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Slow-wave activity enhancement to improve cognition

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Abstract

Slow-wave activity (SWA), and its coupling with other sleep features, reorganizes cortical circuitry supporting cognition. This raises the question: Can cognition be improved through SWA enhancement? SWA enhancement techniques range from behavioral interventions such as exercise, which have high feasibility but low specificity, to laboratory-based techniques such as transcranial stimulation, which have high specificity, but are less feasible for widespread use. We describe the pathways through which SWA is enhanced. Pathways encompass enhanced neural activity, increased energy metabolism, and endocrine signaling during wakefulness, and direct enhancement during sleep. We evaluate the robustness and practicality of SWA enhancement techniques, discuss approaches for determining a causal role of SWA on cognition, and present questions to clarify the mechanisms of SWA-dependent cognitive improvements.

Keywords

NREM sleep; slow-wave activity; memory consolidation; executive function

Non-rapid eye movement sleep as a tool for cognitive enhancement

Non-rapid eye movement (NREM) sleep in humans consists of three stages, N1–N3, which reflect the transition from “light” to “deep” sleep as defined by arousal threshold, as well as physiological and electrophysiological features. N3 sleep, also called slow-wave sleep (SWS), is characterized by low frequency **slow-wave activity** (SWA) [1] (see Glossary) (Box 1). NREM sleep is essential to autonomic, immune, metabolic, and other physiological functions. Here we focus on neurocognitive functions. **Executive function**, learning, and memory appear to be especially sensitive to NREM sleep [2–7]: Increases in high amplitude, low frequency SWA during NREM sleep are associated with improved executive function [6]. Enhanced SWA and the coupling of slow-waves with **spindles** and **sharp-wave ripples**

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during NREM sleep are also critical for memory **consolidation** [8] (Box 2, 3). Recent evidence implicating SWA and NREM sleep in cognitive deficits [9–11] provides empirical motivation to identify SWA enhancement techniques that are feasible for long-term use outside the laboratory. Thus, the goals of this review are two-fold: 1) provide a brief synopsis of the methods for SWA enhancement and give examples of the candidate physiological mechanisms through which they may operate, and 2) to evaluate the efficacy and the general practicality of techniques for enhancing SWA (Box 4). We evaluate evidence that SWA enhancement can improve neurocognitive function and highlight next-step questions that can better define the potential of NREM sleep augmentation in meaningfully modifying cognition.

Box 1

SWA regulates homeostatic sleep drive (Process S)

SWA increases proportionally with the duration of wakefulness: With longer time awake, homeostatic sleep pressure (Process S) builds, resulting in higher SWA [12]. Topographically, SWA is highest in frontal EEG channels, suggesting that during wakefulness, homeostatic sleep pressure builds predominantly in the PFC. Conversely, energy demands in this area are dramatically reduced during SWS [12, 105].

SWA is highest early in the night and decays logarithmically across NREM periods [106] as sleep pressure and extracellular levels of adenosine and SWA-promoting cytokines decrease [107]. In addition to global, wake-dependent fluctuations, SWA also shows local, use-dependent regulation [22]. Local SWA fluctuations derive from neuroglial activity and subsequent metabolic demands [13, 22]. Figure 2 illustrates how SWA propensity is proposed to accumulate under natural (gray) and experimentally increased brain energy consumption during wakefulness (yellow). In contrast, SWA enhancement during sleep diminishes SWA propensity and may thereby lead to no change time spent in SWS. Thus, some SWA stimulation techniques, such as acoustic or transcranial stimulation during sleep, show large increases in SWA EEG power, but minimal increases in whole night SWS (Box 4).

Box 2

NREM sleep and cognition

SWA involves two states: tonic inhibition of neural activity in the **down-state**, along with brief phasic bursts of synchronized excitatory synaptic activity in the “up” state. The down state is characterized by tonic hyperpolarization and synchronized quiescence in which higher frequency activity including spindles (12–16 Hz) and sharp wave ripples (~80 Hz in humans and ~200 Hz in rodents) is reduced. Suppression of higher frequency activity leads to a rebound in spindle and ripple activity in the depolarized up state [1, 8, 108]. Spindles originate from thalamocortical loops that fire in a synchronous oscillatory pattern [1]. Spindles are most evident during N2 sleep, but are also present during N3 sleep, often masked by more dominant SWA [109]. Sharp-wave ripples within CA1 of

the hippocampus are higher frequency bursts that occur preferentially within the trough of the spindle [8].

