Sleep in disorders of consciousness: diagnostic, prognostic, and therapeutic considerations

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Purpose of review
Sleep is important in the evaluation of patients with disorders of consciousness (DOC). However, it remains unclear whether reconstitution of sleep could enable consciousness or vice versa. Here we synthesize recent evidence on natural recovery of sleep in DOC, and sleep-promoting therapeutic interventions for recovery of consciousness.

Recent findings
In subacute DOC, physiological sleep–wake cycles and complex sleep patterns are related to better outcomes. Moreover, structured rapid-eye-movement (REM), non-REM (NREM) stages, and presence of sleep spindles correlate with full or partial recovery. In chronic DOC, sleep organization may reflect both integrity of consciousness-supporting brain networks and engagement of those networks during wakefulness. Therapeutic strategies have integrated improvement of sleep and sleep–wake cycles in DOC patients; use of bright light stimulation or drugs enhancing sleep and/or vigilance, treatment of sleep apneas, and neuromodulatory stimulations are promising tools to promote healthy sleep architecture and wakeful recovery.

Summary
Sleep features and sleep–wake cycles are important prognostic markers in subacute DOC and can provide insight into covert recovery in chronic DOC. Although large-scale studies are needed, preliminary studies in limited patients suggest that therapeutic options restoring sleep and/or sleep–wake cycles may improve cognitive function and outcomes in DOC.

Keywords
coma, minimally conscious state, polysomnography, sleep, vegetative state

INTRODUCTION

The relationship between sleep and consciousness is both paradoxical and profoundly intuitive; sleep is often experienced as an 'off-line' state, yet sleep deprivation produces a pronounced detriment to conscious wakefulness. Although this effect is readily apparent in healthy individuals, sleep physiology has only recently begun to be characterized in patients with disorders of consciousness (DOC). In this review, we detail recent advances in the utility of understanding sleep dynamics in patients with DOC. We first provide a brief framework of the connection between sleep and consciousness before detailing how alterations of sleep features may provide clinical and neurobiological insights into recovery from both subacute and chronic DOC. Finally, we discuss the potential of therapeutic interventions focused on sleep physiology following severe brain injuries.

SLEEP MAINTAINS NEUROPHYSIOLOGICAL PROCESSES CRITICAL FOR HEALTH AND COGNITION

Although the purpose of sleep is an ever-evolving topic, sleep itself is universally recognized as a vital component of health and consciousness. The sleep electroencephalogram (EEG) is broadly divided into rapid eye movement (REM) and nonrapid eye movement (NREM) stages; NREM sleep is further divided into N1, N2, and slow wave sleep (SWS) [1]. REM and

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KEY POINTS

- There is a strong relationship between sleep and consciousness, because of the sharing of anatomical structures and functional networks.
- Almost physiological sleep–wake cycles and patterns of sleep correlate with better outcomes in the subacute phase, and higher residual functioning in the chronic phase of disorders of consciousness.
- Preliminary studies show promise in targeting the restoration of sleep features and sleep–wake cycles for the improvement of wakeful behavior.
- Larger systematic studies are needed to standardize sleep-centered approaches for potential integration into the therapeutic strategy for disorders of consciousness.

NREM are known as nonsynchronized and synchronized sleep, respectively, each with different phylogenetic, ontogenetic, and ethologic significance.

The distinct EEG signatures of each sleep stage provide a noninvasive window into molecular and circuit-level brain function. Sleep, and NREM sleep spindles in particular, have been heavily implicated in circuit development and cortical maturation [2,3], as well as learning and memory [4,5]. Growing evidence suggests that SWS may mediate glymphatic function, which includes clearance of waste metabolites [6▪] and may facilitate repair of DNA damage accumulated during wakefulness [7▪,8]. Cortical slow oscillations and SWS have also been associated with synaptic scaling, a process hypothesized to rebalance global synaptic strengths and cellular homeostasis following wakefulness [9]. Many of these sleep features are mutually modulated by wakeful experience, including the location and density of sleep spindles following learning experiences [5] as well as the amplitude and slope of slow waves following prolonged wakefulness and cognitive engagement [10]. Accordingly, sleep may be not only crucial for arousal and cognition (as summarized in Fig. 1) but also of great value for the clinical evaluation of wakefulness in noncommunicative patients.

