Making memories last:
How sleep promotes neuroplasticity

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in memoriam of Helen Neville

Short title

Sleep, memory and neuroplasticity

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Abstract

Decades of research have demonstrated that sleep benefits memory formation and restores cognitive resources. While the behavioral benefits of sleep are well established, the neurophysiological underpinnings are less clear. In particular, it remains unknown how memories are transferred from short- to long-term storage. While initial theories were largely centered on rapid eye movement (REM) sleep, several contemporary theories converged on the notion that non-REM (NREM) sleep is actively engaged in memory consolidation. NREM sleep is dominated by prominent neuronal oscillations, such as cortical slow waves (< 1.25 Hz), thalamo-cortical sleep spindles (12-16 Hz), and hippocampal ripple oscillations (80-200 Hz). Here we provide an overview of how selective synchronization of neuronal oscillations promotes information reactivation, transfer and consolidation during sleep. We explore the neocortical-hippocampal dialogue in support of information selection and distribution and we discuss the concept of cross-frequency coupling as a neural mechanism of information transfer. In particular, we focus on how time-varying, oscillatory activity can promote a neurophysiological milieu that mediates neuroplasticity. Taken together, we will review evidence of how sleep provides optimal conditions for neuroplasticity and outline that a disruption of sleep can contribute to age- and disease-related memory impairments and cognitive decline.

Keywords

NREM sleep, slow waves, slow oscillations, sleep spindles, sharp-wave ripples, replay, hippocampus, hippocampal-neocortical dialogue, brain stimulation, memory consolidation, memory formation, declarative memory, procedural memory

Sleep and memory formation

Helen never seemed to sleep and had boundless energy. Her interests ranged far and wide and her trainees were primed to have her sense of exploration. One of Helen's key interests was the plasticity of the human brain. In recent years, a multitude of research has revealed the pivotal role of sleep for mediating neuroplasticity in support of long-term memory formation. While sleep was not a topic that Helen studied herself, we are sure she would approve of its relevance for neuroplasticity. With that early career guidance we dedicate this sleep chapter to Helen and review the most recent evidence of the role of sleep in forming lasting memories.

The systematic investigation of how sleep benefits memory formation started almost a century ago and since then it has mainly been governed by three key dogmas (Diekelmann & Born, 2010; Rasch & Born, 2013). First, it had been assumed that sleep's benefit on memory is the result of a passive process that guards new memories by reducing interference. Second, it had been thought that dreams during REM sleep constitute a functional key substrate of memory consolidation; and third, a key emphasis had been on the role of the hippocampus in governing memory processes. In this chapter, we review the origins of these hypotheses and summarize a more contemporary model of sleep-dependent memory consolidation, which posits that memory consolidation is an active – and not a passive — process, which primarily takes place during

non-REM sleep (and not REM) and is dependent more on the neocortex that previously suspected.

In 1924, Jenkins and Dallenbach provided the first empirical evidence for sleep's role in memory formation (Jenkins & Dallenbach, 1924). Over the course of almost two months, they repeatedly tested two participants who had to memorize nonsense syllables across different time intervals ranging from one to eight hours. Notably, they observed that recall performance was better when the participants slept during the retention interval. Initially, these exciting results were interpreted as 'reduced interference' between the memorized and novel information (i.e., that time spent asleep shields new memories by reducing distractions that are abundant in the wake state). However, over time several lines of research questioned this passive theory and began to consider whether sleep itself might play a more active role if memory consolidation (Rasch & Born, 2013).

The interest in sleep-dependent memory formation was further fueled by the discovery of REM sleep by Aserinsky and Kleitman in 1953 (Aserinsky & Kleitman, 1953). The electroencephalogram (EEG) of REM sleep closely resembled electrical patterns as observed during wakefulness, while the participants were immobilized by muscle atonia and only their eye globes rapidly moved under the closed eyelids. An influential hypothesis suggested that since REM sleep is particularly associated with dreams, this might promote memory reactivation and consolidation during REM sleep (Rasch & Born, 2013). This idea

