YALE JOURNAL OF BIOLOGY AND MEDICINE 92 (2019), pp.63-80.

REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

Can Slow-Wave Sleep Enhancement Improve Memory? A Review of Current Approaches and Cognitive Outcomes

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Slow-wave sleep (SWS†) is involved in the overnight consolidation of declarative memories. Recent efforts using auditory stimulation, slow-oscillatory transcranial direct current stimulation (so-tDCS), and pharmacological agents have targeted sleep slow-waves as a method for enhancing cognitive performance. However, no studies thus far have integrated current evidence to provide a preliminary review of the effects of SWS enhancement on memory and other cognitive outcomes. The objective of this review was to synthesize the results of recent experimental studies that have used auditory stimulation, electrical, and pharmacological methods to boost both SWS and cognitive performance. A systematic review was done to identify and consolidate all currently existing empirical studies in this area. We found that each stimulation method could enhance slow-wave power and/or SWS duration in human subjects. Closed-loop, in-phase auditory stimulation enhanced verbal declarative memory in healthy adults. Electrical stimulation using so-tDCS showed some efficacy in promoting verbal declarative memory, picture recognition memory, and location memory. Interleukin-6 and sodium oxybate enhanced declarative verbal memory, while tiagabine and sodium oxybate improved some non-memory measures of cognitive performance. There is some evidence that so-tDCS can also improve certain cognitive outcomes in clinical populations. Overall, future studies should recruit larger sample sizes drawn from more diverse populations, and determine clinical significance and effect sizes of each enhancement methodology.

INTRODUCTION

Slow-wave sleep (SWS), otherwise known as "deep sleep", is a component of non-REM sleep characterized by low-frequency, high-amplitude oscillatory EEG slow-wave activity (SWA) that is well-established to play an important role in the sleep-dependent consolidation of declarative memories [1,2]. The "active system consolidation hypothesis" suggests that slow oscillations, together with sleep spindles, drive the repeated reactivation of newly-encoded memories during SWS and thereby promote their integration into long-term memory storage sites [1]. The mounting theoretical and empirical evidence that points to sleep's importance in facilitating

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†Abbreviations: SWS, slow-wave sleep; PVT, Psychomotor Vigilance Task; so-tDCS, slow-oscillatory direct current stimulation; SWA, slow-wave activity; T8, Tiagabine; WCST, Wisconsin Card-Sorting Task.

Keywords: Slow-wave sleep, Slow-wave enhancement, Sleep slow oscillations, Auditory stimulation, Direct current stimulation, Memory, Sustained attention, Sleep spindles, Cognition, Humans

Author Contributions: Yujie Zhang (first author) completed the literature search and the writing of the review paper itself. She received editorial help from Dr. Reut Gruber (corresponding author).

memory consolidation [3,4] has led to the idea of directly enhancing sleep slow waves by increasing the power or duration of SWS as a potential means for cognitive improvement in human subjects [5]. However, no studies thus far have integrated information from recent experimental studies to provide a structured review of the overall effects of SWS enhancement. Determining the efficacy of experimental methods that enhance slow-wave activity to improve cognitive abilities like memory and executive function are important because the interplay between slow-wave sleep and memory functions is implicated in several serious medical and psychiatric disorders such as Alzheimer's disease [6] and schizophrenia [7] as well as in normal processes like healthy aging [8]. Thus, sleep interventions that can provide daytime cognitive benefits may be of interest to these clinical populations.

The objective of this review was to summarize and synthesize the results of existing empirical studies that used auditory stimulation, electrical stimulation via slow-oscillatory direct current stimulation (so-tDCS), or pharmaceutical interventions to enhance SWS and to modify cognitive outcomes. It was hypothesized that each enhancement method found to be capable of significantly boosting some measured aspect of SWS would also be significantly better than their non-active counterpart at inducing improvements to cognitive outcomes linked to SWS (particularly, aspects of declarative memory). An enhancement in slow wave activity is defined here as either increased SWS duration or increased SWA (slow oscillatory power/amplitude) compared to placebo or sham stimulation. We also included a brief description of the impact of stimulation methods on sleep spindles, as these have been shown to be involved significantly in overnight memory consolidation [9]. Cognitive outcomes that have been evaluated in studies using experimental methods to enhance SWA are verbal declarative memory, [*e.g.* 10], object location memory [*e.g.* 11], and picture memory [*e.g.* 12].

This review first offers a brief overview of each method of SWS enhancement. Within each stimulation method, it describes effects that the enhancement strategy had on sleep variables (including SWS and fast and slow sleep spindles), indicates the primary cognitive outcome variables measured and presents whether there was any cognitive benefit obtained from active stimulation or active medication conditions vs. placebo or sham. Next, it assesses whether changes in performance in cognitive tasks were tied to induced changes in sleep. Lastly, it suggests future research directions based on current evidence and gaps in the empirical literature.

Auditory Stimulation

Auditory stimulation uses 50-millisecond bursts of "pink noise" as a form of sub-arousal sensory stimuli. This stimulation acts to synchronize neuronal cortical activity and thereby increase the size and/or number of slow oscillations (defined as having a frequency <1 Hz) observed during SWS [10]. This method was used in overnight studies and nap studies. In three of the five overnight studies using this technique, auditory stimulation began 5 minutes after participants enter NREM sleep (stage two or deeper) for the first time and ended 210 minutes later [10,13,14]. Papalambros *et al.* [15] and Leminen *et al.* [16] used automated algorithms to target single slow-wave events (see Santostasi *et al*. [17] for a detailed description of stimulation algorithms). In afternoon nap studies, auditory stimulation is delivered intermittently throughout the entire 90-minute nap session [18,19]. In both nap and overnight studies, subjects take part in a sham control condition during which no auditory stimulation is applied but stimulation time points were marked [10].

Transcranial Direct Current Stimulation (tDCS)

Slow-oscillatory transcranial direct current stimulation uses electrodes placed bilaterally at frontal and/or central locations to apply oscillating currents at 0.75Hz (slow wave range) during sleep (see Marshall *et al.* [20] for a detailed description of procedures), with a mastoid (reference) electrode completing the circuit. This technique induces widespread electrical potential fields with a focus on fronto-cortical areas to increase the power and/or duration of slow wave activity (for technical details see Marshall *et al.* [20,21]). In the majority of studies, so-tDCS stimulation began 4 minutes after the first onset of stable NREM sleep stage two, and continuous stimulation was delivered 5 times, each in 5-minute blocks separated by 1-minute stimulation-free rest intervals. In one study, a ramping period of 8 seconds was added to the beginning and end of each stimulation block to reduce skin sensations [22].

