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Modulation of Slow-Wave Sleep: Implications for Psychiatry

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Abstract:	Purpose of review The objectives of this review are to examine and integrate existing empirical evidence regarding the impact of Slow Wave Sleep (SWS) modulation on memory and executive function performance in individuals with psychiatric disorders, and to examine the feasibility of integrating SWS modulation into psychiatric care. Recent findings SWS modulation in individuals with psychiatric disorders resulted in changes to SWS sleep across multiple psychiatric disorders, using all stimulation methods. SWS stimulation was associated with improved cognitive performance. SWS modulation using acoustic stimulation resulted in improved cognitive performance in children with ADHD, and the use of transcranial stimulation was associated with improved cognitive performance in individuals with mild cognitive impairment. Significant relationships between changes in SWS and cognitive improvement were found for individual with mild cognitive impairment following the use of acoustic or transcranial stimulation night. Summary Our review reveals partial support to the potential efficacy of SWS modulation as a transdiagnostic intervention that uses sleep to improve cognitive functions of individuals diagnosed with psychiatric disorders and cognitive deficits. It further highlights multiple barriers pertaining to the feasibility of integrating SWS modulation into clinical practice and proposes ways to improve it.

Dear Dr. Gehrman

Please find attached the revised manuscript by Samantha Scholes, Jose Arturo Santisteban, Yujie Zhang, Armando Bertone, and Reut Gruber "Modulation of Slow-Wave Sleep: Implications for Psychiatry " which is being submitted for possible publication in Current Psychiatry Reports.

In light of the Journal's reviewing and editing of our submission, we hereby transfer copyright ownership of the manuscript to Current Psychiatry Reports in the event that our work is published in the journal. We attest that the manuscript is of original material, has not been published elsewhere, and is not being considered for publication elsewhere.

Sincerely,
Reut Gruber

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Dear Dr. Philip R. Gehrman, PhD
Section/Guest Editor
Current Psychiatry Reports

Thank you for the opportunity to revise our manuscript. The comments provided on our paper have been used to modify and improve the paper. Below you will find a comment by comment response to the reviewer.
We look forward to your decision.
Sincerely,
Reut

Comment 1. This manuscript was very well written and provides a concise review of the current state of the science for slow wave modulation in psychiatric disorders. I especially appreciated the section of the discussion regarding feasibility of implementation in clinical settings.
Response: We really appreciate your feedback. Thank you.

Comment: I have only one minor comment. In the paragraph on page 3, starting line 43, you briefly describe the different methods for slow wave modulation. Although this is basic please include a brief explanation of what it means for a system to be closed loop.

Response The requested information has been added:

Acoustic modulation refers to the use of sounds to evoke SOs and increase the magnitude of slow waves during all sleep cycles without increasing the number of total arousals**. It can be provided through either open- or closed-loop stimulation. Open-loop stimulation refers to the use of sounds to evoke SOs without the sounds being synchronized with any phase of endogenous SOs; whereas closed-loop stimulation uses sounds during the peaks of SOs producing an increase in the amplitude of the ongoing wave and in fast spindle activity during the period of stimulation** [9, 42, 49, 50].

Modulation of Slow-Wave Sleep: Implications for Psychiatry

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Abstract

Purpose of review: The objectives of this review are to examine and integrate existing empirical evidence regarding the impact of Slow Wave Sleep (SWS) modulation on memory and executive function performance in individuals with psychiatric disorders, and to examine the feasibility of integrating SWS modulation into psychiatric care.

Recent findings: SWS modulation in individuals with psychiatric disorders resulted in changes to SWS sleep across multiple psychiatric disorders, using all stimulation methods. SWS stimulation was associated with improved cognitive performance. SWS modulation using acoustic stimulation resulted in improved cognitive performance in children with ADHD, and the use of transcranial stimulation was associated with improved cognitive performance in individuals with mild cognitive impairment. Significant relationships between changes in SWS and cognitive improvement were found for individual with mild cognitive impairment following the use of acoustic or transcranial stimulation night.

Summary: Our review reveals partial support to the potential efficacy of SWS modulation as a transdiagnostic intervention that uses sleep to improve cognitive functions of individuals diagnosed with psychiatric disorders and cognitive deficits. It further highlights multiple barriers pertaining to the feasibility of integrating SWS modulation into clinical practice and proposes ways to improve it.

Keywords: Slow wave sleep; modulation; psychiatric; memory; executive function

Introduction

Memory and executive function (EF) deficits are common in individuals with psychiatric disorders across multiple diagnoses (see Table 1). Both cognitive abilities are critical for the adapting our behaviors in response to the environment, and EF skills (e.g., planning, working memory, cognitive flexibility, inhibition, reasoning, and problem-solving) [1] making them essential for daily functioning. Deficits in either of these domains result in significant and chronic impairments across social, workplace, school, and family contexts [2–5]. Identifying methods that can enhance memory and/or EFs in individuals with psychiatric disorders is necessary to improve their quality of life.

Sleep disturbances are highly comorbid with most psychiatric disorders [6,7] and have been recognized as a transdiagnostic mechanism that contributes to the symptomatology and functional disability associated with psychiatric disorders [8]. Individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression, intellectual disability, mild cognitive impairment, and schizophrenia are additionally affected from multiple sleep disturbances, including slow-wave sleep (SWS) abnormalities (see Table 1). SWS, which is also known as stage (N3) sleep, is the deepest stage of non-rapid eye movement (nREM) sleep along with N1 and N2. SWS is defined by the presence of high-amplitude electroencephalographic activity with a frequency of 0.5 to 2 Hertz (Hz). Oscillatory activity in the spindle frequency range [12-15 Hz] may also be present during SWS [9–11]. Stimulation of the frontal cortex results in induced sleep, EEG slow waves, and slow-wave activity (SWA; quantified based on the power in the delta frequency band, as assessed using power spectral analysis, which is most prominent in the frontal area) [9,12].

TABLE 1: Insert here, includes references 13-40.

The most prominent oscillations during SWS are slow wave oscillations (SO), spindles, and sharp-wave ripples. Sleep spindles are short bursts of oscillations in the 9- to 15-Hz frequency range that are generated by the thalamic reticular neurons and synchronized by corticothalamic feedback. Sharp-wave ripples, produced within the hippocampus, are higher frequency bursts that occur preferentially within the trough of the spindle [41] (for detailed information see [9]).

Recent studies have indicated that SOs during SWS causally contribute to the consolidation of declarative memories and improved EFs [42]. Increases in sleep spindles and hippocampal sharp-wave ripples occur once learning has taken place, and subsequent sleep spindle density is associated with performance on declarative verbal memory tasks [43,44]. More efficient EFs are associated with greater delta power in the first period of nREM sleep. Delta activity reflects neural synchrony within the prefrontal cortex (PFC), which is thought to enhance the cortical connections important for cognition [45–47]. High amplitude, low frequency SWA is associated with better abstract reasoning and working memory abilities in adults, highlighting the beneficial role that delta activity plays in EFs [45].

Advances made in sleep research have demonstrated that SWA can be stimulated during sleep through low-frequency stimulation and/or enhancement of the depolarized slow-wave up-state, and that such SWS/SWA modulation improves memory and EF [41,45,48]. For example, SWS can be modulated experimentally during sleep using acoustic, pharmacological, or electrical stimulation methods. Acoustic modulation refers to the use of sounds to evoke SOs and increase the magnitude of slow waves during all sleep cycles without increasing the number of total arousals. It can be provided through either open- or closed-loop stimulation. Open-loop stimulation refers to the use of sounds to evoke SOs without the sounds being synchronized with any phase of endogenous SOs; whereas closed-loop stimulation uses sounds during the peaks of SOs producing an increase in the amplitude of the ongoing wave and in fast spindle activity during the period of stimulation [9, 42, 49, 50].

[9,42,49,50]. Acoustic modulation has been shown to enhance SWS, leading to improved verbal declarative memory in healthy adults [42,49,51]. Transcranial electrical stimulation, which uses the application of electricity with direct or alternating current, has been used to enhance the duration and the power of SWS [52] and demonstrated to improve verbal declarative memory, picture recognition memory, and location memory [42,52–55] in healthy adults. Pharmacological agents have also been used to modulate SWS [42]. For example, tiagabine, sodium oxybate, and interleukin-6 have been found to increase SWS, and, according to a review article, 44.4% of these studies found that they significantly affect cognitive functioning [42,56–59].