was appealing because the EEG of REM sleep featured much richer spatiotemporal dynamics than non-REM sleep, which is characterized by highly synchronous bursts of slow wave (< 2 Hz; Steriade, Nuñez, & Amzica, 1993) and spindle oscillations (11-16 Hz; De Gennaro & Ferrara, 2003). In particular, the presence of slow waves resembles other states of unconsciousness, such as coma or anesthesia, and, hence, was thought to index an unengaged cortex (Brown, Lydic, & Schiff, 2010). However, in the 1980s several researchers, including Mircea Steriade (Steriade & Amzica, 1998; Steriade, Domich, Oakson, & Deschênes, 1987; Steriade, McCormick, & Sejnowski, 1993; Steriade, Nuñez, et al., 1993) and Gyorgy Buzsaki (Buzsáki, 1996, 1998), started to study the neurophysiological basis of sleep oscillations in more detail and soon came to realize that they might subserve information transfer and directed communication between different cortical and subcortical regions (Sirota & Buzsáki, 2005; Sirota, Csicsvari, Buhl, & Buzsáki, 2003; Steriade, McCormick, et al., 1993). Since then, a wealth of evidence further substantiated these assertions, which now collectively indicates that NREM - and not REM - sleep supports sleep-dependent memory formation (Diekelmann & Born, 2010; Rasch & Born, 2013; Walker & Stickgold, 2006).

Finally, the study of memory is inextricably linked to the hippocampus. Starting with patient H.M., a multitude of memory research has focused on hippocampal processing (Corkin, 2002; Squire, 2009). However, more recently several lines of research uncovered early cortical contributions to memory

encoding and several reports studying sleep dynamics further suggested that cortical contributions might constitute a key element in organizing the hippocampal-neocortical dialogue in support of memory formation (Buzsáki, 1996; Sirota & Buzsáki, 2005).

In this chapter, we review the available evidence that supports the idea that NREM sleep oscillations constitute a functional substrate of memory reactivation, transfer and consolidation during sleep.

The engram: Sleep-dependent memory formation

The engram refers to the physical trace of a memory that is stored in the brain (Kitamura et al., 2017). However, there is no consensus about the level of observation that is needed to unequivocally establish the presence of an engram (Dudai, 2004). Therefore, depending on the chosen imaging modality, engrams have been observed at the level of single cells spiking, local field potentials or even the fMRI signal (Rasch & Born, 2013). Hence, an engram can be found, for example, in the firing pattern of a cell ensemble (Eichenbaum, 2017), at the level of synaptic weights, which reflect short-term plasticity in support of memory maintenance (Stokes, 2015), or at the level of large-scale brain connectivity, where the precise spatiotemporal connectivity pattern could encode a distinct memory.

In particular, the investigations by Karl Lashley demonstrated that memories might not only be characterized by a single engram, but are actually

characterized by a brain-wide distributed pattern (Lashley, 1950). Contemporary imaging further supported this notion and it became increasingly clear that memory systems rely on the functional interaction of widely distributed, but functionally specialized, processing hubs (Buzsáki, 2015; Johnson & Knight, 2015). These networks span sub-cortical and cortical regions and typically include sensory cortices, the hippocampi, and prefrontal and parietal association areas. Furthermore, memory processes are often defined according to the mnemonic information, such as declarative and procedural memories, episodic or semantic memories, or explicit and implicit memories (Diekelmann & Born, 2010; Rasch & Born, 2013). However, it remains unclear if these different types of memories all rely on distinct neural mechanisms or if there is one common denominator that links seemingly different and abstract memory representations.

Taken together, the search for the engram is an overarching goal of contemporary cognitive neuroscience and there is currently little consensus on what level of observation and abstraction is necessary to detect an unequivocal memory representation in the brain (Dudai, 2004; Kitamura et al., 2017).

Systems memory consolidation theory

The systems memory consolidation theory proposes a framework that explains how newly acquired information, which is initially mainly hippocampus-dependent, undergoing a transformation and consolidation during sleep (Diekelmann & Born, 2010). In general, it is believed that newly acquired

information is initially encoded in the hippocampus (Buzsáki, 2015). Over time, these newly acquired memories become less and less hippocampus-dependent, and become progressively more dependent on neocortical association areas (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Walker & Stickgold, 2006). In particular, the prefrontal cortex is thought to constitute a core structure for long-term memory instantiation (Stuss & Knight, 2013). This hypothesis strongly emphasizes the role of hippocampal-prefrontal pathways, which have been studied in great detail over the last three decades (Buzsáki, 1996; Maingret et al., 2016; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009; Sirota et al., 2003). Critically, a large body of evidence stems from recordings in rodents, which poses a problem: Which areas constitute the prefrontal cortex in rodents (Carlén, 2017; Laubach, Amarante, Swanson, & White, 2018)? Even within the field, there is currently only little consensus whether rodents exhibit an equivalent to the human prefrontal cortex, the brain region that underwent the strongest development during evolution. The rodent prefrontal cortex may resemble human medial prefrontal regions, but most likely not portions of the dorsolateral or orbitofrontal cortex (Carlén, 2017).

