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Original Article

ORIGINAL ARTICLE

Modulating overnight memory consolidation by acoustic stimulation during slow-wave sleep: a systematic review and meta-analysis

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Abstract

Study Objectives: The low-frequency high-amplitude oscillations of slow-wave sleep (SWS) are considered to promote the consolidation of episodic memory. Previous research suggests that sleep slow waves can be entrained and enhanced by presenting short acoustic stimuli to the up-states of endogenous waves. Several studies have investigated the effects of these increases in slow-wave activity on overnight memory consolidation, with inconsistent results. The aim of this meta-analysis was to evaluate the accumulated evidence connecting acoustic stimulation during sleep to episodic memory consolidation.

Methods: A systematic literature search was conducted in October 2020 using PubMed, Web of Science, and PsycInfo. The main study inclusion criteria were the application of acoustic slow wave enhancement in healthy participants and an assessment of pre- and post-sleep episodic memory performance. Effect sizes were pooled using a random-effects model.

Results: A total of 10 primary studies with 11 experiments and 177 participants were included. Results showed a combined effect size (Hedges' *g*) of 0.25 ($p = 0.07$). Subgroup models based on young adults ($n = 8$), phase-locked stimulation approaches ($n = 8$), and their combination ($n = 6$) showed combined effect sizes of 0.31 ($p = 0.051$), 0.36 ($p = 0.047$), and 0.44 ($p = 0.01$), respectively. There was no indication of publication bias or bias in individual studies.

Conclusions: Acoustic enhancement of SWS tends to increase the overnight consolidation of episodic memory but effects remain small and—with the exception of subgroup models—at trend levels. Currently, the evidence is not sufficient to recommend the use of commercially available devices.

Statement of Significance

Research suggests that acoustic stimulation during slow-wave sleep can enhance slow oscillatory activity and—as a downstream effect—memory consolidation. It therefore bears potential to be used as a noninvasive, inexpensive tool in the treatment of memory-related disorders. This is the first meta-analysis that quantitatively summarizes memory effects found in studies applying acoustic slow wave stimulation. Overall, the found effect size was small and nonsignificant. However, the number of studies is still relatively small, especially in the older cohort. Additionally, studies suffer from small sample sizes. Hence, caution is advised when dealing with commercial products that are already in use today.

Key words: slow-wave sleep; acoustic stimulation; episodic memory; consolidation

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Introduction

Recalling a memory, for example, a new acquaintance's name, might prove difficult in the evening after a long day. But after a good night's sleep, the same recollection can often come about seemingly effortless. Scientific evidence supports the colloquial experience that sleep has a positive effect on memory functions [1, 2]. In particular, sleep's role in episodic memory consolidation has been highlighted. Episodic memory involves the recollection of specific events in the context of time and space and depends on a neuronal circuit involving the hippocampus as well as neocortical storage sites [3, 4]. Memories are initially fragile and require repeated reactivation of the neuronal network that represents the memory trace. The process of strengthening, stabilizing, and integrating a memory representation is referred to as memory consolidation [5]. With each reactivation of the memory, the circuit involving the hippocampus and neocortical storage sites is reactivated until an integration into existing knowledge networks takes place [6–8]. During this process, the memory becomes gradually less dependent on the hippocampus and more reliant on the neocortex, which in turn makes the memory more stable [4].

Sleep contributes to the consolidation of episodic memory by orchestrating the dialogue between the hippocampus and the neocortex and therefore the reactivation of newly encoded memory representations [2, 9]. Specifically, slow-wave sleep (SWS) has been proposed as a key contributor to memory consolidation. SWS is a sleep stage electrophysiologically hallmarked by low-frequency delta waves (<4 Hz) and slow oscillations (SOs, <1 Hz) that reflect neuronal activity alternating between states of depolarization and hyperpolarization [10]. Depolarized slow oscillatory (SO) up-states mark periods of increased neuronal firing whereas during hyperpolarized down-states, neuronal firing is vastly decreased. Another hallmark of SWS is thalamocortical sleep spindles, oscillatory bursts of 10–15 Hz [2]. SO up-states [11, 12] and sleep spindles [13, 14] have been connected to successful memory consolidation. Temporal coordination of SO up-states and spindles allows for a hippocampal–neocortical dialogue and forms an essential micro-oscillatory event enabling memory consolidation during sleep [2, 9]. This is achieved by hippocampal sharp-wave ripples—high-frequency (100–300 Hz) bursts of activity originating in the hippocampus—that are temporally nested within the trough of the thalamocortical sleep spindle [15], which in turn coincides with the cortical SO up-state [2]. The quality of the SO up-state—spindle synchrony has been shown to predict the success of overnight hippocampal memory consolidation [16, 17].

Considering the role of SWS in episodic memory consolidation, it is not surprising that attempts have been made to experimentally enhance SWS. Methods to enhance SWS focus on entraining the endogenous SO activity by means of external stimulation techniques such as transcranial direct current stimulation [18] (tDCS), transcranial magnetic stimulation [19] (TMS), or acoustic stimulation [20] (AS). AS is arguably the most promising method considering the relative ease of application as well as the low cost and noninvasiveness of the technique (See Fehér et al. [21] for a systematic review on stimulation techniques). In AS protocols, short (typically ~50 ms) acoustic stimuli are administered via headphones or speaker, while a participant is in SWS. Usually, the application of the sound signal is adaptive to the momentary brain state. AS systems typically monitor brain states (semi-) automatically using electroencephalography, and apply stimuli when their predefined requirements are met. Arguably, as stimulation-induced artifacts in the online signal remain low for AS in contrast to other techniques such as tDCS or TMS, AS is most suited for brain state-dependent stimulation approaches. Broadly, there are two differing forms of AS, namely non-phase-locked stimulation (NPLAS) and phase-locked stimulation (PLAS), commonly referred to as open-loop and closed-loop stimulation, respectively. Here, we refer to the differing approaches as NPLAS and PLAS since there is an unresolved debate in the field whether the approaches are truly closed-loop. In a closed-loop approach, an intervention is applied with the outcome of this intervention later informing and adjusting any future interventions. Arguably, in PLAS approaches, the stimulation is informed by ongoing activity, but is not necessarily adjusted by a reinformed outcome (e.g. by implementing refractory periods). The goal of PLAS is to administer sound signals in phase with the endogenous SO up-state to entrain and enhance it. The acoustic stimuli must temporally coincide with the SO up-state to entrain an ongoing SO train. In NPLAS protocols, the auditory stimuli are applied in a rhythmic matter without the necessity of being phase-locked. These protocols often rely on the detection of SWA and apply acoustic stimuli in a fixed interstimulus interval [22]. Importantly, research suggests that if the stimulation does not occur in phase with the up-state, the SO trains might be disrupted [20]. This underlines the necessity for in-phase stimulation systems where the timing of stimulation can be controlled.