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Concurrent memory deficits, EF deficits, and SWS abnormalities are common across different psychiatric disorders. The empirical evidence highlighting the causal link between SWS and cognitive functioning raises the possibility that the modulation of SWS (e.g., by increasing SWS duration and/or slow oscillatory power/amplitude) can be used as a transdiagnostic means to improve the cognitive functioning of individuals with psychiatric populations diagnosed with co-morbid sleep disorder and memory or EF deficits, and thereby improve daytime functioning [42,60]. The objectives of this review are: 1) to examine and integrate existing empirical evidence with regards to the impact of SWS modulation on performance on memory and executive tasks for individuals with psychiatric disorders, and 2) to examine the feasibility of integrating SWS modulation therapy into psychiatric care.

Methods

A systematic search was performed in March 2020 using the MEDLINE (accessed via PubMed), CENTRAL, and EMBASE electronic databases. The criteria used included papers published from March 2017 on that used SWS enhancement methods to induce improvements in cognitive outcomes in psychiatric populations with known relevant deficits in memory, EF, cognition, and SWS (see Table 1). The full search strategies used for each database are presented in Table 2.

INSERT TABLE 2

The search terms yielded 116 articles after exclusion of studies that included non-human participants and those that were not published in English. Titles and abstracts were examined to extract potentially relevant articles, and the abstracts of the extracted articles were examined in more depth by four authors (SS, JAS, YZ, and RG). A study was excluded if it did not involve SWS modulation; if the SWS interference used was not relevant to the psychiatric disorder; or if it was a review article. The full text was retrieved if a decision could not be made based on the article abstraction.

Random search items used were a combination of key words including “slow wave sleep”, “deep sleep”, “delta sleep”, “non-REM sleep”, “nREM sleep”, “nREM3”, “slow oscilla*”, “non-rapid eye movement sleep”, “enhance*”, “boost*”, “modulation”, “closed-loop stimulation”, “acoustic stimulation”, “transcranial electric stimulation”, “pharmaceutical”, “dementia”, “mild cognitive impairment”, “intellectual impairment”, “intellectual disability”, “learning disability”, “learning disorder”, “schizophrenia”, “depression”, “major depressive disorder”, “mood disorder”, “bipolar”, “mania”, “attention deficit hyperactivity disorder”, and “ADHD” . The keywords were combined with Boolean operators ‘OR’ and ‘AND’ to broaden or narrow the search. Furthermore, we reviewed reference lists of original and review articles to search for more studies on the same topic.

Data Extraction

Data was extracted for the characteristics with respect to the trial (author, year of trial conduction, design, duration, randomization, concealment, and blinding), participants (age, gender, diagnosis, and information on other medical comorbidities), intervention (device used, duration, dosimetry, safety and follow-up), measures (sleep, cognitive, and other), and results (changes in sleep, cognition, associations between sleep and cognition, intention to treat analysis, safety, and follow-up).

Results

The literature search yielded three relevant manuscripts and two conference abstracts (see Table 3.1 and 3.2). The psychiatric populations that were investigated included children with ADHD [16] and adults diagnosed with depression [61], mild cognitive impairment [62,63], and schizophrenia [64]. No study published in the last 3 years was found for SWS modulation in individuals with bipolar disorder, intellectual disabilities, or learning disorders.

INSERT TABLES 3.1 and 3.2

The auditory stimulation protocols used in three surviving manuscripts differed in the manner the threshold for amplitude and stimulus intensity, and/or in the timing and duration of stimulation, were determined. Participants with ADHD who underwent acoustic closed-loop stimulation first had their endogenous slow oscillations detected prior to the onset of the first stimulus, which was delivered to each child’s individualized delay time [16]. The second stimulus was delivered 900 ms following the prior stimulus and stimulation stopped after 2.5s. Stimulation was provided for a total of 210 minutes of the

night [16]. In the study conducted with individuals diagnosed with depression, stimuli were delivered when the electroencephalogram (EEG) waves declined below the threshold amplitude for detecting SWS [61]. The thresholds for amplitude and stimulus intensity were determined on an individual basis. Each 30-s epoch with stimulation was preceded and followed by 30-s epochs without stimulation; and these cycles continued throughout the night [61]. Finally, in the study investigating participants diagnosed with mild cognitive impairment, acoustic pulses were targeted to 20 degrees before the peak of the up-state of an endogenous slow oscillation [62]. The stimulation occurred for 50 ms and was delivered in blocks of five, and was applied for approximately 122 minutes of the night [62]. Of the remaining studies included herein, one used transcranial stimulation applied by a battery-driven stimulator (frequency 0.75 Hz) during a single 90-minute nap session of participants mild cognitive impairment [63], and the other used one night of eszopiclone treatment in individuals diagnosed with schizophrenia [64]. The different stimulation methods had different impacts on the sleep and cognitive performance of the participants and varied in the extent to which the changed aspects in SWS were found to be related to the observed changes in cognitive performance.

Impact of different stimulation methods on sleep across different psychiatric populations

Auditory modulation. Auditory stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD [16]: increased SO, delta, slow, and fast spindle band activity; increased SO activity across fronto-central regions; and increased delta oscillation over C3 in the stimulation condition compared to the sham control. Depression [61]: increased overall EEG delta and sleep power density and improved subjective reports of sleep quality. Mild cognitive impairment [62]: 15.1% increase in SO and 11.4% increase in SWA activity during stimulation-ON intervals compared to stimulation-OFF intervals; 8.1% decrease in SO and 6.6% decrease in SWA during stimulation-OFF intervals; and a 22.2% increase in SO, 17.9% increase in SWA, and 5% increase in theta activity during the stimulation night. Schizophrenia: No study included for this population (N/A).

Transcranial stimulation. Transcranial stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: increased SO power and enhanced power in the fast and slow spindle frequency ranges; stronger synchronization between SO and fast spindle power, in particular related to increased spindle power during late-rising SO up-phases, under the stimulation condition compared to sham stimulation. Schizophrenia: N/A.

Pharmacological stimulation. Pharmacological stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: increased spindle density, reduced consistency of SO spindle timing, and reduced SO amplitude on eszopiclone compared to placebo in patients with schizophrenia and in controls.

Impact of SWS modulation on cognition

Auditory modulation. Auditory stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD [16]: faster reaction times in working memory performance under the stimulation condition compared to the sham condition, longer reaction times in performance of procedural memory under the sham condition compared to the stimulation condition in the ADHD group but not in the control group, and improved memory performance for rewarded word-pairs only following stimulation in the control group. Depression: N/A. Mild cognitive impairment [62,63]: no change in cognitive performance under the stimulation/sham conditions. Schizophrenia: N/A.

Transcranial stimulation. Transcranial stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: improved visual recognition performance on a picture-location recall task following a 90-minute nap, with data corrected for sleepiness as a confounding variable. Schizophrenia: N/A.

Pharmacological stimulation. Pharmacological stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: no change.

Associations between changes in SWS and improved cognition

Auditory modulation. ADHD [16]: no significant relationship between the increased SO activity and increase in memory performance. Depression: N/A. Mild cognitive impairment [62]: the degree to which the stimulation enhanced SWA positively correlated with overnight word recall and with total cognitive under the stimulation condition but not the sham condition.

Transcranial stimulation. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: enhanced synchronization of SO and fast spindle power was associated with improved visual recognition performance in individuals diagnosed with mild cognitive impairment. Schizophrenia: N/A.

Pharmaceutical Stimulation. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: on placebo but not on eszopiclone, the spindle density correlated with overnight procedural performance improvements; on eszopiclone but not on placebo, the SO amplitude predicted overnight procedural performance improvements only in individuals with schizophrenia.

Methodological characteristics of the studies

Populations. One study was conducted with school-aged children [16]; two studies were conducted with elderly adults [62,63]; and two studies used a wide age range that included a mix of younger and older adults [61,64]. One study included only male participants [16]; three studies included more males than females [61,63,64], and one study included more females than males [62]. Two of the five studies included a healthy control group [16,64]. One study included 26 participants [64]; two studies had fewer than 20 participants [16,63]; and the other two had fewer than 10 participants [61,62].

