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Targeting Arousal and Sleep through Noninvasive Brain Stimulation to Improve Mental Health

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Abstract
Arousal and sleep represent fundamental physiological domains, and alterations in the form of insomnia (difficulty falling or staying asleep) or hypersomnia (increased propensity for falling asleep or increased sleep duration) are prevalent clinical problems. Current first-line treatments include psychotherapy and pharmacotherapy. Despite significant success, a number of patients do not benefit sufficiently. Progress is limited by an incomplete understanding of the neurobiology of insomnia and hypersomnia. This work summarizes current concepts of the regulation of arousal and sleep and its modulation through noninvasive brain stimulation (NIBS), including transcranial magnetic, current, and auditory stimulation. Particularly, we suggest: (1) characterization of patients with sleep problems – across diagnostic entities of mental disorders – based on specific alterations of sleep, including alterations of sleep slow waves, sleep spindles, cross-frequency coupling of brain oscillations, local sleep-wake regulation, and REM sleep and (2) targeting these with specific NIBS techniques. While evidence is accumulating that the modulation of specific alterations of sleep through NIBS is feasible, it remains to be tested whether this translates to clinically relevant effects and new treatment developments.
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Introduction

Animals and humans, on average, spend about one third of their life asleep. Proposed evolutionary advantages of this state include critical functions for the brain, such as metabolic clearance [1] and neural network organization [2]. On a higher level, sleep modulates behavior, cognition, and emotion [3]. The importance of sleep is also evident with regard to mental health. Particularly, disturbances of arousal and sleep are highly prevalent in patients with mental disorders and represent a transdiag-

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nostic, rather than a disorder-specific, dimension of psychopathology [3]. Beyond this descriptive level, preliminary evidence suggests that targeting arousal and sleep might represent an efficient therapeutic approach to improve mental health.

To date, the first-line treatment for insomnia (difficulty falling or staying asleep) is cognitive-behavioral therapy for insomnia (CBT-I) [4]. This treatment has shown considerable success, and currently a number of activities promoting the implementation and dissemination of CBT-I are underway [5]. Medications for insomnia include benzodiazepines and benzodiazepine-receptor agonists as well as sedating antidepressants and antipsychotics. However, these medications show limited efficacy and side effects, including the risk of tolerance and dependency for benzodiazepines or benzodiazepine-receptor agonists and various side effects for antidepressants and antipsychotics. The first-line treatment for hypersomnia (increased propensity for falling asleep or increased sleep duration) is medication, primarily stimulants, with limited success and adverse side effects.

Recent work suggests that arousal and sleep can be modulated through different types of noninvasive brain stimulation (NIBS). The aim of the present work is to discuss new ways of using NIBS to modulate arousal and sleep to potentially improve mental health. First, relevant aspects of the physiology of arousal and sleep, and current approaches of their modulation through NIBS will be discussed. As a novel aspect of the present work, we propose characterization of patients with mental disorders along the dimension of insomnia and hypersomnia (across diagnostic entities) and more fine-graded alterations of sleep, with the idea of targeting these with specific NIBS techniques. This latter part presents, in the absence of clinical studies, a potential outline for future work.

Sleep Physiology

Sleep in mammals, including humans, is characterized by cyclic alterations of 2 major brain states, i.e., non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Neural networks that regulate arousal and sleep comprise a bottom-up (from the brainstem to the cortex) pathway and a top-down (corticothalamic) pathway. The bottom-up pathway emerges from the ascending reticular arousal system (ARAS) and activates the cortex via well-characterized thalamic and nonthalamic pathways through cholinergic and aminergic neurotransmission. The bottom-up pathway represents the leverage point for pharmaceutical interventions [6]. It is complemented by a corticothalamic top-down pathway, which appears to be modifiable through NIBS techniques [6].