Pharmacological

Pharmaceutical agents have been demonstrated in previous studies to be capable of enhancing slow-wave sleep [23]. Those that have been used in studies assessing both slow-wave sleep and cognitive outcomes include tiagabine [24,25], gaboxadol [26], sodium oxybate [27-29], baclofen [29], olanzapine [30,31], and interleukin-6 [32]. Tiagabine, gaboxadol, sodium oxybate, and baclofen each act to enhance slow-wave sleep by increasing synaptic levels of the major inhibitory neurotransmitter GABA [33]. Olanzapine is a second-generation atypical anti-psychotic medication that serve to increase SWS by acting as an antagonist to the serotonin$_{2C}$ (5-HT$_{2C}$) receptor, which is involved in SWS regulation [34]. In-

terleukin-6 is a proinflammatory cytokine up-regulated during sleep in SWS-rich, later portions of the night that is hypothesized to have neuromodulating influences on sleep-dependent memory consolidation [32]. The precise mechanisms of action of each pharmaceutical agent are beyond the scope of this review (see Mathias *et al.* [35], Lancel *et al.* [36], Lapierre *et al.* [37], Guilleminault and Flagg [38], Sharpley *et al.* [34], and Späth-Schwalbe *et al.* [39] for detailed descriptions of mechanisms involved in each substance).

METHODS

This review employed a systematic review methodology to identify and synthesize all existing empirical studies that have used SWS enhancement methods to induce improvements in cognitive outcomes (*e.g.*, memory, executive function, etc.). Given the limited number of published studies currently available on this topic, it was not possible to use meta-analytical strategies in this review. Key words including "slow-wave sleep", "NREM sleep", "Non-REM sleep", and "slow oscilla*" in combination with "enhance*" or "boost*" were used in a search of various major databases (PsycINFO, MEDLINE, EMBASE, PubMed) in December 2017 (with an addendum in 2018 to include a newly published article by Ong *et al.* [19] and Koo *et al.* [40]. All relevant, published empirical studies that used auditory, electrical, or pharmaceutical enhancement methods to increase slow-wave sleep and that measured subsequent cognitive outcomes were included in the summary tables (see Tables 1-3). Studies involving SWS interference were excluded, as were studies that used non-human subjects. In total, the literature search yielded 28 relevant papers. Nine of these studies used pharmacological strategies as their methodology of choice for SWS augmentation, 12 used electrical transcranial direct current stimulation (so-tDCS), and seven used auditory stimulation. Within the 28 studies included, 21 were overnight sleep studies, and seven were studies of afternoon naps.

RESULTS

The results of this review were organized by method (auditory stimulation, electrical stimulation, and pharmacological methods). Detailed information for each study referenced can be found in Tables 1-3.

Auditory Stimulation

Populations: All seven studies (100%) drew their samples from healthy adults (mean age = 22.0-75.2). Two were studies of 90-minute afternoon naps [18,19], and five were studies of overnight sleep [10,13-16].

Impact of the Auditory Stimulation Paradigm on Slow-Wave Activity and Sleep Spindles

Nap studies. Each of the two nap studies using auditory stimulation were successful in inducing increases in slow wave activity, finding an increase in the average amplitude of slow waves. Ong *et al.* [19] also found an increase in SWS duration in the stimulation condition compared to sham.

Overnight studies. Each of the five overnight studies using auditory stimulation were successful in inducing increases in slow wave activity, finding an increase in the average amplitude of slow waves. No studies found an increase in SWS duration under the stimulation condition, and Papalambros *et al.* [15] found that time spent in SWS was greater in the sham condition than the active stimulation condition.

All seven studies measured spindle activity, and of these studies five found an increase in spindle power or density in the auditory stimulation condition as compared to sham [13,15,16,18,19]. Wiegenand *et al.* [14] found a decrease in spindle power in the stimulation condition. Additionally, spindle activity was correlated with overnight word pair recall performance in two studies [10,16]. One study did not show any impact of auditory stimulation on verbal declarative memory compared with sham [14]. In this study, there was a decrease in spindle power in the stimulation condition. Another study with no group-level differences in memory encoding between stimulation and sham groups found spindles to be uncorrelated with memory benefits [19].

Impact of Auditory Stimulation on Cognitive Outcomes

Declarative verbal memory: A word-pair association task testing verbal declarative recall memory was used in one of the two nap studies [18,19] and all five overnight studies [10,13-16] as the primary cognitive outcome measured. This task involves presenting participants with 40 to 120 moderately semantically related word pairs. Prior to sleep, word pairs were displayed for 4 seconds each. Next, one word of each pair was presented for an unlimited amount of time and participants were asked to immediately recall the appropriate paired word. The same recall test is repeated upon waking, and retention rates serve as a proxy for verbal declarative memory consolidation. Of the six studies where declarative verbal memory was investigated, five (83.3%) (one study of a 90-minute afternoon nap, and four of the five overnight studies) revealed that the post-sleep word-pair retention rate was higher after subjects were in the stimulation condition than after sham [10,13,15,16,18].

Table 1. Auditory Stimulation

Study	Participants	Methods	Cognitive outcomes measured	Other sleep architecture variables considered	Results
Ngo *et al.* (2013) [10]	11 (8 female, mean age 24.2) healthy young adults	Closed-loop in-phase auditory stimulation	WPT[i]; PVT[d]	Stimulation increases fast and slow spindle synchrony with SO[f] cycle, but not amount/power	Stimulation induces trains of SOs[f]; increases SO[f] amplitude, slope, spreading Word pair retention rate significantly higher in stimulation condition Overnight retention of word pairs positively correlated with percentage of SWS during the stimulation period and peak amplitude of fast spindles phase-locked to SO[f] upstate
Ngo *et al.* (2015) [13]	18 (8 female, mean age 23.8) healthy young adults	Sham vs 'driving stimulation' (trains of clicks presented in synchrony with SO[f] up-states)	WPT[i]; PVT[d]; DST[a]; RWT[e]	Phase-locked increase in fast spindle activity only for first stimulus presented	Driving stimulation prolonged SO[f] trains, distinctly increased SO[f] amplitudes. Word pair retention rate significantly higher after stimulation
Weigenand *et al.* (2016) [14]	21 (11 male, mean age 22.2) healthy young adults	Quasi-phase dependent open loop stimulation: starts at a random phase of the SO[f]; second/third click timing relative to first click, chosen to maximize coinciding with evoked SO[f] up states	WPT[i]; PVT[d]; DST[a]; RWT[e]	Stimulation condition: Decrease in slow and fast spindle power; only first click evoked spindle response; non-significant longer time spent in N3	Stimulation condition: Significant increase in SO[f] power
Ong *et al.* (2016) [18]	16 (9 male, mean age 22) healthy young adults	Closed-loop stimulation phase-locked to SO[f] up-state during 90 min afternoon nap: blocks of 5 tones	WPT[i]	Stimulation condition: increased fast spindle activity, similar spindle density/count between conditions	Stimulation condition: Significant increase in SO[f] power, theta activity Forgetting of word pairs significantly less in stimulation condition; modest positive effect on declarative memory

