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New directions in sleep and memory research: the role of autonomic activity

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Over the last 100 years there has been a proliferation of research into the mechanisms of sleep that support cognition. Majority of these studies point to electroencephalographic features during sleep that are linked to plasticity and support valuable cognitive skills, like long-term memory. Importantly, sleep is both a central and an autonomic phenomenon with dynamic shifts occurring in both the brain and the body at sleep onset and throughout a sleep period. Prior work has demonstrated that autonomic inputs during wake modulate cognition. In this Review, we outline a new research direction that links brain-body interactions during sleep to cognitive ability and enhancement and posit that autonomic-central interactions are likely a distinct predictor of sleep-dependent plasticity.

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Introduction

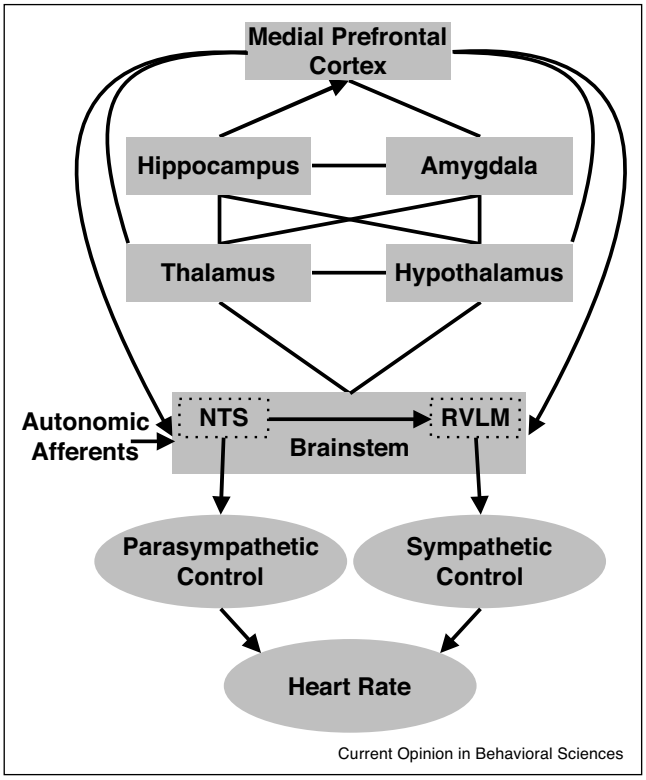
One of the primary functions of sleep is to support cognition; however, the precise mechanisms are not fully understood. The majority of studies examining this question have focused on brain activity of the central nervous system, identifying specific, electrophysiological signatures of non-rapid eye movement (NREM) sleep, for example, sleep spindles (12−15 Hz) and slow oscillations (SOs, 0.5−1 Hz), that are linked to sleep-related plasticity (see Ref. [1] for a review). Given that the transition from wake to sleep induces dramatic changes to both the central and autonomic nervous systems, a newer approach investigates whether autonomic features may also contribute to cognition. Building on previous examinations of the role of autonomic activity during wake for cognition [2,72,3], findings from this nascent field include that distinct autonomic profiles at each stage of sleep appear to influence long-term memory [5•] and that the coupling of central and autonomic activity during sleep also contributes to cognition [6•]. This emergent line of research examining brain-body communication suggests that autonomic activity may be linked with sleep brain activity, and that this interaction is likely a distinct predictor of plasticity, cognitive ability and enhancement. In this brief opinion, we summarize the current state of the field and suggest experimental future directions.

ANS activity during wake mediates cognitive function

The autonomic nervous system is typically known for its role in regulating involuntary bodily functions, namely breathing, heart rate and digestion, and as such, is less recognized for its role in influencing cognitive processing. Yet, seminal work in rodents by James McGaugh and others elucidated the role of ANS activity during wake on different stages of memory formation [7]. These studies demonstrated that altering the peripheral hormone milieu can have a functional impact on acquisition of new information and consolidation of long-term memories [8–11]. Furthermore, vagalectomy studies established that the main artery of influence of ANS activity on cognitive processes is the vagus nerve [12–15], which communicates peripheral information to the brainstem. From the brainstem, vagal afferents project to higher-order, cognitive areas such as hippocampus, amygdala, and prefrontal cortex (PFC). Additionally, descending projections from the PFC to the brainstem and hypothalamic structures allow for bi-directional communication between the central nervous system and the autonomic nervous system through the vagus nerve [7,2] (Figure 1). As such, prominent models of ANS and cognition have focused on modulations of vagal cardiac activity during waking states to understand it's relation to cognition.