Design. All the surviving studies used a crossover design, but with different stimulation and sham/control condition intervals; they included no interval [64], 1-2 nights [61], 1 week [62], or a minimum of 2 weeks [63]. Two of the five studies used randomized crossover sham-controlled designs [62,63]; one study used a counterbalanced design and did not report on blinding [61]; and three studies used a pre-post design with no control group [61–63]. Of the studies that randomized the participants to the sham or stimulation group, none provided information regarding the methods used for randomization, sequence allocation, or concealment.

Blinding. Four of the five studies reported blinding participants to their assigned condition [16,62–64]. Of these, two blinded the sleep technician that scored participants' sleep [16,62]; two blinded the experimenter [16,64]; and none blinded the cognitive outcome assessment.

Control condition. All of the studies included a sham or placebo condition, with all individuals participating in both the sham/placebo condition and the stimulation condition [16,61–64]. Two studies also used healthy control participants [16,64].

Inclusion/exclusion criteria. One study reported having participants with psychiatric comorbidity in addition to the main disorder of interest (ADHD and oppositional defiant disorder or ADHD and conduct disorder) [16]; one study excluded participants with a psychiatric comorbidity [63]; and the other three did not report on psychiatric comorbidity [61,62,64]. Two studies excluded participants with a medical comorbidity [16,63], whereas the other three studies did not report on medical comorbidity [61,62,64]. One study excluded participants with a sleep disorder [63], one study excluded participants who had moderate-to-severe sleep apnea [62], one study excluded participants who had scores above the critical level on two subjective measures (Sleep-Self Report and Children Sleep Habits Questionnaire) [16], and two studies did not report on sleep [61,64].

Intention to treat analyses (ITAs). Two studies reported participant drop-outs, with rates of 11% and 27% [61,63]. None of the included studies reported any ITA.

Pragmatic characteristics of the studies

Number and duration of sessions. All the studies included a one-time exposure to the given stimulation method, with a stimulation duration ranging from 90 minutes to 1 night.

Location of sessions. All studies had participants sleeping in a sleep laboratory.

Need to be off medication. Two studies reported excluding participants on medication [62,63]; one study asked participants to discontinue medication 48h prior to the experiment [16]; one study reported that participants were medicated [64], and one study did not report on medication [61].

Logistics. None of the studies provided information regarding the logistics associated with preparing, instructing, or assisting participants in getting ready, arriving at, or staying in the sleep laboratory; the level of independence required; or any barrier related to such logistical challenges.

Use of specialized equipment/staff. All of the studies required access to specialized equipment and software, as well as highly qualified personnel that can deliver the stimulation with precise timing related to the onset of SWS, and score micro and macro sleep architecture during [63] or after [16,61,62,64] the experiment.

Safety. None of the studies reported any documented side effect, potential harm, or level of patients' inconvenience related to participating in the experiments.

Discussion

One of the most important recent discoveries in cognitive and sleep sciences involves the realization that sleep affects cognitive processes not just as a result of the negative impact of sleep deprivation on these processes, but as an essential part of their successful completion. Given the growing evidence showing that sleep processes contribute to enhancing cognition, we conducted a review of the experimental studies that have examined the impact of three different types of SWS modulation on sleep and cognitive performance among individuals with psychiatric disorders.

Our review provides information regarding the potential efficacy of SWS modulation as a transdiagnostic intervention that uses sleep to improve the cognitive functions of individuals diagnosed with psychiatric disorders and cognitive deficits. Across the different studies, SWS modulation resulted in changes in SWS. Auditory stimulation increased SWS parameters in those with ADHD, depression, and mild cognitive impairment [16,61,62]. Transcranial stimulation increased SO power, enhanced power in the fast and slow spindle frequency ranges, and increased the synchronization between SO and fast spindle power. Eszopiclone increased spindle density but reduced the consistency of SO spindle timing and the SO amplitude.

This review provides partial support for the hypothesis that SWS modulation enhances memory consolidation or EFs in individuals with psychiatric disorders. For example, the study conducted in children with ADHD revealed that the working memory reaction time on the n-back task was improved following acoustic modulation of SWS compared to a sham condition; however, no significant change in procedural or declarative memory was demonstrated [16]. A study conducted in individuals with mild cognitive impairment found significant improvement in performance on visual memory (measured by picture-recognition accuracy) following transcranial stimulation compared to a sham condition, but there was no change in verbal or procedural memory [63] was evideced. The other surviving studies failed to document cognitive improvement following SWS stimulation [61,62,64].

The clinical meaning of the documented cognitive changes is unknown because none of the reviewed studies provided information or reference points regarding the clinical significance of the observed changes in cognitive functioning following SWS stimulation. Furthermore, it remains unknown if or how far these findings may be generalized to reducing cognitive impairments beyond the night of modulation or into one's daily life. Future studies should include clinically meaningful reference points, and document participants' sleep and cognitive functions for a longer period of time and/or in other contexts (e.g., work, school, and daily life).

The reviewed studies provided some support for causal associations between changes in SWS and improvement in performance on cognitive measures. Significant relationships between SO activity and overnight word recall, as well as between SWA and overnight word recall and total cognitive scores were found for individuals with mild cognitive impairment, although there was no significant difference in performance between the stimulation and sham conditions [62]. Enhanced synchronization of SOs and fast spindle power was associated with visual recognition performance following the use of transcranial stimulation in individuals diagnosed with mild cognitive impairment [63]. Eszopiclone increased spindle density in individuals diagnosed with schizophrenia, but had a negative impact on the consistency of SO spindle timing and amplitude, and did not influence procedural memory [64].

Studies conducted with healthy populations used acoustic stimulation for a minimum of 5 nights in order to improve SWS and verbal declarative memory [42,49,51,65,66]. In contrast, both studies in this review investigating the effects of auditory stimulation on cognitive outcomes of adults with psychiatric disorders provided SWS stimulation for only one session [16,62]. Given that a minimum of 5 nights of stimulation is needed in a healthy population to observe improvements, we speculate that this may also be necessary in clinical populations and could potentially explain the relative lack of significant results found here. Likewise, in the studies utilizing transcranial stimulation and eszopiclone, stimulation was provided for either a 90-minute nap or overnight, respectively [63,64]. Future studies should replicate the protocols that have used SWS modulation among healthy individuals. This would allow researchers and clinicians to better characterize the impact of SWS modulation on the cognitive functions of individuals with psychiatric disorders, and further allow for comparison with healthy populations.

Another therapeutic consideration that should be examined in future studies is the extent to which SWS modulation may benefit non-cognitive outcomes, such as symptoms that are key to the psychiatric population of interest. In the present review, only one study investigated the impact of SWS modulation on symptoms related to the disorder [61]. This study used auditory closed-loop stimulation in individuals with depression and found that there was a relationship between power density and depressive symptoms, with stimulation appearing to improve depressive symptoms. Future studies should use various stimulation techniques in clinical populations to better capture the potential positive impact of SWS modulation on other non-cognitive variables.

The inconsistent or insignificant findings found in the present review could also be explained by several methodological limitations. Firstly, the relative lack of studies that used SWS modulation with psychiatric populations constrained our ability to conduct a meta-analysis and limited our ability to draw inferences. Secondly, due to the lack of research comparing these effects within the field, we were unable to draw conclusions regarding the relative effect of such methods compared to other treatment approaches, such as using medications that improve neuroplasticity or optimize the dopamine levels in the PFC [67]. Thus, future research should include efforts to measure changes in SWS and cognitive functions. Ideally, this should also involve comparing changes in cognitive functions between and among the treatment methods, with the goal of better identifying underlying mechanisms of change and assessing how they may differ between interventions. An alternative possibility to be explored is that the changes in SWS might in fact follow from changes in performing cognitive tasks, particularly when this involves a learning phase. Thirdly, the studies included in this review did not analyze important moderating and mediating factors that could have affected the impact of SWS modulation on cognition, such as the presence of a sleep disorder, the severity and chronicity of each patient's psychiatric illness, and the stage of illness. For instance, while SWS modulation may be helpful when a person is in remission, it might not be as helpful in a different context, such as when the person is in an active phase of the disease or in relapse. Many of the psychiatric disorders included herein have comorbid primary sleep disorders [20–22,29,31,68–74], which may have hindered the impacts of SWS modulation on cognitive function. Future studies should exclude participants with sleep disorders or treat the sleep problem using evidence-based methods prior to examining the added benefit of SWS modulation. It is commonly held that randomized controlled trials (RCTs) are the gold standard of treatment evaluation. However, such trials do not necessarily provide evidence that an intervention works through the claimed mechanisms, nor do they guard against multiple other biases. The reviewed studies, including the RCTs, may have suffered from multiple methodological limitations, including the use of small samples **(**leading to underpowered analyses across conditions), the use of numerous comparative analyses and correlations without controlling for multiple comparisons, a lack of randomization (in some cases), non-reporting of randomization methods, the use of crossover designs with minimal or no washout period, and the repeated use of the same measures at baseline and in both conditions (sham and control). These limitations could have resulted in insufficient power to demonstrate significant findings, increased bias, and/or results of limited validity. Finally, the gender distributions were not equal across the studies, most of which included more than 50% males [16,61,63,64]. For the results to be generalizable, the studied sample should reflect the gender distribution of the disorder being investigated. Future research investigating SWS modulation methods will need to encompass larger sample sizes in order to fully explore the effects of each method.

