Exercising the Sleepy-ing Brain: Exercise, Sleep, and Sleep Loss on Memory

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ROIG, M., J. CRISTINI, Z. PARWANTA, B. AYOTTE, L. RODRIGUES, B. DE LAS HERAS, J-F. NEPVEU, R. HUBER, J. CARRIER, S. STEIB, S.D. YOUNGSTEDT, and D.L. WRIGHT. Exercising the sleepy-ing brain: exercise, sleep, and sleep loss on memory. *Exerc. Sport Sci. Rev.*, Vol. 50, No. 1, pp. 38–48, 2022. *We examine the novel hypothesis that physical exercise and sleep have synergistic effects on memory. Exercise can trigger mechanisms that can create an optimal brain state during sleep to facilitate memory processing. The possibility that exercise could counteract the deleterious effects of sleep deprivation on memory by protecting neuroplasticity also is discussed.*
Key Words: physical exercise, sleep, memory, encoding, consolidation, neuroplasticity, sleep deprivation

Key Points

- Exercise and sleep may have synergistic effects on declarative and procedural memory.
- Exercise influences brain processes involved in memory processing during nonrapid eye movement sleep.
- Exercise protects memory from acute but not chronic sleep deprivation in animal studies.
- Exercise protects neuroplasticity from the effect of acute sleep deprivation in animal studies.
- Whether exercise can protect memory from the effect of sleep loss in humans is not known.

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INTRODUCTION

Physical exercise and sleep are two seemingly opposing activities, which have shown, separately, to have positive effects on different types of memory. Most research studying the effects of exercise on memory has focused on cardiovascular exercise (1). Performing exercises such as running or cycling improves our capacity to store information about facts and events (*i.e.*, declarative memory) as well as motor skills (*i.e.*, procedural memory) (1). Similarly, sleep plays an important role in consolidating the declarative and procedural information that we encode during the day, making it less susceptible to interference, and storing it as long-term memory (2). Given the different nature of physical exercise and sleep, one might assume that the enhancing effects that these two activities have on memory are irremediably mediated through different pathways. However, emerging evidence suggests that exercise and sleep can work synergistically to improve memory (3).

The mechanistic underpinnings through which physical exercise and sleep can synergize to impact memory are, however, not well understood. As distinct brain pathways can be engaged during the neural processes that dictate the fate of a memory during wakefulness and sleep, one could argue that the mechanisms by which exercise and sleep improve memory also operate independently. However, mounting evidence indicates that

physical exercise triggers a vast array of physiological processes (4) that modify key aspects of sleep, which have an important role in memory processing (5,6). Hence, it is not inconceivable that the positive effects that exercise has shown to have on different types of memory could be mediated, at least in part, by exercise-induced changes in sleep. Studying the mechanistic interplay between physical exercise and sleep could provide important information to design more effective exercise interventions aimed at maintaining or improving the memory function of sleep.

Lack of sleep reduces work productivity, increases traffic- and work-related accidents, medical errors, and the risk of cognitive impairment (7). Even short periods of sleep deprivation result in maladaptive changes in neuroplasticity, which can impair memory processing (8). Because some of the deleterious effects that sleep loss has on neuroplasticity are diametrically opposed to the positive effects of physical exercise (9–14), it is not inconceivable that, by preserving neuroplasticity, exercise could protect memories against the effects of sleep loss. However, there is still little information regarding how exercise-induced changes in neuroplasticity can impact memory processing in the sleep-deprived human brain. Given the alarming amounts of sleep insufficiency worldwide, its immense societal and economic costs (7), and the strong link between sleep insufficiency and memory deterioration (8), studying interactions between physical exercise, sleep loss, and memory is important.

This brief review examines the hypothesis that physical exercise and sleep can have synergistic effects on memory. We start by providing a basic overview of the mechanisms of sleep involved in memory processing and how exercise modifies them. We will then review emerging evidence supporting the synergistic effect that exercise and sleep can have on declarative and procedural memory. We focus mainly on acute studies using a single bout of exercise performed either before or after memory encoding because this exercise paradigm is ideally suited to study time-locked mechanistic interactions between exercise and sleep and their combined effects on memory. We also discuss potential pathways that could bridge the effects of these two activities on memory, analyzing studies that demonstrate that exercise triggers processes that influence sleep mechanisms modulating memory. Finally, we discuss whether exercise can protect memory from the deleterious effects of sleep deprivation and the potential role of neuroplasticity in mediating such a protective effect.

WHAT IS THE ROLE OF SLEEP IN THE FORMATION OF MEMORY?

Two main hypotheses are currently discussed to explain the role of sleep in memory (2). The synaptic homeostasis hypothesis postulates that a main function of sleep is to maintain global neuroplasticity by downscaling the synaptic activity that has been increased during daytime memory encoding (15). This depotentiation process, in which slow wave sleep (SWS) plays a preeminent role, allows synapses activated during encoding to recover their homeostasis, facilitating memory consolidation, and restoring the capacity of those synapses to be tagged again in future encodings (16). The active system consolidation hypothesis, in contrast, proposes that a primary function of sleep consists of strengthening the synapses that have been activated during encoding through a selective reactivation process of memory replay (17). During this SWS synchronized reactivation process, our brain transfers memory representations from the hippocampus to neocortical areas, where they are progressively strengthened and consolidated into a long-term store (18). Although not mutually exclusive, both hypotheses propose different approaches to explain the memory function of sleep (2).

To comprehend the memory function of sleep, however, it is first essential to understand its architecture. Sleep is characterized by the cyclic occurrence of several nonrapid eye movement (NREM) phases followed by rapid eye movement (REM) phases (Fig. 1A). NREM sleep can be further divided into stages 1, 2, and 3. NREM phases are predominant in early sleep, whereas REM phases are more prevalent in late sleep. These different phases and stages are characterized by electrical patterns of brain activity subserving mechanisms of synaptic plasticity that underlie memory processing (Fig. 1B) (8). Brain activity during NREM 2 sleep is characterized by short bursts of thalamocortical sigma waves called sleep spindles. In contrast, slow (delta) neocortical waves and hippocampal rapid waves superimposed with sharp wave ripples are abundant in NREM 3 sleep, also known as SWS. Both ponto-geniculo-occipital (PGO) and hippocampal theta waves are typically observed during REM sleep. Studying these signals of brain activity provides important insights to better understand the role that each stage of sleep plays in the formation of different types of memory (2) (Fig. 1C).

