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Closed-loop auditory stimulation of sleep slow oscillations: Basic principles and best practices

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ABSTRACT

Sleep is essential for our physical and mental well-being. During sleep, despite the paucity of overt behavior, our brain remains active and exhibits a wide range of coupled brain oscillations. In particular slow oscillations are characteristic for sleep, however whether they are directly involved in the functions of sleep, or are mere epiphenomena, is not yet fully understood. To disentangle the causality of these relationships, experiments utilizing techniques to detect and manipulate sleep oscillations in real-time are essential. In this review, we first overview the theoretical principles of closed-loop auditory stimulation (CLAS) as a method to study the role of slow oscillations in the functions of sleep. We then describe technical guidelines and best practices to perform CLAS and analyze results from such experiments. We further provide an overview of how CLAS has been used to investigate the causal role of slow oscillations in various sleep functions. We close by discussing important caveats, open questions, and potential topics for future research.

1. Introduction

Sleep serves a multitude of biological functions involved in maintaining and restoring our mental and physical health (Dresler et al., 2014; Frank and Heller, 2018; Anafi et al., 2019). It supports cognitive and emotional processes such as memory consolidation (Rasch and Born, 2013; Genzel et al., 2015), as well as vital immunological, endocrine and metabolic functions (Besedovsky et al., 2012; Irwin, 2015; Zoccoli and Amici, 2020). Accordingly, sleep disturbances are both symptomatic of, as well as contributing factors to not only psychiatric disorders such as attention deficit hyperactivity disorder (ADHD, Cortese et al., 2009; Kirov and Brand, 2014; Singh and Zimmerman, 2015), depression (Adrien, 2002; Riemann et al., 2001; Tsuno et al., 2005), anxiety disorders (Mellman, 2006; Staner, 2003), post-traumatic stress disorder (De Boer et al., 2020; Spoormaker and Montgomery, 2008), but also heart and kidney disease (Unruh, 2008), high blood pressure (Sayk et al., 2010), and diabetes (Herzog et al., 2013; Tasali et al., 2008). Sleep, furthermore, supports the removal of toxic metabolites that accumulate throughout the day (Xie et al., 2013), with dysfunction of such metabolic brain clearance potentially increasing the risk for neurodegenerative diseases such as Alzheimer's Disease (Wang and Holtzman, 2020).

The slow oscillation, a hallmark of non-rapid eye movement (NREM) sleep neurophysiology which represents the largest brain wave that can be observed in the electrophysiology of healthy individuals (Steriade et al., 1993; Achermann and Borbély, 1997), has especially been

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associated with many of these biological and cognitive functions of sleep. In particular, when coupled with other oscillatory activity such as sleep spindles (typically in the range of 12–15 Hz), SOs are thought to play a crucial role in memory consolidation and neuroplasticity (Rasch and Born, 2013; Genzel et al., 2015). However, studying the causal relationship between sleep slow oscillations and the different functions of sleep has been challenging due to the difficulty posed by manipulating sleep without disrupting it. In what follows, we will give a comprehensive overview of the neurophysiology as well as the best practices of one increasingly utilized method for systematically enhancing sleep slow oscillations called 'closed-loop auditory stimulation (CLAS)', which allows for the study of the causal mechanisms of sleep function. We will first introduce the theoretical basis of CLAS before providing technical details and guidelines for performing CLAS and analyzing the outcome. In this novel, comprehensive overview of best practices for CLAS, we will discuss the requirements to implement the monitoring and stimulation system, detection algorithms, stimulus characteristics, importance of double-blind methodologies, and applicability of wearable electroencephalography (EEG) systems. We further sketch an analysis pipeline encompassing preprocessing steps, methods for evaluating stimulation-targeting accuracy, and physiological assessment. We close by summarizing previous experiments that utilized CLAS and discussing potential clinical applications, promising novel approaches, and open questions for future research.

1.1. Slow oscillations

Slow oscillations (SO) are large-amplitude, low-frequency waves in the 0.1–1 Hz range. At the cellular level, SOs are associated with fluctuations of the membrane potential of pyramidal neurons in sensory, motor, and association regions between depolarization and extended hyperpolarization, causing the cortex to alternate between active 'up-states' and silent 'down-states' (Steriade et al., 1993). Up- and down-states can be observed as negative and positive deflections in the EEG depending on the electrode montage and origin of the SO. Typically, the down-state is a negative deflection in a surface EEG referenced to neutral positions, e.g. the mastoids. For simplicity, we thus will refer to the down- and up-state of a SO as the negative and positive troughs/peaks of an EEG signal wave. While SOs originate from the cortex (they can be observed in isolated cortical structures, but not in the thalamus of decorticated animals), the thalamus nevertheless actively contributes to their generation (Sheroziya and Timofeev, 2014). SOs also interact with and trigger other sleep oscillations, such as sleep spindles and delta waves, which are thought to play a role in sleep functions, e.g. memory consolidation (Steriade et al., 1993). Modeling and empirical work demonstrated that membrane channels in the reticular nucleus of the thalamus can be inactivated by excitatory inputs from the cortex, thereby disrupting the spindle-generating network, which in turn can trigger cortical down-states (Mak-McCully et al., 2014).

Human research has largely confirmed prior findings on slow oscillations in animal studies: cortical down-states can be recorded in intracranial recordings of patients, and in turn detected as so-called K-complexes in scalp EEG (Achermann and Borbély, 1997; Cash et al., 2009). While K-complexes can occur spontaneously, they have been described as early as the very first sleep EEG studies in the 1930 s as a waveform evoked by auditory stimuli such as knocks on the laboratory door – the name likely stems from the word 'knock' (Loomis et al., 1935, 1939; Halász, 2016). K-complexes are often associated with autonomic arousals as well as an increase in respiratory flow and a decrement in peripheral vascular volume (Tank et al., 2003; Picchioni et al., 2022). In auditorily evoked K-complexes, initial medial geniculate and auditory cortex activation can trigger a local down-state that spreads via thalamocortical and cortico-cortical connections (Cash et al., 2009). The identification of K-complexes as representing cortical down-states thus supports the idea of the K-complex as a sleep-protective process in response to exposure to non-threatening and non-salient stimuli preventing arousals and unnecessary awakenings (Halász, 2016). It should be noted, however, that the identification, differentiation and nomenclature of evoked as well as spontaneous SOs/K-complexes in the EEG and thus the mechanisms and specifics of their biological functions is the subject of a long-standing and still ongoing debate (Amzica, 2010; Cash et al., 2009; Genzel et al., 2014; Halász, 2016; Siclari et al., 2014).

Beyond sleep-protective and restorative processes, in the last two decades SOs have been proposed to be involved in processes of neural plasticity and memory consolidation (Timofeev and Chauvette, 2017; Klinzing et al., 2019). It has been suggested that the sequence of depolarization and hyperpolarization of SOs contributes to an overall downscaling of synaptic strength during sleep, which might be necessary to balance experience-dependent upscaling during wakefulness, with the net effect favoring strong and recently formed memories (Tononi and Cirelli, 2014). Furthermore, the transition from hyperpolarized to depolarized states coupled with synaptic activities during active states is a natural pattern for spike-timing-dependent plasticity, a prominent process to adjust the connection strength between neurons. In particular cortical down-states have been suggested to represent a key component for the induction of long-term potentiation during sleep, thereby supporting memory consolidation (Chauvette et al., 2012). Finally, SOs time the occurrence of sleep spindles, which in turn cluster hippocampal ripples in their troughs. This fine-tuned temporal frame has been proposed to orchestrate the interaction of ripple-associated hippocampal memory replay with neocortical memory representations (Bergmann et al., 2012; Schönauer, 2018; Staresina et al., 2015). Of note, apart from the role of periodic activities such as SO and spindles in memory consolidation, a recent study also highlighted the role of aperiodic brain activity during sleep in facilitating memory processing (Helfrich et al., 2021).

Overall, different aspects of SOs and regional interactions may underlie different respective functions: experimental studies suggest that first-order thalamic nuclei may contribute to the sleep-related gating of sensory inputs, whereas higher-order thalamic nuclei may facilitate an intracortical dialog during sleep, which in addition to cortico-hippocampal interactions may possibly be a key component of sleep-dependent memory consolidation (Sheroziya and Timofeev, 2014).

1.2. Auditory stimulation during sleep

Interventions into sleep physiology to investigate or modulate brain functions such as memory consolidation have been a topic of interest for many years (Malkani and Zee, 2020; Wunderlin et al., 2021; Zhang and Gruber, 2019). The possibility of SO enhancement or suppression in humans and rodents has been highlighted by seminal works using non-invasive stimulation techniques (Binder et al., 2014; Marshall et al., 2006; Massimini et al., 2007; Tononi et al., 2010; Vyazovskiy et al., 2009). Sensory stimulation techniques are particularly suited to convey meaning, which in turn may be used to reactivate memories of various kinds such as in targeted memory reactivation (TMR) studies. While stimulation of any sensory modality can evoke K-complexes with only subtle differences in signal features and topography, auditory stimuli have been shown to be more efficient in this regard compared to visual and somatosensory stimuli (Danilenko et al., 2020; Riedner et al., 2011). Of note, auditory evoked responses are relatively similar in lighter and deeper NREM sleep (Weitzman and Kremen, 1965).

Generally, auditory stimuli are processed via lemniscal (primary) and non-lemniscal (secondary) pathways, with potential arousing effects. The lemniscal pathway processes signals through the brainstem, thalamus, and auditory cortex, with activity detectable in EEG recordings (Atienza et al., 2001). The non-lemniscal pathway integrates auditory data with other sensory information in the reticular formation, assessing priority. Both pathways must converge at the level of the thalamus for conscious perception. While the lemniscal pathway functions similarly during sleep and wakefulness, the non-lemniscal

pathway's communication is limited during sleep, hindering combined processing for conscious perception (Atienza et al., 2001; Hu, 2003). Recently, a simultaneous EEG and magnetoencephalography (MEG) study has demonstrated that auditory information from CLAS reaches ventral frontal lobe areas via non-lemniscal pathways, and that it is the state of ventral frontal regions that is critical for slow oscillation generation (Jourde et al., 2022).

