ANESTHESIOLOGY

Sleep, Pain, and Cognition: Modifiable Targets for Optimal Perioperative Brain Health

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ABSTRACT

The prevention of perioperative neurocognitive disorders is a priority for patients, families, clinicians, and researchers. Given the multiple risk factors present throughout the perioperative period, a multicomponent preventative approach may be most effective. The objectives of this narrative review are to highlight the importance of sleep, pain, and cognition on the risk of perioperative neurocognitive disorders and to discuss the evidence behind interventions targeting these modifiable risk factors. Sleep disruption is associated with postoperative delirium, but the benefit of sleep-related interventions is uncertain. Pain is a risk factor for postoperative delirium, but its impact on other postoperative neurocognitive disorders is unknown. Multimodal analgesia and opioid avoidance are emerging as best practices, but data supporting their efficacy to prevent delirium are limited. Poor preoperative cognitive function is a strong predictor of postoperative neurocognitive disorder, and work is ongoing to determine whether it can be modified to prevent perioperative neurocognitive disorders.

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As older persons increasingly rely on surgical treatment, preventing perioperative neurocognitive disorders including postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder has become a priority for patients, for families, and for perioperative research.[1,2] Defined by an acute, fluctuating disturbance in attention and awareness, postoperative delirium occurs in up to 50% of older patients and is associated with excess hospital costs, higher risk of long-term cognitive impairment, and poor functional outcomes.[3,4] Characterized by cognitive deficits in memory and executive function, delayed neurocognitive recovery (diagnosed within 30 postoperative days) and postoperative neurocognitive disorder (diagnosed within 3 to 12 months) were once considered mainly as research outcomes with questionable clinical impact. However, they are now recognized as key barriers to optimal functional recovery after surgery.[5,6] For decades, strategies to prevent perioperative neurocognitive disorders by targeting isolated perioperative interventions have produced negative or inconclusive results.[7–10] Given that there are numerous potential inciting factors for perioperative neurocognitive disorders, it is likely that multicomponent interventions may be more effective. For example, one of the most successful evidence-based multicomponent prevention strategies is the Hospitalized Elder Life Program (HELP), which has been shown in meta-analysis to consistently prevent delirium in hospitalized older persons.[11] There are 14 core interventions in HELP, highlighting the complex and myriad precipitating factors that can contribute to delirium and the challenges faced by clinicians seeking to employ a comprehensive program. The objective of this narrative review is to highlight and expand upon three key intervenable targets to consider in any multicomponent intervention designed to optimize perioperative brain health: sleep, pain, and cognition (fig. 1).

Sleep

Sleep, Circadian Rhythms, and Brain Health

Sleep is a complex, naturally occurring physiologic state that is critical to survival and health in animals and humans. A fundamental aspect of ensuring optimal physiologic functions, including sleep, is the adherence to ~24-h cycles known as circadian rhythms, which are thought to be ubiquitous to life on earth. If separated from our environmental and lifestyle choices, sleep–wake cycles are governed by our circadian system *via* the sleep-promoter hormone melatonin, which peaks during darkness.[12]

Sleep appears critical to optimal brain health and cognitive function, but only recently has there been increasing attention within the perioperative field.[13,14] What is defined as "normal" sleep varies from individual to individual and with age and comorbid disease. Broadly, the following five dimensions of sleep appear the most relevant to definitions and measurements of sleep health: (1) sleep duration: the total amount of sleep obtained per 24 h, with between 7 and 8 h considered optimal for most; (2) sleep continuity or

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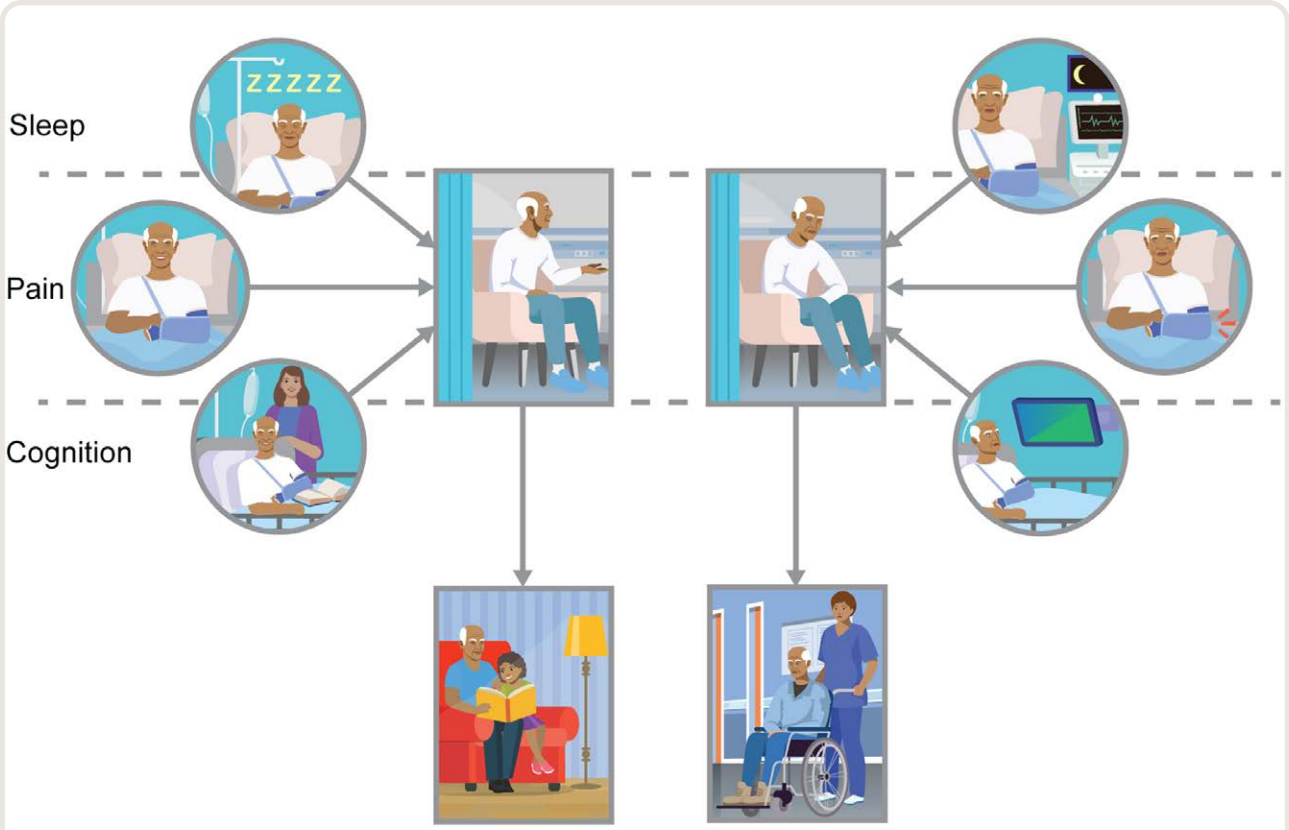

Fig. 1. The impact of sleep, pain, and cognition on perioperative brain health and postoperative recovery. Here depicted is a patient presenting for orthopedic surgery. The scenarios depict how the patient's sleep, pain, and cognition are well managed throughout the postoperative period (*left*). The patient then remains delirium-free in the hospital and returns home at their cognitive and functional baseline (*left center*). Conversely, if sleep, pain, and cognition are poorly managed (*right*), the same patient may experience delirium and/or the inability to return to their cognitive and functional baseline (*right center*).

efficiency: the ease of falling asleep and returning to sleep after awakening; (3) timing of the sleep–wake cycle within the 24-h day; (4) alertness/sleepiness: the ability to maintain attentive wakefulness; and (5) satisfaction/quality: the subjective assessment of "good" or "poor" sleep.[13] All sleep "disorders" or "disturbances" can be understood *via* one or commonly multiple dimensions. For example, insomnia is characterized by difficulty initiating or continuing sleep, but this often leads to lower sleep duration, irregular timings, subjective sleepiness and poor satisfaction/quality.

Unfortunately, as many as one in three people will experience some form of sleep and/or circadian disturbances in their lifetimes; these disturbances often go unaddressed, are increasingly common worldwide, and worsen over time.[15–19] Despite clinicians' familiarity with the diurnal nature of our own sleep and behavioral cycles and the physical and psychologic toll associated with its disruption (*e.g.*, after a busy night on-call), there remains relatively few considerations given to the impact of sleep and circadian disruption in our patients and how it may impact their brain health and overall functional recovery during the perioperative period.