On the basis of myriad functions of sleep, it is unsurprising that even mild disruption of the 24-h sleep–wake cycle negatively affects cognitive performance in healthy individuals [11▪]. In chronic cases, sleep impairment has been associated with systemic inflammation [12], immune dysregulation [13], widespread neuronal loss [14], dementia [15], and increased all-cause mortality [16]. This is especially relevant for patients with brain injuries, in whom sleep disorders are among the most common comorbid complications [17]. In these patients, sleep disorders likely compromise neuronal restoration and repair [18], as well as play a pivotal role in pathologically changing levels of arousal and awareness. Such changes may prevent learning and acquisition of new information [19] thus complicating or even hindering cognitive rehabilitation. Therapeutic restoration and reinforcement of sleep elements may, therefore, have the potential to promote continued recovery of wakeful consciousness and prevent progressive decline following brain injuries.

BEHAVIORAL SLEEP–WAKE CYCLES DENOTE THE TRANSITION FROM COMA TO DISORDERS OF CONSCIOUSNESS

Several studies have demonstrated profound effects of brain injuries on sleep architecture and the sleep–wake cycle, both at early and late stages [20–22,23▪▪,24]. Following brain injury, coma is a transitory and acute state of deep unawareness from which the patient cannot be aroused; coma lasts for a limited period, usually days to weeks [25]. In coma, eyes are closed and the sleep–wake cycle is absent. Among comatose patients who do not fully recover, some progress to states characterized by different levels of consciousness, the vegetative state/unresponsive wakefulness syndrome (VS/UWS) [26] and the minimally conscious state (MCS) [27], which are considered disorders of consciousness (DOC). The evolution from coma to DOC is associated with the presence of eye-opening periods and the re-emergence of circadian rhythms, including behavioral sleep–wake cycles, albeit often in altered forms [28].

Accordingly, recent guidelines of the European Academy of Neurology recommend the inclusion of EEG and EEG-related techniques as part of the multimodal approach in the diagnostic work-up of coma, subacute and chronic DOC [29▪▪]. EEG and polysomnography (PSG) are repeatable, noninvasive and inexpensive techniques that are potentially applicable at the bedside; on the other hand, structural injury and aberrant EEG dynamics often present in DOC make it difficult to apply standard sleep evaluation criteria [1]. Hence, many authors have used modifications and/or proposed alternative scoring criteria tailored to DOC patients [20–22,23▪▪,30].

THE PROGNOSTIC ROLE OF SLEEP IN THE SUBACUTE STAGE OF DISORDERS OF CONSCIOUSNESS

Literature globally supports the hypothesis of a strong relationship between sleep and residual

