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The reuniens nucleus of the thalamus facilitates hippocampo-cortical dialogue

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INTRODUCTION

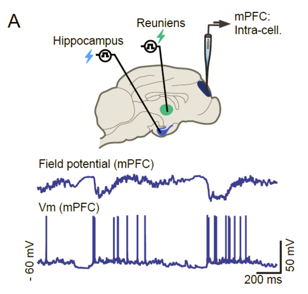
Interactions between the hippocampus and the medial prefrontal cortex (mPFC) are essential for cognition. During sleep, hippocampal and cortical activity is continually synchronized by cardinal sleep oscillations such as slow waves (SWs, 0.1-4 Hz), thalamocortical spindles (10-15 Hz), and hippocampal sharp-wave ripples (SWRs, 100-300 Hz) [1,2].

These rhythms have well-known roles in neuronal plasticity [3,4] and in the consolidation of hippocampus-dependent memories 5. In particular, the hierarchical coupling of slow waves, spindles and SWRs is thought to promote the stabilization of short-term memory4. Consistent with this hypothesis, the temporal coupling of hippocampal and mPFC sleep oscillations results in a selective increase in the recall of hippocampus-dependent memory[5,6].

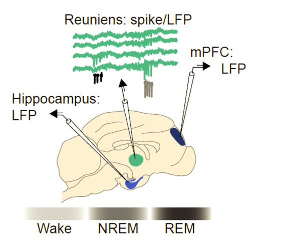
The reuniens nucleus of the thalamus is bidirecationally connected to the mPFC and the hippocampus, making it an ideal hub for coupling of slow waves, spindles and SWRs during sleep. Although evidence for the functional significance of the reuniens in cognitive operations is strong, little is known about the nature of reuniens-prefrontal interactions and their interplay with hippocampal events during sleep.

METHOD

1. In vivo intracellular recordings of the mPFC were obtained during electrical stimulation of the reuniens and hippocampus in animals anesthetized with ketamine-xylazine



2. Field potential recordings of the mPFC and hippocampus were obtained together with spike recordings of the nucleus reuniens during natural sleep/wake cycles



3. A computational model of the prefrontal-thalamic-hippocampal network was implemented using a neural mass model

Interregional synchrony was measured using phase-amplitude coupling and interregional time delays between SWRs, spindles and slow waves together with reuniens spiking and local field potential (LFP) activity.

CONCLUSIONS

The results provides physiological confirmation to the hypothesis that reuniens is a core mediator in hippocampo-cortical dialogue.

1. Reuniens activity during natural sleep was strongly modulated by hippocampal oscillations.

2. Spindles were preceded by increased probability of SWRs.

3. Electrical stimulation of reuniens generated orthodromic and antidromic spiking in mPFC neurons, indicating bidirectional thalamocortical circuitry.

4. Slow waves in reuniens lagged prefrontal slow waves but spindles in reuniens led prefrontal spindles, suggesting a bidirectional, oscillation-dependent dialogue between reuniens and the mPFC.

1. Siapas, A.G., and Wilson, M.A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21, 1123-1128.
2. Isomura, Y., Sirota, A., Özen, S., Montgomery, S., Mizuseki, K., Henze, D.A., and Buzsáki, G. (2006). Integration and Segregation of Activity in Entorhinal-Hippocampal Subregions by Neocortical Slow Oscillations. Neuron 52, 871-882.
3. Chauvette, S., Seigneur, J., and Timofeev, I. (2012). Sleep Oscillations in the Thalamocortical System Induce Long-Term Neuronal Plasticity. Neuron 75, 1105-1113.
4. Diekelmann, S., and Born, J. (2010). The memory function of sleep. Nature reviews. Neuroscience 11, 114-126.
5. Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., and Zugaro, M. (2016). Hippocampo-cortical coupling mediates memory consolidation during sleep. Nature Neuroscience 19.

