NARRATIVE REVIEW ARTICLE

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Brain Structural and Functional Changes Associated With Postoperative Neurocognitive Disorders: Research Update

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Postoperative neurocognitive disorders (PNDs) are frequent and serious perioperative complications in the elderly, and are associated with increased morbidity and mortality, length of hospital stay, and need for long-term care. At present, the pathogenesis of PND is not completely clear, and there are various risk factors including surgical trauma and stress mediating systemic inflammation towards neuroinflammation development which causes brain structural and functional changes namely PND. For elderly patients, perioperative neurological monitoring may provide insights into brain function status. Monitoring may also help clinicians identify potential risks which would ultimately allow timely and effective intervention for better perioperative safety and prognosis for elderly patients. In this review, we summarize the risk factors and potential mechanisms of PND, and discuss preliminary evidence regarding application of electroencephalography, functional near-infrared spectroscopy, functional magnetic resonance, and positron emission tomography imaging in monitoring the central nervous system during the postoperative period. (Anesth Analg 2025;141:1332–1345)

As the population ages and life expectancy increases, there is an increased burden of diseases such as diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, and neurological disorders.[1] Perioperative neurocognitive disorders are common perioperative neurological complications in elderly patients and reflect a change from baseline cognition and in severe cases, a decline in function. Postoperative delirium (POD) manifests in a fluctuating course with symptoms including, but not limited to, inattention, disorientation, changes in arousal level, and alterations in cognition.[1,2] Despite delirium being considered a transient phenomenon, occurring and subsiding on an acute timescale, more permanent negative effects, such as neurocognitive impairment, may occur chronically.[3] Short-term functional recovery and prognosis of patients are adversely affected by these complications leading to increases in length of hospital stay. These events consume health care resources and increase the dependency of care; additional costs may be 52% greater when major neurocognitive disorders (NCDs) occur postoperatively.[4] Not only are there economic burdens, but also there are societal burdens as the lives of caregivers are negatively affected.[4] Other important effects include increased mortality and disability due to long-term neurological disorders.[5] The manifestations of perioperative neurocognitive disorders mainly include: (1) preoperative cognitive impairment; (2) POD: occurring in hospital up to 1-week postprocedure or until discharge (whichever occurs first) and meeting the specific criteria for delirium in the Diagnostic and Statistical Manual-5 (DSM-5)[2]; (3) delayed neurocognitive recovery (dNCR): NCD diagnosed within 30 days after surgery; (4) postoperative NCD: cognitive impairment diagnosed within 12 months after surgery.[2,6]

An important prerequisite for ensuring the safe administration of anesthesia is to monitor patients' physiological states effectively.[7] Successful prediction

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of patients at high risk of developing POD would allow for the reduction or prevention of POD episodes and so methods for identification of potential incitement factors of POD are essential to clinical management. At present, targeting prevention strategies seems the most viable intervention to reduce the incidence of NCDs such as delirium.[8] The approach of improved functional assessment and monitoring of the central nervous system (CNS) in the perioperative period is 1 avenue for future advancement of care.

Various approaches to neurological monitoring in clinical practice are being developed, including measurements of fluid biomarker levels with emphasis on neurofilament light (NfL)[9] and plasma tau levels[10] as indicators of neuronal injury, as well as the use of various neuroimaging modalities such as electroencephalography (EEG),[3] functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). This review aims to summarize the potential mechanisms and risk factors of postoperative neurocognitive disorder (PND) and discuss recent evidence regarding the application of neurological monitoring methods in PND by way of measuring brain structural and functional changes (Table 1).

MECHANISMS OF PND

At present, the exact mechanisms of PND remain unclear. Given the complexity of its etiology, which is due to the numerous pathological mechanisms implicated, there is unlikely to be a single responsible factor. Possible predisposing factors include genetic predisposition to neurodegenerative disorders, vascular diseases, perioperative hypotension, thromboembolism, reperfusion injury, neuronal metabolism, neuroinflammatory reactions, and blood-brain-barrier breakdown.[11] Animal experiments have shown that the effect of anesthesia alone on PND was minimal, but the inflammatory response induced by surgical trauma demonstrated in both animals and humans had a higher correlation with PND,[12–14] likely via neuroinflammation[15] including prostaglandin-mediated effects.[16,17] The apparent increase in inflammation with age highlights a common theme of immune-mediated dysfunction after surgery and in neurological diseases in humans.[10,15,16,18–21]

Other proposed, but as yet unproven, pathological mechanisms promoting PND include the following: (1) Bacteria imbalance in the gut may be an inflammation source to the PND pathology which has been reported that gut microbial dysbiosis in mice after surgery disrupted the intestinal barrier and metabolic abnormalities, resulting in neuroinflammation and dendritic spine loss.[22] This is in line with our previous clinical study showing that gut microbial dysbiosis and intestinal barrier injury led to endotoxemia and systemic inflammation and subsequently exacerbated brain function impairment, in particular whose brain function was already vulnerable;[18] (2) Neuroinflammation associated with mitochondria dysfunction and oxidative stress-mediated neuronal damage;[23] (3) Neuroinflammation-mediated microglia synaptic elimination;[24] and (4) Neuronal pyroptosis caused neuroinflammatory cascades further damaging neurofunction.[25] All these are illustrated in the Figure.