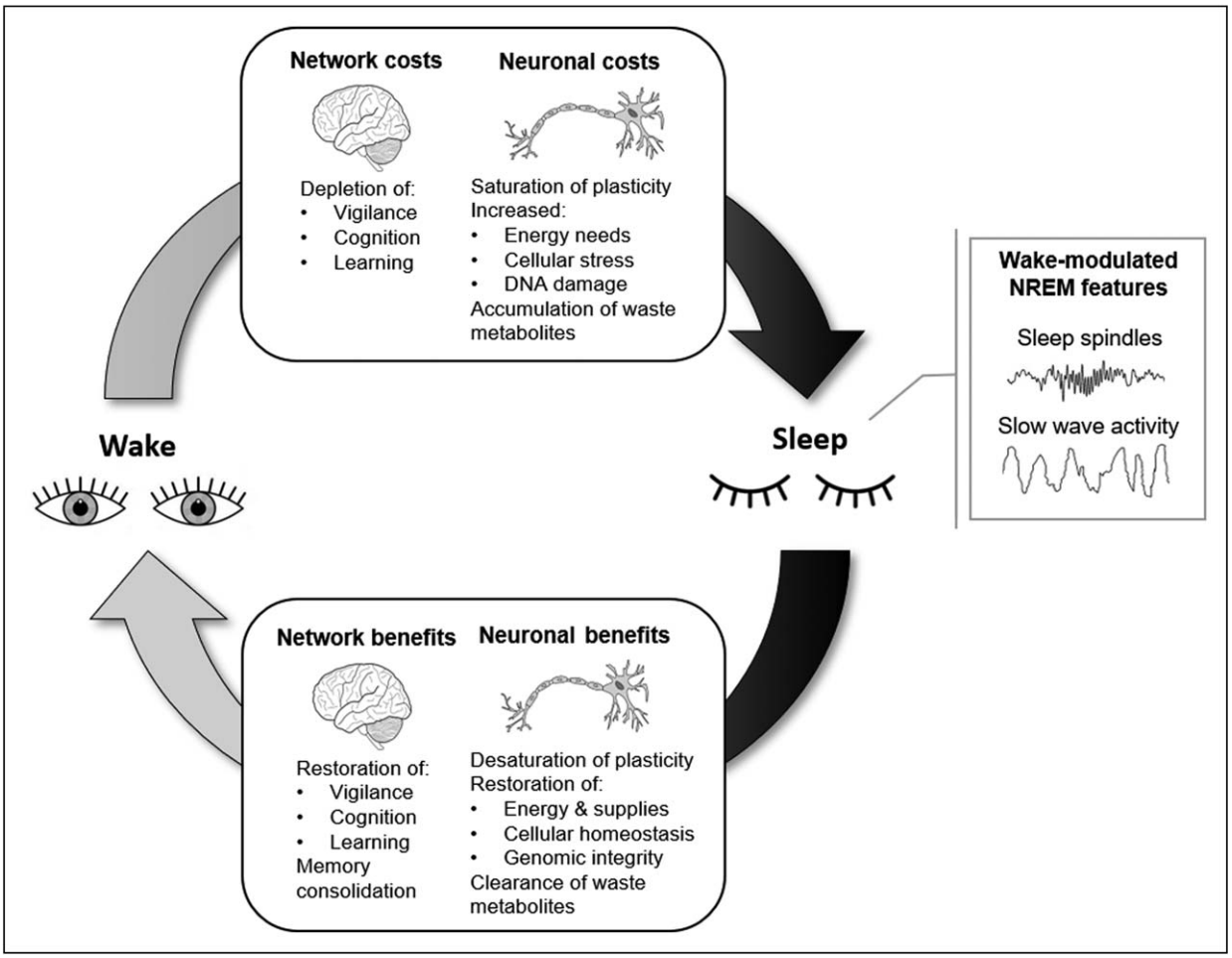

FIGURE 1. Cyclical influences of sleep and wake states on brain function. During wakefulness, active cognitive engagement produces a net increase in synaptic strengths, resulting in greater energy needs, cellular stress, DNA double strand breaks, and the accumulation of waste metabolites. These neuronal costs deplete vigilance and cognitive capacity at the network level, initiating sleep need. Subsequent sleep includes the consolidation of wakeful learning, as reflected in the density and location of nonrapid-eye-movement (NREM) sleep spindles, as well as neuronal and network restoration. Slow wave activity is proposed to reflect homeostatic sleep need and the net rebalancing of synaptic strengths; it is accordingly most intense following prolonged wakefulness and decreases with accumulated sleep time. Homeostatic rebalancing is hypothesized to desaturate neuronal plasticity through a net decrease in synaptic strengths as well as restore neuronal costs incurred during wakefulness. Restoration of neuronal and network function during sleep thereby supports renewed capacity for vigilance and cognitive engagement during subsequent wakefulness.

cognitive functioning as well as level of consciousness in DOC patients [28]. In the milestone work of Landsness *et al.* [30], the authors showed marked differences between sleep in MCS and VS/UWS patients. Specifically, only MCS patients had circadian EEG modification patterns similar to the sleep of healthy subjects, whereas VS/UWS patients preserved only behavioral (alternate eyes-open/eyes-closed periods), but no neurophysiological signs of the sleep-wake cycle. Subsequent studies have challenged this distinction, suggesting that the reality is more complex and that some sleep patterns are present even in VS/UWS patients [31]. Nevertheless, many works have demonstrated that long lasting EEG recordings and PSG can be useful to assess sleep as a reliable prognostic marker and to differentiate MCS from VS/UWS in early stage DOC. Valente *et al.* [20] used the complexity of the 24-h PSG to classify sleep patterns of posttraumatic comatose patients into five classes. These classes did not fit the standard scoring criteria [1] but were correlated with a high predictive value for both survival and functional rehabilitation: five of six (83.3%) patients who exhibited the most complex PSG pattern (i.e. presence of both REM and NREM sleep stages) showed a good outcome (full recovery or mild disability). On the contrary, six patients classified in the two least complex sleep classes showed a poor

prognosis (death, VS/UWS, or severe disability) [20]. Likewise, Arnaldi *et al.* [22] demonstrated that structured sleep predicts positive outcome in early stage DOC patients, even stronger than clinical condition and age. Number and features of sleep spindles may also be related to early prognosis and differentiating MCS from VS/UWS patients [21,32]. In a recent systematic review analyzing brain measures and outcome in DOC patients [33▪▪], although only stimulation-induced oscillatory EEG responses reached significance as an outcome predictor, the authors underlined sleep spindles as a promising variable whose prognostic value should be assessed in future studies.

