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A Sleep Spindle Framework for Motor Memory Consolidation

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Abstract

Sleep spindle activity has repeatedly been found to contribute to brain plasticity and consolidation of both declarative and procedural memories. Here we propose a framework for motor memory consolidation that outlines the essential contribution of the hierarchical and multi-scale periodicity of spindle activity, as well as of the synchronization and interaction of brain oscillations during this sleep-dependent process. We posit that the clustering of sleep spindles in “trains”, together with the temporally organized alternation between spindles and associated refractory periods, are critical for efficient reprocessing and consolidation of motor memories. We further argue that the long-term retention of procedural memories relies on the synchronized (functional connectivity) local reprocessing of new information across segregated, but inter-connected brain regions that are involved in the initial learning process. Finally, we propose that oscillatory synchrony in the spindle frequency band may reflect the cross-structural reactivation, reorganization and consolidation of motor, and potentially declarative, memory traces within broader subcortical-cortical networks during sleep.

Introduction

A plethora of studies using a large variety of methodological approaches in animal models and humans have clearly demonstrated that memory is not a unitary process. On the one hand, declarative memory is defined as our capacity to acquire and recollect facts and events. It is known to depend primarily upon integrity of the medial temporal lobe, and the hippocampus in particular (see 1,2, for reviews). On the other hand, procedural memory is described as our ability to acquire a variety of skills, including simple and complex motor skill behaviors such as shoe lacing or playing a musical instrument, respectively. To study this type of procedural memory, researchers have used a variety of motor sequence learning (MSL) paradigms that test the process by which discrete, independent actions become unified and performed effortlessly as a unitary sequence through repeated practice (see 3,4, for reviews). Changes in performance seen during the acquisition of such skills are known to be incremental, implicit in nature, long lasting and dependent upon anatomical and functional plasticity within motor-related brain structures, including the striatum, cerebellum, motor-related cortical regions, as well as the hippocampus (e.g., 5–8). Yet, following the initial acquisition phase, the newly learned information is then thought to be processed and reactivated offline, such that initially labile memory traces become fixed into the physical structure of the brain through a cascade of events occurring at both the synaptic/cellular and the brain systems levels; a process

called “memory consolidation” (9,10). In fact, studies using MSL paradigms have repeatedly shown that the procedural memory consolidation process of motor skill representations is primarily observed hours or days after the first training session, although Cohen and colleagues (11) have recently reported that the same offline phenomena may also occur rapidly (i.e., on a time scale of seconds) between blocks of practice executed during the initial training session. Some studies have further revealed that such a consolidation process may depend on the type of MSL tasks being acquired, as the offline consolidation of skills acquired unintentionally (implicit learning) has been shown to be time-dependent, while skills acquired intentionally (explicit learning) are greatly dependent upon sleep for this process to occur (12–15). Thus, although the conditions that trigger this latent mnemonic process are still conjectural, most of the work in this field of research has been done using explicit-related MSL paradigms to study its behavioral determinants, neural networks and sleep neurophysiological correlates. Accordingly, this review will focus primarily on findings from sleep studies using explicitly learned materials, spanning declarative and procedural memory domains, to outline the role of sleep in the consolidation of motor skills, and to develop a framework dedicated to MSL consolidation, in particular.

Hierarchical multi-scale periodicity in sleep spindle activity and memory consolidation

There is now ample evidence indicating that sleep plays an active role in the consolidation of both explicit procedural and declarative memories (e.g., 10,16,17, for reviews). Contemporary theories on memory consolidation postulate that the synchronization and interaction between specific brain rhythms during sleep may be responsible for the reactivation-induced strengthening and transformation of newly formed memory representations (18–21). Indeed, it has been suggested that low-frequency ~ 0.5 -1 Hz slow oscillations (SO) during non-rapid eye movement (NREM) sleep drive and synchronize the repeated reactivation of newly encoded memories through spindle-shaped ~ 0.3 -2s bursts of ~ 11 -16Hz oscillatory activity (1,3,22, for reviews). As an electrophysiological hallmark of thalamo-cortical activity during NREM sleep, spindles are thought to be involved in sleep-dependent brain plasticity and memory consolidation through periodic and synchronized rhythmic activity over the brain (5,23,24). However, recent data from our own laboratory, and from other groups, suggest that the hierarchical organization and spontaneous rhythmic occurrence of sleep spindles are critical mechanisms necessary for effective covert memory reprocessing, reorganization and consolidation of memories. We thus propose here a sleep spindle framework for motor memory

consolidation that integrates the rhythmic local reactivation of newly encoded information and the oscillatory interactions between segregated brain regions and nested frequencies for efficient strengthening and integration of new representations into long-term memory networks.