The ability of SWA to group the activity of other brain rhythms, such as spindles and ripples, is thought to accommodate memory consolidation [104]. Sleep-dependent memory consolidation has been associated with the hierarchical interplay of SWA, spindles, and sharp wave ripples [8, 11]. Both spindles and ripples commonly increase after learning, and ripples coincide with replay of cell firing associated with memory traces [104], suggesting involvement in memory reactivation. Within the long-term memory transfer framework, sharp wave ripples, which are generated in CA3 of the hippocampus [108], have been proposed to reflect local information units that are communicated in coincidence with sleep spindles [7, 108]. Enhancement of SWA increases these events and improves memory consolidation, and the involvement of spindles and ripples in memory consolidation depends on SWA [110]. SWA, and in some cases spindles, are posited to organize large-scale neocortical networks involved in other forms of cognition, such as executive functions [6]. These include fluency [4, 5], reasoning [3, 6], and switching [2, 3]. Associations between SWA and these domains of cognition may occur through synaptic scaling by enhancing large scale networks and reducing noise from small-scale networks (Box 3).

Box 3

Theories of synaptic scaling during sleep

Wakefulness is associated with a net increase in cortical synaptic strength, whereas sleep is associated with a net decrease in synaptic strength [38]. These changes may be moderated by factors like energy metabolism and salience [22]. However, sleep may also increase synaptic strength through selective memory reactivation [100, 104].

The synaptic homeostasis hypothesis [38] proposes that synapses are downscaled during sleep back to a level of sustainable neural (i.e. synaptic) homeostasis. Synapses may simply be downscaled through global homeostatic renormalization, or they may be selectively reduced through Hebbian plasticity. In either case, the hypothesis proposes that SWA is responsible for *reducing* the efficacy of all synapses without strengthening synapses. In line with this hypothesis, expression of long-term potentiation (LTP) genes and noradrenaline, which is involved in inducing LTP, are dramatically reduced during sleep [38]. By this model, exercise, cognitive training, and wake brain stimulation are all factors that would increase the weight of a synapse during wakefulness and be locally downscaled during SWA.

In contrast, the active system consolidation model [104] proposes that sleep, including SWA, strengthens specific synapses tagged as relevant by the memory system. Memory traces are repeatedly reactivated across distributed brain regions during sleep and thereby gradually transferred from the limited resources of the hippocampus to the neocortex for long-term storage [111]. The synchronizing effect of SWA on thalamocortical spindles and sharp-wave ripples allows for hippocampus to neocortex transfer of reactivated memory traces [104]. Local information processing units of memory traces represented

by sharp-wave ripples [8] are transferred to the neocortex via neocortical-hippocampal projections of spindles. Support for this model includes findings in both humans and rodents for coordinated grouping of spindles and ripples based on the phase of the slow-wave [8]. Further, replay of neuronal assemblies in the hippocampus coincides with reactivation of neuronal assemblies in the neocortex [112, 113]. Moreover, spontaneous and experimentally manipulated memory reactivation has been demonstrated during NREM sleep, the latter associated with post-sleep memory improvements [102].

Of note, these two processes (general synaptic downscaling, memory-specific synaptic strengthening) are not mutually exclusive, and indeed, may reflect obligate symbiosis.

Box 4

Strengths and weaknesses in the widespread use of SWA enhancement techniques

Heating techniques afford robust enhancements of SWS duration, and have established connections to hormones (i.e. growth hormone) that influence long-term potentiation [33]. Heating methods are feasible and safe outside the laboratory [114]. Additionally, heating, as with other energy metabolism techniques, also minimizes the concern of waking participants during sleep, which is a potential risk with scalp stimulation techniques during sleep. However, it remains unknown whether heating techniques increase SWA, beyond SWS duration, and if so, how.

In contrast to heating techniques, enhancement techniques during sleep such as low frequency transcranial stimulation and acoustic stimulation commonly show robust increases in magnitude of SWA, though interestingly, not SWS amount. One tenable explanation is due to the decreasing sleep drive that would be associated with increasing SWA.