NREM sleep has been implicated in the consolidation of declarative memory. Performing tasks that require the encoding of this type of memory before sleep increases the activity of sleep spindles during NREM 2 sleep, and memory improvements are often correlated with increases in the activity of these short bursts of brain activity (2). Slow waves also are involved in the consolidation of declarative memory, with the activity of these brain oscillations increasing during the sleep succeeding the performance of declarative memory tasks (2). The causal role of slow waves has been confirmed in elegant experiments showing that, unbeknownst to the sleeping participant, i) odor- or tone-induced memory reactivations during SWS can improve declarative memory (19) and ii) manipulating slow wave activity with acoustic or transcranial direct current stimulation during SWS modulates the consolidation of this type of memory (19). SWS is important not only for memory consolidation but also encoding. A sleep rich in slow wave activity before memory encoding ensures that previously potentiated synapses will become again available for the formation of new memories (8).

NREM sleep also has been implicated in the consolidation of procedural memory. Practicing a motor skill during the day leads to increases in the activity of sleep spindles (20,21) and slow waves (22) in areas of the brain engaged in motor skill practice during subsequent NREM 2 and 3 sleep, respectively. In some studies, these increases in sleep spindles and slow wave activity correlate strongly with the capacity to retain the previously practiced motor skill (20–22). Conversely, immobilizing the upper limb as little as 24 h decreases subsequent slow wave activity in areas of the brain innervating the immobilized limb (23), thus, reinforcing the idea that slow wave activity during

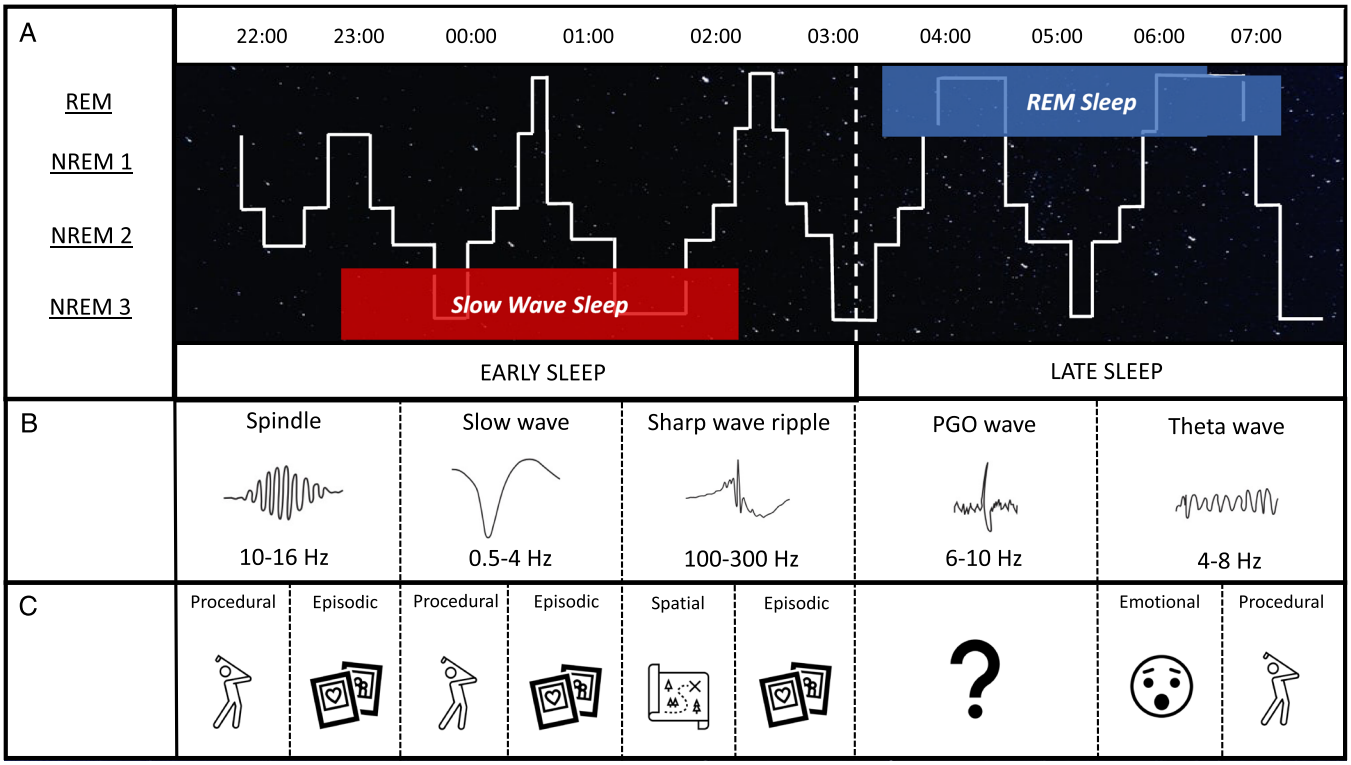

Figure 1. Sleep phases and stages (A), their typical electroencephalographic signals (B), and their relation with different types of memory (C). PGO, ponto-geniculo-occipital.

NREM sleep is modulated locally by events that promote synaptic plasticity during waking such as those triggered by transcranial magnetic stimulation (TMS) (24) or exercise (25). Perturbing slow wave activity during NREM 3 sleep reduces the capacity to increase corticospinal excitability (a marker of synaptic plasticity) in response to motor skill practice, impairing the capacity to obtain further gains in motor learning the following day (16). Taken together, these findings emphasize the importance of SWS to prevent synaptic saturation and restore the capacity to encode new memories (15).

