Title

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Journal

The Annual Review of Pharmacology and Toxicology, 63(1)

ISSN

0362-1642

Authors

Barreto Chang, Odmara L
Possin, Katherine L
Maze, Mervyn

Publication Date

2023-01-20

DOI

10.1146/annurev-pharmtox-051921-112525

Peer reviewed

ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Age-Related Perioperative Neurocognitive Disorders: Experimental Models and Druggable Targets

Odmara L. Barreto Chang,[1] Katherine L. Possin,[2] and Mervyn Maze[1,3]

[1]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California, USA; email: Mervyn.maze@ucsf.edu

[2]Memory and Aging Center, Department of Neurology, and Global Brain Health Institute, University of California San Francisco, San Francisco, California, USA

[3]Center for Cerebrovascular Research, University of California San Francisco, San Francisco, California, USA

Annu. Rev. Pharmacol. Toxicol. 2023. 63:321–40

First published as a Review in Advance on September 13, 2022

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-051921-112525

Keywords

perioperative neurocognitive disorders, postoperative delirium, neuroinflammation, cognitive assessment, perioperative brain health, care pathways

Abstract

With the worldwide increase in life span, surgical patients are becoming older and have a greater propensity for postoperative cognitive impairment, either new onset or through deterioration of an existing condition; in both conditions, knowledge of the patient's preoperative cognitive function and postoperative cognitive trajectory is imperative. We describe the clinical utility of a tablet-based technique for rapid assessment of the memory and attentiveness domains required for executive function. The pathogenic mechanisms for perioperative neurocognitive disorders have been investigated in animal models in which excessive and/or prolonged postoperative neuroinflammation has emerged as a likely contender. The cellular and molecular species involved in postoperative neuroinflammation are the putative targets for future therapeutic interventions that are efficacious and do not interfere with the surgical patient's healing process.

INTRODUCTION

As the population ages, an increasing number of older patients will undergo surgical procedures (1). Advanced age is a major risk factor for postoperative cognitive impairment, resulting in prolonged hospital stay, loss of independence, higher health-care costs, and increased morbidity and mortality (2–4). Among older adults, the relative risk of developing delirium increases with each added year of age (5), becoming particularly prevalent in surgical patients over 75 years old (6). Understanding the pathogenesis of this common postoperative complication will help identify those older surgical patients for whom both preventative and restorative interventions may be required. In this review, we describe the clinical condition and best practices for diagnosis and treatment and describe how preclinical models have established putative mechanisms that constitute druggable targets for testing the efficacy and safety of interventions.

PERIOPERATIVE NEUROCOGNITIVE DISORDERS

In recent years, the nomenclature for cognitive impairment in the perioperative period has been revised to align with the terminology used for cognitive disorders listed in the *Diagnostic and Statistical Manual of Mental Health Disorders* (7) (DSM-5) (**Figure 1**). Perioperative neurocognitive disorder (PND) is the most common complication in older surgical patients, with an estimated 1.6–6.4 million Americans suffering from PND each year (8). PND describes new cognitive impairment or deterioration of existing impairment identified in the period immediately prior to surgery and concluding 12 months after surgery (9) (**Figure 1**). Cognitive impairment within hours after surgery is often classified as emergence excitation or postanesthesia care unit delirium (9, 10). During the postoperative interval, the most common cognitive impairment is postoperative delirium (POD), which can occur in up to 40% of patients older than 60 years (8). POD occurs up to 1 week postprocedure or until discharge from the hospital (whichever occurs first) (9). POD is characterized by fluctuating changes in attention, mental status, or level of consciousness. Irrespective of whether POD occurred, older surgical patients can manifest delayed neurocognitive recovery if new impairment, or increased impairment that was temporally associated with the surgical period, has not resolved within 30 days. If this impairment is present 31 days to 12 months after surgery, it is defined as postoperative neurocognitive disorder (postoperative NCD), which can occur in up to 15% of older patients (10).

It is important to emphasize that outside of the surgical context, NCDs frequently occur in older adults (11) and are a well-established risk factor for PNDs (12–15). The key difference between mild NCD [also called mild cognitive impairment (MCI)] and major NCD (also called dementia) is that in major NCD, the cognitive decline significantly interferes with activities of

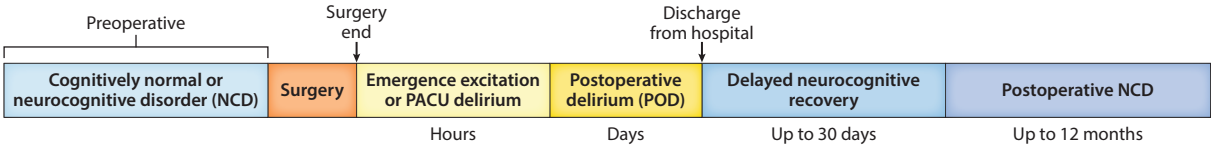

Figure 1

The diagram presents the continuum of the classification of perioperative neurocognitive disorder (PND). Preoperatively, patients are cognitively normal or have a neurocognitive disorder (NCD). After surgery, the cognitive impairment is sometimes classified as emergence excitation or postanesthesia care unit (PACU) delirium while recovering from anesthesia. While patients are in the hospital, cognitive impairment is classified as postoperative delirium (POD). The nomenclature changes to delayed neurocognitive disorder for the period up to 30 days after surgery. After that period and up to 12 months afterward, the cognitive impairment is considered a postoperative NCD. Figure created by Dr. Caroline Prioleau and Sabrina Erlhoff.