Regarding transcranial stimulation techniques, electrical stimulation techniques are more apt for wearable use at night than TMS, and may also be associated with less physical discomfort and arousals. Transcranial stimulation during sleep has shown large positive effects most commonly using oscillatory anodal tDCS, and low frequency tACS and TMS [79, 92, 98, 99]. Nonetheless, there have also been failed replication studies using oscillatory anodal tDCS (0.75 Hz) [94, 95] and tACS (0.75–1 Hz) [93]. Whether these stimulation techniques will be as effective in populations with minimal SWA, relative to healthy young adults remains a question that has been addressed in only a few studies [95, 115].

Considering recent evidence that the precise temporal coupling between slow waves and spindles is necessary for memory consolidation, and is impaired in older adults [116] another important and unaddressed issue is whether or not these techniques beneficially augment the synchronous, interactive dynamics of NREM oscillation. Even if the current methods do not systematically aid in the temporal coupling dynamics, beyond simply the amplitude or density of specific waveforms, the target of manipulating more precise oscillatory coupling becomes an exciting novel intervention target for new stimulation paradigms.

SWA enhancement during sleep has greater experimental control, as the manipulation occurs during sleep, providing a more definitive test of causality. Although there are few studies of olfactory stimulation, this technique has several advantages, particularly when lavender oil is used: published effects to date appear to moderately enhance SWS, and it may be less likely to cause awakenings [80, 87].

Cellular cascade of SWA enhancement

SWA during sleep increases after periods of prolonged wakefulness, reflecting increased homeostatic sleep drive (Box 1). The largest increases are observed over the prefrontal cortex (PFC) [12]. In addition to such global, wake-dependent alterations, SWA can also increase in a local, use-dependent manner [13]. For instance, neuronal populations that are more active during wakefulness show greater SWA during subsequent sleep compared to less active neuronal populations [14, 15]. Following wake neural activity and energy expenditure, presynaptic adenosine triphosphate (ATP) is released into the extracellular space, increasing extracellular levels of sleep-promoting substances [16]. ATP can be converted to adenosine or it can activate signaling of sleep-regulating cytokines such as TNF α (tumor necrosis factor α) and IL1 (interleukin 1 β) by binding to purinergic type 2 receptors throughout the brain [13, 17, 18]. Adenosine inhibits cholinergic wake-active neurons of the basal forebrain, and disinhibits and stimulates sleep-active neurons [16, 19]. Cytokines TNF α and IL1, originating from glia and neurons of the hypothalamus [16], stimulate sleep active neurons in the preoptic area of the hypothalamus and other brain regions critical for the generation of SWA [16]. Adenosine and SWA-promoting cytokines are proposed to disinhibit GABAergic (*γ -amino-butyric-acid*) neurons [16]. GABAergic neurotransmission in turn inhibits and controls large-scale neural activity, manifested as SWA [13, 16, 20]. Functionally, SWA causes grouping of sleep spindles within the **up-state** of the slow-wave [8], a process supporting the consolidation of memories (Box 2), and large-scale synchronous synaptic **scaling**, a process that increases neural network efficiency (Box 3). This cascade of events following SWA enhancement is illustrated in Figure 1 (Key Figure).

Pathways for SWA enhancement and corresponding techniques

Techniques that increase SWA can be categorized by their mechanisms. SWA can be experimentally increased during *wakefulness* in a use-dependent pattern following neural activity, energy metabolism, and endocrine signaling. Conversely, SWA can be stimulated during *sleep* through low-frequency stimulation and/or enhancing the depolarized slow-wave up-state. These main categories may overlap and are not mutually exclusive. In Box 4, we compare the efficacy of different techniques for enhancing SWA and SWS and summarize their strengths and limitations. In what follows, we briefly summarize changes in NREM sleep linked with each of these techniques, and then discuss efficacy and pragmatic aspects. We summarize their effect on SWA, SWS, and spindles and/or sigma activity (12–16 Hz). We focus on non-pharmacological techniques that preserve the characteristics of naturally-occurring SWA and allow NREM oscillations grouped by SWA to interact in an ecologically

valid fashion, since techniques that enhance only “phenotypic” SWA (i.e. GABA agonists) do not seem to enhance memory consolidation [21].

