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Special Article

SPECIAL ARTICLE

State of the clinical science of perioperative brain health: report from the American Society of Anesthesiologists Brain Health Initiative Summit 2018

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Summary

Cognitive recovery after anaesthesia and surgery is a concern for older adults, their families, and caregivers. Reports of patients who were 'never the same' prompted a scientific inquiry into the nature of what patients have experienced. In June 2018, the ASA Brain Health Initiative held a summit to discuss the state of the science on perioperative cognition, and to create an implementation plan for patients and providers leveraging the current evidence. This group included representatives from the AARP (formerly the American Association of Retired Persons), American College of Surgeons, American Heart Association, and Alzheimer's Association Perioperative Cognition and Delirium Professional Interest Area. This paper summarises the state of the relevant clinical science, including risk factors, identification and diagnosis, prognosis, disparities, outcomes, and treatment of perioperative neurocognitive disorders. Finally, we discuss gaps in current knowledge with suggestions for future directions and opportunities for clinical and translational projects.

Keywords: anaesthesia; delirium; geriatrics; neurocognitive disorders; perioperative brain health; postoperative cognitive dysfunction; postoperative complications

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Editor's key points

- A group of physicians and stakeholders interested in cognitive recovery after surgery met to consider current clinical evidence and recommendations regarding perioperative brain health.
- This report summarises the risk factors, identification and diagnosis, prognosis, disparities, outcomes, and treatment of perioperative neurocognitive disorders.
- Pre-existing cognitive impairment is a significant risk factor for the development of perioperative neurocognitive disorders.
- Multicentre randomised clinical trials and observational studies are needed to determine whether the current best practice recommendations can reduce postoperative neurocognitive dysfunction.

Cognitive recovery after anaesthesia and surgery is a concern for older adults, their families, and caregivers. Reports of patients who were 'never the same' prompted a scientific inquiry into the nature of what patients have experienced. The Brain Health Initiative was created by the ASA in partnership with AARP (formerly the American Association of Retired Persons) and stakeholders, including the American College of Surgeons, the American Heart Association (AHA), and the American Alzheimer's Association Perioperative Cognition and Delirium Professional Interest Area. In June 2018, the group held a summit to discuss the state of the science on perioperative cognition, and to create an implementation plan for patients and providers leveraging the current evidence. This group included representatives from the Perioperative Delirium and Cognition Professional Interest Area of Alzheimer's Association International and the American College of Cardiology. This paper summarises the state of the clinical science, including risk factors, identification and diagnosis, prognosis, disparities, outcomes, and treatment of perioperative neurocognitive disorders (PNDs). Finally, we discuss gaps in current knowledge with suggestions for future directions and opportunities for clinical and translational projects.

Background and epidemiology

In recent years, increasing numbers of older adults are undergoing anaesthesia and surgery, with the goal of improving function and quality of life by diagnosing and treating diseases or disorders. In Western countries, approximately 37% of all surgical procedures are performed on patients more than the age of 65 yr; in 2010, this represented more than 19 million patients in the USA.[1] Many patients are affected by PNDs, either in the short term, which includes delirium and delayed neurocognitive recovery (dNCR; also referred to as early postoperative cognitive dysfunction (POCD)), or in the longer term, which includes neurocognitive disorder (NCD) (postoperative), previously called POCD. Our understanding of PNDs has progressed from the first published commentary describing early postoperative 'insanity' in 'predisposed cases' in 1887, through a case series of 'neurological complications' in 1986 (focusing on cardiac surgery) to a vast body of epidemiological and trial data today.[2,3]

Postoperative delirium (POD) is a common adverse cognitive event, occurring in up to 65% of older patients after anaesthesia and surgery.[4] It is characterised by inattention and confusion, which is not only distressing to patients and caregivers, but also may be associated with the need for supportive postoperative care, progression to dementia, and increased mortality risk.[4–8] Delirium is associated with increased healthcare costs: the 1 yr cost of care of patients with delirium is estimated to be 2.5 times the cost of care for similar patients without delirium, and totals more than $164 billion in US annual expenditures.[9]

Postoperative cognitive dysfunction has, to date, been measured as a *research tool* using a battery of neuropsychological tests, but with a range of criteria, and with inconsistent use of controls. Despite the heterogeneity of measurements, a consistent theme is cognitive impairment predominantly in executive function and memory domains of cognition. Within the first week or two after surgery, using age- and time-matched non-surgical controls with osteoarthritis, the incidence of POCD is reported to range from 17% (diagnostic procedure) to 43% (cardiac surgery), and appears to be related to the extent and complexity of the surgery and the challenges of the postoperative environment (disrupted sleep patterns, analgesic and other medications, etc.).[10] In noncardiac surgery patients, the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group identified POCD in 25.8% of patients, compared with healthy non-surgical time-matched community controls.[11] Compared with individual baseline tests, POCD defined by a 2 standard deviation (SD) drop in cognitive test scores (referenced to controls or norms) can be identified in ~12% of older patients 3 months after surgery, whilst POCD defined as a 1 SD drop in cognitive test scores compared with baseline can be detected in ~40% of patients at 6 weeks after surgery[12,13] (Fig. 1). The association between cognitive dysfunction lasting >6 months after anaesthesia and surgery, and the anaesthesia and surgery itself is less clear. Multiple meta-analyses and retrospective studies have failed to show an association between cognitive dysfunction lasting >6 months after anaesthesia and surgery and the anaesthesia itself; however, there are relatively few published long-term prospective studies.[14–19]

