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Understanding the roles of central and autonomic activity during sleep in the improvement of working memory and episodic memory

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The last decade has seen significant progress in identifying sleep mechanisms that support cognition. Most of these studies focus on the link between electrophysiological events of the central nervous system during sleep and improvements in different cognitive domains, while the dynamic shifts of the autonomic nervous system across sleep have been largely overlooked. Recent studies, however, have identified significant contributions of autonomic inputs during sleep to cognition. Yet, there remain considerable gaps in understanding how central and autonomic systems work together during sleep to facilitate cognitive improvement. In this article we examine the evidence for the independent and interactive roles of central and autonomic activities during sleep and wake in cognitive processing. We specifically focus on the prefrontal–subcortical structures supporting working memory and mechanisms underlying the formation of hippocampal-dependent episodic memory. Our Slow Oscillation Switch Model identifies separate and competing underlying mechanisms supporting the two memory domains at the synaptic, systems, and behavioral levels. We propose that sleep is a competitive arena in which both memory domains vie for limited resources, experimentally demonstrated when boosting one system leads to a functional trade-off in electrophysiological and behavioral outcomes. As these findings inevitably lead to further questions, we suggest areas of future research to better understand how the brain and body interact to support a wide range of cognitive domains during a single sleep episode.

autonomic nervous system | working memory | episodic memory | sleep | slow oscillation

The autonomic nervous system (ANS) is divided into two branches, with the sympathetic branch associated with energy mobilization during so-called fight–flight–freeze responses (1, 2) and the parasympathetic branch associated with vegetative and restorative functions during so-called rest–digest responses (3). These branches "work antagonistically, synergistically, and independently to gather information from sensory organs and coordinate responses to internal and external demands" (4). Both the sympathetic and parasympathetic nervous systems communicate with the central nervous system (CNS), forming a system named the central autonomic network. The central autonomic network is a set of CNS structures, including the locus coeruleus (LC), hypothalamus, amygdala, ventromedial prefrontal cortices, hippocampus, and thalamus, that, directly or indirectly, receive inputs from and modulate output to the ANS. The vagus nerve (the 10th cranial nerve) is comprised of ~80% afferent connections (5) that communicate parasympathetic/vagal information from the periphery to the nucleus of the solitary tract in the brainstem and higher-order areas in the central autonomic network (6, 7). Additionally, descending projections from the central autonomic network allow for bidirectional communications between the brain and the peripheral regions (8, 9).

In humans, a noninvasive method to detect ANS activity is heart rate variability (HRV), which examines the variability between individual heart beats (R–R intervals, reflecting ventricular depolarization) in the QRS complex of electrocardiogram (ECG) (10–12). HRV can be calculated in the time domain and the frequency domain. Time-domain measures of HRV include 1) the SD of all R–R intervals (SDNN), a general measure of variability in heart rate, and 2) the root mean square of successive differences (RMSSD), a measure of heart rate fluctuations mediated primarily by the vagus nerve. Frequency-domain measures of HRV include 1) the power of high-frequency HRV (HF-HRV: 0.15 to 0.40 Hz), an indicator of respiratory sinus arrhythmia and parasympathetic vagal activity, and 2) the power of low-frequency HRV (LF-HRV: 0.04 to 0.15 Hz), a mixed signal from both sympathetic and parasympathetic sources. Given the uncertainty in the contribution of signals comprising LF-HRV, relative to the known vagal origins of the HF-HRV signal, research on autonomic activity tends to focus on HF-HRV. For a recent review of the brain areas and neuromodulatory systems comprising the parasympathetic and sympathetic branches, as well as

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their inputs to brain areas devoted to cognitive processing, see Whitehurst et al. (4).

Our review focuses specifically on the evidence supporting a role for the ANS in cognitive processes across wake and sleep. We report on a robust set of findings linking parasympathetic/vagal activity during wake and sleep with the prefrontal–subcortical network regulating cognitive control, executive function, and working memory (WM). We also identify a significant dearth of evidence for autonomic activity facilitating sleep-dependent memory consolidation, a notable gap given the large body of research connecting sleep with the formation of long-term memories. Next, we summarize current knowledge about mechanisms supporting the formation of long-term memories during sleep. Upon this background, we develop the hypothesis that the brain networks and neuromodulatory systems during sleep that support increased efficiency in WM and the consolidation of hippocampal, episodic memories are separate and competing mechanisms. We introduce the Slow Oscillation Switch Model, which gives an outline for how these mechanisms interact during sleep, along with emergent testable hypotheses and new lines of inquiry for further research in this area.

Autonomic Inputs Modulate Cognition

Cognitive processes that rely on top-down inhibitory control in prefrontal–subcortical networks, such as emotional regulation, cognitive control, or executive function, have been associated with parasympathetic/vagal activity. Cognitive control or executive function, the coordination of mental processes and action in accordance with current goals and future plans, is a primary function of the prefrontal cortex. The coordination of cognitive control is implemented by multiple functional circuits anchored in the prefrontal cortex, including the ventromedial prefrontal cortex, anterior cingulate cortex, and a wide range of subcortical regions (13). WM is an aspect of executive function that supports the maintenance and manipulation of a small quantity of information, usually lasts seconds to minutes (14), and shares similar neural mechanisms with cognitive control (15). The scope of this paper will focus on one aspect of executive function, namely WM (for more information on emotional regulation, see refs. 16–19). WM, unlike long-term memory (LTM) that entails the transformation of memory representations or traces, is an information-general, online cognitive process, which has traditionally been considered an unmodifiable trait. Yet, WM training studies have demonstrated that executive function generally and WM specifically can be improved (20) and that these improvements are supported by increased prefrontal efficiency and automaticity of prefrontal–subcortical networks (21, 22).

Research on the role of the ANS in cognition have shown that parasympathetic/vagal activity may be an indicator of the degree to which the prefrontal–subcortical circuit regulates its component systems in response to internal and external demands. Specifically, activity in these inhibitory circuits has been positively associated with resting HF-HRV (9, 23), and optimal functioning of these circuits is hypothesized to predict flexible and adaptive responses to environmental changes (24). One prominent model aimed to explain how the bidirectional communication between CNS and ANS is a critical predictor of adaptive cognitive success is the Neurovisceral Integration Model, developed by Thayer and colleagues (9, 23) (*SI Appendix*, Fig. S1). This model proposes that HRV is an index of prefrontal–subcortical inhibitory influence over a wide range of brain areas supporting cognition, emotion, and physiological reactivity, including executive function, WM, expectation of future outcomes, emotional regulation, emotional response to stress, and peripheral functioning (24).

The Neurovisceral Integration Model gained empirical support from studies showing the relationship between HRV during wakefulness and executive function. Compared to individuals with low resting HF-HRV (reflecting poor parasympathetic vagal tone during awake rest), high–HF-HRV individuals show better WM performance [n-back task (25); operation-span task (26)] and inhibitory control [i.e., Stroop task (27)]. In addition, training-induced changes in cognitive control are associated with improvements in parasympathetic activity, and the reversal is also true that training-induced increases in parasympathetic activity also promote cognitive enhancement. For example, cognitive training (vision-based speed of processing) has been shown to increase HF-HRV and enhance activation in the prefrontal–subcortical network (22). In this study, older adults with amnestic mild cognitive impairment underwent 6 wk of cognitive training. Compared to controls, older adults in the active training group demonstrated increased HF-HRV and decreased prefrontal–striatal connectivity during the task, suggesting an efficient prefrontal–subcortical autonomic regulation. Similar results were reported in healthy participants (28). Furthermore, increasing resting HF-HRV via aerobic training has been reported to parallel improvements in WM performance (27). In this study, participants were randomly assigned to an aerobic training group and a detraining group (reduced exercise condition), with resting HF-HRV and WM measured before and after the exercise intervention. Postintervention, the aerobic training group showed greater HF-HRV and WM performance compared to the detraining control group, suggesting a link between the strengthening of parasympathetic/vagal functioning and WM networks via cardiac exercise.

One potential mechanism for how vagal/parasympathetic activity can benefit prefrontal function and WM is via the modulation of norepinephrine (NE). The last 20 y of research has demonstrated that along with the traditional story that the primary neuromodulator of vagal activity is acetylcholine (ACh), vagal afferents also modulate NE levels in the brain. The vagus nerve represents the main component of the parasympathetic nervous system, and activating ascending fibers of the vagus nerve mediate NE's actions on the brain (29, 30). The terminals of the afferent vagal transmissions are directly within the nucleus of the solitary tract, which convey information to structures that regulate higher-order cognition such as the amygdala, hippocampus, and frontal cortex via a polysynaptic pathway from the LC. Although ACh is the primary neurotransmitter in the peripheral synapses of the vagus nerve, once the information propagates to the LC, NE becomes the primary neuromodulator mediating synaptic communication in the CNS.