In humans, a well-established method to non-invasively examine autonomic activity is heart rate variability (HRV), which measures systematic variation in the beat-to-beat interval [16]. Two main oscillatory components are typically extracted from a spectral analysis of the cardiac signal [17]; one in the low frequency range

Figure 1



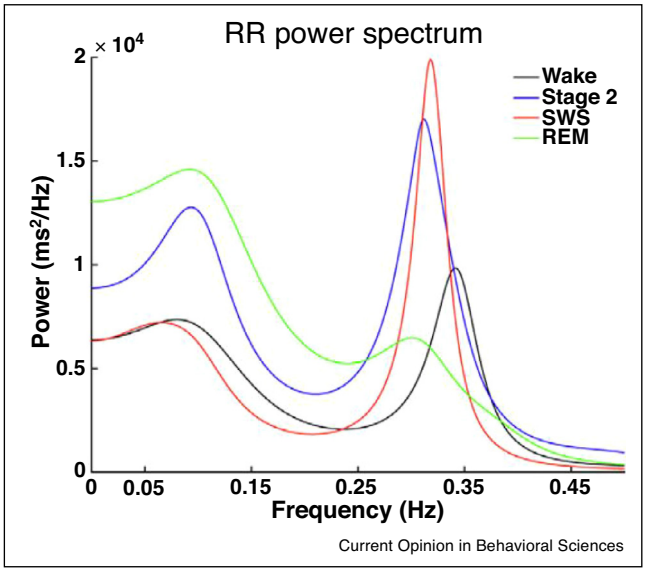
Dialogue between cardiac autonomic centers and higher-order cognition in the central nervous system. Bidirectional innervations between peripheral organs, including the heart, and the central nervous system, beginning at the brainstem, tie memory-related areas in the brain to heart rate and heart rate variability. In this figure, lines denote bidirectional connections and arrows denote mono-directional projections. Note that for clarity, not all areas involved are reported in the current figure. Reprinted from Ref. [5].

(i.e. LF: 0/04–0.15 Hz), partially related to blood pressure and vasomotor tone, and the other in the high frequency range (i.e. HF: 0.15–0.40 Hz), indicative of vagally mediated respiration [18]. HRV during wake has been shown to predict performance on a wide range of cognitive tasks that rely on PFC activity [2]. For example, compared to individuals with low resting HF HRV during wake, high HF HRV individuals perform better on both working memory (n-back task: [19]; operation-span task: [20•]) and cognitive inhibition (i.e. Stroop task; [21]). Additionally, reducing HF HRV, via aerobic de-training, comes at significant cost to executive functioning [21]. More recently, studies have demonstrated that directly stimulating the vagus nerve can increase HF HRV [22], improve verbal memory [23,24], and accelerate extinction learning [25]. These findings align with the neurovisceral integration model which posits the bidirectional communication between the central and autonomic nervous systems, indexed with heart rate variability, is a critical predictor of adaptive cognitive success [2]. Until recently, research approaches specifically focused on the role of waking autonomic activity on PFC related tasks, which while informative, neglected the potential importance of the natural predominance and variation in vagal activity that occurs during sleep.

