Mechanisms of Memory Enhancement Through Closed-Loop Auditory Stimulation During Slow-Wave Sleep: A Literature Review

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Abstract

Memory consolidation during sleep, particularly in slow-wave sleep (SWS), relies on the coordination of slow oscillations (SO) and sleep spindles, which facilitate the transfer of newly acquired information from the hippocampus to the neocortex. Closed-loop auditory stimulation (CLAS) has emerged as a promising non-invasive method for enhancing this process by delivering auditory tones synchronized with SOs. This systematic literature review evaluates the efficacy of CLAS in modulating sleep oscillations and improving memory retention, with a focus on the underlying neural mechanisms, inter-individual variability, and methodological challenges. Following PRISMA guidelines, studies investigating CLAS during SWS in human participants were systematically analyzed. Findings indicate that CLAS enhances slow oscillation amplitude, increases spindle density, and strengthens SO-spindle coupling, leading to improved declarative memory performance. However, its effects on procedural memory remain limited, suggesting that different memory systems rely on distinct oscillatory mechanisms. Moreover, CLAS efficacy varies across individuals due to factors such as baseline SO-spindle activity, age-related changes in sleep architecture, and sleep fragmentation. Despite its potential, several challenges remain, including the need for precise timing of auditory stimulation, long-term effects on sleep homeostasis, and scalability for real-world applications. Advances in real-time electroencephalography (EEG) tracking and machine-learning-based signal processing may improve CLAS accuracy and reliability. Future research should explore personalized stimulation protocols and multimodal approaches to optimize CLAS efficacy for diverse populations. By refining stimulation parameters and integrating technological advancements, CLAS holds promise as a scalable intervention for cognitive enhancement and sleep-based memory improvement.

Keywords: *Slow-Wave Sleep, Closed-Loop Auditory Stimulation, Memory Consolidation, Slow-Wave Activity, Sleep Spindles*

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A list of abbreviations

AI – Artificial Intelligence

CBT – Cognitive Behavioral Therapy

CLAS – Closed-Loop Auditory Stimulation

EEG – Electroencephalography

DBS – Deep Brain Stimulation

GABA – Gamma-Aminobutyric Acid

LTP – Long-term Potentiation

MCI – Mild Cognitive Impairment

MEG – Magnetoencephalography

MST – Motor Sequence Task

N1, N2, N3 – Non-Rapid Eye Movement (NREM) Sleep Stages

NREM – Non-Rapid Eye Movement

PAC – Phase-Amplitude Coupling

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

REM – Rapid Eye Movement

SO – Slow Oscillation

SWA – Slow-Wave Activity

SWR – Sharp-Wave Ripples

SWS – Slow-Wave Sleep

tACS – Transcranial Alternating Current Stimulation

TOPOSO – Topographic Targeting of Slow Oscillations

TSSI – Time Spent in Sleep Initiation

1: Introduction

Why do some memories persist while others fade? A critical answer lies in the brain's activity during slow-wave sleep (SWS), a phase of non-rapid eye movement (NREM) sleep crucial for memory consolidation. During SWS, slow oscillations (SO), high-amplitude, low-frequency waves, coordinate neuronal activity across the hippocampus and cortex, facilitating the stabilization and integration of newly acquired information into long-term memory (Diekelmann & Born, 2010). This interaction is further strengthened by the coupling of SOs with sleep spindles, which synchronize neural communication to enhance memory retention (Ji & Wilson, 2006; Tamminen et al., 2010).

Building on this understanding, recent advances in neuroscience have explored closed-loop auditory stimulation (CLAS) as a non-invasive method to enhance memory consolidation. CLAS delivers auditory tones precisely timed to specific phases of brain oscillations during sleep. By synchronizing these sounds with neural rhythms, CLAS can modulate brain activity to enhance cognitive processes. In the context of memory consolidation, CLAS is typically applied to SOs during SWS, enhancing slow-wave activity (SWA) and promoting stronger SO-spindle coupling. This targeted intervention has demonstrated the ability to boost memory retention, particularly in declarative memory tasks (Ngo et al., 2013; Navarrete et al., 2019). Beyond these laboratory successes, the potential applications of CLAS extend into real-world settings, where it could transform educational practices by improving learning and retention and mitigating age-related cognitive decline in older populations (Langille, 2019; Weiss & Donlea, 2022).

This research investigates how CLAS enhances memory consolidation by modulating SOs and spindle activity during SWS. While prior studies have established the role of SOs and spindles in memory, they have largely overlooked the precise neural mechanisms by which

CLAS interacts with these oscillations and how individual variability influences intervention outcomes. Specifically, this study addresses these gaps by clarifying the underlying neural mechanisms, assessing the impact of precise timing and synchronization of auditory stimuli on memory outcomes, and refining CLAS protocols to optimize efficacy. To address these objectives, the study is guided by the following research question: How does CLAS during SWS enhance memory consolidation, and what are the neural mechanisms underlying its effects? Secondary questions include determining the optimal timing for auditory stimulation to maximize slow-wave enhancement, understanding the distinct roles of SOs and spindles in mediating memory improvements, and exploring how individual variability affects intervention outcomes. By systematically addressing these aspects, this research bridges a critical gap between experimental findings and real-world applications, ensuring that CLAS interventions can be better tailored for diverse populations. The broader implications include potential applications for mitigating cognitive decline, enhancing educational outcomes, and advancing accessible technologies for memory improvement, paving the way for more personalized and scalable interventions.

2: Research Context

2.1: The Role of Sleep in Memory Processing

2.1.1 The Role of Slow-Wave Sleep in Memory Consolidation

Before examining CLAS and its effects on memory function, it is essential to first outline the role of sleep in memory processing.

Memory consolidation during sleep, particularly in SWS, involves the interaction of SOs and sleep spindles (Squire et al., 2015). These oscillatory patterns synchronize neural firing across cortical and subcortical regions, effectively transferring memory traces from temporary hippocampal storage to stable cortical networks (Diekelmann & Born, 2010). The

precise coupling of SOs and spindles enables hippocampal-cortical communication, which serves as a fundamental mechanism for long-term memory consolidation (Tamminen et al., 2010; Fernandez & Lüthi, 2020). While the role of SO-spindle coupling in facilitating memory consolidation is well-documented, questions remain regarding how these mechanisms can be modulated to optimize memory retention, particularly through non-invasive interventions.

2.1.2 Sleep Stages and Their Role in Memory Consolidation

Human sleep alternates between rapid eye movement (REM) and non-rapid eye movement (NREM), cycling approximately every 90 to 110 minutes (Carskadon & Dement, 1989). NREM sleep, which dominates the first half of the night, progresses through three stages (N1–N3), with slow-wave sleep (SWS, or N3) representing the deepest sleep stage. This phase is characterized by high-amplitude, low-frequency delta waves (0.5–3 Hz) and is strongly implicated in declarative memory consolidation (Carley & Farabi, 2016; Rasch & Born, 2013). The distinct characteristics of these sleep stages and their transitions throughout the night are visually represented in Figure 1.

Research indicates that SWS plays a crucial role in memory stabilization, facilitating the reactivation of newly acquired information and its gradual integration into long-term cortical storage (Rasch & Born, 2013). This process is driven by the coordinated interaction of SOs, sleep spindles, and hippocampal sharp-wave ripples (SWR), which collectively structure memory reactivation and transfer (Diekelmann & Born, 2010).

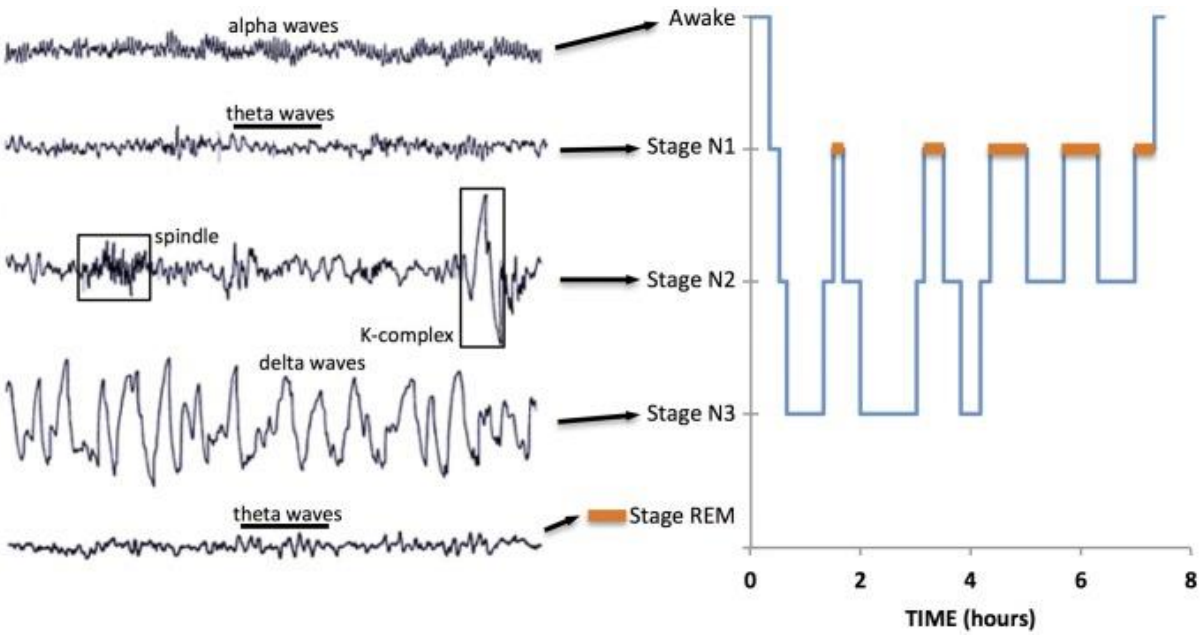

Figure 1. EEG Characteristics of Sleep-Wake Stages (Left) and Typical Nocturnal Sleep Architecture in a Healthy Adult (Right).

The left panel illustrates characteristic waveforms of each stage: alpha activity during wakefulness, theta waves in Stage N1, sleep spindles and K-complexes in Stage N2, and high-amplitude delta waves during slow-wave sleep (Stage N3). REM sleep is marked by low-amplitude, mixed-frequency theta activity. The hypnogram on the right shows the cyclical progression through NREM and REM sleep stages across an 8-hour sleep period, with SWS dominating the early cycles and REM periods extending later in the night. Adapted from *"Physiology of Sleep"* by Carley & Farabi, 2016, *Diabetes Spectrum, 29*(1), 5–9. Copyright © 2016 American Diabetes Association.

2.1.3 Slow Oscillations as a Mechanism for Memory Reactivation

SOs are high-amplitude, low-frequency cortical waves (<1 Hz) that emerge during SWS and provide a global timing signal for neuronal synchronization (Buzsáki et al., 2006). Empirical studies suggest that higher SO amplitude is associated with enhanced declarative memory performance, indicating that the strength of SOs influences hippocampal memory reactivation and neocortical integration (Schabus et al., 2006).