Once reviewed, we next set out to examine the practicality of integrating SWS modulation methods into the clinical care of individuals with psychiatric disorders. The feasibility of an intervention can significantly impact the possibility of evidence translation [75]. We define feasibility as the cumulative impact of different influences that affect the implementation of an intervention within a specific healthcare system or practice. Several barriers are likely to hinder the feasibility of integrating SWS modulation into clinical practice, including the need to train staff to support the intervention,

the significant amount of time needed to deliver the intervention to each individual patient, the need to add professionals that are not part of the standard mental health multidisciplinary team (e.g., sleep technicians or researchers), and the need for unusual and expensive specialized equipment [76]. Characteristics of the modulation that could facilitate its integration into clinical practice include the ability to adapt it to the population(s) of interest, as well as having components of the intervention be manualized in order to help increase efficacy.

Additional issues that could affect the feasibility of the integration of SWS into clinical practice include: 1) the potential impact of psychotropic medications on its outcomes. If medication has to be discontinued in order for this intervention to be effective its applicability to individuals with psychiatric disorders may be limited. This is because they frequently need to stay on their medication in order to remain stable. 2) The nature of the intervention that requires that participants spend the night in an unfamiliar environment (i.e., sleep lab) and might need to be accompanied by staff or family members (due to inability to stay alone). Future studies should explore how to improve the feasibility of disseminating and integrating SWS modulation interventions to individuals with psychiatric disorders by developing methods allowing the use of portable polysomnography (PSG), and by designing a protocol that would allow for integration of SWS modulation into existing inpatient psychiatric units or day programs. This would increase feasibility by reducing the burden associated with having a family member/staff accompany the patient and by increasing the familiarity of the environment from the patient perspective. These modifications could potentially allow for greater dissemination, improved outcomes, and sustainability.

Conclusions

The findings of the review demonstrate that different modulation strategies have an impact on SWS outcomes across different psychiatric populations. This is an important contribution to the evolving evidence supporting a transdiagnostic approach to mental health given the overall challenge in replicating transdiagnostic findings, as well as demonstrating causal impacts of transdiagnostic constructs on outcomes. However, the reviewed studies only partially supported SWS modulation as an effective transdiagnostic intervention that can harness overarching sleep processes across different psychiatric disorders and utilize it to improve cognitive outcomes.

Our second objective was to examine the practicality of integrating SWS modulation methods into clinical care of individuals with psychiatric disorders. Several barriers presently hinder the feasibility of this therapeutic approach into clinical practice. Future studies should investigate improving the feasibility of disseminating and integrating SWS modulation interventions to individuals with psychiatric disorders

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Modulation of Slow-Wave Sleep: Implications for Psychiatry

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Abstract

Purpose of review: The objectives of this review are to examine and integrate existing empirical evidence regarding the impact of Slow Wave Sleep (SWS) modulation on memory and executive function performance in individuals with psychiatric disorders, and to examine the feasibility of integrating SWS modulation into psychiatric care.

Recent findings: SWS modulation in individuals with psychiatric disorders resulted in changes to SWS sleep across multiple psychiatric disorders, using all stimulation methods. SWS stimulation was associated with improved cognitive performance. SWS modulation using acoustic stimulation resulted in improved cognitive performance in children with ADHD, and the use of transcranial stimulation was associated with improved cognitive performance in individuals with mild cognitive impairment. Significant relationships between changes in SWS and cognitive improvement were found for individual with mild cognitive impairment following the use of acoustic or transcranial stimulation night.

Summary: Our review reveals partial support to the potential efficacy of SWS modulation as a transdiagnostic intervention that uses sleep to improve cognitive functions of individuals diagnosed with psychiatric disorders and cognitive deficits. It further highlights multiple barriers pertaining to the feasibility of integrating SWS modulation into clinical practice and proposes ways to improve it.

Keywords: Slow wave sleep; modulation; psychiatric; memory; executive function

Introduction

Memory and executive function (EF) deficits are common in individuals with psychiatric disorders across multiple diagnoses (see Table 1). Both cognitive abilities are critical for the adapting our behaviors in response to the environment, and EF skills (e.g., planning, working memory, cognitive flexibility, inhibition, reasoning, and problem-solving) [1] making them essential for daily functioning. Deficits in either of these domains result in significant and chronic impairments across social, workplace, school, and family contexts [2–5]. Identifying methods that can enhance memory and/or EFs in individuals with psychiatric disorders is necessary to improve their quality of life.

Sleep disturbances are highly comorbid with most psychiatric disorders [6,7] and have been recognized as a transdiagnostic mechanism that contributes to the symptomatology and functional disability associated with psychiatric disorders [8]. Individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression, intellectual disability, mild cognitive impairment, and schizophrenia are additionally affected from multiple sleep disturbances, including slow-wave sleep (SWS) abnormalities (see Table 1). SWS, which is also known as stage (N3) sleep, is the deepest stage of non-rapid eye movement (nREM) sleep along with N1 and N2. SWS is defined by the presence of high-amplitude electroencephalographic activity with a frequency of 0.5 to 2 Hertz (Hz). Oscillatory activity in the spindle frequency range [12-15 Hz] may also be present during SWS [9–11]. Stimulation of the frontal cortex results in induced sleep, EEG slow waves, and slow-wave activity (SWA; quantified based on the power in the delta frequency band, as assessed using power spectral analysis, which is most prominent in the frontal area) [9,12].

TABLE 1: Insert here, includes references 13-40.

The most prominent oscillations during SWS are slow wave oscillations (SO), spindles, and sharp-wave ripples. Sleep spindles are short bursts of oscillations in the 9- to 15-Hz frequency range that are generated by the thalamic reticular neurons and synchronized by corticothalamic feedback. Sharp-wave ripples, produced within the hippocampus, are higher frequency bursts that occur preferentially within the trough of the spindle [41] (for detailed information see [9]).

Recent studies have indicated that SOs during SWS causally contribute to the consolidation of declarative memories and improved EFs [42]. Increases in sleep spindles and hippocampal sharp-wave ripples occur once learning has taken place, and subsequent sleep spindle density is associated with performance on declarative verbal memory tasks [43,44]. More efficient EFs are associated with greater delta power in the first period of nREM sleep. Delta activity reflects neural synchrony within the prefrontal cortex (PFC), which is thought to enhance the cortical connections important for cognition [45–47]. High amplitude, low frequency SWA is associated with better abstract reasoning and working memory abilities in adults, highlighting the beneficial role that delta activity plays in EFs [45].

Advances made in sleep research have demonstrated that SWA can be stimulated during sleep through low-frequency stimulation and/or enhancement of the depolarized slow-wave up-state, and that such SWS/SWA modulation improves memory and EF [41,45,48]. For example, SWS can be modulated experimentally during sleep using acoustic, pharmacological, or electrical stimulation methods. Acoustic modulation refers to the use of sounds to evoke SOs and increase the magnitude of slow waves during all sleep cycles without increasing the number of total arousals. It can be provided through either open- or closed-loop stimulation. Open-loop stimulation refers to the use of sounds to evoke SOs without the sounds being synchronized with any phase of endogenous SOs; whereas closed-loop stimulation uses sounds during the peaks of SOs producing an increase in the amplitude of the ongoing wave and in fast spindle activity during the period of stimulation [9, 42, 49, 50].