A brief overview of sleep

The brain and body undergo large physiological changes across wake, NREM and REM. NREM sleep comprises Stages 2 and 3 and is characterized by a gradual slowing of the electroencephalagram (EEG) signal, including increases in slow wave activity (0−1 Hz) interspersed with bursts of electrical activity in the 12−16 Hz sigma range, also known as sleep spindles. REM sleep, in contrast, is associated with faster, theta activity (4–7 Hz) and phasic bursts of rapid eye movements visible in the electrooculogram (EOG; [26]). Sleep exerts considerable influence over the two branches of the ANS (i.e. sympathetic and parasympathetic nervous systems) and vice-versa with changes in the ANS modulating sleep onset and the transition between sleep stages [27]. Figure 2 shows the power spectrum changes in the RR signal across wake and sleep stages. Sleep onset is partially triggered by a reduction in heart rate and an increase in parasympathetic, HF HRV activity. During NREM sleep, compared to wake and REM, heart rate decreases still and this is coupled with a reduction in overall cardiac activity (total HRV), with a relative dominance of parasympathetic activity (measured in normalized units HF HRV = HF/LF + HF). In REM sleep, both greater total ANS activity and higher relative parasympathetic tone is present, compared with wake and NREM sleep

Figure 2



RR power spectrum changes across wake and sleep stages. Reprinted from Ref. [4•]).

[28,29,30•,31,32•]). In the following sections, we will examine the separate and combined influence of ECG and EEG activity during sleep on cognitive function.

Sleep supports memory formation

Individual sleep stages, electrophysiological features and combinations of features have been consistently shown to play an important role in the maintenance and the formation of long-term memories. Long-term memory formation is supported by dialogue between the hippocampus and the neocortex during offline NREM sleep, with cortical slow oscillations and thalamic sleep spindles reflecting this cortical-subcortical communication [1]. As such, improvement in hippocampal-dependent memory performance is often found to correlate with the amount of slow wave and spindle activity [33–37]. Additionally, both NREM and REM sleep have been shown to benefit non-hippocampal-dependent, perceptual memories [38–40] and boost implicit associative processing [5,41]. Furthermore, emotional memory processing engages both time in REM sleep [42,43] and REM theta frequency [44], as well as NREM sleep features [45–49]. Importantly, along with these distinct EEG features, recent work has implicated peripheral autonomic features in long-term memory processing.

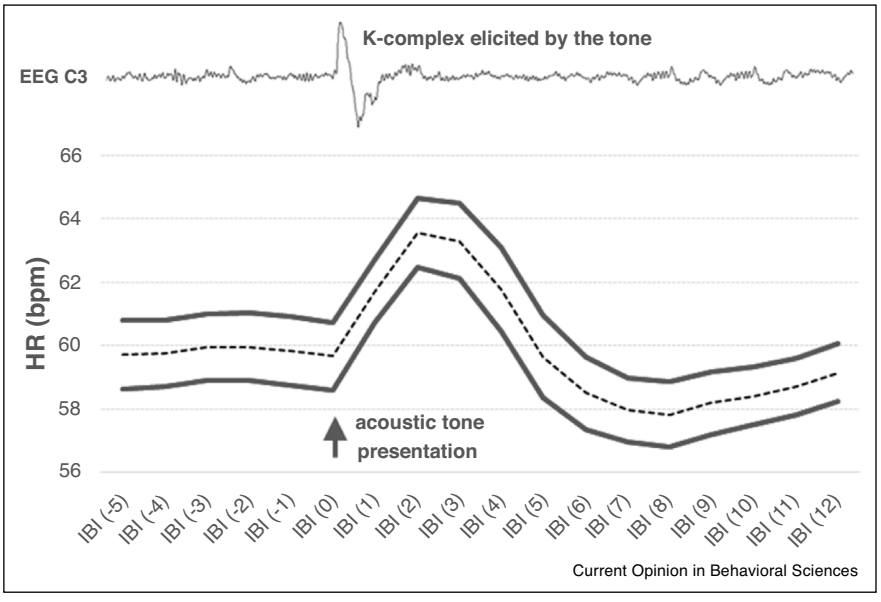
Heart rate variability during sleep enhances long-term memory

Whitehurst *et al.* [5] investigated whether parasympathetic activity during sleep facilitates improvement in long-term memory using the remote association task (RAT), in which distinct memory manipulations (implicit versus explicit) of the RAT task have been shown to rely on REM sleep [41]. In this study, we probed the relative impact of EEG and HRV variables on performance gains. We found autonomic variables during sleep (HF HRV in SWS and REM sleep) accounted for significantly more of the performance increases (73% of explained variance) than the sleep variables alone (46% of explained variance), with HF HRV during REM sleep emerging as the strongest predictor. Additionally, HF HRV during a quiet rest session was not associated with memory improvement. These findings suggest a stronger relation between ANS activity during both NREM and REM sleep and long-term memory than ANS activity during wake and traditional CNS-based sleep features.