The lack of clarity in terminology has led to a proposal for a new nomenclature. This new nomenclature includes memory concerns and functional components; distinguishes POD from other cognitive disorders; and classifies what was previously identified as 'early POCD' as dNCR if it meets the proposed criteria, and replaces longer-term POCD (which was based only on neuropsychological tests) as postoperative NCD mild or major if it meets additional specific criteria. The term PND is the overarching term used to describe all of the conditions. The term POCD will be used in this article when referring to research data derived from neuropsychological testing alone (Table 1 and Fig. 1).[20] There are not yet studies that describe how the incidence of PND using these new criteria differs from prior incidences reported for early or late POCD. Further, it is unclear which cognitive tests are the most sensitive, specific, and best suited for PND detection in clinical practice.

As cognitive decline (up to at least 3–6 months) affects a significant proportion of patients aged >65 yr, and these patients have even higher incidence of POD, the question arises whether the risk of cognitive disorders should be included in 'informed consent'. Commonly used postoperative risk calculators do not include the risks of PND, even though PND often occurs up to 10 times more often than many other postoperative complication risks, such as pneumonia, deep

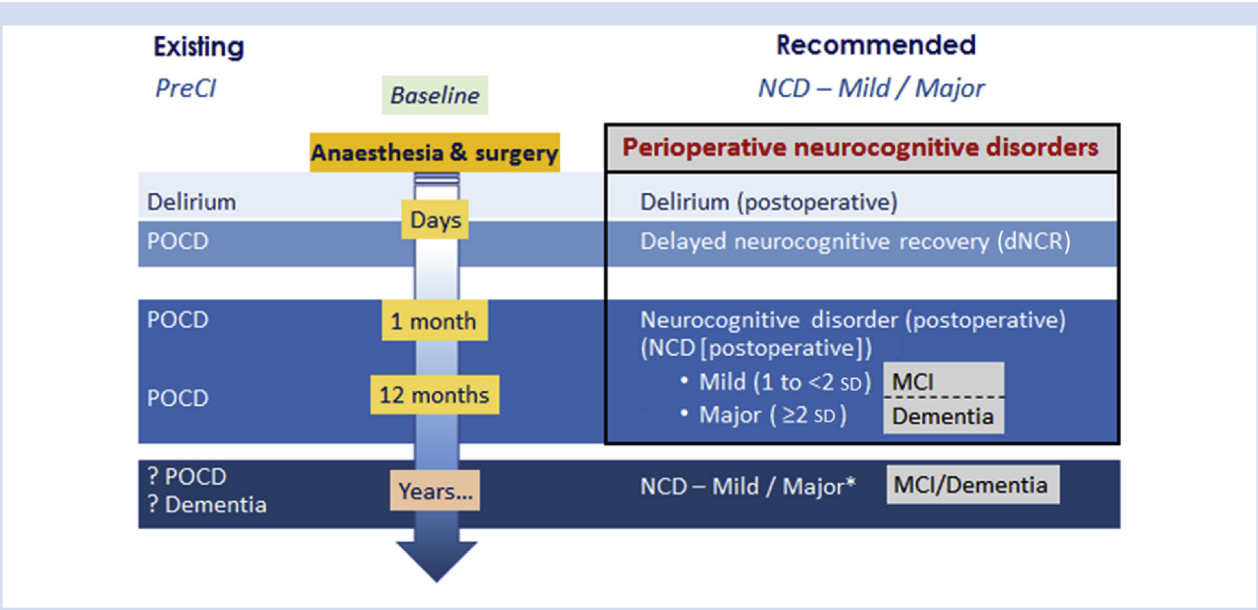

Fig 1. Postoperative cognitive dysfunction and neurocognitive disorders, a crosswalk. MCI, mild cognitive impairment; POCD, postoperative cognitive dysfunction.* Where a new diagnosis is made after 12 months.[20]

vein thrombosis, or death. Thus, it can be argued that it is reasonable for patients to be informed about PND risks, as long- and short-term PND risks are relevant to patients.[21]

Risk factors

Understanding which patients are at heightened risk for developing PNDs (POD, dNCR, and NCD after operation) continues to be an active area of research. Much more is known regarding the risk factors for delirium, this imbalance being at least in part because of lack of consistent definitions in the POCD literature.

Table 1 Perioperative neurocognitive disorders and abbreviations. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

Abbreviation	Definition
PND	Perioperative neurocognitive disorder: includes POD, dNCR, and NCD (postoperative)
POCD	Postoperative cognitive dysfunction: to be superseded (or restricted to a research diagnosis only when based on neuropsychological testing with *no* clinical or functional criteria used)
NCD	Neurocognitive disorder, mild or major per DSM-5 criteria: takes specifier 'postoperative' if a new diagnosis after expected neurocognitive recovery (typically 30 days) and up to 12 months after anaesthesia and surgery
dNCR	Delayed neurocognitive recovery: using criteria for NCD, but in the window of up to 30 days after anaesthesia and surgery; excludes POD
POD	Postoperative delirium: delirium to take specifier 'postoperative' if new onset within 7 days of anaesthesia and surgery