Enhanced Neural Activity and Energy Metabolism

SWA is homeostatically regulated: Activities that increase brain energy consumption during wakefulness increase SWA during subsequent sleep [13, 22] (Box 1). Such activities include active and passive body heating, cognitive training, meditation, and brain stimulation during wakefulness. Similar to prolonged wakefulness, the most widely-studied strategy for enhancing SWS [23], these techniques increase energy metabolism during wakefulness, increase sleep drive, and result in a proportionate increase in SWA during subsequent sleep (Figure 2) [22]. Accordingly, experimentally prolonged wakefulness in the absence of increased neural activation does not increase subsequent SWA [22].

Brain and Body Heating—Brain and body heating from warm baths and heavy exercise result in robust increases in SWS [24–27], whereas inconsistent effects on sleep spindles have been reported [26, 28]. EEG SWA is largely unreported in these studies. Acute exercise leads to small but significant effects on SWS [27], but large effects are found in high fit individuals when the *rate* of energy expenditure is high, rather than when *total* energy expenditure is high, possibly because the former is more strongly related to increased body temperature [29]. Heating via exercise stimulates ATP release [30] and increases adenosine [31] and signaling of sleep-regulating cytokines, such as TNF α and IL1, from the periphery or from astrocytes [20]. Cytokines in the periphery are detected in the CNS through stimulation of the vagus nerve and through active transport of cytokines to the CNS [20]. Heating activates warm-sensitive neurons in the hypothalamus that promote SWA in response to increased core body and skin temperature [32]. Accordingly, exercise combined with body cooling, and warm baths combined with aspirin to maintain body temperature do not change SWA or SWS [25].

Exercise consistently improves memory and executive function [33] through a variety of mediators including insulin-like growth factor-1 (IGF-1), growth hormone release (described below), and brain derived neurotrophic factor (BDNF) [33]. As SWS supports synaptic plasticity, and SWS increases after exercise, SWS is also a likely mediator in the link between exercise and plasticity [34]. One study showed enhancements in both SWA and cognition following physical and social activity [24], but direct evidence for a mediating role of SWA is lacking. Nonetheless, heating techniques are ecologically valid, feasible, and cost-effective approaches that warrant further investigation for their ameliorating effects on cognition through NREM sleep, particularly since they show large effects on global SWS.

Cognitive Activity—Learning commonly leads to changes in NREM sleep, such as increases in spindles, hippocampal sharp-wave ripples and EEG coherence [35]. Salient or repeated learning experiences additionally result in local enhancements of SWA [14, 36, 37]. For instance, training on a visuo-motor task that targeted the right parietal cortex led to local increases in SWA over right parietal derivations [14]. Local, modality-specific SWA enhancements have also been observed for intense training on a working memory task over the left dorsolateral PFC [36]. These studies vary widely in their effects on sleep spindles

[14, 36, 37]. SWA enhancements through cognitive training have been posited to result from increased synaptic strength during the task, and subsequent downscaling during sleep to maintain synaptic homeostasis and organize connections to favor performance on the task the next day [38] (Box 3). In line with this model, improvements in cognitive performance on these tasks depend on the local, modality-specific SWA increase [14, 36, 39].

Meditation—Meditation practice has been shown to increase global SWS and sleep spindles [40]. The effects of meditation on SWA are proposed to result from use-dependent plasticity associated with mental training and focused attention [40, 41]. For instance, meditation is associated with increased theta EEG activity (4–7 Hz) [41], which commonly co-occurs with working memory and memory encoding [42], is a homeostatic indicator of sleep drive during wakefulness, and is associated with enhanced SWA during subsequent sleep [40, 43]. Indeed, meditation is associated with functional activations and connectivity patterns overlapping with those of classic executive control tasks (i.e. higher activity in the orbitofrontal cortex, dorsolateral PFC, thalamus, and cingulate gyrus), and greater functional connectivity of the default mode network [41, 44].

Meditation may be a cost-effective intervention for improving sleep and cognition [25, 45]. For instance, meditation has been shown to improve memory, attention, fluency, and cognitive flexibility [46], but studies have not examined a mediating role of SWA in these cognitive changes. Control experiments testing a causal role of SWA are needed to confirm SWA-enhancing effects but may be less feasible in meditation interventions (see Concluding Remarks). Statistical mediation tested with robust sample sizes would be the first step for identifying the role of SWA in cognitive benefits of meditation.