Autonomic and Central Events (ACE) are coupled during sleep and predict explicit memory

Prior research has hinted at a possible coordination between central and autonomic activity. During wake, volitional effort correlates both with increases in hippocampal activity and heart rate [50]; and phase-locking between central hippocampal theta and autonomic R-waves has been shown in guinea pigs during wake, SWS and REM sleep [51]. During Stage 2 sleep, K-complexes are closely linked to increases and then decreases in heart rate [52]. Figure 3 shows that auditory-evoked k-complexes coincide with marked increases in heart rate. Additionally, ECG activity has been shown to modulate sleep spindle phase [53,54•], and HF HRV has been correlated with slow wave activity in the brain [53].

Figure 3



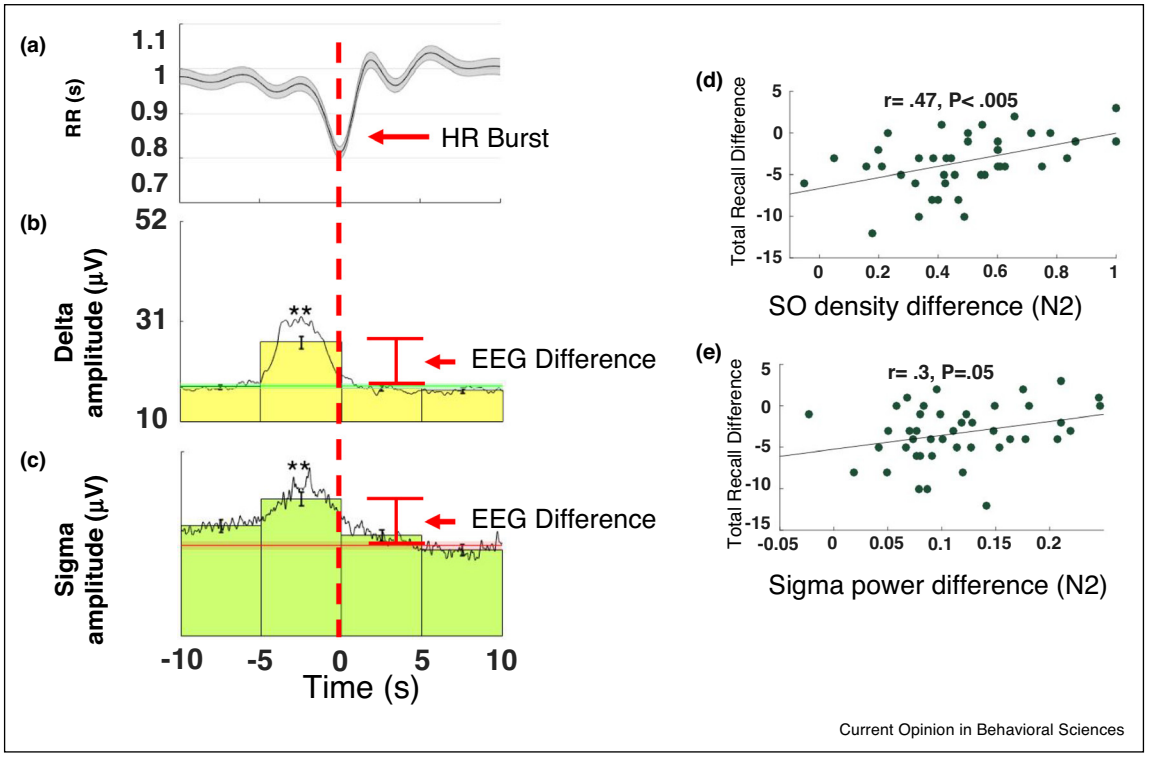
Heart and brain features are linked during sleep. Tone-triggered K-complexes are temporally coupled with a rapid increase and then decrease in heart rate activity. Reprinted from [71•].