Sleep Disturbance and Delirium

There is now increasing recognition for the potential link between sleep disturbances and perioperative neurocognitive disorders including delirium.[20] Sleep/circadian disturbances are more common in older persons and are more pronounced after critical illness and in neurodegenerative diseases such as Alzheimer disease, the very groups most vulnerable to perioperative neurocognitive disorders.[19,21–23]

Sleep disruption before surgery has been shown to predict postoperative delirium. In an observational study of 50 adults undergoing major noncardiac surgery in which sleep patterns were assessed objectively the night before surgery with a wearable actigraphy device, patients who developed postoperative delirium had significantly higher measures of preoperative sleep fragmentation including both the percentage of time spent wake after sleep onset (mean [SD], 44% [22%] *vs.* 21% [20%]; $P = 0.012$) and frequency of nightly awakenings (mean [SD], 17 [9] *vs.* 9 [6]; $P = 0.047$) compared to those without delirium.[24] This finding has been demonstrated in other studies and in a recent meta-analysis of data from 12 studies and 1,199 patients in which the pooled odds ratio for postoperative

delirium for patients with preoperative sleep disturbances was significantly higher than for those without a preoperative sleep disturbance (odds ratio [95% CI], 5.24 [2.28 to 3.69]; $P < 0.001$; $I^2 = 0\%$).[20] Possible shared pathophysiological pathways between sleep disturbance and delirium include altered melatonin metabolism, neurotransmitter imbalance, and reduced neuroprotection from key deficiencies such as vitamin D.[25–29] Undergoing major surgery with preexisting sleep disruption makes it likely these symptoms will be exacerbated during the postoperative recovery period as pain, nausea, light, noise, and immobility ensue.

However, based on current evidence, one cannot conclude causation. The extent to which sleep disturbances may cause delirium or *vice versa* is not yet fully understood, but these two conditions may share a common neuropathology. There is some evidence that poor sleep behavior traits and circadian disruption predicts incident Alzheimer disease, but few large prospective studies exist for sleep and delirium.[19,30] Sleep disruption and problems with rest–activity cycles are also comorbid with many conditions relevant to brain health and perioperative neurocognitive disorders including heart failure and pain, and therefore these issues could potentially be a manifestation of underlying disease such as preclinical neurodegeneration.[31,32] Whether disordered sleep directly increases the risk of delirium or whether it is indicative of an underlying comorbidity that increases risk may be difficult if not impossible to determine. Testing whether treatment of sleep disorders reduces delirium in controlled studies may be the best way to sort out these direct or indirect effects. How this affects the perioperative physician is also evolving. The role of sleep in the preservation of perioperative cognition is an active area of research, and it may be that sleep disruption comes to be seen as a chronic condition in need of optimization rather than reversal.

Sleep-disordered Breathing, Continuous Positive Airway Pressure, and Delirium

Sleep-disordered breathing is a complex, multisystemic disorder that warrants particular mention. In particular, the obstructive variant of sleep apnea (or OSA) is associated with obesity and increased risk for airway difficulties, adverse cardiac events, postoperative respiratory complications, and perioperative neurocognitive disorders.[33] In the general population, OSA is associated with reductions in cognitive reserve, increased risk for cognitive impairment and worsening executive function, and amyloid deposition in key brain regions.[34–36] Because many of these findings share characteristics of perioperative neurocognitive disorders, a link between OSA and perioperative neurocognitive disorders has also been proposed. Possible mechanisms underlying the association between OSA and delirium include abnormalities in sleep architecture leading to sleep disruption, hypoxia, vascular injury, low-grade systemic inflammation, oxidative stress, and decrease in insulin growth factor-1, as has been seen with neuronal injury and apoptosis.[37]

Using objective polysomnography, preoperative sleep-disordered breathing defined by a high apnea–hypopnea index was associated with more than six-fold increased odds for postoperative delirium (odds ratio [95% CI], 6.4 [2.6 to 15.4], $P < 0.001$), including patients without an existing formal OSA diagnosis.[38] In a small cohort of older patients undergoing elective knee replacement, the incidence of delirium was significantly higher in patients with OSA as compared to those without OSA (8 of 15 [53%] *vs.* 19 of 95 [20%]; $P = 0.0123$).[39] However, a recent retrospective observational cohort study of 7,792 surgical patients did not find a significant association between preoperative OSA and postoperative delirium after adjustment for perioperative confounders.[40] Both OSA and postoperative delirium remain greatly underdetected, and on balance of evidence, their relationship still warrants close attention. For example, the Society of Anesthesia and Sleep Medicine currently recommends using preoperative screening tools such as the STOP-Bang preoperative screening for OSA, given the link with increased perioperative complications.[41]

Although the use of continuous positive airway pressure slows the deterioration of cognition, brain function, and mood in nonsurgical patients with OSA, thus far data from the surgical population is less conclusive.[42–44] When patients who were at risk for sleep apnea were randomized in a continuous positive airway pressure group *versus* standard care, the perioperative use of continuous positive airway pressure did not change the incidence of postoperative delirium (12 of 58 [21%] *vs.* 9 of 56 [16%]; odds ratio [95% CI], 1.36 [0.52 to 3.54]; $P = 0.53$).[45] Whereas both preoperative and postoperative residual OSA severity as defined by apnea-hypopnea index were significantly correlated with delirium severity in this sample, continuous positive airway pressure use was not found to be significantly correlated. Further studies with particular attention on continuous positive airway pressure adherence or the use of other respiratory adjuncts such as high-flow nasal oxygen are ongoing and may yield positive results in the future. It remains unclear whether the best strategy to prevent postoperative delirium is to treat the OSA directly using continuous positive airway pressure or to consider OSA patients at high risk and use more general delirium prevention strategies in this group. Currently, it is unknown whether OSA is a risk factor for delayed neurocognitive recovery or postoperative neurocognitive disorder. In the coming years, prospective clinical trials investigating this area will provide much-needed data.[46,47]

Other Postoperative Sleep-related Interventions and Delirium

In terms of pharmacologic interventions to prevent delirium, dexmedetomidine and melatonin have been extensively studied. For intensive care unit (ICU) patients who are mechanically ventilated, sedation with dexmedetomidine may be less likely to be associated with delirium compared to benzodiazepines or propofol.[48,49] Although there are

inconsistent findings between studies, recent meta-analyses suggest that sedation of critically ill patients with dexmedetomidine may reduce the frequency and duration of delirium.[50,51] Although these findings may primarily reflect the benefit of avoiding deliriogenic sedatives, the exact mechanism remains unclear. However, unlike all other sedatives and the commonly used anesthetics, dexmedetomidine appears most likely to preserve sleep architecture as currently inferred *via* electroencephalogram (EEG). In healthy volunteers, dexmedetomidine induced stage N3 non–rapid eye movement sleep in a dose-dependent fashion with an EEG pattern mimicking natural sleep without impairing next-day psychomotor performance.[52] A low-dose dexmedetomidine infusion prolonged total sleep time and increased sleep efficiency and time spent in stage N2 non–rapid eye movement sleep in 76 older ICU patients.[53] In a randomized, blinded, placebo-controlled trial of 700 older noncardiac surgery patients, a low-dose dexmedetomidine infusion given to both ventilated and extubated patients from the time of ICU admission until 8 AM the morning of postoperative day 1 greatly reduced the risk of delirium as compared to placebo (32 of 350 [9%] *vs.* 79 of 350 [23%]; odds ratio [95% CI], 0.35 [0.22 to 0.54]; $P < 0.0001$).[54] Additionally, patients in the dexmedetomidine group reported significantly better sleep quality (2 [0 to 4] *vs.* 4 [2 to 6]); 0 to 11 scale, where lower scores indicate better sleep; the values are shown as medians [interquartile range]; $P < 0.0001$). Finally, oral dexmedetomidine is now a possibility after successful testing in human subjects; however, optimal dosing has yet to be established, and it is not yet approved by the Food and Drug Administration (Silver Spring, Maryland). Subjects taking oral dexmedetomidine displayed both preserved sleep architecture on EEG and next-day psychomotor vigilance.[55] This may open new possibilities outside of the ICU for investigation as to whether dexmedetomidine can be effective as a sleep-promoting agent.