Because of SWS's relevance in memory consolidation, AS approaches assume an increase of post-sleep episodic memory performance brought about by the boosted SO activity and up-state-spindle coupling. Study designs investigating AS effects on memory entail performing a memory task prior to as well as following sleep. This is done once in a real AS condition where acoustic stimuli are applied during SWS and once in a sham condition where no stimuli are applied. The overnight or post-nap change in memory performance is then compared between the stimulation and sham condition expecting a larger memory gain (or less forgetting) in the real AS condition.

Recently, it has been suggested that AS has the potential to be used as a noninvasive, inexpensive method in the treatment of memory-related disorders [23, 24]. This is based on findings that closely link a decline in SWA to the pathophysiological markers of Alzheimer's disease. Furthermore, while episodic memory performance is severely affected in dementia [25], it is also among the first functions to decline with healthy aging [26]. Therefore, AS might help in maintaining episodic memory function in aging. AS has been attempted in both young and older adults with inconsistent findings in both age groups. In young adults, some studies found a positive effect on memory consolidation [20, 27–29], whereas others did not [22, 30, 31]. In older and middle-aged adults, there is a similar inconsistency of results with Papalambros et al. [32] showing an increase in memory consolidation, while Diep et al. [33] and Schneider et al. [34] found no effect. While there are excellent reviews discussing the effects of AS on memory performance [35–37], so far no meta-analysis has been conducted. A meta-analytic approach allows a quantitative overview by statistically synthesizing the outcome of all available studies [38]. Hence, the objective of this meta-analysis was to quantitatively summarize studies investigating

the impact of AS during SWS on episodic memory consolidation and determining its effectiveness.

Methods

Protocol registration

This meta-analysis has been registered with the ResearchRegistry under the unique identifying number researchregistry1004.

Search strategy

The literature search was conducted with the following search term: Sleep AND (slow wave OR slow oscillat*) AND (auditory OR audio OR acoustic* OR sound) AND memory. The databases used were PubMed, Web of Science, and PsycINFO (via OvidSP). Study retrieval and selection were performed in accordance with the PRISMA guidelines [39]. Two independent raters performed the literature search, screened titles, abstracts, and full texts to find a set of eligible studies. Discrepancies and doubts were resolved in consensus. From the final set of studies, both raters extracted the relevant information for analysis.

Study selection

To identify primary studies, the following inclusion criteria were applied:

- Date: primary studies must have been published between 2013 and October 1, 2020. Search results before 2013 were not included as there is widespread consensus in the field of sleep modulation that AS with the goal to boost SOs and episodic memory was pioneered by Ngo et al. [20].
- Language: only articles published in English were considered.
- Publication type: only original research articles were considered, no reviews, meta-analyses, book chapters, dissertations, or comments were included.
- Participants: healthy human participants older than 18 years were included.
- Type of memory task: studies using an episodic (associative) memory task with an encoding session prior to sleep and a retrieval session post-sleep.
- Type of control condition: there must be a control condition where the memory task is assessed prior to and post-sleep with no AS applied during SWS.
- Type of AS: AS with the goal to increase SWS (rather than disrupt) must be administered during sleep stages displaying slow-wave activity (SWS, NREM2).
- Type of acoustic stimuli: acoustic stimuli must be of non-semantical nature as semantical stimuli fall into the field of targeted memory reactivation (for a meta-analysis see Hu et al. [40]).

As common in the field, pre-post task correlations, as well as the standard deviation of difference needed to calculate the effect size [38], were not provided in the publications. Therefore, the authors of all primary studies were contacted and asked to share each participant's pre- and post-memory score in both conditions. Eight authors responded and provided the missing details of 9 experiments. For the remaining two studies, effect sizes were calculated using an estimator (see effect size calculation).

Data extraction

The following variables of interest were extracted from the primary studies: number of participants (n), mean age of participants, age group (young or middle age/older), type of sleep (nap or overnight), type of task (non-related word-pairs or related word-pairs), type of AS (PLAS or NPLAS), mean post-sleep change in performance after sham as well as after AS (m_{sham} and m_{stim}), mean difference and standard deviation of post-sleep performance change between AS and sham (m_{diff} and SD_{diff}), correlation of the post-sleep performance change between AS and sham ($r_{stim/sham}$).