The active systems memory consolidation theory suggests that spontaneous replay of mnemonic information initially strengthens the memory representations in the hippocampus (Antony & Schapiro, 2019; Foster, 2017). Replay refers to the fact that firing sequences that were first observed during the encoding of new information are now spontaneously ‘replayed’ during rest or

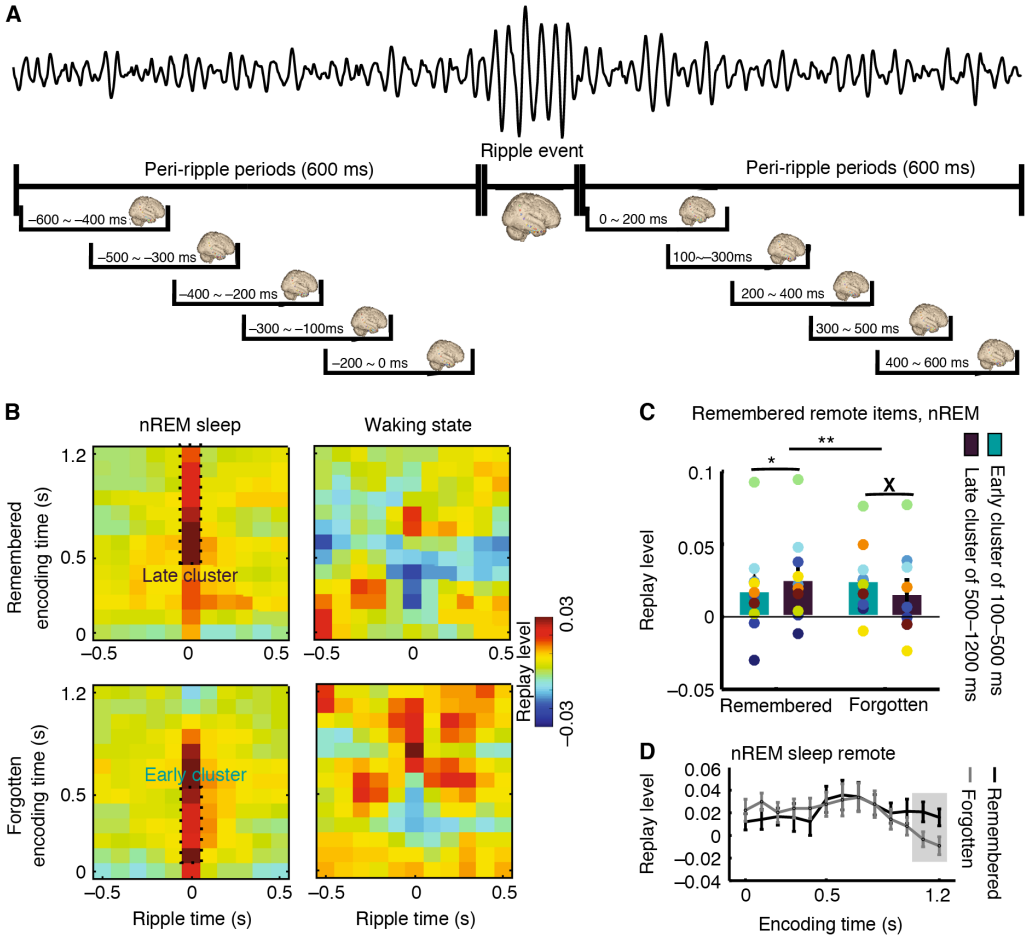
sleep (Foster, 2017; Peyrache et al., 2009). Notably, this replay can also occur in a time-compressed or reversed temporal order. This idea is in line with the idea of neuroplasticity as expressed by Hebb: 'Cells that fire together wire together' (Hebb, 1949). The repeated joint firing of any coalition of neurons in a fixed sequence is thought to strengthen the weak representation of new memories. Critically, replay does not occur in isolation, but is associated with a hippocampal sharp-wave-ripple oscillation (SWR; 100-200 Hz; Buzsáki, 2015). SWR are one of the most synchronized oscillations in the brain and likely reflect the joint firing of several hundred hippocampal cells in a synchronous manner. This high level of synchrony likely constitutes a temporal reference frame for cells to fire and help to structure and strengthen the population firing code that is associated with the encoding of new information.

Evidence in support of this idea came from a recent human intracranial study that utilized direct hippocampal recordings to track both ripples and mnemonic representations (Zhang, Fell, & Axmacher, 2018), which were quantified using representational similarity analysis (RSA; Kriegeskorte, Mur, & Bandettini, 2008). RSA quantifies the similarity (or correlation) between an engram-like pattern during encoding, which can be either defined across time or across space, and as a pattern that re-occurs at a later time point. Critically, Zhang et al. assessed the pattern during sleep, specifically in temporal proximity to the ripple event (**Figure 1**). They observed that ripples and replay of later remembered items were tightly coupled in time, which was less evident for items

that were later forgotten. Hence, the authors established the behavioral relevance of ripple-mediated replay in the human hippocampus (Zhang et al., 2018).