Melatonin is commonly used in the general population and in the ICU for the promotion of sleep. Given its increasing use, some understanding of its role in sleep and circadian rhythms is warranted. As previously mentioned, the sleep–wake cycle is perhaps the most obvious and important behavior under intrinsic circadian output control. However, sleep–wake cycles are also affected by external cues. Of these cues, light is by far most important; others are food, sound, and exercise, many of which are disrupted in sickness and hospital settings. Melatonin is the major sleep-promoting hormone under circadian control. Taking its external cue from low light, its concentration peaks just before sleep initiation. Melatonin levels are measured from the saliva or serum, often in serial measurements, and are an accepted surrogate marker for our "internal time."[56] Critical care settings often involve exposure to light, noise, pain, nausea, or clinical care at night, which may explain the evidence for suppressed nocturnal melatonin peak secretion in ICU patients.[57]

Recent data suggest that delirious patients may also have reduced serum levels of melatonin.[58] For this reason, melatonin supplementation has been investigated as a potential intervention to prevent delirium. In a prospective before–after trial of 500 cardiac surgery patients where prophylactic melatonin was given the night before surgery, the incidence of postoperative delirium was significantly lower in the intervention group (21 of 250 [8.4%] *vs.* 52 of 250 [20.8%]; $P = 0.001$).[59] Although a randomized trial investigating the prophylactic use of the melatonin receptor agonist ramelteon showed some promise in preventing delirium in older medical patients (1 of 33 [3%] *vs.* 11 of 34 [32%], ramelteon *vs.* placebo; $P = 0.003$), it was not shown to prevent postoperative delirium in elective cardiac surgery patients in another trial (19 of 59 [32%] *vs.* 22 of 58 [38%], ramelteon *vs.* placebo; $P = 0.516$).[60,61] Other clinical trials of melatonin or ramelteon have not demonstrated similar success, and a recent meta-analysis of 16 clinical trials concluded that evidence neither supports nor opposes the use of melatonin in the prevention of delirium of hospitalized patients.[62] Trials with individually targeted timing and dosing in those who are most at risk for suppression and misalignment of melatonin secretion may yield improved results. However, this may require accounting for sleep and circadian rhythm regulation before the perioperative period.

Aside from postoperative delirium, the impact of melatonin levels and melatonin supplementation on other perioperative neurocognitive disorders has been less extensively studied. In 97 patients aged 65 to 90 undergoing major orthopedic or abdominal surgery, patients with more than two-fold fluctuations in 6-sulfatoxymelatonin, a main metabolite of melatonin, had a significantly higher incidence of delayed neurocognitive recovery as determined by a cognitive battery 1 week postoperatively (22 of 39 [56%] *vs.* 9 of 56 [16.7%]; $P < 0.01$).[63] In contrast, a study of 36 abdominal surgery patients with a mean age of 70 found no association between abnormal 6-sulfatoxymelatonin levels and the incidence of delayed neurocognitive recovery.[64] In a placebo-controlled trial of 139 patients older than 65 undergoing hip arthroplasty, patients given melatonin beginning the night before surgery and then for the next 5 nights had significantly higher Mini Mental State Exam scores on days 1, 3, and 5, but scores between groups were similar on day 7.[65] It should be noted that delayed neurocognitive recovery as defined as a predetermined decrease from the baseline Mini Mental Status Exam score was not an outcome in this trial. Significantly worse subjectively rated fatigue and sleep quality were found in the control group. In another placebo-controlled trial of 54 patients undergoing breast surgery, patients administered nightly melatonin for 1 month preoperatively until 3 months after surgery did not have significantly different rates of delayed neurocognitive recovery at 2 weeks or postoperative neurocognitive disorder at 3 months, despite subjective improvements in sleep efficiency and total sleep duration.[66] Because of the small sample size and resulting lack of power, as well as the substantial heterogeneity in outcome definition seen in these studies, there is a clear need for further work on the relationship between melatonin and perioperative neurocognitive disorders other than delirium.

Finally, because of the overall paucity of effective sleep-promoting medications, there have now been increased efforts to trial multifaceted nonpharmacologic sleep interventions to prevent ICU delirium. A before–after quality improvement project in 300 medical ICU patients implemented a bundle of environmental changes including ear plugs, eye masks, and soothing music to decrease nighttime sleep disruption and promote daytime wakefulness. In the intervention group, the incidence of delirium was significantly less than in the preintervention group (odds ratio [95% CI], 0.46 [0.23 to 0.89]; $P = 0.02$).[67] Taken as a whole, bundled sleep interventions may reduce the risk of delirium, but more work is needed to confirm these findings in adequately controlled trials and to pinpoint which aspect(s) of the multicomponent sleep bundles are the most effective.

Summary

Sleep and circadian disturbances are important risk factors for the development of neurodegenerative diseases including Alzheimer disease, which in turn are important predisposing factors for postoperative delirium (fig. 2). To what extent sleep disturbances may cause delirium, which sleep disorders are particularly risky, or at which time point in the perioperative course these factors are important are unclear. Certain chronic sleep patterns may predispose to delirium and may in turn make patients more susceptible to acute perioperative sleep disturbances that may precipitate delirium. Additionally, postoperative delirium may cause acute *de novo* sleep disturbances, adding further complexity. More work is needed to untangle these relationships to derive effective interventions. Although the relationship between sleep and circadian health and delirium is beginning to emerge, further work is also needed to understand the consequences of sleep disturbances and delayed neurocognitive recovery and postoperative neurocognitive disorder. Finally, there is a large degree of overlap between sleep disorders, pain, and cognition. Thus, future trials should aim to incorporate multimodal targets incorporating these components.

Pain

Pain and Perioperative Neurocognitive Disorders

The relationship between pain and perioperative neurocognitive disorders and the modification of that relationship by the treatment of pain are incredibly complex (fig. 3). Inflammation and pain are closely biochemically linked, and many of the mediators of the body's response to injury and inflammation in both the peripheral and central nervous

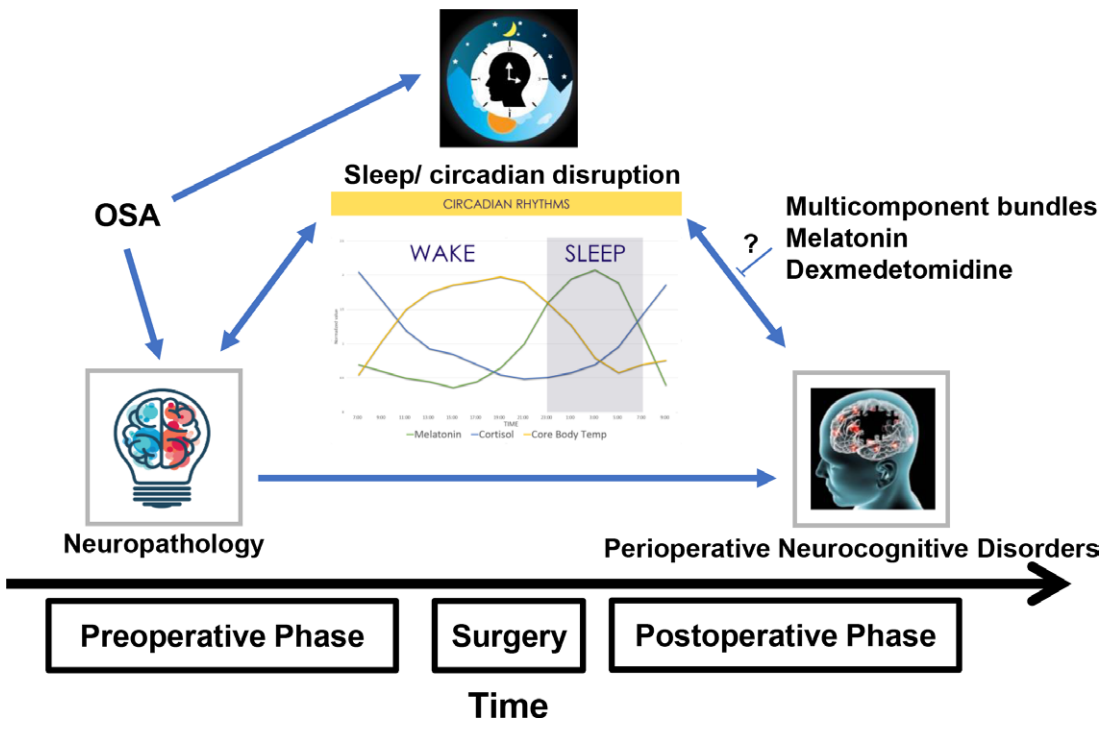

Fig. 2. Sleep and circadian disruption and perioperative neurocognitive disorders. Preexisting sleep disorders and baseline neuropathology may contribute to sleep and circadian rhythm disruption in the perioperative period, which may then be a precipitating factor for perioperative neurocognitive disorders. OSA, obstructive sleep apnea.