Transcranial Stimulation during wakefulness—Excitatory, high frequency (4–20 Hz) or anodal stimulation during wakefulness, using techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS), can increase SWA in a use-dependent pattern. Excitatory transcranial stimulation during wakefulness potentiates synapses and overall energy metabolism of stimulated neurons [47]. Exogenous excitation of neural activity by magnetic or electrical stimulation during wakefulness leads to a proportionate increase in SWA during subsequent sleep [43]. Local SWA enhancements result from both acute and long-term stimulation. For instance, transcranial stimulation with 5 Hz stimulation or paired associative stimulation which combines transcranial motor cortex and median nerve stimulation show increases in SWA [43, 48–50]. One study of TMS treatment for depression found SWA increases after one week of daily stimulation using 20 Hz over the left dorsolateral prefrontal cortex [51]. Studies of transcranial stimulation during wakefulness in healthy controls have found an increase [52] or no change [43, 51] in spindle activity. Similar to the mechanisms of cognitive training, increases in ATP in stimulated neurons leads to increased SWA, and SWA is responsible for synaptic scaling that results in durable changes in synaptic strength of transcranially-stimulated neurons [50].

Transcranial stimulation during wakefulness targeting the dorsolateral or medial PFC enhances memory and other aspects of cognitive performance [53, 54]. Such cognitive enhancements may be modality-specific, depending on the region stimulated [55]. Thus,

measurement of SWA and cognitive performance could provide evidence whether SWA is one of the mediating pathways through which transcranial stimulation during wakefulness influences cognition.

Endocrine Signaling

The endocrine signaling pathway for SWA enhancement occurs downstream from neural activity and energy metabolism. Growth hormone and prolactin are key hormones in regulation of SWA. Behaviors that spontaneously increase growth hormone and prolactin, e.g., exercise [56] (reviewed above) and sexual activity [57, 58], increase SWS. While endocrine signaling during wakefulness is a plausible pathway for enhancing SWS and SWA, more empirical data are needed to clarify the precise mechanisms and magnitude of such effects.

Growth Hormone—Growth hormone is secreted by the anterior pituitary gland largely during SWS and mediates the effects of IL1 on sleep [59]. Growth hormone may be administered exogenously or stimulated endogenously with prolonged wakefulness [60], exercise [61], and growth hormone releasing hormone (ghrelin). Growth hormone releasing hormone stimulates GABA-ergic neurons in the preoptic area of the hypothalamus [16]. Accordingly, increased growth hormone leads to robust increases in SWS and SWA [62], specifically in men, with either no change in spindle activity [62] or a reduction in spindle activity [63].

Growth hormones play a well-established role in protein synthesis and adult neurogenesis [64, 65]. Growth hormone therapy is associated with improved cognitive function in patients with low growth hormone levels and may be an effective treatment for cognitive impairment [64]. SWS may facilitate growth hormone release and thereby influence synaptic plasticity through growth hormone receptors involved in **potentiation** in the hippocampus and elsewhere in the brain [64, 65]. However, SWS increases improve memory [66], independently from whether growth hormone increases or not, suggesting that cognitive benefits from SWS do not depend on growth hormone. It is still possible however that growth hormone by itself increases SWA, leading to large-scale neural synchrony and synaptic scaling with the potential to enhance cognitive function.

Prolactin & Sexual Activity—Prolactin and SWA are tightly linked: Elevated prolactin is associated with higher levels of SWA-promoting cytokines, IL1 β and TNF α [67]. Prolactin plasma levels are highest during sleep [68] and increases in prolactin temporally coincide with slow waves [69]. Although, to our knowledge, there have been no studies of exogenous prolactin on SWA, both exercise and sexual activity increase prolactin secretion in humans and rodents [56–58]. Furthermore, sexual activity increases SWS in male rodents independent of physical activity [70], which could be mediated through endocrine signaling. However, such SWS increases were not found in the one experimental study of humans [71]. Increases in SWS following sexual activity could be related not only to prolactin, but also to prolonged wakefulness [72], physical activity, and reward processes [73] (Figure 2). The specific roles of each of these pathways remain largely unexamined.

Prolactin and sexual activity both have links to cognitive function. Prolactin is positively associated with neurogenesis and cognitive function [74] and frequent sexual activity is cross-sectionally associated with better performance on executive function tasks including fluency and visuo-spatial abilities [75]. Together, these findings support the inclusion of sexual activity in the set of cognitive health-promoting behaviors, along with exercise and sleep health.