These findings are in line with observations from rodent studies that demonstrated that cells fire preferentially during certain ripple phases (Buzsáki, 2015), hence supporting the notion that population oscillations and firing interact bi-directionally (Fröhlich & McCormick, 2010): The firing of thousands of cells gives rise to local field potentials, which in turn serve as a feedback mechanism to guide and structure neuronal firing. Taken together, multiple lines of research now converge on the notion that the hippocampal replay and ripple oscillations are hallmarks of memory consolidation.

[Figure 1]



Hippocampal ripples and replay

(A) Empirical evidence for replay in humans as obtained from intracranial EEG recordings (dots reflect representative intracranial electrodes). Top: One exemplary ripple event and analysis strategy by means of a moving window approach. Evidence for replay (or reinstatement of mnemonic content) is quantified by correlation of the spontaneous pattern with the pattern that was present during encoding. (B) Upper: Selective reinstatement of mnemonic representations during the ripple event (t = 0) during sleep (left) but not during wakefulness (right). Lower: Later forgotten items are characterized by a different pattern. (C) Interaction of encoding time and later remembered/forgotten items. (D) Replay is enhanced for later remembered items in a later time window. From Zhang et al. (2018). Figure reproduced with permission under the Creative Commons Attribution (CC BY) license.

Both replay and ripples are predominantly observed in the hippocampus but recently several groups have reported similar phenomena in the neocortex (Khodagholy, Gelinas, & Buzsáki, 2017; Norman et al., 2019; Peyrache et al., 2009; Vaz, Inati, Brunel, & Zaghloul, 2019). In the classic systems memory consolidation theory, the transfer of mnemonic information from the hippocampus to the neocortex is organized by the two other cardinal sleep oscillations, namely slow waves (Steriade, Nuñez, et al., 1993) and spindles (De Gennaro & Ferrara, 2003; Steriade, McCormick, et al., 1993). Hippocampal ripples do not occur in isolation, but are tightly nested in the trough of cortical sleep spindles (Clemens et al., 2007; Helfrich et al., 2019; Staresina et al., 2015), which in turn are nested in the peak of the slow wave, thus, constituting a hierarchical triple coupling (Latchoumane, Ngo, Born, & Shin, 2017) across three spatial (neocortex, thalamus and hippocampus) and three temporal (~1Hz, ~11-16 Hz, and 100-200 Hz) scales. It was assumed that the ripple triggered a cortical depolarization, which in turn triggered the expression of a spindle in thalamocortical loops (Mak-McCully et al., 2017; Steriade et al., 1987), which then arrived in the neocortex precisely during the 'up-state' of the slow wave as recently demonstrated (Mak-McCully et al., 2017). A multitude of evidence suggested that slow waves and spindles promote the ideal neurophysiological milieu to mediate neuroplasticity to permanently store memories in neocortical circuits (Bergmann & Born, 2018; Niethard, Ngo, Ehrlich, & Born, 2018). Overall, this framework underscores a key role of the ripple in organizing large-scale networks in support of memory

formation (Buzsáki, 2015). Critically, it also emphasized both the role of NREM sleep as well as the active role of sleep in mediating memory formation, hence contradicting the classic notion that sleep only passively guards new memories by reducing interference.

In recent years, several lines of investigation began to question the hippocampus-centric view of the systems memory consolidation theory. For instance, if replay and ripples occur spontaneously, which mechanisms ensure that the cortex is in a favorable state to utilize the supplied information (Sirota & Buzsáki, 2005)? An alternative account suggested that the directionality might be reversed: The cortical slow wave might trigger a thalamic spindle during its 'down-state', which then arrives in the neocortex during the 'up-state', that is, with a delay of half-a-cycle of the slow wave (Helfrich et al., 2019; Staresina et al., 2015). Jointly, these two might then shape the expression of the hippocampal ripple and replay of information. This process would ensure that information would be sent back to the neocortex, when it is in a favorable state for further processing. This mechanism is discussed in more detail in the next paragraph.