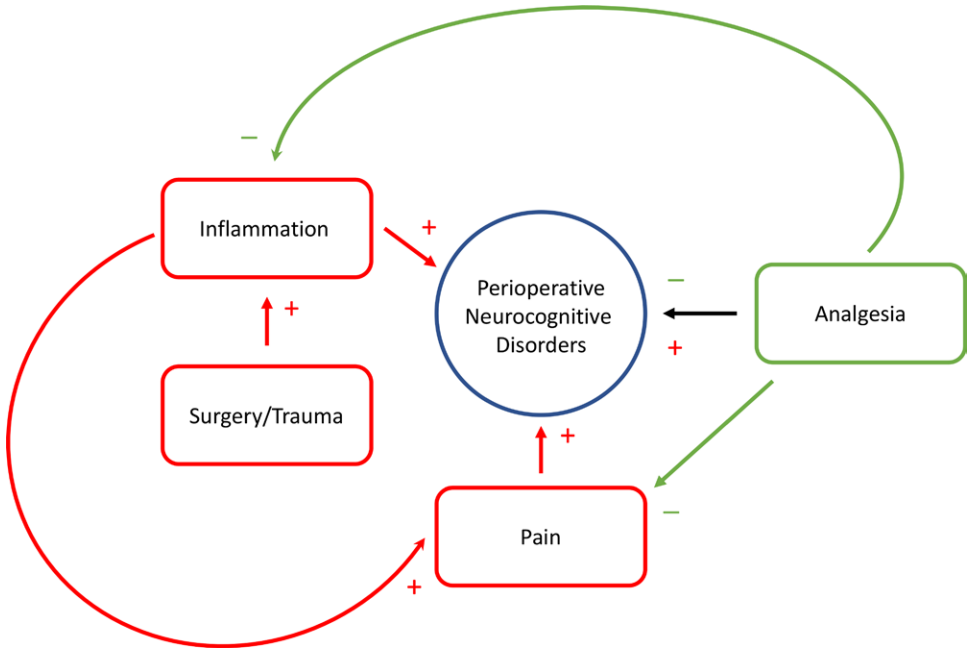

Fig. 3. The relationships between pain, inflammation, and analgesia on the risk for perioperative neurocognitive disorders. *Red lines* and *plus signs* signify processes that may worsen other conditions. *Green arrows* and *minus signs* indicate processes that may ameliorate or improve other conditions.

system including prostaglandins, bradykinins, interleukins, and tumor necrosis factor-α can be elevated in painful conditions.[68,69] This relationship is relevant to perioperative neurocognitive disorders, because one commonly proposed mechanistic framework for both postoperative delirium and delayed neurocognitive recovery is through neuroinflammation.[2,5,6,70,71] In this proposed mechanism, either peripheral or central nervous system injury leads to inflammatory cytokine release, endothelial activation, breakdown of the blood–brain barrier, and activation of microglia, potentially culminating in neuronal injury and subsequent brain dysfunction.[72–74] Another interesting link between pain and cognitive dysfunction comes from the knowledge that cholinergic neurons modulate pain signals, and cholinergic deficiency and anticholinergic medication use have been implicated in both pain hypersensitivity and delirium.[27,75] These biochemical links between inflammation, pain, and neuronal injury or dysfunction are more easily identified in preclinical models than in clinical studies given the difficulties inherent to selecting and sampling the ideal mediators in perioperative patients. Despite this limitation, there are a number of studies supporting an association between pain and subsequent perioperative neurocognitive disorders that are worthy of review.

The majority of clinical studies linking pain to perioperative neurocognitive disorders focus on the potential association between postoperative pain and postoperative delirium. Although this focus is reasonable given their temporal association, the presence of preoperative pain may also play a significant role and should not be overlooked. For example, in a cohort of 333 major noncardiac surgery patients 65 and older, the presence of moderate preoperative pain (odds ratio [95% CI], 2.2 [1.2 to 4.0]; $P < 0.05$) and the presence of severe preoperative pain (3.7 [1.5 to 9.0]; $P < 0.05$) at rest were independently predictive of postoperative delirium.[76] An increase in pain scores from preoperative baseline to postoperative day 1 was also predictive of postoperative delirium (1.1 [1.01 to 1.2]; $P < 0.05$). In 459 older patients undergoing elective orthopedic surgery, the severity of preoperative pain was significantly associated with an increased risk of subsequent delirium (severe pain *vs.* no/mild pain; odds ratio [95% CI], 2.0 [1.4 to 3.0]; $P = 0.013$) for trend between no/mild, moderate, and severe pain).[77] The relationship between pain and delirium may be modified by the presence of underlying depression, because subgroup analysis of patients with depression from this cohort revealed that for every 1-point increase on the postoperative visual analog pain scale, the risk of delirium significantly increased. Interestingly, investigations of alterations in synaptic connectivity in the prefrontal cortex suggest that changes may occur in this region for patients with depression, in chronic pain, and in disorders of executive function, suggesting a potential close neuropathological link between these conditions.[78]

As previously mentioned, the preponderance of clinical evidence associating pain and perioperative neurocognitive disorders involves acute postoperative pain. In a cohort of 541 older patients with hip fracture, cognitively intact patients with any episode of severe postoperative pain at rest (as defined by a score of 4 or greater on a 5-point scale) through postoperative day 3 had a nine-fold increase in the risk of subsequent delirium (risk ratio [95% CI], 9.0 [1.8 to 45.2]; $P = 0.01$).[79] In 361 patients with a mean age of 66 undergoing major noncardiac surgery, postoperative pain at rest was significantly associated with subsequent postoperative delirium (risk ratio, 1.20 [1.04 to 1.37] per 1-point increase on the visual analog scale; $P = 0.015$).[80] In a similar population, patients with high levels of postoperative pain and receiving high doses of opioids had significantly higher rates of delirium, in both patients at low risk for delirium (17 of 34 [50%] *vs.* 35 of 174 [20%]; $P = 0.0004$) and patients at high risk for delirium (23 of 32 [72%] *vs.* 46 of 93 [49%]; $P = 0.031$) compared to patients with lower levels of pain.[81] In contrast, in 89 older patients undergoing major abdominal surgery, uncontrolled pain as defined by a pain score of greater than 5 without adequate medication administration was not found to be significantly associated with delirium (risk ratio [95% CI], 1.0 [0.7 to 1.4]; $P = 0.91$).[82] It should be noted when discussing the evidence linking pain to perioperative neurocognitive disorders that the assessment of pain can be very challenging in patients with impaired cognition, and therefore current guidelines recommend using a multisource, multidimensional approach to the assessment of pain in older persons.[83] Additionally, many of the above-referenced trials do not contain information as to whether chronic pain or opioid use was present preoperatively, limiting the interpretation of these results.

Pain Treatment and Perioperative Neurocognitive Disorders

The adequate diagnosis and management of pain is a core intervention in HELP, as well as multicomponent ICU care guidelines such as the ABCDEF bundle, and is also recommended in consensus guidelines for reducing postoperative delirium from multiple interdisciplinary working groups.[11,84–86] As previously mentioned, data from multiple perioperative studies suggest that the presence of preoperative or postoperative pain or worsening severity of pain in the postoperative period is associated with subsequent delirium. In many of these studies, it is difficult to determine based on their results whether adequate treatment of pain can prevent delirium or conversely whether undertreatment of pain can precipitate delirium. Because low pain scores may indicate either absence of pain or effective treatment of pain, evaluation of the impact of pain treatment on the risk of perioperative neurocognitive disorders requires adjustment for either factor. This relationship is confounded even further when considering the specific medication used to treat pain, because many drugs have been implicated as precipitating factors for delirium, especially opioids.