RISK FACTORS OF PND

Recognized risk factors of PND include age, surgery, preoperative cognitive function, and postoperative pain, amongst others including vascular disease, perioperative hypotension, and inflammation.[26] preoperative neurological conditions that are associated with some degree of cognitive decline may be responsible[27] such as cerebrovascular disease or neurodegenerative diseases such as Alzheimer's disease.[28] Postoperatively elderly patients who are at risk for PNDs often have exacerbated inflammatory responses.[29] The physiological processes responsible for efficiently regulating the stress response of the older person's brain is less effective than in young people.[1,28,30] Brain volume, white matter integrity, and cerebral blood flow also decrease with age.[30,31] Overall the aging brain is more vulnerable to PND development.[1,30,31] Possible triggers include surgical and anesthetic factors such as

Table 1. Summary of EEG and Neuroimaging Modalities

Method	Applications	Temporal resolution	Spatial resolution	Advantages	Disadvantages
EEG	Preoperative mapping, epilepsy, neurodegenerative disorders	-	-	Nonionising radiation, inexpensive, noninvasive	Spatial resolution is low
fMRI	Functional mapping, preoperative maps	Low	High	Capable of imaging functionally, noninvasive	Costly, greater expertise required to utilize
fNIRS	Functional mapping	High	Low	Inexpensive, ionizing radiation absent, real-time, noninvasive	Spatial resolution is low
PET	Functional mapping, preoperative mapping	Low	High	Provides metabolic and functional information, can detect diseases at cellular level	Ionizing radiation, expensive, requires radioactive tracers, lower temporal resolution compared to EEG and fNIRS

Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; PET, positron emission tomography.

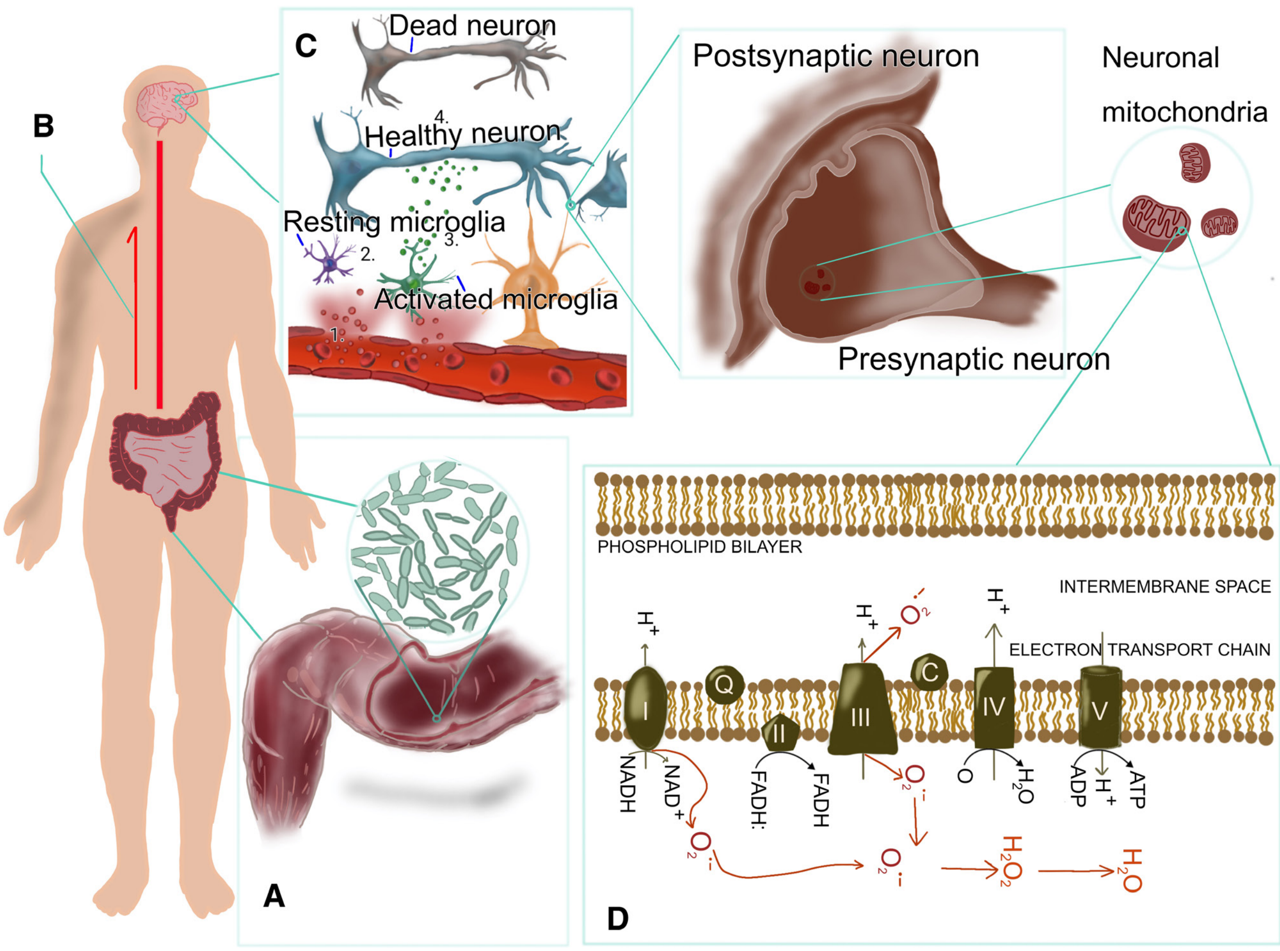

Figure. Potential cellular mechanisms of neurocognitive decline. Surgical trauma causes whole body inflammatory responses and cell death and subsequently leads to remote organ (including intestine) injury and dysbiosis. All these are as follows. A, Gut bacteria microflora imbalance due to anesthetic administration, leading to altered levels of free-floating inflammatory markers. B, Inflammatory markers circulate throughout the body and travel to the brain, crossing the blood-brain barrier. C, Activated microglia secrete neurotoxic factors such as ROS, TNF-α as well as interleukins. These also act in an inflammatory manner causing further microglial activation and a change in the blood-brain barrier permeability to allow immune-cell recruitment leading to further inflammatory mediator secretion. D, Direct neurotoxic insult occurs to healthy neurons leading to neuronal synaptic elimination, mitochondria dysfunction and death as a result of the degradative action of the microglial-secreted neurotoxic factors. Mitochondrial reactive-oxygen species (oxygen free radicals) produced as a byproduct via the electron transport chain cause oxidative damage to synaptic membrane, contributing to neuronal injury or death. ROS indicates reactive oxygen species; TNF-α, tumor necrosis factor alpha.