Enhancement during Sleep

SWA may also be enhanced directly by enhancing neural synchrony and the depolarized up-state during slow-wave sleep. SWA may be directly enhanced through exogenous sensory or transcranial stimulation, or through pharmacological agents, such as GABA agonists. However, GABA agonists have negative carryover effects on next-day cognition [76]. Serotonin 2 receptor (*5-hydroxytryptamine 2, 5-HT2*) antagonists enhance SWA, suppress wake, and promote cognitive function [77, 78], and may represent a more viable candidate pathway for pharmacological sleep augmentation. The effects of 5-HT2 antagonists have been reviewed elsewhere [78].

Exogenous stimuli can modulate neural activity through the sensory systems. For instance, during NREM sleep neurons fire in a synchronized pattern relative to wakefulness [1]. With an exogenous input, activity can be reset. By synchronizing the firing phase of neuronal populations, the summed amplitude and EEG spectral power measured on the scalp is larger [79]. This increase in synchrony and magnitude of waves leads to an increase in SWA power [79, 80]. Low frequency stimulation during sleep is commonly used to amplify SWA in memory consolidation studies [80]. Specific approaches include sensory stimulation with acoustic, olfactory, or vestibular stimuli, and low frequency transcranial stimulation. The common goal of these methods is to modify neural activity to make it more synchronous and thereby enhance SWA power. In contrast to the wake techniques described above that excite neural activity during wakefulness, each of the following techniques is intended to modify neural activity directly during sleep.

Sensory stimulation—Sensory stimulation techniques use rhythmic sensory stimuli, typically presented in low (< 4 Hz) frequencies, to augment slow-waves. Acoustic stimulation involves presentation of low frequency noise phase-locked to the up-state of the slow-wave [80]. Acoustic stimulation increases < 1 Hz SWA during and following stimulation periods [80–84]. In addition, acoustic stimulation further increases coupling of spindles and slow-waves [81]. Interestingly, analysis of visually scored SWS quantity (rather than EEG-measured SWA power) across the night is minimally influenced by such SWA enhancement.

The olfactory system has been exploited to enhance slow-waves during sleep in two ways: via mechanical stimulation, which is effective in rodents but not humans [85, 86], and through scented oils, such as lavender [87]. Mechanical stimulation is conceptually similar to acoustic stimulation, with puffs of air delivered to the nostrils at <1.5 Hz frequencies, with or without scents. Olfactory stimulation through scents involves presentation of scented oils such as lavender at sleep onset and throughout the night. Two studies in humans show

greater SWS with lavender oil presented during sleep [88, 89], one of which further reported co-occurring increased spindles [88]. While the current neurobiological mechanism(s) underlying these effects remains unclear, one suggested route involves interactions with GABA receptors [87], intimating that such sleep oscillatory stimulation involves neural inhibition.

Vestibular stimulation can be accomplished by physical rocking or external stimulation of the vestibular nerves [90]. For example, slow rocking of the bed (0.25 Hz) during a short nap increased frontal SWA (0.6–5 Hz) and spindle activity [91]. Consistent with other low frequency stimulation techniques, vestibular-induced changes in SWA and spindles occurred without significant increases to total SWS time, although the short duration of vestibular stimulation studies may also influence this finding. Exactly how vestibular manipulations modify NREM sleep across an entire night remains currently unexplored.

Acoustic stimulation results in consistent cognitive enhancing effects. Several studies in young adults and one study of older adults showed improved memory retention with acoustically enhanced SWA [81–84]. Studies of SWA enhancement through scented oils and vestibular stimulation have not yet examined effects on cognition. Future olfactory stimulation studies should contrast wake versus NREM sleep presentation of sleep-stimulating scents combined with pharmacological manipulations of GABA, to further understand its SWA-enhancing mechanisms. These studies should also investigate spindle-SWA coupling and cognitive outcomes to determine whether olfactory and vestibular stimulations show the same cognitive benefits as other low frequency stimulation approaches during sleep.

Transcranial Stimulation During Sleep—Non-invasive brain stimulation may also be used to enhance SWA during sleep. For instance, low frequency transcranial stimulation techniques, typically oscillatory anodal tDCS, and low-frequency tACS, and TMS, enhance slow waves by stimulating the cortex in trains of low frequency electrical or magnetic pulses during sleep [92], but see also [93–95], including a study that showed no effect of tACS on intracranially recorded SWA. Anodal tDCS with constant stimulation has also been used in one study to enhance membrane depolarization during periods of existing SWS leading to increases in SWA [96]. Stimulation over the frontal and sensorimotor cortex has moderate sized effects on SWA power [92, 94, 97, 98] and in some cases, also increases spindles [94, 97]. These effects have been observed in young and older adults during the minutes following the stimulation period, although total time spent in SWS tends to remain unchanged or may even decrease due to a reduction in sleep drive following the stimulation period.