Opioids

Amid the enhanced awareness of perioperative neurocognitive disorders and the opioid epidemic, avoidance or minimization of opioids has become an essential consideration in perioperative care. On one hand, opioids remain some of the most effective analgesics for acute pain, especially for severe painful conditions such as after trauma or surgery. On the other hand, opioid-related side effects such as sedation or hallucination may precipitate, worsen, or mimic symptoms of delirium such as disorientation or hypoactive motor and cognitive function. Given these considerations, current guidelines for best practices to avoid delirium advocate for avoiding opioids, at least as first line agents.[70,86] However, data suggest that simply administering fewer opioids may not prevent perioperative neurocognitive disorders. For example, in a retrospective matched cohort study of 86 medical–surgical patients with a mean age of 80 admitted with painful conditions and with an opioid ordered, delirious patients received a significantly lower fraction of the allowed dose ordered than nondelirious patients (11 of 43 [26.14%] *vs.* 21 of 43 [48.21%]; $P < 0.001$).[87] In the cohort study of hip fracture patients mentioned previously in which pain at rest was associated with a nine-fold increased risk of delirium, investigators found that patients administered less than 10 mg of morphine equivalents per day were at significantly increased risk of delirium compared to patients receiving more than 10 mg (risk ratio [95% CI], 5.4 [2.4 to 12.3]; $P < 0.001$).[79] In 236 patients older than 65 undergoing hip fracture repair, opioid consumption during the first 3 postoperative days was not different between patients with and without delirium (mean [SD], 0.66 [0.82] *vs.* 0.49 [0.59] mg/kg morphine equivalents; $P = 0.176$), but patients with delirium did have significantly higher pain scores (mean [SD], 2.6 [1.9] *vs.* 1.7 [1.8]; $P = 0.007$).[88] Although the higher risk of delirium with lower opioid doses does not directly imply that those patients' pain was less well treated, data from these cohorts suggest that increased opioid dose is not associated with an increased risk of postoperative delirium, at least in the context of acute pain. Given the clinical and societal importance of limiting opioid use, it is reasonable to employ multimodal efforts to control pain before resorting to opioids.[89] Ideally, effective analgesia can be accomplished while limiting opioids, but in the event that opioid-sparing techniques such as use of anti-inflammatory agents and regional, neuraxial, or local analgesia are not successful, residual untreated pain may have more of an effect on delirium than further limiting opioid use.

In terms of specific opioids, tramadol and meperidine have been linked to an increased risk of delirium, but there are limited data on the differential impact of the agents more typically used in the perioperative period such as fentanyl

or hydromorphone.[90] The mode of opioid administration may be more relevant. In the cohort study of 333 patients undergoing major noncardiac surgery mentioned previously, patients who only received oral opioid analgesics were found to have a significantly reduced risk of postoperative delirium compared to patients treated with intravenous opioids (odds ratio [95% CI], 0.4 [0.2 to 0.7]; $P < 0.05$).[81] Additionally, a prospective cohort study of 225 patients older than 65 yr undergoing noncardiac surgery found that patients who were treated with oral opioids alone had significantly reduced odds of delayed neurocognitive recovery as assessed by a three-test battery as opposed to those treated with intravenous opioids *via* a patient-controlled system (odds ratio [95% CI], 0.22 [0.06 to 0.80]; $P = 0.02$). This finding came after controlling for a number of patient- and surgery-specific confounders including pre- and postoperative pain levels.[91]

Nonopioid Analgesics

The pathophysiological overlap between inflammation, pain, and neuronal injury makes analgesics with anti-inflammatory effects attractive candidates to prevent delirium in patients with acute postoperative pain. In a randomized trial of 620 older patients undergoing elective total joint arthroplasty, scheduled parecoxib (a selective COX2 inhibitor) for 3 days led to a significant reduction in the incidence of postoperative delirium compared to placebo (19 of 310 [6.2%] *vs.* 34 of 310 [11%]; $P = 0.031$).[92] The parecoxib group also had significantly less delayed neurocognitive recovery, defined by a decrease of more than 2 points on the Mini Mental Status Exam from baseline, than placebo controls on postoperative days 1, 3, and 5 (day 5: 28 of 310 [8.7%] *vs.* 53 of 310 [19.4%]; $P < 0.001$). It should be noted that the Mini Mental Status Exam is limited in its utility as a test for detecting cognitive dysfunction and is not recommended for this purpose by the perioperative neurocognitive disorder nomenclature working group.[1] Although acetaminophen is not considered an anti-inflammatory, it shares some characteristics of nonsteroidal anti-inflammatory drugs including action on the cyclooxygenase pathway and putative blockade of central nervous system prostaglandin production.[93] A randomized, placebo-controlled factorial trial in 121 cardiac surgery patients older than 60 yr found that scheduled intravenous acetaminophen for the first 48 h postoperatively significantly lowered the incidence of delirium as compared to placebo (6 of 60 [10%] *vs.* 17 of 60 [28%]; $P = 0.01$).[94] Patients receiving acetaminophen also had significantly reduced delirium duration (median 1 *vs.* 2 days; $P = 0.03$). The rates of delayed neurocognitive recovery at discharge were not different between groups.

In both the parecoxib and acetaminophen trials, there were either clinically insignificant differences or no differences found between groups in opioid equivalents administered and in postoperative pain scores, suggesting that neither opioid sparing nor superior pain control were the main drivers of the results. It is possible that this finding was instead related to the prevention of neuroinflammation; however, this hypothesis will have to be confirmed in subsequent studies because neither trial included biomarker analyses. Additionally, the possibility that the effect of these interventions occurred through reducing neuroinflammation should be taken in context with the negative findings of multiple clinical trials investigating the intraoperative use of different drugs with both anti-inflammatory and analgesic properties including intravenous lidocaine, magnesium, and steroids to prevent perioperative neurocognitive disorders after cardiac surgery.[95–99]

Gabapentin is another nonopioid analgesic that has been investigated as an intervention to minimize perioperative opioid use. In a large double-blind placebo-controlled trial involving 697 patients with a mean age of 72 yr undergoing noncardiac surgery, the administration of 900 mg of gabapentin preoperatively and for the first 3 postoperative days did result in a small but significant reduction in the amount of morphine equivalents on the first postoperative day (median [interquartile range], 6.7 [1.3 to 20.0] *vs.* 6.7 [2.7 to 24.8] mg; $P = 0.04$).[100] However, there were no differences between the gabapentin and placebo groups in the primary outcome of postoperative delirium (84 of 350 [24%] *vs.* 72 of 347 [20.8%]; $P = 0.30$). Commonly, especially in enhanced recovery pathways, multimodal and opioid-sparing analgesia protocols will combine multiple agents. Data for this approach are limited, but one prospective study of a fast track protocol for 220 older patients undergoing major joint replacement found no cases of postoperative delirium employing a multicomponent strategy including standardized anesthetic and postoperative analgesic protocols utilizing various combinations of paracetamol, gabapentin, tramadol, celecoxib, and ibuprofen across four different centers.[101]

Ketamine is another commonly used opioid-sparing analgesic. Like opioids, ketamine has potential psychotropic effects such as hallucinations, nightmares, or psychosis that are undesirable in patients at risk for perioperative neurocognitive disorders.[102] These effects may be dose-dependent; therefore trials evaluating ketamine's effectiveness in reducing opioid consumption and perioperative neurocognitive disorders focus on low-dose interventions. In a three arm randomized active and placebo-controlled trial of 56 adult patients undergoing major open abdominal surgery, the administration of low-dose (0.25 mg/kg bolus and 0.125 mg · kg^{-1} · h^{-1} infusion) and minimal-dose (no bolus, 0.015 mg · kg^{-1} · h^{-1} infusion) ketamine during the anesthetic and the following 48 h resulted in lower postoperative opioid consumption as compared to placebo (mean [SD], 42.7 [13.4] *vs.* 40.2 [13.5] *vs.* 72.7 [15.3] mg piritramide; $P < 0.0001$).[103] However, patients in the low-dose group had significantly higher Intensive Care Delirium Screening Checklist scores than both the minimal-dose and placebo groups (median [interquartile range], 2 [1 to 3] *vs.* 1 [0 to

1] and 0 [0 to 1], respectively; $P = 0.007$). In 58 patients older than 55 yr of age undergoing cardiac surgery with cardiopulmonary bypass, patients randomized to receive an intravenous bolus of 0.5 mg of ketamine had significantly lower rates of postoperative delirium than placebo controls (1 of 29 [3%] *vs.* 9 of 29 [31%]; $P = 0.01$).[104] In a different study in the same population by the same investigators, they found that the same intervention could possibly reduce the incidence of delayed cognitive recovery at 1 week postoperatively, as defined by a 2 SD decrease on assessments of memory and executive functions, as compared to placebo (7 of 26 [27%] *vs.* 21 of 26 [81%]; $P < 0.001$) after adjusting for training effects using assessment data from concurrent nonsurgical controls.[105]

The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) trial sought to more definitively investigate whether the prophylactic intraoperative administration of ketamine could prevent postoperative delirium, also using a three-armed design.[9] In the trial, 672 patients older than 60 yr undergoing major cardiac and noncardiac surgery were randomized to either low-dose (0.5 mg/kg) or high-dose (1.0 mg/kg) ketamine boluses or placebo given in the time between induction and surgical incision. There was no difference in the incidence of postoperative delirium during the first 3 postoperative days between patients who received any dose of ketamine as compared to placebo (88 of 450 [19.45%] *vs.* 44 of 222 [19.82%]; $P = 0.92$). There was also no significant difference found in delirium rates across all three groups (40 of 227 [17.65%] *vs.* 47 of 223[21.3%] *vs.* 44 of 222 [19.82%] in low-dose, high-dose, and placebo groups, respectively; $P = 0.80$). Furthermore, no significant differences among groups were found with respect to time to delirium onset, severity, or duration of delirium. Postoperative opioid consumption was not significantly different between the three groups at any time point. Last, more patients in the ketamine groups reported experiencing hallucinations (45 of 227 [20%] *vs.* 62 of 223 [28%] *vs.* 40 of 222 [18%] in low-dose, high-dose, and placebo groups, respectively; $P = 0.01$) and nightmares (27 of 227 [12%] *vs.* 34 of 223 [15%] *vs.* 18 of 222 [8%]; $P = 0.03$). Therefore, the results of the PODCAST trial should give providers caution when considering intraoperative ketamine as a means to either reduce the risk of delirium or postoperative opioid consumption, because neither high- nor low-dose regimens were effective for these outcomes, and there was evidence of significant harm from ketamine with regards to its psychotropic effects.