Effect size calculation

To compare the outcome variables of each study, the standardized mean difference (SMD) was calculated by means of Hedges' g [38, 41]. The following steps to calculate g in studies with single group pre-post scores are performed as previously described [38]. First, the standard deviation within (SD_{within}) was calculated by using SD_{diff} and $r_{stim/sham}$ of the test scores (1)

$$SD_{within} = \frac{SD_{diff}}{\sqrt{2(1 - r_{stim/sham})}}. \quad (1)$$

Cohen's d [42] was then calculated using m_{diff} and SD_{within} (2). The variance (V_d) and standard error (SE_d) was calculated as follows ((3), (4)).

$$d = \frac{m_{diff}}{SD_{within}}, \quad (2)$$

$$V_d = \left(\frac{1}{n} + \frac{d^2}{2n}\right) 2 \quad (1 - r_{stim/sham}), \quad (3)$$

$$SE_d = \sqrt{V_d}. \quad (4)$$

Since Cohen's d overestimates effects in small samples, Hedges' g (6) can be computed by applying a correction factor J (5) to d. The same can be applied to the variance (V_g) and standard error (SE_g) of the effect size (7), (8).

$$J = \quad 1 - \quad \frac{3}{4df - 1}, \quad (5)$$

$$g = J * \ d, \quad (6)$$

$$V_g = J^2 * \quad V_d, \quad (7)$$

$$SE_g = \sqrt{V_g}. \quad (8)$$

In contrast to clinical pre-post designs where SD_{diff} and r are commonly reported, this is often not the case in experimental pre-post assessments as used here. Hence, the equations above can only be applied to the studies in which raw data was obtainable. For the two studies where this was not possible, Hedges' g and its SE had to be estimated by different measures. We apply an alternative equation for Cohen's d using an estimate

of SD_{diff} based on the standard deviation of the pre- (SD_{pre}) and post- (SD_{post}) scores resulting in an estimate for Cohen's d defined as d_{rm} (9) [43]. Note that the correlation between memory scores after stimulation and after sham must still be known in this equation. However, r can be estimated from the correlation found in related studies and by running a sensitivity analysis using a range of plausible correlations [38]. Here, the models were calculated for three possible correlation coefficients (0.25, 0.5, and 0.75). Hedges' g and the SE can be computed by replacing d in (3), (6), and (7) with d_{rm}. While these measures are not optimal, they are considered a valid approximation given limited available data [43].

$$d_{rm} = \frac{m_{diff}}{\sqrt{SD_1^2 + SD_2^2 - 2*r*SD_1*SD_2}} * \sqrt{(2 \quad (1 - r_{stim/sham}))}. \tag{9}$$

Selection of statistical model and test of heterogeneity

To pool effect sizes for meta-analytic calculations a random-effects model (RM) was chosen. Since it cannot be assumed that all studies share one common true effect size but are rather represented by a normal distribution, the RM was chosen over a fixed-effects model [38]. Typically, the DerSimonian–Laird method is chosen as an estimator of between-study variance as it is preferred by many meta-analytical programs [38]. However, since the DerSimonian–Laird method is prone to producing false positives [44], especially in meta-analyses with small sample size and high heterogeneity [45], the restricted maximum likelihood estimator was chosen for the RM [38].

Heterogeneity was assessed by the Q-statistic and quantified further by means of the I^2 statistic [38, 46]. The latter describes the percentage of variability in the effect estimates that is attributable to heterogeneity. Heterogeneity was considered moderate if the I^2 statistic was above 50% and substantial when above 75% [47]. As the main differences in the study designs were based on the variables "type of sleep" (nighttime or nap), "memory task" (non-related stimuli or related stimuli), "AS approach" (PLAS or NPLAS), and "age" (young or middle-aged/old), subgroup analyses were additionally performed. This allowed for a subgroup comparison of effect sizes as well as an assessment of how much the differences in these variables contribute to the sample's heterogeneity. For that purpose, a mixed-effects model was calculated. The mixed-effects model combines a fixed-effects model for the between subgroups comparison and an RM for within subgroups effects. This was previously suggested to be more plausible when compared with a strict RM-based subgroup analysis [48].

Risk of bias assessments

A potential publication bias was assessed by means of a funnel plot displaying each primary study's effect size in relation to the SE. Visual inspection as well as Egger's test was used to examine funnel plot asymmetry which would indicate publication bias [49].

The risk of bias in individual studies was assessed via an adapted version of the National Institute of Health's (NIH) quality assessment tool for pre-post studies with no control group [50]. From the original 12 items, 5 were excluded due to their focus on clinical outcomes that do not apply here. The seven remaining items are listed in Supplementary Table S1. The items allow for a classification of a study's quality as good, fair, or poor. Quality assessments were made by the same independent raters who also performed the literature search. The classification of all items except for item 5 was based on subjective criteria of the individual rater and discrepancies were resolved in consensus. Item 5 (sample size) was evaluated based on a power analysis (see results section—Risk of bias in individual studies).

Results

All analyses were performed in R using the packages "meta," "metafor," and "dmetar."

Sample description

The process in which studies were identified, screened for eligibility, and included is shown in Figure 1. A total of 10 primary studies with 11 conducted experiments were included in the meta-analysis. The total sample included 177 healthy participants. Of the 11 included experiments, 3 tested a group of middle-aged and older adults (mean age = 55.7) and 8 a group of younger adults (mean age = 23.6). Three of 11 experiments were nap studies while the rest assessed nighttime sleep. Nine experiments applied a word-pair association task using semantically related stimuli and two used either unrelated or word-nonsense