Several studies using transcranial electrical stimulation (oscillating tDCS (0.75 Hz) or tACS (.75 Hz)) to enhance SWA have shown positive effects on declarative memory consolidation based on a meta-analysis [99]. Evidence for [98] and against [94] cognitive improvements with this technique has been reported in older adults.

Concluding remarks

Reflecting on the Archimedes-lever-like influence of sleep on processes of the brain and the body, augmenting sleep quality and/or quantity represents a target opportunity for the maintenance of human health across the lifespan, as well as treatment and prevention possibilities. Current augmentation techniques offer promise for increasing SWA and SWS. Moreover, these experimentally-induced increases in NREM sleep oscillations result in next-day benefit to cognition, specifically memory consolidation and executive function.

Nevertheless, questions remain regarding the causal role of SWA and overall NREM sleep quality in bringing about cognitive improvements found with enhanced neural activity, energy metabolism, and endocrine signaling approaches (see Outstanding Questions). Although spindles are grouped by slow-waves, SWA enhancement techniques have variable effects on spindles and other aspects of NREM sleep. Moreover, the synaptic processes underlying the link between wake behaviors and NREM sleep remain a topic of debate (Box 3), including whether SWA actively upscales synapses used during wakefulness, or simply downscales all synapses regardless of usage [100] (Box 3). In what follows, we briefly outline how to begin to address these critical, still outstanding questions.

Outstanding Questions Box

- Does synaptic plasticity during NREM SWS, as stimulated by neural activity, energy metabolism, and endocrine techniques, partially mediate improvements in cognition?
- What experimental controls can be used to test a causal role of SWA in enhancement of memory and executive function?
- Are there distinct cognitive benefits of amplifying high magnitude SWA compared to lengthening time spent in SWS?
- Do energy metabolism and techniques that stimulate SWA during sleep differ in their effects on the coupling of NREM sleep oscillations? Under what circumstances are their effects similar?
- Are SWA-based cognitive improvements driven by changes in synaptic strength during slow-wave sleep, and what techniques provide the most robust test for this hypothesis?

SWA Linking Wake Behaviors with Cognition

No intervention studies have specifically tested whether changes in SWA and SWA-spindle coupling co-occur with cognitive changes for the energy metabolism and endocrine techniques reviewed above. Control techniques such as cooling and aspirin used during exercise and warm baths to prevent heating [25] could determine whether these interventions lead to cognitive improvements in the absence of SWA or SWS increases. Such studies would provide compelling evidence that SWA mediates effects of heating on cognition, as opposed to physiological effects of heating occurring during wakefulness. However, this

approach would not rule out wake-related benefits of heating to the brain and cognition independent of SWA. Causality may be more directly established in an animal model inhibiting signaling of SWA-regulating cytokines. For instance, intra-ventricular injection of α melanocyte stimulating hormone inhibits SWA-enhancing effects of IL1 [101]. Such manipulations can help assess whether blocking SWA following increases in energy metabolism and signaling of SWA-promoting hormones minimize benefits to cognition. Identifying valid control conditions in neural activity/energy metabolism and endocrine signaling interventions in humans is an important next step, particularly for therapeutic techniques specific to humans such as meditation. Moreover, some SWA enhancement techniques (i.e. low-frequency stimulation) commonly amplify SWA, whereas heating techniques have reported more consistent lengthening of time spent in SWS. Manipulations of these two aspects of SWA may yield interesting and practical distinctions in their cognitive contributions and their ability to group other features of NREM sleep such as spindles and ripples.

