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REVIEW

The Role of Perioperative Sleep Disturbance in Postoperative Neurocognitive Disorders

Xuan Wang
Dongyu Hua
Xiaole Tang
Shan Li
Rao Sun
Zheng Xie
Zhiqiang Zhou
Yilin Zhao
Jintao Wang
Shiyong Li
Ailin Luo

Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Hubei, People's Republic of China

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Abstract: Postoperative neurocognitive disorder (PND) increases the length of hospital stay, mortality, and risk of long-term cognitive impairment. Perioperative sleep disturbance is prevalent and commonly ignored and may increase the risk of PND. However, the role of perioperative sleep disturbances in PND remains unclear. Nocturnal sleep plays an indispensable role in learning, memory, and maintenance of cerebral microenvironmental homeostasis. Hospitalized sleep disturbances also increase the incidence of postoperative delirium and cognitive dysfunction. This review summarizes the role of perioperative sleep disturbances in PND and elucidates the potential mechanisms underlying sleep-deprivation-mediated PND. Activated neuroinflammation and oxidative stress; impaired function of the blood-brain barrier and glymphatic pathway; decreased hippocampal brain-derived neurotrophic factor, adult neurogenesis, and sirtuin1 expression; and accumulated amyloid-beta proteins are associated with PND in individuals with perioperative sleep disorders. These findings suggest that the improvement of perioperative sleep might reduce the incidence of postoperative delirium and postoperative cognitive dysfunction. Future studies should further investigate the role of perioperative sleep disturbance in PND.

Keywords: perioperative sleep disturbance, cognitive impairment, postoperative delirium, postoperative cognitive dysfunction, neuroinflammation

Introduction

Nocturnal sleep plays an essential role in learning and memory through specific oscillations.[1,2] As an indispensable part of the circadian rhythm, sleep promotes the removal of metabolic wastes to maintain cerebral microenvironmental homeostasis.[3–5] The effects of sleep disruption on brain structure and cognitive performance have attracted increasing attention in recent years. The prevalence of sleep disturbance is 30.6–41.2% in the elderly at home[6] and is much higher in hospitalized patients due to ward environment and patients' primary diseases.[7] Notably, sleep disturbance before admission has been proven to increase the risk of Alzheimer's disease (AD),[8] which would further promote the development of postoperative neurocognitive disorders in elderly patients.[9,10] Contrary to the causes of sleep disturbance at home, perioperative sleep disturbance significantly increases the risk of postoperative complications, including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD).[11,12]

POD and POCD are common postoperative neurocognitive complications in the elderly and belong to perioperative cognitive dysfunction.[13] In view of the extensive

Correspondence: Shiyong Li; Ailin Luo
Email shiyongli@hust.edu.cn; alluo@tjh.tjmu.edu.cn

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use of the terms "POCD" and "POD" to date, we use these terms in this review. POD and POCD share similar risk factors with preoperative neurocognitive disorders (Figure 1) and may co-exist following surgical procedures. POCD is more common in elderly patients with POD.[14] POD and POCD would further cause long-term postoperative cognitive decline in elderly patients.[15,16] Although extensive studies have focused on the potential mechanisms underlying postoperative neurocognitive disorders, to date, they remain unclear. In this review, we summarize the epidemiology, risk factors, potential mechanisms, current diagnosis, and treatments of preoperative and postoperative neurocognitive disorders (Table 1).

Perioperative sleep disturbance may play a crucial role in postoperative neurocognitive disorders in light of the function of sleep in memory consolidation and the effect of sleep disturbance on cognition. However, little attention has been paid to investigating the role of perioperative sleep disturbances in postoperative neurocognitive disorders. Based on the role of sleep in memory and the role of sleep disruption in cognitive impairment, this review elaborates on the potential mechanisms by which perioperative sleep disturbance contributes to POD and POCD. The findings would shed light on the development of potential treatment strategies for POCD.

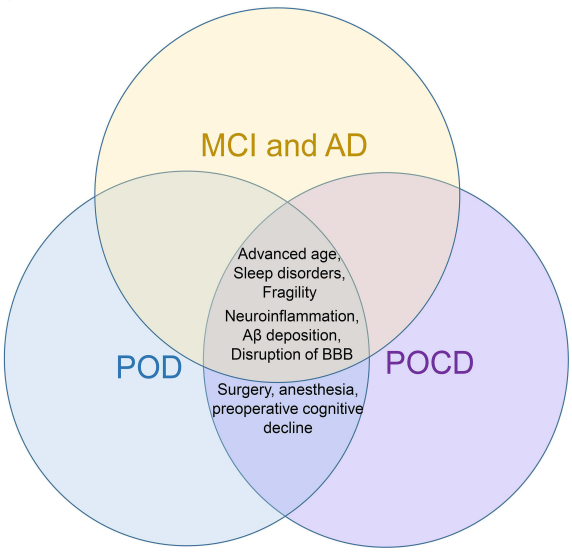

Figure 1 Shared risk factors between preoperative neurocognitive decline and POD and POCD. Shared mechanisms between MCI, AD, POD, and POCD include neuroinflammation, increased amyloid-beta deposition, and disruption of the blood-brain barrier. Common risk factors include advanced age, sleep disorders, and fragility. Moreover, the mutual risk factors for POD and POCD are surgery, anesthesia, and preoperative cognitive decline.