Simultaneous EEG and functional magnetic resonance imaging (fMRI) have shown that in parallel to modulating sleep oscillations, auditory stimulation during sleep triggers widespread modulating activity in cortical areas related to cognitive processing (Schabus et al., 2007; Czisch et al., 2009; Dang-Vu et al., 2011; Fang et al., 2019; Lei et al., 2015). While regional activation during auditory processing was found altered during sleep compared to wake (Portas et al., 2000), humans still appear able to discriminate between sounds carrying different levels of subjective salience in their sleep (Legendre et al., 2019).

Overall, sensory stimulation via auditory pathways appears to be particularly suited to modulate the neurophysiology of sleep: the resulting complex interplay between spontaneous and induced brain activity may build the basis for a targeted modulation of the biological and in particular cognitive functions of sleep.

1.3. Closed-loop auditory stimulation of slow oscillations

Previously, the most common sleep manipulation approaches were based on brain state-independent designs in which stimulation is presented according to a predefined set of parameters and either fully independent of the instantaneous (i.e., < 1-s time scale) brain activity or congruent with macroscopic sleep parameters such as specific sleep stages (i.e., minute-time scale). In contrast, brain state-dependent techniques consider the endogenous activity of the targeted system or oscillation to precisely time the stimulation. For example, the SO positive peak is thought to provide an optimal time window in which auditory processing is supported, both in the case of neutral (Ngo et al., 2013; Schabus et al., 2012) as well as semantically meaningful stimuli (Batterink et al., 2016; Göldi et al., 2019). The stimulation can be applied either in an open-loop fashion or closed-loop, with the latter aiming to manipulate the targeted signal to feed it back into the system, thus closing the loop (Antony et al., 2022).

Closed-loop auditory stimulation (CLAS; in an increasingly smaller fraction of the literature also labeled as ACLS: auditory closed-loop stimulation) has emerged as a promising technique for either enhancing or suppressing specific brain waves during sleep by allowing researchers to selectively target and present tones through the auditory pathway. By assessing brain activity in real-time via EEG, CLAS can precisely identify a particular oscillation during a specific sleep stage, such as SOs during the deepest stage of sleep (NREM3), and subsequently control the timing and phase of auditory stimulation to coincide with specific phases of ongoing sleep oscillations (Fig. 1). Compared to brain-state independent open-loop designs, CLAS approaches result in a much higher specificity in regard to the manipulation of the targeted sleep oscillation and the functional conclusions to be derived. Additionally, by delivering stimulation in synchrony with a specific oscillatory phase, CLAS can minimize variation across stimulation trials both within and between subjects. These advantages render CLAS a suitable tool to test the causal role of specific sleep oscillations in different biological functions of sleep: by manipulating the thalamocortical networks that induce SOs and associated oscillations such as sleep spindles, CLAS can be used in particular to investigate the role of SOs in cognitive functions of sleep (Fig. 1; for an overview see also Zhang and Gruber, 2019; Malkani and Zee, 2020), but could also shed light on basic biological processes such as endocrine regulation, immunological processing and glymphatic brain clearance.

2. How to perform closed-loop auditory stimulation

CLAS experimental setups require three core components: (1) real-time access to ongoing brain activity, (2) a detection algorithm to process the incoming signal and discern the desired brain oscillation(s), and (3) the stimulation device, typically including a soundcard and speakers/earphones that receive the command from the detection algorithm and then administer the stimulus. This section provides a concise overview of these core CLAS components, and examines different strategies to effectively incorporate each. Of note, we do not aim to establish universally applicable rules for implementing CLAS (e.g., best parameters for SO detection), as choices about the specific method and method-specific parameters will depend on the particular aims and circumstances of a study, including characteristics of the target group (e.g. age and health status), equipment (e.g. ambulant or laboratory setting), processing power for the real time analysis, etcetera. Rather, we aim to provide insight with regard to available methods, including advantages and disadvantages of each, to facilitate informed choices. For each individual study or applications of CLAS, adaptation nights are recommended to identify optimal individual parameters, e.g. for individual's SO detection or as an indicator for determining the threshold of stimulus volume below the individual's awakening level that can be used for the upcoming experimental sessions.

2.1. Real-time access to ongoing brain activity

When applying real-time stimulation, any type of delay from the

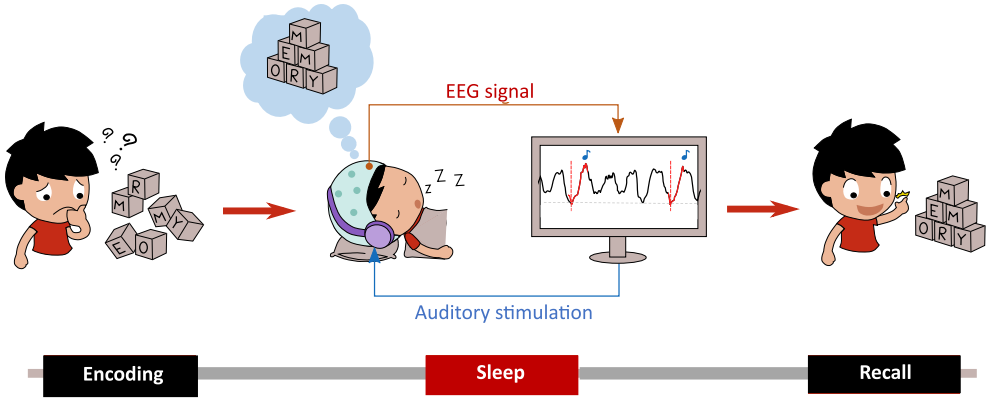

Fig. 1. Schematic illustration of a closed-loop auditory stimulation (CLAS) setup in a sleep study including a memory assessment as a cognitive task. The scalp EEG is recording in real-time and a detection algorithm attempts to detect a specific sleep oscillation (e.g., SOs). During NREM3 and upon the detection of a SO, either an auditory stimulus is presented (stimulation condition) or no stimulation is applied and only the sham markers are placed (sham condition). The threshold for trough detection is shown in a horizontal gray dashed line (monitor screen), and the detected trough is marked by a vertical red dashed line. To assess the effects of CLAS on sleep functionality enhancement, studies usually define a behavioral task, e.g., a memory task which comprises the encoding phase before sleep and a recall phase which is typically after the sleep.

signal acquisition through electrodes to the processing at the sensory organs such as ears should be considered. These delays consist of (1) brain-to-amplifier delay (typically neglectable), (2) amplifier to server (substantial), (3) access-to-processing (e.g., the detection algorithm and filtering), (4) processing-to-triggering (trigger or stimulus initiation) and (5) trigger-to-stimulus (e.g., speaker/headphone delay). These delays may last for several hundreds of milliseconds, and thus might influence the precision and interpretation of stimulation.

The primary CLAS experiments on humans utilized specific amplifiers dedicated to granting access to the analogue EEG signal, which was then fed into an analogue to digital converter to process the real-time signal and subsequently administer the stimulation (e.g., Bergmann et al., 2012 & Ngo et al., 2013). The built-in hardware filters in these setups were advantageous due to the facilitation of filtering without considerable delays. Since then, various software tools such as Event IDE (Okazolab Ltd, Delft, The Netherlands) and open-source alternatives like OpenViBE (RRID: SCR_014156), Fieldtrip (Oostenveld et al., 2011, RRID: SCR_004849), Portiloop (Valenchon et al., 2022), and COsleep (RRID: SCR_017053) were developed that enable real-time access to EEG signals and are designed to be compatible with a wide range of EEG systems.

2.2. Detection algorithm

The simplest approach to target SOs uses a band-pass filter in the SO range, typically 0.25–4 Hz, coupled with an amplitude threshold criterion: a SO is identified if the signal crosses a threshold of − 75 μV for the positive-to-negative and + 30 μV for negative-to-positive transitions (Bergmann et al., 2012; Ngo et al., 2013). This approach is fast and computationally efficient, however, it relies on a simple threshold crossing and thus might not target a reliable phase or time point within the oscillation due to a large overall variation in EEG amplitudes.

Utilizing the stereotypical pattern of SOs, their actual peaks (or troughs) can be detected as a reference to the stimulation time point. In such approaches, a time buffer is used to track the signal further when a threshold is reached until the signal reaches its maximum/minimum within an oscillating-adapted time window. This will only work if sufficient delay is allowed until the actual stimulation is triggered with respect to the detection time point (e.g., at least 200 ms after the lowest SO trough to target its down-to-up state transition period). In addition, the signal state (e.g., optimal conditions in which the signal is within a certain range after the detection time point) can be taken into account to let the algorithm decide if the stimulation time point is realized or skipped (e.g., as implemented in COsleep RRID: SCR_017053).

More advanced approaches have also considered the phase of an oscillation by approximating the SO activity as a narrow-band sinusoidal wave, and utilized signal prediction methods to target the desired phase of an oscillation. For instance, Cox et al. (2014) extracted the instantaneous SO phase using a Hilbert-transform and fitted a sine wave to the most recent signal segment, while a phase-locked loop (PLL) approach was employed by Santostasi et al. (2016) to continuously track SO phase alterations. More recently, Talamini and Van Poppel (2019) utilized an approach to model the full oscillatory dynamics of the signal through a sine fitting procedure on raw data (Pathak et al., 2021; Juan et al., 2023). This avoids signal distortions due to filtering and other data transformations and enhances phase targeting performance throughout the 360^{o} phase range. While the aforementioned methods rely on input from a single EEG channel, a novel approach employed topographic targeting of SOs (TOPOSO) to detect altered SO activity in specific cortical regions (Fehér et al., 2023; Ruch et al., 2022). This method estimates the correlation between the instantaneous voltage distribution of scalp EEG and precomputed voltage maps of the targeted SO down-to-up and up-to-down waves. Compared to their single-channel SO detection approach, TOPOSO resulted in fewer but more specific SO detections and reliably targeted local up-waves over frontal, sensorimotor, and centro-parietal regions. Overall, the advanced approaches might potentially lead to enhanced performance by leveraging their adaptive nature, allowing for more personalized detections, which stands in contrast to relying solely on a consistent amplitude and timing threshold as in earlier approaches. However, the absence of any direct comparison between methods does not allow us to recommend one over the others.