Studies employing electroencephalography (EEG) spectral analysis further confirm that increased SO power correlates with improved post-sleep recall (Niknazar et al., 2022). Additionally, SOs provide a temporal scaffold for the precise alignment of sleep spindles and SWRs, ensuring their coordination in memory replay (Staresina et al., 2023).

2.1.4 Sleep Spindles and Their Role in Memory Retention

Sleep spindles, short bursts of 11-16 Hz oscillations generated in the thalamus, contribute to synaptic plasticity and memory stabilization during NREM sleep (Buzsáki et al., 2006; Diekelmann & Born, 2010). Empirical data demonstrate that spindle density is positively correlated with memory performance, with individuals exhibiting greater spindle activity showing stronger post-sleep recall. Schabus et al. (2006) found that increased spindle density was significantly associated with improved recall of declarative memory tasks, with individuals exhibiting higher spindle activity showing stronger post-sleep retention. Similarly, Tamminen et al. (2010) showed that spindles occurring in phase with SO up-states led to a significant improvement in recall performance, reinforcing the importance of precise SO-spindle coupling in sleep-based memory processing.

2.1.5 Hippocampal Sharp-Wave Ripples and Memory Consolidation

Hippocampal SWRs (80-300 Hz) are brief bursts of high-frequency activity that play a central role in memory replay and neocortical transfer during SWS (Buzsáki et al., 2006; Staresina et al., 2023). Studies indicate that SWRs co-occur with SOs and sleep spindles, further reinforcing their role in coordinating hippocampal-cortical communication during memory consolidation (Diekelmann & Born, 2010; Staresina et al., 2015).

Beyond consolidation, SWRs also contribute to memory retrieval. Norman et al. (2019) found that intracranial recordings in awake human participants have demonstrated SWR activity during memory encoding predicting subsequent recall performance, and an increase in SWR occurrence precedes spontaneous memory retrieval by 1-2 seconds. Moreover,

SWRs facilitate content-specific reactivation in high-order visual areas, highlighting their function in orchestrating hippocampal-cortical interactions necessary for both encoding and recollection of episodic memories (Norman et al., 2019).

2.1.6 The Coupling of SOs, Spindles, and SWRs in Memory Consolidation

EEG-based studies suggest that the precise temporal coordination of SOs, sleep spindles, and SWRs determines the efficacy of memory consolidation (Diekelmann & Born, 2010). Recordings indicate that SOs initiate the sequence, followed by sleep spindles, which then precede hippocampal SWRs, forming a structured network of oscillatory events that optimize long-term storage (Tamminen et al., 2010; Schabus et al., 2006). The interaction between these oscillatory events, known as phase-amplitude coupling (PAC), plays a crucial role in sleep-dependent memory processing (Figure 2).

Findings from multiple studies indicate that greater synchronization among these oscillatory events predicts stronger post-sleep recall performance (Schabus et al., 2006; Tamminen et al., 2010; Staresina et al., 2015). The co-occurrence of these rhythms is believed to enhance synaptic potentiation and facilitate hippocampal-neocortical information transfer, reinforcing the hypothesis that phase-locked oscillatory events are critical for memory consolidation. The measurement of PAC and its role in SO-spindle coupling is illustrated in Figure 2, which highlights how these events align to support memory processes during sleep.

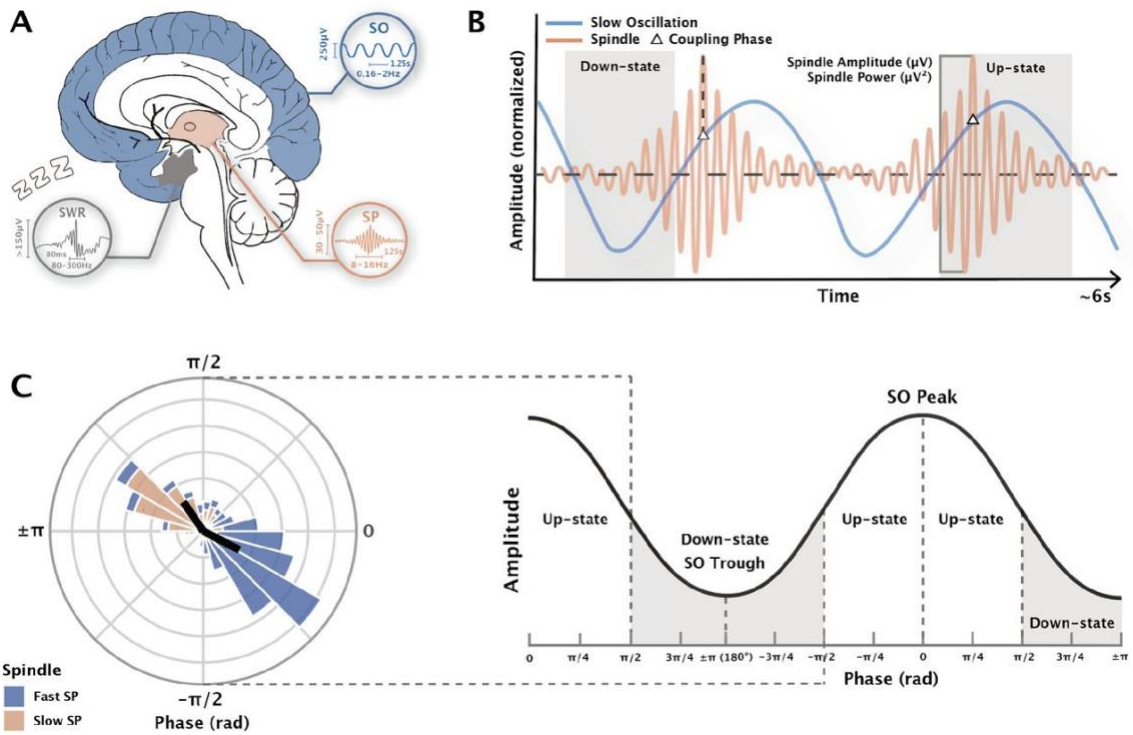

Figure 2. **Measurement of phase-amplitude coupling (PAC) in slow oscillation and spindle events.**

(A) Schematic representation of key oscillatory events involved in sleep-dependent memory consolidation: slow oscillations (SOs; 0.16-2 Hz) generated in the neocortex, sleep spindles (SP; 8-12 Hz) originating from the thalamus, and hippocampal sharp-wave ripples (SWR; 80-300 Hz). **(B)** Example trace showing the temporal coupling of spindle amplitude (brown) to the SO phase (blue). Spindles are predominantly nested within the SO up-state, illustrating phase-dependent modulation of spindle occurrence. **(C)** Circular histogram representing the distribution of spindle events relative to the SO phase. Spindles are concentrated around the SO peak (0 radians), indicating preferred coupling during the up-state. The SO phase diagram (right) further illustrates the up- and down-state transitions used for PAC analysis.

Adapted from *"Does slow oscillation-spindle coupling contribute to sleep-dependent memory consolidation? A Bayesian meta-analysis"* by Ng, T., Noh, E., & Rebecca (2024), *bioRxiv*. https://doi.org/10.1101/2024.08.28.610060. Copyright © 2024 Cold Spring Harbor Laboratory.

2.1.7 Neurotransmitter Regulation of Sleep-Dependent Memory Processing

The coordination of SOs, sleep spindles, and SWRs is influenced by neurotransmitter regulation during sleep. Among the key neurotransmitters, GABAergic inhibition stabilizes SO activity, preventing premature sleep transitions and ensuring synchronized cortical processing (Rasch & Born, 2013). Meanwhile, glutamatergic excitation facilitates long-term potentiation (LTP), strengthening synaptic connections necessary for durable memory storage (Hutchison & Rathore, 2015). Studies further indicate that dopaminergic and cholinergic signaling may influence the strength of SO-spindle coupling, affecting overall memory consolidation efficiency (Feld & Born, 2019). These findings suggest that sleep-based memory consolidation is mediated by oscillatory coordination and neurochemical signaling, offering multiple intervention targets for cognitive enhancement.

2.1.8 Summary of Findings

Declarative memory consolidation depends on the precise timing of SOs, spindles, and SWRs (Diekelmann & Born, 2010). While SOs synchronize cortical-hippocampal communication, evidence suggests spindle density may independently predict memory retention (Schabus et al., 2006; Niknazar et al., 2022). SWRs, traditionally linked to memory replay, may also facilitate retrieval (Norman et al., 2019).

Experimental findings confirm a causal role for SO-spindle coupling. Phase-locked auditory stimulation increases SO power and spindle activity, enhancing recall (Ngo et al., 2013). Additionally, CLAS strengthens SO-spindle synchronization, improving hippocampal-neocortical transfer (Navarrete et al., 2019). However, individual variability in response suggests baseline sleep architecture influences efficacy (Feld & Born, 2019).

Neurotransmitters further modulate memory consolidation, with GABAergic inhibition stabilizing SO activity, glutamatergic excitation supporting synaptic plasticity and LTP, and dopaminergic systems influencing SO-spindle coupling strength (Feld & Born, 2019).

Given the crucial role of slow oscillations and spindles in memory consolidation, researchers have explored methods to enhance these natural processes. One such intervention is CLAS which in principle, can be applied to modulate various brain oscillations. This review focuses specifically on its application to SOs during SWS, given their central role in supporting declarative memory. The next section introduces CLAS, its mechanisms, and its potential applications.

2.2: The Role of CLAS in Sleep-Dependent Memory Consolidation

2.2.1 Closed-Loop Auditory Stimulation as a Memory Enhancement Tool

CLAS applied to enhance memory consolidation delivers auditory tones synchronized with the SO up-phase during SWS (Figure 3). Early research suggests that precisely timed auditory tones can potentially enhance SO amplitude and spindle activity, leading to improved declarative memory performance (Ngo et al., 2013). However, its efficiency varies between individuals, and its impact on different memory types and sleep architectures is still under investigation (Navarrete et al., 2019). Moreover, the reliance on laboratory-based polysomnography for real-time SO phase detection limits the scalability of CLAS. Recent advances in adaptive algorithms, particularly those utilizing artificial intelligence (AI), offer a potential solution by enabling real-time SO phase detection in broader, non-laboratory contexts (Debellemaniere et al., 2018). In addition to these considerations, recent studies have begun to explore aperiodic neural activity as a modulator of SO dynamics, indicating that this component of brain activity may influence stimulation efficacy (Ameen et al., 2024).