Papalambros *et al.* (2017) [15]	13 (3 male, mean age 75.2, range 60-84) healthy older adults	Acoustic closed-loop stimulation phase-locked to SO[f] up-state: blocks of 5 tones	WPT[i]	Non-significant increase in fast spindle power in stimulation condition	Increase in SWA only during ON-intervals; SWA over entire sleep period similar across conditions; Time spent in SWS[h] greater in SHAM condition. Overnight improvement in word recall significantly better in stimulation condition Significant association between induced changes in SWA[g] and percent improvement in recall task
Leminen *et al.* (2017) [16]	15 (7 female, mean age 30.5) healthy adults	Automated acoustic stimulation phase-locked to SO[f] up-state: adjusted and targeted by unsupervised algorithm	WPT[1]; FTT[c]; picture recognition task; face-name association task	Increased spindle activity (density) in stimulation condition	Stimulation condition: significant increase in SO[f] power Overnight improvement better in stimulation condition for WPT[i] only Positive correlation between amount of N2 sleep and performance on WPT[i] (for stimulus night); positive correlation between sleep spindle activity increase and word-pair recall performance
Ong *et al.* (2018) [19]	37 (18 male, mean age 22.5) healthy young adults	Acoustic closed-loop stimulation phase-locked to SO[f] up-state during 90 min afternoon nap:	Memory encoding task following nap, tested for recognition 60-min later in retrieval phase; PVT[d]	Boost in EEG[b] power in spindle activity with stimulation but enhancement not associated with memory benefit	Stimulation condition: significant increase in SO[f] power and SWS[h] duration Magnitude of SO[f] enhancement correlated with greater recollection and hippocampal activation at encoding.

Note: DST[a] = Digit span test, EEG[b] = Electroencephalography, FTT[c] = Finger-tapping task, PVT[d] = Psychomotor vigilance task, RWT[e] = Regensburg word fluency test, SO[f] = Slow oscillation, SWA[g] = Slow-wave activity, SWS[h] = Slow-wave sleep, WPT[i] = Word pair task

Table 2. Transcranial Direct Current Stimulation (tDCS)

Study	Number of participants	Methods	Cognitive outcomes measured	Other sleep architecture variables considered	Results
Marshall *et al.* (2004) [21]	30 (all male, mean age 23.8) healthy adult men	Anodal tDCS[k] applied repeatedly frontocortically, bilaterally (30+ min; 15s OFF 15s ON) during SWS-rich nocturnal sleep	WPT[l]; MTT[c]; d2-test of attention	No significant increase in spindle power in so-tDCS[h] condition	Stimulation condition: increased SWA Stimulation condition: significantly increased retention of word pairs compared to sham
Marshall *et al.* (2006) [20]	13 (7 female, mean age 23.8) healthy young adults	0.75Hz so-tDCS[h], bilaterally at frontolateral and mastoid locations during early nocturnal NREM[d] sleep; five 5-min intervals, 1-min rest intervals (30 min)	FTT[b]; MTT[c]; WPT[l]; non-verbal declarative task; DST[a]	Stimulation increased slow spindle activity in frontal cortex	Stimulation condition: immediately induced slow oscillations, more time spent in SWS Stimulation condition: Significant improvement compared to sham in declarative memory tasks
Göder *et al.* (2013) [45]	14 (mean age 33, range from 30-82) patients with schizophrenia	0.75Hz so-tDCS[h] bilaterally at frontolateral and mastoid locations, sinusoidal currents	MTT[c]; RAVLT[e] (German), DST[a]	-	Stimulation condition: Significantly greater overnight retention of verbal material
Antonenko *et al.* (2013) [41]	15 (7 female, mean age 23.4) healthy young adults	0.75Hz so-tDCS[h] during 90-min nap	WPT[l]; RAVLT[e]; Picture learning task; FTT[b]	No significant difference in spindle power, counts, density, or length in stimulation vs sham conditions	Stimulation condition: enhanced SWA and SWS, (enhanced power in SWA frequency band in first 3 stimulation-free intervals) Stimulation condition: significantly better encoding on WPT[l], RAVLT[e], and picture learning task
Eggert *et al.* (2013) [22]	26 (16 female, mean age 69.1, range 60-90) healthy elderly adults	0.75Hz so-tDCS[h] during overnight early NREM[d] sleep, bilaterally, 30+ minutes stimulation duration	WPT[l]; FTT[b]; RWT[f]; DST[a]	Stimulation condition had no effect on spindle density	Stimulation condition: significantly less NREM[d] stage 3 sleep during five 1-min stim-free intervals
Prehn-Kristensen *et al.* (2014) [11]	12 boys with ADHD (mean age 12.1) 12 healthy boys (mean age 11.9)	0.75Hz so-tDCS[h] during early overnight SWS, bilaterally at frontalateral and mastoid locations	2D object location task (non-verbal declarative memory); DST[a]	-	SO[g] activity in sleep stage 4 significantly higher in stimulation condition Stimulation condition: significantly greater memory consolidation; No difference between stimulated children with ADHD and without ADHD

Sahlem *et al.* (2015) [42]	12 (9 female, mean age 25) healthy young adults	0.75Hz so-tDCS[h], bilaterally during early nocturnal NREM[d] sleep; Five 5-min intervals + 1-min rest intervals (30min); Square-shaped wave	WPT[l]; FTT[b]; RWT[f]	Non-significant increase in slow frontal spindle frequencies in stimulation condition	Non-significant increases in frontal slow delta activity; small decrease in stage 3 sleep 1hr following stimulation compared to sham Stimulation condition: non-significant increase on performance for finger-tapping task
Westerberg *et al.* (2015) [43]	19 (3 male, mean age 73.4, range 65-85) healthy older adults	0.75Hz so-tDCS[h], bilaterally fronto-temporally during 90-min afternoon nap; Five 5-min intervals, 1-min rest intervals (30 min)	WPT[l]; Declarative fact recognition task; Non-declarative object priming task	Central sites: fast-spindle density greater in sham nap	Stimulation condition: increased SO[g] activity in 1-min OFF intervals, increased frontal SO[g] power Stimulation condition: large improvement in word-pair recall performance
Paßmann *et al.* (2016) [44]	21 (11 male, mean age 65) healthy older adults	0.75Hz so-tDCS[h], bilaterally at frontolateral and mastoid locations during early nocturnal NREM[d] sleep; Five 5-min intervals, 1-min rest intervals (30 min)	Visuo-spatial picture location memory task; WPT[l]; FTT[b]; attention test	Increase in fast and slow spindle power after stimulation (1-min OFF segments) NREM[d] sleep stage 4 reduced after stimulation	Stimulation condition: higher SO[g] power at frontal and prefrontal electrodes Stimulation condition: impaired picture recognition on visuo-spatial task compared to sham
Ladenbauer *et al.* (2016) [12]	18 (10 female, mean age 65) healthy older adults	0.75Hz so-tDCS[h], bilaterally at frontocentral locations during 90-min nap	Visuo-spatial picture location memory task WPT[l]; FTT[b]; attention test	So-tDCS[h] significantly increased frontal and parietal fast spindle power and density	Stimulation condition: Increased frontal SO[g] activity (power) at frontal and parietal locations Stimulation condition: significantly better recognition performance of neutral pictures