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The LC has two modes of firing, phasic and tonic, which influences prefrontal function. Tonic firing has been linked to stress or arousal, whereas phasic firing has been linked to responses to novelty and higher-order cognition (31). Phasic and tonic activations are independent, with phasic activity optimized when moderate level of tonic activity (32), while elevated tonic discharge can impair phasic discharge (33). In primates, phasic activation of NE neurons of the LC in time with cognitive shifts could provoke or facilitate dynamic reorganization of target neural networks, permitting rapid behavioral adaptation to changing environmental imperatives (34). Furthermore, it has been recently shown that phasic optogenetic activation of LC protects against deleterious human pretangle tau effects and cognitive decline, while stress-inducing tonic-LC activation worsens its effects (35, 36). Specifically, in the study conducted by Omoluabi et al. (36), mice were injected with pretangled tau and their LC neurons were activated in either phasic or tonic patterns. They found that phasic stimulation rescued mice from behavioral and LC deficits, while tonic stimulation led to worsened symptoms.

Furthermore, studies in rodents and monkeys have shown that optimal excitatory–inhibitory balance of prefrontal NE, maintained by different adrenergic receptors, (e.g., α1 and pre- and postsynaptic α2), has an important beneficial influence on WM performance (37, 38). Experimentally increasing NE concentrations in the prefrontal cortex improves response inhibition performance in rodents and humans (39, 40). This body of research emphasizes the role of increased inhibitory function during distracting conditions that serve to benefit WM specifically (41), while having no benefit for hippocampal memory (42). Interestingly, α2 adrenergic receptors preferentially increased prefrontal NE and maintain its optimal excitatory–inhibitory balance, which in turn improves prefrontal function (43–45), whereas α1 receptors override α2 receptor activity and impair WM function (38). The emerging picture is that different types of adrenergic receptors may play a role in optimizing the overall excitatory–inhibitory balance in the prefrontal cortex. Specifically, NE orchestrates physiological functions that switch the brain and body from a nonstressed state, in which phasic LC activity engages α2 receptors and increases prefrontal WM function, to a stressed state that stimulates tonic firing and α1 receptor activity, impairing WM while maintaining other functions, such as alertness and attention (46).

In humans, a causal link between vagal inputs modulating LC–NE activity and cognitive domains supported by the prefrontal cortex has been established by studies actively manipulating vagal tone using vagal nerve stimulation (VNS) or noninvasive transcutaneous vagus nerve stimulation (tVNS). VNS activates phasic neuron firings in the LC and increases NE levels in the prefrontal–subcortical networks, including the neocortex, hippocampus, amygdala, and other parts of the brain with afferent projections from LC (33, 47–49). In one study, patients treated with invasive VNS performed cognitive tasks with stimulation on or off. Patients demonstrated improved WM performance during the stimulation-on periods compared to the stimulation-off periods (50). More recently, tVNS has shown similar effects to cognitive control (51). In this study, healthy participants performed an inhibitory control (Go/NoGo) task with active tVNS or sham stimulation. In the NoGo condition which required cognitive inhibition, tVNS resulted in significantly reduced amplitude of frontal N2 event-related potentials, a biomarker for demanding cognitive control, suggesting that tVNS may lead to more efficient neural processing with fewer resources needed with successful frontal inhibitory control. Similar effects of tVNS have been demonstrated in another study (52) in which tVNS increased frontal midline theta activity, thought to reflect transient activation of the prefrontal cortex in situations requiring increased executive control of actions.

Given that vagal stimulation enhances phasic LC–NE, and that parasympathetic activity is naturally increased during nonrapid eye movement (NREM) sleep, it is tempting to hypothesize that increases in phasic LC–NE activity with the natural boost in vagal parasympathetic activity during sleep may be one mechanism whereby prefrontal function is regulated and WM capacity enhanced. Taken together, phasic LC–NE during sleep might contribute to increased WM capacity through several possible mechanisms, including by reorganizing neural representations, by the elimination of tau, and/or by increasing phasic activity of LC–NE α2 receptors along with prefrontal function. At the same time, stress-induced tonic LC–NE is disruptive for sleep as well as prefrontal function. The next section will review findings on the relationship between sleep and ANS activity.

Sleep Modulates ANS Activity

The transition from wake to sleep produces the largest shift in autonomic activity we experience every day. Sleep is not one uniform event, and its characterization into organized stages shows specific profiles in central and autonomic activity during each stage. Over a night of sleep, the human brain cycles through two primary phases: NREM and rapid eye movement (REM) sleep. NREM sleep is further divided into stages 1, 2, and 3 (or slow-wave sleep) (53). Stage 1 sleep is a transitional state from wake to sleep, making up 3% of adult nocturnal sleep. About 60% of adult sleep is stage 2 sleep, which is marked by distinct electrophysiological events named sleep spindles and K-complexes. Stage 3, or slow-wave sleep (SWS), makes up about 20% of sleep, and it is marked by slow, high-amplitude oscillations called slow oscillations (SOs, <1 Hz) and slow-wave activity (SWA, 0.5 to 2 Hz). In NREM sleep, cholinergic systems in the brainstem and forebrain become markedly less active; firing rates of LC–NE and serotonergic Raphé neurons are also reduced, compared to waking levels (54). However, the conventional dogma about the relative quiescence of LC–NE neurons during NREM sleep has been challenged by evidence of a transient increase in LC–NE activity during NREM sleep (55). A simultaneous electroencephalogram (EEG)–functional MRI (fMRI) study in humans further revealed that the increased phasic activity of the LC nucleus is temporally related to SO down-to-up transitions (55, 56), suggesting a more complex neuromodulator dynamic during NREM sleep. Activity of LC–NE neurons during NREM sleep is potentially relevant in understanding how autonomic activity during this sleep period may contribute to cognitive enhancement.

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After a bout of SWS, the brain shifts into REM sleep, which makes up about 20% of human sleep and it is marked by sudden bursts of eye movements and faster, low-amplitude alpha (8 to 12 Hz) and theta (4 to 8 Hz) oscillations. During REM sleep, both aminergic populations are strongly inhibited, while cholinergic systems become more active compared to waking levels (57). The transition through stage 2, SWS, and REM occurs in 90- to 100-min cycles across the night, with the first half of the night dominated by SWS and the second half of the night dominated by REM sleep (58).

In peripheral sites, the transition from wake to SWS is associated with a significant drop in heart rate and blood pressure, as well as increased dominance of HF-HRV (59, 60). The blood pressure plunge during NREM sleep compared to wake is beneficial for cardiovascular health, leading some experts to describe sleep as a "cardiovascular holiday" (61). SWS, in particular, is a period of cardiovascular quiescence and may represent an opportunity for the cardiovascular system to recuperate from daytime insults, such as stress-induced blood pressure surges. Indeed, one study comparing amounts of SWS and subclinical markers of cardiovascular disease found that participants who experienced greater SWS showed lower markers of cardiovascular disease after cardiovascular stress (62), suggesting that SWS may buffer autonomic responses to daytime stress that may modify disease risk.

Additionally, sleep, rather than circadian effects, appears to influence ANS activity, as similar HRV profiles have been shown in daytime and nighttime sleep (63), which may also indicate that daytime naps serve as a minicardiovascular holiday. Furthermore, a study comparing HRV profiles during a 50-min nap versus waking rest in supine position reported parasympathetic dominance during sleep only, and not during quiet rest, indicating that the cardiovascular benefits are specific to sleep (64).

Studies have revealed a consistent interdependency between the heart and brain activity, with temporally coincident changes in EEG delta (0.5 to 4 Hz) power and ANS activity (65–70). In fact, modulations in HRV are so closely associated with the onset of SWS that they can be used as a parameter to automatically detect SWS (71). Furthermore, delta band power, a marker of homeostatic sleep drive that dissipates across successive NREM periods, shows inverse coupling with LF/(LF+HF) ratio during nighttime sleep. Generally, the LF/(LF+HF) ratio increases during REM sleep and decreases during SWS (Fig. 1*A*) (66), indicating greater sympathetic activity during REM sleep, with heart rate and blood pressure levels reaching values similar to wake (72). In fact, parasympathetic/vagal activity during NREM sleep and sympathetic activity during REM sleep can exceed average levels of quiet wakefulness (72). Fig. 1*B* demonstrates the power spectrum of RR intervals during quiet wake, stage 2, SWS, and REM sleep (Fig. 1*B*) (73). More recently, causally increased SWA via acoustic SOs stimulation resulted in increased vagal activity (measured by HF-HRV and SDNN) during SWS compared to sham stimulation (74), suggesting a strong interdependency between vagal activity and slow EEG oscillatory events during SWS.