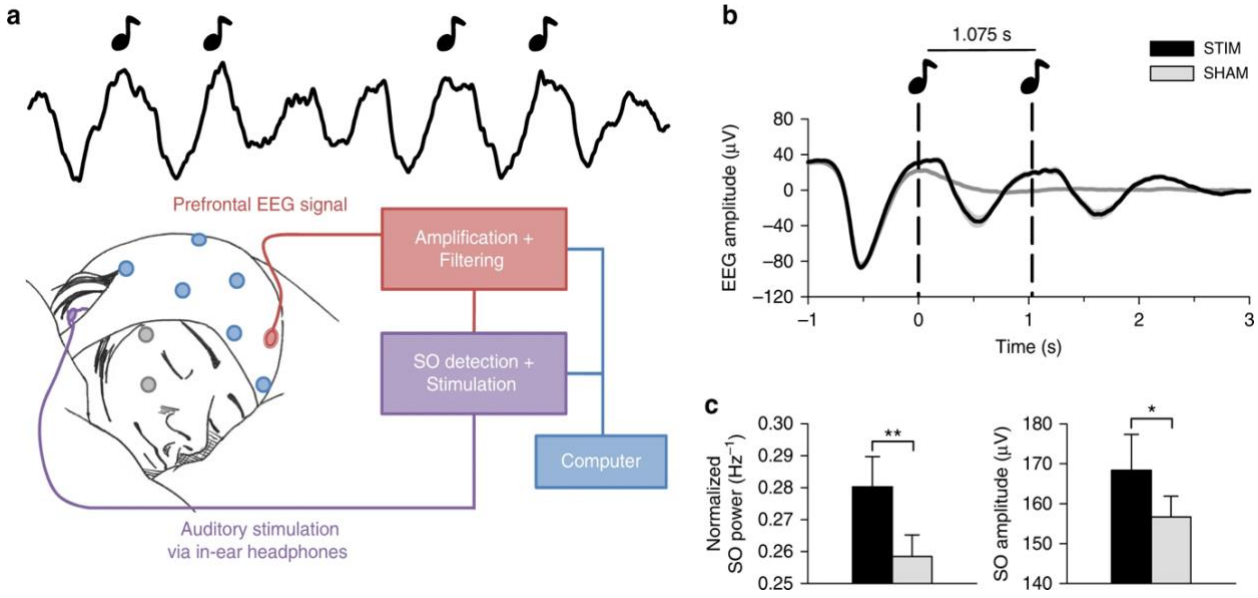

Figure 3. CLAS Mechanism Enhances Slow Oscillations.

(A) Schematic of the CLAS setup: prefrontal EEG signals are amplified, filtered, and processed in real-time by a computer to detect slow oscillation peaks. Auditory stimuli are then delivered via in-ear headphones, timed to the up-phase of detected SOs. **(B)** Example EEG trace showing increased SO amplitude in the stimulation condition (STIM, black line) compared to the sham condition (SHAM, grey line). Auditory tones are triggered at the SO up-phase (dashed lines), with a consistent delay of 1.075s. (C) Quantification of the CLAS effect: stimulation significantly increases normalized SO power (left) and SO amplitude (right) compared to sham ** $p < 0.01$, * $p < 0.05$).

Adapted from "Auditory Closed-Loop Stimulation of EEG Slow Oscillations Strengthens Sleep and Signs of Its Immune-Supportive Function" by Besedovsky, L., Ngo, H.-V. V., Dimitrov, S., Gassenmaier, C., Lehmann, R., & Born, J. (2017), Nature Communications, 8(1). https://doi.org/10.1038/s41467-017-02170-3. Copyright © Nature Publishing Group.

2.2.2 Challenges and Limitations in CLAS Research

While CLAS has shown potential in enhancing memory, its real-world application faces several challenges, and the underlying neural mechanisms remain only partially understood.

A key aspect of its function is the synchronization of SOs and spindles, which is critical for hippocampal-cortical communication and relies on the precise timing, frequency, and volume of auditory stimulation (Fernandez & Lüthi, 2020; Ngo et al., 2013). While much of the research on CLAS has focused on its role in enhancing declarative memory, its potential effects on other types of memory, such as procedural and emotional memory, remain underexplored (Baxter et al., 2023). The effects of CLAS on non-declarative memory systems and its interactions with other sleep stages, such as REM sleep, remain inadequately studied. Moreover, individual differences, including factors such as age, sleep architecture, and baseline SO amplitude, also significantly influence the efficacy of CLAS (Billwiller et al., 2020; Hammer et al., 2021). These variables highlight the need for personalized stimulation protocols to optimize outcomes. Investigating the potential for cross-stage interactions, particularly the role of theta-gamma coupling between SWS and REM, could provide critical insights into how CLAS influences broader neural dynamics (Belluscio et al., 2012; Tononi & Cirelli, 2006). Addressing these gaps will refine CLAS protocols and enhance our understanding of its impact on memory and cognition.

Moreover, research has found that poorly timed auditory tones during sleep significantly reduce intervention efficacy, reinforcing the importance of precise synchronization with SO phases (Debellemaniere et al., 2018). Together, these findings highlight the critical role of timing in optimizing CLAS outcomes and the need for further research to evaluate its potential across diverse memory types.

2.2.3 Neural Mechanisms Underlying CLAS and Memory Consolidation

Understanding the neural mechanisms underlying CLAS is critical for improving its efficacy and expanding its applications. The coupling of SOs and spindles, essential for hippocampal-cortical communication, relies on neurotransmitter systems such as GABA and glutamate, which facilitate synaptic plasticity and memory integration during SWS (Rasch & Born,

2013; Hennies et al., 2016). Preliminary research suggests that these dynamics are integral to CLAS's effectiveness, but further exploration is needed to determine how auditory stimulation influences these neurotransmitter pathways. Insights into these mechanisms could pave the way for protocols that optimize neuroplasticity and extend CLAS benefits beyond declarative memory tasks (Hennies et al., 2016). Further research is essential to evaluate the cumulative effects of repeated CLAS interventions on memory retention and sleep architecture. Clarifying whether prolonged use of CLAS disrupts natural sleep dynamics or enhances its benefits remains a critical area for future investigation (Schneider, 2019).

2.2.4 Translating CLAS to Real-World Applications

The scalability of CLAS is another crucial consideration, particularly for translating its laboratory success into real-world applications. While EEG-based closed-loop systems provide precise stimulation delivery, their reliance on laboratory infrastructure limits accessibility and practicality. Advances in portable EEG systems and smartphone-compatible algorithms for real-time SO detection offer promising avenues for at-home interventions (Fattinger et al., 2017). Wearable devices integrating auditory present non-invasive, user-friendly solutions for widespread use, but challenges such as ensuring user comfort, affordability, and long-term reliability must be addressed (Nguyen et al., 2023). Further refinement of these technologies is essential to facilitate broader deployment and accessibility across diverse populations.

2.2.5 Summary of Findings

CLAS has demonstrated an advanced approach to enhancing memory consolidation during sleep. While research has demonstrated its efficacy in amplifying SOs and spindles and improving declarative memory tasks, significant challenges remain. Addressing questions about timing, individual variability, long-term effects, and interactions with other sleep stages will be essential for refining CLAS protocols. Leveraging advanced methodologies and

multimodal approaches can bridge the gap between experimental findings and real-world applications, advancing both our theoretical understanding and practical implementation of sleep-based cognitive enhancement.

3: Methodology

This study conducted a systematic literature review to synthesize findings from experimental, EEG-based, and behavioral research on CLAS during SWS and its impact on memory consolidation. Integrating data across these domains provided a comprehensive understanding of the mechanisms underlying CLAS and its efficacy in enhancing memory. Following PRISMA 2020 guidelines (Page et al., 2021), the review ensured transparency and rigor in study selection, data extraction, and reporting. The literature search was conducted across PubMed, Google Scholar, and UvA Library databases, using keywords like "closed-loop auditory stimulation," "slow-wave sleep," and "memory consolidation". Peer-reviewed studies published in English, focusing on human participants, were included. Non-peer-reviewed articles and inaccessible full texts were excluded.

Eligibility criteria included studies examining CLAS during SWS in healthy adults, focusing on measurable memory outcomes and employing experimental or observational designs. Studies involving pharmacological interventions, animal models, or non-SWS sleep stages were excluded. A PRISMA flow diagram details steps such as record identification, duplicate removal, title and abstract screening, full-text review, and final inclusion (Appendix 1). Data was extracted using a standardized format, capturing study details (authors, year, design), participant demographics, intervention parameters (timing, synchronization, stimuli characteristics), outcomes (SO amplitude, spindle activity, memory performance), and study limitations.

The synthesis integrated qualitative and quantitative findings, focusing on themes such as neural mechanisms of CLAS, timing of auditory stimuli, and individual variability. Meta-analytic techniques identified trends and measured effect sizes if sufficient data was available. Subgroup analyses explored factors like age and sleep architecture. To address challenges such as heterogeneity and reliance on secondary data, strict inclusion criteria were applied, and methodologies were transparently reported.

This approach was intended to clarify the neural processes modulated by CLAS, assess its practical potential, and provide a foundation for advancing non-invasive sleep-based cognitive interventions. By addressing existing knowledge gaps, the study aimed to contribute actionable insights for both scientific and applied contexts.

4: Results

4.1: CLAS and Its Role in Sleep-Dependent Memory Consolidation

4.1.1 Mechanism of CLAS in Modulating Sleep Oscillations

CLAS has emerged as a promising, non-invasive approach to enhancing sleep-dependent memory consolidation by precisely modulating SO activity during SWS. CLAS operates by delivering auditory cues phase-locked to SO up-phases, reinforcing SO amplitude and SO-spindle coupling, mechanisms critical for memory stabilization (Ngo et al., 2013). EEG and magnetoencephalography (MEG) studies confirm that phase-locked auditory stimulation effectively entrains SO activity, leading to increased amplitude, duration, and synchronization between SOs and sleep spindles (Navarrete et al., 2019). These findings provide direct empirical evidence that CLAS interacts with the core oscillatory mechanisms of SWS, supporting its potential for memory enhancement applications.

Beyond SO-spindle coupling, when specifically directed at the up-phase of SOs, CLAS influences broader oscillatory dynamics. Krugliakova et al. (2020) found that CLAS increased delta, theta, and sigma power, particularly in the right parietal cortex, suggesting region-specific modulation of sleep rhythms. Jourde et al. (2023) further identified CLAS activation of non-lemniscal auditory pathways, which trigger SOs in ventral frontal regions and synchronize cortical-subcortical oscillations, reinforcing memory-related processing beyond auditory networks.

Despite these promising effects, CLAS is subject to inherent regulatory mechanisms that limit excessive cortical activation. These mechanisms likely reflect physiological and neurobiological boundaries designed to preserve brain homeostasis and prevent overstimulation. Ngo et al. (2015) examined whether prolonged CLAS could continuously drive SOs in healthy humans. While results confirmed an enhancement of SO amplitudes, prolonged SO trains, and increased phase-locked spindle activity, excessive stimulation led to rapidly fading phase-locked spindle activity. The authors interpreted this spindle refractoriness as a potential protective mechanism limiting excessive cortical synchronization. These findings highlight the need for optimized stimulation parameters to balance beneficial modulation with natural regulatory processes.