Ladenbauer *et al.* (2017) [46]	16 (7 female, mean age 70.6) patients with mild cognitive impairment	0.75Hz so-tDCS[h], bilaterally at frontolateral and mastoid locations during early nocturnal NREM[d] sleep Five 5-min intervals, 1-min rest intervals (30 min) Procedure identical to [11]	Visuo-spatial picture location learning task; WPT[l]; FTT[b]; attention test	Stimulation condition: Increased fast and slow spindle power; Increased synchronization of fast spindles to SO[g] up-states; Increased sleep stage 2, less stage 1/wake during 1-min stimulation-free intervals	Stimulation condition: Increased frontal and centro-parietal SO[g] power during nap Stimulation condition: significantly better recognition performance of neutral pictures after correcting for sleepiness. Stimulation-induced improvement of visual memory associated with enhanced SO[g]/fast spindle synchronization (functional coupling)
Koo *et al.* (2018) [40]	25 (15 female, mean age 22.4, range 19-26) healthy young adults	Anodal oscillatory stimulation applied bilaterally at frontolateral locations during early nocturnal NREM[d] sleep Five 5-min blocks of so-tDCS[h], 1-min rest intervals (30 min)	Psychomotor vigilance task, RWT, DST, German Learn and Memory Test Battery, WPT, figural paired associates task, 2D-object location task, FTT, MTT	Stimulation condition: so-tDCS significantly increased centro-parietal fast spindle activity in 150-min post-stimulation period	Stimulation condition: overall, no effect on memory retention. Inter-individual difference: High memory quotient group had significantly increased performance on figural paired associates task

Note: DST[a] = Digit span test, FTT[b] = Finger tapping task, MTT[c] = Mirror tracing task, NREM[d] = Non-rapid eye movement, RAVLT[e] = Rey Auditory Verbal Learning Test, RWT[f] = Regensburger word fluency task, SO[g] = Slow oscillation, so-tDCS[h] = Slow-oscillatory transcranial direct current stimulation, SWA[i] = Slow-wave activity, SWS[j] = Slow-wave sleep, tDCS[k] = Transcranial direct current stimulation, WPT[l] = Word pair task

Table 3. Pharmacological

Study	Number of participants	Methods	Cognitive outcomes measured	Other sleep architecture variables considered	Results
Walsh *et al.* (2006) [24]	38 (19 placebo (9 male, mean age 26.0), 19 tiagabine 8mg (8 male, mean age 26.7)) healthy adults	Randomized, double-blind, placebo-controlled, parallel groups design Screening visit + 8 consecutive nights: One screening/adaptation night, one baseline night, four sleep-restriction nights (2 testing days), two recovery nights (1 testing day).	PVT[m]; PAS-AT[k]; Raven's Progressive Matrices, TTCT[u], WCST[v]	MSLT[h]: decrease for placebo group due to sleep restriction but no main group effect	T8[t] consistently increased SWS[s] duration (percentage) during the 4-night sleep T8[t] group: preserved sustained attention performance at baseline levels after sleep restriction (placebo group performance declined); Significantly better than placebo group in key WCST[v] measures
Göder *et al.* (2008) [30]	26 (7 female, 25 inpatients, mean age 30.1, range 19-44) patients with schizophrenia on antipsychotic medication	3 nights: control, baseline and treatment Before the third night: Olanzapine or placebo Before PSG[l] and in morning: neuropsychological tasks; Single blind design	RAVLT[n] (German); Modified RVDLT[p]; MTT[t]	Olanzapine group: Stage 2 sleep spindle density and REM[o] sleep significantly decreased	Olanzapine condition: significant increase in the amount of SWS[s] Spindle density positively correlated with verbal memory recognition performance
Walsh *et al.* (2008) [26]	41 (21 placebo (9 males, mean age 32.0), 20 GBX[e] (10 males, mean age 31.9) healthy adults	Double-blind, parallel group, placebo-controlled design 4 nights of sleep restriction with GBX[e] 15 mg or placebo	PVT[m], Cognitive Testing Battery: memory, attention, executive function; FTT[d]	GBX[e] group: significantly less physiological sleepiness on the MSLT[h], decreased introspective sleepiness and fatigue on KSS[g]	GBX[e] group: significantly more stage 4 and SWS[s] compared to the placebo group
Hall (2009) [27]	58 (28 placebo (11 males, mean age 27.1), 30 sodium oxybate (11 male, mean age 27.1)) healthy adults	Five days and nights in sleep lab: two baseline nights, two nights' sleep deprivation nights followed by 3-hr nap opportunity during following day, one recovery night; 3.5g dose of sodium oxybate or placebo administered on day three and four before nap opportunity	WPT[w]; FTT[d]	Sodium oxybate group: reduced REM[o], reduced homeostatic sleep drive during recovery sleep; Placebo group: slightly more stage 1 sleep,	Sodium oxybate group: Significantly greater amount of SWS[s] Sodium oxybate group: able to maintain baseline encoding levels on WPT[w] with sleep loss (unlike placebo group)