In addition to the detection of low-frequency brain dynamics such as SO, faster rhythms such as spindles may also be targeted (Antony et al., 2018; Choi and Jun, 2022; Hassan et al., 2022; Lustenberger et al., 2016; Zrenner et al., 2018). However, detection of faster sleep oscillations requires high computational power to provide higher timing precision. Nevertheless, in case the phase-specific information is inconsequential to answer the leading research question, and the overall presence of an EEG grapho-element is ample, an alternative computationally efficient algorithm such as enveloped-based detection might be employed.

2.3. Timing

While reliable timing of stimulation is likely essential to maximize its effects, only a few studies have thoroughly investigated the influence of the endogenous brain oscillatory phase on the stimulation. Presenting the auditory stimulus at the up wave of a SO seems optimal to evoke further SOs and spindles (Navarrete et al., 2020). This could prolong a train of previous SO, or enlarge the amplitudes of otherwise intrinsically generated SO, with the elicited SOs resembling endogenous trains of slow waves (Ngo et al., 2013). Cox et al. (2014) directly compared the effects of CLAS phase-locked to the onset of SO up-waves and onset of down-waves and showed a significantly larger induced SO-like positive deflection with higher spindle frequency content for the former. The phase just before the down-to-up state transition was also found to be the best phase of stimulation in a modeling study (Wei et al., 2020), maximizing both the boosting effects on SOs and memory consolidation in case of cues that were associated with training material. In contrast, applying CLAS preferentially during or at the onset of SO down-waves has been shown to acutely disrupt the continuity of a SO train to some degree by delaying or aborting the consecutive SO trains (Ngo et al., 2013; Cox et al., 2014).

The temporal window for favorable stimulation shrinks with aging (Navarrete et al., 2020). Considering the translational potential of CLAS for clinical applications, this highlights the importance of understanding the overall dynamics across different populations and settings for future research and treatments. Importantly, the reason why some stimulation protocols have not returned the most pronounced physiological responses or favorable behavioral results, despite having been delivered within the preferred SO-followed up-wave phase is still unclear. Conceivable explanations range from a specific behavioral task or stimulation parameters (e.g, overly high volume of stimulus that may disrupt one's sleep), oscillatory cross-coupling requirements, the precision of phase-locking approach, or experimenters not blind to the conditions to other unidentified factors (Leminen et al., 2017; Ong et al., 2018; Navarrete et al., 2020).

Regarding repetitions of stimulations, two different stimulation timing protocols have been utilized to date: (1) 'fixed-stimulation' protocol (Fig. 2-A) that has been used by the majority of CLAS studies (Besedovsky et al., 2017; Cox et al., 2014; Diep et al., 2020; Henin et al., 2019; Leminen et al., 2017; Ngo et al., 2013, 2015, 2018; Santiago et al., 2019), and (2) 'block-wise' stimulation-sham alteration approach (Fig. 2-B) (Fattinger et al., 2019; Garcia-Molina et al., 2019; Ong et al., 2016, 2018; Papalambros et al., 2017, 2019; Santostasi et al., 2016). During both procedures, stimulation is commenced upon stable NREM sleep (NREM2 and NREM3) detection and discontinued either manually or automatically if subjects transition into REM, wake, or show signs of arousal. In a fixed-stimulation protocol, following the identification of a SO down- (or up-) wave, acoustic tones or sham triggers are administered at the predicted time of the upcoming SO up- (or down-) waves. Stimulation may be followed by a variably timed pause, where the SO

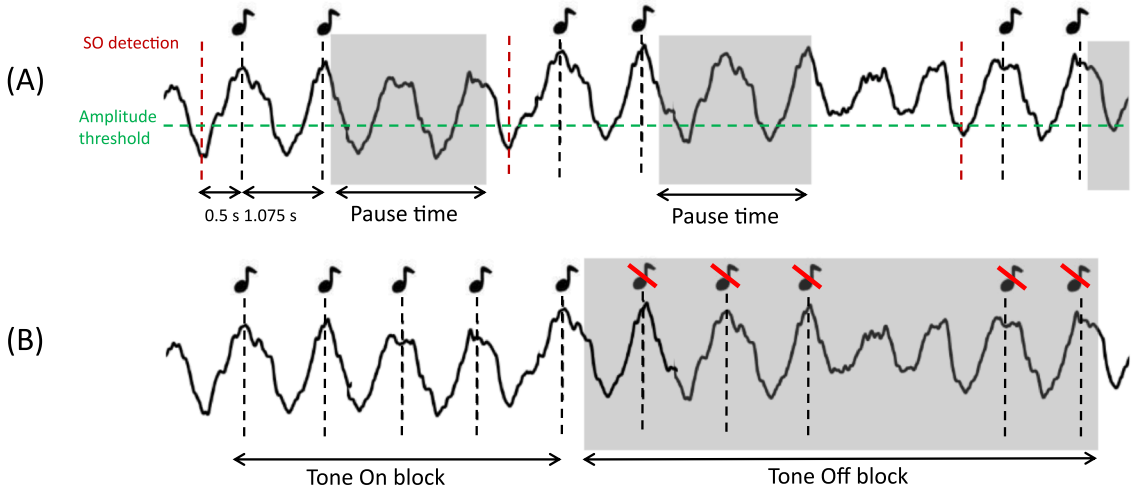

Fig. 2. Schematic of stimulation timing protocols. (A) fixed-stimulation timing protocol (e.g., Ngo et al., 2013). SO down-wave was detected through an amplitude thresholding condition and then stimuli / triggers were played at the predefined time to coincide with upcoming SO up-waves. Each stimulation / sham triggering attempt was followed by a pause period. **(B)** Block-wise stimulation-sham alteration approach (Ong et al., 2016, 2018). SO detection was based on a phase-locked loop (PLL) approach. Each block consisted of a fixed quantity of the detected SOs. Depending on the type of each block, i.e., on or off, either tones were played at the SO up-waves or the triggers were marked. A block-wise approach may also employ fixed duration for each block, instead of a fixed quantity of the detected SOs.

detection is deactivated for a certain duration. Such stimulation-free periods following each stimulus allow for analysis of the immediate effects on the EEG. On the other hand, block-wise approach contains intermittent 'on' and 'off' blocks or segments, each including either a certain 'quantity' of the detected SO events (e.g., Ong et al., 2016, 2018) or a predetermined 'duration', irrespective of the number of the detected SOs within each block (e.g., Huwiler et al., 2022). During the 'on' blocks, stimuli are presented at the targeted SO phase, whereas during 'off' blocks, only sham triggers are marked.

The choice of the stimulation timing protocol is contingent upon the research objectives, as each protocol comes with its own merits and limitations. Typically, in a fixed-stimulation protocol, a single condition (e.g., stimulation or sham) is selected for the entire session and the conditions do not change within the session. However, block-wise protocol allows for within-night comparison of different conditions which might be of interest in some research goals. Nevertheless, conducting a study to directly compare the two approaches may shed more light on the strengths and weaknesses of each method.

2.4. Stimulus parameters

Auditory stimuli can either be meaningful and associated with a particular information or experience, or be context-free such as bursts of noise. In the former case, an identifiable sound might be played during a task of an experiment to reactivate the context associated with the encoded item (e.g., see TMR Table 3), whereas in the latter case the stimulus is intended to activate neural processes independently of specific prior experiences. Following the primary aim to enhance SOs, the majority of CLAS experiments used brief 1/f pink noise bursts, reflecting a softer and more comfortable sound than white noise. While any auditory stimulus (sound, noise, or tone) during sleep can elicit responses resembling SO, pink noise which benefits from a broadband spectrum results in more pronounced evoked potentials and showed lower rates of habituation over repetitive stimulation (Debellemanière et al., 2022). Furthermore, duration of auditory stimulation with noise has mainly been restricted to 50 ms, which to date sufficiently induced an evoked auditory response. In addition, a brief auditory stimulus which fits within a particular phase of an SO can theoretically be repeated more often during short time intervals of stimulation.

Volume is a critical parameter for auditory stimulation (Bellesi et al., 2014): the EEG response can be elicited by stimuli of sufficient softness without accompanying signs of arousal, while higher volume levels increase the probability of arousals and consequently disrupt sleep. Earlier studies used fixed volume settings, e.g., 55 dB sound pressure level (Ngo et al., 2013), however, these studies primarily examined young adult participants. Considering that hearing ability may vary largely between subjects and strongly decays with age, different approaches to adjust the volume individually should be implemented and validated. For example, participants can be asked to identify a comfortable and perceivable volume during wakefulness in a quiet room which is then used as a starting point and increased during sleep (Wang et al., 2022). It is advisable to adjust auditory stimulation volume repeatedly starting from lower volumes (e.g., adaptation nights) and gradually increase it until an evoked response or K-complex is visible without leading to arousal, e.g. during a habituation night before experimental nights. A quick response to discontinue stimulation upon arousal detection is also critical to prevent awakening the participant and to avoid presenting stimuli in a waking state. Thus, relatively slow manual monitoring of polysomnographic signals by an experimenter should be avoided in future studies and a more automatic real-time assessment of different frequency bands to detect arousal or changes in sleep stages should be used to regulate the stimulation volume fully or semi-automated (e.g. in COsleep, RRID: SCR_017053).