4.1.2 Enhancement of SO Amplitude and Spindle Density

Empirical research confirms that enhancing SO-spindle interactions via CLAS leads to measurable neurophysiological changes, reinforcing the hypothesis that SO-spindle coupling is fundamental to sleep-dependent memory processing. Ngo et al. (2013) demonstrated that phase-locked auditory stimulation increased SO power by 9% and spindle density by 30%, leading to significant improvements in memory recall performance.

The stronger effect on spindles, despite CLAS targeting SOs, may be explained by the hierarchical nature of SO-spindle coupling, where enhanced SOs facilitate spindle generation

due to their temporal alignment. Similarly, Navarrete et al. (2019) found that CLAS-enhanced SO-spindle synchronization facilitates hippocampal-neocortical transfer, reinforcing the functional role of these oscillations in memory retention.

Baxter et al. (2021) further explored whether CLAS could evoke coupled SO-spindle events and enhance procedural memory in healthy adults. Their study found that auditory stimulation during NREM sleep significantly increased SO-spindle coupling in a fronto-central cluster of electrodes (clustered t-stat = 49.6, $p < .05$).

Interestingly, although higher stimulation rates were positively correlated with individual memory improvements ($r = .52$, $p < .05$), no significant effect on memory was observed at the group level. This discrepancy suggests that not everyone benefits equally from CLAS-driven SO-spindle modulation. Individual differences in responsiveness may influence how effectively CLAS enhances memory.

4.1.3 CLAS Effects on Declarative Memory Performance

A growing body of research suggests that CLAS effectively enhances declarative memory, particularly in tasks reliant on hippocampal-dependent learning. Schabus et al. (2006) found that higher spindle density following CLAS correlated with greater recall accuracy, supporting the hypothesis that reinforcing sleep spindles strengthens memory retention. Similarly, Ngo et al. (2013) reported that participants receiving auditory stimulation exhibited significantly higher recall of word-pair associations compared to non-stimulated controls, confirming that CLAS enhances hippocampal-cortical interactions underlying declarative memory storage (Figure 4). Tamminen et al. (2010) further demonstrated that spindles occurring in phase with SO up-states improved consolidation efficiency, highlighting the importance of phase-locked oscillatory activity in optimizing post-sleep memory performance.

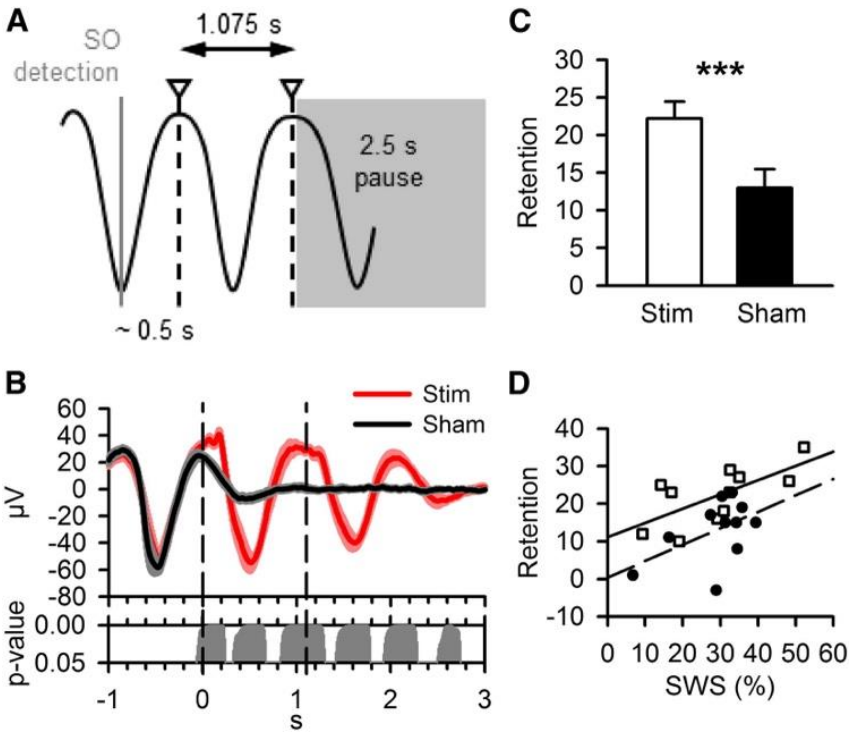

Figure 4. CLAS In-Phase with SO Up States Induces Trains of SOs and Enhances Declarative Memory.

(A) Schematic of the stimulation protocol: auditory stimuli are delivered 1.075 s apart, precisely timed to SO up-states. After three stimulations, a 2.5-second pause prevents overstimulation. **(B)** Averaged EEG traces show increased SO amplitude during stimulation (red) compared to sham (black). Vertical dashed lines indicate stimulus timing. The lower panel shows significant p-values for differences across time points. **(C)** Behavioral results: participants in the stimulation condition (Stim) showed significantly higher memory retention compared to sham (***$p < 0.001$). **(D)** Correlation between the percentage of time spent in slow-wave sleep (SWS) and memory retention, showing a positive relationship in the stimulation condition (open squares) but not in sham (filled circles).

Adapted from "*Auditory Closed-Loop Stimulation of the Sleep Slow Oscillation Enhances Memory*" by Ngo, Hong-Viet V., Martinetz, T., Born, J., & Mölle, M. (2013), *Neuron*, *78*(3), 545–553. https://doi.org/10.1016/j.neuron.2013.03. Copyright © Elsevier

However, findings are not entirely consistent across studies. Henin et al. (2019) reported that while CLAS enhances SOs and spindle activity during sleep, it does not necessarily lead to improvements in memory performance for spatial navigation or verbal association tasks. Their study indicated that although SO-spindle coupling was modulated by CLAS, the increased spindle activity did not translate into a measurable behavioral advantage.

This discrepancy may reflect differences in task demands. The spatial navigation and verbal association tasks used by Henin et al. (2019), while engaging the hippocampus, may also recruit other brain regions or allow alternative strategies, reducing their reliance on hippocampal-cortical reactivation during sleep (Poldrack & Packard, 2003; Iglói et al., 2014). In contrast, declarative word-pair tasks used in studies reporting memory benefits (Schabus et al., 2006; Ngo et al., 2013; Tamminen et al., 2010) depend heavily on hippocampal binding processes, making them more sensitive to enhancements in SO-spindle coupling.

Similarly, Koo-Poeggel et al. (2022) found that although CLAS enhanced SO and spindle activity, it did not significantly improve post-sleep encoding of verbal and non-verbal tasks. The authors attribute this to their focus on new learning after sleep rather than the consolidation of previously learned material. Since encoding depends more on general wakeful learning capacity and less on hippocampal-cortical reactivation during sleep, it may not benefit from CLAS-driven enhancement of sleep oscillations (Diekelmann & Born, 2010). These mixed findings highlight the importance of methodological consistency and task specificity when evaluating CLAS efficacy.

4.1.4 Limited Impact of CLAS on Procedural Memory

While CLAS has demonstrated efficacy in enhancing declarative memory, its impact on procedural memory remains uncertain. Procedural memory consolidation is primarily associated with REM sleep rather than SWS, suggesting that CLAS, which predominantly targets SOs and spindles, may not be as effective for motor sequence learning and other

procedural tasks (Stickgold & Walker, 2013). Baxter et al. (2023) used EEG-based closed-loop stimulation during naps to demonstrate that while CLAS enhanced SO-spindle coupling during naps, it failed to improve motor procedural memory in a finger-tapping motor sequence task (MST). Similarly, Fattinger et al. (2017) examined whether CLAS could improve motor sequence learning and found no significant improvement in procedural memory, reinforcing the idea that procedural memory relies on distinct oscillatory mechanisms, such as theta-gamma coupling during REM sleep.

These findings highlight the stage-specific nature of CLAS effects and suggest that interventions should be tailored to distinct sleep stages and oscillatory targets, as they govern different forms of memory consolidation.

4.1.5 Summary of Findings

CLAS research provides compelling evidence that phase-locked auditory stimulation enhances SO amplitude, increases spindle density, and strengthens SO-spindle synchronization. Studies by Ngo et al. (2013) and Navarrete et al. (2019) confirm that CLAS improves hippocampal-neocortical transfer, supporting the theory that SOs act as a key timing mechanism for memory reactivation. However, not all findings support a direct cognitive benefit of CLAS. While some studies report enhanced declarative memory performance, others (Henin et al., 2019) suggest that SO-spindle enhancement alone does not guarantee behavioral improvements, raising questions about task specificity and methodological variations across studies. Furthermore, the failure of CLAS to enhance procedural learning reinforces the idea that different memory systems rely on distinct sleep-stage mechanisms (Fattinger et al., 2017; Baxter et al., 2023).

Future research should investigate whether combining CLAS with other interventions, such as REM-targeted stimulation or pharmacological neuromodulation, could optimize sleep-based memory enhancement. Additionally, exploring individual differences in responsiveness

to CLAS may help refine stimulation protocols for personalized cognitive enhancement strategies.

4.2: Optimizing CLAS Timing: Phase-Specific Stimulation and Precision Delivery

4.2.1 The Importance of Precise CLAS Timing for Memory Enhancement

The effectiveness of CLAS in enhancing memory consolidation is highly dependent on precise synchronization with the SO cycle. Stimulation delivered at the SO up-phase strengthens hippocampal-cortical communication, optimizing synaptic plasticity and memory retention (Ngo et al., 2013). Conversely, misaligned stimulation disrupts SO coherence, weakens SO-spindle coupling and diminishes cognitive benefits (Fattinger et al., 2017). Given that SO up-phases correspond to peak neuronal excitability, precise phase-locked stimulation ensures maximal plasticity, reinforcing memory traces more effectively than untimed auditory stimulation.

Harrington et al. (2021) further confirmed that phase-targeted CLAS significantly enhances memory by modulating SO activity. Their study demonstrated that stimulation precisely locked to the SO up-phase led to stronger SO power and improved recall performance, while misaligned stimulation resulted in weaker SO-spindle coupling and diminished memory benefits. These findings highlight the necessity of precise phase alignment in optimizing CLAS efficacy and suggest that real-time phase tracking is essential to maximize cognitive benefits.

4.2.2 Phase-Dependent Stimulation Effects on Memory Retention

Studies consistently demonstrate that accurately timed, phase-locked CLAS stimulation enhances declarative memory consolidation. Ngo et al. (2013) found that SO-phase-locked stimulation increased SO amplitude, spindle density, and recall performance, whereas stimulation outside the optimal phase had no significant effect.