Considering more temporally precise levels of analysis, coupling has been shown between individual ANS and CNS events, such as heartbeats and EEG SOs in deep sleep (75). Using a cross-correlation approach, Thomas et al. (69) showed a temporal relation between SWA and high-frequency cardiopulmonary (0.1 to 0.4 Hz) coupling, an ECG-derived biomarker of stable sleep, during NREM sleep. Several studies have also reported on coupling between autonomic and central events whereby short bursts of heart rate are temporally coincident with transient increases in SOs during NREM sleep(73, 76). Rembado et al. recorded vagal-evoked potentials, manifested as the vagal afferents to the cerebral cortex in responses to VNS, in macaque monkey brains during different consciousness states (77). Vagal-evoked potentials were reported to be 300 to 500% larger during NREM sleep, compared to REM sleep and wakefulness (Fig. 1*C*) (77), and, critically, vagal-evoked potentials during NREM were larger for stimuli delivered at the depolarized phase of ongoing delta oscillations, suggesting a close temporal coupling between ANS

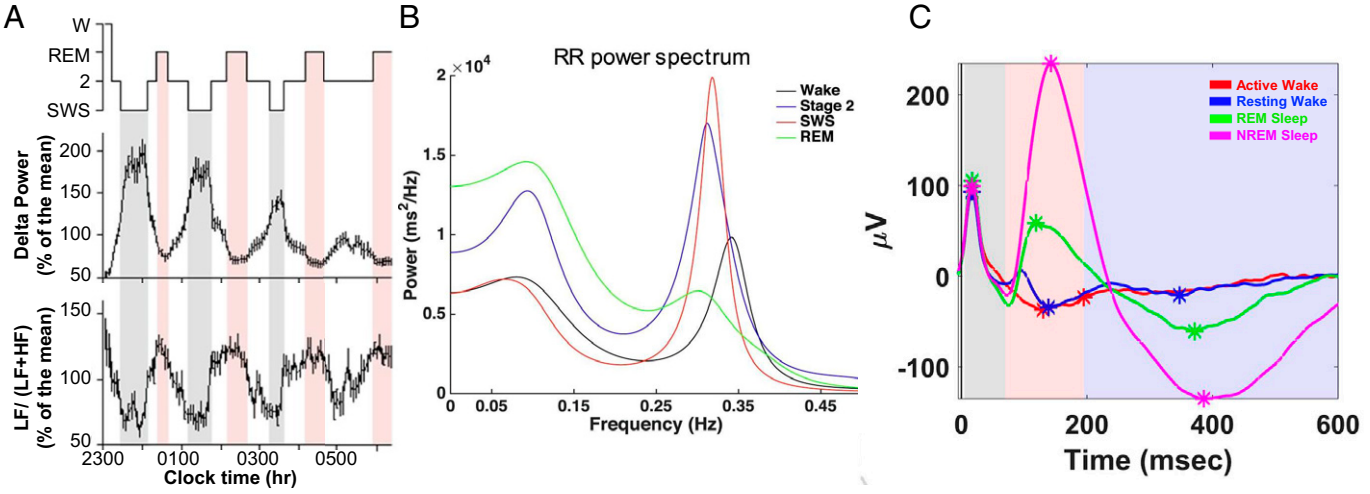

Fig. 1. Parasympathetic/vagal activity is boosted during SWS. (*A*) Delta wave activity and LF/(LF+HF) ratio with a hypnogram during nighttime sleep (66). (*B*) RR power spectrum modulated by sleep stages. NREM stage 2 and SWS demonstrate greater parasympathetic activity indexed by HF-HRV, compared to REM sleep and wake (73). (*C*) Vagal-evoked potentials in the macaque monkey brains by sleep stages (78). NREM sleep demonstrated 300 to 500% greater vagal-evoked potentials, compared to REM sleep and wake.

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and CNS events. These findings demonstrate that CNS–ANS dynamics support the interdependency between cortical and cardiac function during sleep. Moreover, taken together with findings from wake HRV studies, natural surges in parasympathetic activity during SWS suggest that HRV profiles during sleep might account for some degree of cognitive enhancement.

Both SWS and Vagal Tone Benefit WM

Compared to wakefulness, sleep between WM training sessions may be critical for enhancing WM performance (78–82), potentially due to the effect of SOs (83–85) (*SI Appendix*, Fig. S2*A*). Moreover, a recent study using acoustic SO stimulation during nighttime sleep reported that stimulation improved WM as a result of enhanced SWA, compared to individuals whose SWA was not enhanced (86). Not all studies, however, find a positive association between EEG features of SWS and WM improvement (78, 81). One potential reason for the lack of consistent findings may in part be related to the fact that few studies measure ANS activity during sleep and therefore miss the ANS's contribution to the performance change. One recent study accounted for both autonomic and central activity across a sleep period in which subjects' WM was tested before and after a sleep period (78) (*SI Appendix*, Fig. S2*B*). In this study, participants performed the operational-span task in the morning and evening. During the intertest period, subjects either experienced a nap or quiet wake with EEG and ECG recorded (78). Results showed that HF-HRV during SWS predicted WM improvement in healthy young adults, to a greater extent than HF-HRV during wakefulness or than other SWS features, including SOs or SWA. These findings suggest that along with EEG events of SWS, naturally elevated vagal activity during SWS also supports WM improvement in young adults.

Although the sleep-dependent mechanisms of WM improvements remain elusive, based on the current picture, SOs and vagal activity may facilitate WM improvement by increasing prefrontal efficiency and automaticity in prefrontal–subcortical inhibitory networks. Specifically, vagal inputs increase prefrontal phasic-NE activity while SOs up-regulate cortical synapses potentiation. More interestingly, Eschenko et al. showed that LC neurons fire during down-to-up transition, while medial prefrontal neurons fire at the peak of SOs (87), which corresponds to the time of maximal cortical excitability during up-states, suggesting that in prefrontal–LC interactions, LC leads the prefrontal activity. It has been hypothesized that SOs potentiate synapses that were depressed due to persistent activity during the previous day and that potentiation provides a physiological basis for sleep-dependent memory improvement (88). Taken together, optimal levels of NE during sleep might support next-day WM performance by potentiating WM prefrontal activity and thus enhancing prefrontal–striatal WM efficiency.

Another possibility is that SOs and vagal activity facilitate WM by clearance of tau/beta-amyloid plaques in the prefrontal–subcortical executive function networks, driven by phasic LC–NE activity (vagal afferents) and SOs (35). Even among individuals who perform within the normal range of cognitive functioning, mesial temporal tau accumulation is associated with worse cognitive performance (89). This study employed a standardized test to measure cognitive performance, which does not allow us to dissociate the impact of tau on WM per se. Further research is needed to understand whether glymphatic clearance is truly involved with day-to-day sleep-dependent WM improvements in the healthy brain, or whether other mechanisms may also be involved, including SO-mediated restoration of synaptic homeostasis (90) or increasing maximal synaptic efficacy (91).

We now turn to the question of LTM, for which ample evidence supports a role of SWS specifically in consolidation of hippocampal-dependent episodic memories. Yet, evidence for a potential role of ANS activity during sleep in this process remains scarce, a gap that may in fact have explanatory value.

CNS and ANS Contributions to Long-Term Memory

Hippocampal-dependent, episodic memory refers to the conscious recollection of information specific to the time and place of acquisition (92). A growing literature supports the role of sleep in the consolidation of episodic memories and has identified a critical role for specific electrophysiological events during NREM sleep (93). Although there is much debate as to how recent experiences are represented and transformed in cortical and subcortical long-term stores (94–96), there is a consensus that the hippocampus is a fast-learning system that binds recent experiences into representations across different cortical structures during encoding (93). During consolidation, repeated reactivation stabilizes and strengthens memory traces, with sleep being an optimal offline period for consolidation as it facilitates the dialogue between the hippocampus and the neocortex (93). Specifically, during NREM sleep, the memory trace is reactivated by hippocampal sharp-wave ripples nested within thalamic spindles, which are in turn nested within the down-to-up transition of the SO, providing a pathway for neural communication between neocortical and hippocampal cell assemblies. Spindles have recently been recognized as playing a causal role in hippocampal-dependent memory consolidation via pharmacology (97) and targeted memory reactivation (98). Mednick et al. (97) compared zolpidem, a short-acting GABA-A agonist, with placebo and a positive control hypnotic (sodium oxybate) across a night of sleep. Compared with controls, zolpidem increased sleep spindles and enhanced hippocampal-dependent, episodic verbal memory, and the spindle boost mediated the memory improvements. Other pharmacology studies have corroborated these findings (99), implicating GABAergic modulations of the thalamocortical network as important for LTM formation.