Overall, following acute coma, the occurrence of well preserved sleep patterns is often related to a greater sparing of brain structures necessary for the generation of wakeful arousal and cognition [28]. NREM features are related to a functional sparing of reticular-thalamo-cortical pathways [34] and REM of the pontine tegmentum in the brainstem [32]. Hence the presence of physiological sleep patterns is related to better outcomes in subacute DOC patients, probably as it indicates smaller injury, greater resilience of structures/pathways/loops pivotal for sleep (and consciousness), or both.

SLEEP DYNAMICS MAY PROVIDE A WINDOW INTO COVERT RECOVERY IN CHRONIC DISORDERS OF CONSCIOUSNESS

For patients who progress into the chronic phase, identification of recovery remains critically important, as DOC patients have been demonstrated to undergo continued, and often covert, recovery over prolonged timescales [35–37]. During this phase, sleep patterns may serve as an indicator of network capability that might otherwise be obscured by fluctuating arousal or motor impairments during wakefulness [38]. In a study of 44 chronic DOC patients [39], those with either vertex waves or sleep spindles demonstrated significantly higher behavioral responsiveness (as measured by the Coma Recovery Scale – Revised [40], CRS-R) than patients without these features. Interestingly, all patients with the fMRI-validated ability to follow verbal commands demonstrated sleep spindles – a commonality not observed for any other sleep element. Similarly, de Biase and colleagues [41] examined 33 chronic DOC patients, finding that the presence of REM sleep was independently correlated with higher CRS-R scores; this effect was amplified by the concurrent presence of sleep spindles. In a yet larger cohort of 85 chronic DOC patients, presence of SWS was an independent predictor of MCS or VS/UWS diagnosis, correctly classifying 78.8% of patients [23▪▪]. Additionally, sleep spindles were significantly more frequent in MCS compared with vegetative state patients, and CRS-R scores independently correlated with whole-night durations of both N2 and SWS stages [23▪▪]. Across studies, relatively consistent findings regarding sleep spindles highlight the significance of retained integrity of the thalamocortical loops that both produce sleep spindles [42] and support maintenance of arousal [34,43]. Alternately, varying findings regarding the effect size of REM and SWS presence can likely be attributed to the vast heterogeneity of DOC injury patterns combined with the large-scale network recruitment involved in producing these sleep states [44]. Overall, current literature underscores the clinical utility of sleep dynamics in detecting chronic recovery, especially in the face of heavily compromised motor channels that often complicate evaluation of DOC patients [38].

As in healthy individuals, sleep characteristics in DOC may reflect not only integrity of consciousness-supporting brain networks but also functional engagement of those networks during wakefulness [9,45]. In a striking example of this effect in a chronic MCS patient, Thengone *et al.* [35] showed structural and functional brain reorganization (including restored synchronicity of sleep spindles) after the re-establishment of wakeful engagement through a functional communication channel. In another chronic MCS patient (described in detail below), daytime central thalamic deep brain stimulation (CT-DBS) produced reversible improvements in sleep features, including increased sleep spindle frequency and the reappearance of REM and SWS [46▪▪,47]. Although single patient studies, these findings suggest that sleep organization may be a sensitive marker of wakeful brain activation in chronic DOC patients.

Despite strong heritability of many sleep features [48], only two studies have examined the interaction between genetics and sleep patterns in chronic DOC [49,50]. Bedini *et al.* examined the *Period3* gene polymorphism, finding that patients with the Period3$^{5/5}$ variant displayed increased total sleep time and higher CRS-R scores than those with the Period3$^{4/4}$ variant [49,50]. As the *Period3* gene has been implicated in sleep–wake regulation, it is yet unclear whether this and similar polymorphisms may favor recovery via sleep-dependent neuronal repair [18] or through the resilience of wakeful arousal networks that drive homeostatic sleep need [9]. Future genetic studies are needed to uncover the relationship between molecular regulation of sleep–wake processes and recovery in DOC.

THE TREATMENT OF SLEEP DISORDERS: AN ALTERNATIVE APPROACH FOR THE CARE OF DISORDERS OF CONSCIOUSNESS PATIENTS

In light of the demonstrated connection between wakeful recovery and sleep organization in DOC, therapeutic methods that alleviate sleep dysfunction and promote healthy sleep architecture may provide a promising therapeutic option. Of these dysfunctions, sleep apnea, a sleep-related breathing disorder, affects up to 45% of brain-injured patients [51]. Sleep apnea is associated with neurocognitive impairment involving attention, vigilance, long-term memory, visuospatial and executive functions, because of sleep fragmentation and recurrent hypoxemic periods [52]. Treatment of sleep apneas usually determines improvement in cognitive function and even in brain circuitry [53]. Interestingly, temporary functional motor and cognitive improvements were observed in a MCS patient following the treatment of sleep apnea by means of positive airway pressure [54▪▪]. This single case suggests that treatment of sleep apnea may alleviate a comorbidity that is potentially preventing recovery of DOC patients.