Further supporting these findings, Buzsáki et al. (2013) and Schabus et al. (2006) reported that the relative timing of spindles to SO up-phases predicts consolidation success, reinforcing the importance of precisely targeting neural excitability windows. Navarrete et al. (2019) expanded on these results, showing that dynamically adjusting CLAS to real-time SO fluctuations maximized SO-spindle synchronization, strengthening hippocampal-cortical information transfer. Additionally, Debellemaniere et al. (2018) showed that CLAS phase-locking directly correlates with memory performance, emphasizing that precise timing of stimulation influences both neural oscillatory dynamics and behavioral recall. Overall, these findings suggest that CLAS holds promise for enhancing declarative memory by targeting specific sleep stages, but its effectiveness relies on precisely timed, phase-locked stimulation to optimize SO-spindle coupling and support hippocampal-cortical communication.

4.2.3 SO-Spindle Coupling as a Mechanism for CLAS-Induced Memory Improvements

As stated before, SO-spindle coupling is a key determinant of memory consolidation success following CLAS stimulation. Stronger SO-spindle coupling predicts better hippocampal-neocortical transfer and memory recall after CLAS (Schabus et al., 2006; Ngo et al., 2013; Navarrete et al., 2019). Baseline coupling also influences CLAS efficacy, highlighting SO-spindle dynamics as a key target for memory enhancement (Debellemaniere et al., 2018). Recent work by Ruch et al. (2023) highlights the importance of spatial specificity in SO-spindle coupling. Their study introduced the topographic targeting of slow oscillations (TOPOSO) algorithm, a closed-loop stimulation method that targets SO up-phases with high spatial precision. Unlike conventional single-channel stimulation approaches, TOPOSO enhances local SO activity over functionally distinct cortical areas, leading to region-specific spindle synchronization. This suggests that localized CLAS could optimize SO-spindle interactions in brain regions critically involved in memory consolidation, offering a more refined approach to enhancing hippocampal-cortical transfer.

4.2.4 Challenges of Fixed-Interval CLAS Stimulation Protocols

The natural variability in timing and occurrence of SOs, both within a single sleep cycle and across different sleep cycles throughout the night, presents a major challenge for fixed-interval CLAS protocols. Studies show that pre-programmed auditory cues often fail to align consistently with endogenous SO activity, reducing efficacy (Fattinger et al., 2017).

Ngo et al. (2013) demonstrated that memory benefits were significantly greater when stimulation dynamically synchronized with SO fluctuations compared to fixed-interval delivery, highlighting the importance of real-time phase tracking. Additionally, Cox et al. (2017) found that SO frequency varies across individuals and sleep cycles, meaning that pre-determined stimulation risks missing optimal up-phases, leading to inconsistent effects.

In addition, Fehér et al. (2023) found that poorly optimized CLAS parameters can suppress SWS rather than enhance it, shifting slow-wave activity toward the end of the night as a homeostatic response. This finding emphasizes the importance of carefully balancing stimulation intensity and timing to prevent unintended disruptions in sleep architecture.

4.2.5 The Development of Real-Time SO Tracking and Adaptive Stimulation Models

To overcome the limitations of fixed-interval stimulation, real-time EEG-based tracking systems have been developed. Debellemaniere et al. (2018) found that real-time phase tracking produced significantly stronger memory improvements than pre-scheduled stimulation, demonstrating that adaptive CLAS enhances SO-spindle coupling more reliably.

Navarrete et al. (2019) confirmed that adaptive CLAS models, which dynamically adjust stimulation based on real-time SO fluctuations, yield more consistent memory benefits. Their study revealed that phase misalignment as small as 50 ms significantly reduces CLAS efficacy, reinforcing the need for precise real-time adjustments.

4.2.6 Summary of Findings

Empirical studies confirm that precise timing of CLAS stimulation is essential for enhancing declarative memory consolidation. Ngo et al. (2013) and Schabus et al. (2006) show that phase-locked stimulation increases SO amplitude, enhances spindle density, and strengthens hippocampal-cortical transfer. However, Fattinger et al. (2017) and Debellemaniere et al. (2018) demonstrate that fixed-interval CLAS protocols often fail to align with endogenous SOs, leading to reduced memory benefits.

Studies by Navarrete et al. (2019) highlight that real-time adjustments significantly improve memory outcomes compared to fixed-timing interventions, emphasizing the necessity of dynamic phase-tracking in CLAS optimization.

These findings establish that CLAS efficacy is dependent not only on phase-locked SO stimulation but also on the precision of SO-spindle synchronization, underscoring the importance of technological advancements in real-time EEG tracking to maximize cognitive enhancements.

4.3: Individual Variability in CLAS Efficiency

4.3.1 Variability in CLAS-Induced Memory Enhancement

While CLAS has demonstrated efficacy in enhancing sleep-dependent memory consolidation, its effectiveness varies significantly across individuals. Research suggests that differences in baseline sleep architecture, age-related sleep changes, and neurophysiological factors influence how well a person responds to auditory stimulation (Navarrete et al., 2019; Schneider et al., 2020). Understanding these sources of variability is crucial for optimizing CLAS protocols and ensuring its benefits are accessible to a broader population.

4.3.2 Baseline SO Amplitude and Spindle Density as Predictors of CLAS Efficacy

A well-established finding in CLAS research is that individuals with higher baseline SO amplitude and spindle density tend to experience greater memory benefits from stimulation.

Fattinger et al. (2017) observed that participants with stronger endogenous SO activity before CLAS exhibited greater retention improvements, whereas those with lower SO amplitude had weaker responses to stimulation. Similarly, Navarrete et al. (2019) reported that SO-spindle coupling strength before CLAS predicted the degree of memory enhancement, reinforcing the idea that pre-existing sleep characteristics shape CLAS efficacy.

Further, EEG analyses confirm that participants with stronger SO-spindle synchronization show greater hippocampal-neocortical transfer following CLAS, highlighting the role of individual differences in sleep architecture (Schreiner et al., 2021). Recent findings from Koo-Poeggel et al. (2022) emphasize that responses to CLAS depend not only on sleep metrics but also on factors like individual cognitive ability and time of day, which may influence outcomes by affecting baseline encoding strength or sleep architecture, respectively. This suggests that tailoring stimulation parameters to individual factors could enhance its cognitive benefits.

However, whether these variables directly cause improved CLAS-induced memory outcomes or merely correlate with broader sleep quality differences remains an open question. Some researchers propose that greater sleep homeostasis, rather than SO amplitude alone, may underlie these effects (Chen et al., 2025). This raises the possibility that interventions aimed at enhancing overall sleep stability could improve CLAS responsiveness even in individuals with initially weaker SO activity.

4.3.3 Age-Related Differences in CLAS Effectiveness

Age-related sleep changes have been identified as a key factor influencing CLAS efficacy. Schneider et al. (2020) found that older adults exhibited reduced SO-spindle coupling and lower SO amplitude, which correlated with diminished memory enhancement following CLAS. While younger adults benefited significantly from stimulation, older participants showed no improvement in declarative memory. Furthermore, while CLAS increased SO

train duration and phase-locked spindle activity in older adults, these responses were weaker and followed different temporal patterns than those observed in younger subjects (Schneider et al., 2020). These findings suggest that age-related declines in sleep oscillatory dynamics may reduce CLAS effectiveness. Figure 5 illustrates how reduced sleep stability with aging impacts memory function highlighting the progressive changes in sleep oscillations across the lifespan.

Stronger sleep fragmentation and a greater number of microarousals, as seen in older adults, may further compromise SO stability, reducing CLAS's ability to entrain neural oscillations effectively (Mander et al., 2017). Garcia-Molina et al. (2018) found that the reduced effect of CLAS in older adults was partly due to a lower volume of stimulation received, likely a result of altered sleep architecture. Their study suggests that modifications in CLAS protocols, such as adjusting stimulus intensity or timing, may enhance efficacy for older populations. These findings highlight the need for age-specific adaptations of CLAS interventions, potentially in combination with methods designed to improve SO-spindle coupling in aging individuals.

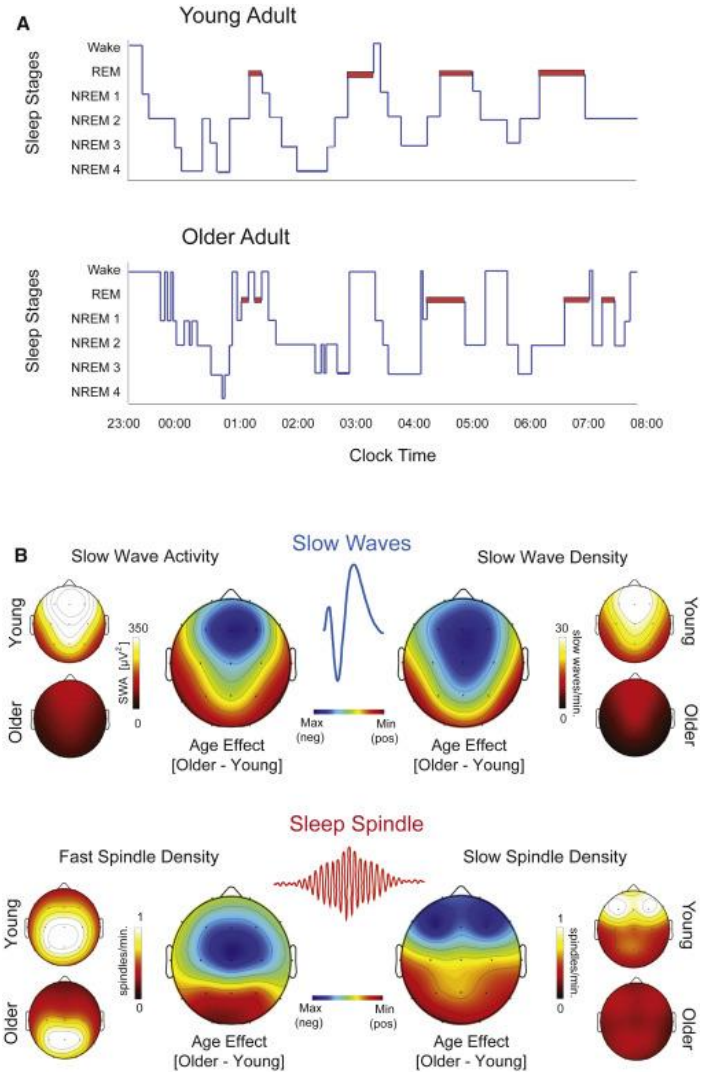

Figure 5. Schematic of Age-Related Changes in Sleep Architecture and NREM Sleep Oscillations.

(A) Hypnograms showing sleep stage transitions across the night in a young and an older adult. Compared to the young adult, the older adult exhibits reduced slow-wave sleep (NREM 3/4), increased wakefulness, and fragmented sleep cycles. **(B)** Topographical maps of slow-wave and spindle activity. Aging is associated with reduced slow-wave activity and density, particularly over frontal regions (top row), and decreased fast and slow spindle density (bottom row). Difference maps (right) indicate significant reductions in both slow waves and spindles in older adults relative to younger adults. Adapted from *"Sleep and Human Aging"* by Mander, B. A., Winer, J. R., & Walker, M. P. (2017), *Neuron, 94*(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004. Copyright © 2017 Elsevier.