The risk factors for delirium are often divided into predisposing and precipitating factors.[22] The predisposing factors are the patient's baseline vulnerabilities and the precipitating factors are the potentially reversible elements that occur throughout the perioperative period. The American Geriatrics Society (AGS) guidelines recommend performing a preoperative assessment of delirium risk factors, including the following five major risk factors: age >65 yr, chronic cognitive decline or dementia, poor vision or hearing, severe illness, and presence of infection.[23] Pre-existing cognitive impairment increases the risk of delirium in the week after surgery.[24–27] Additional risk factors for POD include poor functional status, metabolic derangements, polypharmacy, poorly controlled pain, dehydration, and poor nutrition. Neuropsychiatric conditions, including depression, alcohol abuse, sleep disturbances, and prior history of delirium, are commonly cited factors. It is unknown if predisposing hereditary vulnerabilities, including sex, genetic, or epigenomic factors, place certain patients at higher risk for POD. Whilst an earlier study showed an association between apolipoprotein E ε4 genotype and POD,[28] subsequent studies have not shown this association when controlling for preoperative cognitive impairment.[29–31] Precipitating factors contributing to the development of POD include long duration, urgency, and invasiveness of surgery. Many postoperative risk factors have been identified for the development of delirium, and include admission to an ICU and postoperative complications, including infections and vascular events. Identifying the patients at increased risk for developing POD may facilitate prevention, early diagnosis, and medical decision-making.

Although the exact mechanisms leading to perioperative NCDs have not been elucidated, some risk factors have been identified, including advanced age and lower level of education as a marker of lower cognitive reserve. An important risk

factor for both POD and POCD (and presumably for NCD postoperative) in older surgical patients is baseline cognitive impairment. In patients presenting for elective orthopaedic surgery (hip joint arthroplasty), 32% had previously unidentified preoperative cognitive impairment, and in a study of 340 patients aged >50 yr having coronary angiography, 51.7% had previously unidentified mild cognitive impairment (MCI).[32,33] In both of these studies, the presence of pre-existing cognitive impairment was an independent predictor of post-procedural cognitive dysfunction at 3 months (reported as POCD). Thus, Best Practices consensus papers suggest that baseline cognitive function should be routinely assessed in all older adults before surgery.[34,35] However, exactly how this knowledge should be used to guide medical decision-making and care is unclear.

An underlying medical disease may impact PND risk, especially the cerebral manifestations of vascular disease and hypertension.[36] A history of vascular disease and prior stroke, even without residual impairment, has also been identified as a risk factor for POCD.[36,37] The effect of stenosis of one or more large arteries supplying the brain, brain atrophy, or pre-existing microvascular damage (e.g. subclinical white matter lesions, silent infarcts, and cerebral micro-bleeds) may play a role and requires further study. In a recent systematic review involving 1422 participants, white matter hyper-intensities and subclinical infarcts that may be related to vascular disease or hypertension were associated with POD and POCD, but markers of neurodegeneration, such as global or regional atrophy, were not.[38] The role of these brain MRI markers of neurodegeneration and cerebrovascular pathology in POD and POCD is less clear in noncardiac surgeries.[39] POD has also been shown to be a risk for ultimately developing POCD with patients with the highest delirium severity experiencing the fastest rate of decline.[6,40]

Pathophysiology and biomarkers

Debate remains regarding the pathophysiology of PNDs given the complexity of contributing factors, subtypes, and heterogeneity of these conditions. There are at least four prevailing pathophysiological hypotheses of POD, some of which may also contribute, in part, to postoperative NCD and POCD.

The first of these hypotheses implicates aberrant oxidative cellular metabolism causing neurotransmitter abnormalities/imbalance (i.e. neurotransmitter hypotheses), such as excessive dopamine or reduced acetylcholine availability.[41–43]

The second hypothesis is based on the sympathetic-nervous-system stress response to surgery or hypothalamic–pituitary–adrenal axis alteration, which results in pro-inflammatory cytokine release and negatively alters neurotransmitter concentrations.[44]

The third hypothesis posits perioperative neuroinflammation occurs after surgery and anaesthesia, and plays a role in POD or POCD, as several studies have found significant increases in inflammatory markers in CSF after anaesthesia and surgery.[45–48]

The fourth hypothesis is that POD, and postoperative NCD, may reflect an acceleration of Alzheimer's disease (AD) pathology 'unmasking' neurocognitive dysfunction in patients with underlying cerebrovascular disease or preclinical AD pathology.[49–53]

These four hypotheses are not likely to be mutually exclusive, and could play overlapping roles in individual cases of POD or NCD (Fig. 2). Furthermore, the mechanisms may be synergistically accelerated by transient perioperative abnormalities, such as increased blood–brain barrier permeability, altered cerebral blood flow impacting cerebral glucose and oxygen availability, and pre-existing white matter damage (leucoaraiosis) or alterations in tissue diffusion secondary to chronic ischaemic cerebrovascular disease,[54–58] norepinephrine-mediated stimulation of cytokine production (e.g. interleukin 6),[59] and the role of neuro-inflammation and the impairment of its resolution in AD pathology.[60]

