Journal Club

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# Enhancing Memory Consolidation through Slow Oscillation and Spindle Synchronization

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Review of Ladenbauer et al.

Declines in sleep quality and cognitive function, particularly the formation and retention of hippocampal-dependent memories, are hallmarks of neurodegenerative disorders, such as Alzheimer's disease (AD). These events might be related: converging evidence suggests that sleep plays an active role in memory consolidation, with non-rapid eye movement (NREM) sleep particularly benefiting declarative memories (Ellenbogen et al., 2006). In particular, cortical slow oscillations (SO; 0.5–1 Hz), thalamocortical sleep spindles (slow: 8–12 Hz, fast: 12–15 Hz), and hippocampal sharp wave-ripples (SPW-R; 80–100 Hz), EEG events that characterize NREM sleep, have been shown to facilitate hippocampal-dependent memory consolidation in both rodents (Ji and Wilson, 2007) and humans (Tamminen et al., 2010).

Mounting evidence demonstrates that the coordination of NREM sleep oscillations underlies systems-level consolidation of information from the hippocampus to long-term stores in the neocortex (Clemens et al., 2011; Staresina et al., 2015). Therefore, the functional interaction between slow oscillations and sleep spindles is crucial to consider, and current theory regarding sleep-dependent consolidation takes this coupling into account (Rasch and Born, 2013). Slow oscillations and spindles are phase-coupled during NREM sleep. Spindles are suppressed during hyperpolarized SO down-states but rebound during the depolarizing SO up-states. Spindles are also temporally related to SPW-R, with ripples nested into the troughs of fast spindles, creating spindle-ripple events (Clemens et al., 2011). This temporal coupling of SO, spindles, and SPW-R might be involved in reactivation of hippocampal-dependent memories and consolidation of the memories within neocortical sites.

In human research, noninvasive brain stimulation techniques have emerged as a critical tool to test the causal, as opposed to correlational, relationship between SO, spindle activity, and memory consolidation by allowing modulation of these EEG events during sleep. However, research using transcranial direct-current stimulation (tDCS) has largely studied SO and spindles in isolation, and studies have provided inconsistent data on the benefits of SO and spindles in hippocampal-dependent memory (e.g., Marshall et al., 2006; Paßmann et al., 2016). Moreover, research to date has largely focused on healthy populations, raising the question of how SO, spindles, and their functional coupling affect memory consolidation in neurodegenerative disease.

In a recent publication, Ladenbauer et al. (2017) addressed this question in patients with mild cognitive impairment (MCI), a precursor to AD and other neurological disorders. The authors applied slow oscillatory tDCS (so-tDCS) intermittently to frontal locations during NREM sleep as participants napped. They then examined so-tDCS-related effects on visuospatial, verbal, and procedural memory. Of particular interest was visuospatial memory, which primarily involves the hippocampus and surrounding areas and is affected in MCI (Barbeau et al., 2004). Participants viewed 38 neutral, complex pictures in one of four quadrants and were instructed to memorize both the picture and its location. Either so-tDCS or sham stimulation was applied during the subsequent 90 min nap. Importantly, stimulation was individualized to each participant's sleep to account for sleep fragmentation, such that each stimulation-free interval was prolonged if a participant moved out of NREM sleep.

To determine temporal relationships between SO and fast spindle power, the authors assessed SO-to-spindle phase-amplitude coupling (PAC). PAC examines temporal synchronization between oscillations in any two related regions (Fell and Axmacher, 2011), including dependencies between high- and low-frequency oscillations (cross-frequency coupling). Ladenbauer et al. (2017) found that so-

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tDCS enhanced this coupling, with greater SO-fast spindle synchrony and fast spindle power during SO up-phases. Notably, this functional coupling may have been critical for the reported beneficial impact of so-tDCS on memory: although neither SO nor spindle activity alone correlated with memory performance, SO and fast spindle synchrony in the so-tDCS condition were associated with improved visual recognition.

PAC has been understudied in the SO and spindle frequency ranges, despite evidence that spindles and SPW-R are grouped by SO up-states to facilitate consolidation of episodic memories (Ji and Wilson, 2007). Ladenbauer et al. (2017) directly investigated the possibility that PAC drives SO- and spindle-related benefits for declarative memory. These findings add to growing evidence of the importance of cross-frequency coupling in various types of memory. Phase-locking of theta (4–7 Hz) and gamma (30–100 Hz) frequencies in the hippocampus, for example, have been shown to increase learning of item-context associations in rats (Tort et al., 2009), as well as working memory performance in humans (Fell and Axmacher, 2011). Theta-gamma coupling in the prefrontal cortex is also correlated with spatial working memory in humans, and these benefits appear to be critically dependent on such coupling (Alekseichuk et al., 2016).