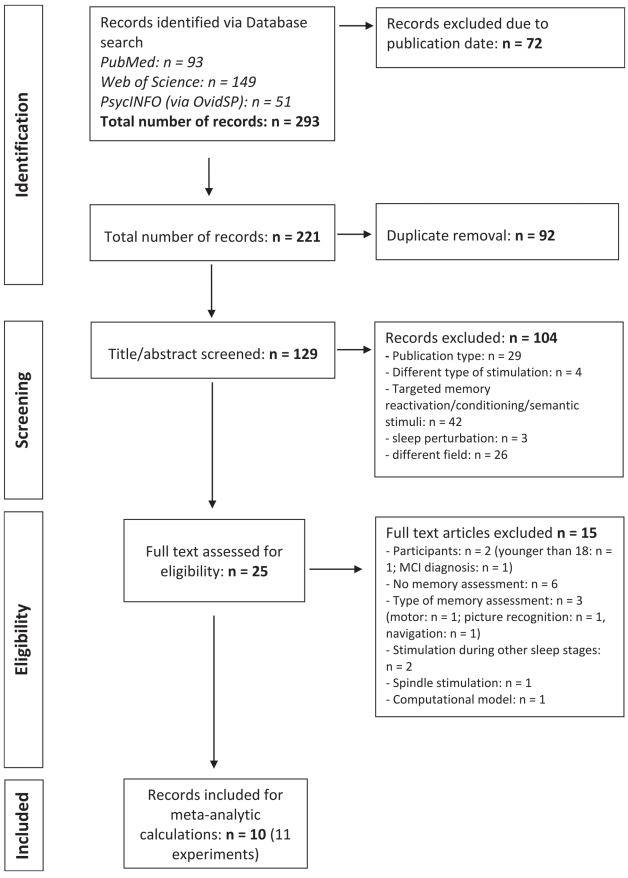

Figure 1. PRISMA flowchart detailing each step of the study selection process.

pairs. The stimulation approaches were either PLAS, referring to the phase-locked application of stimuli (n = 8) or NPLAS, referring to non-phase-specific application of stimuli (n = 3). All studies found a positive physiological effect of AS on slow oscillatory activity such as larger amplitudes and/or steeper slopes of stimulated slow waves. However, while most additionally found an increase of stimulation-locked spindle activity (n = 9), there were also studies where spindle activity decreased (n = 2). Please refer to Table 1 for a specified account of study characteristics.

Main results

Figure 2 provides an overview of effect sizes of each primary study/experiment. Positive effect sizes indicate an increase in memory consolidation in the stimulation condition compared with the sham condition. The combined effect size over all studies was g = 0.25 which did not reach significance but indicated an effect at a trend level (z = 1.82, p = 0.07). According to Cohen's classification, the effect can be considered as small [42]. The use of different correlation coefficients to calculate effect sizes for the two studies where raw data was not obtainable did not alter the combined effect size drastically (r_{low}: g = 0.25, p = 0.078; r_{mean}: g = 0.25, p = 0.070; r_{high}: g = 0.26, p = 0.060). The mean correlation calculated based on the available raw data was 0.4 which is closest to the estimated correlation of 0.5. For the following models, an estimated correlation of 0.5 was therefore assumed.

As the majority of included studies was testing young adults, an additional model 2 was calculated involving only experiments on young adults (n = 8). Here, the combined effect size was 0.31 which remained at a trend level (z = 1.95, p = 0.051). Model 3 included studies with middle-aged or older adults (n = 3) and showed an effect size of 0.11 which was not significant (z = 0.33, p = 0.7). While the effect size in the younger adults group was larger compared with the older adults group (0.31 vs. 0.11, see Figure 3), this difference was not significant (p = 0.6).

As synchronization of stimulation to endogenous slow waves has been suggested to be essential [51], a fourth model was calculated including only studies that used a PLAS approach rather than a non-phase-locked approach. These eight experiments used a PLAS algorithm where the stimulation is timed by the endogenous SO activity in a phase-specific manner (see Table 1). The combined effect size in model 4 was 0.36 which was significant (z = 1.98, p = 0.047). The effect size in model 5 including only studies with NPLAS approaches was 0.03 and was not significant (p = 0.9). Models 4 and 5 showed different effect sizes (0.36 vs. 0.03, see Figure 4) but the difference was not significant (p = 0.1). Finally, a sixth explorative model was calculated focusing on studies with young subjects and PLAS only (n = 6). The combined effect size in model 6 was 0.44 which was significant (p = 0.01, see Figure 5).

The subgroup comparisons between afternoon nap and whole night studies as well as between the different memory tasks were not significant (both p = 0.4). None of the subgroup analyses therefore revealed significant differences in effect sizes. However, sample sizes were small in at least one of each subgroup to be compared (see Table 1; older age group: n = 3; nap studies: n = 3; unrelated-word pair task: n = 2; NPLAS stimulation approaches: n = 3).

Heterogeneity assessment

With the exception of model 5, all models indicated significant levels of heterogeneity (model 1: Q = 30.1, p < 0.01; model 2: Q = 21.2, p < 0.01; model 3: Q = 7.8, p = 0.02; model 4: Q = 26.0, p < 0.01; model 5: Q = 1.05, p > 0.05; model 6: Q = 16.7, p < 0.01). The I^2 statistic further specified the observed heterogeneity to be moderate (66.8% [model 1], 66.9% [model 2], 74.2% [model 3], 73.0% [model 4], and 70.1% [model 6]). Subgroup analyses showed that neither differences in "age group," "type of sleep," "type of task," nor "type of stimulation" could explain the observed heterogeneity.

Publication bias

To evaluate a potential publication bias, a funnel plot displaying every primary study's effect size in relation to the effect size's SE was plotted (Figure 6). If no publication bias is present, the individual studies would be placed symmetrically along the pooled effect size (dotted line) forming the shape of a funnel. Visual inspection of the funnel plot can be interpreted as symmetrical, indicating a lack of publication bias. Statistical testing of the funnel plot asymmetry was performed by means of Egger's test of the intercept which was not significant (p = 0.7). Together these findings indicate the absence of a publication bias.

Risk of bias in individual studies

The assessment of bias in individual studies was based on seven criteria defined by the NIH quality assessment tool for pre-post studies with no control group (see Supplementary Table S2) [50]. All studies depicted an overall rating of either good or fair quality. The only item which was consistently scored as poor was item 5 which asks whether the sample sizes are sufficiently large. This assessment is based on a power analysis that found a power level of 15% when taking into account the mean sample size (n = 16) and an effect size of 0.25 derived from model 1. To achieve a desired power level of 80%, an n of 127 would be needed. Even for the models that found the largest effect sizes (model 4 and model 6), an n of 62 or 42, respectively, would be needed to achieve the same effect size with a statistical power of 80%.