an inflammatory response, changes in cerebral blood flow perfusion or covert stroke,[32–34] increased apoptosis, and increased phosphorylated tau[35,36] but not amyloid production in the brain.[37] All these changes may induce neuronal injury in the brain, leading to postoperative NCDs. In preclinical models, excessive use of anesthetic drugs was found to positively correlate with an increase in the incidence of PND-like behavior[38] but to date, there is limited evidence of this relationship in elderly patients. Patients with acute sleep disturbances or preoperative depressive states are more likely to develop PND.[39]

ELECTROENCEPHALOGRAPHY

As an objective and noninvasive method for monitoring CNS function, EEG records the sum of excitatory and inhibitory postsynaptic potentials spontaneously generated by the pyramidal cells of the cerebral cortex to reflect the overall functional state of the perioperative brain.[40] There are 5 typical EEG bands: gamma, beta, alpha, theta, and delta. Brain electrical activity of awake people is dominated by low-amplitude fast waves (gamma, beta, alpha). The EEG waveform shifts to a low-frequency, high-amplitude pattern with the administration of some anesthetics (such as propofol, etomidate, and inhalation anesthetics).[41]

Bispectral index (BIS) is a frequently used processed EEG (pEEG) monitor, which was originally developed as an anesthetic depth monitor. By measuring the linear components (frequency and power) of EEG and analyzing the nonlinear relationship (phase and harmonic) between component waves, BIS selects some EEG signals that can represent different sedation levels for standardization and digital processing, and finally converts them into a simple quantitative index.

BIS ranges from 100 (awake) to 0 (isoelectric EEG). BIS is normally maintained between 40 and 60 during general anesthesia. Controlling the BIS value within a range considered to be light general anesthesia has been proposed to reduce the incidence of POD and cognitive dysfunction.[42] In a study by Wildes et al,[43] 1232 patients were randomized 1:1 to receive EEG-guided anesthetic administration (n = 614) or usual anesthetic care (n = 618). EEG-guided anesthetic administration did not decrease the incidence of POD among older adults undergoing major surgery. This may be explained by a multitude of factors such as no observed difference in the dose of anesthesia between the 2 groups, patient selection, type of surgery, anesthesia methods, scale used for evaluation of POD, etc, and perhaps more importantly, the limitations of BIS values themselves. A subsequent large study, ENGAGES (Enhancing Neurocognitive Aging with Glucose and Exercise Study)-Canada, found a similar effect in cardiac surgery.[44] The authors randomized 1140 patients to EEG-guided care or not. Similar to the original ENGAGES study, no differences were found in delirium or other outcomes. However, in a dual center study with 139 subjects by Cooter Wright et al,[45] it was suggested that pEEG-based measure of lower brain anesthetic resistance (ie, low Duke Anesthesia Resistance Scale) was related to the increased POD risk in older surgical patients. Payne et al[46] used the trial sequential analysis (TSA), which allows for interim analyses in cumulative meta-analyses to evaluate the accumulated evidence and determine whether further trials are needed, and they analyzed 9 randomized controlled trials (RCTs) involving a total of 4648 participants to assess the effect of pEEG monitoring on POD incidence.

Meta-analysis suggests that pEEG monitoring was not significantly associated with POD incidence (odds ratio [OR] = 0.78; 95% confidence interval [CI], 0.60–1.00).[46] This ultimately suggests that the available data were insufficient to draw firm conclusions regarding the effect of pEEG monitoring on POD. Although the analysis of multiple RCTs investigating the relationship between pEEG monitoring and POD demonstrated no significant effect, limitations in trial methodology and insufficient data emphasize the need for further research in this area. We recommend that the TSA is repeated after the publication of ENGAGES-Canada to review the state of the literature.

Calculation models of all pEEG devices currently in clinical use quantify the EEG based on characteristics such as frequency, time, BIS, as well as entropy which are compared with reference signals that reflect awake, light, and deep anesthesia and brain-dead patients. However, of importance, it appears that signal features differ depending on age, although none of the pEEG devices are standardized for the age of those who are monitored, which affects their overall predictive reliability.[47] Indeed, a relative large adult sample size study showed that the BIS values are correlated positively with age, indicating the BIS algorithm is accurate in older adults.[48] Obert et al[49] also concluded that almost all current neuromonitoring devices were influenced by age, which has the potential to lead to higher than necessary dosage of anesthetics in older individuals. Until we develop bespoke approaches to monitoring the pEEG in the elderly, it is likely that trials investigating the relationship between "depth of anesthesia" and PND will be severely hampered.