NREM oscillations time information reactivation, transfer and consolidation

Sleep oscillations are organized on multiple temporal scales. Most studies focus on the intrinsic or primary frequency of the oscillatory events (11-16 Hz activity) for spindles (De Gennaro & Ferrara, 2003; Steriade et al., 1987). However, upon closer inspection, sleep reveals a multitude of additional temporal scales. For instance, spindles do not occur in isolation, but are tightly coupled to slow waves and ripples (Diekelmann & Born, 2010; Helfrich et al., 2019; Latchoumane et al., 2017), thus, forming a cross-frequency dependency between different primary temporal scales. Furthermore, spindles periodically re-occur every 3-6 s (~0.3 Hz; Antony, Piloto, et al., 2018; Helfrich et al., 2019), hence constituting a second-order temporal structure in the spindle amplitude. This fluctuation of the spindle amplitude is reminiscent of the infraslow oscillation (< 0.1 Hz; Lecci et al., 2017; Watson, 2018) that has been shown to capture slow fluctuations during NREM sleep. Another extended temporal scale is that NREM and REM sleep cycle approximately every 90 min (Rasch & Born, 2013), while sleep and wakefulness are organized in blocks of ~8 h of sleep vs. ~16 h of wakefulness. These examples are not exhaustive but are meant to illustrate the numerous temporal scales that govern sleep physiology.

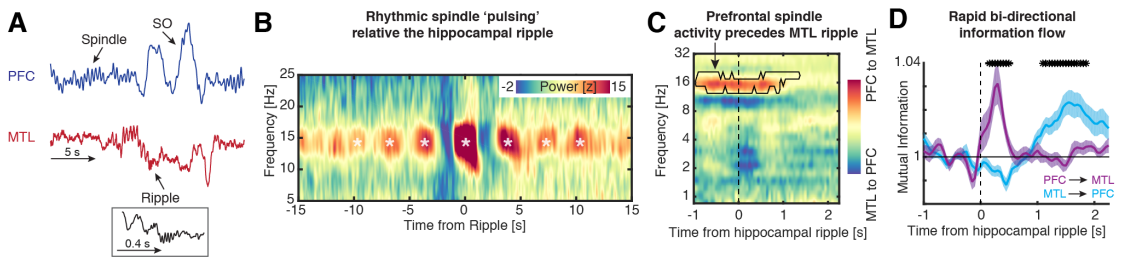
Here we focus on the second-order rhythm of sleep spindles because recent evidence implied that the alternating of high-synchrony ‘spindle’ and low-synchrony ‘no-spindle’ states might actually reveal a fundamental property of the hippocampal-neocortical dialogue (Antony, Piloto, et al., 2018; Antony,

Schönauer, Staresina, & Cairney, 2018; Hanslmayr, Staresina, & Bowman, 2016; Helfrich et al., 2019). As reviewed above, it is reported that slow wave-spindle coupling shapes hippocampal ripples and replay (Latchoumane et al., 2017; Staresina et al., 2015). In this framework, spindles mainly serve as a messenger mechanism that conveys timing information from the neocortex to the hippocampus (Helfrich et al., 2019). However, spindles themselves have also been implicated in mediating neuroplasticity (De Gennaro & Ferrara, 2003) and might reflect a direct functional substrate that cements memories into long-term storage. Hence, spindles have been associated with at least two distinct functions (messenger vs. plasticity mediator) in the brain.

However, this distinction overlooks the fact that comparable long episodes of NREM sleep are actually oscillation-free, that is, there is no apparent spindle or slow wave activity in between two spindles, thus giving rise to a surprisingly desynchronized EEG during NREM sleep, which is characterized by a state of high entropy (Hanslmayr et al., 2016). In contrast, spindles are highly synchronized events that are accompanied by a state of reduced entropy. In the Shannon information theoretical framework (Quian Quiroga & Panzeri, 2009), high entropy is beneficial to imprint new information onto a circuit. Hence, it is conceivable that the inter-spindle interval subserves one function that has previously been associated with spindles, namely mediating plasticity (Antony, Piloto, et al., 2018; Helfrich et al., 2019).

Here, spindles would trigger information reactivation and transfer from the hippocampus to the neocortex. Hippocampal-mediated information transfer peaks after the spindle already subsided, that is, in a state of maximal cortical desynchronization during NREM sleep. In this state, the hippocampus supplies newly encoded memories, which can efficiently be processed in the neocortex, at that point not engaged in a high-synchronous spindle state. Hence, information can efficiently be imprinted onto neocortical circuits in between two spindles (**Figure 2**). This hypothesis is in line with the observation that cue-trigger information reactivation was more efficient during the spindle than during the inter-spindle interval (Antony, Piloto, et al., 2018; Cairney, Guttesen, El Marj, & Staresina, 2018). Therefore, the two most prominent functions that have been associated with spindle activity might be the result of two different temporal scales that govern spindle expression and activity.