Role of Sleep in Learning and Memory

Normal Sleep and Its Physiological Role in Memory and Forgetting

According to electroencephalogram (EEG), sleep is divided into rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep.[17] NREM sleep accounts for 75–80% of the whole sleep and can be divided into four stages: N1, N2, N3, and N4;[18] N3 and N4 are collectively known as slow-wave sleep (SWS).[18] Electricity activities in NREM sleep include slow oscillations (SOs), spindles, and sharp-wave ripples;[19] SOs originate in the neocortex,[20] spindles generate from the thalamus, and sharp waves generate from the hippocampus.[19,21] SOs, spindles, and hippocampal sharp waves couple to promote the transformation from information to long-term memory, indicating the dialogue of the neocortex-thalamus-hippocampus.[22] Moreover, contrary to the alpha waves and beta waves during waking time, the dominating brain waves during sleep are delta waves and theta waves.[19] As one of the hallmarks of SWS, delta waves (1–4 Hz) are similar to SOs (~1 Hz) with higher field potential rhythms.[23] Delta waves have been proved to be beneficial to forgetting, while SOs is of advantage to memory preservation.[23] Additionally, delta electrical stimulation of the neocortex enhances SOs, which strengthens the oscillation of spindles in the thalamus.[5] These oscillations' enhancement promotes the transformation from short-term memory stored in the hippocampus to long-term memory stored in the cortex.[5] Moreover, REM sleep's electricity activities consist of ponto-geniculo-occipital (PGO) waves and theta activities.[24] During REM sleep, melanin-concentrating hormone-producing neurons (MCH neurons), which are located at the hypothalamus and project to the hippocampus densely, selectively promote the forgetting of hippocampal-dependent memory,[2] and activation of MCH neurons impairs hippocampus-dependent memory.[2] In summary, SOs mainly preserve memory by coupling spindles in NREM sleep,[25] delta waves in NREM sleep and MCH neurons in REM sleep contribute to forgetting,[2,25] and unnecessary memories can also be removed by synaptic remodeling to support new learning and memory based on the synaptic homeostasis hypothesis (SHY).[26] Therefore, normal sleep ensures the function of learning and memory through the balance of information retention and forgetting.

Table 1 Epidemiology, Potential Mechanisms, Current Diagnosis and Treatments of Perioperative Neurocognitive Disorder

Perioperative Neurocognitive Disorder	Definition and Classification	Prevalence	Risk Factors	Potential Mechanisms	Diagnosis	Current Treatments
Preoperative neurocognitive disorder	The cognitive disorder not related to the upcoming surgery or anesthesia and can be certified by the patient, family, or medical personnel, including mild NCD and major NCD.[13]	Mild NCD in the elderly: 18.8%, dementia in the elderly: 8.8%.[144] Further, about 8–15% of patients with MCI will progress to dementia every year.[8]	Advanced age, low educational level, coronary heart disease, frailty,[97] sleep disturbance,[8] diabetes, absent physical activity, social isolation, and depression in the elderly.[145]	Deposition of amyloid-beta protein and excessive tau proteins,[106] neuroinflammation, neurovascular dysfunction,[146] decreased hippocampal neurogenesis,[147] glial dysfunction and genotype of Apolipoprotein 4.[113]	Structural magnetic resonance imaging,[148] [18F] fluoro-D-glucose positron emission tomography ([18F] FDG-PET).[149] Montreal Cognitive Assessment (MoCA), Mini-Mental State Exam (MMSE), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[150]	Combination of various treatments: antihypertensive drugs, Mediterranean diet, cognitive rehabilitation training, exercise, psychological therapy, social intereaction.[145,151]
POD	Large fluctuations of performance, cognitive impairment, disturbed circadian rhythm, dysfunction of attention and consciousness, which occurs within one week after surgery or before discharge.[152]	The prevalence of POD in the elderly is 20–29%.[153]	Advanced age, low educational level, preoperative cognitive impairment, sleep disruption, major invasive operation.[154]	Various hypotheses are overlapped: neuroinflammation, excessive neurotoxic substance, imbalanced neurotransmitters, oxidative stress, diurnal dysregulation and disconnected brain networks.[155–158]	Confusion Assessment Method (CAM), Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV TR), International Classification of Diseases (ICD-10).[153]	Nutritional supplement, cognitive training, professional hospital care, management of sleep and pain.[159–161]
POCD	Mild decline of learning and memory, language, attention, perception, as well as the execution of patients after surgery.[162]	After cardiac surgery: 36% at six weeks, 24% at six months, 42% at five years.[95]	Advanced age, postoperative pain, low educational level, major invasive surgery, the use of anticholinergics and opioids.[95,163–165]	Cerebral hypoperfusion and		

hypoxia,[166] microembolus,[167] deposition of amyloid β,[168] neuroinflammation, destructed blood-brain barrier and neuronal apoptosis.[110,169] Clear diagnostic criteria is absent. The evaluation usually depends on neuropsychological scales, including the battery of tests and *Z* scores.[170]

Melatonin,[122] anti-inflammatory therapy, depressant and management of pain and preoperative cognitive training.[97]