daily living (9, 16). In 2020, the estimated US prevalence of dementia was 6.07 million (11.3% of the population aged 65 or older), and the estimated prevalence of MCI was 12.23 million (11). The most common cause of NCD is Alzheimer's disease (AD), followed by cerebrovascular disease and Lewy body disease (i.e., Parkinson's disease dementia and dementia with Lewy bodies); most NCD patients have brain changes associated with more than one cause of dementia (17). Brief cognitive assessments are useful for detecting cognitive impairment, but a more in-depth evaluation is required for differential diagnosis that identifies underlying etiology. Patients with Lewy body disease are at a particularly high risk for POD (18). While differential diagnosis of NCDs is likely beyond the scope of most preoperative clinical settings, extra precautions should be taken for patients with cognitive impairment and warning signs for Lewy body dementia, including rapid-eye-movement sleep behavior disorder, parkinsonism, visual hallucinations, attention fluctuations, and sensitivity to antipsychotic agents (18).

As extant cognitive impairment is a risk factor for PND (15), professional societies such as the American Society of Anesthesiologists, the American College of Surgeons, and the American Geriatrics Society recommend administration of preoperative cognitive assessments for older patients undergoing surgery (19–21). However, these assessments are rarely performed, resulting in underdetection of preoperative cognitive impairment (22–24) and a lost opportunity for targeted interventions to protect brain health.

PREOPERATIVE COGNITIVE ASSESSMENT

Mild cognitive impairment and dementia are substantially underdiagnosed; diagnosis is delayed until moderate or advanced stages of dementia in 50% or more patients (22–24), with greater delays among racial and ethnic minorities (25). For this reason, preoperative cognitive assessment is critical for detecting cognitive impairment and guiding perioperative care. Several reviews have summarized the brief cognitive assessments typically used to detect cognitive impairment prior to surgery (8, 26). Brief (3–15 min) paper-based assessments such as the Mini Mental State Exam, Montreal Cognitive Assessment, Mini-Cog©, verbal fluency, and clock drawing test, among others, have been used as preoperative cognitive screening tools. Yet, cognitive assessments continue to be infrequently incorporated into preoperative clinical workflows (27), and a reconsideration of the types of tools that will be successful is needed.

Commonly used preoperative cognitive assessments can be useful to detect dementia, but sensitivity of these tests is lower for MCI (28). Furthermore, most brief cognitive assessments have been inadequately adapted for different language/cultural/educational groups, and the impact of these demographic variables is rarely considered when determining whether a patient is impaired in preoperative settings. As an example, a brief cognitive assessment that was developed and validated for an English-speaking population with moderate to high education might not be appropriate for a recent immigrant who has limited English proficiency and few years of education. Brief cognitive assessments are needed that are accurate for MCI detection across demographic and social groups, and scoring may need adjustment for education and other demographic variables (29, 30).

It has not been well studied which cognitive tests are most accurate for predicting postoperative cognitive disorders, but there is reason to emphasize testing of executive functions and episodic memory. Executive functions refer to a constellation of cognitive abilities that enable and drive adaptive, goal-oriented behavior. They include working memory, complex attention (e.g., inhibition, mental flexibility, and sustained attention), planning, fluency, and self-monitoring (31). Episodic memory refers to the ability to consciously recall personally experienced episodes. The memoranda can be verbal, spatial, object based, or multimodal (32). Executive functions and

episodic memory are typically the first cognitive domains to be affected in preclinical AD (33), and vulnerability in the neural networks underlying these skills may predispose patients to the neuroinflammatory consequences of surgery. In POD, there are diffusion changes that can be detected by magnetic resonance imaging (MRI) in the periventricular, frontal, and temporal white matter (34) and a decrease in frontoparietal connectivity on EEG (35); these regions and structures are crucial for executive functions (36). Furthermore, disconnectivity involving interhemispheric and frontothalamo-cerebellar networks, as well as microstructural changes of nuclei involved in limbic and memory functions, predisposes patients to delirium after surgery (37). MRI studies suggest that a reduction of thalamic and hippocampal volumes—crucial regions for episodic memory—may be associated with PND (38).

An example of a brief cognitive assessment that is accurate at detecting MCI and sensitive to the memory and executive function impairment of NCDs is the TabCAT Brain Health Assessment (TabCAT-BHA) (36). Subtests include Favorites (associative memory), Match (executive functions and speed), Animal Fluency (language), and Line Orientation (visuospatial). In addition to subtest scores, a composite score summarizes performance, with an emphasis on the memory and executive tests (39). The subtests rely on brain regions vulnerable to surgical insult and NCDs: Favorites has been associated with medial temporal lobe volumes and tau deposition; Match with frontoparietal and basal ganglia network volumes, frontoparietal tau deposition, and corpus callosum white matter integrity; Line Orientation with right parietal volumes and bilateral occipitoparietal tau deposition; and Animal Fluency with left frontal/temporal atrophy (36, 40–42). Furthermore, TabCAT-BHA has been validated in diverse populations, and regression-based norms can be instantly applied that adjust scores for key sociodemographic factors (39, 43).

The TabCAT-BHA is currently in use to improve the detection of NCDs in primary care (44). If a concern for cognitive impairment has been identified by the primary care provider, a medical assistant administers the 10-min test, and results are integrated into the electronic health record (EHR) to guide the primary care provider on the next steps in evaluation in care. Here, we propose a similar efficient workflow adapted for the surgical setting (**Figure 2**). Prior to surgery, adults ages 65 or older or with risk factors for preexisting cognitive impairment are administered a brief, digital cognitive assessment such as the TabCAT-BHA by clinical staff. Results are integrated into the EHR and flagged if the patient has a high likelihood of cognitive impairment, which is a risk factor for PND.