[9,42,49,50]. Acoustic modulation has been shown to enhance SWS, leading to improved verbal declarative memory in healthy adults [42,49,51]. Transcranial electrical stimulation, which uses the application of electricity with direct or alternating current, has been used to enhance the duration and the power of SWS [52] and demonstrated to improve verbal declarative memory, picture recognition memory, and location memory [42,52–55] in healthy adults. Pharmacological agents have also been used to modulate SWS [42]. For example, tiagabine, sodium oxybate, and interleukin-6 have been found to increase SWS, and, according to a review article, 44.4% of these studies found that they significantly affect cognitive functioning [42,56–59].

Concurrent memory deficits, EF deficits, and SWS abnormalities are common across different psychiatric disorders. The empirical evidence highlighting the causal link between SWS and cognitive functioning raises the possibility that the modulation of SWS (e.g., by increasing SWS duration and/or slow oscillatory power/amplitude) can be used as a transdiagnostic means to improve the cognitive functioning of individuals with psychiatric populations diagnosed with co-morbid sleep disorder and memory or EF deficits, and thereby improve daytime functioning [42,60]. The objectives of this review are: 1) to examine and integrate existing empirical evidence with regards to the impact of SWS modulation on performance on memory and executive tasks for individuals with psychiatric disorders, and 2) to examine the feasibility of integrating SWS modulation therapy into psychiatric care.

Methods

A systematic search was performed in March 2020 using the MEDLINE (accessed via PubMed), CENTRAL, and EMBASE electronic databases. The criteria used included papers published from March 2017 on that used SWS enhancement methods to induce improvements in cognitive outcomes in psychiatric populations with known relevant deficits in memory, EF, cognition, and SWS (see Table 1). The full search strategies used for each database are presented in Table 2.

INSERT TABLE 2

The search terms yielded 116 articles after exclusion of studies that included non-human participants and those that were not published in English. Titles and abstracts were examined to extract potentially relevant articles, and the abstracts of the extracted articles were examined in more depth by four authors (SS, JAS, YZ, and RG). A study was excluded if it did not involve SWS modulation; if the SWS interference used was not relevant to the psychiatric disorder; or if it was a review article. The full text was retrieved if a decision could not be made based on the article abstraction.

Random search items used were a combination of key words including “slow wave sleep”, “deep sleep”, “delta sleep”, “non-REM sleep”, “nREM sleep”, “nREM3”, “slow oscilla*”, “non-rapid eye movement sleep”, “enhance*”, “boost*”, “modulation”, “closed-loop stimulation”, “acoustic stimulation”, “transcranial electric stimulation”, “pharmaceutical”, “dementia”, “mild cognitive impairment”, “intellectual impairment”, “intellectual disability”, “learning disability”, “learning disorder”, “schizophrenia”, “depression”, “major depressive disorder”, “mood disorder”, “bipolar”, “mania”, “attention deficit hyperactivity disorder”, and “ADHD” . The keywords were combined with Boolean operators ‘OR’ and ‘AND’ to broaden or narrow the search. Furthermore, we reviewed reference lists of original and review articles to search for more studies on the same topic.

Data Extraction

Data was extracted for the characteristics with respect to the trial (author, year of trial conduction, design, duration, randomization, concealment, and blinding), participants (age, gender, diagnosis, and information on other medical comorbidities), intervention (device used, duration, dosimetry, safety and follow-up), measures (sleep, cognitive, and other), and results (changes in sleep, cognition, associations between sleep and cognition, intention to treat analysis, safety, and follow-up).

Results

The literature search yielded three relevant manuscripts and two conference abstracts (see Table 3.1 and 3.2). The psychiatric populations that were investigated included children with ADHD [16] and adults diagnosed with depression [61], mild cognitive impairment [62,63], and schizophrenia [64]. No study published in the last 3 years was found for SWS modulation in individuals with bipolar disorder, intellectual disabilities, or learning disorders.

INSERT TABLES 3.1 and 3.2

The auditory stimulation protocols used in three surviving manuscripts differed in the manner the threshold for amplitude and stimulus intensity, and/or in the timing and duration of stimulation, were determined. Participants with ADHD who underwent acoustic closed-loop stimulation first had their endogenous slow oscillations detected prior to the onset of the first stimulus, which was delivered to each child’s individualized delay time [16]. The second stimulus was delivered 900 ms following the prior stimulus and stimulation stopped after 2.5s. Stimulation was provided for a total of 210 minutes of the

night [16]. In the study conducted with individuals diagnosed with depression, stimuli were delivered when the electroencephalogram (EEG) waves declined below the threshold amplitude for detecting SWS [61]. The thresholds for amplitude and stimulus intensity were determined on an individual basis. Each 30-s epoch with stimulation was preceded and followed by 30-s epochs without stimulation; and these cycles continued throughout the night [61]. Finally, in the study investigating participants diagnosed with mild cognitive impairment, acoustic pulses were targeted to 20 degrees before the peak of the up-state of an endogenous slow oscillation [62]. The stimulation occurred for 50 ms and was delivered in blocks of five, and was applied for approximately 122 minutes of the night [62]. Of the remaining studies included herein, one used transcranial stimulation applied by a battery-driven stimulator (frequency 0.75 Hz) during a single 90-minute nap session of participants mild cognitive impairment [63], and the other used one night of eszopiclone treatment in individuals diagnosed with schizophrenia [64]. The different stimulation methods had different impacts on the sleep and cognitive performance of the participants and varied in the extent to which the changed aspects in SWS were found to be related to the observed changes in cognitive performance.

Impact of different stimulation methods on sleep across different psychiatric populations

Auditory modulation. Auditory stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD [16]: increased SO, delta, slow, and fast spindle band activity; increased SO activity across fronto-central regions; and increased delta oscillation over C3 in the stimulation condition compared to the sham control. Depression [61]: increased overall EEG delta and sleep power density and improved subjective reports of sleep quality. Mild cognitive impairment [62]: 15.1% increase in SO and 11.4% increase in SWA activity during stimulation-ON intervals compared to stimulation-OFF intervals; 8.1% decrease in SO and 6.6% decrease in SWA during stimulation-OFF intervals; and a 22.2% increase in SO, 17.9% increase in SWA, and 5% increase in theta activity during the stimulation night. Schizophrenia: No study included for this population (N/A).

Transcranial stimulation. Transcranial stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: increased SO power and enhanced power in the fast and slow spindle frequency ranges; stronger synchronization between SO and fast spindle power, in particular related to increased spindle power during late-rising SO up-phases, under the stimulation condition compared to sham stimulation. Schizophrenia: N/A.

Pharmacological stimulation. Pharmacological stimulation had the following impacts on sleep across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: increased spindle density, reduced consistency of SO spindle timing, and reduced SO amplitude on eszopiclone compared to placebo in patients with schizophrenia and in controls.

Impact of SWS modulation on cognition

Auditory modulation. Auditory stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD [16]: faster reaction times in working memory performance under the stimulation condition compared to the sham condition, longer reaction times in performance of procedural memory under the sham condition compared to the stimulation condition in the ADHD group but not in the control group, and improved memory performance for rewarded word-pairs only following stimulation in the control group. Depression: N/A. Mild cognitive impairment [62,63]: no change in cognitive performance under the stimulation/sham conditions. Schizophrenia: N/A.

Transcranial stimulation. Transcranial stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: improved visual recognition performance on a picture-location recall task following a 90-minute nap, with data corrected for sleepiness as a confounding variable. Schizophrenia: N/A.

Pharmacological stimulation. Pharmacological stimulation had the following impacts on cognition across the different psychiatric populations studied. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: no change.

Associations between changes in SWS and improved cognition

Auditory modulation. ADHD [16]: no significant relationship between the increased SO activity and increase in memory performance. Depression: N/A. Mild cognitive impairment [62]: the degree to which the stimulation enhanced SWA positively correlated with overnight word recall and with total cognitive under the stimulation condition but not the sham condition.

Transcranial stimulation. ADHD: N/A. Depression: N/A. Mild cognitive impairment [63]: enhanced synchronization of SO and fast spindle power was associated with improved visual recognition performance in individuals diagnosed with mild cognitive impairment. Schizophrenia: N/A.

Pharmaceutical Stimulation. ADHD: N/A. Depression: N/A. Mild cognitive impairment: N/A. Schizophrenia [64]: on placebo but not on eszopiclone, the spindle density correlated with overnight procedural performance improvements; on eszopiclone but not on placebo, the SO amplitude predicted overnight procedural performance improvements only in individuals with schizophrenia.