Abundant studies on the brain network reveal that NREM sleep mainly facilitates consolidation of declarative memory, especially hippocampus-dependent memory, and REM sleep consolidates the memory of procedure and emotion.[1] Moreover, the glial-lymphatic (glymphatic) pathway is active during sleep and facilitates the flow of cerebrospinal fluid (CSF) from perivascular spaces to the brain parenchyma through aquaporin 4 (AQP4) water channels.[27] The convection velocity between interstitial fluid (ISF) and CSF increases significantly during natural sleep, which elevates the clearance of amyloid-beta (Aβ) protein in the brain of rodents.[28] Additionally, a clinical study also suggests that during NREM sleep, CSF shows pulsed flow with large amplitude to enhance the clearance of cerebral metabolic wastes.[3] Taken together, these findings prove the indispensable role of sleep in the formation and consolidation of memory and forgetting.

Circadian Rhythms and Regulation of Sleep

Circadian rhythms are internal biological processes that occur regularly within a period of approximately 24 hours and are controlled by clock genes.[29] Circadian rhythms have a feedback mechanism. The suprachiasmatic nucleus (SCN) in the hypothalamus serves as a primary pacemaker and controls peripheral cells as well as the circadian rhythms of thousands of downstream genes synchronously after receiving the optical signals from the retina.[30] This process can be modulated by an autonomous transcription and translation feedback loop within the SCN to adapt to the external environment (including light, feeding, and temperature).[31,32] Remarkably, circadian rhythms participate in memory, possibly by outputting gamma-aminobutyric acid from the SCN to learning target sites; this process is independent of sleep and indicates subregional crosstalk.[33] The distribution of CSF and perivascular polarization of AQP4 are also under the control of circadian rhythm.[34] Accordingly, the disturbance of circadian rhythm contributes to hippocampal-dependent cognitive impairment.[35]

As an essential part of circadian rhythm, sleep could be modulated by homeostatic drive, indicating that the body suffers from more pressure induced by adenosine (a degradation product of ATP) to fall into sleep due to sleep insufficiency.[36] Moreover, subsequent NREM sleep after sleep deprivation is longer and deeper to meet homeostatic requirements.[37] However, this homeostatic modulation would be attenuated after chronic sleep restriction.[38] In addition, another modulation of sleep is circadian rhythm involving the periodic release of melatonin.[37] Keeping in line with the pacemaker, the plasma level of melatonin is high during the night but low during the day.[39] However, melatonin secretion is suppressed by even moderate light at night, which may be the precipitating factor of the high prevalence of sleep disorder in the hospital.[40] Periodic release of melatonin not only consolidates clock genes' expression patterns in the hippocampus but also enhances learning efficiency by modulating the synaptic plasticity during the daytime.[41] These studies indicate the importance of normal circadian rhythm in maintaining sleep and awakening.

Role of Sleep Disruption in Cognitive Impairments

Growing evidence indicates that sleep disruption is associated with impairment of spatial memory, verbal fluency, attention, processing speed, and executive function.[42–45] AD is the most prevalent type of major neurocognitive disorder in the elderly. A large proportion of AD victims suffer from sleep disorders,[43] which in turn promotes the development of AD in the elderly.[45] Particularly, insomnia is associated with poor cognitive performances and lower volumes of grey matter,[46] and the atrophy of grey matter in the medial prefrontal cortex (mPFC) is associated with attenuated SOs-spindles coupling and impairment of hippocampal-dependent memory in the elderly.[22] Remarkably, both insufficient sleep duration (less than 6 hours) and excessive sleep duration (more than 9 hours) are associated with cognitive impairment,[47] and sleep fragmentation also accelerates the development of preoperative NCD.[44]

In addition, sleep deprivation also promotes deposition of Aβ protein in the hippocampus[48,49] and increases the ratio of p-tau/total tau, thereby accelerating the occurrence and development of AD.[50] Hence, management of sleep is expected to decrease the incidence of neurocognitive disorders in the elderly.[51] Notably, except for specific effects of surgery and anesthesia on perioperative sleep, there are many similarities between perioperative sleep disturbance and sleep disruption at home.[52–54] Based on the common characteristics of sleep disruption at home and perioperative sleep disturbance, we could provide more directions and choices for future studies investigating postoperative neurocognitive disorders.

Perioperative Sleep Disturbance and Postoperative Neurocognitive Disorders

In contrast to sleep disorders at home, perioperative sleep disturbance refers to disrupted sleep structure or decreased sleep duration at night after admission. Approximately 64% of hospitalized patients suffer from sleep disruption.[7,55] The diagnosis of perioperative sleep disturbance depends on combined subjective questionnaires of sleep and objective examinations, such as eye and hand movement sensors, polysomnography, and EEG.[7,56,57] As for treatments, present measures consist of perioperative psychological support[58] and drugs including benzodiazepine hypnotics,[59] melatonin receptor agonists,[60] and analgesic and narcotic sedatives.[61,62]

Many studies on sleep disturbance at home and cognitive disorders have elucidated the role of perioperative sleep disturbance in POD and POCD.[43] Except for certain effects of anesthesia and surgery, perioperative sleep disturbance may have some similarities with sleep disturbance at home and plays an important role in the development of neurocognitive disorders. Indeed, preoperative and postoperative sleep disturbances are associated with POD and POCD.[12,52,63,64] Based on the role of sleep disruption at home in cognitive impairments and the impact of perioperative sleep disturbance on postoperative neurocognitive disorders, we summarize the potential mechanisms by which perioperative sleep disturbance promotes the development of postoperative neurocognitive disorders.