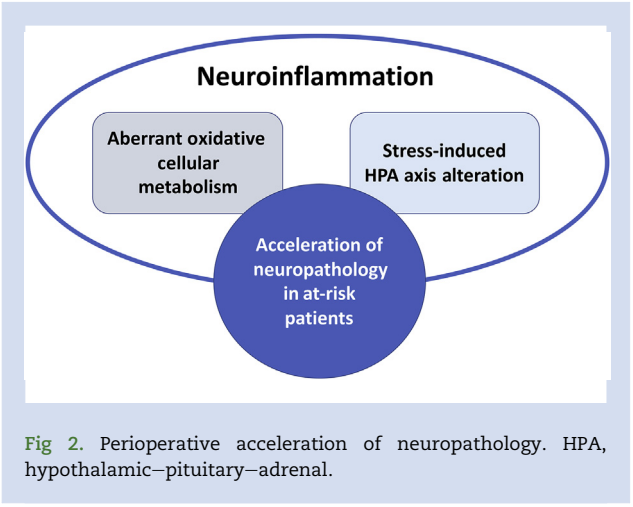

Fig 2. Perioperative acceleration of neuropathology. HPA, hypothalamic–pituitary–adrenal.

Whilst these four hypotheses provide important bases for investigation, the evidence is still mixed or remains unclear as to the precise role of these processes in human PND. For example, we still do not know to what extent the development of neuroinflammation might involve dysregulation of the initial inflammatory response *vs* impaired resolution of inflammation. Perioperative studies have confirmed acute temporal changes in human CSF inflammatory biomarkers after surgery,[47] and recent serial positron emission tomography (PET) imaging in surgical patients shows profound biphasic changes in brain immune activity after surgery associated with changes in cognitive function.[61–64] In contrast, studies that have examined modulating or blocking inflammation have thus far failed to reduce POCD with perioperative steroid treatment,[6566] inflammatory modulation with lidocaine,[67] ketamine,[68] magnesium,[12] or complement pathway blockade.[69] Treatment-based modulation of AD-related pathology has been similarly disappointing. In patients with mild cognitive decline post-cardiac surgery, donepezil, an acetylcholinesterase inhibitor used for Alzheimer's dementia, did not improve composite cognitive performance, although some memory domains did improve.[70]

Solutions to some of these lingering questions may be found in advanced technologies that allow us to construct model systems that illuminate the biological and pathophysiological processes underlying the clinical expression of POD and postoperative NCD. More recently, advances in functional MRI and quantitative electroencephalography have provided the means to conduct *in vivo* research of systems-level POD and NCD (postoperative) pathophysiology and expression. Both modalities provide support for aberrant functional brain network integration underlying POD and NCD (postoperative) expression, specifically the importance of intra- and inter-network connectivity of the default mode network.[71–75] PET

imaging has been explored to detect associations between POD and postoperative NCD clinical expression, severity, and neuropathology (i.e. β-amyloid deposition).[76] PET is expensive and cumbersome (e.g. long duration), and requires repeated imaging in longitudinal studies with total ionising radiation exposure concerns, but recent advances in high-sensitivity assay technologies have enabled some of these possible neuropathological biomarkers to be identified in blood.[77] They have the potential to further elucidate the relative contribution of hypothesised pathophysiological mechanisms and their consequences in POD and postoperative NCD. Further investigation needs to occur to determine which CSF, blood, and neuroimaging biomarkers are optimally sensitive and specific as biomarkers of POD and NCD risk, clinical expression, and recovery.

Pre-surgical cognitive screening

Many studies have identified pre-existing cognitive impairment as a risk factor for PND. Despite a number of studies showing that preoperative cognitive function is a consistent predictor of POCD, routine preoperative assessment of preoperative cognitive function is in its infancy. We are only beginning to learn how to integrate cognitive screenings into busy clinical settings, and how to wisely apply cognitive screening data for perioperative management. Very few hospitals include cognitive screening of older adults as a routine component of their preoperative evaluation. The American College of Surgeons National Surgical Quality Improvement Program and the American Geriatric Society Best Practices Guidelines both recommend assessing cognitive ability for any patient older than 65 yr in order to assess the risk of postoperative dysfunction and to quantify POCD.[35] Recently, the International Perioperative Neurotoxicity Working Group (sponsored by the ASA Brain Health Initiative) also suggested preoperative cognitive screening of all older surgical patients in their Best Practices paper.[34] Even fewer hospitals collaborate with geriatricians, neurologists, or neuropsychologists for more integrated pre- and postoperative care.

Cognitive screening measures as part of pre-surgical evaluations may include variants of short traditional neuropsychological and neurological tools (i.e. clock drawing, three-word memory, counting backwards from 100 by seven, or spelling the word 'world' backwards.[78–80] These simple items assess attention, planning, inhibitory function, and declarative memory abilities, domains commonly compromised by neurodegenerative disorders. In an ideal environment, patients who are identified as impaired on a pre-admission cognitive/memory screen would be referred to interdisciplinary providers for further evaluation (e.g. geriatricians, cognitive neurologists, geriatric psychiatrists, or neuropsychologists). Comprehensive geriatric assessment could be used to identify potentially modifiable risk factors (e.g. Beers Criteria list medications, such as benzodiazepines, anticholinergics, barbiturates, metoclopramide, meperidine, antipsychotics, and polypharmacy), and provide the anaesthesia-surgical team with considerations about the type of cognitive impairment.[81] For instance, vascular dementia may be associated with an elevated perioperative stroke risk. Baseline cognition could be used to better discuss perioperative risks, such as delirium, dNCR, the possibility of a longer hospitalisation, and discharge to a nursing facility rather than home.[82] Preoperative geriatric assessment reports could be available to the anaesthesiology and surgical teams before the surgical procedure so that they can tailor their care (and communications with patients) based on the patients' preoperative profiles. One study showed that providing vascular surgery teams with patient's frailty status reduced mortality at 30, 180, and 365 days.[83] Further study is needed to determine if geriatric assessments would alter patient care and reduce PND.