[Figure 2]



Bidirectional MTL-PFC interactions for inter-areal information transfer
(A) Oscillatory communication between the PFC and MTL. PFC activity is dominated by spindle and slow waves oscillations, while the ripple oscillations can be seen in the MTL. Simultaneous recordings reveal that spindle synchrony precedes ripple expression. (B) Rhythmic spindle pulsing relative to the hippocampal ripple (at t = 0). Note spindles (white asterisks) periodically re-occur every 3-6 seconds. (C) Directional information flow from the prefrontal cortex to the medial temporal lobe prior to the ripple (arrow, black outline highlights the statistically significant time-frequency pairs as determined by cluster-based permutation statistics) indicates that the prefrontal cortex is driving the ripple expression in the medial temporal lobe and that spindle (~16 Hz) serve as a key messenger mechanism to convey the directed influence. (D) Bidirectional information flow relative to the hippocampal ripple. Note that the flow from PFC to MTL is enhanced just after the ripple oscillations, while the expected MTL to PFC flow is only evident after 1 second. Figure reproduced with permission under the Creative Commons Attribution (CC BY) license from (Helfrich et al., 2019).

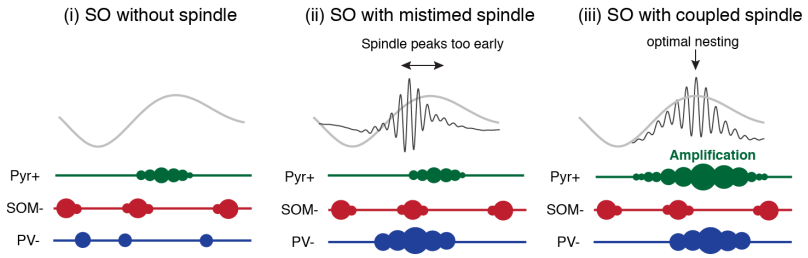
Coordinated neural rhythms and neuroplasticity

How can time-varying neural activity that rhythmically waxes and wanes support the formation of stable and continuous mnemonic representations (Helfrich & Knight, 2016)? A multitude of evidence on cross-frequency coupling implicated that coordinated neural activity might create a neurophysiological milieu that is ideal for information encoding, maintenance and consolidation (Canolty et al., 2006; Axmacher et al., 2010; Canolty & Knight, 2010; Johnson & Knight, 2015). One key assumption is that different neuronal rhythms are associated with different firing patterns of excitatory and inhibitory cells, which

could mediate the storage of newly acquired information (Bergmann & Born, 2018; Canolty & Knight, 2010; Hyafil, Giraud, Fontolan, & Gutkin, 2015; Niethard et al., 2018). However, empirical evidence for this consideration remains surprisingly sparse.

One recent study that employed two-photon calcium imaging combined with electrophysiology during sleep in rodents provided an essential missing piece to the puzzle (**Figure 3**). Niethard and colleagues used wide-field two-photon calcium imaging to track the activity of excitatory (pyramidal cells; Pyr) as well inhibitory somatostatin (SOM) and parvalbumin-positive neurons over posterior cortical areas (Niethard et al., 2018). By recording simultaneous EEG, they were able to relate distinct firing patterns to oscillatory events, such as slow waves and spindles. Importantly, they also studied the interaction of slow waves and spindles. Their results jointly suggest that slow waves and spindles are characterized by a stereotypical firing pattern that consists of Pyr, SOM and PV-cell activity. Critically, only when spindles were perfectly coupled to slow waves, did the authors observe an exponential increase in excitatory firing, which promotes the ideal neurophysiological milieu for neuroplasticity (Bergmann & Born, 2018). Hence, these findings reflect a milestone in explaining how neuronal rhythms interact with cell firing in support of memory formation.

[Figure 3]



Relationship of cell firing and SO-spindle coupling

Schematics of cell-specific activity during a SO and SO-spindle coupling (adapted from (Niethard et al., 2018)). (i) Excitatory activity in pyramidal neurons (Pyr+) is increased during the SO peak, while SOM (somatostatin) interneuron activity is strongest during the state-transitions from the down-to-up-state and vice versa. (ii) The spindle peaks prematurely, hence, is sub-optimally coupled to the SO. Note that spindle activity was associated with activity in PV neurons. (iii) When the spindle coincides with the SO peak then Pyr+ activity was increased by more than 300%. This circuit is thought to optimize synaptic plasticity and support long-term memory retention.