Using explicit MSL paradigms, numerous studies have revealed that both nocturnal and diurnal sleep enhance consolidation of newly acquired motor sequence knowledge, as expressed by post-sleep maintenance or additional performance gains in the absence of further task engagement (3,17,25,26, for reviews). There is also ample evidence that motor memory consolidation is associated with state-like changes in sleep spindle characteristics (i.e., increases in spindle frequency, amplitude and density) following learning. However, most of the findings supporting the role of NREM sleep spindles in memory consolidation have been indirect in nature, with studies focusing on correlations between such spindle characteristics and memory improvements following a night of sleep or a mere daytime nap (5,27–29). To address this issue, researchers have more recently used a different experimental approach, and were able to confer a more causal role of spindles in declarative and procedural memory consolidation by modulating experimentally this type of brain oscillations using transcranial alternating current stimulation (30), or by inducing the reactivation of previously learned materials through olfactory/auditory stimulations using targeted memory reactivation (TMR) paradigms (31–35). Interestingly, TMR work has revealed that cued-memory reactivation during NREM sleep increases spindle activity and related consolidation of both declarative and procedural memories (33,36–39). While previous declarative-memory studies have revealed that sensory stimulation delivered in synchrony with the SO up-states led to enhanced SO amplitudes, phase-locked spindle activity, and overnight memory consolidation (40–44), recent evidence suggests that the effective reactivation of learned cue-associated memory content is dependent upon a precisely-timed cue stimulation that follows an innate, endogenous periodicity of spindle occurrence in the sleeping brain (22,23). Indeed, by using real-time tracking of sleep spindles and systematic delivery of sensory cues at different time points following the offset of the preceding detected spindles, Antony and colleagues (23) found a precise temporal link between sleep spindles and cue-induced memory reactivation, with optimal memory reactivation being strongly linked to sleep spindle rhythmicity.

Additional work has also shown that the distribution of sleep spindles involved in memory consolidation is more localized and spatially restricted to learning-related brain regions than SOs, hence enabling the reactivation of specific memories (45,46). Specifically, the

widespread and in-phase distribution of SOs across brain regions has been thought to temporally coordinate the local spatial expression of spindle activity (47,48). According to this view, SOs would not only provide fine-tuned temporal frames to spindles such that they occur in their excitable up-states, but would also support their brain-wide spatial synchronization, hence facilitating the putative reactivation and consolidation of memories through systematic SO-spindle interactions (49). Indeed, evidence suggests that the coupling between SO and spindle might play a key role in the process of memory consolidation (50–53). Recently, however, it has been proposed that additional oscillatory mechanisms, other than SOs and its coupling with spindles, relating to local spindle rhythmicity may also be of critical importance for the consolidation of both declarative and procedural memories (23,24,54–56). In line with the latter viewpoint, studies have revealed that locally expressed spindles follow two types of rhythms during NREM sleep: the infraslow and mesoscale rhythms. In fact, results from our laboratory (24,56) and that of other researchers have shown that groups of periodically recurring spindles (called “trains”) appear to cycle at an infraslow frequency scale (~ 0.02 Hz) during both light NREM stage 2 sleep (54,55) and deep NREM stage 3 slow-wave sleep (SWS) (23). Such “trains” of sleep spindles closely spaced in time are operationalized in our framework (see Figure 1A) as groups of two or more consecutive and region-specific spindles interspaced by less than or equal to 6 seconds (24), in comparison to those occurring in isolation (i.e., more than 6 seconds from region-specific neighboring spindles). Importantly, we have demonstrated that such groups of spindles play a more critical role than isolated ones in motor memory consolidation, as several metrics related to spindle trains (i.e., length of spindle trains, number of trains, ratio between clustered vs. isolated spindles) were positively correlated with the magnitude of overnight memory improvements. Finally, our findings (24,56) demonstrated that the relationship between spindle trains and procedural memory consolidation is observed during NREM stage 2, but not stage 3, sleep. Hence, this suggests that spindles, which iteratively occur locally within clustered and temporally organized patterns during NREM stage 2 sleep, are most effective in reactivating and further consolidating specific motor memories. Interestingly, support for the latter pattern of results comes from Lecci and colleagues (2017) who have demonstrated that an infraslow rhythmicity of 0.02Hz in spindle activity (every ~ 50 s), more pronounced during NREM stage 2 than stage 3 sleep, is related to offline declarative memory consolidation. Altogether, these findings thus suggest that such a NREM sleep infraslow periodicity in humans may constitute a critical autonomic regulatory mechanism for modulating arousability, and subdividing sleep into cycling periods of environmental alertness and offline memory consolidation. A perturbation of this infraslow periodic clustering of spindle activity

during NREM sleep would therefore be expected to cause inappropriate arousals and memory impairments due to disturbed rhythmicity of spindle trains. Yet, the role of spindle clustering in sleep-dependent consolidation of both declarative and procedural memories awaits further experimental confirmation.