Prospective studies and trials are needed to address the relationships between preoperative cognitive impairment and patient outcomes to inform and identify best practices for the care of our older patients.

Prevention

An expert consensus from the delirium guidelines from the American Geriatric Society and the American College of Surgeons has emphasised non-pharmacological approaches for delirium prevention, as they have the strongest evidence for efficacy and lowest potential for harm. Two of the most effective and widely disseminated multipronged non-pharmacological care bundles are the Hospital Elder Life Program (HELP) and ABCDEF ICU bundle.[84] HELP has consistently been shown to lower the incidence of delirium in general medical patients, decrease the length of stay, reduce falls, and be cost effective.[85–92] The ABCDEF bundle, in a recent multicentre trial, was shown to increase the odds of hospital survival and decrease the number of days with delirium and coma.[84]

Areas of equipoise in the area of anaesthetic management include age-adjusted anaesthetic dosing, use of brain monitoring, and prehabilitation. Anaesthetic requirements decrease significantly with age.[93–95] Anaesthetic drug exposure could contribute to PND, either via neurotoxicity at the molecular and cellular levels, induction of AD-type pathology, neuroinflammation, or indirectly through alterations in physiology (such as cerebral blood flow).[40,52,61,96–100]

Regional anaesthesia could have different implications for PND compared with general anaesthesia; however, clinical data do not support this hypothesis.[101–103] The studies have important limitations: many are older, are limited to neuraxial anaesthesia, and are confounded by the fact that patients also received high doses of i.v. Sedatives.[101,102] Only one study in patients undergoing extracorporeal shock wave lithotripsy truly compared cognitive outcomes in patients randomised to receive regional anaesthesia without sedation.[103] The study was stopped because of difficulty recruiting, with 7% of the general anaesthesia group, and 20% in the neuraxial group found to have POCD at 3 months. However, these results may not generalise to patients undergoing other types of surgery with direct skin incision and greater surgical trauma.

EEG-monitored anaesthesia care utilising processed EEG monitors, such as the bispectral index (BIS) monitor (Medtronic) or SedLine (Masimo) BIS, summarises EEG information with a single number between zero and 100 meant to represent 'anaesthetic depth' with lower numbers thought to represent deeper anaesthesia. The strictly empirical 'black box' construction of these devices has been a source of criticism, as many anaesthesiologists find it difficult to trust a device whose precise mechanism is not known and when it is often unclear whether the number is a true reflection of depth of anaesthesia given potential for artifact. Some of the dissatisfaction and controversy can be attributed to age-dependent changes in the EEG,[104,105] which were not fully understood when the processed EEG algorithms were developed more than 20 yr ago. Some age-dependent EEG changes

can be accounted for by using the 'raw' unprocessed EEG or EEG spectrogram.[104] For example, when older patients are maintained at BIS values between 40 and 60, the device's recommended target range, they are up to 10 times more likely to be in a state of burst suppression than younger patients.[106] The anaesthesia-induced brain state called 'burst suppression' has been linked to an increased likelihood of POD,[107,108] although some studies have found that burst suppression is associated with lower POCD risk.[109] Burst suppression is a deep state of anaesthesia-induced coma, occurring at high anaesthetic doses beyond what is required for unconsciousness.[110] Older patients, even when administered age-adjusted concentrations of anaesthesia, are more likely to be in burst suppression.[104,105] Additionally, there is a marked decrease in alpha band power under general anaesthesia in patients >60 yr old, and decreased intraoperative alpha band power has been associated with both preoperative cognitive impairment and recovery room delirium.[104,111,112] However, it is currently unclear whether intraoperative interventions to maximise or maintain alpha band power under general anaesthesia would reduce POD/NCD, and at least one current study is underway to examine this issue.[113]

Two major trials inform our understanding of the role of processed EEG monitoring on POD. The recent Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery The ENGAGES Randomized Clinical Trial was a large RCT of intraoperative EEG guidance protocol designed to reduce time in burst suppression, and the prior Cognitive Dysfunction after Anesthesia (CODA) trial randomised patients to receive care guided by the BIS monitor processed number or standard of care.[114,115] The ENGAGES EEG-based intervention was not associated with a reduction in delirium; in contrast, the Cognitive Dysfunction after Anesthesia (CODA) Trial (Centre for Clinical Trials number, CUHK_CCT00141) did show a reduction in the incidence of delirium. One explanation for the difference in findings is that, in the ENGAGES study, anaesthetic concentrations were reduced by only 0.11 minimum alveolar concentration (MAC).[115] By comparison, in the CODA trial, anaesthetic concentrations were reduced by 0.36 MAC in the EEG-guided treatment group.[114] This could be interpreted that, if EEG-guided anaesthesia guidance does not markedly reduce anaesthetic dosage, then it will not reduce delirium. Another possible explanation for the conflicting findings is the possibility that patient subgroups may have varying sensitivity to anaesthetic depth. For example, a recent randomised trial of EEG-driven anaesthetic management in hip fracture patients found that anaesthetic depth only impacted cognition in a relatively healthy subgroup (A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients [STRIDE]).[116] Future studies should explore alternative approaches for anaesthetic management, notably the use of the EEG waveform and spectrogram in combination, and be large enough to perform subgroup analyses to explore the likelihood of more vulnerable subgroups.