The specific role of REM sleep in memory processing remains a source of intense scientific debate. REM sleep abolition studies designed to prove the role of this phase of sleep on memory have been often criticized either because they have used stressful protocols or because changes in NREM sleep, which could also explain memory improvements, were not considered (2). Some animal studies have shown that the duration of REM sleep and the activity of PGO and theta waves tend to increase in the sleep succeeding the performance of active avoidance memory tasks, but this relation does not seem generalizable to other memory tasks (2). In humans, the specific role that REM sleep has on memory processing also is controversial, although consensus does exist around the idea that REM sleep could be involved in the stabilization of memories encoded during tasks with procedural requirements and the consolidation of emotional memories (2). For example, a study showed that the benefits of a daytime nap on the consolidation of emotional memories were correlated with the duration of REM sleep and the level of theta activity in prefrontal areas of the brain during this phase of sleep (26). More studies are needed to better understand the specific role that REM sleep plays in the formation of different types of memory.

HOW DOES EXERCISE IMPACT THE SLEEPING BRAIN DURING MEMORY PROCESSING?

Studying whether physical exercise modifies aspects of sleep that can influence memory is essential to determine whether some of the benefits that exercise has on memory are mediated by sleep-related mechanisms or are completely independent. Meta-analyses summarizing the evidence regarding the effects of either acute or chronic exercise on the duration of NREM 1 and 2 have provided equivocal results (27–29). In contrast, the same meta-analyses have shown that a single bout of daytime exercise improves some objective measures of sleep quality, reducing overall sleep latency, and increasing total sleep time and efficiency (27–29). Acute exercise also has been shown to modify aspects of sleep architecture potentially involved in memory formation processes, reducing the latency and total duration of REM sleep and increasing the duration of subsequent NREM 3 sleep (27–29). It should be noted, however, that unless prolonged acute exercise protocols are used, changes in the duration of these stages of sleep in response to a single dose of exercise tend to be modest (<15 min). There also is evidence that chronic exercise interventions involving weeks or months of training reduce sleep latency and awakening time, increase total sleep time and the duration of NREM 3 sleep, and reduce REM sleep.

It is unlikely that such small changes in the duration of NREM 3 and REM could be responsible for the potential sleep-mediated enhancing effect of physical exercise on memory (2). However, exercise, like several other neuromodulation techniques such as acoustic or TMS (19), can trigger changes in neurophysiological mechanisms of sleep involved in memory processing, independent of changes in the time spent in these stages of sleep. This was demonstrated in a recent study (6) in

which 60 min of vigorous cardiovascular exercise performed 6 h before sleep reduced the time in NREM 3 sleep by ~11 min, whereas slow wave activity showed a marked increase in the early stages of sleep. An additional finding of this study was that exercise increased the stability of slow wave power, which could potentially have a positive effect on memory consolidation (30). Although increases in slow wave activity in response to acute exercise have been reported in several other studies, the effects of chronic exercise interventions involving weeks or months of training on slow wave activity remain to be investigated.

Similarly, no studies have investigated the effects of either acute or chronic physical exercise on the activity of the brain signals that characterize REM sleep such as PGO or theta waves. Furthermore, only a few studies have investigated changes in the activity of sleep spindles. One of these studies found that four daytime bouts of 40 min of moderate-intensity cardiovascular exercise increased the activity of fast (13–16 Hz) but not slow (10–13 Hz) sleep spindles (5). In contrast, another study reported no differences in sleep spindle density measured in the 11–16 Hz range during a 60 min daytime nap preceded by 40 min of cardiovascular exercise performed at moderate intensity (3). Discrepancies between these studies could be explained by several factors, including the different frequency bands used to identify sleep spindles, the sleep scoring method, or, simply, the dosage of exercise. Indeed, when sleep pressure is high, as it occurs after a long session of strenuous exercise, the activity of sleep spindles tends to be suppressed, possibly to maximize the restorative effect of slow waves (31). It is, thus, not unlikely that the different dosages of exercise could have contributed to the disparity of results between studies (3,5).

DO EXERCISE AND SLEEP INTERACT TO IMPROVE MEMORY?

A recent study has provided the first direct evidence that exercise and sleep, combined, have synergistic effects on declarative memory (3). The authors used 40 min of cardiovascular exercise of moderate intensity followed by a 60-min daytime nap to determine whether exercise and daytime sleep had summative effects on a visual recognition memory task. Participants were randomly allocated into four experimental groups: exercise plus nap, nap only, exercise only, and neither exercise nor nap. After either exercise or rest, participants were presented with 45 neutral photographs that they had to identify in a recognition test performed after the 60-min nap or after an equivalent period of wakefulness. The recognition test included the original 45 photographs in addition to 45 additional photographs used as distractors. Compared with the groups that either exercised or took a nap only, the exercise plus nap group showed a greater capacity to correctly recognize the photographs previously presented that was associated ($r = 0.46$) with the activity of sleep spindles during the daytime nap. The findings of this study, which align with previous studies demonstrating that delayed retention tests performed after one or several nights tend to show larger exercise-induced improvements in memory than tests performed after a period of wakefulness (1), confirm that exercise and sleep can have synergistic effects on declarative memory.

Evidence for the synergistic effect of exercise and sleep on procedural memory comes from two of our studies (32,33) assessing whether a single bout of cardiovascular exercise performed after practicing a primary serial reaction time task (SRTT) could protect procedural memory from the interfering effects of a secondary SRTT introduced soon after motor practice. In the first study (32), exercise performed 2 h after motor practice abolished the interfering effect of the secondary SRTT. However, because skill retention was assessed after a 24-h period that included sleep, whether memory interference was reduced because of exercise, or the combination of exercise and sleep, could not be determined. In the second study (33), the retention test was performed after a 6-h wakefulness period not including sleep, and, although exercise reduced memory interference, the protective effect was not significant. Although exercise can protect procedural memory from the interfering effect of declarative memory independently of sleep (34), the results of these two studies combined suggest that sleep could have a super additive effect, strengthening the effects of exercise to protect procedural memory from interference (32,33).