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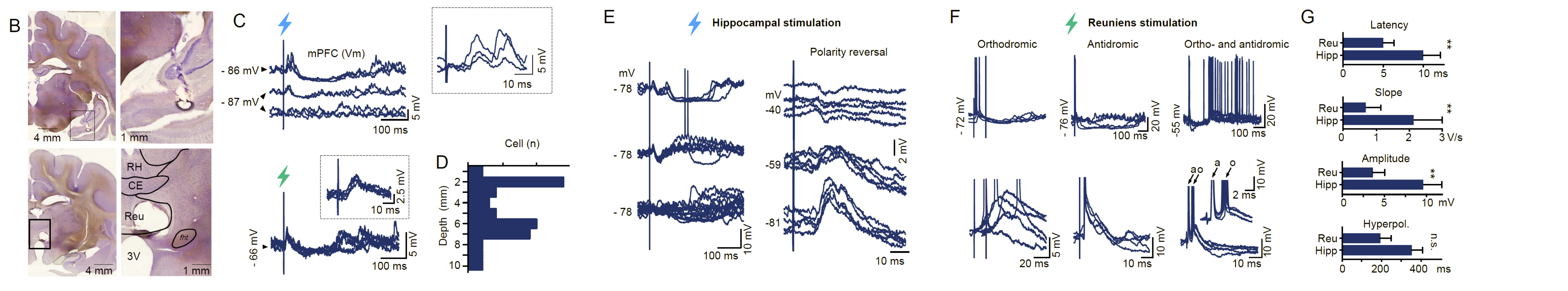
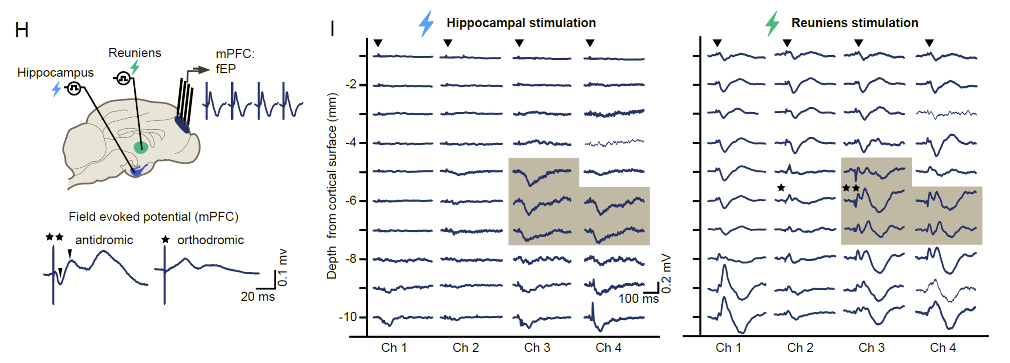
RESULTS

Reuniens stimulation elicits fast, consistent mPFC responses



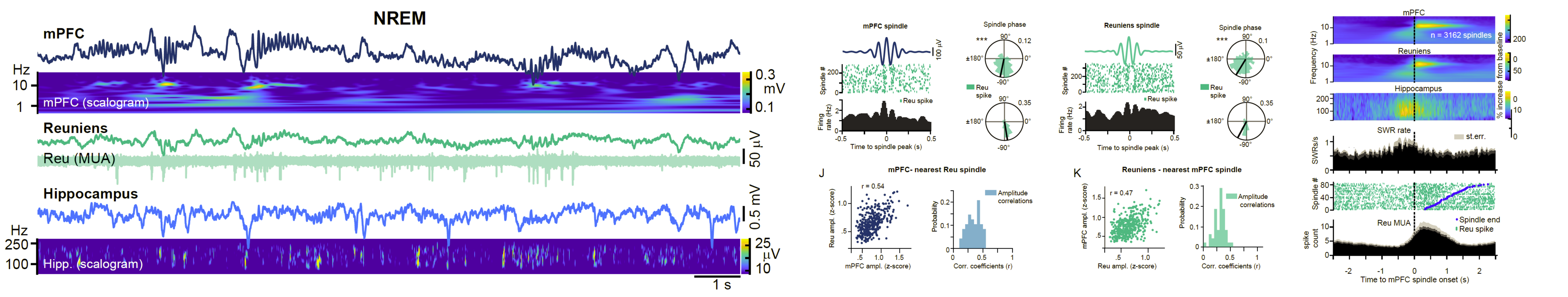
Stimulation of the hippocampus and reuniens elicited synaptic responses in 55% and 51% of recorded mPFC neurons, respectively. Hippocampal stimulation generated variable responses in the same neurons, consisting of complex sequences of either two excitatory postsynaptic potentials (EPSPs) followed by long-lasting hyperpolarization (E, top, left), a depolarization-hyperpolarization sequence (E, middle, left), or no response (E, bottom, left). Reuniens stimulation elicited consistent EPSPs followed by long-lasting hyperpolarization (C, bottom) at earlier latencies than hippocampal stimulation

Reuniens stimulation elicited action potentials that were either orthodromic (85%), antidromic (10%) or both (5%), evidenced by jitter in the latency of orthodromic action potentials and consistent latency of antidromic action potentials (F). Antidromic responses to reuniens stimulation, confirmed by collision tests, were recorded in cells located 6050-6600 μm ventral to the dorsal aspect of the



Reuniens stimulation evoked field postsynaptic potentials in a wider prefrontal territory compared to hippocampal stimulation which was restricted to the ventromedial wall of the mPFC. Early responses to reuniens stimulation (H, I) corresponded to criteria of field potential antidromic responses. Areas in the prefrontal cortex that responded to hippocampal stimulation overlapped with areas exhibiting antidromic responses to reuniens stimulation (I).