The obvious next question is whether these examples of coordination between the ANS and CNS might contribute to memory formation. In order to examine moment-to-moment fluctuations between EEG and ECG, Naji *et al.* [4•] eschewed classic HRV analysis that averages ECG related variables in 3–5 min epochs and ignores heart rate changes/events that occur in short time scales (e.g. quick decreases in heart rate <5 s). Instead, we adopted a high temporal precision time-domain analysis approach to the cardiac signal, which allowed for the identification of bursts in heart rate (HR) that lasted 4−5 s and predominated (~1 per minute) in non-rapid-eye-movement sleep (NREM) (Figure 4a). Using the peak of these HR bursts as the event marker, we examined EEG and ECG within the five second epoch before the peak (pre-burst), and five second epoch after the peak (post-burst). In the pre-burst epoch, we discovered an increase in SWA (Figure 4b) and spindle activity (Figure 4c), as well as density of slow oscillations (0.5−1 Hz). In addition, in the post-burst epoch, there was a surge in vagal activity, assessed by HF HRV during Stage 2 sleep, which was correlated with increased SWA. We labeled these features of EEG/ECG coupling, Autonomic/Central Events (ACEs). Using a regression framework, we assessed the contribution of ACE versus non-ACE activity (EEG periods outside the ACE window) to memory improvement after a sleep period (recall improvement in face-name associations) and found that ACE events (pre-burst: SWA and sigma, post-burst: HF HRV) predicted performance improvement better than either the central events or the autonomic events alone. Correlations between performance improvement and ACE-Slow Oscillations (Figure 4d) and ACE-Spindle (Figure 4e) are shown. These findings introduce a novel example of heart/brain coupling that significantly impacts memory consolidation. Further research is needed to understand the neural dynamics supporting this autonomic-central coupling as well as its precise role in cognition.

Autonomic central coupling predicts perception

Coordination between autonomic and central events during sleep may also contribute to basic perception. Work by Park *et al.* [55] has shown that spontaneous fluctuations in neural responses during wake, measured via magnetoencephalography (MEG), can lock to heartbeats (heartbeat evoked potentials or HEP) and predict visual

Figure 4



Autonomic-Central Events (ACE) predict long-term memory performance. **(a)** Grand average of HR bursts. **(b–c)** Average delta and sigma amplitude in 5-s bins (with the grand average of amplitude overlaid). Asterisks represent significant differences between amplitudes with and without HR burst (baseline, $p < 0.001$). Error bars represent standard error of the mean. **(d–e)** Impact of ACE coupling on memory consolidation. Scatter plots for relationships between the recall improvement in the declarative memory performance and ACE-related difference scores of SO density (3D) and sigma power (3E). Performance (i.e. less forgetting) was positively correlated with increased ACE activity. Adapted from Ref. [4•].

detection. In addition, basic visual processing could be predicted by enhanced HEP responses before stimulus onset. Further, the slowing of post-decisional heart rate has been shown to correlate with the amplitude of pre-stimulus PFC activity [55]. Although HEP is not well understood, these results emphasize the significance of real-time heart-brain interactions for visual detection. In other work, coupling between an autonomic measure (spontaneous pupillary fluctuations) and off-task resting state activity (in regions associated with sympathetic activity) was found to be correlated with trait-level attention [56]. More recently, increasing temporal alignment of EEG-vigilance states and autonomic signals (HR and skin conductance) during resting state corresponded to stronger cortical inhibition [57•]. These findings suggest that adaptive autonomic shifts in response to salient environmental cues may be supported by intrinsic coordination between autonomic-central brain activities.