There exists additional yet indirect evidence in support of the joint effects of exercise and sleep on procedural memory. We, along with other research groups, have shown that a single bout of cardiovascular exercise performed immediately after practicing a visuomotor task can improve the retention of this skill, enhancing its consolidation into procedural memory [see (35) for review]. One finding emerging consistently from all these studies is that exercise-induced gains in procedural memory arose consistently when the retention of the skill was assessed one or several days after motor skill practice once a period of sleep took place. In contrast, when the retention of the motor skill was assessed after a wakefulness period, improvements in procedural memory were diminished (35). At face value, these findings reinforce the hypothesis that sleep interacts with exercise to improve the consolidation of procedural memory. However, these studies were not specifically designed to assess the influence of sleep on memory and, thus, cannot provide direct evidence of its involvement. Improvements in memory arising in the delayed retention tests could have been produced simply by the effect of passage of time on memory stabilization and not the effect of sleep per se.

In summary, despite the growing number of studies supporting a synergistic effect between exercise and sleep to improve memory, the results of such investigations should be interpreted cautiously. First, because all these studies used acute exercise paradigms, the potential interaction between the chronic effects of exercise and sleep on memory remains to be determined. Furthermore, not all types of memories respond equally to the effects of exercise (1) or sleep (2), and, besides individual factors such as age, biological sex, health status, and genotype, other factors concerning the characteristics of both exercise (*e.g.*, frequency, intensity, duration, type, timing) and sleep (*e.g.*, daytime nap, full night sleep) could also influence the potential interactive effects that these two activities, separately, have shown to have on memory.

An additional challenge in studying interactions between exercise and sleep is that exercise and sleep hold bidirectional relations. Exercise influences sleep, but sleep can also affect exercise and, potentially, its effects on neuroplasticity and memory (36). More studies are, therefore, needed to confirm whether

the combination of different forms of exercise and sleep will have synergistic effects on different types of memory.

WHICH MECHANISMS BRIDGE THE EFFECTS OF EXERCISE AND SLEEP ON MEMORY?

Different pathways could explain the mechanistic interplay between exercise and sleep to improve memory (Fig. 2). One potential pathway involves the thermogenic effect of acute exercise on SWS. Increasing body temperature immediately before sleep increases the activity of slow waves, which seem to coordinate an homeostatic response aimed at normalizing both brain and body temperature (37). Evidence for the link between variations in body temperature induced with exercise and SWS comes from a recent study in which four 40-min bouts of moderate-intensity cardiovascular exercise produced persistent increases in both core body temperature and distal-proximal skin temperature gradient during the nighttime sleep after the session of exercise (5). More importantly, increases in temperature gradient were strongly associated ($r^2 = 0.5$) with the increases in slow wave activity triggered by exercise, reinforcing the role that SWS plays in maintaining body temperature (37). Whether temperature-driven increases in slow wave activity in response to exercise could promote improvements in memory consolidation is still to be elucidated (19).

Exercise could also influence the memory function of sleep via autonomic stimulation. Both acute and chronic exercise modulate heart rate (HR) and heart rate variability (HRV). When exercise intensity increases, HR increases linearly and HRV variability decreases progressively until reaching a steady state at submaximal intensity. Exercise recovery is characterized by a progressive return to baseline of HR and a more variable recovery of HRV. Chronic exercise is thought to improve vagal stimulation and the synchrony between the sympathetic and parasympathetic action of the autonomic nervous system, reducing basal HR and increasing HRV variability. Intense exercise before sleep promotes increases in HR and also high-frequency (0.15–0.40 Hz) HRV (HF-HRV), a marker of parasympathetic activity, during sleep (4). Recent studies have shown that both HR and HF-HRV are coupled with sleep spindles and slow wave activity during NREM sleep and, more importantly, that HF-HRV during SWS and REM sleep is strongly associated with the consolidation of declarative memory (38). It is, therefore, possible that exercise-induced changes in HR and HRV could modify aspects of sleep architecture involved in memory processing.

Converging evidence in support of a potential role of neuroplasticity in bridging the combined effects of these two activities on memory has started to emerge in the literature. This evidence supports the view that exercise promotes neuroplasticity mechanisms that have a direct impact on NREM sleep–related memory processes. We have shown that a single bout of exercise increases corticospinal excitability (25) and the peripheral concentration of brain derived neurotrophic factor (BDNF) (39), two markers of neuroplasticity that correlate with improvements in procedural memory after acute exercise (40). In addition, human and animal studies have shown that increasing corticospinal excitability using TMS (24), and BDNF using *in vivo* cortical BDNF microinjections (41) increase the activity of slow waves only in the areas of the brain targeted by these interventions. Altogether, these studies reinforce the view that exercise promotes changes in synaptic plasticity that have a direct effect on slow wave activity during NREM sleep. Other studies have shown that both acute (42) and chronic exercise (43) improve the connectivity between hippocampal and neocortical areas, which could

