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REVIEW

Impact of Sleep Deprivation in the Neurological Intensive Care Unit: A Narrative Review

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Abstract

Sleep is fundamental for everyday functioning, yet it is often negatively impacted in critically ill patients by the intensive care setting. With a focus on the neurological intensive care unit (NeuroICU), this narrative review summarizes methods of measuring sleep and addresses common causes of sleep disturbance in the hospital including environmental, pharmacological, and patient-related factors. The effects of sleep deprivation on the cardiovascular, pulmonary, immune, endocrine, and neuropsychological systems are discussed, with a focus on short-term deprivation in critically ill populations. Where evidence is lacking in the literature, long-term sleep deprivation studies and the effects of sleep deprivation in healthy individuals are also referenced. Lastly, strategies for the promotion of sleep in the NeuroICU are presented.

Keywords: Sleep, Sleep deprivation, Intensive care unit, Brain injury, Critical illness

Introduction

Sleep is a complex physiological phenomenon necessary for restoration, growth, cognition, and survival. Sleep is particularly important among patients recovering from critical illness. Unfortunately, patients in the intensive care unit (ICU) frequently experience sleep deprivation (reduced quality and/or quantity of sleep compared to healthy subjects) [1, 2]. After reviewing methods for measuring sleep, this review highlights common causes of sleep deprivation in the ICU and its impact on the functioning of major organ systems. While there is a focus on topics pertinent to the neurological ICU (NeuroICU), we note that much of the literature comes from general critical care rather than a neurocritical patient population.

Methods

A narrative review of published literature was performed. Relevant abstracts were identified using the PubMed and Google Scholar databases. Search terms included 'sleep deprivation,' 'critical care,' 'neurological ICU,' and 'neurocritical care.' Search terms for effects on individual organ systems followed the format of 'sleep and X' with X being 'heart,' 'cardiovascular,' 'blood pressure,' 'hypertension,' 'obstructive sleep apnea,' 'lung,' 'ventilator,' 'neuromuscular,' 'immune,' 'cytokines,' 'glucose,' 'metabolic,' 'temperature,' 'cognitive,' 'brain,' 'psychiatric,' 'delirium,' and 'pain.' References known to the authors were also considered. Abstracts were reviewed, and articles whose abstracts addressed sleep deprivation were evaluated in full. A total of 210 articles published between 1958 and 2019 were deemed relevant for inclusion after this evaluation.

Measuring Sleep in the NeuroICU

Polysomnography (PSG) is the gold standard for measuring sleep. It involves simultaneous electroencephalogram (EEG), electromyogram, and electrooculogram and is interpreted according to American Academy of Sleep

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Medicine scoring guidelines [3]. Portable PSG is feasible in the ICU, but limited by cumbersome and costly equipment and the difficulties in interpretation among the critically ill [4]. Standard staging criteria in these patients have not been shown to reliably distinguish between sleep and wake as the K complexes and sleep spindles that classically characterize stage 2 sleep are often absent [5]. Thus, revised PSG scoring schemes have been proposed for the critically ill, mechanically ventilated population [6, 7].

For critically ill patients, although total sleep quantity varies, sleep is consistently highly fragmented and much less time is spent in the deeper (slow wave and REM) sleep stages as compared to healthy individuals [8–10]. ICU patients also exhibit disrupted circadian rhythms, with nearly 50% of sleep occurring during the daytime [11]. Those with sepsis have varying severity of encephalopathy and lack definable sleep–wake periods on EEG [5]. Furthermore, common ICU medications such as benzodiazepines, analgesics, and antipsychotics can lead to spindle coma patterns, burst suppression, and slowing on EEG [12], making sleep staging difficult.

Unfortunately, sleep has been especially challenging to describe in the NeuroICU population given the presence of preexisting neurological injuries that further complicate EEG interpretation. A recent study by Foreman et al. to evaluate sleep in the NeuroICU found that 65% of patient EEG recordings could not be scored, typically due to the lack of a distinguishable posterior dominant rhythm [13]. Using scorable recordings, the authors found that patients spent significantly more time in lighter (N1) than deeper sleep stages as compared to normal values. Moreover, sleep was abnormally distributed across the day–night cycle—similar to findings in critically ill patients without neurological injury. Studies of patients with subarachnoid hemorrhage (SAH) [14] and traumatic brain injury (TBI) [15] have also noted grossly abnormal or even absent sleep architecture in the majority of subjects; greater degrees of abnormality correlated with poorer prognosis.