Benedict *et al.* (2009) [32]	17 (all male, mean age 25.4) healthy adult men	20 0.1-ml puffs (10/nostril) of IL-6[f] (recombinant human IL-6[f], 0.8mg diluted in 2ml of PBS) or placebo administered intra-nasally before overnight sleep to subjects at 30-s intervals, to a total dose of 2ml of IL-6[f]	Verbal learning task (neutral and emotional texts); 2D object-location memory task; FTT[d]	Significant changes were not found for either the low or high frequency spindle bands	Second half of the night: Significantly longer SWS[s] (min) during the second half of the night; significantly higher average SWA[r] at fronto-central site during second half of the night. IL-6[f] group: Significant improvement on declarative verbal learning task for emotional content words (but not neutral content words)
Walsh *et al.* (2010) [28]	58 (28 placebo (11 male, mean age 27.1), 30 sodium oxybate (11 male, mean age 27.1)) healthy adults	Five-day protocol: Two baseline/ screening nights, two sleep deprivation nights (each followed by a 3h daytime sleep opportunity), and a recovery night. Placebo or 3.5g sodium oxybate administered prior to each of the two daytime sleep opportunities	PVT[m]; DSST[c]; WCST[v]; WPT[w]; FTT[d]	Sodium oxybate group: Lower power in 12-Hz and 13-Hz bins on Day 3, 12-Hz bin on Day 4; Shorter stage 4 sleep, less SWS[s], less REM[o], lower total sleep time; Reduced homeostatic sleep drive on Night 5	Sodium oxybate group: greater amount of stage 3, stage 4, and SWS[s] during daytime sleep after deprivation; Higher SWA[r] power density on Day 3 and 4 in 1-9 Hz range (exception of 2-Hz bin on Day 4) Sodium oxybate group: shorter median reaction time on PVT[m] on Day 4
Vienne *et al.* (2012) [29]	13 (all males, mean age = 23.5) healthy young adult men	Five weekly sessions of three consecutive nights; 30mg/kg of sodium oxybate, 0.35mg/kg BAC[a], or placebo before nap or before experiment night	PVT[m]; WPT[w]; 2D face-location memory task; FTT[d]	Sodium oxybate and BAC[a] conditions: increase in total sleep time and EEG delta/ theta power, decrease in sleep latency also observed during REM[o] and wakefulness	Sodium oybate and BAC[a] conditions: increase in SWS[s] during first NREM[j] sleep episode Significant correlation between total sleep time during nap and PVT[m] mean reaction time in BAC[a] condition
Feld *et al.* (2013) [25]	14 (all male, mean age 21.9) healthy young adult men	Two overnight experimental sessions scheduled ≥14 days apart for same participants; oral administration of placebo or tiagabine (Gabitril 10 mg, Teva GmbH, Germany)	WPT[w]; Emotional picture memory consolidation task; FTT[d]; PVT[m]	Fast spindle activity and slow frontal spindle activity significantly reduced following tiagabine, especially those occurring phase-locked to SO[q] cycle	Significant longer time in SWS[s] in tiagabine condition; Significantly increased mean power density in slow oscillation, delta, and theta frequency bands. Tiagabine condition: Significantly reduced accuracy of finger tapping

Lazowski *et al.* (2014) [31]	25 (10 placebo (5 male, mean age 46), 15 olanzapine (6 male, mean age 46)) patients experiencing major depressive episode on stable medication	Placebo or oral olanzapine (2.5mg on Day one, 5mg at Day two; during Day 2–4, dosing was titrated to a maximum of 20 mg). Mean dose of olanzapine=6.67mg at end of study; range=5-10mg.	CANTAB[b]: Spatial Working Memory, Spatial Span, and Reaction Time tasks	Sleep continuity improvement in olanzapine group vs placebo (including sleep efficiency, total sleep time, number awakenings, time spent awake)	Olanzapine condition: decreased latency to SWS[s] but no significant difference in SWS[s] duration or percentage

Note: BAC[a] = Baclofen, CANTAB[b] = Cambridge Neuropsychological Test Automated Battery, DSST[c] = Digit symbol substitution test, FTT[d] = Finger-tapping task, GBX[e] = Gaboxadol, IL-6[f] = Interleukin-6, KSS[g] = Karolinska Sleepiness Scale, MSLT[h] = Multiple sleep latency test, MTT[i] = Mirror tracing task, NREM[j] = Non-rapid eye movement, PASAT[k] = Paced Auditory Serial Addition Test, PSG[l] = Polysomnography, PVT[m] = Psychomotor vigilance task, RAVLT[n] = Rey Auditory-Verbal Learning Test, REM[o] = Rapid eye movement, RVDLT[p] = Rey Visual Design Learning Test, SO[q] = Slow oscillation, SWA[r] = Slow-wave activity, SWS[s] = Slow-wave sleep, T8[t] = Tiagabine; TTCT[u] = Torrance Tests of Creative Thinking, WCST[v] = Wisconsin card-sorting task, WPT[w] = Word pair task

Relationship Between Changes in Sleep Parameters and Changes in Verbal Declarative Memory After Auditory Stimulation

Five of the seven auditory enhancement studies (71.4%) found that improvements in verbal declarative memory and enhanced slow oscillatory power both occurred as a result of auditory stimulation [10,13,15,16,18]. Four of the seven studies reported significant correlations between cognitive outcomes and induced changes in SWA [10,15,16,19]. Ngo *et al.* [10] found that change in overnight retention of word pairs (*i.e.*, verbal declarative memory) was positively correlated with both the percentage of SWS during the stimulation period and fast spindle power. Papalambros *et al.* [15] found a significant association between improvements in verbal declarative memory and induced changes in SWA, but not spindle density, time spent in SWS, or total average SWA. Leminen *et al.* [16] found a positive association between subjects' performance on the verbal declarative memory task and the amount of N2 sleep and spindle activity that they experienced on stimulus nights. Finally, Ong *et al.* [19] found that the magnitude of SO enhancement, but not increases in spindle activity, was correlated with better performance on a picture encoding task. The remaining three studies [13,14,18] did not report a correlation between cognitive change and change in any sleep variable, despite two of the three studies [13,18] finding higher word-pair retention rates and SO amplitudes under auditory stimulation conditions.

Transcranial Direct Current Stimulation (tDCS)

Populations: Twelve studies used slow-oscillatory transcranial direct current stimulation to enhance slow-wave sleep and cognitive outcomes. Nine of the 12 so-tDCS studies (75.0%) involved participants who were healthy adults where the mean age ranged from 22.4-73.4 [12,20-22,40-44]. Three studies (25.0%) involved clinical populations [11,45,46]. Of these studies, one examined boys with ADHD where the mean age of participants was 11.9 [11], another involved patients with mild cognitive impairment where the mean age was 70.6 [46], and the last drew its sample from patients with paranoid schizophrenia where the mean age was 33 [45].

Impact of so-tDCS Electrical Stimulation on Slow-Wave Activity and Sleep Spindles

Nap studies: All three nap studies using slow-oscillatory transcranial direct current stimulation (so-tDCS) were successful in inducing slow wave activity [12,41,43], and one of the three also found that SWS duration was higher under the stimulation condition compared to sham [41].

Overnight studies*:* Five of the nine overnight studies

(55.6%) using so-tDCS were successful in inducing slow wave activity [11,20,21,44,46], and one of the five also found that SWS duration was higher under the stimulation condition compared to sham [20]. Of the remaining three studies, one did not report whether there were changes in sleep parameters [45], one found that so-tDCS did not significantly alter EEG activity in the acute stimulation period [40] and two found tDCS to decrease the amount of NREM stage three sleep subjects experienced [22,42].