Discussion

This systematic review and meta-analysis was the first to quantify the efficacy of AS on overnight episodic memory consolidation. A total of 10 primary studies with 11 distinct experiments were included. The combined overall effect size of AS on episodic memory consolidation was 0.25, which can be considered a small effect [42]. The effect was not significant but a trend was indicated (p = 0.07). Risk of bias assessments revealed that studies were of acceptable quality and that there was no publication bias. A subgroup model assessing the combined effect size of studies with younger adults only (n = 8) found an effect size of 0.31 at a trend level (p = 0.051) which was larger than in the overall model but can still be considered as small. The subgroup model assessing only studies that applied a PLAS algorithm (n = 8) showed an effect size of 0.36 which was significant (p = 0.047). Lastly, an explorative model including studies with young subjects and in-phase stimulation (n = 6) showed the largest effect size, which was 0.44 and significant (p = 0.01).

This meta-analysis showed that AS during SWS has an effect on overnight memory consolidation which remains small and at trend levels. Furthermore, the lack of publication bias indicated

Table 1. Characteristics of included primary studies

Study	N	Mean age	Type of sleep	Memory task*	Stimulation approach	Main Physiological effects†		Memory effect‡
						Sleep slow waves	Sleep Spindles	
Ngo et al. [20]	11 (8f)	24.2	Nighttime sleep	120 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	2 × 50 ms stimuli with 1,075 ms ISI (0.93 Hz), targeting SO peaks *Stim period*: 210 min	SO_E ↑ P_{SO} ↑ A_{SO} ↑ Den_{SO} -- Sl_{SO} ↑ Dur_{SO} -- P_{SWA} -- P_{δ} ↑	↑ SSA & FSA	↑
Ngo et al. [27]	18 (8f)	23.8	Nighttime sleep	120 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	1–4 × 50 ms stimuli with 973.0 ± 11.7 ms ISI (adaptive), targeting SO peaks *Stim period*: 210 min	SO_E ↑ P_{so} ↑ A_{SO} ↑ Den_{SO} -- P_{δ} --	↑ FSA	↑
Ong et al. [28]	16 (7f)	22	Afternoon nap	40 semantically related word-pairs; 1 × encoding‖, immediate cued recall (learning to criterion: 60%) Retrieval: cued recall	5 × 50 ms at ~1 Hz (adaptive), targeting SO peaks *Stim period*: nap	SO_E ↑ A_{SO} ↑ P_{SWA} ↑	↑ FSA	↑
Weigenand et al. [22]	21 (10f)	22.2	Nighttime sleep	120 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	3 × 50 ms. 2nd stimulus after ~0.9 s (adaptive), 3rd stimulus after 1,075 ms, targeting SO peaks *Stim period*: 210 min	SO_E ↑ P_{SO} ↑ A_{SO} ↑ P_{δ} ↑ P_{SWA} ↑	↓ SSA ↓ FSA	--
Leminen et al. [29]	15 (7f)	30.5	Nighttime sleep	120 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	1 × 50 ms stimuli, targeting SO peaks *Stim period*: entire night	SO_E ↑	↑ SA	↑
Papalambros et al. [32]	13 (10f)	75.2	Nighttime sleep	88 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	5 × 50 ms at ~0.83 Hz (adaptive), targeting SO peaks *Stim period*: entire night	SO_E ↑ P_{SWA} ↑	↑ SA	↑
Henin et al. [31] Exp. 1	12 (6f)	23.3	nap	100 word-pairs (unrelated); 1 × encoding§ and immediate cued recall without feedback Retrieval: cued recall	1 × 50 ms stimuli, targeting SO peaks *Stim period*: nap	SO_E ↑	↑ SA	--
Henin et al. [31] Exp. 2	19 (9f)	23.3	Nighttime sleep	120 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	2 × 50 ms stimuli with 1,075 ms ISI (0.93 Hz), targeting SO peaks *Stim period*: 210 min	SO_E ↑ Den_{SO} --	↑ SSA & FSA	--
Choi et al. [30]	13 (0f)	26.3	nap	54 semantically related word-pairs; 1 × encoding§ and 2 × immediate cued recall (1st feedback-based/2nd no feedback) Retrieval: cued recall	N × 50 ms stimuli with unspecified ISI upon sleep spindle detection Stim period: nap	P_{SO} ↑ P_{δ} ↑	↑ SA	--
Diep et al. [33]	24 (0f)	39.9	Nighttime sleep	120 word-nonsense word-pairs; 1 × encoding¶ (learning to unspecified criterion) Retrieval: cued recall	Commercial use device; continuous 50 ms stimuli with 1,000 ms ISI, synchronized to the first detected SO peak per stage N3 *Stim period*: entire night	NA for stimulation period; overall: P_{SWA} ↑	↓ SSA	--

Table 1. Continued

Study	N	Mean age	Type of sleep	Memory task*	Stimulation approach	Main Physiological effects†		Memory effect‡
						Sleep slow waves	Sleep Spindles	
Schneider et al. [34]	17 (9f)	55.7	Nighttime sleep	80 semantically related word-pairs; 1 × encoding§ and feedback-based immediate cued recall Retrieval: cued recall	2 × 50 ms stimuli with 1,091.47 ± 21.06 ms ISI, targeting SO peaks *Stim period*: 210 min	SO_E ↑ A_{SO} -- $P_{so\ (0.9\ Hz)}$ -- Den_{SO} --	↑ FSA	↓

Stim, stimulation; SO, slow oscillatory; SO_E, entrainment of slow oscillations; SOs, slow oscillations (0.5–1 Hz); δ, delta waves (1–4 Hz); SWA, slow-wave activity (0.5–4 Hz); P, power; A, amplitude; Den, density; Dur, duration (time between two succeeding positive-to-negative zero crossings); SA, spindle activity; SSA, slow spindle activity; FSA, fast spindle activity; ISI, interstimulus interval; ↑ = significant increase/gain; ↓ significant decrease/loss; -- no effect.