2.5. Blinding

An important confound in conducting manipulation studies involving humans, such as CLAS, is the blinding of subjects and experimenters to the stimulation condition, e.g., SO positive peak targeting and sham. Amnesia for events that happened during certain sleep states is common, with the event more readily remembered if awakened a few seconds or minutes after (Siclari et al., 2013). It is thus unlikely, though conceivable, that subjects are aware of stimulation at some point of an experiment. Nevertheless, the challenge arises when it comes to the experimenters. Blinding of the experimenters to the stimulation condition remained unaddressed by most CLAS studies. So far, only a few studies followed rigorously double-blinded CLAS replication experimental protocol to investigate the influence of CLAS on declarative memory consolidation (Henin et al., 2019; Lustenberger et al., 2022). Automatized approaches (e.g. COsleep, RRID: SCR_017053) are

particularly suited to facilitate double-blinded experimentation and stimulation.

2.6. Towards CLAS in home settings

The non-invasive nature and feasibility of automation favor the development of therapeutic solutions in home settings. Recently, a few studies investigated the applicability of CLAS technology transfer to home settings (Ferster et al., 2019; Henao et al., 2022; Nguyen et al., 2022; Sun et al., 2022; Xi et al., 2023; Zeller et al., 2023). In an early approach, upon the automatic detection of SO up-waves during deep sleep, a block-wise stimulation including 15 tones with 1-second inter-stimulus interval was employed, which enhanced SWA in 86% of participants (Garcia-Molina et al., 2019). In another study, Ferster et al. (2019) introduced a mobile EEG system for real-time CLAS in home settings and found SO enhancement comparable to lab-based studies. In a follow-up study, they proposed two novel algorithms based on PLL and phase vocoder (PV) to detect the phase and frequency of the input signal and subsequently enhance smaller SO amplitudes (e.g., 20 – 60 μV) in older adults and those suffering from neurodegenerative disorders such as Parkinson's disease (PD) (Ferster et al., 2022). In one of the rare longitudinal studies in the field, healthy adults aged 62–78 years underwent a randomized, cross-over, double-blinded study at home over six weeks, comprising two weeks of sham, and two weeks of stimulation, separated by two weeks as a washout period in between (Lustenberger et al., 2022). This study also resulted in enhanced slow-wave activity (SWA).

Furthermore, the applicability of CLAS in home settings may not be limited to scalp EEG. Henao et al. (2022) utilized an in-ear EEG system to apply CLAS in home settings, by comparing the feasibility of SO detection using in-ear sensors with the SOs obtained in the scalp EEG during simultaneous recordings. Their approach may still require further developments to guarantee the absence of any confound in the topography maps.

However, translating laboratory-based CLAS procedures to home-usable technologies introduces several challenges. Solutions require a minimally sensing EEG system such as a wearable with a reasonable comfort level and ease of operation for a naïve user. EEG signal quality, unconventional EEG montages, and restricted computational power may pose additional challenges for real-time signal analysis. Furthermore, the reliability of wireless signal transmission in most wearable systems tends to be inferior to that of wired transmission. This is undesirable in CLAS procedures which are highly dependent on a short and jitter-free loop lag in transmitting the real-time signal. Finally, considering the impracticality of including an adaptation session, unsupervised CLAS in real-life environments such as a home setting requires devising stimulus gating procedures to reliably avoid stimulation outside stable NREM episodes as well as adaptive algorithms to detect the brain oscillation of interest with more individualized parameters (e.g., see Nguyen et al., 2022).

Taking the above requirements and challenges into account, home-based CLAS adaptations have been and are currently being developed. One such adaptation has been presented by the group of Talamini and colleagues at the university of Amsterdam. It incorporates EEG recordings through frontal electrodes from a commercial headband (ZMax, Hypnodyne, Sofia, Bulgaria) and wireless signal transmission to a computational unit, such as a tablet or a PC, in real-time. This solution runs an experimental control software (a custom version of EventIDE, Okazolab Ltd, London, UK) through the computational unit, performs online signal processing to detect SOs via a modeling-based CLAS algorithm, and subsequently applies the stimulation automatically (Talamini et al., 2016; Talamini and Korjoukov, 2018). Preliminary results indicate a precise targeting of a specific SO phase when compared with the laboratory outcomes, in addition to the feasibility of boosting SWA over longer stretches of sleep, using precisely targeted, sub-arousal sounds (Talamini et al., publication in preparation).

3. How to analyze closed-loop auditory stimulation

The analysis pipeline of CLAS studies typically begins with sleep scoring to identify the NREM2 and NREM3 stages during which SO and spindle activities are dominant (Fig. 3 - A), followed by a pre-processing step (Fig. 3 - B). Subsequently, the viability of the applied CLAS might be assessed through two crucial factors: first, an assessment of phase targeting performance (Fig. 3 - C), secondly, a precise assessment of the electrophysiological response (Fig. 3 - D). Stimulus targeting performance can be evaluated in terms of phase targeting accuracy and precision by assessing the phase angle at stimulus onset in an SO range filtered signal, displaying the results using phase-plots or histograms showing the distribution of the results. Of note, bandpass filtering of the signal in the SO range may create an artifactual offset in targeted phase if the bandwidth deviates to one side of the dominant frequency systematically across trials. Hence, dynamic filtering, in which each trial is filtered in a range spaced symmetrically around that trial's frequency may be considered. Electrophysiological responses can be evaluated through a variety of methods in which the stimulation's evoked response is compared with a control condition.

3.1. Pre-processing

In accordance with established protocols in sleep research, EEG signals are pre-processed with a band-pass filter in a range encompassing the typical sleep oscillations of interest, e.g., 0.1–30 Hz and epochs contaminated with arousals or artifacts are excluded. Subsequently, for the purpose of stimulus-locked analysis, EEG signals should be epoched into trial windows time-locked to the onset of stimulus presentation. Retaining a pre-stimulus period is helpful for baseline correction.

3.2. Stimulation targeting analysis

In a CLAS approach, auditory stimuli should be presented at a specific time or phase angle such that they coincide with the targeted oscillatory phase, for instance SO positive peaks, while considering different types of delay, such as software, hardware, and audio system delays. Phase-plots are polar histograms indicating the phase angles at which the auditory stimuli were actually presented. They can be used to determine SO detection errors as a measure of the deviation of 'detected' from the 'targeted' phase angle.

A few cautionary points ought to be taken into consideration when using phase-plots. Phase-plots require narrow-band filtering, e.g., between 0.7 and 1 Hz, whereas SOs have broader spectral components in the range of 0.5–4 Hz. Therefore, phase plots only result in an approximation of SOs and the evaluation of phase plots as the estimates of SWA might induce temporal jitter. Additionally, while stimulation in the vicinity of SO positive peak has been demonstrated to be efficient in boosting SWA (Navarrete et al., 2020), stimulus presentation also elicits early responses within a few milliseconds, i.e., transient responses that have an impact on the ongoing brain oscillation and thus cause a phase shift in SWA (Van Diepen and Mazaheri, 2018) or potentially other frequency bands (Weitzman and Kremen, 1965). The applicability of the phase plots in evaluating CLAS studies has been initially introduced by Cox et al. (2014). Phase-plots were used in this study as a tool to indicate the accuracy and precision of the proposed modeling-based SO detection algorithm to target various SO phases.

3.3. Electrophysiological responses

Effects of CLAS on brain activity can be evaluated through various types of analyses, including stimulus-locked analyses that investigate the short-term evoked responses to the stimuli, and non-stimulus locked methods to assess global effects of stimulation over relatively longer stretches of the EEG signal. In the latter category, power spectral analysis can, for instance, be employed to evaluate the impact of stimulation