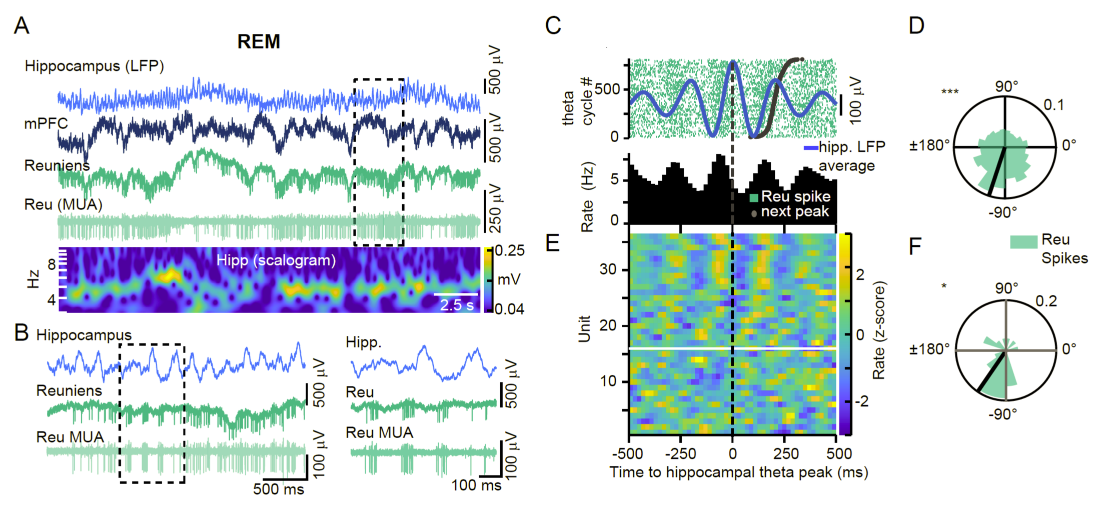
Reuniens and hippocampal activity precede mPFC spindles



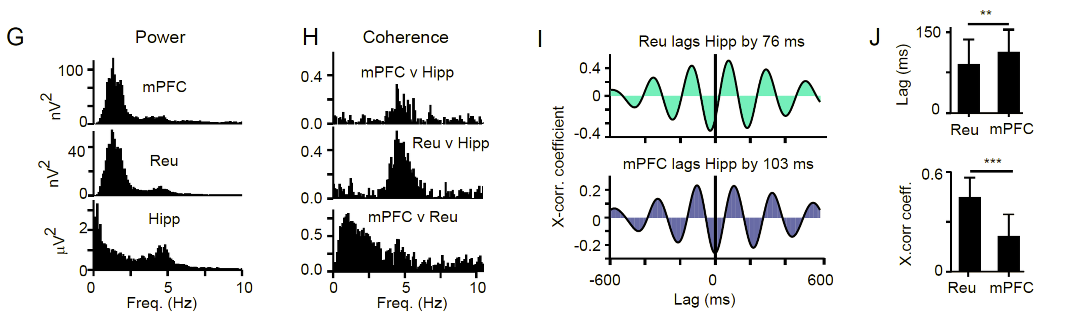
The mean phase preference of reuniens single-units was advanced for reuniens spindle cycles relative to mPFC spindle cycles. For pairs of co-occurring reuniens and mPFC spindles, spindle amplitudes were significantly correlated.

We observed increased hippocampal ripple power and increased reuniens spindle power preceding the onset of spindles in the mPFC. The histogram of SWR incidence in the same time window, referenced to the onset of mPFC spindles, indicated increased SWR incidence prior to the onset of mPFC spindles. Reuniens multi-unit activity increased prior to the onset of mPFC spindles

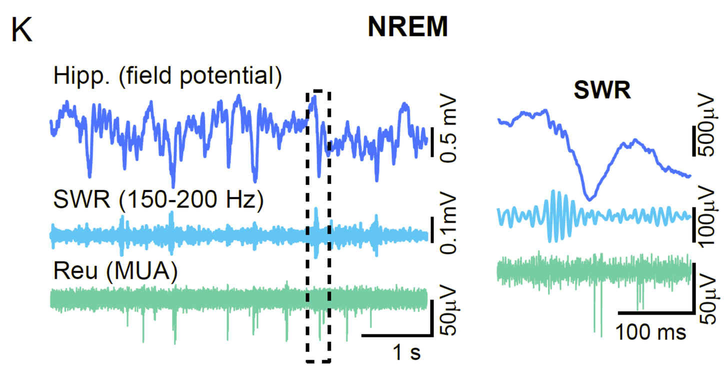
Hippocampal oscillations modulate reuniens activity