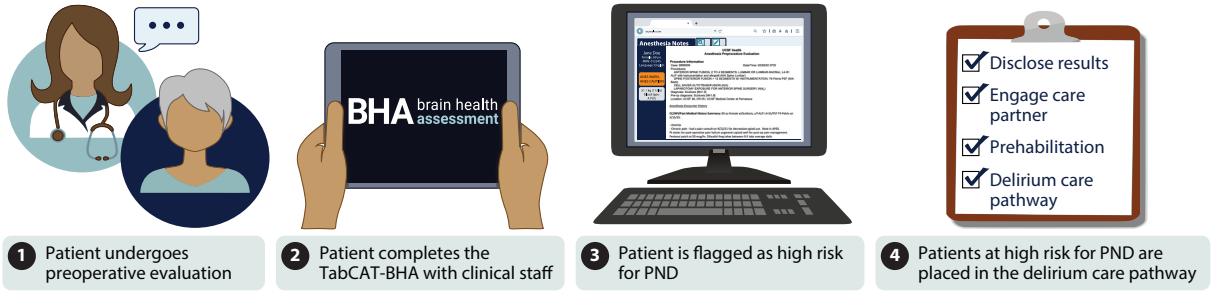

Figure 2

Proposed care pathway for older adults undergoing surgery. Adults ages 65 or older or with risk factors for preexisting cognitive impairment are administered a brief digital cognitive assessment prior to surgery. Results are integrated into the electronic health record and flagged if the patient has a high likelihood of cognitive impairment. After cognitive impairment has been established, the anesthesiologist or another clinician on the team discloses this finding to the patient with a care partner present. Prehabilitation and delirium care pathways are incorporated for patients at high risk for perioperative neurocognitive disorder (PND). Figure created by Dr. Caroline Prioleau and Sabrina Erlhoff.

MONITORING COGNITIVE TRAJECTORIES

Patients and families commonly complain of postoperative cognitive decline. While accurate monitoring of the cognitive trajectory is important for appropriate diagnosis and treatment, it can be difficult to quantify change and monitor for recovery without a reliable preoperative baseline. Sensitive and reliable tests can establish a neurocognitive baseline to monitor postoperative cognitive dysfunction and trajectories, including decline, recovery, and response to treatment (45–47). Reliable change is measured by defining a change in performance between cognitive scores and adjusting for the expected variance of the test (39). Unfortunately, most paper-based cognitive tests that are used in the preoperative setting are designed for screening but are poor for measuring cognitive change over time. Computer-based cognitive batteries are often better suited for following long-term trajectories because of their better psychometric properties and higher measurement precision (48). The TabCAT-BHA, for example, exhibits excellent long-term stability for patients with MCI and dementia and outperforms standard paper-based tests in this regard (39).

PERIOPERATIVE BRAIN HEALTH CARE

After cognitive impairment has been established, the anesthesiologist or another clinician on the team discloses this finding to the patient with a care partner present (**Figure 2**). The risk of PND is discussed, including confusion, inattention, and memory problems that may occur after the operation. The desirability of proceeding, especially with an elective procedure, should be discussed with the surgical provider and the patient. Next, the care partner should be engaged to participate in medical decision-making, to be present during the postoperative period to assist with orienting and providing a comforting environment for the patient, and to develop a caregiving plan if the patient develops POD.

If time allows prior to surgery, prehabilitation may be considered for older adults at high risk for PND (**Figure 2**). Prehabilitation aims to enhance health, optimize comorbidities, treat sleep disorders, and address modifiable risk factors before surgery via a variety of interventions that typically focus on nutrition, exercise training, and reducing stress and anxiety. Reversible causes of cognitive impairment, including medication side effects, sleep apnea, depression, and other medical conditions, can be treated prior to surgery (49–51). While more research is needed to understand whether prehabilitation reduces the risk of PND (52, 53), there is evidence that prehabilitation programs can decrease hospital length of stay and improve functional capacity (54, 55). Recent research has suggested that cognitive training may offer some benefit (56), although not all studies concur (57). Delirium care pathways should be triggered for patients at high risk for PND (**Figure 2**). These delirium care pathways include a cautious approach to anesthesia that starts by avoiding deliriogenic medications and optimizing intraoperative anesthetic care. Postoperatively, these pathways also include healthy nutrition, delirium screening, and nonpharmacological protocols that emphasize patient orientation, early access to glasses and hearing aids, sleep-wake cycle regularity, promotion of mobility, and pain control (8, 58). While adopting these multidisciplinary interventions can be challenging, they can be feasibly performed in the perioperative setting (59, 60).

In summary, clinical perioperative brain health care has seen recent advancements in consistent nomenclature, consensus on evidence-based perioperative care pathways, and new tools that facilitate accurate and actionable assessment of cognition in clinical settings. More research is needed to elucidate the mechanisms of PNDs and how baseline vulnerabilities, including NCDs, affect postsurgical disease progression. Furthermore, gaining insights into new interventional targets to protect perioperative brain health is an active area of work and the focus of the remainder of this review.