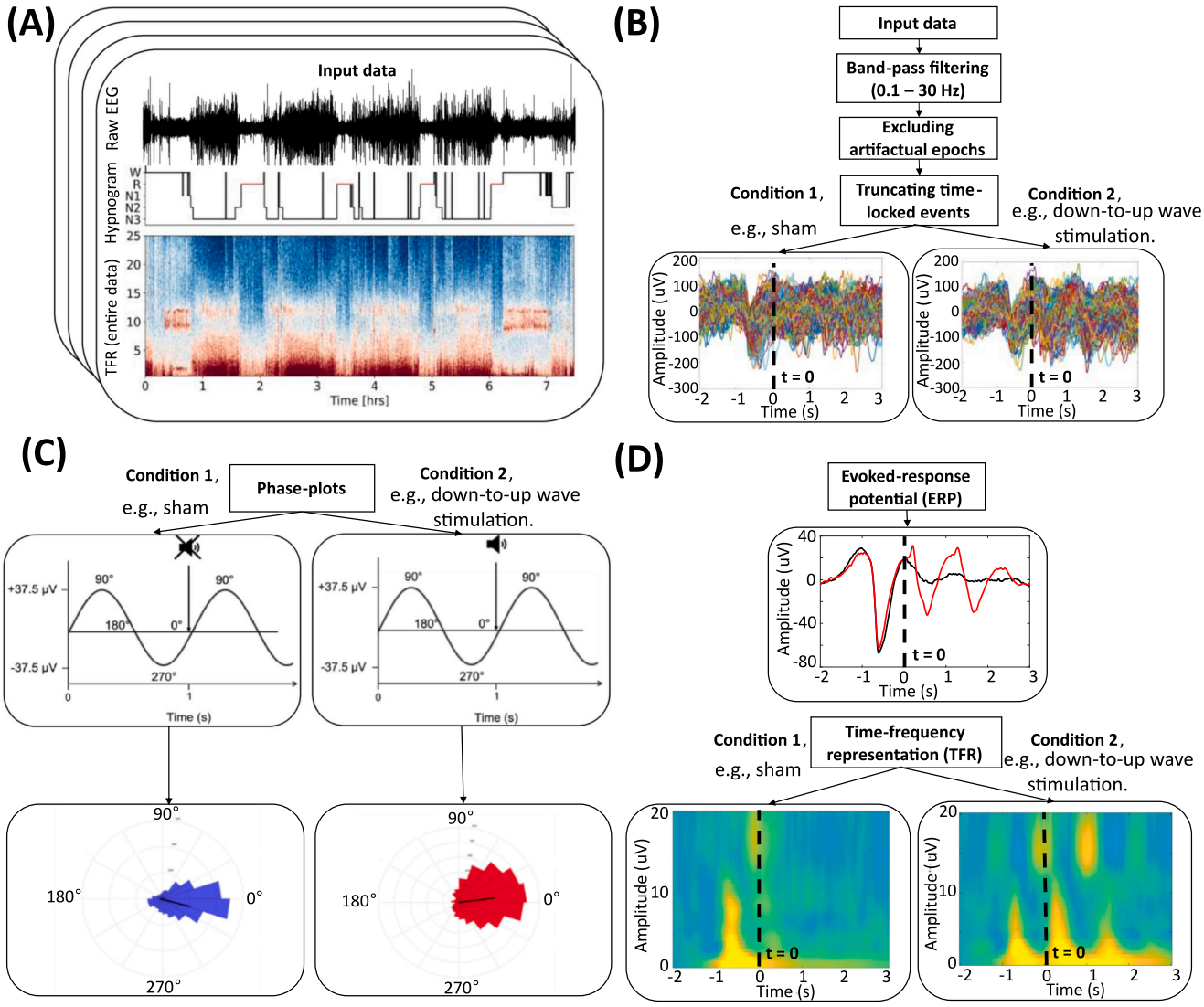

Fig. 3. Analysis pipeline for CLAS studies. (A) Input EEG data and the corresponding hypnogram. Similar to other areas of sleep research, the analysis of CLAS studies typically begins by sleep scoring polysomnography (PSG) data to identify the NREM2 and NREM3 stages. Subsequently, the identified epochs are pre-processed to detect and analyze the oscillations of interest. **(B)** Pre-processing step comprises band-pass filtering of the EEG signals in the common sleep frequency range (0.1–30 Hz), removing artifactual epochs, and creating events time-locked to the stimulus presentation time while preserving a short pre-stimulus interval. This is followed by evaluating the efficacy of stimulation. **(C)** phase-targeting performance can be assessed using phase plots for each study condition, separately. As a case in point, the phase-targeting performance of the sham condition may be compared with a stimulation (e.g., SO down-to-up wave stimulation). The representation is retrieved from Juan et al. (2023) **(D)** electrophysiological response to the stimulus is assessed using various methods such as evoked-response potential (ERP), and time-frequency representation (TFR). The red signal represents the ERP of the stimulation trials, whereas the black signal corresponds to the ERP of sham trials. The TFR of the stimulation condition indicates the entrainment of SOs and the coupled spindle activity when compared with the TFR of the sham trials. The results were created by averaging all trials (sham and stimulation conditions, separately) of a single subject over Fz, Cz, Pz, AFz, F3, Fp1, F4, C3, Fp2, C4, P3, Fpz, and P4 channels from Ngo et al. (2013).

on power in the targeted frequency band. One may compare the SO and spindle band power enhancement across different conditions (e.g., as in Ngo et al., 2013). Additionally, to assess phase-locked activity in the time-domain, evoked-response potential (ERP) analysis can be employed. For this, events of the same condition time-locked to the acoustic stimulus/trigger presentation and baseline-compensated to a pre-stimulus interval are averaged. Consequently, the ERP signal captures the 'phase-locked' activity among all trials, whereas it counteracts the perturbed time-varying portion of the signal within each trial (Makeig, 1993; Tallon-Baudry and Bertrand, 1999). The majority of CLAS literature employed ERP to contrast the SO entrainment after stimulation with the endogenous SO activity and showed that the 'in-phase' stimulation (presenting cues at the SO up-wave) results in maximum effect (Debellemaniere et al., 2018; Garcia-Molina et al., 2018; Henin et al., 2019; Leminen et al., 2017; Ngo et al., 2013, 2015, 2018; Ong et al., 2016, 2018). While ERP may not assess EEG patterns such as SOs on an individual level, it represents the differential impact of stimulation conditions on a very high amplitude EEG dynamic like SO. Nevertheless, stimulation consequences at the level of ERP may reflect average alterations on individual SO waveforms in addition to the impacts on the stimulus-locked synchronization of such waveforms. As such, SO-like deflections in an ERP do not necessarily result from an induction or amplitude enhancement of SOs in individual trials but might also denote temporal consistency of SO dynamics in relation to stimulation, while such consistency (synchronization) is not present in the spontaneous SO dynamic. Most reports did not account for the naturally ongoing SO dynamics in epochs time-locked to the phase-targeted stimulus, whereas a few studies computed ERP by

excluding spontaneous SO dynamics (e.g., Cox et al., 2014).

It is also feasible to analyze the electrophysiological responses to the stimulus using time-frequency representation (TFR). For this, after a baseline correction based on a pre-stimulus/pre-trigger interval, the significance of difference among conditions determines whether the desired outcome of stimulation such as an increment in SO and spindles power after stimulation is reached. Typically, a cluster-based permutation test is the appropriate statistical test to assess the significance of difference between conditions (Maris and Oostenveld, 2007).

TFR was employed in several CLAS studies. As a case in point, Ong et al., (2016, 2018) employed TFR to depict the impact of CLAS on the increment of SWA and theta band power approximately throughout the epoch, whereas the spindle activity enhancement was observed limited to SO positive peaks. Similarly, Garcia-Molina et al. (2018) investigated the TFR for stimulation, sham, and stimulation minus sham conditions to indicate the temporal power changes in SWA and spindle bands after the stimulation. Moreover, in one of the scarce studies that account for the non-random baseline dynamics in stimulus-locked epochs, researchers assessed the cortical network's reaction to an auditory stimulus time-locked to stimulus onset at the SO up-and down-waves using TFR (Cox et al., 2014).

4. Applications

Given its opportunity to manipulate sleep patterns non-invasively without disturbing the sleeper, CLAS can be applied in studies investigating the causal role of sleep in basic research as well as in clinical settings where sleep slow oscillations are thought to be of importance. Of the different functions of sleep that have been investigated in recent years, memory consolidation has arguably received the most attention, however, also emotion regulation (including the experience of nightmares), glymphatic brain clearance, immunological processing, energy metabolism, and endocrine regulation are promising fields of application. In the following subsections, we will give a brief overview of research that has already been performed to test CLAS in memory consolidation and for clinical applications (see also Tables 1–3). While we do not aim for a full systematic review, we ensured the comprehensiveness of our originally selected set of studies by conducting a literature search in Google Scholar and PubMed with the following sets of keywords: 'auditory closed loop stimulation', 'acoustic closed loop stimulation', 'closed loop auditory stimulation', 'closed loop acoustic stimulation', and 'closed loop targeted memory reactivation'. Any additional pertinent papers that emerged from this search were included.

4.1. Memory consolidation in healthy populations

CLAS has originally been introduced as a tool to demonstrate a causal role of sleep slow oscillations in memory consolidation: Ngo et al. (2013) showed that CLAS enhanced the SO amplitude, slope, and spreading, as well as the memory consolidation while keeping the sleep macro-architecture intact. Additionally, CLAS was found to increase the coupling between SOs and sleep spindles, aligning with previous work indicating that the synchrony between sleep spindles and SOs rather than the number of fast spindles is critical for memory consolidation (Cox et al., 2012; Ruch et al., 2012; Timofeev et al., 2002). Moreover, Ngo et al. (2018) targeted sleep spindles rather than SOs and again observed an increased coupling between SOs and sleep spindles, although it did not convey an improvement in memory consolidation. Similarly, the comparison between the 2-click (i.e., presenting stimuli at the predicted time of the two consecutive upcoming SO up-waves) and continuous clicks (i.e., presenting stimuli at the SO up-waves as long as the down-to-up wave of the endogenous SWA were detected in real-time) showed no differences in memory consolidation or coupling between SOs and sleep spindles (Ngo et al., 2015), indicating the presence of mechanisms that may prevent overdrive of SO activity, such as spindle refractoriness. This further emphasizes the important relationship between SOs and sleep spindles (Cox et al., 2012; Ngo et al., 2013; Ruch et al., 2012; Timofeev et al., 2002).

While early studies of CLAS as a tool to enhance memory consolidation have used a word-pair task either following a full night of sleep (Ngo et al., 2013) or a short nap (Ong et al., 2016), a study by Leminen et al. (2017) suggested that the type of memory task is crucial in finding significant effects on memory consolidation. The study compared four different memory tasks and found that only the word-pair task showed a significant improvement after CLAS, suggesting that other memory tasks, such as procedural finger tapping, picture recognition and face-name association tasks may not benefit from CLAS. Henin et al. (2019) demonstrated that despite a strong increase in SO and spindle activity during sleep, CLAS did not result in an improvement of memory performance in either a virtual reality spatial navigation or word-pair task. Additionally, Diep et al. (2020) aimed to improve cognitive function beyond sleep-dependent memory consolidation and found that higher slow-wave activity responders showed improved verbal fluency and working memory after CLAS. Although the findings are limited and inconclusive, the study suggests the potential for CLAS to improve other memory domains, such as working memory. Finally, Ong et al. (2018) combined CLAS with fMRI to investigate the impact of CLAS on declarative memory encoding. Although no memory benefit was detected, their work shows that SO enhancement and increased sleep spindle activity were positively correlated with hippocampal activation at encoding.

Most CLAS memory experiments have been conducted on healthy young adults (Cox et al., 2014; Leminen et al., 2017; Ngo et al., 2013, 2015; Ong et al., 2016). However, in particular the elderly population often experiences reductions in NREM3 (Edwards et al., 2010; Ohayon et al., 2004), as well as declines in memory abilities (Schaie et al., 1998), which raises the question of whether CLAS can improve NREM3 in this age group and consequently enhance their declarative memory consolidation. In a study by Papalambros et al. (2017), participants aged 60–84 years underwent CLAS to test their declarative memory. Results showed an increase in SO and spindle activity during acoustic stimulation, leading to improved word recall. In contrast, Schneider et al. (2020) found no beneficial effect on declarative and procedural memory consolidation in middle-aged participants, despite prolonged endogenous SO trains and phase-locked sleep spindles. This discrepancy could be due to differences in the temporal dynamics of stimulation effects on SOs and spindles between the age groups, and emphasizes the importance of exploring CLAS in different age and health groups.