The ability to interpret unprocessed EEG waveforms or the EEG spectrogram from processed monitors may be valuable to many anaesthesiologists to better manage anaesthetic brain states in older patients (see eegforanesthesia.iars.org and icetap.org). Anaesthetic requirements tend to be highly individualised and to become even more so with age.[117] Older patients might uniquely benefit from the individualised real-time feedback of anaesthetic brain state provided by the EEG spectrogram or raw waveform pattens.[104,118,119]

Avoiding cerebral hypoperfusion is another area of investigation in preventing PND. Appropriate cerebral perfusion in older patients is complicated by the fact that many older patients have hypertension, which can shift cerebral pressure autoregulation.[120] Studies have shown a relationship between intraoperative hypotension and increased incidence of delirium or cognitive decline.[121–123] Conflicting results have also been reported.[124,125] Studies of intraoperative hypotension are complicated by the fact that there is no consensus on what constitutes hypotension,[126] which perhaps underscores again that patients' cerebral autoregulatory curves are highly individualised.[120,127,128] It follows that the only way to ensure adequate brain perfusion in a given patient would be to measure or monitor it in some way.

Cerebral perfusion can be measured continuously in real time using near-infrared spectroscopy (NIRS). In several studies, an intraoperative decline in NIRS values has been associated with POD and cognitive change.[129,130] A recent study found that anaesthetics titrated with a combination of BIS and cerebral oximetry reduced POCD in older adults.[131] Studies of NIRS-guided anaesthesia have been limited by small size, inappropriate tests/criteria, and short follow-up periods.[96,132,133] Another approach might be to identify individualised cerebral pressure autoregulatory thresholds and strictly maintain arterial blood pressure above those levels.[120]

Medications as a preventative measure have been an active area of study. Intraoperative dexmedetomidine has been investigated as a prevention strategy based on its reduction in the incidence of delirium when used for ICU sedation.[134–136] Three studies of intraoperative dexmedetomidine with differing study characteristics produced different results.[137–139] In an orthopaedic surgery, infusion of dexmedetomidine throughout surgery reduced POD compared with conventional treatment.[138,139] However, in both cardiac and noncardiac surgery studies, infusion during surgery and into recovery had no effect on POD incidence.[137,138] A subsequent systematic review and meta-analysis that examined the efficacy of perioperative dexmedetomidine on POD did a subgroup analysis on these three studies and found that perioperative administration of dexmedetomidine may decrease POD.[134] A recent review supported this, but found no evidence that dexmedetomidine reduced POCD.[140] Clonidine decreased delirium severity in a small thoracic surgery cohort in one study without changing its incidence.[141] Ketamine has been investigated as a preventative adjunct for POD because of its analgesic properties, opioid-sparing properties, and effectiveness as an antidepressant drug. Although a small single-centre trial of intraoperative ketamine in cardiac surgical patients found a reduction in POD,[142] a subsequent large multicentre trial found no difference in POD.[68] A recent multicentre RCT of medical and surgical patients aged $\geq$70 yr compared the antipsychotic drug haloperidol or placebo on top of non-pharmacological strategies to prevent POD.[143] There was no difference in delirium incidence, duration, or severity. Melatonin has shown conflicting results as a preventative agent for POD in a few small RCTs.[144] Tryptophan was not effective in reducing either delirium incidence or duration in a randomised control trial.[145] The multiple negative trials for pharmacological prevention of delirium raise the possibility that we need to better understand the pathophysiology of delirium in order to prevent specific pathophysiological processes that play an aetiological role in delirium.

Clinical trials are currently under way to examine the influence of cognitive and physical prehabilitation programmes on postoperative cognitive outcomes.[146–148] The combination of these prehabilitation efforts with intraoperative brain monitoring is a promising approach to reducing PNDs.

Diagnosis

POCD has historically been classified solely for research purposes on the results of a battery of neuropsychological tests designed to identify decline across several cognitive domains using cut points.[10] One of the major difficulties with the different definitions for POCD is that they do not align with the clinical neuropsychiatric criteria for cognitive impairment used by psychiatrists and neurologists, and described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[149] A working group of perioperative clinicians and researchers convened recently to align the terms used to describe postoperative cognitive impairment with the larger field of clinical cognitive impairment in a new consensus statement.[20] The new paradigm is consistent with the DSM-5[149] and the National Institute on Aging–Alzheimer's Association guidelines.[150,151]

The diagnosis paradigm includes an objective assessment of impairment or decline in one or more domains compared with controls or normative data, a subjective complaint (patient or informant), and an assessment of activities of daily living (ADL). NCDs are defined as mild (MCI) or major (dementia). Mild NCD requires an objective impairment of 1–2 SDs below controls/norms, a subjective complaint, and preserved ADL, whilst major NCD requires an objective impairment of $\geq$2 SDs below controls/norms, a subjective complaint, and impaired ADL. Objective impairment, as defined in the DSM-5 for NCD, requires a deficit in one or more cognitive domains.

POD is included in the overarching PND group of disorders, and retains the current definition (DSM-5). The diagnosis of delirium according to the DSM-5 requires an acute and fluctuating disturbance in attention and awareness, and an additional disturbance in cognition, with evidence of an underlying organic aetiology or multiple aetiologies. The symptoms are not better explained by pre-existing dementia and not diagnosed in the face of a severely reduced level of arousal.