Impact of Surgery and Anesthesia on Perioperative Sleep

Perioperative sleep disturbances occurring in different periods may have various effects on postoperative neurocognitive disorders. To clarify this, we should first understand the impact of surgery and anesthesia on perioperative sleep and circadian rhythm. Surgery and anesthesia may accelerate the development of postoperative neurocognitive disorders.

Sleep disruption after admission is caused by noise, inadequate light, medical devices, and pain.[7] The characteristics of EEG during anesthesia are different from those during physiological sleep, and the neural circuits involved in anesthetic sedation are also different from those in physiological sleep.[65] Moreover, some general anesthetics, including isoflurane and propofol, disrupt the circadian rhythm of melatonin secretion.[66] However, there are also many similarities between anesthesia and normal NREM sleep, including increased dominating slow waves and sleep spindles.[67] These similarities may promote the recovery of preoperative sleep loss.[68] Nevertheless, REM sleep is significantly reduced at the first night after surgery and would return to preoperative baseline at the third night after surgery.[69] These findings indicate that superimposed effects of anesthetic and surgery, at least partially, contribute to postoperative sleep disorders in patients.

Furthermore, melatonin's secretion is elevated by desflurane during the day and may be associated with stimulation of the sympathetic nerve.[66] Interestingly, the use of isoflurane during the day causes significant suppression of circadian rhythm genes, including BMAL1, CLOCK, PER2, and CRY2, with only minimal inhibition at night;[70] Three kinds of gas anesthetics all show no effect on the secretion of melatonin at night.[71] Besides, circadian rhythm involving the circadian activity level has been proven to be severely disturbed after large surgery.[72] For instance, melatonin concentration is reduced on the first night after surgery, and treatments of melatonin could prevent related sleep disturbances.[73] These findings verify different effects of anesthesia and surgery on sleep during day and night, indicating that anesthesia and surgery during the night conform to the normal circadian rhythm and have smaller impacts on circadian rhythms.

Association Between Perioperative Sleep Disturbance and POD

Sleep disturbance at home is an independent risk factor for POD,[74] and perioperative sleep disturbance increases the risk of POD[11,75] (Table 2). Moreover, one study argued that perioperative sleep disturbance could be used as a predictor of POD in elderly patients in the ICU after heart surgery.[76] Indeed, the improvement of sleep in elderly patients could reduce the risk of POD, further verifying the potential role of sleep disturbance in POD.[77]

There are confounding factors for establishing a link between preoperative sleep disturbance and POD. Postoperative pain is inevitable following major surgery, and improper management of pain not only decreases the total sleep duration[78] but also impacts the cognitive scores.[79] The secretion of melatonin, an important regulator of circadian rhythm, is delayed during anesthesia and surgery,[80–82] and the delay lasts up to the first night following surgery.[73] Postoperative supplementation with melatonin prevents

Table 2 Clinical Studies on Examining the Effect of Perioperative Sleep Disturbance on POD

Clinical Study	Sleep Disorders (Preoperative/ Postoperative)	Surgery Type	Findings
Prospective study	Perioperative insufficient sleep	Thoracic surgery	Sleep deprivation may be a trigger for POD.[171]
Prospective study	Preoperative and postoperative sleep disruption	Major non-cardiac surgery	Preoperative, but not postoperative, sleep disturbance in hospital is correlated with POD.[75]
Prospective study	Perioperative sleep disruption	Not specifically	Community sleep disruption before admission is the independent risk factor of POD. Perioperative sleep disruption will further increase the risk.[74]
Meta- analysis	Preoperative sleep disturbance	Not specifically	The risk of POD in patients suffering from preoperative sleep disturbance is approximately 5 times more likely to develop POD.[172]
Retrospective study	Postoperative sleep disturbance	The operation for proximal Femoral Fracture	Postoperative sleep disorders could be an independent predictive factor of POD in patients 60 years of age or older.[173]

related sleep disturbances[83,84] but fails to reduce the incidence of POD in elderly patients with nosocomial hip fractures.[85] Interestingly, preoperative treatment with melatonin reduces the incidence of POD,[86] indicating that early management of sleep disturbance after admission would be beneficial to postoperative cognitive outcomes.

Although no definitive conclusion has been reached, we speculate that preoperative sleep disturbance would promote the occurrence of POD and further increase the long-term cognitive impairment in patients after discharge.[74,87] With regard to the relationship between perioperative sleep disturbance and POD, mutual crosstalk rather than a causal link is more likely.

Association Between Perioperative Sleep Disturbance and POCD

Acute sleep deprivation caused by the ward environment or patients' diseases is very common in the hospital and leads to damaged sleep structure and decreased sleep duration.[88,89] Nevertheless, only a few studies have investigated the role of perioperative sleep disturbance in POCD. In view of the high incidence and harmful outcomes of POCD, more attention should be paid to the role of perioperative sleep disturbance in POCD.