Despite the growing list of studies demonstrating a role for ANS activity in executive function and WM, links to LTM are sparsely reported, and no studies have endorsed a role for ANS during sleep in hippocampal-dependent episodic LTM specifically. One study showed that overnight improvement in nonhippocampal-dependent procedural memory was correlated with LF-HRV and SDNN during

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sleep (100). In addition, parasympathetic activity (HF-HRV) during REM sleep strongly predicted improvement in implicit priming in a creativity task (101). Studies examining the impact of HRV during wakefulness on episodic LTM also show mixed results. One study demonstrated that people with poor vagal autonomic functioning (low resting HRV) show greater false memory errors (102). In addition, cardiac vagal tone has been shown to positively correlate with better memory for emotionally charged stimuli (103, 104), albeit no relation with memory for neutral stimuli. In contrast, several studies showed that HRV during wakefulness does not predict episodic memory performance (105–107). Taken together, the emerging picture of the role of CNS and ANS inputs for cognitive enhancement is that SWS is an optimal brain state for the stabilization of episodic, long-term, nonemotional memories, as well as for the improvement of executive function, but not necessarily via the same mechanisms.

How Do Working and Long-Term Memory Interact during Sleep?

While studies have shown that both SWS (including SWA and SOs) and vagal activity during SWS contributes to WM, and that SO–spindle-ripple complexes contribute to episodic LTM, the relation between WM and episodic LTM remains unclear. On one hand, studies have shown positive associations between WM and LTM, such that WM increases LTM recognition and WM capacity constrains LTM encoding (108). On the other hand, Hoskin et al. demonstrated that episodic memory reactivation during wake intrudes on WM maintenance (109). Specifically, participants learned word lists, and they either got tested immediately after encoding (short-term WM) or performed a distractor task during which the episodic memory was reinstated (LTM reactivation). They showed that the delay period introduced additional information that negatively influenced WM maintenance. This suggests coordinated activity patterns across a broad swath of cortical regions, including the prefrontal cortex, triggered by memory reactivation may steal resources from WM maintenance. Thus, WM and episodic memory may be supported by separate and potentially competitive neural mechanisms, namely, the LC–NE prefrontal–subcortical network and the GABAergic thalamocortical hippocampal network, respectively.

At the neuromodulatory level, along with LC–NE enhancement of WM (VNS studies), animal studies have implicated this system during and immediately following encoding novel experiences (110, 111) and in wake-dependent gene expression regulating synaptic potentiation that supports learning (112). However, while reversible inactivation of LC during the Morris water maze task demonstrated significant impairments in spatial memory encoding and WM, consolidation and retention of spatial memory were not affected (113). Together, these findings suggest that the LC–NE system may play an important role in early acquisition of new experiences and in cognitive control efficiency, but not in consolidation and retrieval of LTM.

In humans, recent findings in the tVNS literature have corroborated a selective functional role of the LC–NE system in cognitive control, but not in LTM. A meta-analysis of 19 tVNS studies (114) showed significant effects of acute tVNS on cognitive inhibitory control, particularly as task difficulty increases, but no evidence supporting the effectiveness of tVNS on LTM performance, attention, or other cognitive domains. Specifically, Mertens et al. (115) found that tVNS had no effect on either immediate or delayed word recognition memory in young and middle-aged adults. Furthermore, using pharmacology, Lozano-Soldevilla et al. (116) administered a GABAergic benzodiazepine (lorazepam) to healthy adults and reported dose-dependent decreases in WM, driven by decreased gamma and alpha power, suggesting an antagonistic relation between GABA and LC–NE prefrontal–subcortical networks.

Competition between these networks may be especially prevalent during offline sleep (117, 118). During hippocampal ripples, signatures of LTM replay and consolidation, Logothetis et al. (117) demonstrated deactivations in brainstem regions regulating the ANS. These fascinating results may mean that during sleep-dependent memory consolidation, ripple/spindle complexes may orchestrate a privileged interaction state between hippocampus and cortex by silencing the output from diencephalic, midbrain, and brainstem regions (*SI Appendix*, Fig. S3). Interestingly, the deactivation of the basal ganglia, the pontine region and the cerebellar cortex, is consistent with prior evidence of competition between episodic and procedural memory systems (119). In the reverse direction, Novitskaya et al. (118) experimentally increased NE by phasic-LC stimulation and blocked the generation of ripple-associated cortical spindles, thus interfering with spatial LTM consolidation. Moreover, Marzo et al. (120) have shown that phasic stimulation of LC in anesthetized rats transiently suppressed spindles while evoking sustained spiking in the medial prefrontal cortex that resembled NE-dependent prefrontal activity during the delay period of WM tasks. It is also well documented that NE input shifts the thalamocortical network from a synchronized state associated with SOs and spindles to a desynchronized state characterized by increased neuronal responsiveness to synaptic inputs, which is more optimal for encoding and sensory processing (121).

Thus, a bidirectional, mutual antagonism between thalamo–hippocampal–cortical and prefrontal–subcortical–autonomic systems during NREM might underlie the reported behavioral trade-off between episodic LTM and WM. To test this possibility, Chen et al. used a GABA-A agonist, zolpidem, to investigate the directionality of the interplay between the vagal and spindle systems during overnight sleep and their effect on WM improvement and episodic memory consolidation (122). Along with enhancing spindle activity and episodic LTM consolidation, zolpidem also showed vagal suppression and less WM improvement compared with placebo (*SI Appendix*, Fig. S4*A*). Vagal activity during SWS positively correlated with WM improvement (*SI Appendix*, Fig. S4*B*) but negatively correlated with LTM retention (*SI Appendix*, Fig. S4*C*). Effective connectivity estimation (123, 124) demonstrated that cortical oscillations in the spindle range showed causal suppression over vagal autonomic activity both in the zolpidem and placebo conditions, the magnitude of which was associated with a trade-off between enhanced episodic LTM at the cost of reduced WM improvement. Additionally, spindle–SO coupling was associated with

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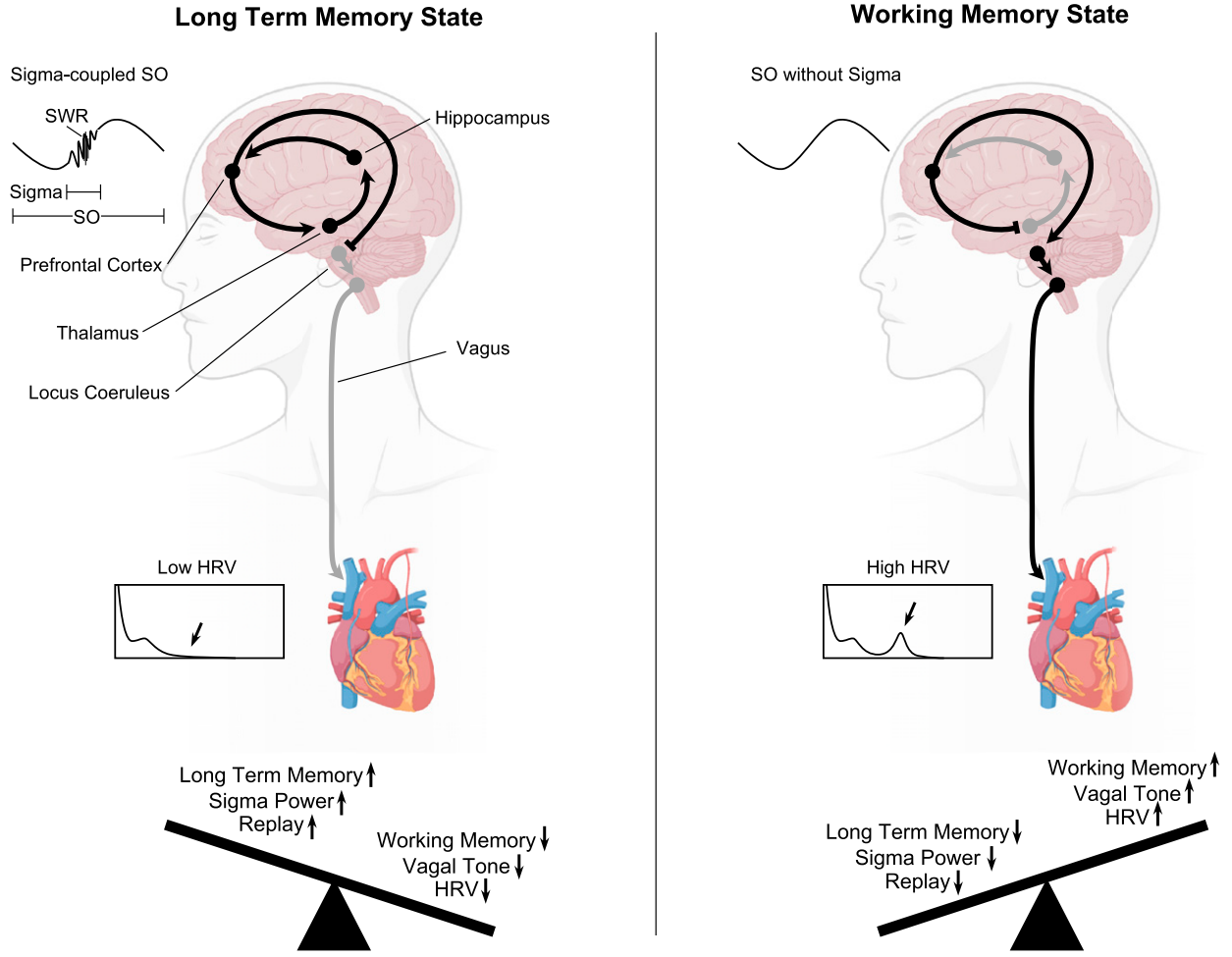
a similar behavioral trade-off, with greater spindle–SO coupling associated with less WM improvement. These findings are consistent with the notion that GABAergic hippocampal–thalamocortical communication and LC–NE frontal–subcortical–autonomic communication compete for resources during SWS sleep and that this interaction can be biased toward LTM consolidation by increasing spindles/sigma, in this case pharmacologically, and presumably other methods would have predictable effects. For example, we hypothesize that VNS would bias the interaction in the opposite direction by enhancing vagal activity and WM improvement at the expense of spindles coupled with SOs and LTM performance.