Other tools such as actigraphy and bispectral index (BSI) have been considered as alternatives to PSG to measure sleep but present their own challenges of accuracy and reliability [16]. Actigraphy (which estimates sleep using a motion sensor worn on the wrist or ankle) is a convenient, noninvasive technique that can be used for extended periods of time; however, it likely overestimates sleep in a largely bedridden, sedated population [17]. It may be useful for assessing sleep fragmentation [18, 19]. Originally employed to monitor anesthesia in the operating room, BSI uses a single foam EEG sensor applied to the forehead. The BSI is calculated as a weighted sum of several EEG parameters and is scaled from 0 to 100, with larger values corresponding to a higher likelihood of alertness. BSI monitoring may predict depth of sedation in critically ill patients with brain injury [20], but further research is necessary to demonstrate its correlation with depth of sleep in this population [21].

Causes of Sleep Disturbance in the NeuroICU

Numerous studies have evaluated the causes of sleep disruption in the ICU setting. Environmental contributors include patient care, noise, light, and medications. Patient factors, including illness severity, mechanical ventilation requirement, and pain, can also play important roles.

Patient Care

In a recent cross-sectional, questionnaire-based study assessing sleep quantity and quality among 2005 hospitalized (ICU and other) patients in the Netherlands, 85% reported at least one nocturnal awakening, and 20% experienced sleep disturbance due to awakenings by hospital staff [22]. Our search yielded only two studies that quantify the number of care events occurring during patient sleep in the ICU. Using PSG and time-synchronized environmental monitoring, Gabor and colleagues found activities occurring approximately eight times per hour of sleep, accounting for just 7% of total arousals and awakenings (68% of sleep disruption events did not have an identifiable cause; 21% were due to sound) [8]. Tamburri et al. found an average of 42.6 interactions per night (7 p.m. to 7 a.m.), but did not directly measure sleep via PSG [23]. Nevertheless, patient care activities consistently rank as a major source of sleep disturbance in surveys of ICU survivors, even more so than noise level [5]. Although many patient care activities are unavoidable or temporally fixed, efforts have been proposed to minimize and reschedule as possible to reduce sleep disruption (see "Strategies for Sleep Promotion in the NeuroICU"). Specific to the NeuroICU, hourly neurological assessments (neurochecks) are performed on many patients and are often cited to justify increased nursing needs [24]. In conjunction with neuroimaging surveillance requiring travel off-unit, neurochecks have been demonstrated to impact surgical decision making in patients with primary intracerebral hemorrhage (ICH) [25] and severe TBI [26]. The appropriate duration and frequency of these neurochecks for most diagnoses is often at attending provider discretion [26]. Evidence from patients admitted for ICH suggests that the initial 12 h is a period of frequent and prognostically important neurological change [27], while TBI patients appear to be at highest risk of expansion of a traumatic intracerebral hematoma within 24 h from onset [28].

Noise and Light Levels

While the typical ICU is noisier than the levels recommended by the Environmental Protection Agency [29] and World Health Organization [30] (50–90 dB vs the recommended 20–45 dB) [31, 32], studies utilizing PSG have found that environmental noise causes less than 20% of all arousals and awakenings among ICU patients [5, 33]. Work by Stanchina et al. demonstrating that sleep disruption is caused by the relative noise difference from baseline to peak suggests opportunities for effective intervention with white noise if absolute noise levels cannot be reduced [34]. Environmental light exposure appears to play a smaller role in sleep disruption than patient care activities or noise, and its effect may be mediated by inadequate daytime light exposure [5, 35].

Medication and Pharmacological Effects

Generally speaking, medications can disrupt sleep both physiologically and during their administration. In general, sedation shares characteristics with sleep (similar receptor and network effects, muscle hypotonia, altered mentation, respiratory depression) but does not produce the full spectrum of restorative benefits found in sleep [36, 37]. Benzodiazepines, while frequently prescribed for insomnia, have actually been found to suppress REM and deeper N3 sleep stages in favor of lighter N2 sleep in healthy individuals [38]. Similarly, opioids have a sedating effect, but decrease total sleep time and time spent in deeper sleep stages [39, 40]. Other sleep-disrupting medications commonly administered to ICU patients include vasopressors [41] and beta-blockers [42] via their impacts on melatonin production; antidepressants [43, 44], which can decrease time spent in REM sleep; continuous intravenous drips and diuretics, which may increase the frequency of toilet visits or require uncomfortable indwelling urinary catheters [16]; and corticosteroids, which reduce REM sleep and increase the incidence of nightmares [45].