A possible explanation for negative findings in memory consolidation studies is that CLAS may not evidently distinguish between stimulation of large-amplitude SOs and delta-waves (Kim et al., 2019; Ngo and Born, 2019). As delta waves have been discussed to augment the mechanism underlying the forgetting of memories (Kim et al., 2019; Ngo and Born, 2019), inadvertent enhancement of delta waves might lead to inadequate outcomes regarding memory consolidation. Nevertheless, given the clear physiological effects of CLAS, the sleep-dependent cognitive or mental enhancement using CLAS should be investigated more thoroughly. This is important due to the impact of CLAS on non-cognitive measures such as cortisol level alterations which are thought to be co-associated with cognitive and mental health as well as sleep-mediated memory functions (Diekelmann and Born, 2010).

Furthermore, the importance of stimulation protocols for considering ongoing oscillatory activity other than the SO itself has been highlighted by studies examining auditory processing in the face of spindle dynamics. It has been suggested that spindles during NREM2 and NREM3 may epitomize a protective element against sleep disruption, as a higher number of naturally occurring spindles and prolonged periods of heightened spindle activity were associated with higher sleep continuity in the face of noise (Dang-Vu et al., 2010; Lecci et al., 2017). During a spindle event, the processing of incoming auditory information appears largely blocked by thalamic neurons not transmitting sensory

Table 1
A detailed description of experimental parameters of CLAS studies on memory consolidation. ADHD: attention deficit hyperactivity disorder, aMCI: amnestic mild cognitive impairment, CLAS: closed-loop auditory stimulation, fMRI: functional magnetic resonance imaging, N/A: not available, SD: standard deviation, SEM: standard error of mean, SO: slow-oscillation, SWA: slow-wave activity, VR: virtual reality.

Author	Subjects	Stimulation parameters	Measures	Design	Results
Ngo et al. (2013)	11 healthy subjects (8 females) Mean age 24.2 years ± 0.9 SEM	50 ms pink noise, phase-locked to SOs up-waves delivered at a fixed delay; 2-click system.	120 associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SO amplitude; Improvement of declarative memory consolidation after CLAS.
Ngo et al. (2015)	18 healthy subjects (8 females) Mean age 23.8 years ± 0.6 SEM 16 healthy subjects (10 females) Mean age 24.3 years ± 0.76 SEM	50 ms pink noise, delivered at a fixed delay; 2-click and continuous clicks systems clicks	120 associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	No difference between 2-click and overdrive protocol; Improvement of declarative memory consolidation after CLAS.
Ong et al. (2016)	16 healthy subjects (7 females) Mean age 22 years ± 1.4 SEM	50 ms pink noise, phase-locked to SOs up-waves; Block-wise stimulation-sham alteration 5-click system.	40 semantically associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights	Enhancement of SO amplitude; Improvement of memory consolidation after CLAS.
Leminen et al. (2017)	15 healthy subjects (7 females) Mean age 30.5 years (SD: N/A)	50 ms pink noise, delivered at the fixed delay; 1-click system	240 semantically associated word-pair task 30 associated face-name task 6 blocks of 10 loops of 5-unit-long finger-tapping task 119 picture recognition task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SO and spindle activity; Improvement of only word-pair task recall after CLAS.
Papalambros et al. (2017)	13 healthy subjects (10 females) Mean age 75.2 (SD: N/A)	50 ms of pink noise phase-locked to SOs up-wave; 5-click system.	88 moderately associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs and spindle activity; Improvement of memory consolidation after CLAS.
Ngo et al. (2018)	34 healthy subjects (18 females) Mean age 25.1 years ± 3.4 SD	25 ms of pink noise at individual's fast spindle peak frequency; 7-click system.	Associated word-pair task	Experiment 1: Within-subject comparison, two conditions (spindle and arrhythmic stimulation), counterbalanced Experiment 2: Within-subject comparison, two conditions (spindle stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs and spindle activity; No improvement of memory consolidation after CLAS.
Ong et al. (2018)	37 healthy subjects (19 females) Mean age 22.5 years ± 2.3 SD	50 ms of pink noise phase-locked SOs up-wave; 2-click system.	80 picture-recognition task Psychomotor vigilance task	Encoding in fMRI after a nap with or without stimulation, followed by recognition. counterbalanced Two experimental nap sessions.	Enhancement of SOs and spindle activity positively correlated with hippocampal activity at encoding; No improvement of memory after CLAS.
Henin et al. (2019)	Overall 31 healthy subjects (15 females) Mean age 23.5 years ± 0.6 SEM Experiment 1: 12 healthy subjects (6 females) Mean age 23.3 ± 2.7 SEM Experiment 2 (replication): 19 healthy subjects (9 female) Mean age 23.3 years ± 3.4 SEM	50 ms of pink noise, phase-locked to SOs up-wave. 1-click system.	Experiment 1: 100 unrelated associated word-pair task and spatial navigation task Experiment 2: 120 semantically associated word-pair task	Experiment 1: within-subject comparison, two conditions (stimulation and sham, randomized and counterbalanced), Two experimental afternoon nap sessions Experiment 2: within-subject comparison, two conditions (stimulation and sham, randomized and counterbalanced) Two experimental nights; double-blind protocol (subjects and experimenter unaware of conditions)	Enhancement of SO and spindle activity; No improvement of memory consolidation on either the VR or word-pair tasks after CLAS.
Papalambros et al. (2019)	9 subjects (5 females) with aMCI Mean age 72.0 years (SD: N/A)	50 ms pink noise phase-locked to SO up-waves; 5-click system.	Associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SWA after CLAS in both groups; No significant memory improvement.
Diep et al. (2020)	24 healthy subjects (0 females) Mean age 39.92 years ± 4.15 SD	50 ms audio tones (type not specified) phase-locked to SOs up-wave. continuous-click protocol.	120 associated word-pair task 6 Tower of London measures 60 s verbal fluency task Go No Go task (124 times Go and 57 times No Go)	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights. double-blind protocol (subjects and experimenter unaware of conditions)	Enhancement of SOs, delta activity; Improvement of working memory and verbal fluency after CLAS in high-SWA responders.

(*continued on next page*)

Table 1 (*continued*)

Author	Subjects	Stimulation parameters	Measures	Design	Results
Schneider et al. (2020)	17 healthy subjects (9 females) Mean age 55.7 years ± 1.0 SEM	50 ms of pink noise phase-locked to SOs up-wave; 2-click system.	Psychomotor vigilance task Associated word-pair task Finger-tapping task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs and spindle activity; No improvement of memory consolidation after CLAS.
Prehn-Kristensen et al. (2020)	14 subjects (0 females) with ADHD Mean age 10.2 years ± 0.4 SEM 15 healthy subjects (0 females) Mean age 11.1 years ± 0.4 SEM	50 ms pink noise phase-locked at SO up-waves; 2-click system.	48 unrelated associated word-pair task Serial reaction time task n-back task	Within-subject and between-group comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs after CLAS in both groups; Improvement in declarative memory task only in the control group; Improvement in working memory only in the ADHD group.
Harrington et al., 2021	12 healthy subjects (0 females) Mean age 20.03 years ± 2.02 SD	50 ms pink noise, delivered at a fixed delay phase-locked to SO up-waves; 2-click system.	80 unrelated associated word-pair task	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs after CLAS; No improvement in declarative memory consolidation.
Koo-Poeggel et al. (2022)	16 healthy subjects (9 females) Mean age 25.63 years ± 0.58 SD	50 ms pink noise, 2-click system, first at the SO down-to up-wave, the second after a fixed interval of 1075 ms.	Verbal tasks: 100 semantically non-associated word pairs, verbal learning and memory test; Non-verbal task: 16 figural pairs	Within-subject comparison, two conditions (stimulation and sham), pseudo-randomized, counterbalanced; Two experimental afternoon nap sessions	Enhancement of SOs and spindles after CLAS; CLAS did not influence memory encoding at group level; Variables such as time of day and subjects' cognitive ability may affect the responsiveness to CLAS

information to cortical regions (Schabus et al., 2012), a process thought to be a noradrenergic super-modulation of the thalamus on an infra low (~1-min) time scale by the locus coeruleus (Osorio-Forero et al., 2021). It has been postulated that blocking any unnecessary processing of new incoming stimuli could prevent interference of new information with existing memory traces that undergo internal transformation during active system consolidation (Diekelmann and Born, 2010). A study which delivered acoustic stimuli during ongoing endogenous spindle activity was found to evoke a single K-complex (Choi et al., 2019). Meanwhile, targeting the SO positive peaks with CLAS using stimuli in the spindle frequency range did not acutely entrain spindle activity but resulted in a delayed increase in the spindle frequency range during the consecutive SO up-wave (Ngo et al., 2018). Finally, the cross-frequency coupling of SO and spindle activity could be enhanced locally with CLAS application (Krugliakova et al., 2020). These studies demonstrate that the specifics of CLAS effects are still unclear, but analyses for stimulation optimization are under way (Navarrete et al., 2022). So far, only a few studies have focused on investigating memory consolidation by directly targeting sleep spindles rather than SOs (e.g., Ngo et al., 2018) and found enhanced slow-wave amplitude and fast spindle power following offset, revealing the complex interface of different brain oscillations during sleep. Nevertheless, more research on CLAS of sleep spindles could help investigate the effect of their interactions with SOs on declarative memory consolidation.