SWA Enhancement and Spindle Changes

Studies of SWA enhancement during sleep have more consistently reported changes in SWA, spindle oscillations, and their coupling. However, results have varied widely within and between techniques regarding spindle activity, with similar methods often showing discrepant findings. For instance, transcranial stimulation during sleep has shown increases [97] in spindle activity, no change [94, 98], and in one case a decrease in fast spindle activity [98]. These discrepancies need to be systematically investigated. On the other hand, studies examining coupling of spindles with slow-waves have more consistently found positive effects on memory [81] in line with the view that slow-waves group spindles, and their temporal coupling is essential for memory consolidation [81]. Assessing EEG temporal dynamics is important not only for identifying slow wave-spindle coupling, but also because the co-occurrence of slow-waves and spindles depends on time of the night [23]. Future interventions using heating and other energy metabolism techniques would benefit from investigating coupling of NREM features to understand whether improvement in NREM sleep quality may support memory consolidation and other aspects of cognition.

SWA and Synaptic Plasticity

There is consensus that NREM sleep plays a critical role in cognitive function. How active a role SWA plays, however, is unclear [38], as discussed in Box 3. Wakefulness is associated with a net increase in synaptic strength and sleep is associated with a net decrease in synaptic strength [38]. Sleep-related changes may be moderated by the salience of activities that occurred during wakefulness [102–104], leading to the strengthening of used synapses and memory representations that depend upon them. However, it has also been postulated that synaptic circuits involved in memory formation are reactivated and strengthened through upscaling or potentiation during NREM sleep [104]. Importantly, selective memory-representation strengthening, and synaptic downscaling need not be mutually exclusive during NREM sleep. Increasing clarity of the interaction between synaptic strengthening and downscaling during NREM sleep will advance our understanding of how sleep augmentation methods may improve cognition and neural function. Indeed, sleep augmentation methods provide tools for better understanding these fundamental neural mechanisms. In addition,

multimodal neuroimaging techniques, including newly emerging human molecular neuroimaging of cellular functions such as protein synthesis, offer powerful additions for identifying the neural mechanisms underlying sleep's benefit to next-day cognition.

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Glossary

Down-state

hyperpolarized state of sleep slow waves characterized by tonic, reduced excitatory activity

Consolidation

Strengthening of memories over time following encoding, which results in long-term durable traces

Executive Function

Behavioral index of cognitive processing responsible for goal-driven planning, initiating, and monitoring

Potentiation

The increase in size of a postsynaptic potential after persistent stimulation

Sharp-wave ripples

Bursts of high frequency activity primarily in the hippocampus posited to reflect reactivation of memories during sleep

Slow-wave activity (SWA)

Electroencephalographic (EEG) activity within the slow wave (< 1 Hz) and delta (1–4 Hz) frequencies, which is most prevalent during Stage N3 sleep (slow-wave sleep)

Spindles

Electrophysiological feature of NREM sleep characterized by 12–16 Hz (sigma) activity originating from synchronized thalamo-cortical loops

Scaling

Synaptic plasticity that homeostatically renormalizes all synapses in a neuronal network in response to global changes in activity

Up-state

Depolarized state of slow waves characterized by brief, phasic bursts of excitatory post synaptic activity

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Highlights

- NREM sleep contributes to consolidation of memories and restored executive function. The involvement of NREM features in cognition depends on SWA.
- Enhancing SWA in older adults and clinical populations with cognitive deficits may effectively improve cognition through sleep.
- Techniques promoting energy metabolism, such as exercise, and endocrine signaling, such as growth hormone, are known to enhance SWA and cognition. SWA may therefore mediate the link between these approaches and cognition.
- Brain and body heating and transcranial stimulation during sleep are promising approaches to characterize the functions of SWA to improve cognition.

Figure 1 (Key Figure). Cascade of events resulting in behaviorally induced NREM SWA and the central nervous system consequences

Neural activity results in ATP release, which either converts to adenosine or activates astrocyte signaling of SWA-promoting cytokines, IL1 and TNF α . GABA-ergic neural inhibition leads to neural synchrony characterizing SWA. This groups phasic bursts of activity through thalamocortical spindles and hippocampal ripples that change the firing rate of synapses to consolidate memories and restore daytime function. Ellipses list examples of wake-based (yellow) and sleep-based (blue) techniques that enhance SWA through this cascade.

Figure 2. Process S under baseline conditions (gray) and under increased brain energy consumption (yellow)

Sleep drive and propensity for SWA accumulate during wakefulness and dissipate during sleep (gray). Sleep drive accumulates more rapidly with increased brain energy consumption, as with increased neural activity and energy metabolism (yellow). Thus, slow-wave activity is higher following sleep onset. A similar function would be hypothesized for endocrine signaling.