Overall, electrical stimulation enhanced SWA in six of the nine studies of healthy adults [12,20,21,41,43,44] and in two of the three studies of clinical populations (patients with MCI [46] and boys with ADHD [11]).

Ten of 12 tDCS studies reported on spindle activity in tDCS conditions compared to sham [12,20-22,40-44,46], and seven of these ten studies (70%) found some impact of stimulation on spindle activity [12,20,40,42-44,46] (six of the ten were statistically significant [12,20,43,44,46]). In seven studies (of which one mathematically but not statistically significant), stimulation increased spindle activity (power, density, and/or frequency) in the frontal, central, or parietal sites [12,20,40,42-44,46]. All but one study [40] in which increases in spindle activity were found in the stimulation condition also found increases in SWA.

Evidence for Declarative Memory, Picture Recognition Memory, and Location Memory Enhancement Using so-TDCS

Declarative verbal memory: 11 out of the 12 studies included a variation of a verbal recall declarative memory task (word-pair association task [12,20-22,40-44,46] or Rey-Auditory Verbal Learning Test [41,45]). The Rey Auditory Verbal Learning Test involves a list of 15 semantically unrelated nouns which were orally presented 5 times for 1 second each. A free recall test was conducted after every presentation. After another unrelated list of words (interference list), subjects were asked to recall the list of original words [47]. Of all 11 nap and overnight so-tDCS studies involving verbal declarative memory, 5 (45.5%) found a significantly greater retention of verbal material after so-tDCS [20,21,41,43,45]. Two of the three nap studies found a significantly greater retention of verbal material after so-tDCS [41,43]. Three of the nine overnight studies (33.3%) found a significantly greater retention of verbal material after so-tDCS [20,21,45].

Picture recognition memory*:* Seven so-tDCs articles (three nap studies, four overnight studies) also examined picture, picture-fact recognition, or figure-pair association memory (non-verbal declarative memory) [12,20,40,41,43,44,46]. Four of these studies (57.1%) found a significant improvement in recognition memory across all participants under active stimulation [12,20,41,46]. One study [40] found that so-tDCS only improved non-verbal declarative memory for participants with a high memory quotient, one [44] found picture recognition was worse under the stimulation condition, and one [43] showed no significant difference between stimulation and sham. Two of the three nap studies found a significant improvement in picture recognition memory [12,41]. Two of the four overnight studies found a significant overall improvement in picture recognition memory [20,46].

Location memory*:* One of the five (25.0%) so-TDCs articles that examined location memory found a significant improvement under the stimulation condition [11]. This study was also the only one whose participants were children (boys with ADHD and healthy controls), while the four studies finding no effect of stimulation on location memory drew samples from a young adult [40] or older adult population [12,44,46].

Relationship Between Changes in Slow-Wave Activity and Changes in Cognitive Measures After so-tDCS

Four of the 11 studies using so-tDCS (36.4%) found that improvements in verbal declarative memory and enhanced SO power/SWS duration both occurred with anodal slow oscillatory electrical stimulation [20,21,41,43]. Electrical stimulation which successfully enhanced SO power was also found to be efficacious in enhancing picture recognition memory in two studies [12,46], as well as location memory in another [11]. There were no additional correlations between cognitive outcomes and induced changes in SWA in any study.

Pharmacological

Populations: Participants were healthy adults (range of mean ages = 21.9-31.9) in seven of the nine studies (77.8%) [24-29,32]. Two remaining studies involved a clinical population (patients with major depression (mean age = 46) [31] and patients with schizophrenia (mean age = 30.1) [30].)

Tiagabine, Olanzapine, Gaboxadol, Sodium Oxybate, Baclofen, and Interleukin-6 Each Efficacious in Enhancing SWS Duration but Studies Reporting on Spindles Find Negative Impact of Medications

Eight of the nine studies (88.9%) using pharmacological methods were successful in enhancing SWS duration [24-30,32] but none directly enhanced the power of slow oscillations. The one study that found no significant effect of the active medication [31] did find a decreased latency to SWS, but no overall increase in SWS duration or percentage. Two studies used tiagabine as the active

pharmaceutical to be tested [24,25], two used olanzapine [30,31], one used gaboxadol [26], two used sodium oxybate [27,28], one used sodium oxybate in combination with baclofen [29], and one used interleukin-6 [32]. All studies compared their active ingredient to a placebo group. Overall, all seven pharmacological studies involving healthy adults (range of mean ages = 21.9-32.0) were successful in increasing SWS duration. Of the two studies involving clinical populations, olanzapine was efficacious in enhancing SWS duration in patients with schizophrenia on stable antipsychotic medication where the mean age was 30.1 [30]. However, olanzapine was unable to boost SWS duration in patients currently experiencing a major depressive episode and on stable medication (mean age = 46) and only decreased their average latency to SWS [31].

Three of the nine studies (33.3%) reported on spindles, with two finding a significant decrease in spindle power (sodium oxybate [28] and tiagabine [25]) after active medication and one finding no difference between conditions (interleukin-6 [32]).

Impact of Tiagabine, Sodium Oxybate, and IL-6 on Several Cognitive Domains

Sustained attention*:* Sustained attention was measured in five pharmacological studies using the Psychomotor Vigilance Task (PVT) [48]. The PVT is a simple 10-minute visual reaction time test measuring sustained attention where the subject responds to the appearance of a light at random intervals. PVT scores were greater in the active pharmaceutical group than in the placebo group in two of the five studies (40%) where it was measured (one tiagabine [24], one sodium oxybate [28], all with healthy adult subjects).

Concept formation and executive function: The Wisconsin Card-Sorting Task (WCST) measures concept formation and executive function by continuously presenting stimuli (sets of four cards) and feedback until subjects identify predetermined criterion principles [24]. The number of trials subjects take to reach the first criterion principle, the total number of trials, total errors, and total number of perseverative errors are the outcomes of interest. This measure was used by one study using tiagabine as the active pharmaceutical [24], and one study using sodium oxybate [28]. Only the tiagabine study [24] found that the active medication resulted in improvements on WCST measures (*i.e.,* T8 subjects committed fewer total errors, fewer perseverative errors, needed fewer trials to complete the first category, and needed fewer trials to complete the entire task). The other study by Walsh *et al.* [28] found no significant effect of sodium oxybate on WCST results.

Declarative verbal memory: One study of healthy young men [32] showed that intranasal interleukin-6 enhanced declarative verbal memory for emotional content words compared to placebo. In this verbal learning task, participants were presented with one emotional and one neutral text (between 202-255 words, ~95 content words) to read and memorize. Immediate free recall tested initial encoding by asking subjects to write down the text from memory as closely as possible to the original. After sleep, recall was tested again in the same fashion. Performance on this task was determined by the percentage of correct content words recalled by participants. One study using sodium oxybate also found encoding of word pairs (declarative verbal memory) was less impaired after sleep loss when active medication was administered compared to placebo [27].