Due to the absence of unified diagnostic criteria for POCD, there are few clinical studies directly pertaining to perioperative sleep disturbance and POCD (Table 3).

Table 3 Clinical Studies on Exploring the Role of Perioperative Sleep Disturbance in POCD

Study Characteristics	Sleep Disorders (Preoperative/ Postoperative)	Surgery	Findings
Prospective study	Preoperative and postoperative sleep quality	Abdominal surgery	The quality of postoperative sleep assessed by actigraph and visual analog scale is worse and the number of awakenings is higher in patients with POCD.[92]
Randomized clinical trial	Preoperative and postoperative sleep	Hip arthroplasty	The supplementation of perioperative melatonin may improve early POCD in elderly patients.[174]
Randomized clinical trial	Preoperative and postoperative sleep	Mastectomy for breast cancer	The supplementation of perioperative melatonin can improve the quality and time of perioperative sleep but not postoperative cognitive function.[175]

Some scholars consider postoperative sleep disturbance a phenotype of POCD.[90,91] POCD is associated with increased perioperative awakening times and subjective poor sleep quality in hospitalized patients.[92] The occurrence of perioperative sleep disturbance may be partly due to altered rhythm of melatonin secretion.[93] However, there is a lack of clinical evidence to support the role of melatonin in perioperative sleep disturbance-related POCD.

Moreover, during normal aging, the duration of total sleep and slow-wave sleep is decreased, but sleep fragmentation and the difficulty of falling asleep are increased.[94] Advanced age is a known risk factor for POCD,[95] suggesting potential undiagnosed sleep disturbance in the elderly before admission. Sleep quality is worse in hospitals, thus inducing overlapping pathophysiological pathways.

Potential Mechanisms Underlying Perioperative Sleep Disturbance-Associated POCD

A wealth of preclinical studies have indicated a close association between perioperative sleep disturbance and POCD. However, the specific mechanisms require further exploration. In this section, we summarize preclinical evidence on the adverse effect of perioperative sleep disturbance on cognition (Table 4) and the potential mechanism of perioperative sleep disturbance in POCD (Table 5). We describe anatomical changes in the brain and illustrate potential mechanisms associated with perioperative sleep disturbance-induced POCD.

Perioperative Sleep Disturbance-Induced Structural Changes

In parallel with peripheral inflammation, the integrity and function of the blood-brain barrier are impaired by sleep restriction and surgery,[96] which are known to be involved in POCD.[97] According to MRI findings, sleep fragmentation induces hippocampal atrophy due to decreased neurogenesis in the dentate gyrus (DG) and neuronal loss in the cornu ammonis (CA),[98] which is thought to be the origin of slow waves. MPFC atrophy during aging has been used to predict the impairment of slow-wave activity and NREM-associated and hippocampal-dependent memory.[22] Furthermore, sleep disturbance decreases hippocampal-prefrontal cortex functional connectivity and thus impairs memory consolidation.[22,99] Strikingly, individuals with inadequate sleep duration exhibit decreased white matter integrity and cognitive impairment.[100] Moreover, as mentioned above, perioperative sleep disturbance includes changes in structure and duration. Therefore, perioperative sleep disturbances may induce extensive abnormalities in the brain.

The glymphatic pathway is a recently discovered cerebral structure, and its function is similar to that of the peripheral lymphatic system.[101] Its clearing activity in protein waste products is dependent on the exchange of CSF-ISF and polarized expression of AQP4 on astrocytic endfeet;[27] the glymphatic pathway is most active during NREM sleep[3,102] and is enhanced during general anesthesia.[103] As a noxiously neurotoxic substance, Aβ is

Table 4 Preclinical Studies on Investigating the Association Between Sleep Disturbance and Cognitive Impairments

Animals of the Laboratory Experiment	Sleep Disruptions	Behavioral Tests	Results and Possible Mechanisms
Elderly C57BL/6J male mice	24 h sleep disturbance	Fear context test	Sleep disturbance may selectively impair hippocampus-dependent learning and memory.[42]
Adult C57BL/6J mice	6 days of Chronic sleep restriction	None	The function of BBB is impaired by 6 days of CSR and can be reversed by 24 hours of recovery sleep.[96]
Adult male Sprague Dawley Rats	48 h of sleep deprivation	Morris water maze (MWM)	Sleep deprivation impairs spatial memory by stimulating glial cell activation and the release of pro-inflammatory cytokines.[111]
Adult male Sprague Dawley Rats	CSR (Chronic sleep restriction)	None	CSR results in the chronic elevations of IL-1β and TNF-α and inhibition of brain-derived neurotrophic factor (BDNF), which may be involved in cognitive impairment.[135]
Adult male Sprague Dawley Rats	48 h of sleep deprivation	MWM	Sleep deprivation promotes the activation of complement C3a/ C5a units that are combined with the respective receptors in the spatial memory impairment and gliosis mediated neuroinflammation in the hippocampus.[176]

Table 5 Preclinical Studies on Exploring the Association Between Perioperative Sleep Disturbance and Postoperative Neurocognitive Disorder