The Slow Oscillation Switch Model

The Slow Oscillation Switch Model (Fig. 2) proposes that the brain switches between separate and nonoverlapping SWS mechanisms that support LTM and WM processing. Given that SOs have been implicated in both sleep-dependent WM and LTM processes (84, 125), we hypothesize that the shared resource for which they compete may indeed be SOs. In this way, when coupled with ripple-nested spindles, SOs promote LTM and suppress other processes and when uncoupled facilitate WM by enhancing prefrontal–autonomic networks. The Slow Oscillation Switch Model posits that during NREM the brain toggles between two states, the LTM state and the WM state, via a complex interaction at the synaptic (GABA vs. NE activation) systems (thalamocortical–hippocampal vs. frontal–midbrain–autonomic) and oscillatory level (spindle-coupled SOs vs. uncoupled SOs). Although the LTM system relies on a wide range of neurotransmitter/receptor interaction, we focus on the role of GABA in this model due to its important role in sleep physiology and interaction with NE.



	Long Term memory	Working memory
Brain Regions	Thalamus, Hippocampus, Prefrontal Cortex	Prefrontal Cortex, Locus Coeruleus
Neuromodulators	GABA	Norepinephrine
Sleep Mechanisms	Coupling between Sharp Wave Ripple (SWR)-Sigma-Slow Oscillations (SO) reflects LTM systems consolidation.	Uncoupled SO during SWS reflects Prefrontal Cortex inhibitory network activation and greater autonomic vagal HRV.

Fig. 2. Slow Oscillation Switch Model (123). The model represents the proposed brain regions, primary neuromodulators, and sleep mechanisms involved in the LTM state and the WM state that toggle throughout NREM sleep. During the LTM state, consolidation occurs via spindle-coupled SOs, which leads to reduced vagal autonomic activity and less WM improvement. During the WM state, greater efficiency occurs during uncoupled SOs associated with increased vagal autonomic activity, which leads to reduced central sigma-dependent activity and less LTM consolidation.

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During the LTM state, consolidation occurs via spindle-coupled SOs, which leads to increased hippocampal–thalamo–cortical communication, increased ripple–spindle complexes, while reducing the prefrontal–autonomic inhibitory networks. During the WM state, SOs without spindles promote greater neural efficiency within the prefrontal–subcortical–autonomic network. The competitive dynamics between these networks are theoretically guided by animal studies showing antagonistic relations between brain regions that regulate autonomic activity versus memory replay (117, 118) and evidence for a periodic switch between spindles and autonomic activity (126).

We further hypothesize that spindles may act as a gating mechanism that regulates SOs resources for other processes. Given that ∼20% of SOs during NREM are spindle-coupled (127), this leaves plenty of resources to be divided among other processes. Recent work analyzing the spatiotemporal characteristics of SOs has established that they can be categorized into three types, global, frontal, and local SOs, with global SOs more often cooccurring with spindles (127). Global SOs have been shown to support long-range communication, increase spindle coupling and predict LTM consolidation (128), whereas frontal SOs have lower amplitude than global SOs, spread only within the frontal cortex, and may be promising candidates for modifying prefrontal–subcortical–autonomic networks that support WM. We hypothesize that frontal SOs may also be a carrying wave for restorative processes that facilitate prefrontal glymphatic clearance, as studies have reported that SOs are temporally coupled with and precede cerebrospinal glymphatic clearance (129, 130), but these studies have not distinguished between SO categories. Frontal SOs may regulate vagal activity, thereby promoting phasic LC neuron firing and tau clearance (35). A recent study showed that auditory stimulation not only boosts frontal SOs but also increases vagal HRV (131). Together, vagal activity might increase prefrontal efficiency and automaticity of WM functional networks by glymphatic clearance that preferably occurs during frontal SOs. These speculations are experimentally testable, and more research is needed to further elucidate sleep's complex, and potentially competitive, dynamics that support a wide range of cognitive domains.

Concluding Remarks and Future Directions

WM is the ability to hold a small amount of information active and relevant for a short amount of time, whereas episodic memory is a seemingly unlimited bank of autobiographical experiences, each of which can be explicitly evoked. Sleep, specifically brain activity during SWS, has been shown to influence both types of memory processes. Additionally, vagal activity measured by HF-HRV is associated with WM, while studies investigating the effect of ANS on episodic memory yield inconsistent results. The mechanism underlying how CNS and ANS activity during sleep coordinate to facilitate both types of cognitive processes is unknown. To bridge this gap, we present the Slow Oscillation Switch Model, which states that sleep is a competitive arena in which episodic LTM and WM vie for limited resources. Although this model is thought to occur naturally, the inner workings of the system are revealed experimentally in studies that amplify one side of the trade-off (e.g., pharmacologically increasing spindles or ripple-triggered stimulations of LC) with predictable reductions in vagal activity and postsleep WM performance or ripple/spindle coupling and LTM.

If sleep acts like a switch that toggles between the LC–NE prefrontal–subcortical autonomic processes and the GABAergic thalamocortical–hippocampal replay, one question is what determines the priority of the switch mechanism. We consider two possibilities—a natural periodic switch versus an experience-dependent bias. Lecci et al. (126) demonstrated a periodic alternating pattern between spindle bursts and heart rate accelerations, occurring every 50 s, supporting a possibility that the Slow Oscillation Switch mechanisms alternate periodically under tonic conditions. Alternatively, learning, emotional experiences, novelty, or cognitive load might determine prioritization. Consistent with this idea, more demanding memory tasks show a greater number of spindles during subsequent sleep (132). Similarly, intensive WM training can increase frontal SOs and vagal activity to a higher degree, compared to less-intense WM training (22, 84). Futures studies investigating how our brain and body coordinate to control this switch would allow further understanding of the competitive dynamics between different memory domains.

WM has traditionally been considered an unmodifiable trait, yet WM training studies have demonstrated that executive function in general and WM specifically does improve (20), and recent studies show that sleep supports this improvement (78, 82). The underlying mechanisms of this benefit, however, are unclear. Furthermore, we know little about how prefrontal–subcortical autonomic networks might coordinate SOs and vagal activity to facilitate WM. One study suggested an association between cognitive control, vagal activity, and automaticity in the prefrontal–subcortical autonomic networks. Lin et al. showed that cognitive training decreased functional connectivity in the bilateral striatum–prefrontal networks while increasing vagal activity, thereby facilitating performance in trained and untrained tasks, with fewer resources needed for successful cognitive inhibitory control (22). However, how such dynamics are modulated during sleep or SOs remains unexplored. Future neural imaging studies with simultaneous EEG–fMRI are crucial to allow understanding of the neural mechanisms underlying WM plasticity during specific sleep events.