Dexmedetomidine, a selective alpha 2-adrenoreceptor agonist, is increasingly utilized in the NeuroICU due to its analgesic, sedative, and anxiolytic effects while maintaining patient arousability and minimizing respiratory depression [46, 47]. While dexmedetomidine is more expensive, several studies have found it to be more cost-effective than traditional sedatives overall as it is associated with reduced ICU stay costs and shorter times to extubation [48–50]. Interestingly, compared to other commonly used sedative–anesthetics such as propofol; in rats, dexmedetomidine may induce a sedative response more similar to natural sleep although it seems to increase the proportion of states resembling light (stages 1 and 2) rather than deep sleep (stage 3 and REM) [51, 52].

Patient-Specific Factors

A number of patient-specific factors also contribute to sleep deprivation. Illness severity has been positively correlated with sleep disruption (e.g., in sepsis) [53]; however, this finding has not held true in studies of ICU patients across diagnoses [5, 54]. Pain, either related to illness severity or on its own, is associated with poor sleep and increased arousals due to discomfort [55, 56]. In fact, pain causing loss of sleep may trigger an unfortunate feedback loop in which lack of sleep leads to hyperalgesia, which in turn inhibits adequate rest [57]. Specific to the NeuroICU, intracranial devices such as external ventricular drains and continuous EEG may cause additional discomfort, though this remains speculation.

One area that has been thoroughly investigated is that of mechanical ventilation, and the mode most conducive to sleep. Mechanical ventilation can disrupt sleep due to mismatch between patient demand and ventilator supply (inadequate support leading to dyspnea or excessive support leading to apnea). Studies by Parthasarathy et al. [58] and Toublanc et al. [59] found that when compared to assist control ventilation (ACV), pressure support ventilation (PSV) led to episodic hyperventilation with resulting decreased partial pressure of carbon dioxide, causing apneic events. However, work by Cabello and colleagues showed no differences in sleep architecture between non-sedated ICU patients on clinically adjusted PSV, automatically adjusted PSV, or ACV. The authors therefore suggested that it is not PSV itself that causes sleep disruption but the specific ventilator settings: They used lower levels of pressure support, standard minute ventilation, and tidal volume across all modes as compared to previous authors in an effort to better mimic physiological conditions [60]. Other studies looking at proportional assist ventilation [61]—in which pressure is applied in proportion to the patient's own inspiratory effort—and neurally adjusted ventilatory assist—in which pressure is applied in proportion to the electrical activity of the patient's diaphragm—also find improved sleep quality [62]. Thus, evidence from multiple studies indicates that patient–ventilator mismatch, rather than any given ventilator mode, is most responsible for sleep disruption. However, it can be challenging to find the appropriate settings most reflective of patient physiology, and clinical conditions (e.g., intracranial pressure crises in the setting of hypercarbia) may demand certain ventilator modes. Additionally, when generalizing the results of critical care ventilation studies to neurological patients one must consider the underlying need for ventilation (e.g., airway protection versus hypoxemic respiratory failure). Moreover, NeuroICU patients may already experience frequent spontaneous hyperventilation and periodic breathing apneas from their primary injuries, making it difficult to

apply optimal ventilator settings based on studies in non-neurological populations.

The impact of noninvasive ventilation on sleep in the critically ill population has received far less attention than invasive ventilation. It appears that poor sleep quality on PSG in the early stages of noninvasive ventilation is correlated with eventual failure (patient death, endotracheal intubation, persistent noninvasive ventilation requirement after 6 days) [63]. Of particular interest in the NeuroICU is the impact of ventilation mode on sleep in patients with neuromuscular disease. Much of the respiratory research in this population is done using noninvasive ventilation [64]. Similar to findings with invasive ventilation, Fanfulla and colleagues found that noninvasive pressure support set with physiological parameters (tailored to the patient's respiratory effort via measurement of esophageal pressure) among neuromuscular patients with chronic respiratory failure improves nighttime gas exchange, sleep architecture, and sleep efficiency [65].