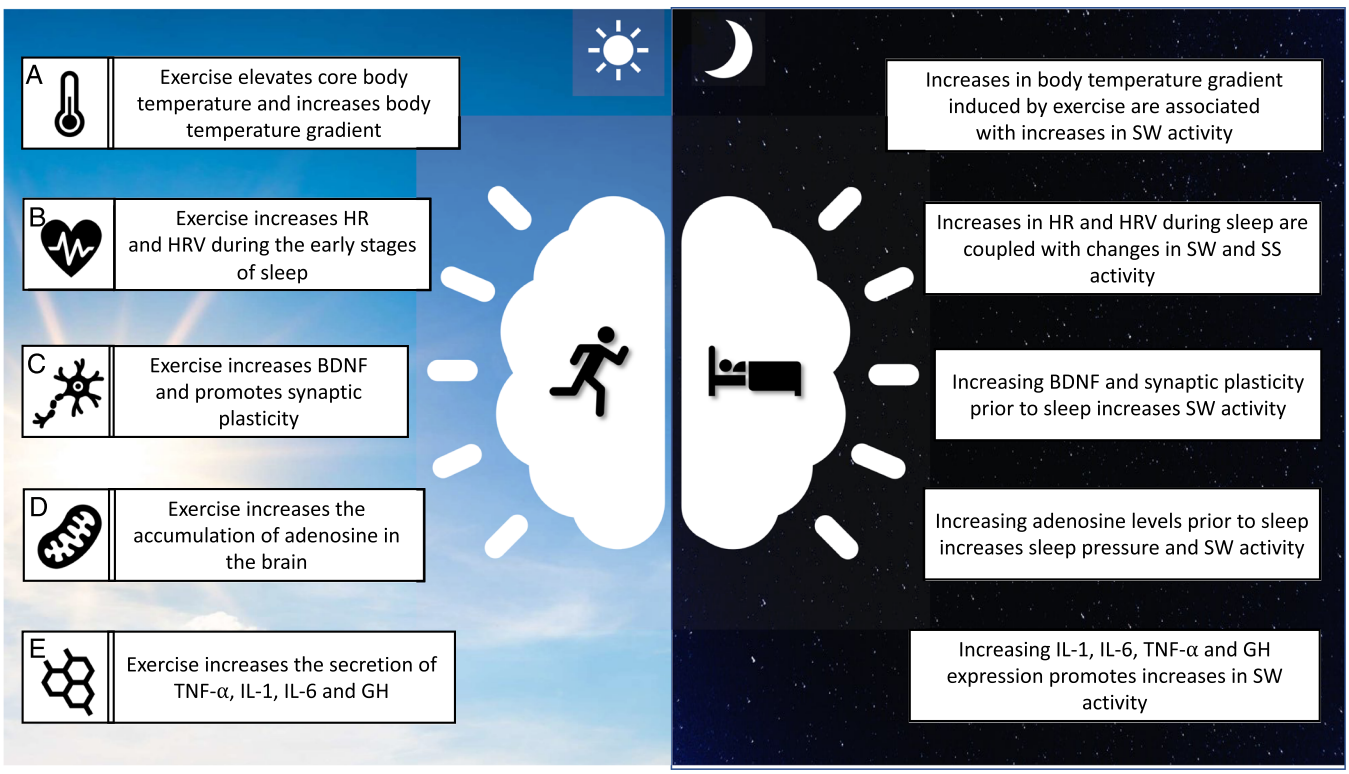

Figure 2. Potential mechanistic pathways through which exercise could modify mechanisms of sleep involved in memory processing. Body temperature (A), autonomic regulation (B), neuroplasticity (C), adenosine (D), and cytokines and hormones (E). SS, sleep spindles; SW, slow wave.

potentially improve the transfer of memory representations between these two areas during the SWS coordinated process of memory replay proposed by the active system consolidation hypothesis (18). Whether neuroplasticity-mediated increases in slow wave activity underlie the effects that exercise has on memory processing is, however, still not known (19).

Another pathway by which exercise could improve memory processing through NREM sleep modulation involves adenosine, a key mediator of sleep homeostasis. Adenosine accumulates in basal forebrain and cortical regions during prolonged wakefulness, inhibiting arousal and increasing sleep pressure. Importantly, adenosine accumulation, which has been implicated in synaptic transmission and neural excitability processes, contributes to the hippocampal memory deficits commonly observed with sleep deprivation (44). Animal studies have shown that, in parallel with a depletion of energy stores, extracellular adenosine levels increase markedly in areas of the brain involved in sleep regulation after a single bout of high-intensity exercise (45). Importantly, adenosine accumulation during wakefulness promotes slow wave activity during NREM sleep, possibly to reduce brain metabolism and facilitate the replenishment of high energy compounds that have been used during waking such as adenosine diphosphate and adenosine triphosphate (45). It is, thus, not unconceivable that the accumulation of adenosine in response to exercise could trigger a metabolic-mediated pathway to promote slow wave activity and influence memory consolidation (19).

Acute exercise increases the concentration of several cytokines and hormones that have sleep modulatory attributes, including the cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha α (TNF-α), as well as the growth hormone (GH) (46). The exogenous administration of IL-I, TNF-α, GH, and, to a lesser extent, IL-6 increases the duration of SWS and the activity of slow waves (46,47). In contrast, interventions that interfere with the synthesis or secretion of these cytokines and GH tend to reduce the duration of SWS and slow wave activity (46,47). Although the effects of exercise on cytokines and GH expression and their instrumental role in sleep regulation are well established (46,47), the action of these molecules with pleiotropic effects targeting multiple bodily systems is extremely complex. Furthermore, there is evidence that cytokine expression can change transiently with acute exercise, but also be modulated more permanently with chronic exercise (48). More studies, thus, are needed to understand how both acute and chronic exercise-induced changes in cytokine and hormonal expression could influence mechanisms of sleep involved in memory.

DOES EXERCISE PROTECT MEMORY AGAINST SLEEP DEPRIVATION?

Sleep deprivation has shown to have profound negative effects on neuroplasticity and memory. For example, in humans, sleep loss has shown to impair synaptic plasticity, reducing the capacity to increase corticospinal excitability in response to motor learning (49). Furthermore, peripheral BDNF levels have shown to be reduced significantly after only one night of sleep deprivation (16) and among people with chronic insomnia (50). It is noteworthy that the detrimental effects that sleep deprivation has shown to have on memory and neuroplasticity seem to go in the opposite direction of the positive effects of physical exercise (9–14). Exercise cannot replace the many memory functions of sleep, but given the tremendous societal cost of sleep deprivation (7), it would be of enormous interest to determine whether exercise could mitigate the deleterious effects that sleep loss has on memory.