VALIDITY OF ANIMAL MODELS FOR PNDs

Findings from animal models can be extended to the target clinical population if certain factors are satisfied (61). Construct validity, also referred to as etiologic validity, considers the relevance of methods that create the model to the factors that produce the clinical disease. For PNDs, the model should be triggered by aseptic trauma (mimicking the surgical intervention), usually within the context of heightened vulnerability, in which risk factors, which are similar to those that enhance the prevalence of the clinical condition, are introduced. Face validity considers whether the model recapitulates, with high fidelity, critical biochemical, neuropathological, and behavioral features of the disease. For the clinical features to be similar to those of PND, the assessment of animal behavior must reflect the clinical cognitive domains that are typically impaired; it is unlikely that a single animal behavioral assessment will suffice for the features that are evident in the heterogeneous syndrome of PNDs. Predictive or pharmacological validity is established when the model responds to treatments in a way that predicts the effects of those treatments in humans; once established, the model can be used as a tool for screening for efficacy of prospective interventions. We focus on models involving rats and mice as these are the most common species used for PND preclinical research (62).

PROVOKING THE PHENOTYPE IN ANIMAL MODELS OF PND

The surgical trauma must be accomplished aseptically, under a general anesthetic regimen that itself does not modify the pathogenesis, resulting in an injury that does not interfere with mobility that is required in a subsequent behavioral assessment of cognition. As sepsis itself can produce cognitive disturbances, possibly through molecular mechanisms that differ from those of aseptic trauma, it is crucial that surgery be performed under sterile conditions. Apart from asepsis, the surgical intervention must avoid other pathogenic pathways, such as ischemic-reperfusion injury, which itself can cause cognitive decline (63), possibly through a different mechanism. Some sedative hypnotics can affect cognitive function independent of the surgery; a notable class are the benzodiazepines, which can directly affect both neuroconnectivity (64) and immune responses (65) and confound the influence of trauma on these potential mechanisms of PND. Furthermore, as prolonged exposure to volatile anesthetic agents can itself produce cognitive disturbances (66), the surgical intervention needs to be of short duration when performed under general anesthesia with these agents. Because neither neuraxial anesthesia (67) nor the type of general anesthetic (68) has been shown to influence the risk for delirium or postoperative cognitive impairment, respectively, these features have not been explored in preclinical models. As it is unethical to produce surgical trauma without anesthesia, models that seek to determine the putative modulatory effects of anesthetics on postsurgical behavior require the use of surgical surrogates, such as damage-associated molecular patterns (DAMPs), to trigger the phenotype (69) and that can be administered to a nonanesthetized animal. Behavioral assays that measure attentiveness and/or memory usually require assessment in a freely moving animal; therefore, it is important to ascertain that the surgical intervention (especially one involving the musculoskeletal system) does not interfere with mobility.

ENHANCING THE VULNERABILITY IN ANIMAL MODELS OF PND

As advanced age is the dominant risk factor for the development of PNDs (2), older animals are frequently used in translational models (70) for construct validity; use of young adult rodents may still be useful to understand surgery-induced changes in normal animals as a comparator to define why risk factors such as age influence the development of this postoperative complication. In

the International Study of Postoperative Cognitive Dysfunction investigation, perioperative respiratory infection was identified as a significant risk factor (71); consequently, some investigators have incorporated respiratory infection with mycoplasma into their models (72). Surgical patients with metabolic syndrome have an increased risk for POD following either noncardiac (73) or cardiac surgery (74); similarly, posttraumatic cognitive decline was exacerbated in a rat model of metabolic syndrome (75). Some studies have found that obese surgical patients have more exaggerated PND (76); this observation has been replicated in animal models of diet-induced obesity (77). Perioperative disrupted sleep hygiene and/or obstructive sleep apnea increases the probability for developing POD (78), and this finding has been recapitulated in animal models of sleep deficiency (79). Postoperative administration of opiate narcotics increases the risk for POD (80) and the duration of memory impairments and can be included in the model for those reasons (81). There is increasing interest in the possibility that surgery may hasten the onset or progression of AD symptoms (82) and that similar postoperative neuropathological changes to those of AD are observed (83); these observations led to the use of transgenic animals to explore the pathological and behavioral changes that surgery induces in this AD-permissive genetic background in which the postoperative cognitive impairment is longer lasting than in wild-type animals (84). Modification of the intestinal microbiome may also increase vulnerability for posttraumatic cognitive impairment (85), and rectification of an unstable intestinal microbiome results in an improvement in cognitive function (86). Cancer has been shown to be associated with increased risk for the development of cognitive impairment in an animal model (87); this finding is now being studied clinically (88).

BEHAVIORAL ASSESSMENT OF COGNITIVE DOMAINS IN ANIMAL MODELS OF PND

The complex cognitive processes required to develop thoughts and produce actions in humans involve domains that include attention, perception, executive functions, learning, memory, and language; additionally, emotional and motivational processes influence cognitive performance (89). Rather than targeting the entire spectrum of cognition, investigators have sought assessments that quantify the impairments that are present in PNDs. POD is the most common PND; its clinical features include inattention, disorganized thinking, altered levels of consciousness, disorientation, memory impairment, perceptual disturbances, and psychomotor agitation or retardation. Of these clinical features of POD, only inattention and memory impairment can reliably be measured through behavioral assessment in rodents. The domain of executive function, incorporating the faculties of working memory and attention, is often dysfunctional in PNDs (90).