The new nomenclature provides for a common language to discuss PNDs, and uses definitions designed to allow comparison to the larger medical literature. It remains to be determined if the alignment of PND with MCI (mild NCD) and dementia (major NCD) will promote improved multidisciplinary management of older individuals, what the limitations of the new nomenclature are, and how inclusion of subjective decline impacts diagnosis.

Healthcare disparities

Research in POCD and NCD (postoperative) has been most active amongst English speakers, with limited European languages included as part of the ISPOCD.[11] This is mostly attributable to the limited availability of neuropsychological tests that are translated into and validated in other languages. Currently, it is unclear what diagnostic battery is least affected by healthcare disparities. For example, even for a common tool, such as the Mini-Mental State Examination (MMSE), the degree of difficulty of each sub-item can differ in different cultures, leading to variability in sensitivity and specificity in identifying cognitive impairment.[152] There are some studies on POCD from Asia, but with limited follow-up.[153] It is of great importance for future studies to examine NCD (postoperative) across different countries and cultures to reduce the large knowledge gap in this area.

Cognitive disorders can affect different races differentially. In one study, dementia incidence was highest for African Americans (26.6/1000 person years) and American Indian/Alaska Natives (22.2/1000 person years), followed by Latinos (19.6/1000 person years), Pacific Islanders (19.6/1000 person years), and whites (19.3/1000 person years). Dementia incidence was lowest for Asian Americans (15.2/1000 person years).[154] The rate of NCD amongst different races and ethnicities may also be affected by factors, such as socioeconomic status, co-morbidities, and education levels. One study showed that disparities in educational attainment are one of the factors that are associated with the higher incidence of AD in African Americans.[155]

Subjective cognitive complaints may also differ amongst races. In one study involving 1250 older African Americans, 48.3% had subjective cognitive complaints. There were many factors associated with having subjective cognitive impairment, including hearing loss, stress, depression, and poor health.[156] Whether postoperative subjective cognition is impacted by preoperative objective cognitive ability is unknown and is an important area of future research. More research is needed to understand the rate of PND and risk factors for PND in different races.

POD is currently an active area of research. A recent review article examining different studies on the prevention and treatment of delirium reported high-quality perioperative intervention studies from North America, Europe, and Asia.[157] Although there are still few studies that specifically examine disparities in delirium research, and even more so in the field of POD, one can still glean potential future research questions from prior studies. In a study by Kales and colleagues[158] of the pattern of recorded diagnosis of delirium in acute inpatient units in Veterans Affairs hospitals across the USA, African Americans were more likely to be given a diagnosis of organic psychosis rather than delirium. The diagnosis of organic psychosis was associated with longer length of stay and a higher rate of discharge to a nursing home. Africa as a region is under-represented in POD and NCD (postoperative) research[159]; most literature on cognitive disorders from this region is about neurological sequelae of infection, including human immunodeficiency virus, typhoid fever, and malaria.[160] As the ageing population in Africa increases, the available expertise for diagnosing and treating delirium in this region will need to increase to meet the demand.

Prognosis and outcomes

POD has been associated with decline in cognitive performance in the weeks to months after surgery in several well-done studies.[6,8,40,161,162] One year after surgery, there is often recovery in cognitive function. However, many patients with delirium do not recover to baseline cognitive status, although there is some disagreement between studies.[6,8,40,161,162] Few prospective studies have examined cognitive outcomes beyond 1 yr, but the largest study of patients undergoing noncardiac surgery found greater cognitive decline beginning at 2 yr after surgery in patients with delirium compared with patients who did not develop delirium.[6] This same group

found that patients with the highest delirium severity had the fastest rate of decline, with a dose–response relationship between delirium severity and long-term cognitive decline.[40] Similarly, patients with cognitive dysfunction early after cardiac surgery also have worse cognitive function 5 yr later than patients who did not develop early POCD.[13] Several studies have shown a 'dose–effect' with greater cognitive decline in patients with higher delirium severity scores.[40,162] Some studies have found that delirium after surgery is associated with incident dementia.[5,163–165] With regard to functional status, there appears to be a greater decline in functional status after surgery amongst patients with POD.[166–168] Trajectories of recovery are also non-linear, with greatest decline in the weeks to months after surgery.[167,168] Questions remain as to whether POD simply reveals an underlying vulnerability and ongoing, inexorable cognitive decline *vs* a causative effect. It is also not known if delirium prevention or treatment efforts impact subsequent cognitive status.