The work by Ladenbauer et al. (2017) is of particular relevance for neurodegenerative disorders characterized by memory and sleep impairments, such as MCI and AD. Cognitive decline in AD has been associated with atrophy of brain structures important for the generation of SO, spindles, and SPW-R, including the hippocampus and thalamus (Mouton et al., 1998; de Jong et al., 2008). Impaired SO and spindle generation may contribute to the severe memory impairments seen in AD. Reduced gray matter and amyloid-$\beta$ deposition in the medial prefrontal cortex have been associated with reduced NREM slow-wave activity ($<$1 Hz) and reduced functional connectivity between the hippocampus and prefrontal cortex (Mander et al., 2013, 2015). Importantly, these reductions predict reduced overnight memory retention, suggesting that disruptions in spindles and SO contribute to rapid memory declines in neurodegenerative disorders.

Disruptions in PAC, rather than SO and spindle dysregulation alone, might be an important consideration in neurodegenerative disorders. Spindle synchrony across the thalamus and cortex is dependent on active corticothalamic input, and atrophy in these regions may impair PAC. GABAergic neurons of the thalamic reticular nucleus impart rhythmic IPSPs onto thalamocortical neurons, which in turn fire spindle-frequency excitatory input to the cortex (Neske, 2015). Animal research has demonstrated that removal of cortex disrupts synchronization of SO and spindles (Contreras et al., 1996), suggesting that cortical atrophy impairs PAC. Further, the thalamic reticular nucleus communicates with structures in the brainstem and parts of the limbic thalamus, regions that are known to be affected in AD (Braak and Braak, 1991). Therefore, it is possible that AD-related atrophy of cortical and thalamic regions reduces SO-to-spindle coupling in neurodegenerative disorders.

Understanding the role of PAC in memory consolidation may be the next critical step in uncovering the underlying causes of sleep-related cognitive decline. Research has consistently shown that memory-relevant electrophysiological coherence is impaired in MCI/AD during wake (Hogan et al., 2003; Bazzigaluppi et al., 2017), and research on SO and spindles raise the possibility that similar impairments occur during sleep and lead to sleep-dependent memory consolidation impairments. The findings of Ladenbauer et al. (2017) suggest that so-tDCS may be an avenue for individualized treatment of memory decline by modulating SO-to-spindle PAC.

Although Ladenbauer et al. (2017) focus on the coupling of specific sleep parameters, future work might also consider possible interactions with factors such as sleep quality. For example, sleep fragmentation is common in older adults and magnified in MCI (Lim et al., 2013). It has been shown to impair LTP and learning in rodents (Wallace et al., 2015). Importantly, increased sleep continuity (i.e., less fragmentation) has been associated with improved declarative learning in healthy older adults (Gosselin et al., 2016). To minimize sleep fragmentation in their study, Ladenbauer et al. (2017) individualized stimulation to each participant's sleep. In this study, so-tDCS increased Stage 2 and marginally decreased Stage 1 (light) sleep as well as wake after sleep onset. Interestingly, these changes in sleep architecture did not correlate with visual memory performance. Nonetheless, so-tDCS may still have decreased sleep fragmentation. In turn, enhanced sleep continuity could have benefited visual memory performance independently from SO-to-spindle PAC. Therefore, future research should consider whether brain stimulation not only increases individual events, such as spindles or SO, or coherence between events, but also sleep quality as a whole.

The findings of Ladenbauer et al. (2017) further our understanding of sleep-dependent memory consolidation, including a lesser-examined feature of sleep (i.e., phase-amplitude coupling) that may be critical for hippocampal-dependent memory consolidation. While SO and spindles on their own have been related to memory performance, the specific association of PAC with improved visual recognition suggests that functional coupling may be vital for effective reactivation and consolidation of information during sleep. Future work should aim to develop an intervention strategy using noninvasive brain stimulation methods, such as tDCS, for individualized treatment of sleep and memory impairments. Enhancing SO and spindle synchronization provides promising future directions for benefitting sleep and memory processes in neurodegenerative disorders, such as AD, that are characterized by dysregulated sleep and impaired sleep-dependent memory consolidation.

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