The complexity of raw EEG spectrograms and the information contained within is far more than the single number output currently provided (such as a BIS value). There are marked reductions in signal power across all frequencies with increasing age.[50] Due to potential gray matter and/or skull conductance decreasing with age, EEG changes in elderly sometimes show a decrease in amplitude and lower power spectral density.[47,51,52] Patients had a significantly increased incidence of delirium after wakening when their EEG changed from slow to fast waves with more beta wave rather than alpha.[53] In addition, it was also reported that patients with more preoperative comorbidities or existing cognitive impairment had lower alpha power in the frontal lobe during anesthesia than "healthy" patients.[54,55] In addition, patients with low alpha wave power were more prone to EEG burst-suppression during anesthesia.[56] EEG change, for example, the increase in delta or theta activity exceeded 50% or the fast frequency amplitude decreased by more than 50%, has specificity of 91.5% for predicting POD, especially in patients undergoing cardiovascular surgery, but sensitivity was low (20.4%),[57] suggesting that EEG changes associated with POD occurrence has not been established yet and further study with different surgical population and settings is needed.

In a study by Tanabe et al,[20] preoperative and postoperative cognitive testing, EEG, blood biomarkers, and preoperative MRI were collected from 70 surgical patients. They reported that those who developed POD had higher alpha power, increased alpha-band connectivity, and increased radial diffusivity in the preoperative period.[58] Increased preoperative functional connectivity (FC) in preoperative EEG was hypothesized to represent a compensatory mechanism for underlying structural neurodegeneration before surgery. Delirium was associated with a profound increase in EEG slowing (increased power from 0.5 to 6 Hz) that correlated with inflammatory burden consistent with the role of inflammatory mediators described within the mechanisms section.[20]

Specific manifestations of perioperative EEG spectrograms (eg, EEG alpha power) can potentially be used as indicators of brain health. However, Shortal et al[59] found no significant correlation between EEG suppression time and anesthesia recovery time or cognitive task performance in healthy adults aged 22 to 40 years old. Clearly, this study does not represent the conditions in older patients because younger volunteers are different than older surgical patients with multiple comorbidities. In a retrospective cohort study by Fritz et al,[60] patients with EEG suppression at lower volatile anesthetic concentrations have an increased incidence of POD. Indeed, for the elderly brain, improvements in PND prognosis and subsequent reduction in PND incidence, potentially by lowering anesthesia dosage, while introducing more accurate neurological monitoring is paramount in progressing this field. This area of research is summarized in Table 2.[43,45,49–56,58,59,61] In addition, event-related potentials (ERPs) are commonly used to assess cognitive function.[62] Cochrane database review reported 6 RCTs with 2929 participants and found the EEG or ERP indices-guided anesthesia decreased the risk of neurological complications including delirium and cognitive impairment.[63] The auditory evoked potentials (AVP) study found similar changes in cognitive function after either intravenous or inhalation anesthesia.[64] When the visual evoked potentials (VEPs) were used to assess cognitive function after sevoflurane anesthesia, the finding is inclusive. Interestingly, it has been reported recently that delirium is associated with loss of feedback cortical connectivity using AVP.[65] Other changes observed in the Dynamic Causal Modelling approach include modulated interneuron function, consistent with theoretical prediction about the mechanisms of delirium.[66]

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

fNIRS is a method of noninvasive neurological monitoring that evaluates the level of neurological activity in the brain by exploiting differences in infrared absorbances of oxy/deoxyhemoglobin. fNIRS essentially reflects neural metabolic activity at any given point in time. Neurovascular coupling is the process by which many functional neuroimaging modalities work. Neurons of the brain receive oxygen via the blood and in the process of cognition, there is a fluctuating level of cerebral blood flow in various active regions of the brain, the changes of which may be measured in the content of blood oxyhemoglobin and deoxyhemoglobin. Based on the difference in near-infrared light (700–900nm) absorbance between oxyhemoglobin and deoxyhemoglobin, fNIRS calculates the relative concentrations of oxy/deoxyhemoglobin in local brain regions in real time through absorption spectrum according to the Beer-Lambert law, thus indirectly reflecting brain neural activity state. fNIRS has a good correlation with fMRI data with high spatial resolution (10–20 mm) and temporal resolution (10 Hz). It is a portable technique, has real-time and continuous readings, and has high repeatability of results. It should be pointed out that the technique only measures a small and superficial area of cortex, and its usefulness is yet fully known and warrants further study.

The NIRS technique's regional cerebral oxygen saturation ($rScO_2$) measurement continuously reflects the balance of cerebral oxygen supply and demand. Low $rScO_2$ values indicate that energy substrate delivery may be not enough to meet metabolic requirements, such as hypoperfusion or hypoxia, while high $rScO_2$ values are to do with high perfusion or increased metabolic activity. It is important to understand that NIRS measures intravascular hemoglobin oxygen saturation (diameter <100μm), not intracellular oxygenation.

A preoperative $rScO_2$ value below a certain threshold (50%–60%) indicates increased risk of neurological and systemic complications after surgery; in 1 study this threshold independently predicted postoperative mortality at 30 days and 1 year.[67] For septic shock patients, the best cutoff value for $rScO_2$ max in predicting delirium was 77.5% although the sensitivity was low (0.44) and specificity was high (0.897). The best cutoff value for $rScO_2$min in predicting delirium was 65.5% (sensitivity: 0.556 and specificity: 0.744). Roberts et al[68] have shown that significant decreases in $rScO_2$ in patients with one-lung ventilation during thoracic surgery may be associated with an increased incidence of postoperative complications and POD, delayed neurocognitive recovery, and prolonged length of hospital stay. Rogers et al[69] conducted a multicenter RCT to evaluate whether fNIR-based interventions during cardiopulmonary bypass can reduce the incidence of postoperative cognitive dysfunction (POCD) in patients undergoing cardiac valve surgery. There were no differences between the intervention and control groups in cognitive or psychomotor function, nor were there differences in levels of biomarkers for brain, kidney, and myocardial injury or adverse events. This area of research is summarized in Table 3.[68,69,71,72]