Regional or Neuraxial Analgesia

A successful regional nerve block may be very effective for postoperative pain control when placed in an appropriate candidate. If this effective analgesia can be obtained while also sparing the use of opioids, then it is theoretically possible that regional nerve blocks can prevent delirium in multiple ways. The best available data for this approach come from studies in orthopedic surgery patients. In 207 patients at intermediate- or high-risk of delirium undergoing hip fracture surgery who were randomized to undergo a fascia iliaca or sham block administered on admission and repeated every 24 h until delirium occurrence or discharge, the use of the fascia iliaca block resulted in a significantly reduced incidence of delirium (11 of 102 [10.78%] *vs.* 25 of 105 [23.8%]; risk ratio [95% CI], 0.45 [0.23 to 0.87]).[106] Additionally, patients who received fascia iliaca blocks experienced lower delirium severity (mean [SD], 14.34 [3.6] *vs.* 18.61 [3.4) DRSR-98 score; $P < 0.001$) and shorter delirium duration (mean [SD], 5.22 [4.28] *vs.* 10.97 [7.16] days; $P < 0.001$). For patients undergoing total knee arthroplasty, a cohort study of 85 patients demonstrated that analgesia *via* a femoral nerve catheter in addition to patient-controlled analgesia (PCA) was associated with lower rates of postoperative delirium as compared to PCA alone (7 of 28 [25%] *vs.* 31 of 51 [61%]; $P = 0.002$).[107] After controlling for preoperative cognitive function, the odds of postoperative delirium were significantly higher in the PCA group than patients who received a femoral nerve catheter in addition to their PCA (odds ratio [95% CI], 7.02 [2.06 to 23.97]; $P = 0.002$). The use of intraoperative spinal anesthesia as an alternative to general anesthesia has been proposed to reduce anesthetic exposure for patients at risk for postoperative delirium. Interestingly, this may not always be the case, because patients under spinal anesthesia with supplemental monitored anesthesia care may still receive high doses of intravenous sedatives.[108] This makes the interpretation of trials investigating the benefit of neuraxial anesthetics on postoperative delirium challenging. A large randomized controlled trial is currently underway specifically examining whether spinal anesthesia or general anesthesia is superior for older patients undergoing hip fracture surgery, with postoperative delirium as a secondary outcome.[109]

For operations on the thorax or abdomen, analgesia *via* the use of an epidural catheter can be very effective, albeit with the inherent risk of hypotension.[110] In a trial of 70 patients older than 70 yr of age randomized to either combined general and epidural anesthesia followed by epidural PCA with bupivacaine and sufentanil compared to general anesthesia and PCA alone, the use of epidural PCA did not significantly reduce the incidence of delirium (8 of 31 [26%] *vs.* 8 of 33 [24%]; $P > 0.05$).[111] A higher proportion of patients in the PCA group demonstrated poor scores on the Abbreviated Mental Test than the epidural PCA group on postoperative day 4 (number of patients with scores ≤ 8, 9, and 10 was 5, 11, and 17 *vs.* 1, 5, and 25; $P < 0.05$) and postoperative day 5 (5, 13, and 15 *vs.* 1, 7, and 23; $P < 0.05$). In a secondary analysis of the PODCAST trial, the investigators found that patients who received postoperative epidural analgesia did not have a significantly reduced odds of postoperative delirium within the first 3 postoperative days compared to those without an epidural after adjusting

for several confounders including age and type of procedure (adjusted odds ratio [95% CI], 0.65 [0.32 to 1.35]; $P = 0.247$).[112] A *post hoc* analysis was performed in which patients treated with an epidural were less likely to experience any episode of delirium during the study follow-up, after adjustment for the same confounders (adjusted odds ratio [95% CI], 0.36 [0.17 to 0.78]; $P = 0.009$). Because postoperative delirium is often defined by any single episode of delirium, and this analysis was conducted post hoc, it is unclear how impactful this finding is.

Finally, the use of epidural analgesia has been included in studies evaluating the effectiveness of enhanced recovery pathways for colonic surgery. In one trial, 240 open colorectal surgery patients older than 70 yr were randomized to a fast-track protocol (consisting of preoperative dietary, hydration, and bowel preparation interventions, thoracic epidural anesthesia and postoperative epidural PCA with ropivacaine only, and postoperative mobilization and dietary interventions) or traditional care (notably consisting of general anesthesia and postoperative fentanyl).[113] Patients in the fast-track group had a significantly lower incidence of postoperative delirium within the first 5 days (4 of 117 [3.4%] *vs.* 15 of 116 [12.9%]; $P = 0.008$).

Summary

Severe or uncontrolled preoperative or postoperative pain and increased levels of pain from the preoperative to postoperative period are all associated with postoperative delirium. Proper diagnosis and adequate treatment of pain remains a key component of preventative strategies for postoperative delirium. Although multimodal analgesic strategies including nonopioid analgesics and regional or neuraxial analgesia have demonstrated success in effectively controlling pain and potentially reducing opioid requirements, at this time the quality of evidence underlying any one analgesic approach to prevent delirium is low. Evidence is stronger, however, that undertreatment of pain is more of a significant risk factor for postoperative delirium than treatment with potentially deliriogenic medications. There are few data available on the relationship between pain, pain treatment, and delayed neurocognitive recovery or postoperative neurocognitive disorder.

Cognition

A disturbance in cognition, either temporarily or longer term, is a defining feature of postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder.[1] An emerging component of perioperative care now consists of perioperative multicomponent strategies to enhance recovery. In this context, preoperative optimization and the goal of the best possible functional recovery for surgical patients increasingly includes measures taken to protect perioperative cognitive function.[114] Thus, the detection of perioperative neurocognitive disorders and evaluation of strategies employed to prevent them relies on a thorough understanding of the cognitive areas affected in the perioperative period, the development of validated instruments to measure perioperative cognition, and the current state of evidence for strategies to improve postoperative cognitive function.

Baseline Cognitive Performance and Perioperative Neurocognitive Disorders

The degree of preexisting organ dysfunction is an important risk factor for many types of postoperative complications.[115–117] The same can be said for brain function, because poor baseline cognition is a strong predictor of future cognitive dysfunction. Although there is continuing debate as to which cognitive test or battery of tests is best suited for the perioperative period, there is strong evidence that patient performance on a preoperative cognitive test can predict perioperative neurocognitive disorders. Screening tests such as the Mini-Cog and Mini Mental Status Exam, which were originally designed to detect mild cognitive impairment or dementia, have been used to evaluate perioperative cognitive function. In two longitudinal cohort studies of surgical patients older than 65 yr, investigators found that a preoperative Mini-Cog score indicative of moderate cognitive dysfunction (3 or lower or 2 or lower) was associated with a significantly higher risk of postoperative delirium (odds ratio [95% CI], 2.4 [1.2 to 4.9]; $P = 0.015$; and 4.5 [1.3 to 15.7]; $P = 0.017$, respectively) and more days with postoperative delirium (mean [SD], 4 [6] *vs.* 1 [2] days; $P = 0.012$).[118,119] In 425 older hip fracture surgery patients, those with a Mini Mental Status Exam score of less than 24 had a significantly increased incidence of postoperative delirium (76 of 141 [54%] *vs.* 73 of 284 [26%]; $P \leq 0.001$).[120] In a similar population, a higher preoperative Mini Mental Status Exam score was associated with a lower incidence of postoperative delirium (odds ratio [95% CI], 0.67 [0.52 to 0.86]; $P = 0.002$).[121]