Even though significant progress has been made over the past decade, there is still much to understand about the role of sleep in different cognitive domains. Here, we present a scenario in which episodic LTM and WM are supported by separate circuitry that vie for limited resources during sleep. Importantly, we highlight the potential that SOs could be further divided into subcategories implicated in different functions, as electrophysiological events that share the same frequency may have separate functions, a possibility recently explored by Ngo and colleagues, showing a functional dissociation between delta and SOs, with delta waves facilitating forgetting whereas SOs are more likely to couple with spindles and facilitating episodic LTM consolidation (133, 134). We propose that identifying autonomic-central

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biomarkers during sleep for different cognitive processes and understanding their competitive dynamics may facilitate novel insights to memory models and provide new targets to combat neurodegenerative disease.

Data, Materials, and Software Availability. There are no data underlying this work.

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1. M. A. Hagenaars, M. Oitzl, K. Roelofs, Updating freeze: Aligning animal and human research. *Neurosci. Biobehav. Rev.* **47**, 165–176 (2014).
2. K. Miki, M. Yoshimoto, Role of differential changes in sympathetic nerve activity in the preparatory adjustments of cardiovascular functions during freezing behaviour in rats. *Exp. Physiol.* **95**, 56–60 (2010).
3. S. E. Taylor *et al.*, Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight. *Psychol. Rev.* **107**, 411–429 (2000).
4. L. N. Whitehurst, A. Subramoniam, A. Krystal, A. A. Prather, Links between the brain and body during sleep: Implications for memory processing. *Trends Neurosci.* **45**, 212–223 (2022).
5. S. Breit, A. Kupferberg, G. Rogler, G. Hasler, Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. *Front. Psychiatry* **9**, 44 (2018).
6. M. Kalia, J. M. Sullivan, Brainstem projections of sensory and motor components of the vagus nerve in the rat. *J. Comp. Neurol.* **211**, 248–265 (1982).
7. K. K. Sumal, W. W. Blessing, T. H. Joh, D. J. Reis, V. M. Pickel, Synaptic interaction of vagal afferents and catecholaminergic neurons in the rat nucleus tractus solitarius. *Brain Res.* **277**, 31–40 (1983).
8. F. Shaffer, R. McCraty, C. L. Zerr, A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Front. Psychol.* **5**, 1040 (2014).
9. J. F. Thayer, R. D. Lane, Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. *Neurosci. Biobehav. Rev.* **33**, 81–88 (2009).
10. R. E. Kleiger, P. K. Stein, J. T. Bigger, Jr, Heart rate variability: Measurement and clinical utility. *Ann. Noninvasive Electrocardiol.* **10**, 88–101 (2005).
11. S. Laborde, E. Mosley, J. F. Thayer, Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. *Front. Psychol.* **8**, 213 (2017).
12. M. Malik, Heart rate variability. *Ann. Noninvasive Electrocardiol.* **1**, 151–181 (1996).
13. V. Menon, M. D'Esposito, The role of PFC networks in cognitive control and executive function. *Neuropsychopharmacology* **47**, 90–103 (2021).
14. A. Baddeley, Working memory. *Science* **255**, 556–559 (1992).
15. T. S. Braver, J. R. Gray, G. C. Burgess, "Explaining the many varieties of working memory variation: Dual mechanisms of cognitive control" in *Variation in Working Memory*, A. Conway, C. Jarrold, M. Kane, A. Miyake, J. Towse, Eds. (Oxford University Press, 2007), pp. 76–106.
16. J. F. Brosschot, B. Verkuil, J. F. Thayer, Generalized unsafety theory of stress: Unsafe environments and conditions, and the default stress response. *Int. J. Environ. Res. Public Health* **15**, 464 (2018).
17. P. Lehrer *et al.*, Heart rate variability biofeedback improves emotional and physical health and performance: A systematic review and meta analysis. *Appl. Psychophysiol. Biofeedback* **45**, 109–129 (2020).
18. M. Mather, J. Thayer, How heart rate variability affects emotion regulation brain networks. *Curr. Opin. Behav. Sci.* **19**, 98–104 (2018).
19. D. P. Williams *et al.*, Resting heart rate variability predicts self-reported difficulties in emotion regulation: A focus on different facets of emotion regulation. *Front. Psychol.* **6**, 261 (2015).
20. M. Melby-Lervåg, C. Hulme, Is working memory training effective? A meta-analytic review. *Dev. Psychol.* **49**, 270–291 (2013).
21. S. J. Brooks, R. Mackenzie-Phelan, J. Tully, H. B. Schiöth, Review of the neural processes of working memory training: Controlling the impulse to throw the baby out with the bathwater. *Front. Psychiatry* **11**, 512761 (2020).
22. F. Lin, K. L. Heffner, P. Ren, D. Tadin, A role of the parasympathetic nervous system in cognitive training. *Curr. Alzheimer Res.* **14**, 784–789 (2017).
23. J. F. Thayer, R. D. Lane, A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* **61**, 201–216 (2000).
24. J. F. Thayer, F. Åhs, M. Fredrikson, J. J. Sollers 3rd, T. D. Wager, A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neurosci. Biobehav. Rev.* **36**, 747–756 (2012).
25. A. L. Hansen, B. H. Johnsen, J. F. Thayer, Vagal influence on working memory and attention. *Int. J. Psychophysiol.* **48**, 263–274 (2003).
26. E. Mosley, S. Laborde, E. Kavanagh, Coping related variables, cardiac vagal activity and working memory performance under pressure. *Acta Psychol. (Amst.)* **191**, 179–189 (2018).
27. A. L. Hansen, B. H. Johnsen, J. J. Sollers 3rd, K. Stenvik, J. F. Thayer, Heart rate variability and its relation to prefrontal cognitive function: The effects of training and detraining. *Eur. J. Appl. Physiol.* **93**, 263–272 (2004).
28. L. Xiu, R. Zhou, Y. Jiang, Working memory training improves emotion regulation ability: Evidence from HRV. *Physiol. Behav.* **155**, 25–29 (2016).
29. C. K. McIntyre, J. L. McGaugh, C. L. Williams, Interacting brain systems modulate memory consolidation. *Neurosci. Biobehav. Rev.* **36**, 1750–1762 (2012).
30. T. Miyashita, C. L. Williams, Epinephrine administration increases neural impulses propagated along the vagus nerve: Role of peripheral β-adrenergic receptors. *Neurobiol. Learn. Mem.* **85**, 116–124 (2006).