Animals	Perioperative Sleep Disorders	Surgery	Results and Possible Mechanisms
Elderly C57BL/6J male mice	Preoperative 8 hours of sleep disturbance	Tibial fractures	Preoperative sleep disturbance aggravated postoperative cognitive impairment and inflammation in the central nervous system.[52]
Adult male Sprague Dawley Rats	Preoperative 96 hours of REM sleep deprivation	Only sevoflurane anesthesia	Preoperative sleep deprivation aggravates hippocampal memory impairment by enhancing neuroinflammatory level.[63]
Elderly ICR mice	Postoperative sleep fragmentation	Tibial fracture	Postoperative sleep fragmentation exacerbates hippocampal inflammation and cognitive impairment.[64]
Adult C57BL/6J male mice	Preoperative and postoperative 24 hours of sleep fragmentation	Tibial fracture	Perioperative sleep fragmentation leads to a significant increase of hippocampal inflammation but without further cognitive impairment.[177]
Elderly C57BL/6J male mice	Preoperative circadian rhythm disorder	Only isoflurane anesthesia	Preoperative circadian rhythm resynchronization by administrating melatonin improved cognitive dysfunction induced by isoflurane in aged mice.[12]

mainly cleared through the glymphatic system.[3] The level of Aβ in the ISF is elevated in the dark, and the amplitude of elevation is inversely proportional to the NREM sleep time.[32] Additionally, sleep deprivation inhibits the inflow of apolipoprotein E (APOE) in CSF and clearance of APOE in ISF,[104] suggesting that sleep deprivation reduces the removal of Aβ in CSF. Notably, it was reported that even the deprivation of one-night sleep would significantly increase cerebral Aβ levels in middle-aged men;[49] Excessive cerebral Aβ increases the wakefulness of mice, which in turn affects the sleep-wake cycle.[105] Moreover, Aβ plaques also trigger the mislocalization of AQP4 and decrease CSF influx, thus forming a vicious circle.[104] Notably, Aβ accumulation in the brain is associated with neuropathological changes that contribute to cognitive dysfunction in MCI, AD, and POCD.[106–108] Based on these findings, we hypothesize that perioperative sleep disorder contributes to POCD by impairing the waste protein clearance of the glymphatic system. However, it was reported that general anesthesia, especially high-dose agents, could inhibit the glymphatic system; thus, further investigation is needed to determine whether perioperative sleep disturbance triggers original changes in the glymphatic system and whether appropriate anesthetics promote glymphatic influx.

Taken together, these findings suggest that perioperative sleep disturbances induce structural changes in the brain and possibly contribute to cognitive impairment. Future studies are needed to ascertain whether there is a causal link between anatomical abnormalities in the brain and perioperative sleep disturbance-associated POCD.

Potential Signaling Pathways

Morphological changes in the brain detected by imaging methods are usually caused by pathological abnormalities at the cellular and molecular levels. With regard to pathological changes in POCD, neuronal injury and overactivated microglia and astrocytes have been observed in animal models.[109,110] Coincidentally, sleep deprivation upregulates the expression of proinflammatory cytokines in the hippocampus,[111] facilitates microglial activation by suppressing melatonin secretion,[112] promotes Aβ deposition,[113] and increases the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[114] Furthermore, sleep deprivation impairs the microglial activity of synaptic pruning, which is essential to form the functional neural circuits in learning.[115] Overactive neuroinflammation is usually considered the culprit of POCD.[109,110] Studies examining the effect of sleep disturbance on POCD have revealed that acute preoperative sleep disruption increases the level of proinflammatory cytokines, which consequently impairs cognitive performance.[52,64] Moreover, surgical procedures upregulate proinflammatory cytokines in the peripheral plasma and hippocampus and induce or exaggerate neuroinflammation.[97,116–118] Furthermore, the inflammatory environments, in turn, deteriorate sleep quality.[119] In

other words, a vicious circle is formed. Additionally, sleep deprivation activates neurotoxic complement components C3a and C5a, which disturb the hippocampal brain-derived neurotrophic factor (BDNF) pathway and adult neurogenesis, eventually impairing spatial memory.[120] Considering the complicated effect of general anesthetics on immune function,[121] it is a great challenge to distinguish which factor (sleep disturbance, surgical procedures, or general anesthetics) is the last straw to prime the neuroinflammatory cascade.

In addition, astrocytic ATP and adenosine A1 receptor activity contribute to sleep deprivation-induced deficits in hippocampal synaptic plasticity and hippocampus-dependent spatial memory.[122] Interestingly, the astrocyte circadian clock regulates inflammatory Chi3l1 induction and further reduces the phagocytosis of microglia in the context of AD neuropathogenesis.[123] Microglia-derived factors could induce the transition of astrocytes to neurotoxic phenotype A1 astrocytes.[124] In light of the complicated crosstalk between microglia and astrocytes, it is difficult to identify the initial changes in sleep deprivation-induced cognitive impairment. In summary, perioperative sleep disturbance, particularly acute sleep deprivation, may induce overactivated microglia and astrocytes, thus resulting in postoperative cognitive impairment.

In addition to the indirect modulation effect of microglia and astrocytes, sleep disruption can directly impair neuronal excitability and synaptic plasticity.[18] Specifically, acute sleep deprivation reduces dendritic spine density in the hippocampal neurons and results in long-term memory impairment, while recovery sleep ameliorates spine loss and memory impairment.[125] Moreover, sleep deprivation induces abnormal hippocampal neuronal autophagy and apoptosis, which contribute to cognitive impairment.[126] Reduced neurogenesis and BDNF mediated by overactivated microglia are associated with sleep disruption-induced spatial memory impairment.[111] Therefore, direct and indirect neuronal injuries are involved in sleep deprivation-induced hippocampal-dependent learning and memory.