At an intermediate mesoscale ($\sim 0.2\text{--}0.3$ Hz) between the infraslow periodicities of spindle trains and spindle oscillations themselves ($\sim 11\text{--}16$ Hz), there is also converging evidence that spindles within trains undergo periods of refractoriness of about 3–6 seconds (23). This finely-tuned alternance between region-specific spindle events and refractory periods has recently been proposed to be of paramount importance for optimal segregation of spindle events and interference-free reprocessing of memory traces. In fact, such temporally-coordinated spindles and periods of refractoriness are thought to be critical for efficient reprocessing and offline consolidation of both declarative and non-declarative procedural memories, respectively, during SWS-rich deep sleep (23,57) and light NREM stage 2 sleep (5,56). However, the question as to whether spindles belonging to the same “trains” mediate the repeated reactivation of a unique memory content, or whether they trigger reactivation of several previously learned memories, remains unanswered. Thus, in future studies it would be of interest to apply EEG/fMRI decoding-classification approaches (e.g., 58–62), in order to compare the neural correlates of memory reactivations within and between spindle trains.

Neural substrates associated with spindle-related memory consolidation

Growing evidence suggests that newly acquired declarative and non-declarative procedural memory traces are reprocessed offline within neural circuits involving the hippocampus and other learning-related cortical and subcortical brain structures during memory consolidation, and that this mnemonic process engages two complementary neurophysiological mechanisms: “synaptic” and “systems” consolidation processes (1,5,63–68). At the synaptic level, it has recently been demonstrated that, irrespective of the memory system, post-learning sleep is characterized by enhanced temporal synchrony between cortical SO and spindle activity, topographically restricted to the brain regions that were initially involved during learning (50,52,53). More specifically, it has been proposed that the topographical cortical organization of spindle patterns, occurring independently at specific recording sites or nearly simultaneously across multiple cortical regions (45,46,69,70), may relate respectively to the reprocessing of local memory units or to the synchronized concurrent reprocessing of inter-related memory units. Cortical SOs are assumed to underpin the temporally-coordinated

reactivation of task-specific brain regions, and to orchestrate the synchronized local reprocessing of independent memory components, hence allowing the consolidation of combined memory representations by strengthening the associations between inter-connected brain areas and their related spindle activity (see 20,22, for reviews). This viewpoint is in accord with several sleep studies in the procedural domain, in which authors have reported a spatio-temporal distribution of SO and nested spindle activity over the cortex, as well as evidence of reactivation of the memory traces time-locked to spindles over localized cortical and subcortical brain regions recruited during the learning phase (5,19,28,71,72). More research is needed in humans, however, to determine whether this topographical expression of sleep spindles reflects cortical and subcortical reactivation of newly acquired memory representations, and whether brain-wide patterns of concurrent spindles may constitute an informative metric for categorizing specific memory trace reactivations.

In addition to the repeated reactivation-induced strengthening and stabilization of the newly acquired memory trace at the local synaptic level, there is accumulating evidence supporting the existence of a gradual reorganization of temporary formed representations over distributed and long-lasting brain networks (e.g., 73,74) (see also 9,16, for reviews). In accordance with this systems level concept, work from our laboratory looking at procedural memory consolidation has revealed that motor memory traces are not only strengthened during sleep, but undergo qualitative representational changes (e.g., plasticity within the striatum) time-locked to spindle activity as well (18,19). This reorganization in brain activity further correlated with overnight performance improvements, thus suggesting that sleep-dependent strengthening and transformation of memory traces may be beneficial for enhanced integration and long-term retention of memory representations. By conducting EEG deep-brain source reconstruction and functional connectivity analyses (i.e., EEG coherence analyses) during sleep spindle epochs, Boutin et al. (2018) have also provided additional evidence that spindle oscillations may be involved in sleep-dependent motor memory consolidation by locally reactivating and functionally binding segregated, but inter-connected, brain regions such as the hippocampus, striatum, thalamus, and motor-related cortical areas. Together, these findings thus suggest that oscillatory synchrony in the spindle frequency band may underlie the reactivation, reorganization and consolidation of memory traces within broader subcortical-cortical networks during sleep (see Figure 1B for schematic illustration of the role of cross-structural functional connectivity in motor memory consolidation). Yet more research is needed

in order to extend and generalize these findings to anatomically and functionally distinct memory systems, i.e., the declarative memory system.