It is very likely that similar considerations also apply to cross-frequency coupling as observed during encoding and wakefulness (Canolty & Knight, 2010; Hyafil et al., 2015; Johnson & Knight, 2015). During wakefulness, the two most prominent rhythms are the theta (4-8 Hz; Colgin, 2013) and the gamma (~40-80 Hz; Fries, 2015) rhythms, which have been associated with a range of cognitive operations, but have repeatedly been implicated with memory encoding, maintenance and retrieval processes in the brain (Axmacher et al., 2010; Watrous, Deuker, Fell, & Axmacher, 2015). It would be an important advance to link these population oscillations to specific firing patterns in the human brain, however, current single unit recording techniques in humans do not allow a clear differentiation into putative excitatory and inhibitory cells (Fried, Rutishauser, Cerf, & Kreiman, 2014; Rutishauser, 2019). Comparative work in non-human

primates or rodents might provide the necessary means to bridge the explanatory gap between firing patterns, population oscillations, and behavior.

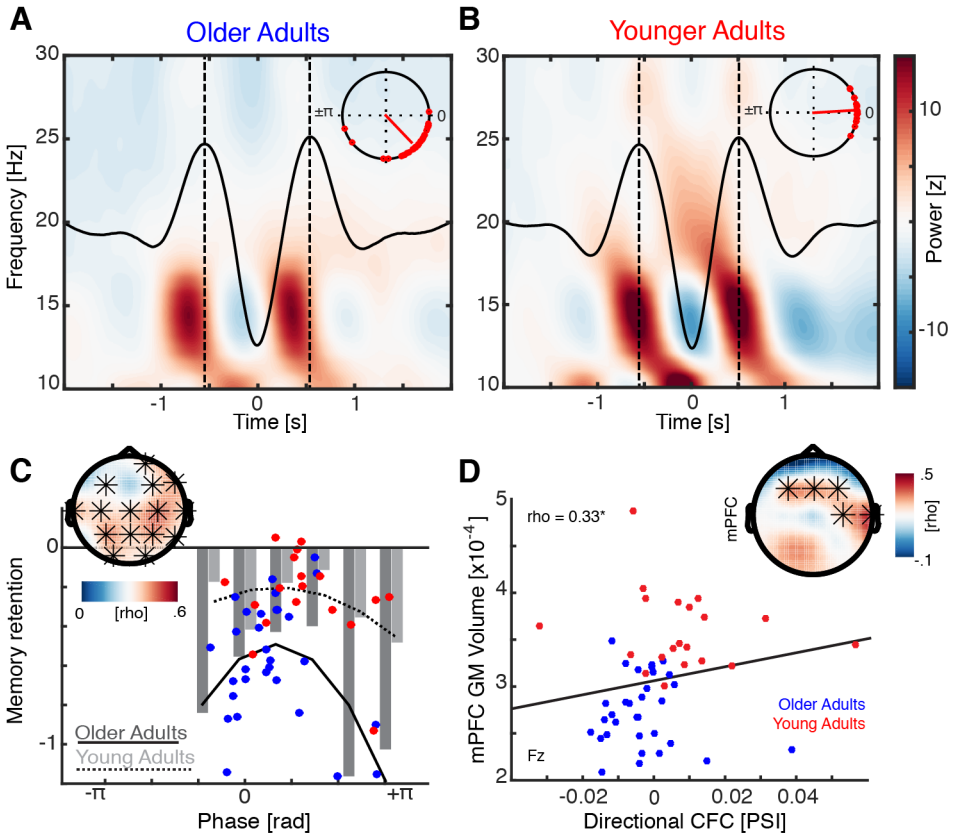
Boosting sleep-dependent memory consolidation through electrical brain stimulation to alleviate age- and disease-related decline

If neuronal oscillations are causally involved in forming new memories and mediating neuroplasticity, then one intriguing hypothesis is that modulation of these oscillatory patterns should impact memory formation (Hanslmayr, Axmacher, & Inman, 2019). In a seminal experiment conducted approximately 15 years ago, researchers stimulated the prefrontal cortex in humans with slow (0.75 Hz) oscillating currents during sleep (Marshall, Helgadóttir, Mölle, & Born, 2006). Marshall et al. reported that active stimulation improved memory recall performance the next day and critically, this was accompanied by an increase in slow wave as well as spindle power. In particular, the latter finding was very encouraging, since it demonstrated that the oscillatory signatures do not occur in isolation, but are reciprocally coupled (Clemens et al., 2007; Staresina et al., 2015). Hence, if one modifies one of cardinal sleep oscillations, then one will also impact coupled interactions. However, in the wake of these initially very promising results, several groups failed to observe similar effects and the evidence to date remain equivocal, as both successful and failed replications have been reported in the literature (Ladenbauer et al., 2017; Lafon et al., 2017; Lustenberger et al., 2016). Nevertheless, this line of research is actively being

developed because it provides the unique opportunity to non-invasively modulate memory pathways that might be impaired in age- and disease-related cognitive decline (Wilckens, Ferrarelli, Walker, & Buysse, 2018). Two recent studies provided further support for this possibility.