This question was recently addressed in a series of animal studies, which investigated the protective effects of chronic exercise in reducing memory impairments induced with sleep deprivation protocols targeting REM sleep and, possibly to a lesser extent, other phases of sleep (9,10,12,14,36,51–58) (Table). Taken together, the results of these studies demonstrated that exposing rodents to voluntary or forced treadmill-based cardiovascular training for some weeks protected memory from the deleterious effects of an acute episode (12–96 h) of sleep deprivation. Importantly, the protective effect was observable in a wide variety of memory tasks (Table), suggesting that the effect could be generalized to different types of memory. Furthermore, the effect was demonstrated not only in male rodents but also in female rodents, who tend to be more susceptible to the deleterious effects of sleep loss on memory. These animal studies provide the first evidence that chronic exercise can protect memory against the effects of sleep deprivation.

One animal study did not find evidence of a protective effect of exercise on sleep loss (36). In this study, however, instead of acute sleep deprivation, a chronic sleep restriction protocol was used (Table). Mice in the sleep deprivation groups underwent an 11-week partial sleep restriction protocol involving 4 h of sleep avoidance per day. Under normal sleep conditions, 11 wk of exercise resulted in improvements in acquisition and recall in the Morris water maze task. In contrast, exposing animals to chronic sleep restriction abolished the learning and memory improvements resulting from exercise. Perhaps the effects of exercise were not strong enough to protect memory against chronic sleep deprivation. Alternatively, it is possible that sufficient sleep is required for the exercise to improve memory. Because the chronic sleep restriction protocol and training occurred concurrently, it is possible that the effects of sleep loss hampered the neuroplastic response to exercise that was needed to protect memory (36). Taken together, the findings of animal studies exploring the protective effect of exercise (Table) suggest that although chronic exercise can possibly protect memory from an acute episode of sleep deprivation, it is less clear that exercise can confer protection against the more pervasive effects of chronic sleep restriction.

Most human studies investigating interactions between exercise, sleep deprivation, and cognition have used exercise to protect executive function against fatigue rather than to preserve memory. In one study (60), participants underwent either an exercise or a rest condition on two separate visits. During the exercise condition, participants engaged in 10-min bouts of vigorous exercise every 2 h during a 40-h period of total sleep deprivation. In the rest condition, exercise was replaced by a reading activity. Participants were more alert immediately after exercise than after rest. However, electroencephalographic data collected 50 min after each exercise bout revealed that exercise increased slow wave (delta) activity during wake, which is a sign of increased sleep pressure and decreased alertness. More importantly, impairments in working memory associated with sleep deprivation were similar in both conditions. These results suggest that although short bouts of exercise may transiently

TABLE. Animal studies studying the protective effects of exercise on memory or neuroplasticity against the effects of sleep deprivation.

Study	Exercise	SD, h	Outcomes	Main Findings
Estrada 2019 (51)	**Type:** running wheel **Length:** 45 d **Frequency:** daily **Duration:** np **Speed:** np	12	**Memory:** Barnes maze test (24 h after acquisition).	Exercise protected memory from the effects of SD, preventing an increase in the number of working memory errors both in young and older animals and in reference memory errors in older animals.
Fernandes 2013 (52)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30 min **Speed:** 8–18 $m \cdot min^{-1}$	96	**Memory:** inhibitory avoidance (24 h after acquisition). **Neuroplasticity:** hippocampal expression of GAP-43, synapsin I, synaptophysin, PSD-95.	Exercise protected memory from the effects of SD, preventing the downregulation of GAP-43 after SD. Changes in synapsin I, synaptophysin, and PSD-95 expression did not change with exercise nor SD.
Mohammadi-poor-ghademabad 2019 (9)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** np **Duration:** 30–45 min **Speed:** 10–15 $m \cdot min^{-1}$	72	**Memory:** Morris water maze (2 h after acquisition). **Neuroplasticity:** hippocampal expression of miR-1b, pri-miR-1b, and BDNF mRNA.	Exercise protected memory from the effects of SD, preventing the downregulation of miR-1b and BDNF mRNA after SD. miR-1b levels were associated with memory protection.
Rajizadeh 2020 (54)	**Type:** forced treadmill **Length:** 10 d **Frequency:** 1 per day **Duration:** 60 min **Speed:** np	72	**Memory:** Morris water maze (24 h after acquisition); novel object recognition test (45 min after acquisition).	Exercise protected memory from the effects of SD in both the Morris water maze and novel object recognition test in ovariectomized female rats.
Rajizadeh 2019 (55)	**Type:** voluntary wheel **Length:** 4 wk **Frequency:** 1 per day **Duration:** 60 min **Speed:** 18 $m \cdot min^{-1}$	72	**Memory:** Morris water maze (24 h after acquisition).	Exercise protected memory from the combined effects of SD with and without demyelination, preventing further decays in memory after SD.
Rajizadeh 2018 (53)	**Type:** voluntary wheel **Length:** 4 wk **Frequency:** np **Duration:** np **Speed:** np	72	**Memory:** Morris water maze (24 h after acquisition); novel object recognition test (45 min after acquisition); passive avoidance test (24 h after acquisition).	Exercise protected memory from the effects of SD in the Morris water maze, novel object recognition, and passive avoidance tasks.
Saadati 2014 (10)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	72	**Neuroplasticity:** hippocampal expression of BDNF mRNA and protein.	Exercise prevented mRNA and protein BDNF downregulation after SD.
Saadati 2015 (56)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	72	**Memory:** Morris water maze (2 h after acquisition).	Exercise protected memory from the effects of SD.
Sahin 2021 (58)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** np	48	**Memory:** Morris water maze (24 h after acquisition). **Neuroplasticity:** hippocampal Grin2a, Grin2b, c-Fos, and BDNF mRNA expression as well as MDA.	Exercise protected memory from the effects of SD, but there were no differences among groups in any of the measures of neuroplasticity and oxidation (MDA).
Salari 2015 (57)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	24	**Memory:** Morris water maze (24 h after acquisition).	Exercise protected memory from the effects of SD in both intact and ovariectomized female rats.
Vollert 2011 (59)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 7 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	24	**Neuroplasticity:** hippocampal, cortical and amygdala expression of oxidative enzymes GLO-1 and GSR-1.	Exercise prevented upregulation of the GLO-1 and GSR-1 after SD, suggesting a protective effect of exercise against the oxidative effect of SD on brain structures involved in memory processing.
Zagaar 2012 (12)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	24	**Memory:** radial arm water maze (30 min after acquisition). **Neuroplasticity:** hippocampal E-LTP as well as basal and stimulated calcineurin, BDNF, and P-CaMKII expression.	Exercise protected memory from the effects of SD, preventing the impairment of E-LTP and the downregulation of basal and stimulated expression of BDNF and P-CaMKII after SD.
Zagaar 2013a (11)	**Type:** Forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	24	**Neuroplasticity:** Hippocampal E-LTP as well as basal and stimulated calcineurin calcineurin, BDNF and P-CaMKII expression.	Exercise prevented the impairment of E-LTP and the downregulation of basal and stimulated BDNF and P-CaMKII expression after SD.
Zagaar 2013b (14)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 $m \cdot min^{-1}$	24	**Memory:** radial arm water maze (24 h after acquisition). **Neuroplasticity:** hippocampal L-LTP as well as basal and stimulated CaMKIV, MAPK/ERK, P-CREB, and BDNF expression.	Exercise protected memory from the effects of SD, preventing the impairment of L-LTP and the downregulation of basal expression of CaMKIV, MAPK/ERK, P-CREB, and BDNF, as well as the stimulated expression of BDNF and P-CREB after SD.