More than half of the studies (55.6%) found no significant differences on any of the cognitive measures between active medication and placebo [25,26,29-31], and one study [25] found a detrimental effect of tiagabine on procedural memory as measured by a finger-tapping task.

Relationship Between Changes in Slow-Wave Duration and Changes in Cognitive Domains after Tiagabine, Sodium Oxybate, or IL-6 Intervention

Two studies (one using tiagabine as the active medication [24], one using sodium oxybate [28]) found both increased sustained attention (mean PVT reaction time) and increased SWS duration under active medication conditions compared to placebo. Improved executive function and concept formation (as measured by Wisconsin Card Sorting Test) was also found in one study when SWS duration was increased by tiagabine [24]. Encoding of declarative verbal memories was also shown to be improved in one study when SWS was increased by sodium oxybate [27]. Similarly, interleukin-6 enhanced both declarative verbal memory for emotional content words and SWS duration [32]. No additional correlations were found between cognitive outcomes and induced changes in SWS duration in any study.

DISCUSSION

The objective of this review was to summarize and synthesize the results of recent studies that have used auditory stimulation, electrical, and pharmacological methods to induce the enhancement of SWS and cognitive abilities. The main findings were: 1) all three of these stimulation methods were capable of promoting slow-wave power and/or SWS duration in human subjects; 2) closed-loop, in-phase auditory stimulation resulted in improvement in verbal declarative recall memory; 3) electrical stimulation via so-tDCS showed mixed efficacy in improving verbal declarative memory and picture recognition memory, and had limited efficacy in promoting location memory; 4) pharmacological methods of SWS

enhancement showed limited efficacy in improving verbal declarative memory, sustained attention, or executive function.

Impact of Auditory Stimulation, Electrical, and Pharmacological Methods on Slow-Wave Power and SWS Duration

Auditory stimulation that used a closed-loop, in-phase paradigm and had sound pulses phase-locked to the slow-wave up-state enhanced SWA and was better than sham stimulation at inducing greater slow-wave power. This was also true in the one study where quasi-phase dependent open loop stimulation was used instead of closed-loop stimulation [14]. Most nap and overnight so-tDCS stimulation studies were successful in inducing increased SWA, and several also found increased SWS duration. The large majority of pharmacological enhancement studies were also able to prolong SWS duration in their active medication condition, though none increased slow-wave power.

Impact of Enhancement Strategies on Cognitive Outcomes

Auditory stimulation successfully enhanced verbal declarative recall memory as measured by a word-pair association task in most nap and overnight studies reviewed [10,13-16,18,19]. All studies which were successful in enhancing verbal declarative memory used a closed-loop, in-phase stimulation paradigm, while the only study [14] which used an open-loop auditory stimulation paradigm was unsuccessful in enhancing verbal declarative memory. From these results, it may be concluded that closed-loop auditory stimulation locked to sleep slow-wave up-states is efficacious in enhancing verbal declarative memory. There is no current evidence that auditory SWA enhancement methods can improve picture recognition memory, sustained attention, executive function, or location memory.

Electrical brain stimulation showed mixed efficacy in enhancing verbal declarative memory as measured by a word-pair association task or the Rey Auditory Verbal Learning Test, with slightly under half of so-tDCS studies reviewed finding a significant improvement after stimulation [20,21,41,43,45]. This method also showed some efficacy in improving picture recognition memory, with 57.1% of so-tDCS studies where this outcome was investigated finding improvements after active stimulation compared to sham [12,40,41,46]. One so-tDCS study found a significant improvement in location memory under the stimulation condition [11]. No studies have yet shown so-tDCS to be capable of enhancing sustained attention or executive function abilities.

Only one study using interleukin-6 [32] and one study using sodium oxybate [27] out of six pharmacological studies that included a measure of verbal declarative memory were found to be successful in of boosting declarative verbal memory, suggesting that pharmaceutical agents have limited efficacy in enhancing verbal declarative memory. Tiagabine [24] and sodium oxybate [28] were the only compounds found to improve sustained attention as measured by the Psychomotor Vigilance Task. Tiagabine also improved concept formation/executive function in one study as measured by the Wisconsin Card Sorting Task [24]. No other SWS-boosting pharmacological agent enhanced sustained attention or executive function. Currently, there is no evidence that any pharmacological method for enhancing SWS can improve picture recognition memory or location memory.

Studies that used electrical or auditory SWS enhancement methods were primarily efficacious in enhancing slow-wave power, and were both capable of improving aspects of declarative memory. Meanwhile, studies using pharmacological methods were capable of increasing the duration of slow-wave sleep but not slow-wave power and had only limited success in enhancing cognitive performance. These results suggest that enhancing slow-wave power may play a more important role as a tool for improving memory than enhancing overall slow-wave duration.

Impact of Enhancement Strategies on Sleep Spindle Activity

Many auditory and electrical enhancement studies boosted sleep spindle power [12,13,15,16,18-20,40,43,44,46] but results were mixed in terms of how exactly they are implicated in the linkage between stimulation methods, SWA enhancement, and cognitive outcomes. Spindle activity was found to be increased alongside verbal declarative recall memory in each study where auditory stimulation was successful in enhancing both cognitive outcomes and SWA [10,13,15,16,18], suggesting that spindles had a positive impact on verbal declarative memory. The only auditory stimulation study in which SWA enhancement did not increase verbal declarative memory [14] found a decrease in spindle power in the stimulation condition, providing further evidence for the importance of spindles in facilitating SWA-mediated memory improvement.

It is difficult to determine whether spindle activity was impacted by pharmacological agents used to increase SWS as only a minority of studies reported on spindles [25,28,32]. However, the two studies that found spindle power to be decreased by active medication [36,37] suggest that the pharmaceutical mechanisms of action that allow tiagabine and sodium oxybate to increase SWS may have a negative impact on spindle power.

The fact that spindle activity was increased in each

study where auditory stimulation enhanced SWA and cognitive outcomes, but spindle activity was decreased in several pharmacological studies where SWS duration was enhanced and no cognitive improvements arose, suggests that the simultaneous enhancement of sleep spindles may be necessary for augmented SWS to effectively improve cognitive performance. This idea is supported by recent evidence showing that sleep spindles are modulated by SO-upstates and that it may be the functional coupling between slow oscillations and spindles (instead of either sleep parameter individually) that leads to improved memory consolidation [49]. However, there were also several so-tDCS studies where spindle activity was not significantly improved despite improvements in SWA and cognitive outcomes [21,41,42], which complicates this conclusion and is a worthwhile avenue for future studies that seek to explore sleep and memory enhancement via so-tDCS.