Patients with POCD in the weeks to months after surgery may be at risk for longer-term adverse outcomes. In a long-term follow-up of noncardiac surgery patients enrolled in the ISPOCD study, cognitive dysfunction after surgery was associated with long-term mortality and persistent cognitive dysfunction 1–2 yr after surgery.[169,170] However, a Danish registry study did not find a relationship between POCD and registry dementia.[171] The mortality findings were confirmed in a subsequent study of >1000 patients undergoing noncardiac surgery and in a prospective longitudinal study of outcome after coronary artery bypass graft surgery.[36,37] In terms of functional status and quality of life, participants with cognitive dysfunction after noncardiac surgery in the ISPOCD study had a higher risk of leaving the labour market prematurely and a longer period of social transfer payments.[169] Similarly, a large study of >700 patients undergoing cardiac surgery showed that cognitive impairment at 6 weeks and 1 yr after operation was associated with reduced functional status, increased depression, and lower general health perception.[172] These associations appear to be sustained, with lower neurocognitive scores 5 yr after cardiac surgery strongly correlated with quality of life.[173] Although most studies use formal neuropsychological testing, there are apparent discrepancies between subjective patient complaints and objective testing.[173–175]

Treatment

There is a dearth of well-executed trials on PND treatment once it has been diagnosed. Most available evidence is extrapolated from studies on prevention strategies and their effects on PND severity and duration. The expert consensus from the delirium guidelines of the American Geriatric Society and the American College of Surgeons emphasises non-pharmacological approaches in the treatment of POD. Whilst HELP has consistently been shown to lower the incidence of delirium, the effect of the programme on the duration and severity of delirium has been variable between studies.[85–91] Additionally, HELP needs to be further studied in patients in the postoperative setting to better understand its effect on POD. Total or partial compliance with the ABCDEF bundle days can increase the number of delirium-free days.[84] Further studies are needed to elucidate how the implementation of these approaches after the onset of delirium will affect the course, severity, and morbidity of delirium. With the development of an online application to convert delirium severity scores by commonly used instruments, there now exists a possibility of forming meta-analyses on studies that have delirium severity and duration as secondary outcomes.[176]

The most commonly used pharmacological treatments for delirium are typical and atypical antipsychotics. A recent landmark, randomised, double-blind, placebo-controlled trial compared the use of haloperidol and ziprasidone against placebo for the treatment of established delirium.[175] No difference in delirium- or coma-free days was found between groups, effectively showing a lack of efficacy for haloperidol and an atypical antipsychotic in the treatment of delirium. A recent meta-analysis, conducted before the trial, also showed antipsychotics neither decreased delirium duration nor severity in both general medical and postoperative patients.[177] Another multicentre RCT published after the meta-analysis found no effect of prophylactic haloperidol on delirium severity or duration.[143] A comparison of typical *vs* atypical antipsychotics did not find a consistent trend in improvement of symptoms to recommend one over another.[177]

Other drugs used in the treatment of delirium include melatonin and cholinesterase inhibitors. In retrospective cohort studies, melatonin and ramelteon have been associated with decreased use of antipsychotics, but no difference in severity.[144] A multicentre RCT investigating rivastigmine, a cholinesterase inhibitor, as an adjuvant to haloperidol was halted early, as mortality was increased in the rivastigmine group in addition to longer duration of delirium.[178]

Studies specifically investigating how to mitigate dNCR and NCD (postoperative) are lacking. Reasonable avenues include measures used in other forms of NCD. These include cognitive training, physical exercise, optimising nutrition, social engagement, and optimising vascular and metabolic risk factors.[179] It is not known if multipronged non-pharmacological bundles used to prevent and treat delirium would have a similar effect on dNCR and NCD (postoperative). In addition, it is not clear if preventing or treating delirium may reduce subsequent rates of dNCR or NCD (postoperative). There is no evidence for treating dNCR and NCD (postoperative) with medications, such as anticholinergics or N-methyl-D-aspartate receptor antagonists.

Discussion

More rigorously designed multicentre randomised clinical trials and larger-scale observational studies are needed to determine whether the current best practice recommendations reduce the development of all forms of PND. Future clinical research should focus on whether specific clinical interventions along the perioperative continuum can bridge the scientific knowledge gap between purported mechanisms of cognitive impairment observed in preclinical studies (e.g. neuroinflammation, CNS neurotransmitter alterations, calcium dysregulation, apoptosis, and anaesthetic- and surgery-induced changes in β-amyloid and tau pathology). The role of biomarkers in predicting the development of POD, dNCR, and NCD (postoperative) should also continue to be explored. Research should also focus on identification of noninvasive biomarkers (i.e. plasma, saliva, or urine), and also on more proximal measures of CNS function (i.e. functional neuroimaging, electroencephalography, and CSF biomarkers). Further, given the limitations of neuroscience research techniques, it will be important to conduct future studies that

combine techniques to obtain insights unobtainable by single methods.

A significant risk factor for the development of POD[180] or other PNDs[11] is pre-existing cognitive impairment. However, very few medical centres have incorporated cognitive screening into their routine preoperative evaluation of older surgical patients. More clinical research is needed to determine who would benefit from such cognitive screening, and to develop neuro-psychometric testing protocols that can be easily administered and yet be of value for risk stratification. Prospective studies are needed to determine whether such testing alone or in combination with other preoperative geriatric care bundles can improve clinical outcomes. The strong impact of advanced age and pre-existing cognitive impairment on POD, dNCR, and NCD (postoperative) also underscores the importance of healthy ageing, which is also supported by the AHA/American Stroke Association presidential advisory to promote optimal brain health throughout life.[181]

Whilst significant gaps exist in the optimal management of geriatric surgical patients, best practice guidelines exist that summarise for clinicians what is known. The AGS and the American College of Surgeons have been leaders in these projects. The ASA has committed to this process through the Brain Health Initiative and the larger community of groups that serve older adults, such as AARP and AHA. Public health work and implementation science will be used to realise the goal of excellence in geriatric care, and improvements in perioperative advice to older patients, relatives, and caregivers. In the coming decade, metrics derived from these programmes will drive advances in perioperative geriatric cognition.

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