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TABLE. *(Continued)*

Study	Exercise	SD, h	Outcomes	Main Findings
Zagaar 2016 (13)	**Type:** forced treadmill **Length:** 4 wk **Frequency:** 5 per week **Duration:** 30–60 min **Speed:** 10–15 m·min^{-1}	24	**Neuroplasticity:** hippocampal L-LTP as well as basal and stimulated CaMKIV, P-CREB, and BDNF expression.	Exercise protected memory from the effects of SD, preventing the impairment of L-LTP and the downregulation of basal expression of CaMKIV, P-CREB, and total CREB, as well as the stimulated expression of BDNF, P-CREB, and CaMKIV after SD.
Zielinski 2013 (36)	**Type:** forced treadmill **Length:** 11 wk **Frequency:** 6 per week **Duration:** 60 min **Speed:** 18–21 m·min^{-1}	11 wk (4 h·d^{-1})	**Memory:** Morris water maze (24 h after acquisition). **Neuroplasticity:** hippocampal c-Fos and BDNF cell activity.	Exercise improved spatial learning and recall, but SD mitigated the improvement. Exercise did not prevent the effects of SD on hippocampal c-FOS and BDNF cell activity.

Most studies used adult female rats and the multiple platform method to induce sleep deprivation. However, the study by Zielinski *et al.* used male mice and a rotating drum surrounded by water, and the study by Estrada *et al.* used *Octodon degus* female rodents and disrupted the sleep cycle with either a soft tactile stimulus or a gentle jostling of the cage.

CaMKII-IV, calcium-calmodulin–dependent protein kinase II and IV; c-Fos, cellular FBJ osteosarcoma protein; E-LTP, early long-term potentiation; GAP-43, growth associated protein 43; GLO-1, glyoxalase 1; Grin2a/b, glutamate ionotropic receptor (NMDA) type subunit 2a/b; GSR-1, glutathione reductase 1; L-LTP, late long-term potentiation; MAPK/ERK, mitogen-activated protein kinase/extracellular signal–regulated kinase; MDA, melondialdehyde; miR-1b, micro ribonucleic acid 1b; np, not provided; P-CaMKII-IV, phosphorylated calcium-calmodulin–dependent protein kinase II and IV; pri-miR-1b, primary micro ribonucleic acid; PSD-95, postsynaptic density protein; P-CREB, phosphorylated cAMP-response element-binding protein; SD, sleep deprivation.

reduce sleepiness and fatigue associated with sleep loss, they cannot preserve cognition during an extended period of sleep deprivation.

In another study, Slutsky *et al.* (61) investigated the effects of a single bout of acute exercise performed at mild intensity on cognitive performance after 24 h of sleep deprivation. Two groups of young, active healthy adults were randomized to a control or an exercise group, which exercised 15 min on a stationary bicycle. After 24 h of sustained wakefulness, cognitive testing, including memory assessment, was performed before and after the resting control period or the acute exercise intervention. Exercise did not produce any benefit on memory performance; however, the study had one important caveat. The sleep deprivation protocol did not cause significant impairments in cognitive performance other than a moderate increase in reaction times in a psychomotor vigilance task. Because the sleep deprivation protocol used was not taxing enough to affect memory, the potential protective effects of exercise could not be demonstrated.

In a chronic exercise study (62), 16 healthy young men underwent 7 wk of cardiovascular training performed three times per week. The impact of a 40-h total sleep deprivation protocol on different aspects of executive function, including vigilance, attention, inhibition, and working memory, was assessed at baseline and after training. Training reduced the degradation of vigilance and attention performance associated with sleep deprivation but not its deleterious effects on inhibition and working memory. At face value, these findings indicate that the protective effects that chronic exercise has shown in animal studies (Table) cannot be directly extrapolated to humans. However, like in the human study described previously (60), this study assessed the effects of exercise on working memory. Working memory, which defines our ability to retain but also actively manipulate pieces of information over short periods of time, is usually considered more an aspect of executive function and attention than a memory function per se. More human studies are, therefore, needed to determine the potential protective effect of exercise against the effects of sleep loss on different types of memory.

DOES EXERCISE PROTECT NEUROPLASTICITY AGAINST SLEEP DEPRIVATION?