Attentiveness

The 5-choice serial reaction time task (5-CSRTT) is a robust method for measuring impairment in attentiveness that can be performed in both rats (91) and mice (92); this preclinical test was specifically developed to mirror the inattentiveness that is present in children with attention deficit hyperactivity disorder and has been shown to have both predictive (93) and construct validity (94). In this attentiveness paradigm, the rodent is required to perform a nose poke into one of five holes in response to a brief (2 s) flash of light from that hole; correct spatial location results in a food reward. Both accuracy and speed of stimulus discrimination define the attentional capacity to monitor a horizontal array of food-rewarding apertures. Training is performed over several days (typically involving a total of ~25 sessions), and animals that can successfully respond with 80% accuracy are subsequently used for the experiments. Indices that are monitored in the test situation include accuracy (percentage of correct responses), omission rate (failure to respond),

and latency to nose poke. Additionally, a distracting stimulus (e.g., noise) can be introduced to challenge attentional processes that are directed to the relevant visual stimulus. Limitations of the 5-CSRTT include a requirement for adequate visual sensory function and that the operant nature of the task in which early satiety (established by an increase in latency for the food pellet to be retrieved) may limit motivation.

Memory

Working memory in humans refers to the ability to represent information in mind and use it in service of our immediate goals. An example of a clinical test of this function is Digit Span, which requires the examinee to repeat back a string of digits in forward or backward order (31). Absent language as a parameter in animals, the tasks that are used involve memory in maze-like paradigms (95). The delayed Y-alternation test (96) exploits the tendency of rodents to choose an alternate, other that the originally explored, arm to enter on successive trials, with an intertrial delay of a specified time (usually seconds).

Episodic memory refers to recollection of what has been personally experienced, with a retention time that is longer than for working memory. In the Novel Object Recognition (NOR) test (97), the novelty-seeking curiosity of rodents is exploited. In an acquisitional session, the animal is confronted with two identical objects, and they devote approximately equal time to exploring each individual object. In the retention phase, the animal explores a situation in which one of the familiar objects is substituted with a novel object; the test requires the animal to discriminate between the novel and the familiar object. If the animal can recall the objects to which it was previously exposed, it spends significantly more time exploring the novel object; if episodic memory is impaired, the animal is unable to distinguish which is the novel object and spends approximately equal time with each. Care with respect to the nature of the objects, the discriminability of the stimulus, the length of the sessions, intertrial intervals, and environmental conditions must be exercised (98). The NOR test can also be reconfigured to measure working memory by shortening the retention interval (99).

The most common histopathological feature of preclinical models of PND is neuroinflammation, especially of the hippocampus, a critical region for spatial episodic memory in rodents and humans (100). Spatial memory behavioral tasks are usually performed within a maze; the Morris water maze (MWM), the Barnes maze (BM), and the radial arm maze (RAM) are discussed further because of their popularity in laboratories that use preclinical models of PND. In the MWM, visual cues surround a circular pool to guide the rodent to a submerged platform that is obscured by the opaque nature of the fluid when the animal is introduced into the pool from different starting locations (101). Because the wound from the surgical trauma must not be contaminated, trials in the pool cannot be undertaken before it has healed. Similarly, any limitation in swimming speed from the surgical trauma will confound the assessment. Similar spatial memory deficits were observed on the MWM in a transgenic mouse model of AD as those on a virtual MWM in patients with MCI due to AD, providing face validity evidence for this test (102). In the BM, the rodent is required to escape from a brightly lit circular platform by locating the correct hole (of the 20 that are radially arranged) that leads to a small dark recessed chamber (103). In the RAM, eight arms radiate from a circular central platform on which the animal is placed; the goal of the task is to select the arm that contains a food pellet (104). In the acquisition or learning phase for each of the spatial memory paradigms, the performance of the task is assessed by the time it takes to reach the platform, hole, or arm; in the retention phase of the task, the reference memory probe is assessed by the preference for a quadrant, hole, or arm when the platform, recessed chamber, or food pellet is removed.

For emotive (associative) memory, a form of implicit memory, a trace fear conditioning paradigm is used in which an unconditional stimulus (mild foot shock applied from the grid floor) is paired with either contextual or auditory cues in the acquisition phase (105). In the test phase of the task, placement of the rodent in the same context or subjected to the same auditory cue, but without the shock, provokes a fear response in which the animal freezes (no movement except for breathing) in anticipation of a foot shock. A decrease in the time spent freezing in response to an auditory cue indicates a lesion in the amygdala, while a lesion in the hippocampus limits freezing in response to the contextual cue.

DRUGGABLE TARGETS ESTABLISHED IN ANIMAL MODELS OF PNDs

Successful interventions for PNDs require a thorough understanding of the cellular and molecular species involved; studies in animal models have generated two plausible pathogenic mechanisms: inflammation and oxidative stress. In the following description of the pathogenesis of PND, the cellular and molecular targets for interventions with disease-modifying entities are identified. Symptom mitigation is not considered because of the difficulty of aligning postoperative clinical symptoms with animal models.

Inflammation

Based on the similarity of the innate immune response to trauma between surgical patients and animal models (106), as well as meta-analyses associating the degree of inflammation with outcomes in patients (107), both construct and face validities are satisfied. The dynamic nature of the inflammatory response to trauma requires consideration of temporal changes rather than exhaustively describing each immune-related cell or cytokine that is altered by surgery; without appropriately timing the intervention, its efficacy may not become evident, a problem that has plagued immunotherapy for dynamic diseases such as sepsis (108). Therefore, the stages of the immune response to surgical trauma are now considered (**Figure 3**).