4.3.4 The Impact of Sleep Stability and Fragmentation on CLAS Responsiveness

Beyond age-related factors, sleep stability and homeostatic sleep pressure play a crucial role in determining CLAS efficacy. Schabus et al. (2006) and Schneider (2019) found that individuals with more stable sleep architecture exhibited stronger memory benefits from CLAS, whereas those with fragmented sleep cycles had more variable and weaker responses. This variability is likely due to disruptions in the coordination of SOs and sleep spindles, which are essential for memory consolidation (Schabus et al., 2006). Participants with highly fragmented sleep demonstrate reduced synchronization between SOs and spindles, leading to diminished CLAS-induced memory benefits.

Moreover, individuals with higher sleep homeostasis, marked by greater SO amplitude and spindle density, tend to show stronger CLAS-induced memory enhancements (Chen et al., 2025). These findings suggest that improving sleep stability may enhance the efficacy of CLAS, particularly in individuals prone to disrupted sleep cycles.

Building on this, recent advances in sleep-tracking technology offer promising solutions to minimize sleep disturbances during CLAS interventions. Henao et al. (2022) demonstrated that in-ear EEG sensors offer a less invasive method for detecting slow oscillations. Compared to traditional scalp EEG, this approach reduces discomfort and minimizes sleep disturbances, potentially leading to more stable sleep and improved responsiveness to CLAS interventions. Similarly, Bressler et al. (2023) introduced a wearable EEG-based CLAS system that successfully measured sleep-related neural activity without disrupting sleep onset. Another promising device, ZMax EEG, has been developed as a headband-based system designed for home use, offering a practical alternative to traditional polysomnography (Mahdad Jafarzadeh Esfahani et al., 2023). By enabling real-time monitoring of sleep oscillations in non-laboratory environments, ZMax EEG and similar wearable devices may play a crucial role in improving the accessibility of CLAS interventions.

Unlike conventional scalp EEG, this home-use device provided a more user-friendly alternative, minimizing discomfort-related sleep fragmentation. Together, these technologies could optimize CLAS responsiveness by enabling real-time monitoring of sleep oscillations while reducing disruptions caused by traditional EEG setups.

4.3.5 Summary of Findings

CLAS efficacy is significantly influenced by individual differences in sleep architecture, age, and SO-spindle dynamics. Studies indicate that higher baseline SO amplitude and spindle density predict greater memory benefits, while age-related reductions in SO-spindle coupling limit CLAS effectiveness in older adults (Fattinger et al., 2017; Navarrete et al., 2019; Schneider et al., 2020).

However, the causal mechanisms underlying these effects remain unclear. Some studies suggest that sleep stability, rather than SO power alone, may determine CLAS responsiveness (Chen et al., 2025). This raises important questions about whether interventions aimed at improving sleep homeostasis could enhance CLAS-induced memory benefits, even for individuals with lower baseline SO activity.

Additionally, while sleep fragmentation is associated with weaker CLAS-induced memory benefits, it remains uncertain whether individuals with disrupted sleep cycles can still benefit from adaptive CLAS interventions designed to account for sleep variability (Schabus et al., 2006; Schneider, 2019). Future research should explore whether combining CLAS with interventions that stabilize SO activity, such as pharmacological modulation or targeted behavioral strategies, could improve its efficacy in more variable sleepers.

These findings highlight the need for personalized CLAS protocols that account for individual sleep profiles, ensuring that stimulation is optimized for maximal cognitive enhancement across diverse populations.

5: Discussion

5.1 The Role of SO-Spindle Coupling in Memory Consolidation

This study provides strong empirical support for the role of SO-spindle coupling in sleep-dependent memory consolidation. The findings align with the active system consolidation hypothesis, reinforcing that precise temporal coordination of SOs and sleep spindles facilitates the transfer of newly encoded information from the hippocampus to the neocortex (Born & Wilhelm, 2012). The observed enhancement of SO amplitude, increased spindle density, and strengthened hippocampal-cortical communication with CLAS further validate its efficacy in promoting declarative memory formation (Ngo et al., 2013; Navarrete et al., 2019).

While these findings confirm that CLAS modulates sleep oscillatory dynamics, its effects on broader cognitive functions remain unclear. Although declarative memory benefits are well-documented, CLAS has demonstrated limited efficacy in enhancing procedural memory, with studies showing no significant improvement in motor sequence learning tasks (Baxter et al., 2023; Fattinger et al., 2017). This suggests that SO-spindle coupling alone may not be sufficient for all forms of memory consolidation, necessitating further research into stimulation strategies tailored to different memory domains.

5.2 Mechanistic Specificity and Long-Term Effects of CLAS

A key limitation of CLAS studies is the unclear mechanistic specificity of its effects. While CLAS consistently increases SO amplitude and spindle density, it remains uncertain whether these enhancements directly facilitate long-term synaptic plasticity or merely reinforce transient neural entrainment. Some studies indicate that increases in SO power alone do not predict improvements in recall, suggesting that SO-spindle coupling, rather than SO amplitude, is the primary driver of CLAS-induced memory benefits (Tamminen et al., 2010; Staresina et al., 2023).

Beyond mechanistic uncertainty, the long-term effects of repeated CLAS use remain largely unexplored. If nightly stimulation leads to compensatory adaptations in neural oscillations, its effectiveness may diminish over time. Some research suggests that CLAS induces an entrainment-like effect, aligning slow waves with the stimulation periodicity (Garcia-Molina et al., 2018), while others indicate that prolonged use triggers a regulatory mechanism preventing hypersynchronization, ultimately reducing SO-spindle coupling (Ngo et al., 2015). Future studies should determine whether CLAS produces sustained neuroplastic benefits or if homeostatic mechanisms limit its impact on sleep-dependent memory consolidation.

5.3 Optimizing CLAS Timing for Maximum Efficacy

One of the most significant challenges in CLAS research is the need for precise timing of auditory stimulation. CLAS is most effective when delivered at the SO up-phase, where neuronal excitability and synaptic plasticity are maximized (Fattinger et al., 2017; Debellemaniere et al., 2018). However, fixed-interval stimulation protocols fail to account for individual differences in SO morphology, leading to inconsistent results (Cox et al., 2017). Studies demonstrate that even slight phase misalignments (as small as 50ms) significantly reduce CLAS efficacy (Navarrete et al., 2019).

Adaptive real-time EEG tracking presents a potential solution by dynamically adjusting stimulation timing to align with endogenous oscillatory fluctuations. However, several challenges remain, including EEG signal noise, phase misalignment errors, and computational delays that reduce precision. Future research should focus on machine learning-based signal processing techniques to improve real-time SO detection algorithms, thereby enhancing the precision of auditory cue delivery and optimizing CLAS efficacy.

5.4 Inter-Individual Variability and Personalized CLAS Protocols

CLAS responsiveness varies significantly across individuals, suggesting that personalized stimulation protocols may be necessary to optimize efficacy. Studies show that individuals

with higher baseline SO amplitude and spindle density experience greater memory benefits, whereas those with lower endogenous SO-spindle coupling show weaker effects (Fattinger et al., 2017; Navarrete et al., 2019). These findings raise the question of whether tailoring CLAS interventions, such as adjusting stimulation intensity, incorporating multi-night interventions, or combining CLAS with pharmacological approaches, could enhance outcomes for individuals with weaker baseline SO activity.

Age-related changes in sleep architecture present another critical factor influencing CLAS efficacy. Older adults exhibit reduced SO power, increased sleep fragmentation, and weaker SO-spindle coupling, which contribute to diminished responsiveness to auditory stimulation (Schneider et al., 2020). Given that cholinergic and dopaminergic neuromodulation plays a role in sleep-dependent memory processing (Feld & Born, 2019), future research should explore whether pharmacological interventions targeting these neurotransmitter systems can enhance CLAS efficacy, both in aging populations and in individuals with impaired sleep architecture. Additionally, strategies aimed at improving sleep quality more broadly, such as behavioral interventions or non-invasive neuromodulation, may also support better responsiveness to CLAS.

Moreover, sleep stability plays a crucial role in determining how effectively CLAS enhances memory consolidation. Individuals with high sleep fragmentation exhibit reduced synchronization between SOs and spindles, leading to weaker CLAS-induced memory benefits (Schabus et al., 2006; Schneider, 2019). Wearable EEG-based CLAS systems, such as in-ear EEG sensors, may provide a less intrusive alternative to traditional polysomnography, reducing disruptions in sleep continuity and improving stimulation outcomes (Henao et al., 2022; Bressler et al., 2023).

5.5 Potential Adverse Effects of CLAS on Sleep Architecture

Although CLAS is designed to enhance sleep-dependent memory consolidation, poorly optimized stimulation parameters may inadvertently disrupt sleep architecture. Research has shown that inappropriate CLAS settings can suppress SWS instead of enhancing it, shifting SO activity toward the end of the night as a homeostatic compensation mechanism (Fehér et al., 2023). Additionally, excessive stimulation can trigger an intrinsic regulatory response, leading to diminished phase-locked spindle activity over time (Ngo et al., 2015). These findings highlight the need for careful optimization of CLAS parameters to prevent unintended disruptions in natural sleep oscillatory dynamics.

Another key consideration is whether repeated nightly CLAS use alters overall sleep quality. While most studies focus on short-term effects, it remains unknown whether long-term stimulation impacts REM sleep, theta-gamma coupling, or broader sleep-stage interactions. Future research should investigate how CLAS interacts with other sleep stages, particularly whether cross-stage interactions (e.g., SWS-to-REM transitions) influence its efficacy.

5.6 Broader Applications of Real-Time CLAS Beyond Memory Consolidation

Recent research by Yoon et al. (2023) extends the potential applications of real-time CLAS beyond memory consolidation. Their study developed a system that synchronizes auditory stimulation with an individual's respiratory rhythms, aiming to facilitate sleep initiation. By aligning stimulation to the breathing cycle, the intervention significantly reduced time to sleep onset (TSSI) and modulated autonomic nervous system activity. These findings suggest that real-time CLAS approaches could also support sleep regulation mechanisms, offering new avenues for interventions targeting sleep onset difficulties.

5.7 Summary of Key Insights

CLAS enhances SO-spindle interactions and declarative memory retention, but its effects on procedural memory remain limited. Precise timing is crucial, as misaligned stimulation reduces efficacy, highlighting the need for real-time phase-tracking solutions. The mechanisms underlying CLAS-induced memory enhancement, including its impact on SOs and sleep spindles, are visually summarized in Figure 6, which outlines the step-by-step process of how CLAS influences memory consolidation.