Cognitive function is not controlled by any 1 singular brain region, rather it is orchestrated by a wide distribution of spatially separated but temporally correlated regions represented as a functional network. Thus, it is important to consider and be aware of the functional interactions between related brain regions as cognitive function appears to reflect the synchronized effort of complex interacting networks. The

Table 2. Characteristics of EEG Studies

Year	First author	Participants (n)/ mean age in years ± SD	Type of study	Country	Design	Main findings
2024	Al-Qudah et al[57]	n = 886/64, n = 275/67	Retrospective	United States	Cohort study	EEG change has specificity of 91.5% for predicting POD, especially in patients undergoing cardiovascular surgey,but sensitivity was low (20.4%), suggesting that EEG changes may have been remedied secondary to intraoperative therapeutic intervention.
2022	Tanabe et al[51]	n = 91	Prospective	United States and Australia	Observational study	The complexity of EEG signals is diminished in proportion to the severity of delirium implying reduce cortical information.
2022	Cooter Wright et al[45]	n = 104/73, n = 35/74	Prospective	United States	Dual Center Study	pEEG-based measure of lower brain anesthetic resistance (ie, low Duke Anesthesia Resistance Scale) was related to the increased postoperative delirium risk in older surgical patients.
2021	Obert et al[49]	n = 180	Retrospective	United States	Observational study	The index values of the Treaton device were significantly decreased with age. These findings were independent of the administered dose of anesthetics.
2021	Koch et al[58]	n = 41/74.8 ± 5.4, n = 196/72.3 ± 5.3	Prospective	Germany	Observational study	Lower preoperative SEF, lack of EEG slowing deficiency during transition from preoperative state to unconscious state, and lower EEG power in the relevant frequency bands in both states were associated with the occurrence of POD.
2020	Tanabe et al[52]	n = 53	Prospective	United States, UK and Australia	Cohort study	Both amyloid-b and tau pathology were associated with slowing in the alpha peak frequency. In addition, slowing in the peak alpha frequency was associated with CSF Ab42/40 ratio, phosphoTau (pTau181) and Tau181/Ab42. And Alpha peak frequency was not associated with neurodegeneration. Amyloid-tau and neurodegenerative pathologies correlate with distinct electrophysiological signatures.
2020	Kaiser et al[54]	n = 589/63.6	Prospective	New Zealand and New Zealand	Observational study	Comorbidities and age are independently associated with decreasing frontal EEG alpha and broadband power during general anesthesia.
2020	Shao et al[56]	n = 155/48.69 ± 18.57	Retrospective	United States	Observational study	Lower frontal alpha-band power is strongly associated with a higher propensity for burst-suppression and, therefore, a higher potential risk of postoperative neurocognitive impairment.
2019	Hernaiz et al[61]	n = 54/69.52 ± 7.35	Prospective	United States	Sub-Study	EEG intraindividual variability was significantly associated with cognitive reserve, brain integrity, and a domain of processing speed/working memory.
2019	Wildes et al[43]	n = 614/65.0–74.7, n = 618/64.7–75.8	Prospective	United States	Randomized clinical trial	Compared with usual care, EEG-guided anesthesia administration did not reduce the incidence of postoperative delirium in older adults undergoing major surgery.
2019	Hesse et al[53]	n = 125/63, n = 501/65	Prospective	United States and New Zealand	Observational study	The lack of significant spindle power in the EEG emergent trajectories was strongly associated with PACU delirium, especially in cases involving ketamine or N_2O
2019	Shortal et al[59]	n = 27/22–39.5	Prospective	United States	Cohort study	EEG suppression by itself is not a significant determinant of recovery time or degree of cognitive impairment after anesthesia recovery in healthy adults.
2017	Giattino et al[55]	n = 15/69(5.5), n = 35/69 (6)	Prospective	United States	Cohort study	The lower intraoperative α power of the frontal lobe can be used as a physiological indicator to identify the elderly with lower preoperative cognitive function.
2015	Purdon et al[50]	n = 155	Retrospective	United States	Observational study	The age-related changes in EEG are consistent with the neurobiological and neuroanatomical changes known to occur during typical aging. An unprocessed EEG and its spectrogram can explain age and individual patient characteristics.

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; PACU, postanesthesia care unit; pEEG, processed EEG; POD, postoperative delirium; SEF, spectral edge frequency.

hippocampal region is the focus of many studies in mild cognitive impairment (MCI), due to its importance in relation to cognitive function. The prefrontal cortex is also associated with cognitive function and research has illustrated an inversely proportional relationship between hippocampal volume and

Table 3. Characteristics of fNIRS Studies

Year	First author	Participants (n)/ Mean age in years ± SD	Type of study	Country	Main findings
2021	Roberts et al[68]	n = 60/63, 3 ± 13; n = 57/61, 9 ± 14	Prospective	United States	Intraoperative cerebral oxygen desaturations were significantly associated with poorer early cognitive recovery, higher risk of postoperative delirium, and longer hospital stay.
2021	Peng et al[70]	n = 25/53. 84 ± 16.01 n = 23/54. 60 ± 16.35	Retrospective	China	For septic shock patients, the best cutoff value for rScO2 max in predicting delirium was 77.5% although the sensitivity was low (0.44) and specificity was high (0.897). The best cutoff value for rScO2min in predicting delirium was 65.5% (sensitivity: 0.556 and specificity: 0.744).
2019	Nguyen et al[71]	n = 42/75. 9 ± 3.6, n = 42/74.3 ± 4.4	Prospective	Korea	The right hemisphere connectivity in the resting state was significantly higher in the MCI group than in the HC group, while the left hemisphere connectivity in the verbal fluency test was significantly lower in the HC group.
2019	Bu et al[72]	n = 26/69. 27 ± 3.64, n = 28/70.15 ± 3.5	Prospective	China	The decreased level of effective connectivity of brain regions in the mild cognitive impairment group may be a sign of impaired cognitive function.
2017	Rogers et al[69]	n = 106/70.0, n = 98/65. 9	Prospective	UK	There was no difference between the groups for the 3 core cognitive domains (attention, verbal memory, and motor coordination) or for the noncore domains psychomotor speed and visuospatial skills.