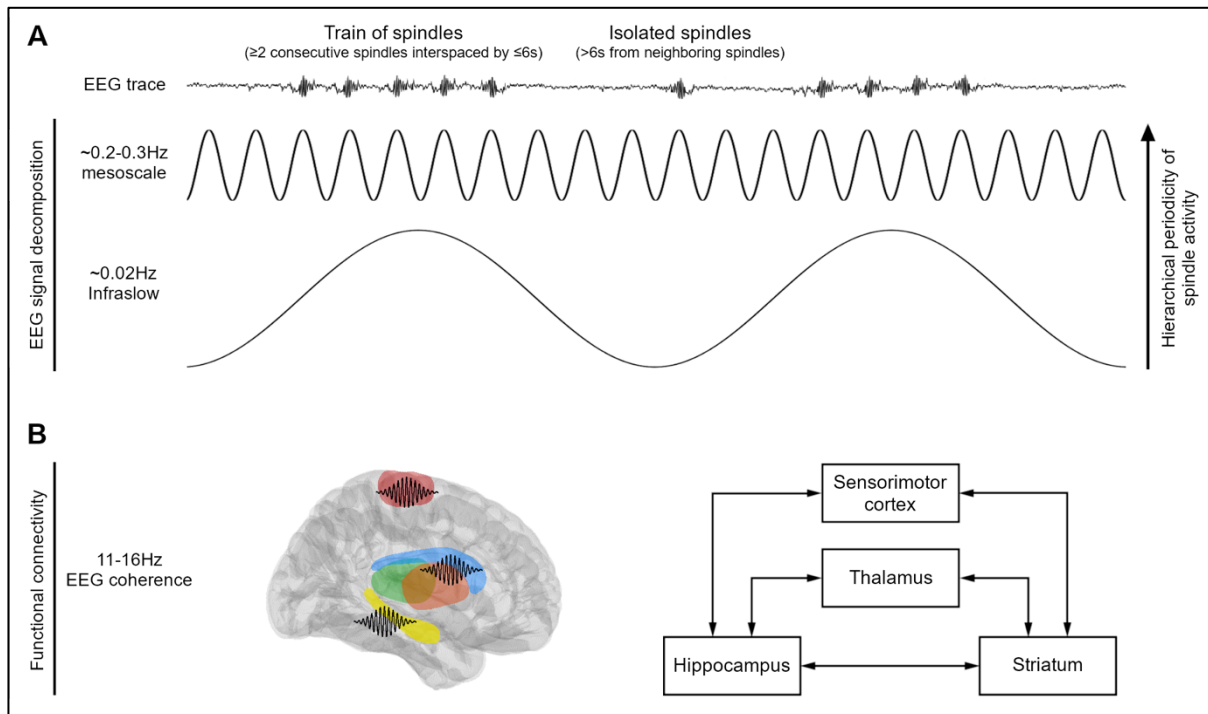


Figure 1. Sleep spindle framework for motor memory consolidation. (A) Illustration of the clustering and hierarchical rhythmicity of spindle activity during NREM stage 2 sleep. Here we define clusters of sleep spindles closely spaced in time as “trains”, and operationalized spindle trains as groups of two or more consecutive and region-specific spindles interspaced by less than or equal to 6 seconds. Isolated spindles, in contrast, are those occurring more than 6 seconds apart from their region-specific neighbors in time. Recurring spindle “trains” cycle at an infralow frequency scale of about 0.02Hz. In addition, a finely-tuned alternance between spindles and associated refractory periods within trains, oscillating at an intermediate mesoscale rhythm of about 0.2-0.3Hz, allows efficient and interference-free motor memory reprocessing and consolidation. (B) Oscillatory synchrony in the 11-16Hz spindle frequency band is thought to reflect cross-structural reactivation, reorganization and consolidation of motor memory traces within subcortical-cortical networks involving the hippocampus (yellow), striatum (putamen in orange and caudate nucleus in blue), thalamus (green) and motor-related cortical regions (red).