More specifically, the transition from wakefulness to NREM sleep is characterized by progressive deactivation of the ARAS, a reduction of activity in broad areas of the brain, and the emergence of cortical slow oscillations (1 Hz). Slow oscillations, via corticothalamic connections, orchestrate other sleep-specific oscillations including low-frequency high-amplitude δ waves (1–4 Hz), resulting from an alteration of hyperpolarized down- and depolarized up-states of the cortex, and sleep spindles (12–16 Hz), both characteristic for NREM sleep. Slow oscillations, δ waves, and sleep spindles have been related to important functions of sleep, such as neural development, sensory processing, and synaptic plasticity [7]. REM sleep is characterized by a selective activation of the cholinergic component of the ARAS (along with a persistent deactivation of the aminergic component), resulting in a relative activation of some brain areas, including the limbic (emotional) system and electroencephalographic (EEG) activation similar to wakefulness along with a persistent deactivation of other areas, such as frontal cortical areas. This paradoxical brain activation pattern might generate the REM sleep-related perception of vivid emotional and sometimes bizarre experiences (limbic activation) along with reduced cognitive control and consciousness (frontal deactivation).

NIBS for Modulation of Arousal and Sleep

The development of NIBS techniques offers the possibility to target the top-down pathway and, presumably, to modulate arousal and sleep. The following section provides an overview of the use of different NIBS techniques in the context of arousal and sleep with a focus on transcranial magnetic stimulation (TMS), transcranial current stimulation and auditory stimulation.

TMS induces a magnetic field that passes through the skull and modifies cortical activity [8]. Stimuli can be single or repetitive pulses. TMS can be suprathreshold, directly inducing action potentials, or subthreshold, only modulating excitability. TMS can be used to trigger specific oscillations, such as sleep slow waves and sleep spindles [9]. However, TMS during sleep requires a complex setup and is currently of limited relevance for therapeutic application. At this point, it is rather a research method contributing to the understanding of sleep and arousal mechanisms [6].

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Transcranial current stimulation applies a weak electric current to the scalp. The applied current is not strong enough to directly induce neural firing. Rather, it induces local shifts in cortical excitability and the probability of generating action potentials [10–12]. These effects can extend to connected neural networks [13, 14]. The most common protocols are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). During tDCS, a constant current flows from one electrode to another and the excitability of the targeted cortical area is shifted in a certain direction. In general, anodal stimulation exhibits excitatory, while cathodal stimulation exhibits inhibitory effects [15]. The effects of tDCS primarily depend on the polarity, position, and duration of the application [16]. In contrast, during tACS, the flow of electric charges periodically reverses its direction from anodal to cathodal polarity. Note that oscillatory stimulation can also be induced via rhythmically waxing and waning direct current stimulation (transcranial oscillatory direct current stimulation; tODCS). In vitro studies have shown that the rhythmic stimulation of tODCS or tACS can entrain fluctuations of excitability at the applied frequency in the underlying neural tissue [12]. Evidence in humans for changes in phase-dependent excitability during tACS has recently been provided by phase-dependent motor evoked potentials [17–19] and phase-dependent TMS-evoked potentials measured from the scalp [20]. Several studies have demonstrated that tDCS has the potential to modulate aspects of arousal and sleep. For instance, tODCS in the EEG δ frequency range during slow-wave sleep increased δ activity and improved sleep-related declarative memory consolidation [21]. Moreover, a repetitive anodal tDCS protocol applied bilaterally to the frontal cortex prior to sleep increased indices of arousal during wakefulness (high-frequency resting-state EEG power) and reduced the total sleep time in healthy humans [22] as well as in a patient with hypersomnia [23], but not in patients with insomnia [24], which is indicative for brain state-dependent effects of the protocol. In contrast to TMS, transcranial current stimulation is easy to apply, even in a home setting, with only minor side effects when using protocols within standard safety limits [6]. However, a major disadvantage is that transcranial current stimulation leads to considerable artifacts in EEG recordings, which limits the investigation of direct effects on sleep. Moreover, the exact mechanisms and the reliability of effects are currently under debate [e.g., 25].

Auditory stimulation uses tones to modify cortical activity. In principle, all senses, including vision, hearing, scent [26], and touch, can be used for sensory stimulation [6], yet in humans auditory stimulation appears to be particularly well suited to modulate sleep. More specifically, auditory stimulation is the most reliable way to induce single slow oscillations (K-complexes) in humans [27–29]. Moreover, the auditory system is most sensitive to monitoring the environment and detecting threats during sleep [30]. By contrast, in animals like rodents, this sentinel role may be also played by the olfactory system, which may explain why olfactory stimuli are particularly effective in inducing slow waves in rodents [31, 32]. Recently, the rhythmic presentation of auditory stimuli (clicks) synchronized to the peaks (up-states) of slow waves (closed-loop setting) has been demonstrated to entrain slow waves and to increase the consolidation of declarative memories formed before sleep [33]. Other protocols, such as stimulation in the down-states, are currently being investigated. The technique seems to be well tolerated and promising for further deciphering of sleep mechanisms. However, it remains to be further clarified whether induced slow waves indeed show the same or similar physiological properties, for instance with regard to travelling, homeostatic aspects, underlying neural activity patterns, or molecular processes, and the same or similar potential functions, such as synaptic refinements, as intrinsic slow waves. Moreover, the potential clinical utility remains to be investigated.

