Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

A Dual Role for Sleep Spindles in Sleep-Dependent Memory Consolidation?

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Review of Ngo et al.

Memories for facts and events (i.e., declarative memories) are not immediately integrated into the long-term storage centers of the brain, but must instead undergo consolidation, a neurocognitive process whereby initially labile memory information becomes progressively resistant to interference and decay. There is now substantial evidence that declarative memory consolidation is enhanced during sleep, particularly during slow-wave sleep (SWS) (Rasch and Born, 2013). The <1 Hz slow oscillation (SO), which characterizes electroencephalographic (EEG) recordings of SWS, is central to sleep-dependent memory gains. SOs reflect highly synchronized neuronal activity and consist of depolarising up states, when neurons show sustained firing, and hyperpolarizing down states, when neurons are silent. Generated in mainly prefrontal cortical areas, SOs typically occur in individual cycles (i.e., complete down-to-up state transitions) and spread across the entire neocortex. Via efferent pathways, SOs synchronize neuronal activity in other memory-relevant brain regions, including the thalamus, where sleep spindles (~10–15 Hz EEG activity) are generated (Steriade and Timofeev, 2003).

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Research linking SOs to memory consolidation prompted researchers to ask whether boosting SOs in SWS can produce additional memory gains. Using a sophisticated computerized technique known as closed-loop stimulation (CLoS), Ngo et al. (2013) were able to enhance SO activity by repeatedly delivering two auditory clicks in-phase with two consecutive SO up states during SWS. Whereas a sham stimulation condition resulted in mostly single SO cycles (as typically observed in SWS), CLoS formed trains of three successive SO cycles in which one cycle immediately followed the next, suggesting a resonating response of the SO-generating network to in-phase auditory stimulation. Moreover, compared with sham stimulation, CLoS enhanced power in the fast spindle band (12–15 Hz) during SO up states and improved declarative memory retention. CLoS administered out-of-phase with SO up states had no such effects.

Paroxysmal spike-wave seizures emerge from cortical SOs during sleep, with this transition characterized by a speeding of the SO rhythm and increased neuronal synchronization (Steriade and Amzica, 1998). Enhancing the SO rhythm and synchronized excitability with CLoS should therefore carry an increased risk of hypersynchrony and seizure-like activity within the cortico-thalamic system. But CLoS was not associated with any paroxysmal episodes in Ngo et al. (2013), indicating the presence of a healthy brain mechanism that prevents the development of hypersynchronicity during SO activity.

In a recent issue of *The Journal of Neuroscience*, Ngo et al. (2015) present a neurophysiological study that explored how the sleeping brain counters SO induction to prevent hypersynchronicity. To this end, the authors aimed to overdrive CLoS with a previously untested driving stimulation protocol. In Study 1, healthy participants took part in two experimental nights consisting of a driving stimulation night and a sham stimulation night, counterbalanced in order and separated by an interval of at least 7 d. On both experimental nights, participants performed a memory task that involved the successive presentation of 120 German word pairs and immediate cued recall test before going to bed. On the driving stimulation night, auditory stimulation commenced ~5 min after the participant displayed SWS (as confirmed via online EEG monitoring). The stimulation protocol was based on a sophisticated algorithm which, upon detecting a SO negative half-wave peak (down state), delivered a 50 ms click of pink noise that coincided with the upcoming SO up state. Additional clicks occurred each time the EEG signal crossed the negative half-wave threshold during a 1 s time window that began with the preceding click presentation, with up to four clicks occurring in succession. Stimulation was paused during non-SWS and was stopped entirely ~ 210 min after onset. On the sham stimulation night, SO negative half-waves

were detected and marked but no clicks were presented.

In Study 2, an additional cohort of healthy participants followed the same experimental procedures, except that sham stimulation was replaced with a two-click stimulation protocol in which only two clicks occurred in-phase with the up states of the detected and subsequent SO (as in Ngo et al., 2013). Thus, the authors were able to examine how driving stimulation, designed to drive trains of numerous succeeding SO cycles via the presentation of multiple clicks, affected SO activity and memory consolidation relative to two-click stimulation. This comparison, together with EEG data from Studies 1 and 2, was intended to unravel the mechanisms limiting SO induction and hypersynchronicity in the sleeping brain.