Animal studies have investigated the potential role of neuroplasticity in mediating the protective effects that exercise has shown to have on memory against sleep deprivation. The results of those studies (Table) revealed that 4 wk of exercise prevented sleep deprivation–induced downregulation of several key signaling molecules involved in neuroplasticity mechanisms underlying memory and learning processes in the rat hippocampus (9–14). At a functional level, exercise also prevented the inhibition of early and late long-term potentiation (11,12,14), a mechanism needed for the formation of long-term memory. Interestingly, another study demonstrated that exercise reduced the increase in oxidative stress enzymes induced by sleep deprivation in the rat hippocampus, cortex, and amygdala (59), suggesting that the protective effects on neuroplasticity could be mediated by an antioxidant effect of exercise. Importantly, some of these studies found correlations between these markers of neuroplasticity and the improvements in memory and learning induced by exercise (9,36). This reinforces the hypothesis that the protective effects of exercise on memory against sleep deprivation could be mediated, at least in part, by a preservation of neuroplasticity (8).

Two animal studies failed to show a general protective effect of exercise on neuroplasticity against sleep loss (36,52). Fernandes *et al.* (52) showed that 4 wk of exercise prevented the downregulation of the growth associated protein 43 but not of other synaptic plasticity proteins (synapsin I, synaptophysin, and postsynaptic density protein 95) in the rat hippocampus. However, it is possible that, because in this study rats were euthanized 5 d after the last exercise session, the detraining period washed out potential neuroplasticity adaptations. The only animal study that did not show a protective effect of exercise on memory against sleep deprivation (36) also failed to demonstrate a general protective effect on neuroplasticity. Eleven weeks of exercise increased cell activity (c-Fos protein expression) and BDNF levels in the mice hippocampus, both of which correlated with spatial memory. However, the group exposed to the 4 h·d^{-1} sleep restriction protocol showed no increase in c-Fos or BDNF

in response to exercise. It is important to reiterate that this study used a chronic sleep restriction protocol and not an acute episode of sleep deprivation. Again, these results suggest that, by promoting neuroplasticity, exercise could potentially protect memory from an acute episode of sleep loss but not from the effects of chronic sleep restriction.

FUTURE DIRECTIONS

Perhaps the most important message emerging from this review is that there is still much to learn about the interaction between exercise and sleep in the context of memory processing. We need more evidence to confirm that these two activities synergize to improve memory and that the effect observed in some recent studies (3,32,33) is robust and generalizable. Importantly, we also need more studies looking at this issue from the other side of the interaction, this is, how sleep can affect the mechanisms of exercise that can impact memory processing.

Once this bidirectional interaction is confirmed, future studies should focus on investigating interactions between different types (*e.g.*, cardiovascular vs resistance) and parameters (*e.g.*, intensity, timing) of exercise as well as sleep (daytime napping vs full nighttime sleep) using different memory paradigms (declarative vs nondeclarative). An additional yet necessary step will consist of identifying potential individual moderators that could influence such an interactive effect (*e.g.*, age, biological sex, fitness level, genotype).

Another important gap in knowledge remains with respect to the potential interaction between chronic exercise and sleep and their combined effect on memory. Compared with acute studies, chronic exercise studies are not well suited to study time-locked mechanistic interactions between exercise and sleep, and their combined effects on memory (40). However, chronic exercise studies could provide important insights by incorporating mediation analyses to delineate changes in the trajectories of biomarkers of both sleep and memory over the course of long-term exercise interventions. This may help determine whether the repeated exposure to exercise promotes memory improvements through change in sleep mechanisms.

There is a paucity of information regarding how exercise affects sleep mechanisms that regulate memory, and our knowledge of the pathways through which exercise could modify sleep to enhance memory processing is still sparse. We have identified potential pathways involving mostly acute exercise and SWS (Fig. 2), but these mechanisms need to be confirmed with more experimental evidence and should be regarded only as a starting point to guide future lines of inquiry. There are many other potential pathways that could mediate the combined effects of exercise and sleep on memory that, because of the lack of more robust evidence, we did not discuss here.

To date, most research has been focused exclusively on studying how exercise changes the duration of different phases and stages of sleep, but this approach provides little mechanistic insight regarding how exercise could potentially change sleep to improve memory. We need more studies looking at markers of sleep architecture associated with memory processing and how different types of exercise modify them. These investigations should go beyond the use of electroencephalography as a standalone technique and combine other techniques (*e.g.*, continuous monitoring of blood biomarkers during sleep) to obtain a more comprehensive picture of the different pathways that could mediate the interactive effects of exercise and sleep on memory.

Exercise cannot replace the memory function of sleep; however, we still see great value in exploring interactions among exercise, sleep loss, neuroplasticity, and how these interactions affect memory. We need more studies investigating the impact of exercise on the sleep deprived human brain and exploring the possibility that exercise could be used as a preventive measure to protect memory from the deleterious effects of acute episodes of sleep loss. Both acute and chronic exercise studies could be used to investigate short- and long-term mechanisms underlying the protective effect against sleep loss.

Given the well-known deleterious effects of sleep deprivation on health, subjecting individuals to chronic protocols of partial sleep restriction applied over several days to study the protective effects of exercise on memory is not advisable. A potential solution to partially circumvent this limitation is to explore the effects of exercise on memory in sleep-restricted individuals (*e.g.*, insomniacs, shift workers).

SUMMARY

Emerging data support a synergistic effect of exercise and sleep on both declarative and procedural memory, but the evidence is still limited, and data come exclusively from studies using acute exercise interventions. The exact mechanisms bridging the potential synergistic effects of these two antagonistic activities on memory remain largely unknown and may involve different overlapping pathways. However, converging evidence suggests that exercise could trigger different pathways that modify the activity of slow waves during NREM sleep, which have been associated with memory consolidation processes. Recent animal studies provide strong evidence that chronic exercise stimulates positive changes in neuroplasticity and protects different types of memory from the effects of a single bout of sleep loss but not from a chronic sleep restriction protocol. The evidence supporting a protective effect of exercise against the effects of sleep loss on memory in humans is still equivocal, and, thus, more research is needed.

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