Psychiatry Is Changing

To date, patients suffering from mental disorders are categorized according to diagnoses of the International Classification of Diseases of the World Health Organization (ICD, 10th edition) or the American Diagnostic and Statistical Manual (DSM, 5th edition). Diagnoses are established based on a set of clinical symptoms, observable over a defined period of time. Strengths of this categorical ICD/DSM approach include standardization of the diagnostic process, a high reliability of diagnoses, and a high practicability for clinicians. However, disadvantages comprise a high heterogeneity of psychopathology within diagnostic categories and limited utility for further revealing the neural mechanisms of clinical complaints. This is thought to limit the development of more individualized and, potentially, more effective treatments [34].

A potential solution is a shift from today's categorical diagnostic process to a dimensional approach, which might better reveal the neurobiological underpinnings of the clinical symptomatology. In this vein, the American National

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Institute of Mental Health (NIMH) has proposed a domain-based approach for the investigation of mental health problems. This approach is called Research Domain Criteria (RDoC) and its goal is to integrate different levels of information (from genetics to behavior) to improve our understanding of the neurobiology of mental health problems. While the ICD/DSM systems center on the description of complex clinical syndromes, which are unlikely to share a common neurobiology, the RDoC approach centers on defined domains of behavior, which are thought to map to identifiable neural mechanisms. It is important to note that RDoC has primarily been developed for research purposes, not as an immediate replacement of ICD/DSM in clinical practice. Specifically, it proposes a framework for future research based on 5 domains of human behavior and functioning: negative and positive valence systems, cognitive systems, social processes, and arousal/regulatory systems. The current work centers on the domain arousal/regulatory systems, particularly on arousal and sleep.

Sleep and Mental Disorders

Most patients with mental disorders experience problems sleeping, yet these problems can differ substantially within one diagnostic group. Sleeping problems can, in a first step, be classified as difficulty falling or staying asleep (insomnia) or excessive sleepiness (hypersomnia) (Fig. 1).

For decades, the clinical treatment for sleep problems has been typically based on the sleep complaint and not on the diagnostic entity of a mental disorder. For instance, insomnia is treated with cognitive behavioral interventions or hypnotics across diagnostic groups. This is an example of a longstanding transdiagnostic approach in clinical practice. However, progress is hampered by limited insights into the underlying neurobiology of insomnia and hypersomnia and, respectively, by a poor translation of such insights into clinical practice. The following section aims to move one step in that direction. Particularly, we propose characterization of sleep on a brain oscillation level to inform the development of new and more individualized treatment options.

Insomnia

Insomnia is defined by difficulty falling asleep or maintaining sleep or premature early morning awakening. Many patients with mental disorders – across diagnoses – suffer from insomnia, including for instance those with posttraumatic stress disorder (PTSD), anxiety disorder, or major depression [3].

The current first-line treatment is CBT-I, as supported by meta-analyses and reflected in all current guidelines [4, 35]. CBT-I has proven effective in the majority, but not all patients. Benzodiazepines and benzodiazepine receptor agonists, which are among the most widely prescribed drugs worldwide, are effective for short-term use but interfere with relevant sleep functions, such as synaptic refinements [36], and, importantly, are often associated with tolerance effects and the development of dependency. Other medications for insomnia include sedative antidepressants or antipsychotics, which are associated with various side effects [37]. There is, to date, a certain level of stagnation in the development of new treatments, which might be overcome through a better neurobiological characterization of insomnia.