Impact on Organ Systems in Critically Ill Patients

There are few data about the impact of sleep deprivation on critically ill patients as most research in this area is conducted with healthy (and typically male) subjects. What follows is an overview of the impact of sleep deprivation on specific organ systems with extrapolation to the critically ill population when possible (see Fig. 1). It emphasizes experimental studies of short-term sleep deprivation, but some long-term sequelae will be highlighted as ICU stays may be extensive or precipitate chronic problems. Notably, experimental studies of short-term sleep deprivation differ significantly in the length of sleep deprivation assessed, subject environment and behaviors, and measurement time points, which makes comparison across studies challenging. For the purposes of our discussion, short-term or acute sleep deprivation refers to sleep deprivation of less than one-week duration, while long-term or chronic deprivation is on the order of months. When possible, studies conducted in obstructive sleep apnea (OSA) patients will be discussed, as the fragmented nature of their sleep serves as an organic model system for fragmented sleep in ICU patients [66].

Cardiovascular System

Elevated blood pressure is a recognized consequence of short-term sleep deprivation. Many studies have found increases in blood pressure and heart rate after a single night of experimental deprivation [67–69], though effects can vary with subject posture during deprivation and

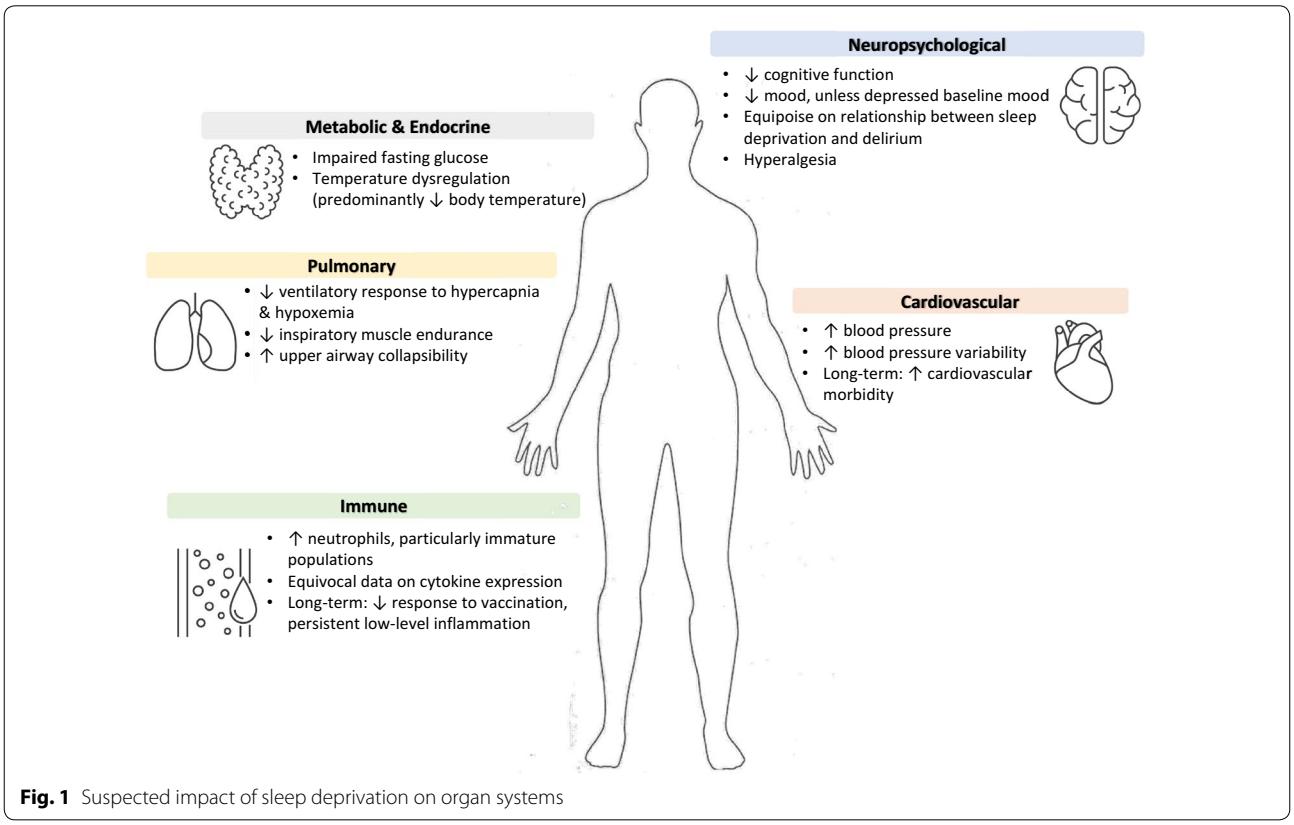

Fig. 1 Suspected impact of sleep deprivation on organ systems

vital sign measurement [70, 71]. Hospitalization itself is also associated with higher morning blood pressure in older adults [72]. The hypertensive effect of sleep deprivation has been attributed to an increase in sympathetic activity [73], a reduction in maximum endothelium-dependent vasodilation [52], and an upward resetting of the baroreflex set point [50, 57]. This relationship between sleep deprivation and blood pressure has particular relevance for NeuroICU patients with strict blood pressure parameters, e.g., patients with hypertensive and aneurysmal bleeds. In addition to its hypertensive effect, sleep deprivation is also correlated with increased blood pressure variability [74], which may worsen stroke outcomes [75, 76].