Methodological characteristics of the studies

Populations. One study was conducted with school-aged children [16]; two studies were conducted with elderly adults [62,63]; and two studies used a wide age range that included a mix of younger and older adults [61,64]. One study included only male participants [16]; three studies included more males than females [61,63,64], and one study included more females than males [62]. Two of the five studies included a healthy control group [16,64]. One study included 26 participants [64]; two studies had fewer than 20 participants [16,63]; and the other two had fewer than 10 participants [61,62].

Design. All the surviving studies used a crossover design, but with different stimulation and sham/control condition intervals; they included no interval [64], 1-2 nights [61], 1 week [62], or a minimum of 2 weeks [63]. Two of the five studies used randomized crossover sham-controlled designs [62,63]; one study used a counterbalanced design and did not report on blinding [61]; and three studies used a pre-post design with no control group [61–63]. Of the studies that randomized the participants to the sham or stimulation group, none provided information regarding the methods used for randomization, sequence allocation, or concealment.

Blinding. Four of the five studies reported blinding participants to their assigned condition [16,62–64]. Of these, two blinded the sleep technician that scored participants' sleep [16,62]; two blinded the experimenter [16,64]; and none blinded the cognitive outcome assessment.

Control condition. All of the studies included a sham or placebo condition, with all individuals participating in both the sham/placebo condition and the stimulation condition [16,61–64]. Two studies also used healthy control participants [16,64].

Inclusion/exclusion criteria. One study reported having participants with psychiatric comorbidity in addition to the main disorder of interest (ADHD and oppositional defiant disorder or ADHD and conduct disorder) [16]; one study excluded participants with a psychiatric comorbidity [63]; and the other three did not report on psychiatric comorbidity [61,62,64]. Two studies excluded participants with a medical comorbidity [16,63], whereas the other three studies did not report on medical comorbidity [61,62,64]. One study excluded participants with a sleep disorder [63], one study excluded participants who had moderate-to-severe sleep apnea [62], one study excluded participants who had scores above the critical level on two subjective measures (Sleep-Self Report and Children Sleep Habits Questionnaire) [16], and two studies did not report on sleep [61,64].

Intention to treat analyses (ITAs). Two studies reported participant drop-outs, with rates of 11% and 27% [61,63]. None of the included studies reported any ITA.

Pragmatic characteristics of the studies

Number and duration of sessions. All the studies included a one-time exposure to the given stimulation method, with a stimulation duration ranging from 90 minutes to 1 night.

Location of sessions. All studies had participants sleeping in a sleep laboratory.

Need to be off medication. Two studies reported excluding participants on medication [62,63]; one study asked participants to discontinue medication 48h prior to the experiment [16]; one study reported that participants were medicated [64], and one study did not report on medication [61].

Logistics. None of the studies provided information regarding the logistics associated with preparing, instructing, or assisting participants in getting ready, arriving at, or staying in the sleep laboratory; the level of independence required; or any barrier related to such logistical challenges.

Use of specialized equipment/staff. All of the studies required access to specialized equipment and software, as well as highly qualified personnel that can deliver the stimulation with precise timing related to the onset of SWS, and score micro and macro sleep architecture during [63] or after [16,61,62,64] the experiment.

Safety. None of the studies reported any documented side effect, potential harm, or level of patients' inconvenience related to participating in the experiments.

Discussion

One of the most important recent discoveries in cognitive and sleep sciences involves the realization that sleep affects cognitive processes not just as a result of the negative impact of sleep deprivation on these processes, but as an essential part of their successful completion. Given the growing evidence showing that sleep processes contribute to enhancing cognition, we conducted a review of the experimental studies that have examined the impact of three different types of SWS modulation on sleep and cognitive performance among individuals with psychiatric disorders.

Our review provides information regarding the potential efficacy of SWS modulation as a transdiagnostic intervention that uses sleep to improve the cognitive functions of individuals diagnosed with psychiatric disorders and cognitive deficits. Across the different studies, SWS modulation resulted in changes in SWS. Auditory stimulation increased SWS parameters in those with ADHD, depression, and mild cognitive impairment [16,61,62]. Transcranial stimulation increased SO power, enhanced power in the fast and slow spindle frequency ranges, and increased the synchronization between SO and fast spindle power. Eszopiclone increased spindle density but reduced the consistency of SO spindle timing and the SO amplitude.

This review provides partial support for the hypothesis that SWS modulation enhances memory consolidation or EFs in individuals with psychiatric disorders. For example, the study conducted in children with ADHD revealed that the working memory reaction time on the n-back task was improved following acoustic modulation of SWS compared to a sham condition; however, no significant change in procedural or declarative memory was demonstrated [16]. A study conducted in individuals with mild cognitive impairment found significant improvement in performance on visual memory (measured by picture-recognition accuracy) following transcranial stimulation compared to a sham condition, but there was no change in verbal or procedural memory [63] was evideced. The other surviving studies failed to document cognitive improvement following SWS stimulation [61,62,64].

The clinical meaning of the documented cognitive changes is unknown because none of the reviewed studies provided information or reference points regarding the clinical significance of the observed changes in cognitive functioning following SWS stimulation. Furthermore, it remains unknown if or how far these findings may be generalized to reducing cognitive impairments beyond the night of modulation or into one's daily life. Future studies should include clinically meaningful reference points, and document participants' sleep and cognitive functions for a longer period of time and/or in other contexts (e.g., work, school, and daily life).

The reviewed studies provided some support for causal associations between changes in SWS and improvement in performance on cognitive measures. Significant relationships between SO activity and overnight word recall, as well as between SWA and overnight word recall and total cognitive scores were found for individuals with mild cognitive impairment, although there was no significant difference in performance between the stimulation and sham conditions [62]. Enhanced synchronization of SOs and fast spindle power was associated with visual recognition performance following the use of transcranial stimulation in individuals diagnosed with mild cognitive impairment [63]. Eszopiclone increased spindle density in individuals diagnosed with schizophrenia, but had a negative impact on the consistency of SO spindle timing and amplitude, and did not influence procedural memory [64].

Studies conducted with healthy populations used acoustic stimulation for a minimum of 5 nights in order to improve SWS and verbal declarative memory [42,49,51,65,66]. In contrast, both studies in this review investigating the effects of auditory stimulation on cognitive outcomes of adults with psychiatric disorders provided SWS stimulation for only one session [16,62]. Given that a minimum of 5 nights of stimulation is needed in a healthy population to observe improvements, we speculate that this may also be necessary in clinical populations and could potentially explain the relative lack of significant results found here. Likewise, in the studies utilizing transcranial stimulation and eszopiclone, stimulation was provided for either a 90-minute nap or overnight, respectively [63,64]. Future studies should replicate the protocols that have used SWS modulation among healthy individuals. This would allow researchers and clinicians to better characterize the impact of SWS modulation on the cognitive functions of individuals with psychiatric disorders, and further allow for comparison with healthy populations.

Another therapeutic consideration that should be examined in future studies is the extent to which SWS modulation may benefit non-cognitive outcomes, such as symptoms that are key to the psychiatric population of interest. In the present review, only one study investigated the impact of SWS modulation on symptoms related to the disorder [61]. This study used auditory closed-loop stimulation in individuals with depression and found that there was a relationship between power density and depressive symptoms, with stimulation appearing to improve depressive symptoms. Future studies should use various stimulation techniques in clinical populations to better capture the potential positive impact of SWS modulation on other non-cognitive variables.