*The encoding phase is always pre-sleep and the retrieval phase is post-sleep.

†Effects during real stimulation period compared to sham.

‡Increase in memory consolidation in the AS condition vs. the sham condition.

§4s/stimulus-pair.

‖5s/stimulus-pair.

¶Unspecified duration of stimulus-pair display.

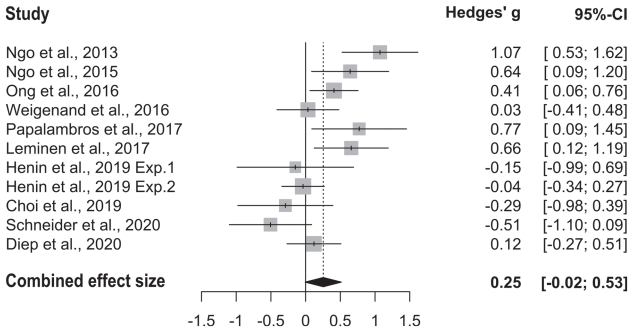

Figure 2. Forest plot depicting the effect of AS during SWS on episodic memory consolidation. Each study's effect size is represented by a square in proportion to the respective weight. The summary measure is indicated by a dotted line and a black diamond. Model 1 included all primary studies (n = 11) with effect size calculations based on raw data (n = 9) as well as an approximated estimate when raw data was not obtainable (n = 2). For each study, Hedges' g, as well as its 95th confidence interval, is depicted on the right.

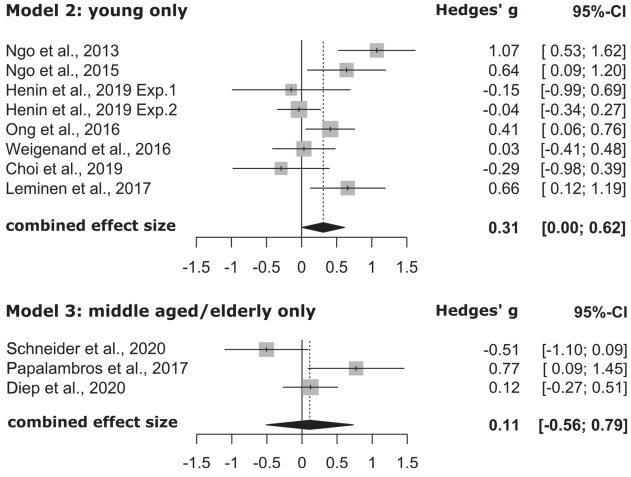

Figure 3. Forest plots depicting the combined effect size (Hedges' g) separated by the subgroups young adults and older adults. Model 2 included studies with younger adults (n = 8), while model 3 contained studies with middle-aged or older adults (n = 3). The summary measures are indicated by a dotted line and a black diamond for each of the groups. Hedges' g, as well as its 95th confidence interval, are depicted on the right for each individual study as well as the overall effect per group.

that these studies display a representative sample of the available evidence.

The results might further suggest that the effect of AS on overnight episodic memory consolidation could be stronger in younger adults than in older adults as well as in studies applying phase-locked algorithms compared to non-phase-locked algorithms. However, this claim remains speculative as the respective subgroups did not differ significantly from each other. Nevertheless, the number of studies assessing effects in older adults (n = 3) as well as studies applying NPLAS is small (n = 3) which might explain the lack of effect when compared with the other subgroups (both n = 8).

When focusing on AS effects on overnight memory consolidation in different age groups, an argument can be made for both the case that it might work better in younger adults as well as the opposite that it might work better in older adults. The assumption that AS effects might be stronger in younger adults is in line with findings from Schneider et al. [34] who compared the same AS approach between a younger and an older cohort. While physiological effects were found in both younger and older adults, they were markedly reduced in older adults. Specifically, increases in SO measures were short-lived in older adults while there was a sustained effect in younger adults. Critically, SO up-state/spindle coupling was only enhanced by AS in younger but not in older adults. Based on their findings, the authors concluded that susceptibility to AS might differ as a function of age. The reasons for this are not fully uncovered but might include neuronal degradation, decreased thalamocortical connectivity, or slowed-down cell refractoriness [34]. This is further supported by one study finding no group effect of AS on memory consolidation in cognitively impaired patients [52]. Presumably, susceptibility to AS might be even more diminished in pathological aging since age-related declines in sleep physiology are particularly pronounced in patients suffering from cognitive decline when compared with an age-matched healthy group [23, 53]. AS effects on memory are however not

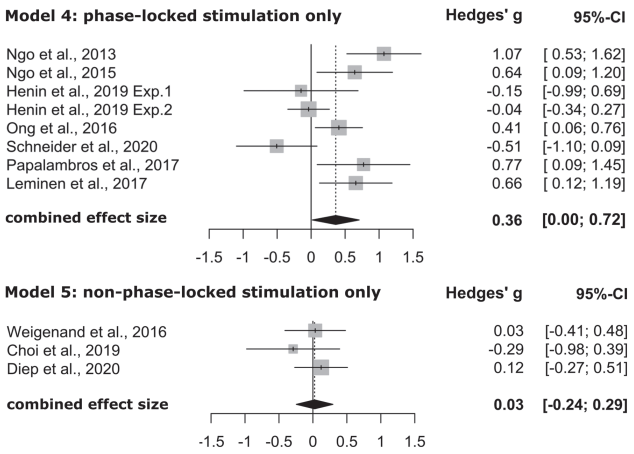

Figure 4. Forest plots depicting the combined effect size (Hedges' *g*) separated by the subgroups PLAS (model 4, *n* = 8) and NPLAS (model 5, *n* = 3). Hedges' *g* and its 95th confidence interval are displayed on the right for each of the studies as well as for the summary effect (black diamond).