Basic scientific work over the past decades indicates that insomnia is characterized by persistent (24 h) hyperarousal as a final common pathway [38, 39], as indicated, for instance, by decreased slow-wave sleep, increased fast-frequency (EEG β range) power during NREM sleep [40], and increased indices of local wakefulness during sleep [41]. However, these studies show a substantial variance across patients with insomnia and it appears to be important to further characterize individual alterations of sleep. The following paragraphs discuss how specific alterations of sleep might inform new treatment developments (Fig. 1).

Sleep Slow Oscillations. Slow-wave sleep has been shown to be reduced in at least some patients with insomnia compared to controls [42]. Several NIBS techniques have been demonstrated to increase slow oscillations, and it is plausible, although it has not been demonstrated, that increasing slow oscillations might improve the complaint of nonrestorative sleep and potentially thereby related daytime complaints. Particularly, decreased slow-wave sleep may relate to an accumulation of β-amyloid peptide in the cortex and deficits of memory consolidation [43]. Of further interest is that inducing sleep slow waves, e.g., through acoustic stimulation, in patients with mild cognitive impairment and slow-wave deficits might improve memory and even decelerate the progression of neurodegeneration and prevent or delay the onset of dementia (Fig. 1). As a potential mechanism, slow-wave sleep-dependent increases in metabolic clearance have been proposed [1]. Though compelling in theory, the direction of effects is insufficiently understood and it remains unclear whether the induction of sleep slow waves is feasible in elderly individuals and whether or not this might be considered a preventive intervention or treatment in the future. Of particular interest, we recently proposed a synap-

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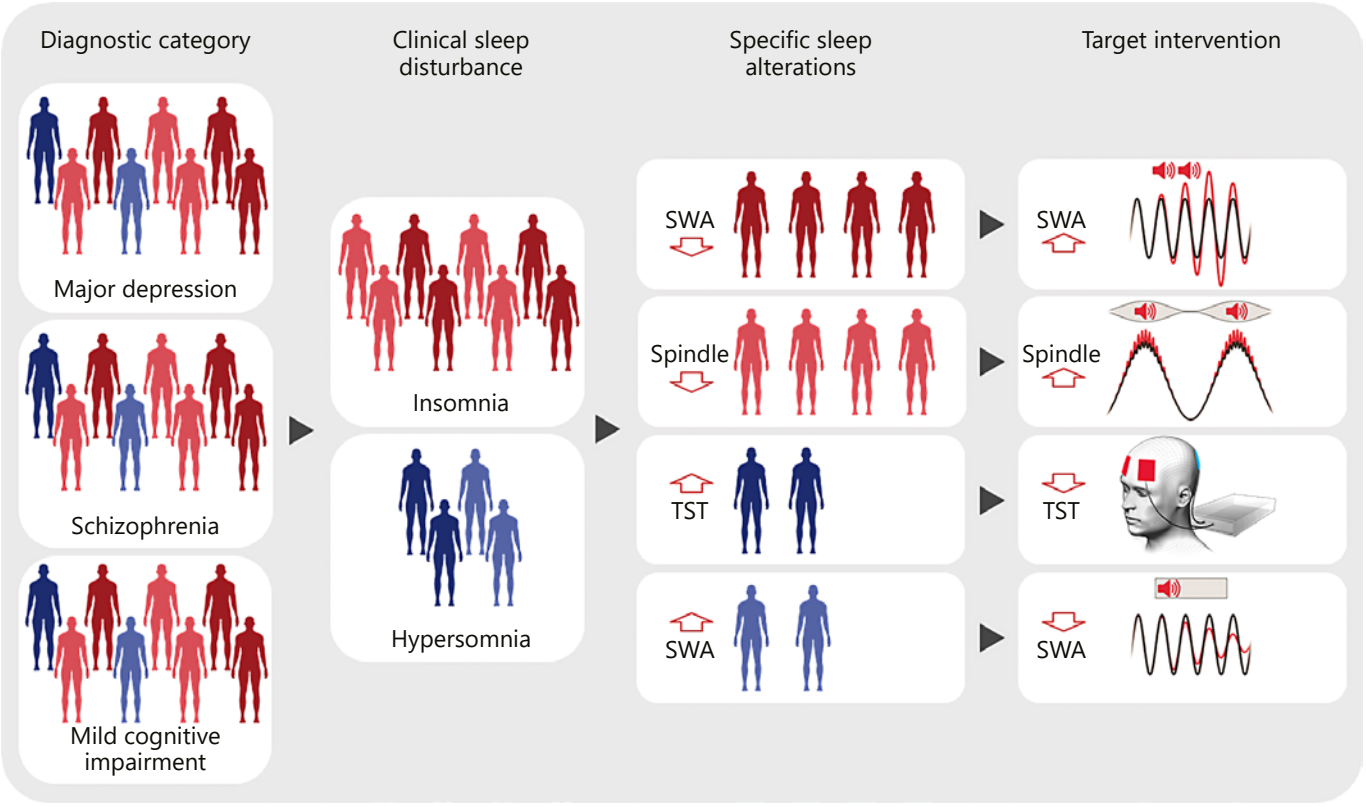