A link between chronic sleep deprivation and increased cardiovascular morbidity has also been demonstrated across numerous epidemiologic studies [77–79], and since ICU length of stay (LOS) can be prolonged, we will briefly discuss the relationship here. This relationship holds true in OSA, in which higher numbers of apneic events correlate with increased blood pressure variability during wakefulness, a phenomenon which may precede the development of persistent hypertension [80]. OSA patients also have increased sympathetic activity and resting heart rate. An elevation in blood pressure and inflammation—which also increases with chronic lack of sleep [81]—may underlie this relationship, increasing cumulative cardiovascular risk. For example, levels of C-reactive protein (CRP), an inflammatory marker shown to be an independent predictor of future myocardial infarction and stroke in apparently healthy individuals [82, 83], are higher after experimental sleep deprivation [84]. Newly diagnosed OSA patients have also been found to have elevated levels of CRP, with severity proportional to the CRP level [85].

Pulmonary System

The impact of sleep deprivation on pulmonary function is relevant in the NeuroICU given the proportion of patients who require ventilatory support [86, 87] and the prevalence of sleep-disordered breathing among stroke and transient ischemic attack patients [88]. As compared to ventilated non-neurological patients, those with neurological disease experience poorer outcomes with longer ICU and ventilator days, more tracheostomies, and higher mortality rates [89].

Most studies have found a reduced ventilatory response to hypercapnia and hypoxemia after 24 h of sleep deprivation [90–92], although this finding has been disputed by a newer study performed with stricter control of subject behavior and environment [93]. Short-term sleep deprivation has also been shown to lessen inspiratory muscle endurance. In humans, Chen et al. found a significant reduction in maximal voluntary ventilation after 30 h of sleeplessness, with no change in respiratory muscle strength, forced expiratory volume in one second, and forced vital capacity [94]. Studies in rats [95] and exploratory work in humans [96] have suggested that the underlying mechanism is impairment of respiratory motor plasticity (i.e., inspiratory drive in response to hypoxia) with sleep deprivation, a finding that may be especially problematic among patients hospitalized for brain injury.

Experimental sleep deprivation has also been found to increase upper airway collapsibility, which can cause or contribute to preexisting OSA and lead to challenges in extubation [97–99]. This finding may be pertinent for neurological patients with pharyngeal muscle weakness. Studies on patients with OSA have also demonstrated that cerebral blood flow (CBF) decreases during obstructive apneas [100–102], and intracranial pressure increases in linear proportion to the length of an apneic event [103]. The reduction of CBF in OSA may be attributed to damage to brain areas essential for vascular regulation (including the insular, cingulate, and medial frontal cortices; raphe and ventrolateral medulla) and an unexplained blunting of the typical vasodilator response to increased $PaCO_2$ [104]. Such results highlight the possible complications of sleep deprivation for NeuroICU patients with ischemic brain injury, but may not be generalizable as the authors do not correlate apneas with sleep disruption.

Immune System

Conventional wisdom considers sleep essential to maintaining the body's immunologic defenses. However, aside from response to vaccination—consistently shown to be lower in sleep-deprived individuals [105–107]—loss of sleep has not consistently demonstrated impacts on other aspects of the immune system. Short-term sleep deprivation studies largely assess the effect of varying degrees of sleep deprivation and recovery on specific cell types and cytokines. Long-term sleep deprivation has also been associated with persistent, low-level inflammation that can increase risk of conditions such as cardiovascular disease [108] and arthritis [109] and has been associated with increased risk of pneumonia [110]—at least in observational studies. The significance of these individual changes in the larger context of illness recovery or infection response is difficult to evaluate.