In summary, CLAS has been used to probe the role of slow oscillations and their relationship with sleep spindles in memory consolidation with a broad range of memory tasks, however a recent meta-analysis reported a steady decline in effect size of memory studies using CLAS over the last decade (Harlow et al., 2023). The inconsistent results of CLAS in enhancing memory consolidation raise questions about the role of the type of memory task and the subtleties of stimulation protocols interacting with different types of oscillations in the effectiveness of CLAS. Further investigation of these interactions is necessary to fully understand the potential of CLAS in memory improvement.

4.2. Clinical applications

Deep sleep and related slow-wave activity play an important role in overall health and well-being, as many physiological processes, including the cardio-metabolic, endocrine, and immune functions, are affected by it (Besedovsky et al., 2012; Irwin, 2015; Mancia, 1993; Zoccoli and Amici, 2020). Accordingly, enhancing slow oscillations via CLAS is a promising tool to boost these functions of sleep. For example, CLAS has also been demonstrated to reduce cortisol levels (Grimaldi et al., 2019; Besedovsky et al., 2017) and modulate the immune system, as stimulation of SOs overnight reduced blood T and B cell counts, which could indicate beneficial redistribution of these immune cells to lymphoid tissues (Besedovsky et al., 2017). Although negative results of CLAS have been reported for glucose homeostasis, consecutive food intake, or energy expenditure (Santiago et al., 2019), overall, these studies illustrate CLAS as a useful method in exploring the clinically relevant aspects of sleep and slow-wave activity, and its potential to be utilized as a therapeutic tool in the future.

Sleep disruption often occurs simultaneously with neuro-developmental disorders or neurological diseases (Cortese et al., 2009; Hu et al., 2017; Kirov and Brand, 2014; Krystal, 2012; Mander et al., 2016; Singh and Zimmerman, 2015). While most studies on the impact of CLAS on memory consolidation have been conducted in healthy participants, there have been a few studies on CLAS in different patient populations (Fattinger et al., 2019; Papalambros et al., 2019; Prehn-Kristensen et al., 2020). In patients with epilepsy, CLAS has been shown to effectively manipulate NREM3 without having a significant impact on spike activities and without compromising sleep quality (Fattinger et al., 2019). Additionally, studies have demonstrated that CLAS in patients diagnosed with benign epilepsy with centrotemporal spikes would lead to a reduction in focal interictal epileptic spikes, potentially by inducing thalamocortical refractoriness (Klinzing et al., 2021). CLAS has also been proven to effectively increase SWA in an amnestic mild cognitive impairment (aMCI) target group (Papalambros et al., 2019). However, only half of the patients benefited from improved memory consolidation (Papalambros et al., 2019). Moreover, in a study of ADHD patients, CLAS was found to boost procedural and working memory performance but did not influence declarative memory tasks when compared to a healthy control group (Prehn-Kristensen et al., 2020). Finally, the first study on the use of CLAS to enhance positive therapy memories in post-traumatic stress disorder is currently ongoing, and preliminary findings demonstrate that the procedure is well tolerated by patients (Van Marle et al., 2017). Additionally, SO phase targeting was accurate despite the reduced SO power in these patients (De Boer et al., 2020) and resulted in similar stimulus-evoked responses to those found in healthy subjects. Altogether, while these initial studies exploring CLAS as a non-invasive therapeutic method have modest clinical outcomes, they highlight the usability of the technique in populations with disturbed sleep, and illuminate how CLAS as a form of

Table 2
A detailed description of experimental parameters of CLAS studies with (potential) clinical applications. BMI: body mass index, CLAS: closed-loop auditory stimulation, oGTT: oral glucose tolerance test, SD: standard deviation, SEM: standard error of mean, SO: slow-oscillation, SWA: slow-wave activity.

Author	Subjects	Stimulation parameters	Measures	Design	Results
Besedovsky et al. (2017)	14 healthy subjects (0 females) Mean age 24 years ± 2.16 SD Mean BMI 23 kg/m^2 ± 2.14 SD	50 ms pink noise, delivered at an individual delay phase-locked to SO up-waves; 2-click system.	Absolute counts of T and B lymphocytes in the blood	Within-subject comparison, two conditions (stimulation and sham), counterbalanced	Enhancement of SOs after CLAS; Reduction in T and B cell counts and cortisol, increment in aldosterone levels but no difference in growth hormone after CLAS.
Santiago et al. (2019)	22 healthy subjects (0 females) Mean age 24.36 years ± 0.80 SEM Mean BMI 22.51 kg/m^2 ± 0.35 SEM	50 ms pink noise, delivered at an individual delay phase-locked to SO up-waves; 2-click system.	oGTT blood samples, thermogenesis, energy expenditure, and food intake	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs after CLAS; No differences in glucose homeostasis, energy expenditure or consecutive food intake.
Grimaldi et al. (2019)	20 healthy subjects (15 females) Mean age 24.7 years Mean BMI 25 kg/m^2 ± 3.5 SD	50 ms pink noise phase-locked to SO up-waves; 5-click system.	Heart rate variability, cortisol level, and blood pressure	Within-subject comparison, two conditions (stimulation and sham), counterbalanced Two experimental nights.	Enhancement of SOs and spindle activity after CLAS; Reduction in cortisol and increment of parasympathetic activity after CLAS.
Diep et al. (2021)	25 healthy subjects (16 females) Mean age 32.9 years ± 8.2 SD	50 ms audio tones phase-locked to SO up-waves and subsequent 1-s inter-tone-intervals; Automatic delivery of tones	Subjective alertness (sleepiness scale) and fatigue (Samn-Perelli fatigue scale), Objective measures of alertness (multiple sleep latency test) and attention (psychomotor vigilance task)	Within-subject comparison, two conditions (stimulation and sham), counter-balanced, double-blind protocol (subjects and experimenter unaware of conditions) Two experimental nights (consecutive)	Enhancement of SWA energy; Improvement in alertness after each stimulation night; Improvement in objective attention measures the day after two consecutive stimulation nights
Krugliakova et al. (2022)	18 healthy subjects (9 females) Mean age 23 years ± 1.4 SD	50 ms pink noise at the ascending phase of SOs (~35^o after zero-crossing in the positive direction)	Enhanced SWA by means of different stimulation techniques as an electrophysiological marker of recovery during sleep	Within-subject comparison, two conditions (stimulation and sham), counterbalanced, Two experimental nights	Enhancement of SOs after CLAS; Acceleration of SWA decline over night after CLAS that is associated with enhanced attentional performance; Recovery improvement during sleep after CLAS; Different types of SOs contribute differently to the recovery process
Huwiler et al. (2022)	Overall 51 healthy subjects (0 females) Study 1: 23 subjects Mean age 40.25 years ± 13.69 SD, Study 2: 9 subjects Mean age 50.36 years ± 6.74 SD, Study 3: 19 subjects, Mean age 45.29 years ± 11.00 SD	50 ms pink noise, delivered at an individual delay phase-locked to SO up- and down-waves; Block-wise stimulation-sham alteration (10 s on/off blocks)	Heart rate variability, electrocardiogram R peaks, SWA	Within-night comparisons, Various conditions, e.g.,: phase-specific, rhythmic, and sound modulated One experimental night	Enhancement of SWAs after CLAS regardless of the stimulation phase; SWA improvement is more pronounced at the beginning of a stimulation block; Increased heart rate variability; Potential application of CLAS to regulate cardiovascular restorative conditions during sleep; More restful cardiovascular conditions after CLAS.
Diep et al. (2022)	24 healthy subjects (0 female) Mean age 39.9 years ± 4.1 SD	50 ms audio tones phase-locked to SO up-waves; Automatic delivery of tones with individualized sensitivity of 20–65 dB	Heart rate variability, normalized RR intervals, SWA	Within-subject comparison, two conditions (stimulation and sham), counter-balanced, double-blind protocol (subjects and experimenter unaware of conditions) Two experimental night	Enhancement of SOs after CLAS; Heart rate variability improvement after CLAS

therapy might present a new and safe way to improve deep sleep (Talamini and Juan, 2020). A recent study indeed demonstrated that using CLAS to boost posterior SO during NREM sleep decreased the likelihood of dreaming, thus opening up the possibility to suppress nightmares in clinical populations (Juan et al., 2023).

Encouraging with respect to clinical CLAS application, preliminary findings using a wearable implementation of modeling-based CLAS in patients with post-traumatic stress disorder (paper in preparation) show that SO phase can be accurately targeted in home environments. This type of application could offer major healthcare benefits, providing a low-cost, broadly applicable treatment option for a highly prevalent and currently undertreated disorder.

5. Conclusions, limitations and future outlook

Sleep affects the mind, brain and body in multiple and complex ways (Dresler et al., 2014; Frank and Heller, 2018; Anafi et al., 2019). The underlying processes are still poorly understood; however, they can gradually be uncovered by interfering with different brainwaves and evaluating the effects. An increasing body of evidence demonstrates that

Table 3
A detailed description of experimental parameters of real-time targeted-memory reactivation (TMR) studies on memory consolidation. SD: standard deviation, SO: slow-oscillatory.