Fig. 1. Conceptual framework of modulating distinct aspects of sleep to improve mental health. The figure is divided into 4 columns and is based on a seminal visualization of the Research Domain Criteria (RDoC) concept [67]. Column 1 depicts the current classification of patients into diagnostic entities of mental disorders, which share several diagnostic criteria but demonstrate significant inhomogeneity with regard to underlying neurobiological alterations. Column 2 shows the proposed redistribution of patients (across diagnostic entities) to the major clinical sleep complaints, i.e., insomnia and hypersomnia. Column 3 demonstrates selected alterations of sleep on a brain oscillation level. This level is thought to map more closely to common neural mechanisms than the level of disorders. Column 4 shows examples of a targeted modulation of alterations of sleep through NIBS techniques. As an example, a patient classified as having mild cognitive impairment (column 1) might show the clinical complaint of insomnia (column 2) and attenuated sleep slow waves (column 3), which might be targeted through auditory-closed loop stimulation to increase sleep slow waves (column 4). Please note that the figure aims to show the concept of the current work and certainly represents an oversimplification of potential clinical complaints, underlying mechanisms and pathways to treatment. SWA, slow wave activity. TST, total sleep time.

tic plasticity model of therapeutic sleep deprivation in major depression, which suggests that slow-wave sleep-related shifts in synaptic plasticity might drive the well-characterized rapid antidepressant effects of therapeutic sleep deprivation in major depression (please refer to (Box 2) 1 for further information).

Sleep Spindles. Patients with insomnia, in the absence of another disorder, demonstrate an enhancement of sleep spindles rather than an attenuation, as indexed by increased EEG σ activity in the sleep spindle range in comparison to controls [40]. A possible, though speculative, explanation is a compensatory sleep-protecting increase in sleep spindles to counteract persistent hyperarousal in insomnia. With regard to mental disorders, patients with schizophrenia show deficits in the generation of sleep spindles [50], which relate to cognitive deficits [51]. Here, increasing sleep spindles might present a new path to treat cognitive deficits that strongly affect the quality of life and respond insufficiently to existing treatments. Interestingly, sleep spindles appear to be increasable through tACS informed by real-time detection of sleep spindles in healthy humans [52]. The authors also reported an increase in sleep-related motor memory consolidation, which correlated with the stimulation-induced change in fast spindle activity. Future studies are needed to test whether sleep spindles can be enhanced in patients with sleep spindle deficits, and whether this can improve related dysfunctions, such as cognitive deficits.

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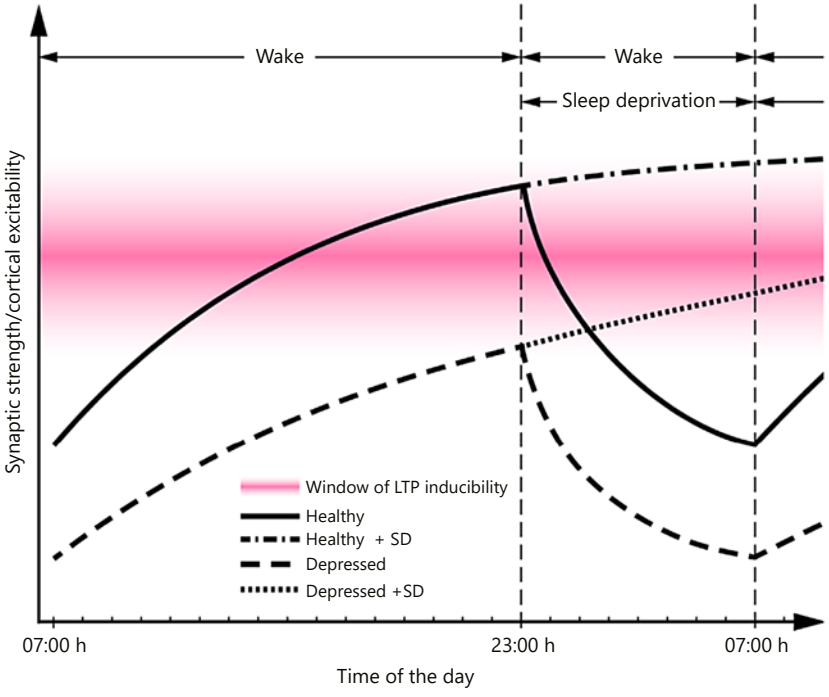
Box 1. Therapeutic sleep deprivation in major depression