Cross-frequency interactions in the sleeping brain support memory consolidation

Accompanying the multi-scale oscillatory hierarchy of NREM sleep spindle activity described above, it has been proposed that cross-frequency coupling and hierarchical nesting of NREM sleep rhythms may be of particular importance for the consolidation of declarative memories (see 21,49, for reviews). Current trends postulate that SOs coordinate the bidirectional hippocampo-cortical information flow in a phase-dependent manner, with spindle oscillations nested in the depolarizing up-phase of the SOs, together with hippocampal-dependent sharp wave-ripples (SWR; $\sim 80-140$ Hz) nested into spindle troughs (1,2,21,49,75).

Initiated by SOs, synchronized spindle-ripple interactions are thought to enable hippocampal and associated coherent cross-structural reactivations and offline sequential replay of training-related neuronal patterns in a time-compressed representation (2,64,65,76,77). This triple phase-locking of cortical SO, thalamo-cortical spindle and hippocampal SWR is assumed to improve memory consolidation by facilitating the induction of persistent synaptic plastic changes (78) and by mediating the long-term storage of hippocampal-dependent memory information into pre-existing networks (49). The functional coupling of these three rhythms has been further shown to occur cross-regionally during NREM sleep (e.g., 49,75,79). Hence, cross-frequency coupling has been considered the neurophysiological mechanism underlying local synaptic potentiation and inter-regional communication, both required for memory consolidation (e.g., 9,10,16, for reviews) through global synchronization and communication within cortical (49,75,80) and subcortical networks (65,77). Moreover, it has been suggested that the hippocampus is also involved in this coupling process by initiating and orchestrating cross-structural memory reactivation for the strengthening of declarative memory traces within subcortical-cortical networks during sleep (65,77), while its contribution is suggested to diminish throughout the consolidation process (61,74,81) (see also 82, for a review). This is consistent with previous procedural-memory studies, which have pointed out the role of the hippocampus in the temporary storage of newly acquired motor sequence knowledge and of its contribution to offline memory reactivation and reorganization within distributed networks during sleep, then followed by its progressive disengagement in motor sequence memory representation (5,18,19,61,83). Hence, akin to theories proposed for declarative memories, we conjecture that the hippocampal to subcortico-cortical memory tradeoff associated with reactivations during spindle-ripples events may reflect the concomitant consolidation of motor memory representations and hippocampal trace clearance, in order to prevent synaptic saturation and the ability to learn new information during succeeding periods of wakefulness (84–86). Yet, direct experimental evidence supporting this mechanism in human is also lacking for both declarative and procedural memory systems.

Concluding remarks: A framework for sleep-dependent motor memory consolidation

Based upon substantial evidence accumulated from work investigating the role of NREM sleep oscillations in human motor memory consolidation, we propose here a framework that highlights the contribution of sleep spindle activity in this mnemonic process (see Figure 1). We first suggest that the clustering and temporally organized alternation between spindles and associated refractory periods during NREM stage 2 sleep are essential for efficient

reactivation and interference-free reprocessing and consolidation of motor memories (24,56) (see (23), for evidence in relation to declarative memories). More specifically, we conjecture that spindle-related memory reactivations follow two periodic rhythms that can be decomposed into a $\sim 0.02\text{Hz}$ infraslow periodicity of spindle “trains” and a $\sim 0.2\text{--}0.3\text{Hz}$ mesoscale rhythm for the iterative and region-specific occurrence of sleep spindles within trains. We further highlight the fact that such neurophysiological events show a topographical distribution over cortical and subcortical structures involved during the initial learning phase, and that their temporally-coordinated occurrence is assumed to reflect synchronized oscillatory activity (functional connectivity) across multiple learning-specific brain regions and associated integration of new information into pre-existing knowledge structures. At the systems level, it is then suggested that oscillatory synchrony in the 11-16Hz spindle frequency band underlies the cross-structural reactivation, reorganization and consolidation of memory traces within subcortical-cortical networks involving the hippocampus, striatum, thalamus and motor-related cortical regions for sequential motor memories (5,18,19), and potentially, the hippocampus and other cortical regions that were activated during the acquisition phase in the case of declarative memories. Altogether, we thus argue that the integrity of the mechanisms supporting the synchronization and interaction of brain rhythms during sleep is fundamental to the proper consolidation and long-term storage of coherent memory representations. However, more research is needed to pinpoint the neurobiological mechanisms responsible for the endogenous neuromodulation of the infraslow and mesoscale rhythms in the human brain across the adult lifespan, and to determine from a developmental perspective whether these rhythms develop through childhood and adolescence along with learning/cognitive functions and brain maturation (27,87).

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