In addition to tests of global cognitive function, poor performance on targeted tests of executive function can also predict postoperative delirium in older patients undergoing major noncardiac surgery (odds ratio [95% CI], 1.23 [1.06 to 1.43]; $P < 0.01$ for a three-test composite and log mean ratio [95% CI], 1.27 [1.11 to 1.46]; $P < 0.01$ for color trial 2).[122,123] Preoperative test performance is also associated with persistent cognitive deficits, because older hip arthroplasty patients who performed less than 2 standard deviations on at least two of seven neuropsychological tests had higher incidences of both delayed neurocognitive recovery at 7 days (23 of 91 [25.3%] *vs.* 26 of 195 [13.3%]; $P = 0.012$) and of postoperative neurocognitive disorder at 3 months (13 of 87 [14.9%] *vs.* 14 of 197 [7.1%];, $P = 0.039$) and 12 months (5 of 83 [9.4%] *vs.* 2 of 188 [1.1%]; $P < 0.001$).[124] In a cohort of 566 older surgical patients, lower preoperative scores on an 11-test cognitive battery was identified as the dominant risk factor for postoperative delirium

after adjustment for other established predictors (risk ratio [95% CI], 2.0 [1.5 to 2.5] for each 0.5 SD decrease; $P < 0.05$).[125] Last, preoperative test performance may also help identify patients at risk for long-term cognitive decline, because a higher preoperative Mini Mental Status Exam score was associated with a lower risk of dementia 5 yr after cardiac surgery (odds ratio [95% CI], 0.68 [0.54 to 0.84]; $P < 0.001$).[126] Based in part on the findings of these studies, the Perioperative Neurotoxicity Working Group recommends evaluating baseline cognition using a screening test in patients older than 65 or who are at otherwise high risk for perioperative neurocognitive disorders.[127] They do not recommend one screening test in particular, however, because more work is needed to assess the predictive power and clinical utility of these screening tests in perioperative patients.

Cognitive Reserve

Cognitive reserve can be described as resiliency of an individual's cognitive processes in the face of injury. In contrast to cognitive performance assessed at one point in time, cognitive reserve is characterized by the accumulation or loss of cognitive abilities over the lifespan. Differences in cognitive reserve have been theorized to explain observed differences between patients in phenotypes or degrees of impairment seen after similar pathologic findings of neurologic injury such as stroke or Alzheimer disease, and the concept can be applied to perioperative neurocognitive disorders (fig. 4).[128] Cognitive reserve is typically described in terms of years of education attained, occupational complexity, and cognitive lifestyle behaviors. There is some evidence to suggest that differences in cognitive reserve may predict perioperative neurocognitive disorders. In two cohort studies of hospitalized older patients, each year of education obtained was associated with a significantly decreased risk of delirium (odds ratio [95% CI], 0.91 [0.87 to 0.95]; $P < 0.01$; and 0.76 [0.62 to 0.95]; $P = 0.016$, respectively).[129,130] Low educational attainment was also found to be a strong predictor of postoperative delirium in older patients after hip fracture surgery or hip replacement (odds ratio [95% CI], 3.59 [1.14 to 11.25]; $P < 0.05$).[131] However, a large cohort study of similar patients did not find an association between years of education or multiple other markers of cognitive reserve and postoperative delirium.[132] It should be noted that this cohort exhibited a

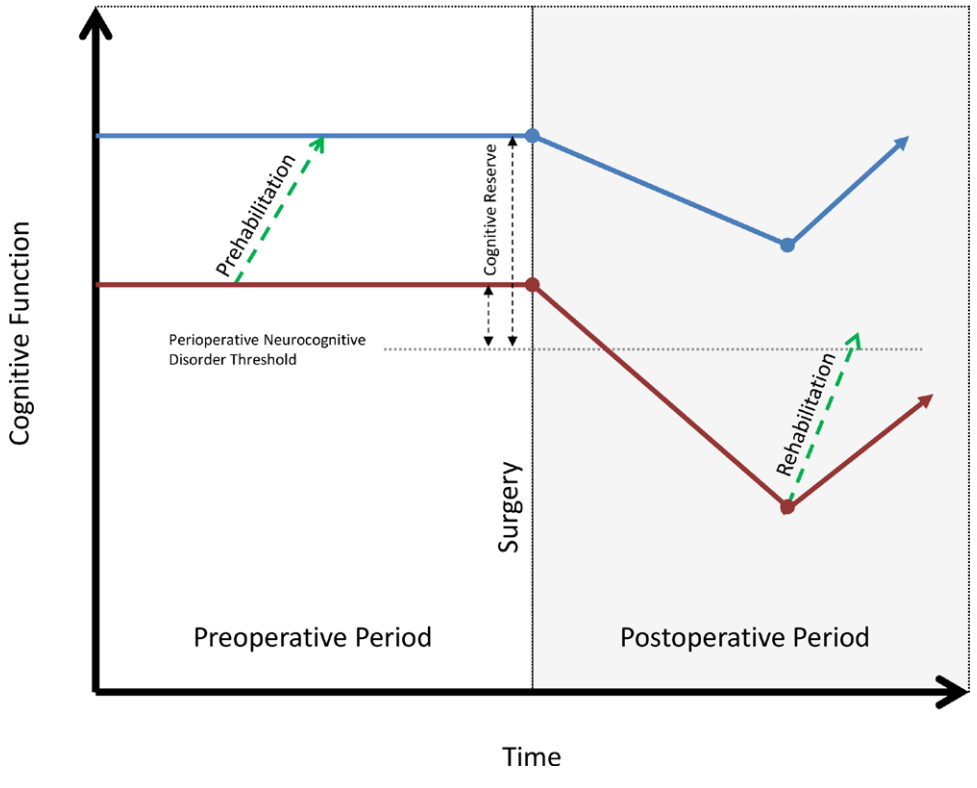

Fig. 4. Cognitive trajectories and perioperative neurocognitive disorders. Depicted are theoretical cognitive trajectories of a patient with high baseline cognitive reserve (*blue line*) and a patient with low baseline cognitive reserve (*red line*). Both patients experience an event in the perioperative period leading to a decrease in cognitive function, but only the patient with low baseline reserve may manifest symptoms. The *green dashed lines* represent the theoretical mechanism through which cognitive interventions in the pre- and postoperative phases may influence cognitive reserve and either prevent or aid recovery from perioperative neurocognitive disorders. Adapted from Stern.[128]

high median years of education (15 yr), suggesting that this effect may not be as evident in highly educated populations.

Educational attainment may also predict long-term postoperative cognitive function. In a large longitudinal cohort of older patients undergoing major noncardiac surgery, educational achievement of high school or higher was associated with a significantly lower risk of delayed neurocognitive recovery at 1 week (odds ratio [95% CI], 0.6 [0.4 to 0.9]; $P = 0.002$), but not for postoperative neurocognitive disorder at 3 months.[133] In another large prospective cohort of major noncardiac surgery patients of which 355 were older than 60, patients with postoperative neurocognitive disorder at 3 months had slightly fewer mean years of education (mean [SD], 13.2 [2.4] or 13.7 [2.8] years; $P = 0.013$).[134] Less well characterized than educational level is the relationship between baseline cognitive lifestyle behaviors and perioperative neurocognitive disorders. In a cohort of 141 patients with a mean age of 71 yr, greater participation in preoperative cognitive lifestyle behaviors including reading books, using email, or playing computer games was found to be protective against delirium after elective orthopedic surgery (increase of one activity per week; odds ratio [95% CI], 0.92 [0.86 to 0.98]; $P = 0.006$).[121]

Prehabilitation to Prevent Perioperative Neurocognitive Disorders

Prehabilitation refers to the attempt to optimize preoperative modifiable risk factors to improve functional outcomes after surgery, often focusing on preoperative physical, nutritional, and psychologic health. Of these three domains, physical prehabilitation has been the most studied. Although there are inconsistent results among trials and uncertainty with regards to whether physical prehabilitation can reduce postoperative complications, multiple clinical trials in abdominal and orthopedic surgery have demonstrated improved postoperative physical capacity in patients who participated in home-based exercise regimens as compared to usual care.[135] Nutritional prehabilitation, consisting mainly of nutritional supplements and dietary counseling, may potentially accelerate the return to preoperative functional capacity in colorectal surgery when added to a physical prehabilitation program.[136] Both physical deconditioning and poor nutritional status are elements of frailty, which has been shown in retrospective studies to be strongly associated with postoperative delirium and possibly postoperative neurocognitive disorder.[137,138] Such elements may be modifiable. In a six-armed randomized trial of 246 older prefrail or frail adults, physical, cognitive, nutritional, or combined intervention training were all shown to reduce future frailty scores to a significantly larger degree than a usual care control.[139] If physical and nutritional prehabilitation can improve postoperative functional outcomes and reverse frailty in older persons, it is then possible that these interventions may prevent perioperative neurocognitive disorders. Data from clinical trials evaluating this potential effect are limited, however. In a single center before and after unblinded study of 627 patients undergoing major abdominal surgery, the incidence of postoperative delirium was found to be significantly lower in patients who underwent a multicomponent intervention to improve physical and nutritional health and reduce frailty factors as compared to patients who did not receive this intervention (22 of 267 [8.2%] *vs.* 42 of 360 [11.7%]; adjusted odds ratio [95% CI], 0.56 [0.32 to 0.98]; $P = 0.043$).[140]