Intriguingly, one night of continuous wakefulness (therapeutic sleep deprivation) leads to a dramatic decrease in depressive symptoms in 50–60% of patients with MDD. The benefit is however limited due to a frequent relapse after subsequent nighttime sleep. Scientifically, sleep deprivation presents a unique paradigm to study rapid mechanisms of antidepressant response and relapse, which are most likely different from those of today's standard treatments. We recently proposed a new framework of mechanisms [44] which integrates two prominent lines of research on MDD and sleep, the synaptic plasticity hypothesis of MDD [45, 46] and the synaptic homeostasis hypothesis of sleep-wake regulation [47]. The figure depicts the proposed interplay between the time course of net synaptic strength (homeostatic plasticity; solid and dotted lines) and the inducibility of synaptic LTP (associative plasticity; red window). According to the synaptic homeostasis hypothesis, wakefulness leads to an upscaling and sleep to a downscaling of net synaptic strength. Whereas in healthy controls SD eventually leads to synaptic saturation and deficient LTP inducibility [48], SD is proposed to compensate for attenuated synaptic strength and to evoke an antidepressant effect in patients with MDD via a shift into a window of more favorable LTP inducibility. Of interest, selective attenuation of sleep slow waves through visual detection and, potentially, also automated detection and suppression through NIBS – without actual sleep deprivation – might exert antidepressant effects through an alteration of brain plasticity [49]. LTP, long term potentiation; MDD, major depressive disorder; SD, sleep deprivation [44].



Phase Amplitude Coupling. Recent work highlights an inherently coupled, hierarchical organization of brain oscillatory activity during sleep (cross-frequency coupling). For instance, recent studies corroborate the notion that the phase-amplitude coupling of sleep slow waves and sleep spindles serve critical functions of sleep, such as memory consolidation [53] and changes in neural plasticity [54, 55]. Our own unpublished data suggest an attenuation of phase-amplitude coupling in patients with insomnia compared to controls, which might relate to the perception of nonrestorative sleep. It would therefore be of interest to test whether the strengthening of phase-amplitude coupling through NIBS might improve the perception of nonrestorative sleep and functions of sleep in patients with insomnia.

REM Sleep. Patients with insomnia appear to show a greater fragmentation of REM sleep than controls [56]. The duration of REM sleep, rather than other polysomno-

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graphic parameters, predicts the perception of poor sleep in patients with insomnia [57]. Moreover, patients with insomnia show a bias towards wake perception after experimental awakening from REM sleep [58]. Other work suggests that a fragmentation of REM sleep relates to deficits in dissolving distress in patients with insomnia [59]. In patients with mental disorders, increased REM sleep (e.g., shortened REM sleep latency and increased duration of REM sleep) has been observed across several disorders, including major depression, PTSD, and anxiety disorders [3]. These alterations might represent an index of or contribute to cognitive and emotional deficits in afflicted patients [60]. To date, NIBS studies that modulate REM sleep are scarce. For instance, Voss et al. [61] demonstrated that tACS in the EEG γ frequency range during REM sleep increases EEG γ activity and induces self-reflective awareness in dreams in healthy individuals [61]. This intervention – if further replicated – would be of interest to increase cognitive control over and reduce nightmares, for instance in patients with PTSD. In turn, it can be speculated that decreasing EEG γ activity during REM sleep might decrease self-reflective awareness and promote the perception of restorative sleep under conditions of insomnia.