The impact of sleep deprivation on natural killer (NK) cells, which play a critical role in early defense against viruses and tumor cell cytotoxicity [111], has been studied extensively with great variability in results. Several authors report a decline in NK cell function with sleep deprivation, and a return to baseline after one night of

recovery sleep [112–114]. One study did not find NK cell function recovery after resumed sleep [115], and one found an *increase* in NK cell activity after severe sleep deprivation (64 h) [116]. This variation might be explained by the difference in timing of blood draws across experiments, which may be confounded by the natural circadian rhythm of NK cell activity, and the small number of subjects in each of these studies (10 or fewer).

Neutrophils have been found to be persistently elevated after sleep deprivation, even with return to normal sleep [117, 118]. These cells are the 'first responders' at a site of potential injury or infection and therefore serve as a marker of acute inflammation. Christoffersson et al. demonstrated an enrichment of immature populations and a reduced capacity to produce reactive oxygen species in response to bacterial and pharmacologic stimuli, suggesting the promotion of a less effective yet pro-inflammatory state with one night of total sleep deprivation [119]. Notably, elevated neutrophil-to-lymphocyte ratios in peripheral blood have been shown to be predictive of poor outcomes among patients with TBI [120], acute ICH [121], and stroke [122].

Data on cytokine expression are equivocal. Levels of pro-inflammatory proteins ICAM-1, E-selectin, IL-1b, IL-6, and TNF-a, have been found to increase after one night of total sleep deprivation in most [123, 124] but not all studies [125]. A meta-analysis of 72 studies evaluating CRP ($n > 34{,}000$), IL-6 ($n > 30{,}000$), and TNF-a ($n = 672$) levels after sleep deprivation found higher levels of CRP with sleep disturbance and the extremes of short or long sleep, higher IL-6 with sleep disturbance and the extreme of long sleep, and no changes in TNF-a. Notably, neither experimental sleep deprivation nor sleep restriction was associated with statistically significant changes in any of the three inflammatory markers in this meta-analysis [60]. Regarding neurological injury specifically, acute elevation of CRP following ICH is associated with higher mortality and poor functional outcome [126], although the etiology underlying the rise in CRP in ICH is likely multifactorial.

Ultimately, increases and decreases in immune cell activity and cytokine levels are seen with inadequate sleep. Regarding acute brain injury (ABI) specifically, the pro-inflammatory milieu of biomarkers that can occur with sleep deprivation is also associated with poorer outcomes. Additional research is required to fully comprehend the physiological significance of these changes, but raises the possibility that sleep normalization and restoration of the circadian rhythm may be targets for improving outcomes in ABI. Furthermore, given the potential for inflammatory markers to predict or influence prognosis after brain injury, future studies may explore the value of sleep indices such as sleep quality or fragmentation as mediators of clinical outcomes.

Metabolic and Endocrine Systems

Acute sleep deprivation alters glucose metabolism and modulates hormone levels [127, 128]. Among hospitalized patients, shorter sleep duration and worse sleep efficiency (measured via wrist actigraphy) are associated with hyperglycemia and impaired fasting glucose [129]. This is important to consider among those with acute neurological injury due to the association between hyperglycemia and worse outcomes in patients with ischemic stroke [130], TBI [131], and SAH [132–134].

Several experimental studies have demonstrated that the loss of sleep greater than one hour per night can decrease glucose sensitivity by 20–40% among healthy subjects [44, 135]. This phenomenon may occur through the modulation of both hepatic and peripheral metabolic pathways after just a single night of sleep restriction to 4 h [136]. Changes in glucose metabolism likely contribute to the correlation between chronic sleep loss and type 2 diabetes observed in epidemiological studies [137].

Thermoregulation is also very important in the NeuroICU. Hyperthermia and fever (temperature > 38 °C) is a cause for concern among patients with stroke and TBI [138] and occurs in up to half of these patients [139–141]. Cooling techniques and pharmaceutical management can be used to target normothermia and even hypothermia. Although sleep deprivation has been associated with declines in body temperature [142–144], it is difficult to clarify the relevance of this finding in the context of acute neurological injury, which itself causes temperature dysregulation [145].

Neuropsychological Effects

It is known that sleep deprivation impacts neuropsychological function in healthy individuals. The impact of sleep deprivation on various aspects of neuropsychological functioning among ICU patients is not as well studied, and what we do know is addressed as follows:

Cognitive Function

Cognitive performance declines with sleep deprivation and fragmentation in healthy individuals [146]. A wide range of cognitive tasks—attention, working memory, short-term memory, learning, and situational awareness—are negatively impacted by lack of sleep and worsen as sleep-deprived subjects spend more time on task [147]. In a landmark meta-analysis of 19 studies evaluating the neurocognitive consequences of sleep deprivation in 1932 non-critically ill patients, Pilcher et al. found that a person at the 50th percentile (composite of motor, cognitive, and mood domains) in the sleep-deprived

group performs at approximately the same level as a person at the 9th percentile in the non-sleep-deprived group [148]. In healthy individuals, improvement in cognitive impairment can be seen with adequate rest [149, 150].