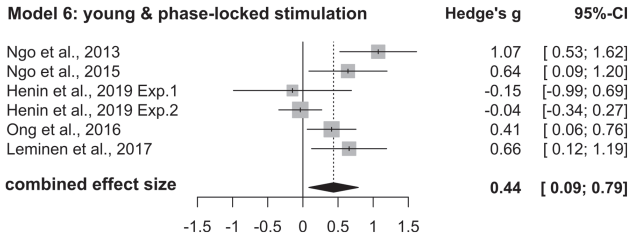

Figure 5. Forest plots depicting the combined effect size (Hedges' *g*) found in an exploratory model 6 that focused on studies with young adults and PLAS only (*n* = 6). Hedges' *g* and its 95th confidence interval are displayed on the right for each of the studies as well as for the summary effect (black diamond).

entirely absent in the older cohort as one study found a substantial memory effect after AS [32]. Interestingly, this is the only study in this meta-analysis that assessed AS effects in a group of elderly participants (mean age: 75.2) whereas the other two assessed a group of middle-aged adults (mean ages: 55.7 [34] and 39.9 [33]). One potential reason for the observed effect could be that the default amplitude for the detection of SOs was drastically lower than in Schneider et al. [34]. This is particularly important as SO amplitude is more impacted by age than the incidence rate of SOs is [54] which means that potential targets might be missed when the amplitude threshold is not adaptive enough [23]. Therefore, the evidence does not conclusively suggest that AS effects might be stronger in younger adults. From a theoretical perspective, it might also be plausible to assume the opposite, that AS—when optimized—is more effective in older adults than in younger adults. Presumably, there is no need to boost SOs in a healthy, young brain as it already functions on a homeostatically optimized level. However, when the brain loses its optimized functions—as is the case in aging and even more in pathological aging—the potential for improvement might rise.

The studies included in this meta-analysis used different approaches of AS. Subgroup analyses revealed that there was no significant difference between the model using PLAS and the model using NPLAS approaches. However, the number of studies in the NPLAS model might be too small to draw a reliable conclusion. Based on our analyses it cannot be stated with certainty that a specific form of AS approach is more suitable

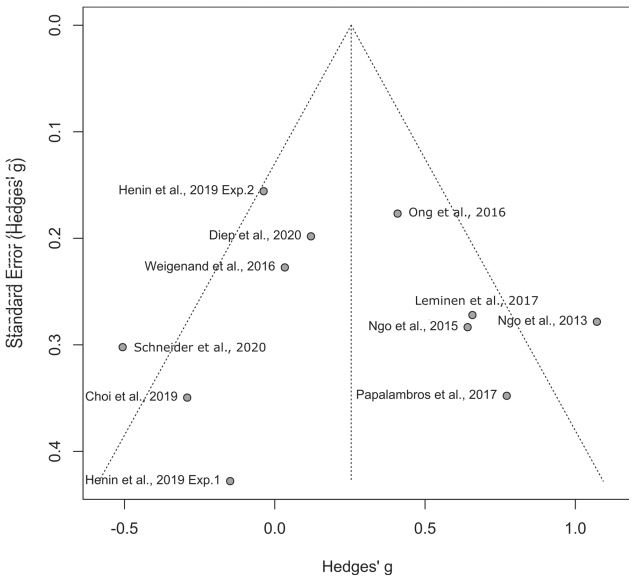

Figure 6. Funnel plot exploring publication bias. The horizontal and vertical axes represent the effect size (Hedges' *g*) and the SE of the effect size, respectively. The studies appear roughly symmetrical within the funnel suggesting a lack of publication bias.

than another. However, the only models in this meta-analysis showing a significant effect size were the ones using PLAS studies only (PLAS approach and all ages *n* = 8, PLAS approach and young only *n* = 6). Therefore, a strong case can be made that the timing of stimulation seems to be of essence in AS effects on memory. This claim is in line with research suggesting that especially the transition from the down-state to the up-state might provide a window of opportunity to maximize AS effects [51]. Furthermore, one study found that in older adults the optimal window for stimulation was substantially reduced [55]. This finding does not only provide evidence for the claim that timing of stimulation seems to be essential but also further explains why successful application of AS in older adults might be more challenging.

The majority of primary studies (*n* = 9) included in this meta-analysis used a verbal paired-associates task consisting of moderately related word-pairs such as "solution–problem." This type of task had been shown to be sensitive to effects of sleep [12, 18] in studies preceding the first AS study [20]. Paired-associate learning depends on the episodic memory system [56] which critically involves the hippocampus [4]. However, using word-nonsense pairs instead of semantically linked associations has been suggested to better engage the hippocampal memory system by minimizing semantical influences that are not hippocampus-dependent [57, 58]. Inherent semantics of the word-pairs and the influence of previous experiences could imply that the hippocampus' role in the encoding and consolidation of these memory traces might be drastically reduced. Since sleep-dependent memory consolidation requires hippocampal reactivation [2, 9], effects might be stronger when the hippocampal demand of the task is higher. Diep et al. [33] followed that reasoning and used a word-nonsense-pair task with the goal of rendering it more hippocampus-dependent. The authors did not find an effect of AS on the word-nonsense memory associations. However, as stated by the authors, this might have been due to a high task difficulty. When the task

is already too difficult at encoding, consolidation is likely to be drastically impeded.