Systemic inflammation is provoked by high molecular group box protein 1 (HMGB1), a DAMP that is passively released from physically disrupted traumatized tissue as it shuttles between the cytoplasmic and nuclear compartments, dictated by its posttranslational modifications. Subsequently, active, exocytotic release of cytosolic HMGB1 from immunocytes occurs under the influence of proinflammatory cytokines (109). Depending on its posttranslational redox state, released HMGB1 can bind up to 14 different pattern-recognition receptors, including the receptor for advanced glycation end products (RAGE) and Toll-like receptors (TLRs) on chemotactically attracted immunocytes [including circulating bone marrow–derived monocytes (BM-DMs)]. Through RAGE-dependent signaling pathways, the transcription factor nuclear factor κB (NF-κB) localizes to the nucleus, resulting in the upregulation of proinflammatory cytokine genes, including *TNFα*, *Il1β*, and *Il6*; the cognate proteins of these genes peak in the circulation within hours of the trauma (110). Animal studies have revealed that neutralizing HMGB1 (69), tumor necrosis factor α (TNFα) (111), IL-1β (110), or IL-6 (112) at this early stage can block the development of postoperative cognitive decline (**Table 1**); however, a thorough understanding of the effect of early immunotherapy on healing of traumatized tissue is required before considering these as therapeutic interventions. Glycyrrhizin, a natural triterpene glycoconjugate derived from the root of licorice, has been shown to bind to HMGB1 and to prevent proinflammatory cytokine activity (113) and postoperative cognitive decline (114); again, caution should be exercised before extending this finding to the clinical setting because of the possible adverse effects of glycyrrhizin on wound healing.

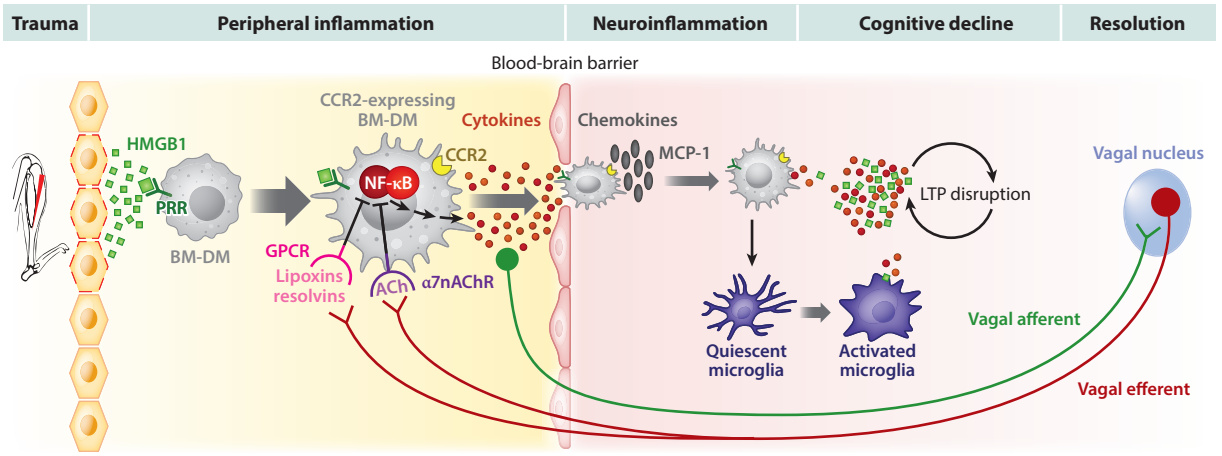

Figure 3

Inflammatory mechanisms involved in perioperative neurocognitive disorders. Aseptic trauma to the tibia provokes the release of high molecular group box protein 1 (HMGB1) from the traumatized tissues. HMGB1 binds to pattern-recognition receptors (PRRs) on circulating bone marrow–derived monocytes (BM-DMs), resulting in nuclear translocation of nuclear factor κB (NF-κB) and the subsequent upregulation of genes for proinflammatory cytokines and its release into the circulation; HMGB1 also upregulates the chemokine MCP-1. High levels of circulating proinflammatory cytokines can permeabilize the blood-brain barrier, promoting the influx of C-C chemokine receptor type 2 (CCR2)-expressing BM-DMs into the brain parenchyma via the chemoattraction of MCP-1 to CCR2 receptors. Under the influence of BM-DMs, resident quiescent microglia in the brain become activated; together, these tissue macrophages release proinflammatory cytokines and HMGB1, which can disrupt long-term potentiation (LTP), a synaptic plasticity mechanism required for learning and memory. Inflammation is resolved through efferents from the vagus nerve that inhibit NF-κB nuclear translocation via the action of acetylcholine (ACh) and lipoxins/resolvins, which are mediated by the α7 nicotinic acetylcholine receptor (α7nAChR) and G protein–coupled receptors (GPCRs), respectively. Figure created by Dr. Caroline Prioleau and Sabrina Erlhoff.

The next stage is the transformation of systemic inflammation into neuroinflammation (**Figure 3**). Despite the obstacle presented by the blood-brain barrier (BBB) to unfettered passage of inflammatory molecules and immunocytes (115), the brain can still receive instruction from the innate immune response to peripheral injury through the circulating proinflammatory cytokines IL-1β and TNFα, which can signal the central nervous system by binding to cognate receptors on either the afferent vagus nerve (116) or endothelial cells in the BBB (117) to provoke neuroinflammation. Additionally, the BBB can be permeabilized by high levels of circulating TNFα, which decreases cadherin and ZO-1, proteins that are involved in establishing the BBB's tight junctions (118). Another immunological mechanism for enhancing BBB permeability is through the activation of mast cells (119). Restoring the integrity of the BBB (and preventing postoperative neuroinflammation) can be accomplished with a mast cell stabilizer such as disodium cromoglycate (119) (**Table 1**). Other strategies designed to strengthen the BBB include blocking the angiotensin II receptor type 1 that is upregulated in the hippocampus postoperatively (120) and by neutralizing IL-17A (121), although such an intervention may adversely affect peripheral inflammation and wound healing (**Table 1**).