Abbreviations: fNIRS, functional near-infrared spectroscopy; HC, healthy controls; MCI, mild cognitive impairment; SD, standard deviation.

hippocampal—prefrontal cortex connectivity: as the hippocampal volume reduces in size it is believed that the increased prefrontal connectivity acts as a compensatory mechanism in MCI.[73] Nguyen et al monitored hemodynamic responses of the prefrontal cortex during resting state whilst assessing patients using verbal fluency tests and examined FC in both cognitively normal seniors and patients with MCI using the fNIRS system.[73] Their findings showed that the level of interspheric connectivity was significantly stronger than that of intrahemispheric connectivity in normal seniors, while there was no significant difference in patients with cognitive impairmentt.[71] Bu et al[72] evaluated the effective connectivity of the brain by fNIRS technology and found that the effective connection level of brain regions in patients with cognitive impairment was significantly reduced compared with nonimpaired individuals, suggesting that the reduction of effective connection may be a physiological marker of cognitive dysfunction. From simple changes in frontal cortex blood flow to the study of functional interactions between different brain regions, fNIRS provides a new perspective and new opportunity for the study of cognitive disorders.[72] At present, there are some studies on fNIRS in PND, but more research is needed. To date, studies have mainly focused on changes in regional blood oxygen and considered how varying methods (each with different capabilities) can provide differing resolutions. Furthermore, when combining modalities, it is possible to obtain greater insight by way of exploiting the strengths as well as weaknesses of the various neuroimaging methods (Table 1). However, certain limitations towards clinical outcomes have been documented.[74]

FUNCTIONAL MAGNETIC RESONANCE IMAGING

A powerful tool for studying white matter, MRI can provide more abundant, accurate and objective parameters. MRI provides clinicians with a unique opportunity to study small and subtle neuroplasticity changes in the brain. Functional MRI (fMRI) is an imaging technology that reflects the blood oxygenation level of tissues and organs and can also measure oxygenation levels related to neuronal activity in the brain under different cognitive conditions.

Resting-state fMRI (rs-fMRI) does not require performance of specific tasks during scanning, but fMRI can be used during the performance of a task (ie, task-based fMRI; tb-fMRI). Default mode network (DMN) describes a network of brain regions that appear to be active "at rest" and show greater activity in rs-fMRI than in tb-fMRI. DMN brain regions include posterior cingulate cortex (PCC), medial frontal cortex, bilateral superior frontal gyri, bilateral angular gyri, bilateral mesial temporal and lateral temporal cortices.

Research on fMRI use in PND is currently in the exploratory stages. It has been suggested that POCD occurrence may be related to a reduction of thalamus and hippocampus volume as well as a decrease in cerebral blood flow, while preexisting white matter lesions were also reported to relate to the development of POD.[20,75] In a pilot study following 19 subjects by Mohanty et al,[76] it was suggested that changes in

FC may serve as neural correlates of cognitive changes after surgery. Family Wise Error (FWE) correction for multiple comparisons was applied to ensure statistical validity and the reported peak FWE values indicate that the observed correlations were statistically significant.[76] This pilot study serves to contribute to the growing body of evidence on the relationship between FC, cognitive changes, and the perioperative period. Wu et al[77] also found that there are more connections among brain regions in dNCR patients than in non-dNCR patients. By performing rs-fMRI examination before surgery in 74 elderly noncardiac patients (≥60 years of age), Jiang et al[78] found that a random forest machine learning model based on DMN and central executive network (CEN) resting-state FC (RSFC) features can predict dNCR after noncardiac surgery, which may be beneficial for early prevention of dNCR. Abu-Omar et al[79] used fMRI to compare perioperative prefrontal activation in patients undergoing on-pump and off-pump coronary artery bypass grafting. They found that patients who underwent on-pump, but not off-pump surgery, had a significant relative reduction in prefrontal activation which was related to intraoperative cerebral microembolic load. fMRI may prove to be a useful tool of perioperative cerebral injury monitoring that may help in the evaluation of potential cerebroprotective strategies. In the early diagnosis of dementia patients with MCI with MRI, the sensitivity and specificity in the temporal lobe were 0.65 and 0.69, respectively; the sensitivity and specificity in hippocampus were 0.62 and 0.70, respectively.[80]

Changes in intrinsic RSFC of the DMN region are related to cognitive function and memory.[81] Lan et al[82] analyzed the amplitude of low-frequency fluctuation (ALFF) and FC to estimate differences in brain functional parameters. This study investigated functional alterations in older patients with knee osteoarthritis before and after knee arthroplasty using rs-fMRI and found that those suffering from knee osteoarthritis had decreased ALFF within the DMN together with increased ALFF in the bilateral amygdala and cerebellum posterior lobe (CPL) preoperatively and decreased ALFF within the left precuneus gyrus and middle temporal gyrus postoperatively.[82] The power of fMRI is apparent; however, large sample size studies are required to ensure robustness of the evidence.