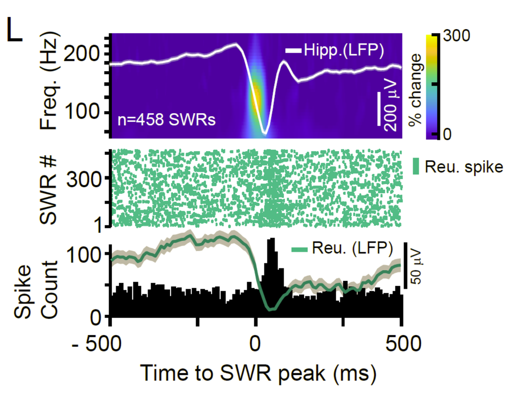


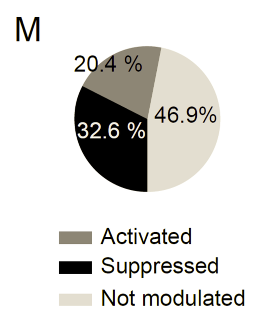
The wavelet spectrogram of the hippocampal trace demonstrates prominent theta-band activity during REM with periodic locking of reuniens multi-unit activity to hippocampal theta cycles (B). Analysis of reuniens firing around the peak of hippocampal theta cycles, shows significant phase-locking of reuniens single-unit activity to the theta rhythm during REM (C-F).



Power spectra of mPFC, reuniens, and hippocampal signals during REM are characterized by prominent peaks in the theta range, with coherence between mPFC-hippocampus, reuniens-hippocampus, and mPFC-reuniens recording pairs in the theta range during REM (G, H). mPFC-reuniens recordings were further comodulated by a slow, irregular potential observed in A and in the broad low frequency peak (4H, bottom). mPFC signals lagged hippocampal signals by a longer delay than reuniens signals lagged the hippocampus (J, top) and peak cross-correlation coefficients were significantly higher for reuniens-hippocampus recording pairs than for reuniens-mPFC.(J, bottom).

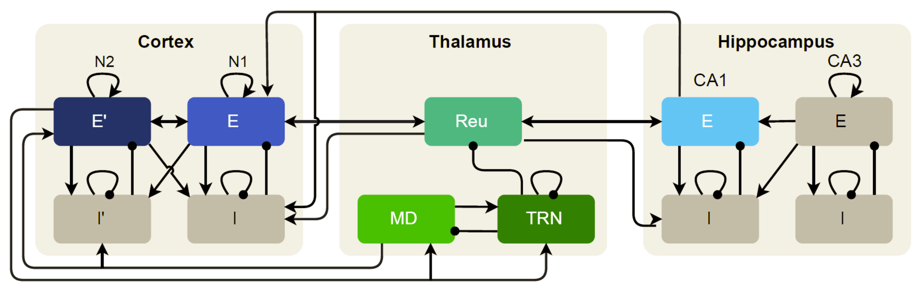






Peri-event analysis of reuniens spiking activity around SWRs in one recording session. The time frequency representation shows the mean wavelet transform of 458 detected SWRs, estimated by Morlet wavelets (top). Overlayed traces show the grand average LFP in the hippocampus (white) and reuniens (green), referenced to the onset of the SWR. Raster of reuniens spikes (every 10th sweep) and associated peri-event spike histogram, referenced to the onset of the SWR (bottom). Proportion of reuniens single-units modulated by SWRs (10/49 activated, 16/49 suppressed).

Hippocampal-thalamocortical model



To explore the parameters that control interregional synchrony during NREM sleep, we constructed a neural mass firing rate model consisting of two cortical networks (N 1 & 2), representing mPFC layers 5 and 6, respectively, and two hippocampal (CA1-CA3) and three thalamic networks (TRN, MD, and Reu).

Slow waves and sharp waves are spontaneously generated in the isolated CA3 and cortical networks respectively as a result of adaptation and excitatory-to-excitatory recurrent connections.

Slow wave-spindle coupling angles were nonuniformly distributed for both cortical and reuniens spindles indicating strong coupling with slow waves. In quantitative match to the experimental data, reuniens spindles occured mainly around the slow wave peak (active phase) while cortical spindles mainly occur around the slow wave trough. The slow wave-spindle coupling strength is also higher for reuniens than cortical spindles (F).

Slow waves in the thalamocortical network were also accompanied by large negative deflections and a subsequent peak in CA1 network (G). Phase locking analysis revealed that, consistent with the experimental data, SWRs are phase-locked to slow waves, occurring mainly before slow wave peaks (active phase, H). The bidirectional projections between reuniens and CA1 coordinate the communication between these two networks so that the membrane potential of the reuniens neurons increases after SWRs (I). Reuniens spindles were also preceded by an increase in the SWR rate (J).