Through the permeabilized BBB, circulating BM-DMs translocate into the brain parenchyma after trauma (122), attracted by the chemokine MCP-1, which is upregulated by HMGB1 (69). The resident microglia sense the changes induced by cytokine signaling and the influx of BM-DMs and become activated (123), polarize to a proinflammatory state (M1), and release proinflammatory cytokines, which disrupt synaptic plasticity processes associated with learning and memory

Table 1 Table of druggable targets

Pathogenesis	Target	Intervention	Adverse event(s)	Reference
Inflammation	HMGB1	Monoclonal Ab	Poor healing	69
	IL-1β	Receptor antagonist	Poor healing	110
	TNFα	Monoclonal Ab	Poor healing, infection	111
	IL-6	Tocilizumab	Poor healing	112
	HMGB1	Glycyrrhizin	Hypertension	114
	Mast cell, BBB	Sodium cromoglycate	Rash, joint pain, headache	119
	BBB, angiotensin II receptor 1	Candesartan	Cold and flu-like symptoms	120
	BBB, IL-17A	Secukinumab	Nasopharyngitis	121
	Bone marrow–derived monocytes	Clodrolip	Infection	122
	Microglia	PLX5622	Loss of CNS homeostasis	125
	Microglia	Mixed-lineage kinase 3 inhibitor	NK	127
	Microglia	Kv1.3 inhibitor	NK	128
	Microglia	Atorvastatin	Cold and flu-like symptoms	130
	Microglia	Pioglitazone	SOB, fatigue, micturition problems	131
	Increase BDNF	Cannabinoids	Psychotomimetic	133
	Increase BDNF	Exercise	NK	86
	A1 astrocytes	Cholecystokinin	Abdominal pain, flushing	136
	A1 astrocytes	Minocycline	GI problems, dizziness	137
	Resolution	AT-Rv1D1	NK	141
	Resolution	Maresin	NK	142
	Resolution, oxidative stress	Omega-3 PUFAs	GI problems, back pain	143
	Resolution	α7nAChR agonist	NK	146
	Resolution	Dexmedetomidine	Bradycardia, hypotension, sedation	149
Oxidative Stress	COX-2	COX-2 inhibitor	Insomnia, GI problems, rhinitis	153

Abbreviations: α7nAChR, α7 nicotinic acetylcholine receptor; Ab, antibody; AT-Rv1D1, aspirin-triggered resolvin 1D1; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; COX, cyclooxygenase; CNS, central nervous system; GI, gastrointestinal; HMGB1, high molecular group box protein 1; IL, interleukin; NK, not known; PUFA, polyunsaturated fatty acid; SOB, shortness of breath; TNFα, tumor necrosis factor α.

(124); chemokines are also released, which attract more immunocytes, thereby prolonging neuroinflammation (125).

Notwithstanding the adverse consequences of neuroinflammation through interruption of synaptic plasticity, neurotransmission, and even neuroapoptosis, the cellular constituents may also be a mechanism for regeneration and repair, for example, through release of trophic substances such as brain-derived neurotrophic factor (BDNF) from the reparative M2 microglia phenotype (126). Thus, while elimination of microglia with an antagonist directed at the colony stimulating factor-1 receptor (PLX5622) can prevent postoperative cognitive decline (125), this is unlikely to be translatable into clinical utility because of the crucial surveillance function of microglia. Rather, strategies aimed at selectively preventing activation of microglia are more appropriate; for example, blocking the mixed-lineage kinase 3 (127) or the Kv1.3 ion channel (128) can prevent microglia activation and postoperative cognitive decline while leaving intact the peripheral inflammatory response and wound healing—an ideal combination (**Table 1**). Conversion of microglia into the M2

phenotype has been accomplished with peroxisome proliferator–activated receptor γ (PPARγ) agonists in other brain injuries (129); pretreatment with the PPARγ atorvastatin reduced activated microglia and cognitive impairment (130), while pretreatment with pioglitazone, another PPARγ, prevented the development of the surgical phenotype and increased expression of BDNF (131) (**Table 1**). It is noteworthy that BDNF dysregulation features prominently in postoperative cognitive impairment (132), and lower levels are present in comorbidities (e.g., type 2 diabetes, obesity) that increase the risk for developing postoperative cognitive impairment. Acute administration of cannabinoids can increase levels of BDNF (133) and can prevent postoperative impairment through cannabinoid 2 receptor signaling (134). Interestingly, nonpharmacologic interventions that increase BDNF levels (e.g., exercise) also prevent postoperative cognitive impairment (86).

In much the same manner that activation of microglia can result in proinflammatory (M1) or proregenerative (M2) phenotypes, the A1 reactive astrocyte phenotype can lose its trophic function and becomes neurotoxic (135). In an aged mouse model of PND, surgery induces astrocytes to express complement 3, a marker of the A1 phenotype (136). Despite the suppressant effect of either minocycline (137) or cholecystokinin (136) on the A1 phenotype and postoperative cognitive impairment, the nonspecific nature of these interventions precludes assigning causality (**Table 1**).