Another therapeutic strategy includes regulation of circadian rhythmicity and sleep–wake cycles, which are involved in the regulation of metabolism, as well as mood and cognitive functions. Uncoupling of circadian rhythmicity with natural light–dark cycles has been shown to impair cognition in otherwise healthy individuals [55], whereas the entrainment of physiologic circadian rhythms has been suggested to support recovery in critically ill patients [56]. Physiological circadian rhythmicity has been demonstrated to relate to better functioning of DOC patients [57▪▪] and has been suggested as a prerequisite for recovery following coma [58▪▪]. In DOC, smaller deviations in circadian period length and timing of melatonin secretion from healthy standards have been correlated with higher CRS-R scores [57▪▪]. De Weer *et al.* [59] first demonstrated that fast light variations drive, albeit temporarily, an increase in arousal and motor activity in DOC patients; in this line, Blume and Schabus [57▪▪,60] then improved circadian rhythms in brain-injured patients by means of bright light stimulation. The use of bright light stimulation and/or the management of environmental lights has the advantage of being noninvasive, inexpensive, and easily applicable at the bedside.

Some pharmacological approaches have also shown encouraging results, although often anecdotal. A pilot study in a relatively small sample of brain-injured patients suggested that modafinil, a central nervous system stimulant used for narcolepsy and refractory sleep apnea may have a positive effect on residual cognitive function [61]. Some works have proposed the use of agonists of orexin, a regulatory hypothalamic neuropeptide affecting feeding and sleep, as potentially useful in regulating arousal [62]. Additional evidence supports a positive paradoxical alerting effect of zolpidem, an imidazopyridine derivative commonly used as a sedative hypnotic in refractory insomnia, even if DOC patients with brainstem lesions seem to be unresponsive (see Sutton and Clauss [63] for a global review).

Overall, neuromodulatory stimulations are the most intriguing and hopeful alternative therapeutic approaches to DOC [64]. In pioneering work, Schiff and colleagues [65] presented a double-blinded crossover study of daytime central thalamic deep brain stimulation (CT-DBS) in a chronic MCS patient; CT-DBS was shown to enhance thalamocortical output and produce significant functional recovery, including improvements in arousal, limb control, and oral feeding behaviors [65]. Although sleep dynamics were not reported in this study, daytime CT-DBS in a similar MCS patient [46▪▪,47] was found to produce significant improvements in sleep patterns against the natural trends of age-related sleep decline [66]. In the latter patient, both wakeful responsiveness and sleep organization significantly regressed following discontinuation of treatment [46▪▪], suggesting a causal relationship between wakeful CT-DBS and sleep organization. Critically, in these patients, CT-DBS was initiated at approximately 6 and 19 years postinjury, respectively, demonstrating that some MCS patients retain the potential to benefit from neuromodulatory stimulation years to decades into an MCS diagnosis.

In addition to invasive techniques, Monti *et al.* [67] reported a first-in-man safety and feasibility study of noninvasive ultrasonic thalamic stimulation in which a 25-year-old man demonstrated early-stage emergence from MCS. Unfortunately, EEG and/or PSG was not reported, but there is strong suggestion that this improvement could be related to a parallel improvement in sleep architecture through up-regulation of the thalamocortical pathway. However, as the authors declared, we can neither be sure of this interpretation nor whether the patient spontaneously emerged from MCS.

As a whole, there are no standardized protocols to date that include the treatment of sleep disorders in the guidelines for DOC, even if the treatment of secondary medical comorbidities is generically recommended to improve the condition of DOC patients [68]. Nevertheless, a small yet growing body of evidence suggests that therapeutic strategies that integrate the improvement of sleep and sleep–wake

cycles are desirable to maximize the potential for recovery in DOC patients.

CONCLUSION

Sleep dynamics are an important marker of neuronal integrity and capacity in DOC patients, both at subacute and chronic phases. Early evidence demonstrates that therapeutic strategies that alleviate sleep dysfunction, whether through wakeful neuronal activation or sleep-focused interventions, may improve recovery in DOC patients. Future systematic investigations of the effect of these interventions on outcomes from severe brain injuries are needed to elucidate the molecular and circuit-level mechanisms underlying the relationship between sleep and recovery in DOC. Such studies have the potential to greatly impact both therapeutic strategy and recovery trajectories for DOC patients.

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Conflicts of interest

There are no conflicts of interest.

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