The inconsistent or insignificant findings found in the present review could also be explained by several methodological limitations. Firstly, the relative lack of studies that used SWS modulation with psychiatric populations constrained our ability to conduct a meta-analysis and limited our ability to draw inferences. Secondly, due to the lack of research comparing these effects within the field, we were unable to draw conclusions regarding the relative effect of such methods compared to other treatment approaches, such as using medications that improve neuroplasticity or optimize the dopamine levels in the PFC [67]. Thus, future research should include efforts to measure changes in SWS and cognitive functions. Ideally, this should also involve comparing changes in cognitive functions between and among the treatment methods, with the goal of better identifying underlying mechanisms of change and assessing how they may differ between interventions. An alternative possibility to be explored is that the changes in SWS might in fact follow from changes in performing cognitive tasks, particularly when this involves a learning phase. Thirdly, the studies included in this review did not analyze important moderating and mediating factors that could have affected the impact of SWS modulation on cognition, such as the presence of a sleep disorder, the severity and chronicity of each patient's psychiatric illness, and the stage of illness. For instance, while SWS modulation may be helpful when a person is in remission, it might not be as helpful in a different context, such as when the person is in an active phase of the disease or in relapse. Many of the psychiatric disorders included herein have comorbid primary sleep disorders [20–22,29,31,68–74], which may have hindered the impacts of SWS modulation on cognitive function. Future studies should exclude participants with sleep disorders or treat the sleep problem using evidence-based methods prior to examining the added benefit of SWS modulation. It is commonly held that randomized controlled trials (RCTs) are the gold standard of treatment evaluation. However, such trials do not necessarily provide evidence that an intervention works through the claimed mechanisms, nor do they guard against multiple other biases. The reviewed studies, including the RCTs, may have suffered from multiple methodological limitations, including the use of small samples **(**leading to underpowered analyses across conditions), the use of numerous comparative analyses and correlations without controlling for multiple comparisons, a lack of randomization (in some cases), non-reporting of randomization methods, the use of crossover designs with minimal or no washout period, and the repeated use of the same measures at baseline and in both conditions (sham and control). These limitations could have resulted in insufficient power to demonstrate significant findings, increased bias, and/or results of limited validity. Finally, the gender distributions were not equal across the studies, most of which included more than 50% males [16,61,63,64]. For the results to be generalizable, the studied sample should reflect the gender distribution of the disorder being investigated. Future research investigating SWS modulation methods will need to encompass larger sample sizes in order to fully explore the effects of each method.

Once reviewed, we next set out to examine the practicality of integrating SWS modulation methods into the clinical care of individuals with psychiatric disorders. The feasibility of an intervention can significantly impact the possibility of evidence translation [75]. We define feasibility as the cumulative impact of different influences that affect the implementation of an intervention within a specific healthcare system or practice. Several barriers are likely to hinder the feasibility of integrating SWS modulation into clinical practice, including the need to train staff to support the intervention,

the significant amount of time needed to deliver the intervention to each individual patient, the need to add professionals that are not part of the standard mental health multidisciplinary team (e.g., sleep technicians or researchers), and the need for unusual and expensive specialized equipment [76]. Characteristics of the modulation that could facilitate its integration into clinical practice include the ability to adapt it to the population(s) of interest, as well as having components of the intervention be manualized in order to help increase efficacy.

Additional issues that could affect the feasibility of the integration of SWS into clinical practice include: 1) the potential impact of psychotropic medications on its outcomes. If medication has to be discontinued in order for this intervention to be effective its applicability to individuals with psychiatric disorders may be limited. This is because they frequently need to stay on their medication in order to remain stable. 2) The nature of the intervention that requires that participants spend the night in an unfamiliar environment (i.e., sleep lab) and might need to be accompanied by staff or family members (due to inability to stay alone). Future studies should explore how to improve the feasibility of disseminating and integrating SWS modulation interventions to individuals with psychiatric disorders by developing methods allowing the use of portable polysomnography (PSG), and by designing a protocol that would allow for integration of SWS modulation into existing inpatient psychiatric units or day programs. This would increase feasibility by reducing the burden associated with having a family member/staff accompany the patient and by increasing the familiarity of the environment from the patient perspective. These modifications could potentially allow for greater dissemination, improved outcomes, and sustainability.

Conclusions

The findings of the review demonstrate that different modulation strategies have an impact on SWS outcomes across different psychiatric populations. This is an important contribution to the evolving evidence supporting a transdiagnostic approach to mental health given the overall challenge in replicating transdiagnostic findings, as well as demonstrating causal impacts of transdiagnostic constructs on outcomes. However, the reviewed studies only partially supported SWS modulation as an effective transdiagnostic intervention that can harness overarching sleep processes across different psychiatric disorders and utilize it to improve cognitive outcomes.

Our second objective was to examine the practicality of integrating SWS modulation methods into clinical care of individuals with psychiatric disorders. Several barriers presently hinder the feasibility of this therapeutic approach into clinical practice. Future studies should investigate improving the feasibility of disseminating and integrating SWS modulation interventions to individuals with psychiatric disorders

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Table 1. Slow wave sleep (SWS) and cognitive deficits in individuals with psychiatric disorder in comparison to healthy individuals

Psychiatric Disorder	SWS characteristics	Cognitive Deficits
ADHD (13–18)	Adults • No differences found in SWS percentage or duration Youth • Mixed evidence regarding whether SWS percentage is lower or the same • No difference in SWS duration • SWA increased in centro-parietal-occipito brain regions	• Executive functions (*) Decision-making Fluency Planning Reaction time and variability Response inhibition Selective attention Set shifting Vigilance • Working memory (**) • Declarative memory (**) • Procedural memory (**)
Bipolar Disorder (6,19,20)	Adults: • Shorter SWS duration per night Youth: • Longer SWS latency (duration)	Euthymic state: • Language • Psychomotor speed • Executive functions (*) Attention Problem-solving Verbal interference Set-switching Working memory • Declarative memory (*) Verbal memory Non-verbal memory Manic state: • Language (letter fluency and semantic fluency) • Visual scanning • Executive functions (*) Speeded set-shifting Perseveration • Declarative memory (*) Verbal memory Depressed state: • Verbal fluency
Depression (6,19,21–26)	Adults: • Lower amplitude delta power • Shorter time spent in SWS (percentage and minutes) per night • Decreased SWA time in first sleep cycle	• Concentration • Motivation • Executive functions (*) Attention Processing speed Inhibition

	Youth: • Shift of SWS from 1st to 2nd sleep cycle • Decreased delta sleep ratio (ratio of average slow wave counts per minute in first NREM sleep stage to the average counts per minutes in the second NREM sleep stage), reflecting abnormal slow wave homeostatic regulation	Problem-solving Planning • Declarative memory (*) Verbal memory
Intellectual Disability Costello syndrome, Angelman syndrome, Prader-Willi syndrome, Fragile X syndrome, Smith-Magenis syndrome, Rett syndrome (27–30)	• Depending on the disorder, alterations of sleep spindles are observed consisting of being either reduced (in number, activity), absent, or extremely increased (in number, activity) • Higher in SWS percentage • SWS significantly higher bursts (1-3HZ)	• Declarative memory (*) Verbal memory Visuospatial memory Phonological memory • Retrieval/recognition of complex information • Executive functions (*) Inhibition Shifting Emotional control Initiation Working memory Planning Organization Monitoring Decision-making Problem solving Selective attention Sustained attention Divided attention
Mild Cognitive Impairment (31–36)	• Lower SWS percentage, delta and theta power during NREM • Lower spindle density	• Declarative memory (**) Episodic memory Visuospatial memory (**) Verbal memory (**) • Procedural memory (**) • Executive functions (*) Attention Working memory Planning Problem solving
Schizophrenia (37–40)	• Inconsistent evidence regarding whether SWA is lower or the same • Lower spindle power, amplitude, duration, and quantity	• Executive functions (*) Planning Working memory Processing speed • Declarative memory (*) Verbal memory • Verbal fluency • Procedural memory (**)

This table presents a summary of SWS abnormalities and a summary of cognitive deficits with or without relation to SWS documented across multiple empirical studies. All studies conducted compare the psychiatric group to a healthy control group, unless otherwise stated. (*) represents cognitive deficits related to SWS (**) represents cognitive deficits that have been studied with regards to SWS modulation.		

Table 2
Search strategies used for each database

1. Topic: “slow wave sleep” OR “deep sleep” OR “delta sleep” OR “non-REM sleep” OR “nREM sleep” OR “nREM3” OR “slow oscilla* OR “non-rapid eye movement sleep”
2. Topic: “enhance*” OR “boost*” OR “modulation” OR “closed-loop stimulation” OR “acoustic stimulation” OR “transcranial electric stimulation” OR “pharmaceutical”
3. Topic: “dementia” OR “mild cognitive impairment”
4. Topic: “intellectual impairment” OR “intellectual disability” OR “learning disability” OR “learning disorder”
5. Topic: “schizophrenia”
6. Topic: “depression” OR major depressive disorder”
7. Topic: “mood disorder” OR “bipolar” OR “mania”
8. Topic: “attention deficit hyperactivity disorder” OR “ADHD”
9. (#1 AND #2 AND #3) OR (#1 AND #2 AND #4) OR (#1 AND #2 AND #5) OR (#1 AND #2 AND #6) OR (#1 AND #2 AND #7) OR (#1 AND #2 and #8)

Table 3.1. Summary of included papers: population, stimulation type and details, and study design.