Relative to sham stimulation in Study 1, driving stimulation produced a greater number of SO trains, increased SO amplitudes, and improved declarative memory retention in the post-sleep test. However, the enhancing effects of driving stimulation for SO trains, SO amplitudes, and memory performance did not exceed those of two-click stimulation in Study 2, suggesting that SO-generating networks enter a state of refractoriness against stimulation and thus prevent an overdriving of SO activity. Furthermore, in the driving stimulation condition of both Studies 1 and 2, the intervals after auditory stimulation (i.e., the time elapsed until detection of the next SO negative half-wave) were shorter when they followed a solitary SO induced by a single click than when they followed trains of two, three, or four SOs induced by multiple clicks. When comparing only the intervals that followed trains of two, three, or four SOs resulting from multiple clicks, by contrast, no difference was detected. This pattern suggests that there is no additional influence of multiple clicks on network refractoriness, and led the authors to conclude that two-click stimulation is sufficient for a complete state of refractoriness to emerge within SO-generating networks.

Which properties of the sleeping brain contribute to refractoriness against stimulation and, on a broader scale, a mechanism to prevent hypersynchronous episodes? Regardless of the CLoS protocol, Ngo et al. (2015) observed a pronounced increase in fast spindle activity during the SO up state that followed the first click, whereas no such effect occurred in response to subsequent clicks. As described by the authors, this finding suggests that thalamic spindle-generating networks develop an immediate resistance to stimulation. Notably, the thalamocortical cells that underlie refractory periods related to thalamic spindle generation are thought to confer relative refractoriness to the entire thalamocortical network, which includes the cortical networks that generate SOs (Destexhe et al., 1998).

A point not raised by Ngo et al. (2015) is that a mechanism inhibiting SO induction may also be of critical importance to memory. The synaptic homeostasis hypothesis proposes that SOs promote a global proportional downscaling of synapses potentiated throughout the preceding day as a result of learning (Tononi and Cirelli, 2014). Consequently, highly potentiated neuronal circuits retain their relative strength compared with weakly potentiated circuits, which may even become silent if downscaled below a particular threshold. This process improves the signal-to-noise ratio within neural circuits and thus facilitates efficient memory storage. From this perspective, while a transient increase in SO activity would enhance global synaptic renormalization and improve the signal-to-noise ratio accordingly, an overdriving of SO activity would cause excessive downscaling and have a damaging impact on memory. Indeed, the typical overnight decrease in the slope of SOs, thought to reflect the progressive renormalization of potentiated synapses, is impaired in children with continuous epileptic spike-wave activity in SWS, suggesting an epilepsy-related disruption of synaptic homeostasis (Bölsterli et al., 2011). More recent work has also revealed a link between interictal epileptiform discharges during non-rapid eye movement (NREM) sleep and poor declarative memory performance the following day (Galer et al., 2015). Impairments in the mechanism that limits SO generation may therefore underlie seizure activity and associated memory disruptions in neurological disorders.

Relatedly, sleep spindles have been heavily implicated in declarative memory consolidation (Lüthi, 2013). An alternative but nonexclusive model of sleep-dependent consolidation, known as the active systems model, proposes that spindles and SOs work in unison to stabilize memories in localized cortical networks via covert memory reactivations (Born and Wilhelm, 2012). Together with previous work, the findings of Ngo et al. (2015) suggest that spindles may have a multifaceted role in offline memory processing. By contributing to a mechanism that inhibits an overdriving of SO activity and hypersynchronicity while at the same time supporting memory reactivations in sleep, spindles may work to both prevent excessive global downscaling and strengthen individual memories.

It is important to note, however, that spindles are associated with reduced sensory responsiveness in sleep (Lüthi, 2013). In one study, Dang-Vu et al. (2011) reported that tone-evoked fMRI responses in thalamus and auditory cortex observed during wakefulness persisted in NREM sleep, except during spindles when activation was significantly reduced. From this perspective, if spindles help to prevent hypersynchrony during CLoS, one may expect an increase in spindle activity (and related reduction of sensory responsiveness) to persist throughout the entire stimulation period, rather than diminishing after the first click as observed by Ngo et al. (2015). Future work should therefore examine in more detail the relationships between spindles, sensory processing, and SO induction.

In summary, Ngo et al. (2015) reported that CLoS with a driving stimulation protocol brought no greater enhancement to SO activity or memory consolidation than a two-click protocol. These findings indicate that SO-generating networks build up refractoriness to repetitive stimulation and, on a broader scale, suggest the presence of a healthy brain mechanism that counters SO induction to prevent hypersynchronous episodes. An increase in phase-locked spindle activity to the first stimulation click, but not any subsequent click, signified immediate spindle refractoriness to stimulation, which may project to SO-generating networks and, thereby, underpin this protective brain mechanism.

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