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Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms

Highlights

- Spindles in-phase with slow oscillation up-states boost hippocampus-dependent memory
- Phase coupling of slow oscillations, spindles, and ripples underlies memory formation
- Thalamic spindle stimulation drives cross-regional co-occurrence of spindles
- Thalamic inhibition phase-locked to slow oscillation up-states impairs memory

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In Brief

Latchoumane et al. demonstrate a causal role of sleep spindles in memory formation. They show that optogenetic induction of thalamic spindles, when phase-locked to the slow oscillation up-state, enhances the triple coupling of slow oscillations-spindles-ripples together with hippocampus-dependent memory consolidation.

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Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms

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SUMMARY

While the interaction of the cardinal rhythms of non-rapid-eye-movement (NREM) sleep—the thalamo-cortical spindles, hippocampal ripples, and the cortical slow oscillations—is thought to be critical for memory consolidation during sleep, the role spindles play in this interaction is elusive. Combining optogenetics with a closed-loop stimulation approach in mice, we show here that only thalamic spindles induced in-phase with cortical slow oscillation up-states, but not out-of-phase-induced spindles, improve consolidation of hippocampus-dependent memory during sleep. Whereas optogenetically stimulated spindles were as efficient as spontaneous spindles in nesting hippocampal ripples within their excitable troughs, stimulation in-phase with the slow oscillation up-state increased spindle co-occurrence and frontal spindle-ripple co-occurrence, eventually resulting in increased triple coupling of slow oscillation-spindle-ripple events. In-phase optogenetic suppression of thalamic spindles impaired hippocampus-dependent memory. Our results suggest a causal role for thalamic sleep spindles in hippocampus-dependent memory consolidation, conveyed through triple coupling of slow oscillations, spindles, and ripples.

INTRODUCTION

Sleep is known to support the consolidation of memory (Rasch and Born, 2013). The <1 Hz cortical slow oscillation (Steriade et al., 1993), thalamo-cortical spindles (Steriade et al., 1986) (7–15 Hz), and hippocampal sharp wave-ripples (Buzsáki et al., 1992) (100–250 Hz) represent the cardinal rhythms of non-rapid-eye-movement (NREM) sleep, and all these rhythms have been implicated in the consolidation of declarative (i.e., hippocampus-dependent) memory during sleep (Fogel and Smith, 2011; Friedrich et al., 2015; Logothetis et al., 2012; Marshall et al., 2006; Ngo et al., 2013; Schreiner et al., 2015; Wang et al., 2015). Importantly, it has been proposed that consolidation of hippocampus-dependent memory during NREM sleep essentially relies on the hierarchical nesting of these rhythms (Diekelmann and Born, 2010; Dudai et al., 2015; Phillips et al., 2012). Phase-locking occurs such that ripples accompanying neural memory reactivation in the hippocampus nest into the excitable troughs of the spindle oscillation, which themselves nest into the excitable up-state of the slow oscillation (Clemens et al., 2007; Siapas and Wilson, 1998; Sirota et al., 2003; Staresina et al., 2015). This phase-locking presumably favors the redistribution of the representation from predominantly hippocampal toward neocortical networks that serve as long-term storage sites (Diekelmann and Born, 2010; Dudai et al., 2015).

Several studies have demonstrated a causal relationship between increased slow oscillation and memory consolidation in humans (Marshall et al., 2006; Ngo et al., 2013). Using timed electrical stimulation in rats, Maingret et al. (2016) provided evidence that reinforcing the endogenous temporal coordination between hippocampal sharp wave-ripples, cortical slow waves, and spindles can enhance the consolidation of hippocampus-dependent spatial memory. However, so far, there is no experimental evidence demonstrating a causal influence specifically of thalamic activity on the phase-locking between cortical slow oscillations and the subordinate rhythms—thalamo-cortical spindles and hippocampal ripples—in the process of memory formation. This is even more surprising as thalamic spindles emerging first during ontogeny (Khazipov et al., 2004), as well as in the course of human nocturnal sleep (Aeschbach and Borbély, 1993; Clemens et al., 2007), are suspected to play a central role in forming memory during sleep.

Using closed-loop, optogenetic stimulation of the thalamic reticular nucleus (TRN) to induce spindle activity in mice (Figure 1A), we show that only spindles induced during the slow oscillation up-state—that is in-phase coupling—enhance memory for previously learned hippocampus-dependent tasks, whereas spindles occurring out-of-phase with the slow