Sleep deprivation also causes oxidative stress by downregulating the α7 nicotinic acetylcholine receptor and downstream PI3K/AKT/GSK-3β in the hippocampus.[127] In addition, as anti-inflammatory and anti-oxidative factors, Nrf2 and HO-1 are also downregulated by sleep deprivation.[127] The PI3K/AKT/Nrf2/HO-1 pathway has been confirmed to be involved in POCD.[128] Moreover, activation of the Nrf2/HO-1 pathway improves cognitive impairments induced by sleep deprivation,[129] and the elevated expression of NADPH oxidase in the hippocampus and cortex induced by sleep fragmentation promotes hippocampal memory impairments.[130] NADPH oxidase in the central nervous system produces redundant reactive oxygen species (ROS), thus promoting the development of POCD.[114]

BDNF is involved in hippocampus-dependent memory formation and consolidation by regulating synaptic plasticity and hippocampal neurogenesis.[131] On the one hand, the BDNF signaling pathway plays a key role in maintaining homeostasis of REM sleep without sex difference.[132–134] On the other hand, abnormal sleep reduces the expression of BDNF. One study suggests that the reduction of peripheral BDNF possibly contributes to cognitive impairment in insomnia patients whose sleep duration is less than 6 hours.[132] Notably, the expression level of BDNF in the hippocampus, but not in the neocortex, is lower in chronic sleep restriction and sleep deprivation models.[135,136] Considering the role of the abnormal BDNF pathway in POCD,[137–139] abnormal changes in the BDNF signaling pathway induced by sleep disturbances, especially preoperative sleep disturbances, are possibly further exaggerated by other perioperative stress and contribute to cognitive impairment following surgery.

Sirtuin 1 (SIRT1) in the hippocampus is reduced after total sleep deprivation or surgery.[140,141] Interestingly, melatonin enhances memory by restoring the activity of SIRT1 after total sleep deprivation.[140] Our study and other studies found that the reduction of SIRT1 was associated with postoperative cognitive impairment by activating the neuroinflammatory pathway and inhibiting neurotrophic factors.[141,142] Considering our previous findings that SIRT1 mediated abnormal tau modification in an aged POCD model,[143] it is plausible that SIRT1 is involved in sleep disturbance-related POCD. Future studies are needed to validate this hypothesis.

Based on sleep disturbance-induced neuropathogenesis ranging from morphological changes to abnormal signaling pathways, we conclude that perioperative sleep disturbance induces extensive changes that possibly contribute to POCD. The potential mechanisms are shown in Figure 2.

Conclusions

Perioperative sleep disturbances are prevalent among surgical individuals. Clinical findings indicate that perioperative sleep disturbances increase the risk of POD and POCD, especially in the elderly population. We summarize the potential mechanisms underlying perioperative sleep-disturbance-associated neurocognitive disorders. There are