Inter-individual variability in SO dynamics, age-related declines in SO power, and sleep fragmentation all affect outcomes, emphasizing the need for personalized interventions. Further research should clarify long-term effects, refine stimulation models, and explore wearable EEG and AI-driven algorithms for scalable applications, while also investigating CLAS potential in reducing sleep onset latency. Optimizing stimulation parameters and combining CLAS with other interventions will be essential for maximizing its cognitive benefits.

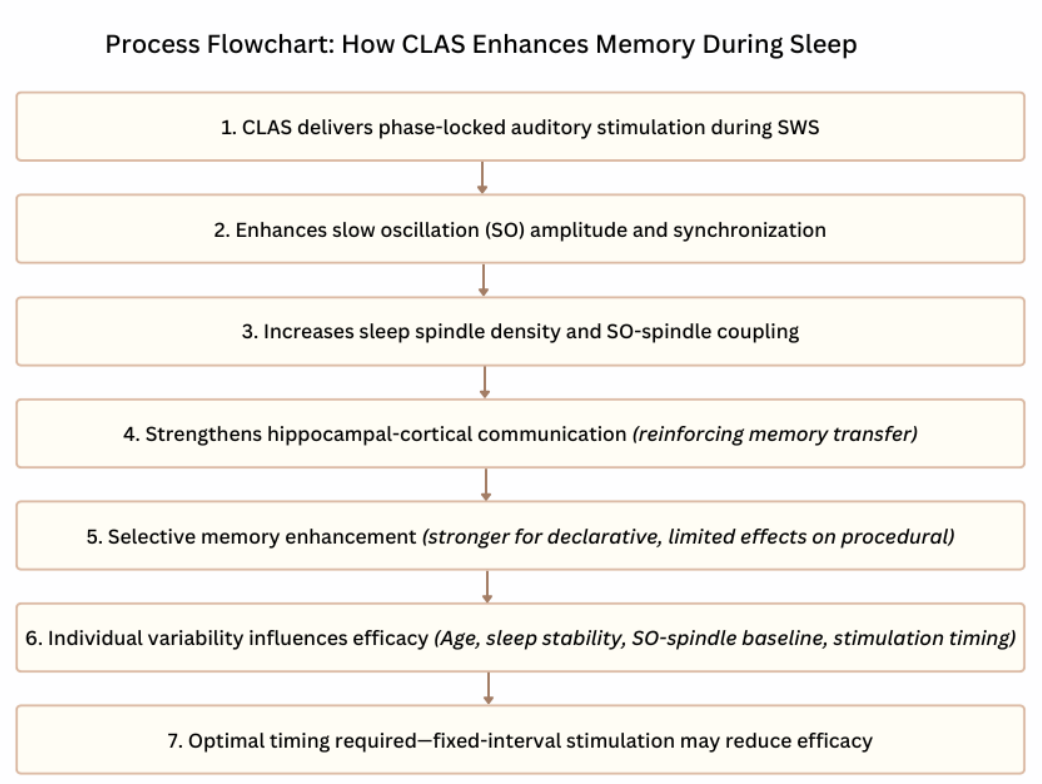

Figure 6. Process Flowchart: How CLAS Enhances Memory During Sleep

CLAS delivers phase-locked auditory stimuli during slow-wave sleep (SWS), increasing slow oscillation (SO) amplitude and synchronization. This, in turn, enhances sleep spindle density and strengthens SO-spindle coupling, facilitating hippocampal-cortical communication critical for memory transfer. The process leads to selective memory enhancement, particularly for declarative memory. Individual differences, such as age, sleep stability, baseline SO-spindle activity, and stimulation timing modulate the efficacy of CLAS. Precise timing is essential, as fixed-interval stimulation may reduce effectiveness.

6: Conclusion and Broader Implications

6.1 Advancing Sleep-Based Cognitive Enhancement

This study provides compelling empirical evidence that CLAS is a viable tool for enhancing sleep-dependent memory consolidation. By modulating SO-spindle coupling, CLAS strengthens hippocampal-cortical communication, leading to measurable improvements in declarative memory retention (Ngo et al., 2013; Navarrete et al., 2019). These findings reinforce the notion that targeted sleep interventions can actively enhance memory processing, offering exciting possibilities for cognitive neuroscience and applied neurotechnology. However, several translational challenges must be addressed before CLAS can be effectively implemented outside controlled laboratory environments.

6.2 Challenges in Real-World CLAS Applications

One of the primary obstacles in real-world applications is ensuring the reliability of phase tracking in wearable EEG systems. While emerging at-home CLAS technologies such as SleepLoop and ZMax EEG show promise, their accuracy in detecting SO phases must be validated against gold-standard polysomnography (Mahdad Jafarzadeh Esfahani et al., 2023). By integrating AI-driven adaptive stimulation, these technologies can enhance the precision

of CLAS interventions in home-based environments, reducing reliance on traditional sleep labs. Additionally, personalized stimulation protocols will be necessary to account for individual differences in sleep architecture, cognitive ability, and responsiveness to auditory stimulation. As CLAS moves toward commercialization, ensuring user-friendly, high-precision technology will be essential for maximizing its effectiveness in diverse populations.

6.3 Applications in Education and Clinical Neuroscience

Beyond laboratory settings, CLAS presents significant potential for educational applications. Given its ability to enhance declarative memory, CLAS could be integrated into structured learning programs, particularly in fields requiring strong memory retention, such as language acquisition and medical education (Clark et al., 2024). However, successful implementation will require optimizing stimulation timing based on individual sleep schedules and learning objectives. Furthermore, the effectiveness of CLAS in improving long-term retention beyond short-term recall enhancements remains an open question that future research should explore. In clinical contexts, CLAS has been investigated as a potential intervention for cognitive decline in individuals with mild cognitive impairment (MCI) and early-stage Alzheimer's disease (Navarrete et al., 2019; Schneider et al., 2020). However, age-related reductions in SO-spindle coupling may limit its efficacy in older populations, necessitating tailored stimulation protocols or adjunctive pharmacological interventions. Given the increasing prevalence of neurodegenerative disorders, further research into how CLAS can be optimized for cognitive rehabilitation will be crucial in determining its feasibility as a therapeutic tool.

6.4 Ethical Considerations and Societal Impact

As neurotechnology like CLAS become more widespread, ethical considerations regarding data privacy, accessibility, and regulatory oversight must be carefully addressed. There is a risk that CLAS could exacerbate cognitive disparities if access to advanced sleep-enhancing technologies remains restricted by socioeconomic factors (Veit, 2018). Regulatory

frameworks must ensure that CLAS interventions are equitably distributed and that safeguards are in place to prevent potential misuse or over-commercialization. Additionally, transparency in data collection and algorithmic decision-making in real-time EEG processing will be critical for maintaining ethical integrity in CLAS applications.

6.5 Future Research Directions

Future research should prioritize longitudinal studies to assess whether repeated CLAS use leads to cumulative neuroplastic benefits or whether homeostatic mechanisms diminish its effects over time. In parallel, lifespan-oriented studies may help clarify how CLAS influences cognitive processes during key developmental stages and aging.

Beyond NREM sleep, a promising avenue involves applying CLAS during REM sleep, particularly to enhance procedural learning (Jaramillo et al., 2023). Investigating cross-stage sleep dynamics, such as how transitions between SWS and REM sleep affect CLAS efficacy, could also reveal synergistic effects on memory consolidation and restoration.

Given the variability in individual responsiveness, combining CLAS with interventions that stabilize SO activity, such as pharmacological modulation or targeted behavioral strategies, may improve outcomes, especially in individuals with fragmented or unstable sleep. Pairing CLAS with GABA agonists or other agents known to enhance SWS may also synergistically support oscillatory dynamics and memory (Feld & Born, 2019). Future work should further examine whether compensatory neural mechanisms emerge with prolonged CLAS use, potentially limiting its long-term impact.

Significant opportunities lie in technological innovation. The development of machine-learning-driven adaptive stimulation models could refine CLAS timing by enhancing SO phase detection and tailoring stimulation to individual profiles. Integration of wearable data (e.g., Oura, Whoop) and long-term sleep tracking may further boost predictive accuracy.

Translating CLAS beyond the lab will also require continued improvements in wearable EEG systems, real-time detection capabilities, and at-home usability.

From a biological targeting perspective, age-related declines in SO power may reduce CLAS efficacy. Investigating pharmacological strategies (e.g., GABAergic or glutamatergic modulation), as well as non-invasive neuromodulation techniques such as transcranial alternating current stimulation (tACS) or, in severe cases, deep brain stimulation (DBS), could enhance responsiveness in aging populations (Rasch & Born, 2013; David et al., 2020; Aktürk et al., 2022). Multi-modal interventions that combine CLAS with cognitive training, mindfulness, cognitive behavioral therapy (CBT), or VR-based biofeedback also hold the potential for improving cognitive outcomes in both healthy and clinical populations.

CLAS's applications may also expand beyond SOs. Studies have shown that stimulation of alpha oscillations modulates power, frequency, and connectivity (Hebron et al., 2024), while phase-locked CLAS during REM can modulate both alpha and theta rhythms (Jaramillo et al., 2023). These findings point to the possibility of targeting other frequency bands (e.g., theta, gamma) to influence emotional regulation, executive function, attention, or sensorimotor integration.

Finally, future research should aim to identify biomarkers of CLAS responsiveness, including SO-spindle coupling strength, sleep architecture, or even genetic factors, to guide personalized stimulation protocols. Testing CLAS in clinical populations, such as individuals with insomnia, mild cognitive impairment, or neurodegenerative conditions, will be critical to evaluating its real-world therapeutic impact (Navarrete et al., 2019; Schneider et al., 2020). Neurofeedback techniques could also be explored to enhance slow oscillation expression prior to sleep, optimizing CLAS efficacy.

6.6 Final Thoughts

While CLAS represents a groundbreaking approach to sleep-based memory enhancement, its broader application will depend on continued technological, methodological, and ethical advancements. By integrating real-time EEG tracking, personalized stimulation protocols, and multimodal cognitive interventions, CLAS has the potential to revolutionize memory enhancement in both research and clinical settings. As research progresses, CLAS could transition from an experimental tool to a widely accessible neurotechnology, fundamentally reshaping how sleep is leveraged for cognitive optimization.