31. J. A. Ross, E. J. Van Bockstaele, The locus coeruleus-norepinephrine system in stress and arousal: Unraveling historical, current, and future perspectives. *Front. Psychiatry* **11**, 601519–601519 (2021).
32. G. Aston-Jones, J. D. Cohen, An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annu. Rev. Neurosci.* **28**, 403–450 (2005).
33. K. Janitzky, Impaired phasic discharge of locus coeruleus neurons based on persistent high tonic discharge-A new hypothesis with potential implications for neurodegenerative diseases. *Front. Neurol.* **11**, 371 (2020).
34. S. Bouret, S. J. Sara, Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci.* **28**, 574–582 (2005).
35. M. Mather, C. W. Harley, The locus coeruleus: Essential for maintaining cognitive function and the aging brain. *Trends Cogn. Sci.* **20**, 214–226 (2016).
36. T. Omoluabi *et al.*, Novelty-like activation of locus coeruleus protects against deleterious human pretangle tau effects while stress-inducing activation worsens its effects. *Alzheimers Dement. (N. Y.)* **7**, e12231 (2021).
37. A. F. Arnsten, P. S. Goldman-Rakic, Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science* **230**, 1273–1276 (1985).
38. B. P. Ramos, A. F. T. Arnsten, Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. *Pharmacol. Ther.* **113**, 523–536 (2007).
39. S. R. Chamberlain *et al.*, Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol. Psychiatry* **65**, 550–555 (2009).
40. D. M. Eagle, A. Bari, T. W. Robbins, The neuropsychopharmacology of action inhibition: Cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology (Berl.)* **199**, 439–456 (2008).
41. A. F. T. Arnsten, T. A. Contant, Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. *Psychopharmacology (Berl.)* **108**, 159–169 (1992).
42. J. Sirviö, P. Riekkinen, Jr, I. Vajanto, E. Koivisto, P. J. Riekkinen, The effects of guanfacine, α-2 agonist, on the performance of young and aged rats in spatial navigation task. *Behav. Neural Biol.* **56**, 101–107 (1991).
43. J. A. Giovannitti, Jr, S. M. Thoms, J. J. Crawford, Alpha-2 adrenergic receptor agonists: A review of current clinical applications. *Anesth. Prog.* **62**, 31–39 (2015).
44. C.-L. Ma, X. Sun, F. Luo, B.-M. Li, Prefrontal cortical α2A-adrenoceptors and a possible primate model of attention deficit and hyperactivity disorder. *Neurosci. Bull.* **31**, 227–234 (2015).
45. M. Wang *et al.*, Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* **129**, 397–410 (2007).
46. C. W. Berridge, R. C. Spencer, Differential cognitive actions of norepinephrine a2 and a1 receptor signaling in the prefrontal cortex. *Brain Res.* **1641**, 189–196 (2016).
47. D. L. Hassert, T. Miyashita, C. L. Williams, The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. *Behav. Neurosci.* **118**, 79–88 (2004).
48. D. R. Hulsey *et al.*, Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. *Exp. Neurol.* **289**, 21–30 (2017).
49. R. Raedt *et al.*, Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. *J. Neurochem.* **117**, 461–469 (2011).
50. L. Sun *et al.*, Vagus nerve stimulation improves working memory performance. *J. Clin. Exp. Neuropsychol.* **39**, 954–964 (2017).
51. M. Pihlaja, L. Failla, J. Peräkylä, K. M. Hartikainen, Reduced frontal nogo-N2 with uncompromised response inhibition during transcutaneous vagus nerve stimulation-more efficient cognitive control? *Front. Hum. Neurosci.* **14**, 561780 (2020).
52. M. Keute *et al.*, Effects of transcutaneous vagus nerve stimulation (tVNS) on conflict-related behavioral performance and frontal midline theta activity. *J. Cogn. Enhanc.* **4**, 121–130 (2020).
53. C. Iber, S. Ancoli-Israel, A. Chesson, S. Quan, *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specfications* (American Academy of Sleep Medicine, 2007).
54. C. B. Saper, T. C. Chou, T. E. Scammell, The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends Neurosci.* **24**, 726–731 (2001).
55. O. Eschenko, S. J. Sara, Learning-dependent, transient increase of activity in noradrenergic neurons of locus coeruleus during slow wave sleep in the rat: Brain stem-cortex interplay for memory consolidation? *Cereb. Cortex* **18**, 2596–2603 (2008).
56. T. T. Dang-Vu *et al.*, Spontaneous neural activity during human slow wave sleep. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 15160–15165 (2008).
57. F. Marrosu *et al.*, Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Res.* **671**, 329–332 (1995).
58. W. Plihal, J. Born, Effects of early and late nocturnal sleep on declarative and procedural memory. *J. Cogn. Neurosci.* **9**, 534–547 (1997).
59. P. Bušek, J. Vanková, J. Opavský, J. Salinger, S. Nevsímalová, Spectral analysis of the heart rate variability in sleep. *Physiol. Res.* **54**, 369–376 (2005).
60. E. Tobaldini *et al.*, Heart rate variability in normal and pathological sleep. *Front. Physiol.* **4**, 294 (2013).
61. J. Trinder, J. Waloszek, M. J. Woods, A. S. Jordan, Sleep and cardiovascular regulation. *Pflugers Arch.* **463**, 161–168 (2012).
62. R. C. Brindle *et al.*, Cardiovascular stress reactivity and carotid intima-media thickness: The buffering role of slow-wave sleep. *Psychosom. Med.* **80**, 301–306 (2018).
63. L. N. Whitehurst, M. Naji, S. C. Mednick, Comparing the cardiac autonomic activity profile of daytime naps and nighttime sleep. *Neurobiol. Sleep Circadian Rhythms* **5**, 52–57 (2018).
64. P.-C. Chen, N. Sattari, L. N. Whitehurst, S. C. Mednick, Age-related losses in cardiac autonomic activity during a daytime nap. *Psychophysiology* **58**, e13701 (2021).
65. M. Ako *et al.*, Correlation between electroencephalography and heart rate variability during sleep. *Psychiatry Clin. Neurosci.* **57**, 59–65 (2003).
66. G. Brandenberger, J. Ehrhart, F. Piquard, C. Simon, Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep. *Clin. Neurophysiol.* **112**, 992–996 (2001).
67. T. B. J. Kuo, C. C. H. Yang, Scatterplot analysis of EEG slow-wave magnitude and heart rate variability: An integrative exploration of cerebral cortical and autonomic functions. *Sleep* **27**, 648–656 (2004).
68. S. D. Rothenberger *et al.*, Time-varying correlations between delta EEG power and heart rate variability in midlife women: The SWAN Sleep Study. *Psychophysiology* **52**, 572–584 (2015).