Causal Effects of SWA Enhancement Methods on Cognitive Improvement

Most auditory stimulation studies found that improvements in verbal declarative memory and enhanced slow oscillatory power co-occurred as a result of auditory stimulation [10,13,15,16,18]. Moreover, several of these studies reported significant correlations between cognitive outcomes and induced changes in SWA [10,15,16,19]. These results suggest that an increase in slow-wave power is causally implicated in the mechanism that allows auditory stimulation to improve verbal declarative memory.

The causal connection between SWA enhancement mediated by so-tDCS and improvements in verbal declarative memory is somewhat less clear than with auditory stimulation, as no significant correlations were found between cognitive outcomes and SWA enhancement in any study. Nevertheless, significantly improved performance on at least one cognitive task was noted in nearly every study (Paßmann *et al.* (2016) [44] was the only exception) where so-tDCS successfully increased SWA [11,12,20,21,41,43,46]. This provides some evidence for a causal relationship between so-tDCS-mediated SWA enhancement and benefits to verbal declarative memory, picture recognition memory, and location memory.

Of the pharmacological enhancement methods, tiagabine, sodium oxybate, and interleukin-6 each induced increases in SWS duration that led to improvements in several cognitive outcomes [24,27,28,32]. However, the causal connection between pharmacologically-enhanced SWS and cognitive performance is quite ambiguous as 44.4% of the studies found an increase in SWS duration without a concurrent increase in any cognitive variable [25,26,29-31]. Moreover, no studies found a correlation between increases in SWS duration and improvements in any cognitive domain.

Impact of Enhancement Methods on Healthy and Clinical Populations

There is evidence that closed-loop auditory stimulation can improve SWA and verbal declarative memory in healthy adults (particularly young adults, as only one study [15] examined older adults). No auditory stimulation studies examined clinical populations.

The evidence is mixed as to whether so-tDCS is efficacious in enhancing SWA and verbal declarative memory in healthy populations, as three studies of healthy young adults [20,21,41] and one study of healthy older adults [43] found benefits to verbal declarative memory using so-tDCS, but three studies of older adults [12,46,44] and one study of young adults [42] found no such effect. Based on these results, it may be concluded that so-tDCS is most efficacious in younger populations as a SWS enhancement strategy to boost verbal declarative memory. As suggested by Paßmann *et al.* [44], delayed SWS onset in older adults may mean that having electrical stimulation begin almost immediately after the onset of NREM stage two sleep is too early and leads to increased arousal rather than increased SWS.

There is evidence that so-tDCS is efficacious in improving SWA and certain areas of cognitive performance in patients with schizophrenia, boys with ADHD, and patients with mild cognitive impairment (MCI). Specifically, verbal declarative memory was improved in the study of patients with paranoid schizophrenia [45], object location memory was improved in the study of boys with ADHD [11], and picture recognition memory was improved in a study of patients with MCI [46].

Every pharmacological study involving healthy participants enhanced SWS duration, but only sodium oxybate [27,28], tiagabine [24], and interleukin-6 [32] were found in at least one study to improve cognitive performance in any domain. There is evidence that olanzapine can increase the amount of SWS experienced by patients with schizophrenia [30] but this study did not find that this improvement in SWS duration led to significant improvements in declarative verbal memory, visual declarative memory, or procedural memory compared to placebo. Olanzapine also failed to increase SWS duration (but did decrease latency to SWS) and did not provide cognitive benefits to patients currently experiencing a major depressive episode [31].

Clinical Future Directions

The investigation of auditory stimulation as a method of enhancing slow-wave activity (SWA) and cognitive outcomes has focused exclusively thus far on healthy populations. Future studies should test the efficacy of au-

ditory stimulation as a method to boost SWA and verbal declarative memory in clinical populations. As a physiologically natural, non-invasive enhancement method, auditory stimulation could be used in clinical populations with verbal declarative memory deficits such as in patients with schizophrenia [50].

A limitation of previous studies is that participants were not retested at later time points to examine whether any improvements in cognitive outcomes were maintained over time. This is of particular relevance for clinical populations to determine whether these interventions can result in sustained therapeutic benefits. Follow-up studies should be done to determine whether any significant improvements in overnight declarative memory consolidation abilities were maintained in participants where any stimulation method successfully enhanced slow-wave activity and memory.

SWS/SWA enhancement methods were only applied over one nap or overnight session. Future research should determine whether having multiple nights or sessions of closed-loop auditory stimulation, slow-oscillatory direct current stimulation, or pharmacological interventions could further increase the magnitude of cognitive benefits. Debellemaniere *et al.* [51] recently found that auditory closed-loop stimulation increased SO power at the same level for ten consecutive nights, inviting future exploration of this method in terms of sustained cognitive improvements.

No slow-wave sleep enhancement study thus far has tested whether improvements in cognitive measures generalize to other cognitive tasks or to tasks of daily life. The generalizability of improvements in measures of cognitive performance such as the word-pair association task, the picture recognition memory task, or the Psychomotor Vigilance Task should be examined in future studies. If improved performance in in-lab tasks translates to improved performance in real-world tasks (such as academic or occupational performance immediately after a stimulation session), there would be stronger evidence for the clinical utility of slow-wave sleep enhancement methods.

Methodological Issues

One important methodological limitation of current studies is their small sample size and narrow range of demographics included, as most studies examined healthy young adults. Future studies should expand the use of SWS enhancement to larger and more clinically diverse samples to provide more conclusive evidence for the efficacy of these methods in enhancing SWA and cognitive outcomes.

The effect sizes of all cognitive improvements using all slow-wave sleep enhancement methodologies should also be evaluated in further research, as it is unclear whether any of the statistically significant differences in memory performance found in previous studies were also clinically significant. By determining relative effect sizes, a more conclusive comparison could be made between the different enhancement methods.

Slow-oscillatory transcranial direct current stimulation has shown mixed results in its ability to improve SWA and cognitive outcomes. While a number of studies have found positive effects of so-tDCS [11,12,20,21,41,43,45,46] several studies have found no effect or a negative effect of active stimulation on memory [22,42,44] and recent evidence has found that inter-individual factors may predict whether so-tDCS is effective in enhancing cognitive performance [40]. Such mediating and moderating factors (such as spindle activity or participant characteristics) that may contribute to whether stimulation methods targeting sleep slow waves leads to cognitive improvements are worthy targets of further investigation.

CONCLUSION

Closed-loop in-phase auditory stimulation, slow-oscillatory transcranial direct current stimulation, and several pharmacological substances including tiagabine, sodium oxybate, and interleukin-6 were found in this review to be capable of enhancing slow-wave activity/SWS duration and improving performance in several cognitive domains. Future research should put emphasis on involving broader clinical populations, investigating the role of spindles and other mediators in the connection between SWA enhancement and cognitive benefits, and determining effect sizes of each enhancement strategy.

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