Bolstered by the theory that increasing cognitive reserve can protect against neurologic injury and experimental data suggesting that neurogenesis and neuroplasticity still occur in later life, numerous investigators have evaluated whether cognitive exercise can improve cognitive performance in older persons.[141–144] Perhaps the most notable example is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, which demonstrated that 10 h of computerized cognitive training led to sustained improvements in processing speed over the following 10 yr.[145] In perioperative research, attempts have been made to apply this technique to prevent perioperative neurocognitive disorders. In a randomized trial of 141 abdominal surgery patients older than 60, 3 h of supervised memory exercises 1 to 4 weeks before surgery significantly reduced the incidence of delayed neurocognitive recovery at 1 week compared to usual care (11 of 69 [15.9%] *vs.* 26 of 72 [36.1%]; $P = 0.007$).[146] In contrast to its success in older adults in the general population, computerized cognitive training appears to be less feasible in older surgical patients.[147] Although a small feasibility trial of 45 older cardiac surgery patients noted high degrees of patient interest and enjoyment with a computerized cognitive prehabilitation program, there were low rates of adherence (39% during the preoperative period), and no effect on the incidence of postoperative delirium or delayed cognitive recovery was found.[148] In a recent randomized trial of 251 patients older than 60 undergoing major noncardiac nonneurologic surgery, preoperative computerized cognitive exercise did not significantly reduce the risk of postoperative delirium as compared to usual care in the primary analysis. However, a *post hoc* per-protocol analysis excluding patients who never used the cognitive exercise program revealed a significantly reduced incidence of postoperative delirium favoring the cognitive exercise group (16 of 121 [13.2%] *vs.* 29 of 126 [23%]; $P = 0.04$).[149] It should be noted that for this trial and the feasibility trial that used the same cognitive exercise platform, the median length of time spent training was ~4.5 h, which falls short of "recommended dose" of 10 h of cognitive exercise in the ACTIVE trial. Further investigation is necessary to determine whether adherence to cognitive prehabilitation can be improved and whether cognitive prehabilitation can reduce delirium and/or other perioperative neurocognitive disorders in an adequately powered trial.

Postoperative Cognitive Training

Postoperative cognitive training may also prevent perioperative neurocognitive disorders. A randomized trial of 47

lung transplant patients with a mean age of 65 yr demonstrated greater score improvements at 12 weeks on the Forward Digit Span (mean [SD], 0.93 [1.09] *vs.* 0.04 [0.52]; $P = 0.004$) and Verbal Fluency tests (mean [SD], 1.32 [1.82] *vs.* 0.1[1.53]; $P = 0.033$) with the use of a computerized program for 8 weeks after surgery.[150] Among 46 lung transplant recipients with a mean age of 66 yr, the use of 8 weeks of computerized cognitive training started 4 weeks after surgery resulted in significantly higher scores on the digit span forward test (mean [SD], 0.93 [1.09] *vs.* 0.04 [0.52]; $P = 0.0044$) and verbal fluency (mean [SD], 1.32 [1.82] *vs.* 0.10 [1.53]; $P = 0.0331$).[150] It should be noted, however, that these mean differences are less than the SD for the group, which is a common benchmark used in previous studies to define perioperative neurocognitive disorders. The best known multicomponential intervention to prevent hospital delirium, HELP, includes the provision of cognitively stimulating activities at least three times daily as a core intervention.[151] In a before–after study of 179 consecutive abdominal surgery patients older than 65 in which a modified version of HELP was implemented that focused only on nutrition, mobilization, and cognitively stimulating activities including discussing current events or word games, the delirium rate was significantly reduced in the intervention group (0 of 102 [0%] *vs.* 13 of 77 [16.7%]; $P < 0.001$).[152] A similar approach employing daily cognitively stimulating conversation and word games was employed in a randomized pilot trial in 50 older hip or knee arthroplasty patients. The investigators found that patients in the intervention group had a significantly lower incidence of delayed neurocognitive recovery as defined by a decrease of 2 points or more from the baseline Mini Mental Status Exam score as compared to usual care controls (3 of 25 [12%] *vs.* 11 of 25 [44%]; $P = 0.012$).[153]

Summary

Poor baseline cognition, defined by either poor preoperative performance on screening tests of cognitive function or decreased markers of cognitive reserve, is strongly associated with perioperative neurocognitive disorders. As such, the routine use of a validated screening test in the preoperative period has been recommended to help identify at-risk patients. Although physical and nutritional prehabilitation may improve postoperative functional capacity and reverse frailty in nonoperative patients, more investigation is necessary to determine whether these interventions can prevent perioperative neurocognitive disorders. Cognitive prehabilitation has been shown to reduce delirium incidence in one clinical trial, but further studies are needed to replicate this finding, to determine the optimal training regimen, to improve adherence, and to investigate whether the technique can prevent delayed cognitive recovery and/or postoperative neurocognitive disorder. Postoperative cognitive exercise may improve postoperative cognition and prevent postoperative delirium, but high-quality evidence from adequately powered clinical trials is needed to better determine these effects.

Conclusions

The increasing awareness of the long-term negative consequences of perioperative neurocognitive disorders on functional outcomes after surgery has led to the development of multicomponent interventions to optimize postoperative brain health. Decades of perioperative research targeting isolated intraoperative interventions focusing on altering the exposure to anesthesia or surgery have not yet been able to identify a singular intervention to successfully prevent perioperative neurocognitive disorders. Given the

Table 1. Summary of Evidence and Future Directions

Summary	Questions for Future Research
Sleep	
Chronic sleep disorders including obstructive sleep apnea are associated with future delirium.	Can improving preoperative sleep quality reduce delirium risk?
	Can increasing perioperative adherence to continuous positive airway pressure prevent delirium?
Perioperative sleep disruption is a precipitating factor for delirium.	Can restoring circadian rhythm, either naturally or with the use of melatonin, prevent delirium?
	Can preferential use of dexmedetomidine prevent postoperative delirium in patients requiring postoperative sedation?
Pain	
Preoperative pain is a risk factor for postoperative delirium.	Can optimization of preoperative pain lower the risk of postoperative delirium?
Poorly treated postoperative pain can precipitate postoperative delirium.	Do multisource tools for pain assessment identify patients at risk for delirium?
	Does the use of multimodal analgesia prevent postoperative delirium?
Little evidence exists describing the association between postoperative pain and longer term perioperative neurocognitive disorders.	Is poorly controlled pain associated with delayed neurocognitive recovery?
	Does chronic postoperative pain increase the risk of postoperative neurocognitive disorder?
Cognition	
Poor preoperative cognitive function is one of the strongest predictors of perioperative neurocognitive disorders.	Which cognitive screening test(s) best predict perioperative neurocognitive disorders?
	Does preoperative cognitive trajectory predict perioperative neurocognitive disorders?
Perioperative cognitive exercise may prevent postoperative delirium.	Can cognitive prehabilitation prevent perioperative neurocognitive disorders?
	Which type of cognitive exercise is best suited to prevent perioperative neurocognitive disorders? What is the most effective dose?

multiple predisposing and precipitating risk factors for postoperative delirium and the incomplete overlap with risk factors for delayed neurocognitive recovery and postoperative neurocognitive disorder, it is likely that a multicomponent approach encompassing all phases of the perioperative period (preoperative, intraoperative, and postoperative) may be more effective. Going forward, critically needed perioperative research into three targets for optimal perioperative brain health: sleep, pain and cognition, will enable providers to better identify high-risk patients and confidently employ interventions into well defined care plans (table 1). When this can be achieved, perioperative medicine may reach its goal of an ideal recovery for both the bodies and minds of surgical patients.

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Competing Interests

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