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69. R. J. Thomas *et al.*, Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram: Possible implications for assessing the effectiveness of sleep. *Sleep Med.* **15**, 125–131 (2014).
70. C. C. H. Yang, C.-W. Lai, H. Y. Lai, T. B. J. Kuo, Relationship between electroencephalogram slow-wave magnitude and heart rate variability during sleep in humans. *Neurosci. Lett.* **329**, 213–216 (2002).
71. Z. Shinar, S. Akselrod, Y. Dagan, A. Baharav, Autonomic changes during wake-sleep transition: A heart rate variability based approach. *Auton. Neurosci.* **130**, 17–27 (2006).
72. J. Trinder *et al.*, Autonomic activity during human sleep as a function of time and sleep stage. *J. Sleep Res.* **10**, 253–264 (2001).
73. M. Naji, G. P. Krishnan, E. A. McDevitt, M. Bazhenov, S. C. Mednick, Coupling of autonomic and central events during sleep benefits declarative memory consolidation. *Neurobiol. Learn. Mem.* **157**, 139–150 (2019a).
74. C. Diep, S. Ftouni, S. P. A. Drummond, G. Garcia-Molina, C. Anderson, Heart rate variability increases following automated acoustic slow wave sleep enhancement. *J. Sleep Res.*, 10.1111/jsr.13545 (2022).
75. J. Lechinger, D. P. J. Heib, W. Gruber, M. Schabus, W. Klimesch, Heartbeat-related EEG amplitude and phase modulations from wakefulness to deep sleep: Interactions with sleep spindles and slow oscillations. *Psychophysiology* **52**, 1441–1450 (2015).
76. P. C. Chen, L. N. Whitehurst, M. Naji, S. C. Mednick, Autonomic/central coupling benefits working memory in healthy young adults. *Neurobiol. Learn. Mem.* **173**, 107267 (2020b).
77. I. Rembado *et al.*, Cortical responses to vagus nerve stimulation are modulated by brain state in nonhuman primates. *Cereb. Cortex* **31**, 5289–5307 (2021).
78. P.-C. Chen, L. N. Whitehurst, M. Naji, S. C. Mednick, Autonomic activity during a daytime nap facilitates working memory improvement. *J. Cogn. Neurosci.* **32**, 1963–1974 (2020a).
79. K. Kuriyama, K. Mishima, H. Suzuki, S. Aritake, M. Uchiyama, Sleep accelerates the improvement in working memory performance. *J. Neurosci.* **28**, 10145–10150 (2008).
80. E. Y. Y. Lau, M. L. Wong, K. N. T. Lau, F. W. Y. Hui, C. H. Tseng, Rapid-eye-movement-sleep (REM) associated enhancement of working memory performance after a daytime nap. *PLoS One* **10**, e0125752 (2015).
81. K. J. MacDonald, H. A. Lockhart, A. C. Storace, S. M. Emrich, K. A. Cote, A daytime nap enhances visual working memory performance and alters event-related delay activity. *Cogn. Affect. Behav. Neurosci.* **18**, 1105–1120 (2018).
82. K. Zinke, H. Noack, J. Born, Sleep augments training-induced improvement in working memory in children and adults. *Neurobiol. Learn. Mem.* **147**, 46–53 (2018).
83. F. Ferrarelli *et al.*, An increase in sleep slow waves predicts better working memory performance in healthy individuals. *Neuroimage* **191**, 1–9 (2019).
84. F. Pugin *et al.*, Local increase of sleep slow wave activity after three weeks of working memory training in children and adolescents. *Sleep (Basel)* **38**, 607–614 (2015).
85. N. Sattari, L. N. Whitehurst, M. Ahmadi, S. C. Mednick, Does working memory improvement benefit from sleep in older adults? *Neurobiol. Sleep Circadian Rhythms* **6**, 53–61 (2019).
86. C. Diep *et al.*, Acoustic slow wave sleep enhancement via a novel, automated device improves executive function in middle-aged men. *Sleep,* **43**, zsz197 (2020).
87. O. Eschenko, C. Magri, S. Panzeri, S. J. Sara, Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb. Cortex* **22**, 426–435 (2012).
88. I. Timofeev, S. Chauvette, Sleep slow oscillation and plasticity. *Curr. Opin. Neurobiol.* **44**, 116–126 (2017).
89. C. Groot *et al.*, Mesial temporal tau is related to worse cognitive performance and greater neocortical tau load in amyloid-β-negative cognitively normal individuals. *Neurobiol. Aging* **97**, 41–48 (2021).
90. G. Tononi, C. Cirelli, Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* **81**, 12–34 (2014).
91. S. Chauvette, J. Seigneur, I. Timofeev, Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. *Neuron* **75**, 1105–1113 (2012).
92. M. Moscovitch, R. Cabeza, G. Winocur, L. Nadel, Episodic memory and beyond: The hippocampus and neocortex in transformation. *Annu. Rev. Psychol.* **67**, 105–134 (2016).
93. B. Rasch, J. Born, About sleep's role in memory. *Physiol. Rev.* **93**, 681–766 (2013).
94. L. Nadel, M. Moscovitch, Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* **7**, 217–227 (1997).
95. A. P. Yonelinas, C. Ranganath, A. D. Ekstrom, B. J. Wiltgen, A contextual binding theory of episodic memory: Systems consolidation reconsidered. *Nat. Rev. Neurosci.* **20**, 364–375 (2019).
96. A. D. Ekstrom, A. P. Yonelinas, Precision, binding, and the hippocampus: Precisely what are we talking about? *Neuropsychologia* **138**, 107341 (2020).
97. S. C. Mednick *et al.*, The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. *J. Neurosci.* **33**, 4494–4504 (2013).
98. S. A. Cairney, A. Á. V. Guttesen, N. El Marj, B. P. Staresina, Memory consolidation is linked to spindle-mediated information processing during sleep. *Curr. Biol.* **28**, 948–954.e4 (2018).
99. J. Zhang *et al.*, The effect of zolpidem on memory consolidation over a night of sleep. *Sleep* **43**, zsaa084 (2020).
100. F. J. van Schalkwijk *et al.*, Procedural memory consolidation is associated with heart rate variability and sleep spindles. *J. Sleep Res.* **29**, e12910 (2020).
101. L. N. Whitehurst, N. Cellini, E. A. McDevitt, K. A. Duggan, S. C. Mednick, Autonomic activity during sleep predicts memory consolidation in humans. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 7272–7277 (2016).
102. N. Feeling *et al.*, Resting state heart rate variability and false memories. *Int. J. Psychophysiol.* **159**, 17–22 (2021).
103. K. Mattarozzi, V. Colonnello, J. F. Thayer, C. Ottaviani, Trusting your heart: Long-term memory for bad and good people is influenced by resting vagal tone. *Conscious. Cogn.* **75**, 102810 (2019).
104. J. Wendt, M. Weymar, M. Junge, A. O. Hamm, A. Lischke, Heartfelt memories: Cardiac vagal tone correlates with increased memory for untrustworthy faces. *Emotion* **19**, 178–182 (2019).
105. D. Aguillard *et al.*, Investigating fractal dimension, heart rate variability, and memory during different image sequencing regimes in young adults. *Chaos.* **30**, 113116 (2020).
106. L. E. Paige, J. M. Wolf, A. Gutchess, Evaluating heart rate variability as a predictor of the influence of lying on memory. *Memory* **30**, 785–795 (2020).
107. A. Zeki Al Hazzouri, T. Elfassy, M. R. Carnethon, D. M. Lloyd-Jones, K. Yaffe, Heart rate variability and cognitive function in middle-age adults: The coronary artery risk development in young adults. *Am. J. Hypertens.* **31**, 27–34 (2017).
108. K. Cotton, T. J. Ricker, Working memory consolidation improves long-term memory recognition. *J. Exp. Psychol.* **47**, 208 (2021).
109. A. N. Hoskin, A. M. Bornstein, K. A. Norman, J. D. Cohen, Refresh my memory: Episodic memory reinstatements intrude on working memory maintenance. *Cogn. Affect. Behav. Neurosci.* **19**, 338–354 (2019).
110. K. Kobayashi, Y. Yasoshima, The central noradrenaline system and memory consolidation. *Neuroscientist* **7**, 371–376 (2001).
111. J. L. McGaugh, Making lasting memories: Remembering the significant. *Proc. Natl. Acad. Sci. U.S.A.* **110** (suppl. 2), 10402–10407 (2013).
112. K. Tully, V. Y. Bolshakov, Emotional enhancement of memory: How norepinephrine enables synaptic plasticity. *Mol. Brain* **3**, 15 (2010).
113. B. Khakpour-Taleghani, R. Lashgari, F. Motamedi, N. Naghdi, Effect of reversible inactivation of locus ceruleus on spatial reference and working memory. *Neuroscience* **158**, 1284–1291 (2009).
114. C. Ridgewell *et al.*, The effects of transcutaneous auricular vagal nerve stimulation on cognition in healthy individuals: A meta-analysis. *Neuropsychology* **35**, 352–365 (2021).
115. A. Mertens *et al.*, Transcutaneous vagus nerve stimulation does not affect verbal memory performance in healthy volunteers. *Front. Psychol.* **11**, 551 (2020).
116. D. Lozano-Soldevilla, N. ter Huurne, R. Cools, O. Jensen, GABAergic modulation of visual gamma and alpha oscillations and its consequences for working memory performance. *Curr. Biol.* **24**, 2878–2887 (2014).
117. N. K. Logothetis *et al.*, Hippocampal-cortical interaction during periods of subcortical silence. *Nature* **491**, 547–553 (2012).
118. Y. Novitskaya, S. J. Sara, N. K. Logothetis, O. Eschenko, Ripple-triggered stimulation of the locus coeruleus during post-learning sleep disrupts ripple/spindle coupling and impairs memory consolidation. *Learn. Mem.* **23**, 238–248 (2016).
119. R. A. Poldrack, P. Rodriguez, How do memory systems interact? Evidence from human classification learning. *Neurobiol. Learn. Mem.* **82**, 324–332 (2004).
120. A. Marzo, N. K. Totah, R. M. Neves, N. K. Logothetis, O. Eschenko, Unilateral electrical stimulation of rat locus coeruleus elicits bilateral response of norepinephrine neurons and sustained activation of medial prefrontal cortex. *J. Neurophysiol.* **111**, 2570–2588 (2014).
121. D. A. McCormick, Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends Neurosci.* **12**, 215–221 (1989).
122. P.-C. Chen, H. Niknazar, W. A. Alaynick, L. N. Whitehurst, S. C. Mednick, Competitive dynamics underlie cognitive improvements during sleep. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2109339118 (2021).
123. K. J. Friston, Functional and effective connectivity in neuroimaging: A synthesis. *Hum. Brain Mapp.* **2**, 56–78 (1994).
124. K. J. Friston, Functional and effective connectivity: A review. *Brain Connect.* **1**, 13–36 (2011).
125. C. V. Latchoumane, H.-V. V. Ngo, J. Born, H.-S. Shin, Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. *Neuron* **95**, 424–435.e6 (2017).
126. S. Lecci *et al.*, Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. *Sci. Adv.* **3**, e1602026 (2017).
127. P. Malerba, L. N. Whitehurst, S. B. Simons, & S. C. Mednick, Spatio-temporal structure of sleep slow oscillations on the electrode manifold and its relation to spindles. *Sleep* **42**, zsy197 (2018).
128. H. Niknazar, P. Malerba, S. C. Mednick, Slow oscillations provide the spatio-temporal framework for long-range neural communication during sleep. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122515119 (2022).
129. N. E. Fultz *et al.*, Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* **366**, 628–631 (2019).
130. L. M. Hablitz *et al.*, Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Sci. Adv.*, **5**, eaav5447 (2019).
131. S. Huwiler *et al.*, Effects of auditory sleep modulation approaches on brain oscillatory and cardiovascular dynamics. BioRxiv [Preprint] (2022). https://www.biorxiv.org/content/10.1101/2022.02.16.480303v1 (Accessed 23 September 2022).
132. S. Gais, M. Mölle, K. Helms, J. Born, Learning-dependent increases in sleep spindle density. *J. Neurosci.* **22**, 6830–6834 (2002).
133. J. Kim, T. Gulati, K. Ganguly, Competing roles of slow oscillations and delta waves in memory consolidation versus forgetting. *Cell* **179**, 514–526.e13 (2019).
134. H. V. V. Ngo, J. Born, Sleep and the balance between memory and forgetting. *Cell* **179**, 289–291 (2019).

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