Building on these ideas, we investigated the impact of off-task heart-brain interactions during sleep on the speed of visual processing [6•]. For each autonomic/central event (ACE), we calculated individual differences in the delay interval between the peak of the SO and the peak of the HR burst (i.e. SO-HR timing), during a daytime nap. Next, we found that temporal processing speed, measured by the duration of a target-to-mask interval, was highly correlated with SO-HR timing (i.e. shorter SO-HR timing correlated with faster perceptual processing) during the nap. These results suggest that the timing between coupled autonomic and central events during sleep may be used to assess temporal processing speed within an individual and contribute to a growing literature on the importance of heart-brain coupling for a wide range of cognitive processes. An important question is whether this timing phenomenon is global and transversal, thus pervading all cognitive functions, or rather domain-specific and thus not mandatorily reflected in all domains. One potentially insightful research direction to address this question would be to examine age-related changes in SO-HR timing. Given the classical global slowing hypothesis of aging [58], as well as specific findings of deterioration in temporal processing in auditory [59] and visual [60] function, the correlative finding of decreased SO-HR timing in older adults would be consistent with considering this measuring as a global biomarker.

Concluding remarks and future directions

We have described how large scale neural activity and cognitive processing can be shaped by brain-body interactions. We reviewed recent studies showing that autonomic and central events are coupled during sleep and that they both distinctly and jointly predict higher-order cognitive processing. Throughout, we placed these findings in the context of a long-standing literature supporting the role of autonomic activity for cognition. We add that in considering these relationships during sleep, we can further extend the impact of the autonomic system on cognitive function and marry this literature with a rapidly growing sleep and cognition field. To this point, much research is still needed. For example, to date studies have only examined measures of parasympathetic/vagal activity during sleep and have ignored the sympathetic nervous system. This is mainly because sympathetic responses are more methodologically cumbersome to collect during sleep. Yet, importantly, previous work has demonstrated that the relationship between the sympathetic and parasympathetic system is not unidimensional but intricate and multifaceted [61], which suggests that the relative complexities between these two systems are important in explaining behavioral outcomes. As such, in future examinations, it will be important to model both vagal and sympathetic fluctuations during sleep to fully understand the influence of autonomic activity on cognitive function. Additionally, distinct subfields of cognitive science could especially benefit from considering autonomic inputs. Specifically, both autonomic activity [62] and sleep [63] have long been implicated in emotional processing; however, the role of autonomic fluctuations across sleep has yet to be considered. Future experimental investigations detailing shifts in autonomic activity during emotional experiences and across sleep stages may provide increased insight into the processing and maintenance of affective experiences. Furthermore, given the pursuit of non-invasive methods to boost SWA and subsequent memory performance, it will be interesting to explore the extent to which these methods simultaneously enhance parasympathetic activity during NREM sleep, as well as ACE coupling. So far, only one such analysis has been undertaken with positive results, whereby acoustic stimulation phase-locked to Slow Waves enhanced SWA and led to a concomitant increased parasympathetic activity (%HF HRV) [64•]. It remains to be seen whether boosting HRV and SWA with stimulation will also enhance memory improvement, over and above natural sleep. Lastly, both autonomic [65,66] and sleep dysregulation [67–69,70•] have been separately implicated in age-related and pathological cognitive decline. Yet, few practical treatment options have emerged from either area alone. Identifying autonomic-central biomarkers during sleep and using state and trait classifiers to predict cognitive trajectories may facilitate novel insights into cognitive aging and provide new targets to combat neurodegenerative disease.

Contributions

All authors contributed to the data interpretation, drafted the manuscript, provided critical revisions and approved the final version for submission.

Conflict of interest statement

Nothing declared.

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This study examined autonomic–central interactions by analyzing EEG and ECG during wake and daytime sleep. The authors identified bursts of ECG activity that lasted 4–5 s and predominated in NREM sleep, and found an increase in delta (0.5–4 Hz) and sigma (12–15 Hz) power and an elevated density of slow oscillations (0.5–1 Hz) about 5 s before peak of the heart rate burst, as well as a surge in vagal activity, assessed by high-frequency (HF) component of RR intervals, and that these Autonomic/Central Events (ACE) positively predicted post-nap improvement in a declarative memory task above and beyond non-ACE sleep activity.

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