In the first study employing whole-head scalp EEG recordings, it had been observed that older participants perform worse than younger participants on a declarative hippocampus-dependent overnight memory task, in which new associations between words and nonsense words are encoded (e.g., “bird” and “jubu”; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Mander et al., 2013). Critically, both older and younger participants exhibited a comparable number of slow waves and spindles, and differences in their morphological features did not explain differences in task performance. However, it had been noticed that spindles peak prematurely in older participants – hence, indicating that the cardinal sleep oscillations in older participants were systematically mistimed, but not absent (Helfrich et al., 2018). Importantly, a difference that was a small as 50 ms predicted impaired memory formation in older participants (**Figure 4**). Furthermore, this functional deficit directly correlated with the amount of grey matter atrophy in the medial prefrontal cortex.

[Figure 4]



Impaired slow-wave spindle coupling predicts memory deficits
(A) SO trough-locked time-frequency representation (TFR) reveals elevated spindle power just prior to the SO peaks (dashed lines) in older adults. The inset highlights the average SO-spindle coupling phase across 32 older adults. (B) SO trough-locked TFR demonstrates that states of high spindle power coincide with SO peaks in younger adults. Same conventions as in panel A. (C) The precise SO-spindle coupling phase predicts overnight memory retention. In both groups, less forgetting was associated with more optimal coupling closer to the SO up-state (around 0°). (D) The strength of the directional influence of the SO phase on spindle power correlates with grey matter (GM) volume in the mPFC, hence, suggesting that age-related atrophy impairs the temporal coordination of SOs and spindles and hence, impairs memory performance. The graphs are reproduced with permission from (Helfrich et al., 2018).

In a second related study, the findings were recently replicated (Muehlroth et al., 2019) These results were encouraging because they implied that older participants exhibited all necessary substrates of successful overnight memory

consolidation, such as slow waves and spindles, but these events were misaligned (Bergmann & Born, 2018; Helfrich et al., 2018; Muehlroth et al., 2019). This finding raises the question of whether it is possible to resynchronize these two events and alleviate memory disorders (Wilckens et al., 2018). Results that support this notion had recently been reported by another group in patients with mild cognitive impairment, where non-invasive brain stimulation was successfully used to increase both the coupling strength as well as to readjust the timing of the slow wave and spindle interaction (Ladenbauer et al., 2017). While this study is encouraging, the reviewed evidence is by no means conclusive and large trials are required to assess the efficacy of non-invasive stimulation protocols in alleviating age- and disease-related deficits in sleep oscillation coordination.

However, we speculate that this will be an emergent issue in future years, since evidence is mounting that impaired slow wave spindle coordination is also implicated in tau- and amyloid-pathologies in the medial MTL and PFC, respectively (Winer et al., 2019). For instance, Winer et al. reported that cortical slow wave spindle coupling is reduced in patients with increased tau burden in the medial temporal lobe, which might signal a selective disruption of the hippocampal-neocortical dialogue during sleep. Given the societal burden of neurodegenerative diseases and the lack of treatment options, it is likely that the option of non-invasive electrical modulation will be further explored in the future to improve memory functions in patients with neurodegenerative diseases.

Conclusions

Taken together, we reviewed how cardinal sleep oscillations support active systems memory consolidation and discuss three main points: First, memory consolidation during sleep is a fundamentally active and not passive process. In other words, the sleeping brain generates prominent oscillatory patterns, which subserves the consolidation of new memories and the permanent storage in neocortical association cortex (Diekelmann & Born, 2010; Helfrich et al., 2019; Rasch & Born, 2013). Second, the reviewed evidence emphasizes a key role of the neocortex in organizing information transfer from the hippocampus. In contrast to previous views, this framework posits that the hippocampal-neocortical dialogue is an 'invited' dialogue, thus, forming cortico-hippocampal-cortical loops that ensure that mnemonic information arrives in the neocortex at favorable time points for subsequent processing (Antony, Schönauer, et al., 2018; Buzsáki, 2015; Sirota & Buzsáki, 2005). Third, contemporary theories highlight the role of NREM sleep for memory formation, which is in stark contrast to previous considerations, which favored REM sleep. Currently, the role of REM sleep is not well understood (Boyce, Williams, & Adamantidis, 2017; Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012). In particular, since REM sleep in humans is not characterized by prominent oscillation as REM sleep in rodents, where strong theta oscillations are evident (Gonzalez et al., 2018). It will be of great interest for future work to see what the

role of REM sleep is in organizing the hippocampal-neocortical dialogue in support of memory consolidation.

Acknowledgements

This work was supported by a NINDS grant R37NS21135 (R.T.K.).

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