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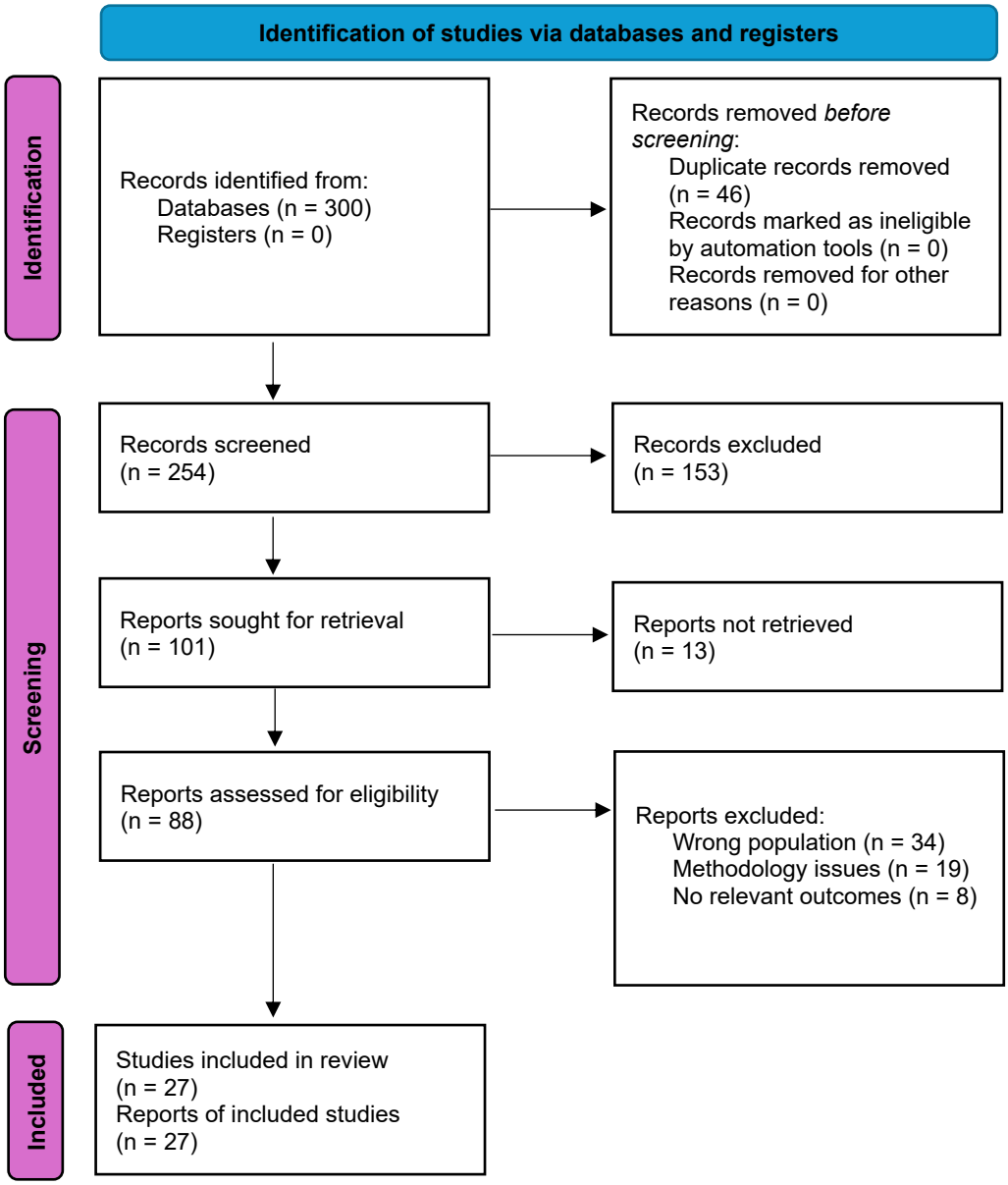
Appendix 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71



Appendix 2. Comparison of Methodological Approaches and Findings in Key CLAS Studies

Study	CLAS Timing	EEG Effects	Memory Task	Findings
Baxter et al. (2021)	Afternoon nap, phase-locked to SO up-state	Increased coupled SO-spindle events, stimulation rate correlated with memory improvement	Finger tapping Motor Sequence Task	Higher stimulation rate positively correlated with memory improvement ($r = .52$, $p < .05$); centro-parietal SO-spindle density also correlated with memory improvement ($r^2 = .29$, $p = .05$)
Baxter et al. (2023)	During sleep, synchronized with SO up-phase	Enhanced SO-spindle coupling	Motor sequence learning	Improved motor procedural memory consolidation, with increased coupling between slow oscillations and spindles
Bressler et al. (2023)	Alpha-phase-locked auditory stimulation during transition from wakefulness to sleep	High-precision phase tracking of oscillations, modulation of alpha and theta activity	None	Demonstrated feasibility of using a wearable EEG device for real-time closed-loop neuromodulation, showing that auditory stimulation can be delivered at intended phases with minimal disruption to sleep onset
Choi et al. (2020)	Weak vibrational closed-loop stimulation	Improved SWS depth, increased delta power	Declarative memory recall	Enhanced SWS depth, autonomic stabilization,

				and improved memory retention
Clark et al. (2024)	During sleep, over three consecutive nights per week for two weeks	Increased SO amplitude and entrainment, enhanced SO-spindle coupling	Language learning tasks (word recall) and discovery learning tasks	35% improvement in word recall and 26% enhancement in discovery learning performance with CLAS compared to control
Debellemaniere et al. (2018)	During N3 sleep	Improved SO coherence	Cognitive function assessment	CLAS using a wireless dry-EEG device accurately detected N3 sleep and enhanced slow oscillations without adaptation over 10 nights
Fattinger et al. (2017)	SO phase-locked auditory stimulation	Increased SO amplitude	Motor procedural memory	No significant improvement in procedural memory performance
Fehér et al.(2023)	Auditory stimulation during SWS, targeting frontal SOs	30% reduction in SWS, increase in lighter NREM sleep, shift in slow-wave activity timing	None	CLAS suppressed SWS without reducing total sleep time, demonstrating a homeostatic shift in SOs and highlighting the need for precise parameter optimization to avoid unintended disruptions
Garcia-Molina et al. (2018)	Auditory stimulation during SWS,	Enhanced slow-wave activity	None	CLAS effectively enhanced slow-

	dynamically adjusted based on sleep depth	(+16.1%, $p < 0.01$) in younger adults; increased spindle power		wave activity in younger adults, but no effect was observed in older adults due to differences in sleep architecture and stimulation received
Harrington et al. (2021)	Phase-locked auditory stimulation during SWS	Increased slow oscillation rhythm, phase-coupled spindle activity, and slow oscillation power	Semantically-incongruent word associations	CLAS enhanced SO and spindle activity but did not improve memory retention for semantically incongruent associations, suggesting task-specific limitations of CLAS benefits
Hebron et al. (2024)	EEG-based alpha phase-locked stimulation	Modulated alpha power, frequency, and connectivity	Sleep onset regulation	Alpha CLAS interfered with sleep onset dynamics in a phase-dependent manner, demonstrating the ability to influence cortical rhythms beyond SWS
Henao et al. (2022)	Auditory stimulation synchronized to SOs using in-ear EEG	Successfully detected and enhanced slow oscillations in real-time	None	In-ear EEG sensors provided a viable alternative to scalp electrodes, demonstrating the feasibility of non-invasive CLAS for sleep

				modulation and potential clinical applications
Henin et al. (2019)	During daytime naps and overnight sleep, stimuli were delivered during the up-phase of SOs	Enhanced SO and spindle activity	Virtual reality spatial navigation task and word-pair associates task.	Despite enhancing sleep oscillations, no improvement in memory performance was observed
Jaramillo et al. (2024)	Phase-locked auditory stimulation during REM sleep (phasic and tonic stages)	Modulation of alpha and theta oscillations, phase-dependent changes in power and frequency	None	CLAS successfully targeted specific phases of alpha and theta oscillations during REM sleep, demonstrating its potential to investigate the functional role of REM sleep rhythms
Jourde et al. (2023)	Auditory stimuli were delivered during specific phases of SOs detected in real-time during sleep.	Activated ventral frontal areas, enhanced slow oscillations	None	CLAS engages non-lemniscal pathways to modulate slow oscillations, impacting sleep-dependent processes
Koo-Poeggel et al. (2022)	Auditory stimulation during an afternoon nap, phase-locked to SO up-states	Enhanced slow oscillatory and spindle activity	Word pairs and figural memory encoding	CLAS did not improve post-sleep encoding at the group level; individual differences such as cognitive ability and time of day influenced responses
Krugliakova et	During NREM	Enhanced	None	CLAS locally

al. (2020)	sleep, targeting the up-phase of slow waves over the right sensorimotor area	delta, theta, and sigma power; increased delta-sigma coupling in the stimulated region		modulated cross-frequency coupling, suggesting potential for targeted sleep interventions
Leminen et al. (2017)	During Non-REM sleep	Increased slow-wave activity and spindle power	Word-pair association task	Enhanced memory consolidation compared to control condition
Navarrete et al. (2019)	Auditory clicks delivered during the positive phase of SOs	Increased SO amplitude and spindle likelihood, with optimal effects near the SO peak phase	None	Enhanced SOs and spindles when timed to specific SO phases, with age-related differences in optimal timing
Ngo et al. (2013)	During the up phase of SOs	Increased SO amplitude and spindle density	Word-pair association task	Enhanced retention of word pairs following stimulation
Ngo et al. (2015)	During SWS, phase-locked to SO up-state	Enhanced SO amplitudes, prolonged SO trains, increased phase-locked spindle activity	Word-pair memory recall	Demonstrated an intrinsic mechanism preventing hypersynchronicity; stimulation improved SO dynamics but did not exceed the effects of limited-click stimulation
Nguyen et al. (2023)	Real-time during sleep onset	SO and spindle activity increased	General cognitive function	Wearable CLAS improved declarative memory consolidation in younger adults, but showed variability in

				older participants
Papalambros et al. (2017)	Auditory stimulation during the upstate of slow waves in non-REM sleep	Increased slow-wave activity and spindle power during stimulation intervals	Verbal paired-associate memory task	Improved overnight word recall correlated with changes in slow-wave activity
Ruch et al. (2022)	Auditory stimulation targeting local SOs (TOPOSO algorithm) during NREM sleep	Localized enhancement of slow oscillations, improved precision in targeting functionally distinct SOs	None	CLAS successfully modulated local slow oscillations with topographic specificity, demonstrating that conventional stimulation methods may lack spatial precision in SO targetingopoopo
Schneider et al. (2020)	Auditory stimulation during SWS	Enhanced slow oscillation power in younger adults; diminished effect in older adults	None	Younger adults showed increased slow oscillation power with CLAS; older adults exhibited reduced responsiveness, indicating age-related differences in susceptibility to auditory stimulation during sleep.
Westerberg et al. (2015)	Auditory stimulation during SWS	Enhanced slow-wave activity	Word-pair association task	Improved recall of word pairs following stimulation
Yoon & Sang Ho Choi (2023)	Auditory stimulation dynamically	Modulated respiratory instability and	None	CLAS reduced time to sleep onset (TSSI)

	adjusted to respiratory rhythm during sleep initiation	heart rate variability		and influenced autonomic nervous system activity, demonstrating a potential application for improving sleep initiation through respiratory entrainment