Critical illness itself—independent of sleep deprivation—appears to have an effect on cognitive performance. ICU survivors exhibit cognitive impairments across a similarly wide range of domains so-called post-intensive care syndrome. Between 25 and 78% of ICU survivors experience neurocognitive impairments, with acute respiratory distress syndrome patients particularly afflicted [151–154]. While cognitive function has been found to improve in the first year after discharge, long-term studies assessing outcomes several years post-ICU stay have found persistent impairment after 6 years [155]. The extent of this cognitive impairment is notable: Jackson et al. found impairments in visual domains, psychomotor speed, and verbal fluency in ICU survivors at 6-month follow-up that were clinically equivalent to mild dementia [156]. The mechanisms by which this impairment occurs in the ICU include hypotension, hypoxemia, hyperglycemia, and delirium during admission [73]. The relationship between sleep deprivation and cognitive impairment in this setting has not been investigated directly.

Psychiatric Effects

Sleep deprivation for one night has been observed to alleviate depressive symptoms in 40–60% of patients with preexisting depression [157], though this effect is limited by relapse with recovery sleep [158]. However, sleep deprivation of healthy subjects impairs mood as assessed using the Profile of Mood States rating scale [64, 159]. Underlying confinement to a laboratory setting can have a negative impact on mood [49, 160], which may confound findings in sleep studies lacking controls [69]. There is evidence to suggest that sleep deprivation may reset circadian clock gene abnormalities that contribute to depression [161]. Perhaps sleep deprivation can only have a beneficial effect in depressed patients with preexisting circadian rhythm disturbances.

In addition to new cognitive symptoms, ICU survivors may also display post-traumatic stress disorder (PTSD), depression, and anxiety. Depression and anxiety have a documented prevalence of 17–43% [62, 162] and 23–48% [163], respectively. Estimates of the prevalence of ICU-PTSD vary from 19% in systematic review [164] to 64% (although these authors ultimately felt the variability among studies to be too significant to draw strong conclusions) [165, 166]. These new psychiatric symptoms can have long-lasting effects on sleep; for instance, PTSD often causes persistent distress and nightmares [167].

While sleep deprivation outside of the ICU has a negative effect on mood and subjective stress [168], its effects in the ICU are more speculative. Studies of daily sedation interruption have found an improvement in PTSD symptoms, theoretically by facilitating the formation of factual rather than delusional memories which are characteristic of the condition [169]. It remains unclear whether sleep deprivation, which has different physiological consequences from sedation interruption, would alter psychiatric symptoms in the same way.

Delirium

Delirium is a clinical syndrome of fluctuations in consciousness, attention, and cognition. It is an independent predictor of mortality [170–172], increased hospital LOS [50, 173, 174], and persistently worsened physical and mental status after discharge [175, 176]. There is significant overlap in the risk factors, pathophysiology, and presentation of sleep deprivation and delirium, particularly the hypoactive subtype which is characterized by lethargy and sedation [177].

Three neuroanatomical pathways of attention have been proposed [178, 179], and those same regions evidence abnormalities (utilizing functional magnetic resonance imaging [180], positron emission tomography [181], and EEG [182]) in both sleep deprivation and delirium [183]. Both conditions also appear to share the neurochemical alterations of cholinergic deficiency and dopaminergic excess, although the former has only been seen in rat models [57].

Despite these similarities, no studies have definitively shown that sleep deprivation is itself a risk factor for delirium, although there is equipoise on the topic [184]. Notably, sleep-promoting interventions have been shown to reduce the number and duration of delirium episodes among general medical ward [185], medical ICU [186], and surgical ICU [187, 188] patients.

Pain Perception

There appears to be a bidirectional relationship between pain perception and sleep deprivation. The conventional perspective is that pain impairs sleep, but sleep deprivation may also interfere with pain processing. Correlational studies in fibromyalgia patients have found more arousal episodes during sleep as compared to healthy controls [189], as well as an inverse relationship between subjective sleep quality and sensitivity to pressure pain [190]. In the acute setting, poor sleep has also been associated with a significantly greater pain experience among hospitalized burn patients [191]. Experimental work in healthy subjects has found that 24 to 40 h of total sleep deprivation causes either no [192, 193] or a generalized hyperalgesic effect [194], with a return to baseline following a night of recovery sleep [195]. The disruption of slow

wave sleep seems particularly important in lowering the pain threshold [196, 197].