Local Sleep and Wakefulness. Research over the past decades supports the notion that sleep, beyond its uniform appearance, is a highly local process of neural activity patterns. For instance, local islands of sleep have been observed in awake rats [62] and, in turn, local indices of wake-like activity have been observed in sleeping animals and human patients with intracerebral recordings prior to epilepsy surgery [63]. Preliminary evidence (small sample size, i.e., $n = 8$) suggests that patients with insomnia show increased indices of local wakefulness (elevated high-frequency EEG activity in sensory and sensorimotor areas) during NREM sleep compared to controls [41]. This has not been replicated yet and therefore further and larger studies are needed. Currently, further methods need to be developed to determine aspects of local sleep and wakefulness in individuals with and without alterations of sleep. Finally, it would be of great value to refine NIBS techniques to modify local sleep/wake activity patterns and to test whether new treatments can be developed.

Hypersomnia

Hypersomnia is defined as an increased propensity for falling asleep or an increased sleep duration. It may be associated with increased daytime fatigue and decreased alertness and vigilance. Hypersomnia can occur in the context of neurological disorders, such as narcolepsy or brain injury. Hypersomnia can also, though much less frequently than insomnia, occur as part of a mental disorder. For instance, at least some patients with attention deficit hyperactivity disorder experience increased sleepiness [64]. This is potentially related to specific sleep disorders [65]. Also other patients, for example those with major depression, subjectively report hypersomnia [66]. However, it is important to note that hypersomnia (i.e., increased propensity for falling asleep or increased sleep duration), should be carefully disentangled from frequently occurring inactivity and extended bed time in the absence of actual hypersomnia.

Current treatments for hypersomnia include activation of behavioral interventions and various medications, including antidepressants, dopaminergic compounds, modafinil, methylphenidate, and amphetamines. It is important to note that evidence for the efficacy of these approaches is limited and no medication has currently been approved for the treatment of hypersomnia (apart from narcolepsy), indicating the need for additional research. Again, further characterization of the underlying neurobiology might help to develop new treatments.

Recently, a repetitive stimulation protocol of bifrontal anodal tDCS prior to sleep has been shown to decrease total sleep time in healthy humans [22] and in a patient with organic hypersomnia after reanimation [23]. Future studies are needed to test whether this protocol or further refined protocols can be used to improve hypersomnia.

Conclusions and Future Directions

Sleeping problems are highly prevalent in patients with mental disorders. Current treatments include cognitive behavior therapy and medication. For decades, the clinical choice of treatment has been based on the clinical sleep complaint, i.e., insomnia or hypersomnia, and not on the diagnostic entity of a mental disorder. As such, the treatment of sleep complaints is an example of an early transdiagnostic approach prior to newer dimensional developments in psychiatry, yet progress is limited by insufficient insight into the neurobiology of insomnia and hypersomnia as much as by a poor translation of such insight into clinical practice.

The novel approach of this work is that we propose further characterization of patients based on more fine-graded characteristics of sleep, such as alterations of sleep slow-wave activity, sleep spindles, cross-frequency coupling, local sleep-wake aspects, and REM sleep, with the goal of treating these with specific NIBS techniques (Fig. 1). There is mounting evidence that the modulation of different aspects of sleep through NIBS is feasible, yet

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Box 2. Research agenda

Studies are needed to…

- further refine non-invasive brain stimulation (NIBS) protocols to modulate distinct aspects of sleep, such as sleep slow waves, sleep spindles, cross-frequency coupling, local sleep-wake regulation or aspects of REM sleep
- test whether the modulation of distinct aspects of sleep through NIBS translates to functional relevance, e.g. with regard to memory or emotion regulation
- investigate whether these interventions have the potential to treat clinical sleep complaints
- examine whether the modulation of sleep has the potential to improve mental health outcomes
- assess if NIBS protocols of interest, if effective, are safe and practicable for clinical applications

future studies are needed to test whether these interventions can be considered as treatment for sleeping problems and whether this might improve the overall treatment for patients with mental disorders (Box 2).

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

C.N. has served as an advisor for Lundbeck and Vifor Pharma. All of the other authors have no conflict of interests to declare.

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Author Contributions

T.G., E.H., and C.N. conceptualized and wrote the first version of this paper. All of the authors provided significant contributions to refining the content, approved the final version, and are accountable for the integrity of this work.

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