In this meta-analysis, studies using an episodic memory task were included due to the theory-driven connection between this specific form of memory and SO activity [2]. With the exception of two studies [28, 32], all primary studies additionally had participants perform one or more cognitive tasks. These tasks involved assessments of vigilance [20, 22, 27, 30, 31, 33, 34], verbal fluency [22, 27, 30, 33], digit span [22, 27], working memory (n-back [30, 33], tower of London [33]), and inhibition [33] as well as finger tapping [29, 30], navigation [31], picture recognition [29], and face-name association tasks [29]. In the majority of cases, no differences in performance were found between the stimulation and sham condition. One study found an enhancement in finger tapping speed after AS compared with sham [30], while the second study that applied a finger tapping task did not find such an effect [29]. Only one other study showed effects of AS on two additional cognitive tasks, namely the 2-back as well as verbal fluency task [33]. Verbal fluency, however, was not positively influenced by AS as assessed in three other studies [22, 27, 30]. These findings generally support the idea that AS might mainly influence hippocampus-dependent episodic memory. However, there was no effect found in a spatial navigation task [31] as well as a face-name association task [29], which both rely on hippocampal activity [59, 60]. Furthermore, the two studies that found effects on a finger tapping [30] and n-back/verbal fluency task [33] both used an NPLAS algorithm and both did not find an effect on episodic memory performance. Whether there is a connection between these discrepant findings remains—due to the low number of studies—speculative and a question for future research to resolve.

A recent finding on the opposing roles of SOs and delta waves in memory processing might offer another explanation for the variance of effects found in the 11 experiments of this meta-analysis. Animal models showed that SOs support the consolidation of memories whereas delta waves support their forgetting [61]. This dissociation has been brought forward in the explanation of inconsistently found memory effects using tDCS during sleep [62]. The authors argue that it is possible that tDCS might have also stimulated delta waves which in theory would enhance forgetting. tDCS approaches cannot be as fine-tuned as AS approaches due to the induced artifacts on the electrophysiological data (Fehér et al. [21]) which makes it difficult for a phase-locked-stimulation system to read out the brain activity under stimulation. Even though in AS approaches SOs are the target of stimulation, the possible interactions with delta waves and forgetting are not fully uncovered yet and might give further insight in the absence of memory effects found in some studies.

As mentioned above, a case can be made that PLAS (as compared with NPLAS) could be essential in the modulation of overnight memory consolidation. Due to the small sample size in the two PLAS models, it remains an open question whether there are concrete conditions under which in-phase stimulation works best. Models 4 and 6 investigated the overall effect of studies applying PLAS in all available studies as well as in young adults, respectively. Model 6 showed the largest effect size and included two experiments where no memory effects were found [31] and four studies where an increase in memory consolidation was observed [20, 27–29]. Although the small sample size does not allow for definitive specifications of concrete conditions under which stimulation works better or worse, one could speculate that the use of a nap (instead of a whole night), unrelated-word-pairs (instead of related word-pairs), and 1-pulse in-phase stimulation (instead of 2-pulse/continuous in-phase stimulation) could have led to a lack of effect found in Henin et al. [31]. However, the authors recognized these possible limitations and conducted a second experiment where 2-pulse stimulation was applied in a whole night study design and a related word-pairs memory task was used. Contrary to what would have been expected if indeed these conditions were non-ideal—they did not find an effect of PLAS on overnight memory consolidation. Furthermore, among the four studies that found an increase in overnight memory consolidation, one also applied AS during a nap [28] and another also used 1-pulse in-phase stimulation [29]. For these reasons, we argue that—at this point—more research is needed in order to make definitive statements about specific conditions under which stimulation might work best.

Limitations and future research

Some level of bias might have been introduced to this meta-analysis by the observed moderate heterogeneity. Although subgroup analyses revealed that neither age, type of sleep (nap/nighttime), task (related/non-related word-pairs), nor AS approach (PLAS/NPLAS) were able to explain the heterogeneity, the validity of these analyses remains questionable due to the small group sizes. The moderate heterogeneity might also be due to the low number of experiments included in this meta-analysis (n = 11) as well as their relatively low sample sizes [38]. The low number of included studies is generally a limitation of this meta-analysis as single studies with extreme effects might have substantial impact on the overall effect. However, as supported by both the funnel and forest plots (Figures 2 and 5), no study gives an obvious reason for concern.

As revealed by a power analysis assuming a mean effect size of 0.25 and a mean sample size of 16, the included studies are underpowered. Substantially larger sample sizes would be needed to show sufficient power. In combination with the effect sizes remaining small in all models, critical assessments should be made when dealing with commercially already available products. While it cannot be stated that these devices do not work [63], this meta-analysis suggests that more research is needed to provide a clear understanding of the approach's efficacy.

AS and its effect on memory is still a relatively young field. Future studies should address open questions such as the potential role of AS in forgetting of memories. AS could potentially boost delta waves, rather than slow waves, when approaches are not fine-tuned enough, leading to potential forgetting instead of consolidation [61]. This could explain the failure to increase memory performance by means of AS. Furthermore, future studies should use highly hippocampus-dependent tasks. This would address the question as to whether AS specifically boosts hippocampus-dependent memory systems, which would be in line with theories on sleep-dependent memory consolidation [2, 9]. However, finding the balance between a manageable task difficulty and maximized hippocampal involvement might prove challenging, as more hippocampus-dependent tasks might generally be more difficult. Lastly, especially in older adults, studies need to assess how to perfect AS algorithms. Contemporary PLAS Algorithms are optimized to work for younger adults. It is preferable to have a fine-tuned amplitude-independent algorithm that takes into account that older adults' sleep physiology

is more complex than that of younger adults [23]. When this challenge is met, AS could be used in therapeutic or prevention settings. Episodic memory is among the first functions to decline with aging [26] and is severely affected in Alzheimer's disease and other forms of cognitive decline [25]. AS could support cognitive trainings in elderlies which could potentially help in maintaining memory performance on a more stable level. If certain limitations of AS—especially in older adults—are addressed, it bears the potential to be used as a noninvasive, inexpensive tool in the treatment of memory-related disorders.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Data Availability

Data partially available on request: The data underlying this article will be shared on reasonable request to the corresponding author. The raw data underlying this article were provided by authors of primary studies by permission. Data will be shared on request to the corresponding author with permission of the respective authors.

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