Author	Subjects	Stimulation parameters	Measures	Design	Results
Cox et al. (2014)	12 healthy subjects (11 females) Age range 18–23 years	Maximum of 500 ms real-world sound stimuli (doorbell, barking dog, footsteps, etc.) at SO up- and down-waves.	2-alternative forced choice task	Within-subject comparison, one condition (up- or down-wave closed-loop TMR) One experimental evening nap session.	No differential brain or behavioral responses.
Shimizu et al. (2018)	37 healthy subjects (16 females) Mean age 25.14 years ± 5.75 SD	Acoustic cues were played at the time of down- to up-wave transition.	Virtual reality navigation task	Within-subject comparison, two conditions (closed-loop TMR and sham) Three experimental nap sessions	Increased spectral power in sleep spindle band; Improvement in navigation efficiency.
Göldi et al. (2019)	22 healthy subjects (18 females) Mean age 20.85 ± 0.28 SD	1/3 of words were played phase-locked to SO up-waves 1/3 of words were played phase-locked to SO down-waves 1/3 of words were not replayed	120 Declarative foreign vocabulary learning task	Within-subject comparison, one condition (up- and down-wave closed-loop TMR) One experimental night.	Increased spectral power in theta and sleep spindle band; Improvement of recall after closed-loop TMR.
Wang et al. (2022)	16 healthy subjects (0 females) Mean age 24.4 years ± 0.8 SD	Auditory cues (first syllable of the words) were played binaurally phase-locked to SO up- and down-waves.	40 declarative paired-associates learning tasks	Within-subject comparison, two conditions (up- and down-wave closed-loop TMR) Two experimental nights.	No difference in memory performance between the up- and down-wave cueing conditions, and between the cued and non-cued words.
Ngo and Staresina (2022)	24 healthy subjects (14 females) Mean age 21.3 ± 0.5 SD	Two prototypical image sounds (500-ms long) were played at SO up- and down-waves and a novel sound served as a control.	120 verbs associated with 6 gray-scale images for episodic memory task; 240 gray-scale images as the localizer task	Within-subject comparison, one condition (up- or down-wave closed-loop TMR) One experimental night.	Up-wave TMR decreases overnight forgetting of target image representation when compared to down-wave TMR.

CLAS is effective in enhancing SOs during NREM sleep with highly replicable EEG effects. Given that animal research has been using closed-loop stimulation techniques for many years to unravel the details of neural processing with great precision (Aksamaz et al., 2022; Girardeau et al., 2009; Latchoumane et al., 2017; Maingret et al., 2016; Moreira et al., 2021, 2022), transferring knowledge between human and animal research is essential to shed more light on the working mechanisms and possibilities of CLAS in both basic science and clinical research.

CLAS has been developed in particular to strengthen memory consolidation. While some studies were able to show enhancing effects (especially using task-related TMR stimuli), many were not (particularly, non-task-related sound stimuli and replications), indicating that the impact of CLAS on memory might overall be minor (Wunderlin et al., 2021). Conflicting results between memory consolidation studies highlight the necessity of further developing standardized protocols with more replications and larger sample sizes, as well as more rigorous study designs (e.g. double-blinding) to examine the functional effects of CLAS on memory consolidation. Beyond memory processes, CLAS has been applied to modulate several physiological processes with potential clinical applications, e.g. to reduce cortisol levels in addition to nocturnal T and B cell migration to lymphoid tissues for immune-adaptive function while increasing parasympathetic activity and aldosterone levels, benefitting the overall physical health of humans (see Table 2).

Applying auditory stimulation to the brain in a closed-loop manner has inspired and facilitated a wealth of investigations examining previous unknowns of oscillatory sleep dynamics. However, studies conducted so far have also revealed several physiological limitations and constraints posed by this type of stimulation. The first limiting factor to be considered relates to the homeostatic balance the brain constantly seeks to maintain. In a recent study by Fehér et al. (2023), deep sleep suppression through CLAS resulted in a shift of SWA towards the end part of the night, showing the homeostatic response of the brain. According to the synaptic homeostasis hypothesis, waking time results in a net increase in synaptic strength which is downregulated again by SWA during subsequent sleep (Cirelli, 2017; De Vivo et al., 2017; Tononi and Cirelli, 2006). With the brain aiming to maintain a sustainable equilibrium, it is possible that experimentally enhancing SWA could lead to an unwanted detrimental outcome. Interestingly, previous studies in humans have found that while slow-wave activity could be acutely boosted during stimulation trials or periods, these increases often seemed to level out over the entire night (Ngo et al., 2013; Papalambros et al., 2017; Schneider et al., 2020), which would hint at an inherent limit of SO activity that the brain is willing to engage in. However, enhancing total night SWA was possible in some studies (Diep et al., 2020; Garcia-Molina et al., 2018; Santiago et al., 2019) and may therefore be conditional on specific stimulation parameters. Thus, the question of whether 'more' stimulation appears to entail better effects, and if so, of what nature, has yet to be conclusively answered. In the case of spindles, a CLAS protocol administering acoustic stimuli to four consecutive SOs demonstrated that this could not exceed the increase in spindle activity compared to a two-stimuli protocol (Ngo et al., 2015). This limitation, which is based on a refractory period of spindle-expressing thalamic networks (Antony et al., 2018), could thus pose a physiological constraint on the maximum possible increase that may be achieved by experimental manipulation using this stimulation technique. Nevertheless, considered to date, CLAS presents a practical experimental tool to explore the limitations not only of its own applicability but also of inherent physiological constraints and oscillatory dynamics of the brain.

Furthermore, some inconsistent results may be associated with the neglected (albeit minor) variances in the 'type' of the targeted SOs. Recently, an unsupervised approach to classify SOs based on their scalp distribution as well waveform characteristics resulted in three distinct SO categories (Navarrete et al., 2023). It was shown that, while CLAS results in higher occurrence of large, widely distributed, and steep SOs (category 1), it is potentially associated with the decreased likelihood of flat, smaller, and more localized SOs (categories 2 and 3). The diversity in the response of different SO types to CLAS, along with potentially different neuronal mechanisms, could account for certain incongruent findings to date. Another explanation may be related to the stimulation

technique: to further sharpen the 'closed-loop' terminology, a clearer distinction between the closed- and 'open-loop state-dependent' approaches has recently been made (Antony et al., 2022). According to the authors, a closed-loop state-dependent stimulation requires continuous monitoring and intervention to maintain a specific state (e.g., as in Ngo et al., 2015), whereas in an open-loop state-dependent stimulation, the intervention either does not directly affect the state or does not adapt itself over time (e.g., as in Antony et al., 2018).

The majority of CLAS literature has evaluated short-term effects of the method. However, the long-term impacts of CLAS on sleep, mood, and behavior remained largely unexplored: only a few longitudinal studies have investigated CLAS applications over time in real-life settings (Barnes et al., 2023; Debellemaniere et al., 2018; Lustenberger et al., 2022; Xi et al., 2023). Lustenberger et al. (2022) could successfully enhance low-frequency SWA using a wearable system and found that the level of response to CLAS may be predicted by baseline SWA. However, unintended effects were observed, including reduced REM sleep duration and decreased mood on the following day. Nevertheless, this study included a limited sample size (16 participants) and restricted age range (62–78 years old). Future work should aim for replications with larger sample sizes and broader age ranges to provide clearer insights on the long-term effects of CLAS, from memory consolidation to clinical applicability. While wearables offer an immense potential for understanding the effectiveness of CLAS for various applications, their associated challenges as mentioned in Section 2.6 should be carefully considered in future studies to ensure the reliability and validity of findings.

So far, CLAS has been restricted to oscillations in NREM sleep. However, given the role of REM sleep e.g. in emotion regulation (Genzel et al., 2015), it seems promising to extend the stimulation of sleep oscillations to REM as well. CLAS has recently shown applications in enhancing theta wave (3–7 Hz) activity within REM sleep (Harrington et al., 2021), resulting in extended suppression of theta wave after a short boost and prolonged beta power enhancement. This possibility of CLAS to manipulate theta oscillatory activity during REM sleep might extend recent advances in the use of CLAS during NREM sleep to modulate dream experiences (Juan et al., 2023), paving the way for new, physiology-focused nightmare therapies. Moreover, emotion during memory encoding plays a critical role in memory consolidation, and in particular REM sleep has been shown to play a crucial role in the consolidation of emotionally charged memories (Genzel et al., 2015). Therefore, the effects of sleep on the consolidation of emotional memory are another topic for future research to explore: studies on CLAS targeting REM sleep theta rhythms, might extend insights on the role of REM sleep in emotional processing.

Overall, CLAS has demonstrated substantial potential for the advancement of sleep research, by non-invasively, yet noticeably, evoking sleep oscillations. Given the role of sleep and in particular slow-wave sleep for mental health, future research should assess the applicability of CLAS as a novel non-invasive therapeutic solution to enhance deteriorated sleep quality in ADHD, autism, MCI, or patients with depression. Ultimately, CLAS may be utilized as a prevention strategy or therapy for people with early Alzheimer's Disease to augment neurotoxin removal during sleep and, as a result, slow down the progression of the disease (Lim et al., 2014; Ngo et al., 2020).

Best practices and future directions:

- CLAS system implementation requires 1) a real-time brainwave access system, 2) an oscillation detection algorithm, and 3) a stimulation system. Detection algorithms with different complexity levels may be employed depending on the available infrastructure and processing power.
- While identifying universally optimal parameters for implementing CLAS is unrealistic, individualized optimal parameters can be attained by analyzing data from an adaptation night or employing adaptive algorithms that adjust to the specific properties of the individual's brain oscillation of interest.

(*continued on next column*)

(*continued*)

- The analysis of CLAS results involves the following essential steps: 1) applying standard pre-processing techniques to generate time-locked events, 2) evaluating the performance of phase-targeting, 3) assessing the electrophysiological response, and 4) conducting behavioral assessments (if applicable).
- Future studies should evaluate short- and long-term effects of CLAS on memory consolidation and clinical applications in longitudinal designs across a large diverse population, employing double-blind approaches and adaptive algorithms using wearable EEG systems.
- The distinction in the response of different types of SOs to CLAS may explain some of the inconsistent findings to date. In the analysis pipeline, upcoming studies may consider the actual subtype of the targeted SO.
- CLAS may be employed for targeting other brain oscillations during NREM and REM. An interesting area of research could be emotional memory processing through CLAS of REM sleep theta rhythms.

CRediT authorship contribution statement

Conceptualization: MJE, SF, HVN, MD; Data curation: MJE, SF; Funding acquisition: MD, HVN; Methodology/Software: MJE, FDW, LT; Supervision: FDW, LT, MD; Visualization: MJE, SF; Writing – original draft: MJE, SF; Writing – review & editing: MJE, SF, HVN, JS, FDW, LT, MD.

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