.
A subset of VMT neurons were inhibited around the 50 ms mark.

VMT firing rates were higher during ripples that were followed by prefrontal slow waves, compared to weakly coupled ripple-slow wave events. Slow wave were preceded by a depth-negative component, indicating increased cortical activity. Ripples that occured 100 ms prior to slow waves were de-

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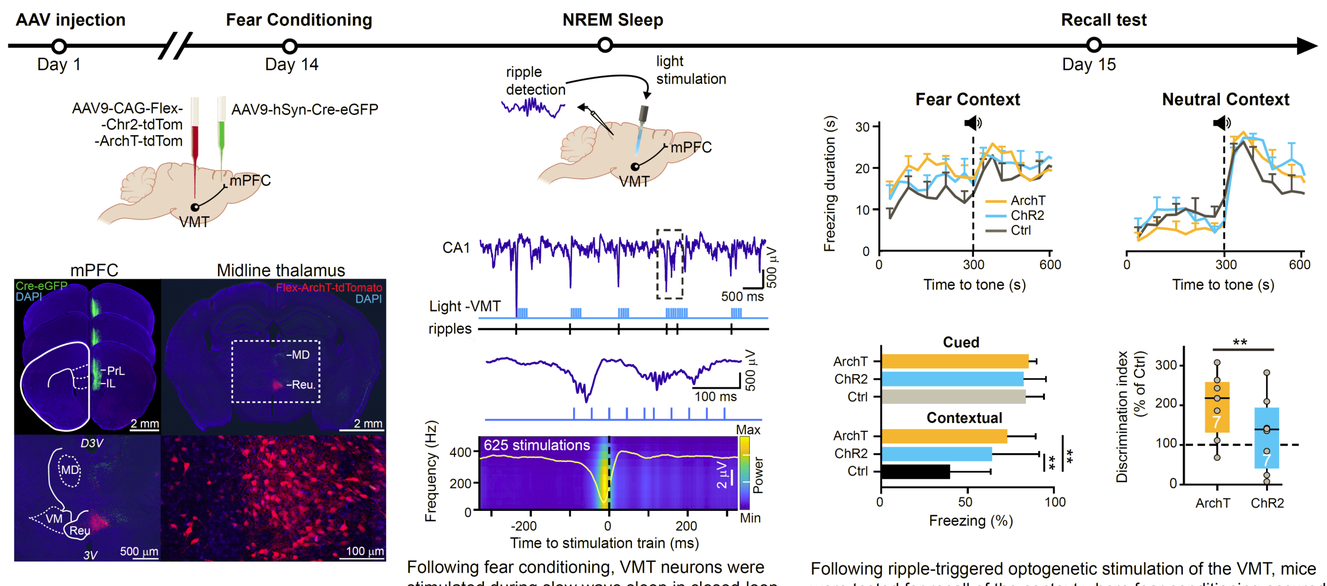
3. Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci. 2005 Feb;6(2):119-30.
4. Maingret, N., Girardeau, G., Todorova, R., Goutierre, M. & Zugaro, M. Hippocampo-cortical coupling mediates memory consolidation during sleep. Nat. Neurosci. 19, 959–964 (2016).
5. Xu W, Südhof TC. A neural circuit for memory specificity and generalization. Science 339(6125):1290-5 (2013)

thalamic stimulation during ripples enhances memory specificity

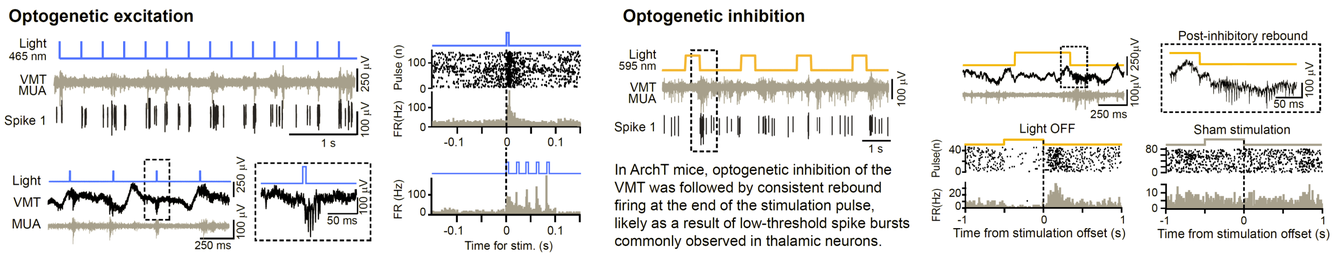


Using AAV-mediated delivery, opsins were conditionally expressed in VMT neurons projecting to the mPFC in three groups of mice: ChR2 - excitatory, ArchT-inhibitory and Ctrl-control mice.

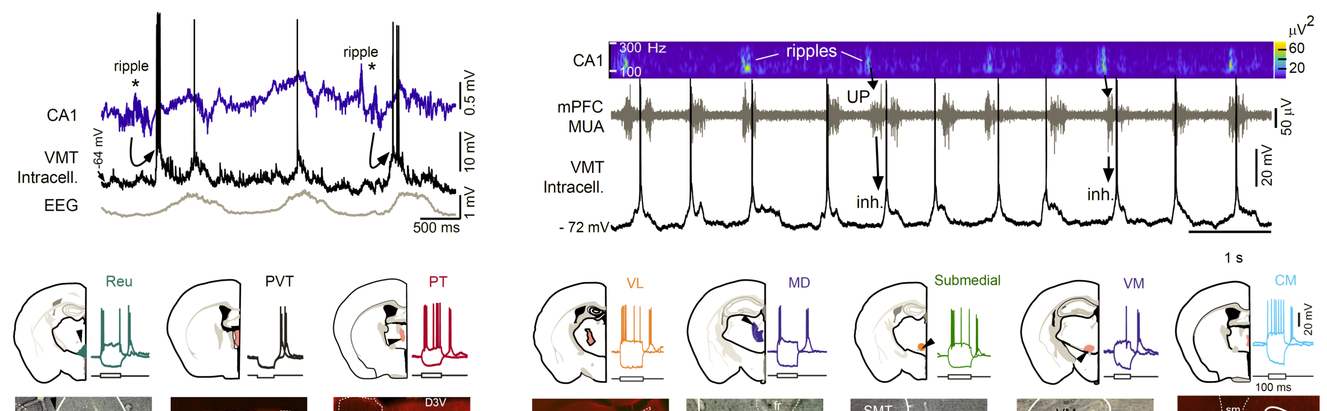
Following fear conditioning, VMT neurons were stimulated during slow wave sleep in closed-loop configuration. Ripples, detected from hippocampal recordings, were used to trigger a light source to deliver time-restricted stimulation to the VMT.

Following ripple-triggered optogenetic stimulation of the VMT, mice were tested for recall of the context where fear conditioning occured. Compared to controls, ArchT and ChR2 mice displayed higher discrimination of fear and neutral contexts. ArchT mice were more likely than Chr2 mice to display fear responses in the appropriate context.

optogenetic inhibition of the thalamus is followed by rebound firing



ripple-triggered UP states drive multiple thalamic targets of the mPFC



In vivo intracellular recording of the VMT in anesthetized mice. VMT neurons from reuniens, paraventricular and parataeniai nuclei were depolarized following the onset of hippocampal ripples.

Multiple thalamic targets of the mPFC were inhibited during the prefrontal UP state triggered by hippocampal ripples. Ripple-triggered UP states delayed low-threshold spike bursting, in comparison to low-threshold spike bursts occuring during global UP states. VL-ventrolateral, MD-mediodorsal, VM-ventromedial, CM-centromedian.

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