Study	Population Studied	Gender	Age	Diagnosis	Stimulation Type	Intervention Details	Study Design	Control	Interval between conditions	Intention to Treat Analysis?
Prehn-Kristensen et al. (2020) (16)	14 children diagnosed with ADHD, 15 healthy matched controls	100% male	ADHD: *M* = 10.2 years, *SD* = 0.4 years; Control: *M* = 11.1 years, *SD* = 0.4 years	Kiddie-SADS-PL; DSM-IV-TR	Acoustic	One overnight session of 210 minutes of stimulation presented through in-ear headphones (50ms pulses of pink noise [1/f])	Non-randomized, double-blind placebo-controlled	Sham	NR	No
Papalambros et al. (2019) (62)	9 individuals diagnosed with mild cognitive impairment	44% male	Range: 62-86 years, *M* = 72 years, *SD* = 8.7 years.	Changes in cognition compared to previous level among cognitive domains; preserved independence in functional activities; no impairment in social/occupation functioning.	Acoustic	One overnight session of 122 minutes of stimulation presented through flat headphones (50ms pulses of pink noise [1/f]).	Randomized, blinded crossover sham-controlled	Sham	1 week apart	No
Danilenko et al. (2019) (61)	7 individuals diagnosed with depression	71% male	Range: 21-68 years; no other information provided	NR	Acoustic	One overnight session of stimulation (time not reported) presented through miniaturized	Placebo-controlled, crossover	Sham	1-2 nights	Yes

						headphones (50ms pulses of pink noise [1/f]).				
Ladenbauer et al. (2017) (63)	16 individuals diagnosed with mild cognitive impairment	56% male	Range: 53-81 years, *M*: 71 years, *SD*: 9 years	Mayo Clinic criteria of subjective complaints; Alzheimer's Disease test battery; German version of Auditory Verbal Learning Test.	Transcranial	One 90-minute nap session of stimulation applied by a battery-driven stimulator (frequency 0.75 Hz).	Randomized, crossover sham controlled	Sham	Minimum 2 weeks	Yes
Mylonas et al. (2019) (64)	26 individuals diagnosed with schizophrenia, 29 healthy matched controls	81% male	*M*: 32 years, *SD*: 8 years; no other information provided	NR	Pharmacological	Eszopiclone, one night (dosage not reported).	Non-randomized, double-blind placebo-controlled crossover	Placebo	Consecutive nights	No
Notes: DSM-IV-TR: Diagnostic and Statistical Manual, fourth edition, text revision. Kiddie-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime. NR: not reported.										

Table 3.2. Summary of included papers: randomization, blinding, and results

Study	Randomized	Randomization Method	Blinding					Sleep	Cognitive	Change			Association between changes in sleep and cognition
			A	B	C	D	E			SWS	Other Sleep	Cognition	
Prehn-Kristensen et al. (2020) (16)	N	N	Y	Y	Y	Y	N	PSG	Declarative memory: unrelated word-pairs. Procedural motor memory: Serial Reaction Time task; Working Memory: *n*-back task.	Increased oscillatory activity in SO; increased delta, slow, and fast band activity [Values not reported; stats: (SO: $F_{(1,27)}$ = 31.7, p < .001; delta: $F_{(1,27)}$ = 5.1, p = .033; slow spindle: $F_{(1,27)}$ = 11.4, p = .002; fast spindle: $F_{(1,27)}$ = 22.7, p < .001)].	Increased nREM2 sleep (ADHD vs HC: 236.8 +/- 10.05 vs. 269.1 +/- 9.87 minutes; p = 0.11)	Working memory reaction time on n-back task was faster for children with ADHD after stimulation (vs. after sham) [786 +/- 57.7 vs. 889 +/- 71.1; p = 0.017]	Not Examined
Papalambros et al. (2019) (62)	Y	N	N	Y	N	Y	N	PSG; self-report questionnaire assessing sleep quality and alertness (measures not named).	Declarative memory - verbal paired-associate test, NIHTCB to assess working memory, picture memory,	Within-night effects of stimulation were examined by comparing changes in on compared to off intervals. Increased SO by approximately 15% and SWA by	No significant differences in spindle characteristics, or self-reported sleep quality.	Overnight change performance better in stim condition but not significant [stim: 1.4 (0.4), sham 0.11 (1.3), p=0.56]. Morning	Positive correlation between overnight word recall (r=0.78, p=.012), SO activity (4=.072, p=.029), sigma power (r=0.72, p=.028), with the degree to

									language, and executive attention.	approximately 11% in stimulation ON condition ($p<.001$), trend for increase in SWA during ON intervals throughout first four cycles of sleep (condition: $p=.005$, cycle: $p<.001$, condition*cycle: $p=.070$), re-organization of power in which stimulation resulted in SWA enhancement during ON intervals followed by reduction in OFF intervals with no net effect on NREM SWA.		NIHTB scores were the same between conditions.	which stimulation enhanced SWA in ON vs OFF intervals. Amount of stimulation based SWA increase also correlated with NIHTB total cognitive scores in stimulation condition ($r=0.75$, $p=.031$). No associations found between word recall and spindle characteristics or sleep macrostructure in either conditions.
Danilenko et al. (2019) (61)	N	N	N	N	N	N	N	PSG, HDRS-7-SR (sleep quality), and LSEQ.	NA	Acoustic stimulation led to increased delta sleep power density (frequency bands: 0.5-2.5), statistics not provided.	Greater overnight power density associated with improvement on wakening subscale of LSEQ.	NA	Greater overnight power density associated with decreased depressive symptoms ($p <$ .02).

Ladenbauer et al. (2017) (63)	Y	N	N	Y	N	N	N	Actigraphy, sleep diaries, questionnaires of sleep habits (German version of Morningness-Eveningness-Questionnaire), sleep quality (Pittsburgh Sleep Quality Index), daytime sleepiness (Epworth Sleepiness Scale) and the Essen questionnaire on age and sleepiness.	Visuospatial memory: yes/no recognition task, including picture memory and location memory; verbal memory: associative word pair recall task; procedural memory: sequential finger tapping task.	Increased SO in stimulation condition in frontal (d = 1.16, p < .001) and centroparietal (d = .70, p = .006). Increase fast spindle power in stimulation condition (frontal: d = 1.02, p < .001; centroparietal: d = .50, p=.041). Increased frontal slow spindle power after stimulation (d=0.82, p=.001). Enhanced slow oscillatory-to-spindle coupling, and amplified spindle power during depolarizing slow-oscillation up-phase.	During 1 min stimulation-free intervals, significant difference in nREM2 (p = .021), where percentage increased after stimulation. Wake time after sleep onset and NREM1 was reduced (p = .062 and p = .091).	Significant improvement from stimulation on picture recognition accuracy (visual memory; p=.039, n2= 0.308); no significant differences on location retrieval performance, verbal memory, procedural memory.	Visual memory performance was associated with synchronization between SO and fast spindle power (values not reported)
Mylonas et al. (2019) (64)	N	N	Y	Y	Y	N	N	PSG	Procedural memory	Eszopiclone led to increased spindle density (p < .001), reduced consistency of SO-spindle timing (p <	NR	Eszopiclone did not lead to a significant improvement on procedural memory in individuals	SO amplitude predicted overnight procedural memory improvement, only in individuals

									.001), and reduced SO amplitude (p < .001).		with schizophrenia (p = .05)	with schizophrenia, when taking eszopiclone (amplitude by group interaction: p = .04; schizophrenia: r = .44, p = .03).
Notes: Blinding: A – blinding of personnel; B – blinding of participants; C – blinding of participants and personnel; D – blinding of sleep scoring; E – blinding of cognitive assessment; ADHD: attention deficit/hyperactivity disorder; HDRS-7-SR: Hamilton Rating Scale for Depression, 7 items, short form; HC: healthy control; LSEQ: Leeds Sleep Evaluation Questionnaire; NIHTCB: National Institutes of Health Toolbox Cognitive Battery; NREM1: stage 1 non-rapid eye movement; NREM2: stage 2 non-rapid eye movement; PSG: polysomnography; SWA: slow wave activity; SWS: slow wave sleep. NA: not applicable. NR: not reported. Studies had no follow up period and did not examine safety (harm) outcomes.												

COI Gruber

COI Zhang

COI Santiseban

COI Bertone

COI Scholes