In a prospective cohort study reported by Browndyke et al,[83] older apolipoprotein E (APOE4) carriers showed greater intrinsic functional brain connectivity associated with brain regions before surgery, a greater decline in connectivity than noncarriers in many of these regions after major noncardiac surgery. Also in the study of Browndyke et al,[84] cognitive tests and rs-fMRI before and 6 weeks after cardiac surgery were compared in elderly patients and found that changes in RSFC in specific DMN regions were positively correlated with worse postoperative cognition. In another study, they found that a postoperative increase of working memory load-associated local coherence was negatively correlated with postoperative overall cognition.[85] Additionally, it has been suggested that DMN activity and connectivity may become important diagnostic markers or potential intervention targets for PND.[84] Rs-fMRI results at 48h after total knee replacement under general anesthesia showed that 23% of patients had reduced connections to at least 1 functional network in the area of interest and 15% of patients had reduced connections to all functional networks in the area of interest. Preoperative cognitive ability and ventricular volume can predict the reduction of FC of brain regions in elderly patients after surgery.[61,86] van Montfort et al[87] revealed that the Rs-fMRI networks break down and become less efficient during delirium as well as causing loss of hub function of the right PCC, which is positively correlated to the duration of the disorder. Kyeong et al[88] compared seed-based connectivity of the suprachiasmatic nucleus between 34 delirious patients and 38 nondelirious controls. A dysregulation of the DMN and mental coordination processing areas by the circadian clock may be an underlying pathophysiology of sleep-wake cycle disturbance and symptom fluctuation in delirium.[88] The DMN activation and FC changes by rs-fMRI may have good application prospects in early PND diagnosis and in the exploration of PND pathogenesis. The summary of this area of research is presented in Table 4.[75,76,82,84,85,89–93]

POSITRON EMISSION TOMOGRAPHY

PET imaging studies in the neurocognitive setting have unveiled significant alterations in brain metabolism and neuroinflammatory responses underscoring the complexity of CNS changes associated with cognitive dysfunction. In a study by Silva et al,[94] exploring neuroinflammation in cases of peripheral acute bacterial infection of older patients with cognitive dysfunction, PET imaging with a TSPO ligand revealed nuanced patterns. Cognitively healthy participants exhibited higher neuroinflammation in subcortical regions, specifically the choroid plexus, compared to those with cognitive impairment.[94] Surprisingly, participants with dementia and/or delirium showed weaker neuroinflammatory responses, suggesting an immunosuppressive brain environment in these cases.[94] These findings suggest that choroid plexus microglia activation might be a potential biomarker for cognitive function. Researchers and clinicians can utilize PET scans to assess the state of microglia activation in this region, potentially aiding in the diagnosis and monitoring of cognitive disorders. It would be beneficial to explore novel PET tracers specifically designed to target microglia markers, enhancing the accuracy and specificity of microglia-related PET imaging.

Table 4. Characteristics of fMRI Studies

Year	First author	Participants (n)/ mean age in years ± SD	Type of study	Country	Main findings
2024	Tornero et al[80]	23 articles	systematic review	Spain	In the early diagnosis of dementia patients with mild cognitive impairment with magnetic resonance imaging, the sensitivity and specificity in temporal lobe were 0.65 and 0.69, respectively; the sensitivity and specificity in hippocampus was 0.62 and 0.70, respectively.
2020	Lan et al[82]	n = 15/71. 2 ± 4.2, n = 23/71. 4 ± 4.1	Prospective	China	Preoperatively, the KOA patients exhibited increased FC between the left precuneus gyrus and the right supplementary motor area compared to the controls. The significantly altered ALFF values were not correlated with cognitive changes.
2019	Oren et al[89]	n = 25/29, n = 28/ 71.8	Prospective	Israel	The correlation between intra-HC and inter-HC RSFC was altered with cognition and aging. Importantly, older adults who had lower posteffort RSFC between the laHC and the pHC demonstrated a decline in an episodic memory 2 y later.
2019	Mohanty et al[76]	n = 19	Prospective	United States	FC can identify neural correlates of cognitive changes after operation.
2018	de Vos et al[90]	n = 77/68.6 ± 8.6, n = 173/66.1 ± 8.7	Prospective	Netherlands	Moderate to good AD classification can be obtained using RSfMRI scans. FC matrix, FC dynamics, and ALFF are the most discriminative, and the combination of all resting-state measures slightly improves classification accuracy.
2017	Browndyke et al[84]	n = 12/69, 7 ± 7.3; n = 12/70, 4 ± 7.9	Prospective	United States	Changes in RSFC in specific DMN regions were positively associated with overall cognitive changes at 6 wk after cardiac surgery, suggesting that DMN activity and connectivity may be an important diagnostic indicator of POCD or an intervention target for potential POCD treatment.
2017	Huang et al[75]	n = 48/69. 02 ± 5.81, n = 45/67.81 ± 5.62	Prospective	Denmark and Sweden	Within 48 h after surgery, at least a quarter of the sample of older Adults showed significant functional network decline. The correlation between preoperative cognition, brain integrity and postoperative acute functional network changes.
2017	Browndyke et al[85]	n = 25/66.7, n = 26/67.2	Prospective	United States	A postoperative increase in working memory load-associated local coherence was negatively correlated with postoperative overall cognition.
2016	Li et al[91]	n = 21/68, 19 ± 9.07; n = 20/68, 15 ± 8.67; n = 25/64, 52 ± 6.44	Prospective	China	Alzheimer's patients have damage to the limbic system network. In patients with AD, impaired WM connections and the GM volume of these networks are associated with impaired emotional memory and EEM effects.
2015	Das et al[92]	n = 30/71.60, n = 39/70.62	Prospective	United States	Compared with the control group, the anterior and posterior MTL networks are affected in MCI, to different degrees. In addition, cortical thickness in the brain regions defined by these networks was reduced in MCI.
2013	Xie et al[93]	n = 18/22 mo (rats)	Prospective	China	Splenectomy performed under neuroleptic anesthesia triggers a cognitive decline which is associated with changes in spontaneous neuronal activity in the cortex and hippocampus.

