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Sleep Spindles and Memory Reprocessing

James W. Antony[1], Monika Schönauer[1], Bernhard P. Staresina[2], Scott A. Cairney[3*]

1. Department of Psychology, Princeton University, USA
2. School of Psychology, University of Birmingham, UK
3. Department of Psychology, University of York, UK

* Correspondence: scott.cairney@york.ac.uk (S.A. Cairney)

Twitter: @sacairney

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Abstract

We propose a framework for the memory function of spindle oscillations during sleep. In this framework, memories are reinstated by spindle events, and further reprocessed during subsequent spindle refractory periods. We posit that spindle refractoriness is crucial for protecting memory reprocessing from interference. We further argue that temporally-coordinated spindle refractory periods across local networks facilitate the consolidation of rich, multimodal representations, and that localized spindle refractoriness optimizes oscillatory interactions that support systems consolidation in the sleeping brain.

Sleep spindles and memory consolidation

Sleep spindles are ~1 s bursts of 11-16 Hz oscillatory activity that characterize non-rapid eye movement (NREM) sleep and have been repeatedly linked to memory consolidation [1]. More specifically, spindles are thought to support a covert reactivation of newly formed memories, prompting their integration into cortical sites for long-term storage. Yet, the nature of the operations underpinning spindles' role in sleep-dependent memory processing is poorly defined. Here, we attempt to fill this gap by presenting a framework to explain how spindles might facilitate overnight consolidation.

Memory reinstatement refers to the re-emergence of learning-related neural activity, and is linked to spindle activity in sleep [1]. Here, we propose that newly formed memories are reinstated during spindle events and further reprocessed during subsequent spindle refractory periods. Crucially, spindle refractoriness blocks additional reinstatement of other memory traces, enabling reprocessing to unfold without interference from unrelated information. Spindle refractory periods occur locally, supporting reprocessing across interrelated memory units and optimizing oscillatory interactions underpinning systems consolidation.

Memories are reprocessed during spindle refractory periods

Central to our framework is that spindles provide a neurobiological scaffold for memory reinstatement and subsequent reprocessing in sleep. There are multiple lines of evidence in support of this idea. In the EEG, spindle activity during regular overnight sleep can robustly discriminate between categories of information (e.g., faces vs. houses) encoded in a prior learning phase [2]. Furthermore, inducing memory reactivations in NREM sleep evokes a transient increase in spindle activity, during which the content of reactivated memories can be reliably decoded [3]. Inhibiting spindles during reactivation correspondingly eradicates the retention benefits associated with sleep [4]. Thus, spindles appear to promote the spontaneous reinstatement and reprocessing of newly formed memories.

Another key component of our framework is that effective information processing requires limited interference. Spindle refractoriness may play a central role in this context by safeguarding memory reprocessing from additional reinstatement. In the human brain, spindles undergo refractory periods of 3-6 s [5], which places limits on memory reactivation [6].

As a corollary to the presumed protective role of spindle refractoriness, one could expect that the likelihood of reinstatement of other, unrelated traces would increase as time passes from a spindle oscillation. Indeed, the memory benefits of cueing reactivations in NREM sleep, an established index of successful reactivation, are eradicated when cues are presented immediately after the spindle offset [5].

Local refractory periods facilitate localized reprocessing

Much of the sleep research in humans relies on scalp electroencephalography (EEG), which represents the global signal summed across large parts of the brain. Of note, however, spindles are predominantly local phenomena [1]. Everyday memories are rich, multimodal representations, formed of many units and encoded across numerous neural regions. As such, we furthermore argue that spindles support consolidation by mediating the reinstatement and reprocessing of discrete memory traces in local networks. Indeed, spindle-coupled neural reactivations are topographically-restricted to the cortical areas activated during learning [7], and cued memory reactivations elicit spindles across learning-specific brain regions [8].

Importantly, we propose that localized spindle refractory periods gate reinstatement in a temporally-coordinated manner, facilitating highly synchronized periods of mnemonic reprocessing across multiple, interrelated memory units. The concurrent reprocessing of component memory traces will then sum to promote the consolidation of coherent representations (see **Figure 1**). Within our framework, inhibiting spindles in local networks is expected therefore to block the reinstatement and subsequent reprocessing of regionally-dependent memory units.

Spindle refractoriness optimizes spindle-ripple interactions

Another possible role of spindle refractoriness is optimizing oscillatory interactions across regions and nested frequencies during NREM sleep. The *Active Systems* model, for instance, postulates that memory consolidation in sleep is driven by finely-tuned interactions between spindles, slow oscillations (SOs, < 1 Hz), and sharp wave-ripple complexes (hereafter, ripples; ~80-100 Hz in humans [1]). More specifically, under the global control of cortical SOs, thalamocortical spindles cluster hippocampal ripple events representing local memory units, facilitating crosstalk between cortical and subcortical memory systems [9].