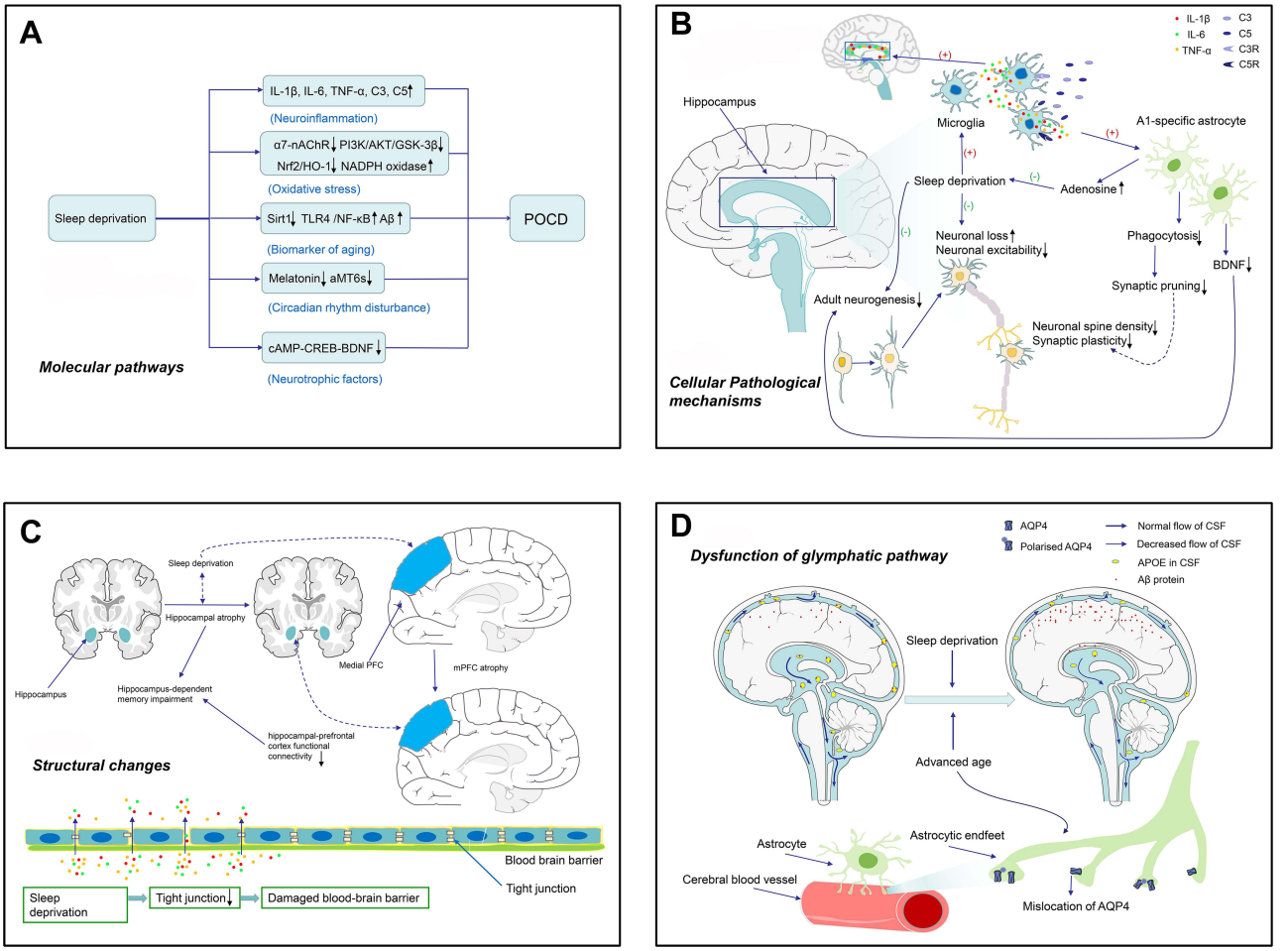

Figure 2 Potential mechanisms of sleep disturbance in postoperative neurocognitive disorders. (**A**) Signaling pathways associated with sleep deprivation-induced POCD, including neuroinflammation, oxidative stress, elevated biomarkers of aging, disturbed circadian rhythm, and decreased neurotrophic factors. (**B**) Sleep deprivation leads to several cellular pathological mechanisms in the hippocampus. Complements C3 and C5 in the hippocampus are elevated as a result of sleep deprivation, which activates microglia. Activated microglia further release IL-1β, TNF-α, and IL-6 to exaggerate neuroinflammation. Moreover, sleep deprivation activates neurotoxic astrocytes (A1-specific astrocytes) and weakens astrocytic phagocytosis and their function of synaptic pruning. Activated microglia and astrocytes promote neuronal loss. Sleep deprivation causes decreased spine density of neurons and impaired synaptic plasticity, and decreased BDNF after sleep deprivation also restrains hippocampal adult neurogenesis. All of these cellular pathological changes induced by sleep deprivation accelerate the development of POCD. (**C**) Structure changes. The blood-brain barrier is damaged by sleep deprivation through decreased tight junctions. Atrophy of the hippocampus and medial prefrontal cortex, as well as decreased hippocampal-prefrontal cortex functional connectivity, may indicate a higher risk of POCD. (**D**) Dysfunction of the glial-lymphatic pathway. Sleep deprivation causes decreased exchange of the cerebrospinal fluid (CSF) to the interstitial fluid (ISF), which promotes Aβ accumulation. Apolipoprotein E (APOE) in the CSF is reduced after sleep deprivation, resulting in depressed elimination of Aβ. Moreover, advanced age and accumulated Aβ lead to mislocalization of aquaporin 4 (AQP4) expressed in the endfeet of astrocytes, thereby forming a vicious circle to accelerate the development of POCD.

extensive overlapping neuropathological changes, such as neuroinflammation, ROS generation, and reduction in BDNF and SIRT1, between sleep disturbance-induced cognitive impairments and POCD. Some preclinical studies have shown that restoring sleep could alleviate the injury and improve cognitive function. These findings indicate that early screening and timely intervention of perioperative sleep disturbances would be a far-reaching way to prevent POCD. Moreover, appropriate operative time and anesthetic medication may also contribute to maintain perioperative circadian rhythm and reduce the risk of postoperative neurocognitive disorders.

Abbreviations

Aβ, amyloid-beta; AD, Alzheimer's disease; APOE, apolipoprotein E; AQP4, aquaporin 4; BDNF, brain-derived neurotrophic factor; CA, cornu ammonis; CSF, cerebrospinal fluid; DG, dentate gyrus; EEG, electroencephalogram; ISF, interstitial fluid; MCH, melanin-concentrating hormone; mPFC, medial prefrontal cortex; NADPH, nicotinamide adenine dinucleotide phosphate; NREM, non-rapid-eye-movement; POD, postoperative delirium; POCD, postoperative cognitive dysfunction; PND, perioperative cognitive dysfunction; PGO, ponto-geniculo-occipital; REM, rapid-eye-movement; ROS, reactive oxygen species; SCN,

suprachiasmatic nucleus; SHY, synaptic homeostasis hypothesis; SOs, slow oscillations; SIRT1, Sirtuin1; SWS, slow-wave sleep.

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Disclosure

The authors report no conflicts of interest in this work.

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