The resolution phase of inflammation is an active process involving both humoral and neural mechanisms. Humoral factors include specialized proresolving mediators (SPMs) that are broadly classified as lipoxins, resolvins (D/E series), and protectins/maresins, which are biotransformation products of the fatty acids arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (138). As these fatty acid precursors can also give rise to proinflammatory mediators such as prostaglandins and leukotrienes, precise temporal coordination is required to toggle or class switch between proinflammatory and proresolving states depending on the phase of inflammation (139). In conditions such as diabetes and metabolic syndrome, and with advanced age, biotransformation processes do not appropriately class switch, resulting in a dysregulated inflammatory response that is both exaggerated and prolonged, as was noted postoperatively in a rat model of the metabolic syndrome (140). SPMs bind to G protein–coupled receptors on circulating lymphocytes and monocytes, as well as tissue macrophages, to limit inflammation through inhibition of NF-κB, increased phagocytosis, efferocytosis, and conversion to reparative cellular phenotypes.

Pretreatments that increase levels of SPMs can attenuate inflammation and prevent postoperative cognitive impairment in PND models (**Table 1**). For example, administration of an aspirin-triggered D series resolvin (AT-RvD1) prevented cognitive decline in vivo and relieved the impediment to long-term potentiation in hippocampal brain slices ex vivo (141). Prophylactic administration of maresin decreased systemic inflammation, entry of BM-DMs into the hippocampus, and cognitive impairment while sustaining the proresolving cytokine IL-10 and wound healing (142). As both EPA and DHA are derived from omega-3 polyunsaturated fatty acids (PUFAs), administration of fish oil (containing omega-3 PUFAs) perioperatively (3 days before until 7 days after the operation) improved cognition (assessed by the MWM), reduced peripheral inflammation, and resisted oxidative stress injury (143).

Neural mechanisms for resolving inflammation are mediated by the release of acetylcholine—under the influence of postganglionic vagal efferents—which binds to α7 nicotinic acetylcholine receptors (α7nAChRs) on circulating BM-DMs as they traverse the spleen (144); α7nAChR signaling inhibits nuclear translocation of NF-κB and proinflammatory cytokine production. Interruption of this pathway with anticholinergic drugs enhances inflammation and cognitive impairment (145). The cholinergic inflammation-resolving pathway has been exploited through direct vagal stimulation (146) or by administration of the synthetic α7nAChR agonist (146, 147) to limit postoperative inflammation and cognitive impairment (**Table 1**). Dexmedetomidine,

a sedative hypnotic that limits postoperative cognitive decline in humans (148), produces its ameliorative action through its vagomimetic properties (149).

The neural and humoral inflammation-resolving processes may have in common the upregulation of netrin-1 (150), which transduces its resolving action through neogenin 1; thus far, no interventions have been shown to modulate the levels of these key proteins to facilitate resolution of inflammation.

Oxidative Stress

Elaboration of reactive oxygen species (ROS) and depletion of antioxidants (needed to neutralize the toxic intermediates) reflect oxidative stress, which occurs after tissue trauma and has been associated with cognitive decline (151). Peripheral oxidative stress can disrupt the BBB and thereby facilitate the development of neuroinflammation; additionally, central oxidative stress is induced by the release of ROS and nitric oxide (a reactive nitrogen species) from activated microglia. Therefore, it is unclear whether oxidative stress is a unique process, a consequence of the inflammatory response to trauma, or a feedforward mechanism for prolonging neuroinflammation (152). Cyclooxygenase (COX) inhibitors, particularly of the COX-2 isoform, can reduce postoperative cognitive decline in rats (153) and are used for the management of postoperative inflammatory pain, although their efficacy for ameliorating postoperative cognitive impairment in patients has yet to be reported (NCT02689024).

CONCLUSION

Recent advances in clinical and preclinical investigations of PND have led to improved patient care and new intervention targets. In the clinical field, achievements include the standardization of nomenclature in alignment with the DSM-5, consensus on evidence-based perioperative care pathways, and new tools that facilitate rapid and accurate assessment of cognition that can detect preoperative cognitive impairment for risk stratification as well as establish a baseline for subsequent changes in the cognitive trajectory. In validated animal models, promising cellular and molecular targets have been identified in the innate immune response to aseptic trauma that are ripe for testing interventions for both efficacy and safety. Via the translation of discoveries in the preclinical environment and more widespread implementation of brain health pathways, the recent developments outlined in this review provide hope for better protection of brain health for vulnerable adults undergoing surgery.

DISCLOSURE STATEMENT

O.L.B.C. served as a clinical investigator for the OLIVER clinical trial from Medtronic. K.L.P. received research funding from Quest Diagnostics. M.M. is a co-holder of the patent for the use of dexmedetomidine as a sedative agent; he has not and will not receive royalty payments for the sale of dexmedetomidine as a sedative agent.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Caroline Prioleau and Sabrina Erlhoff for their expert help in designing each of the figures. O.L.B.C. received funding from the National Institute of Neurological Disorders and Stroke (3UH3NS10557-03S1) and the Weill Pilot Award for Junior Investigators in Neurosciences. K.L.P. received grants from the National Institute of Neurological Disorders and Stroke (3UH3NS10557), the National Institute on Aging, Global Brain Health Institute,

Quest Diagnostics, Administration for Community Living, Rainwater Charitable Trust, and Merck Foundation.

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