Assimilating our framework and this broader oscillatory hierarchy, we argue that spindle-ripple interactions and associated reinstatement events are separated by periods of spindle refractoriness, facilitating mnemonic reprocessing and neocortical integration. Although ripples can emerge independently of spindles, we propose that their occurrence alone is insufficient to support reinstatement. Indeed, reducing spindle-ripple cooccurrence, but not ripples or spindles independently, impairs the memory benefits of sleep [10]. Correspondingly, optogenetic induction of spindles enhances spindle-ripple coupling and sleep-dependent consolidation [9].

Temporal coupling between spindles and ripples occurs both locally [11] and cross-regionally [9]. While localized spindle-ripple interactions would subserve the reinstatement of highly specific memory units, cross-regional interactions might work to strengthen connections between the component traces of broader representations. Under the current framework, enhancing the temporal coupling of spindle-ripple events in local areas would facilitate the retention of only regionally-specific memory elements, whereas cross-regional enhancement would strengthen associations between them.

A role for theta oscillations?

An outstanding issue in the field of memory consolidation is the functional significance of theta activity during NREM sleep. Recent work has suggested that theta oscillations, in unison with sleep spindles, support the reinstatement and stabilization of newly-formed memory traces [4]. Yet, transient variations in theta activity during mnemonic processing have not emerged in other work [3, 5], raising questions about the specific conditions in which theta synchronization is necessary for consolidation. Interestingly, in [4] and related studies, the critical memory associations contained substantial linguistic components, which might depend on theta-related mechanisms to a greater extent than non-linguistic representations. Related to this possibility, theta synchronization during wakefulness provides an electrophysiological index of lexical integration [12]. A systematic assessment of the oscillatory dynamics underpinning memory reinstatement and reprocessing will be an important endeavor in future research.

Conclusion

We have outlined a framework to explain the role of sleep spindles in memory consolidation. First, we proposed that spindle refractoriness gates memory reinstatement in NREM sleep, which allows mnemonic reprocessing to unfold without interference from other, unrelated information. Second, we proposed that local control of spindle refractoriness gates reinstatement in a temporally-coordinated manner to allow synchronized reprocessing across the component traces of broader representations. Third, we assimilated our framework with the hierarchical oscillatory structure of NREM sleep, arguing that spindle refractoriness optimizes the timing of spindle-ripple events and associated memory reinstatement. Testable predictions for our framework are outlined in **Box 1**. We encourage a global effort to address the mnemonic function of sleep spindles, and hope that this will provide important new insights into the fundamental biology of memory.

Box 1. Predictions for Future Research

Here we outline the core questions relating to our framework and offer experimental predictions:

- **Do spindle refractory periods support memory reprocessing?** Disrupting reprocessing after spindle events (e.g. via auditory interference) should produce greater memory impairments when disruption follows a short (< 1 s) vs long (> 2 s) delay.
- **Do local spindles reflect localized memory reinstatement?** For instance, inhibiting spindle events (e.g. via electrical stimulation) in the fusiform face area should impair the consolidation of memories for faces, but not memories for objects.

- **Do localized and cross-regional spindle-ripple events serve different purposes?** Enhancing temporal coupling of local spindle-ripple events via closed loop optogenetic approaches [9] should strengthen regionally-specific memory units, whereas enhancing cross-regional coupling should strengthen associative links between local memory traces.
- **Do the neural correlates of reinstatement differ according to the nature of reactivated associations?** Cueing the reactivation of linguistic versus non-linguistic associations should evoke stronger responses in the theta band, with linguistic representations relying on increased theta synchronization.

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Figure Legends

Figure 1. Integrated view of memory reactivation during NREM sleep. A) Hypothetical paired-associate learning task involving images of common objects, scenes, and faces. The lateral occipital complex (LOC), parahippocampal place area (PPA), and fusiform face area (FFA) represent object, scene and face information, respectively. B) Schematic of coincident

neural events from LOC, PPA, FFA and local field potentials from the hippocampus (HC). Sleep spindles occur preferentially in the slow oscillation (SO) up-state, and can be seen as the high-frequency rhythm imposed over the SO. In the schematic, reinstatement of the 'House in Woods – Pewter Mug' memory occurs during a hippocampal ripple, which is coincident with the troughs of spindles over PPA and LOC. After this reactivation event, refractoriness prevents another spindle from occurring for a few seconds, meaning hippocampal ripples may be ineffective at inducing reinstatement. This enables memory reprocessing to continue without disruption from unrelated traces. The refractory period may be accompanied by a gradual decline in reprocessing, and an increasing potential for the reactivation of other memories. Once refractoriness fades, the reinstatement and reprocessing cycle is repeated, allowing, in this example, the 'Sunglasses – Woman in Hat' memory to be reactivated.