Strategies for Sleep Promotion in the NeuroICU

The critical care environment and circumstances surrounding admission to the ICU will disrupt sleep for many patients. Without data demonstrating a direct and significant impact on patient outcomes, sleep cannot take precedence over patient care activities. Nevertheless, there are several opportunities to address some of the causes of sleep deprivation discussed above.

Patient care may be consolidated and discretionary care activities (e.g., baths, phlebotomy, dressing changes) performed during the daytime. Hourly neurochecks may be limited to the most crucial initial 12 h after presentation or surgery, or for an extended period in patients more likely to require intervention, such as those with vasospasm or malignant cerebral edema. Basic noise reduction interventions such as earplugs and white noise machines have been shown to promote longer and better quality sleep [198, 199]. New ICUs can consider noise reduction in their designs [200]. Quiet time to allow naps in the afternoon and evening hours is a simple policy that may increase patient satisfaction with sleep [201], especially as patient satisfaction is becoming an important benchmark of care.

Inappropriate light deprivation or exposure may be corrected through the adjustment of window blinds, use of personal eyeshades, and appropriate timing of artificial light sources. The timing of indoor lighting to reflect or augment the physiological 24-h circadian sleep–wake cycle has been demonstrated to improve mood in seasonal affective disorder and non-seasonal depression [202]. A small pilot study with hematopoietic stem cell transplant survivors found that full-spectrum white light administered for 30 min every morning for 4 weeks improved cancer-related fatigue as compared to non-stimulating dim red light [203]. For Alzheimer's disease and related dementia patients residing in healthcare facilities, lighting schemes that favor stimulating light with blue undertones in the morning appear to improve sleep time and efficiency [204]. Artificial light exposure during the daytime has been shown to decrease the incidence and duration of delirium [184]. Although more research is necessary to determine the benefits of circadian lighting schemes in the ICU setting, past work has shown subjective patient satisfaction with dynamic lighting environments without clear sleep benefits [205].

Patients receiving continuous sedation should receive daily sedative interruptions—when not limited by clinical contraindication—given its association with decreased duration of mechanical ventilation and LOS [206]. For mechanically ventilated patients, the ventilation mode should be tailored to pulmonary requirements. Given the association between sleep-disordered breathing and stroke/transient ischemic attack, simple interventions including avoidance of the supine position if possible, administering low concentrations of oxygen, and continuous positive airway pressure for hemorrhagic stroke patients may also be implemented [207]. Complementary therapies including massage [208–210] and music [211] have been found to promote sleep in the ICU setting, and should be further investigated.

Ultimately, ICU staff must be educated regarding the benefits of minimizing sleep deprivation for their patients. The exact form and quantity of interventions undertaken may vary by ICU, but increased awareness of this issue, real-time identification of areas for improvement, and active intentions to address them are necessary.

Conclusion

During their hospital admission, critically ill patients suffer from sleep disturbance due to environmental and personal factors, with detriment to various organ systems. Although the relevance of specific sleep-deprivation-related impacts to hospital and long-term outcomes requires further characterization, it is clear that low-quality sleep harms patients' subjective well-being.

Critically ill patients with brain injuries face several unique challenges related to sleep deprivation. In the NeuroICU, patients are subject to hourly neurochecks and uncomfortable devices, in addition to the issues with the hospital environment, mechanical ventilation, and medications that other ICU patients experience. Impacts on the endocrine system such as glucose regulation and thermoregulation, in addition to potentially compounding the effect of sleep deprivation on preexisting neurological injury in neuropsychological domains, are particularly relevant in the NeuroICU population. Several straightforward interventions are possible to improve patient sleep quality and quantity. It should be noted that the major limitation of this review is the paucity of data derived from the NeuroICU patient population. Therefore, the continued optimization of care will require further investigation in this specific population regarding the impact of sleep deprivation on outcome measures and the utility of various interventions on sleep specifically in the neurocritically ill.

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Authors' Contribution
VA Chang was responsible for primary review of the literature and drafting of the manuscript, as well as providing final approval for submission. RL Owens provided revisions and feedback and was involved in final approval for submission. JN LaBuzetta was responsible for conception of the manuscript, extensive revisions and feedback, and providing final approval for submission.

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