Abbreviations: AD, Alzheimer's disease; ALFF, amplitude of low-frequency fluctuation; DMN, default mode network; EEM, emotional memory enhancement; FC, functional connectivity; fMRI, functional magnetic resonance imaging; GM, gray matter; HC, healthy control; KOA, knee osteoarthritis; laHC, left amygdala hippocampal complex; MCI, mild cognitive impairment; MTL, medial temporal lobe; pHC, posterior hippocampus; POCD, postoperative cognitive dysfunction; SEF, spectral edge frequency; RSFC, resting-state FC; SD, standard deviation; WM, white matter.

Additionally, combining PET with other imaging modalities such as computed tomography (CT) scan may provide a comprehensive view of both structural and functional changes in the brain. This multimodal approach has the potential to offer a more nuanced understanding of cognitive disorders, aiding in both research and clinical applications. For example, Nitchingham et al[95] used PET and CT imaging to meticulously compare hospitalized patients with and without delirium, uncovering significant hypometabolism in both cortical and subcortical regions among delirium-positive individuals. This observation highlighted potential disruptions in glucose metabolism linked to thalamic dysfunction and abnormalities within the DMN.[95] Notably, the regions displaying reduced metabolic activity, such as the thalamus and PCC, are closely associated with attention, awareness, and various cognitive functions. The correlation between metabolic activity and neuropsychological assessments in their study is consistent with documented cognitive impairments in delirium patients.[95,96] Hypometabolism in the PCC might underpin the inattention observed in delirium, a hallmark clinical feature.[96] The vulnerability of the PCC, which exhibited high metabolic activity even at rest made the region particularly susceptible to factors that impair cerebral metabolism, further emphasizing the intricate relationship between altered cerebral metabolism and cognitive dysfunction in delirium. Mathias et al[97] investigated delirium-positive geriatric patients undergoing PET imaging, and observed that after resolution of delirium PET imaging remained accurate for diagnosing neurodegenerative diseases. Patients received amyloid PET at an early stage, and 40% of those with impaired cognitive function received an etiological diagnosis within just 3 months, 3.5 times higher than those who did not receive amyloid PET (11%).[98] The studies mentioned above may suggest that PET imaging, especially fluorodeoxyglucose (FDG) PET, holds promise in unraveling the complexities of cognitive dysfunction for more precise diagnosis, monitoring, and personalized interventions per se. Pertinent studies in this field of research are presented in Table 5.[94–97,99,100]

Understanding these neurobiological mechanisms is crucial for developing targeted interventions and improving outcomes for individuals at risk of POD. Further research in this area holds the potential to refine diagnostic strategies and enhance our understanding of the underlying pathophysiology, ultimately leading to more effective management approaches. PET imaging not only serves as a valuable research tool to deepen our understanding of cognitive disorders but also holds promise as a diagnostic and therapeutic monitoring tool in the context of cognitive impairments. Continued advancements in PET techniques and the development of specific tracers can further enhance our ability to study and target various brain regions.

CONCLUSIONS

At present, there is still a lack of recognized effective perioperative monitoring methods and standards for the CNS. Identifying PND is currently based on clinical consultation and objective neuropsychological cognitive assessment tools, but also now includes assessments of subjective cognitive complaint and daily function. As such, the clinical relevance and patient impact are beginning to be reported and become evident in the literature. Due to the complexity of the mechanisms of perioperative brain injury, the solutions may also be multifaceted. EEG, fNIRS, fMRI, and PET can be seen as important components

Table 5. Characteristics of PET Studies

Year	First author	Participants (n)/ mean age in years ± SD	Country	Main findings	PET tracer
2023	Altomare et al[98]	n = 794/71	Switzerland	Patients received amyloid PET at an early stage, and 40% of those with impaired cognitive function received an etiological diagnosis within just 3 mo, 3.5 times higher than those who did not receive amyloid PET (11%).	[18F]flute metamol and [18F]florbetaben
2022	Silva et al[94]	n = 4/ 83.7; n = 4/83.5; n = 4/83.3; n = 7/ 80.0	Portugal	Dementia and/or delirium is associated with a reduced neuroinflammatory response to acute systemic bacterial infection which can be the result of an immunosuppression in the brain.	[11C]-PK11195
2021	Nitchingham et al[95]	n = 20	Australia	In patients with acute illness but without clinical dementia, delirium is accompanied by regional cerebral hypometabolism.	18F-FDG
2020	Mathies et al[97]	n = 88/82. 0 ± 5.7	Germany	There was no difference in the fraction of correct PET-based categorization between patients with delirium in remission and those without delirium.	18F-FDG
2020	Katsumi et al[99]	n = 36/74.4 ± 3.9	United States	No significant relationship was identified between postoperative delirium and [11C]-PBR28 binding.	[11C]-PBR28
2018	Klinger et al[100]	n = 38/69; n = 40/69.4; n = 12/71; n = 18/71	United States	Postoperative cognitive dysfunction was not associated with 6-week cortical amyloid deposition.	18F-florbetapir
2017	Haggstrom et al[96]	n = 13	Australia	FDG PET can provide substantial insight into the neural mechanisms and metabolic disturbances in delirium.	18F-FDG

Abbreviations: FDG, fluorodeoxyglucose; PET, positron emission tomography; SD, standard deviation.

in clinical settings to promote effective monitoring of perioperative brain health. Although evidence that these monitoring tools may improve patient prognosis is currently controversial, it is too early to dismiss their potential since the goal is to gain insights into brain functional status is largely not optimized yet but advancing.

In conclusion, EEG, ERP, and fNIRS have the advantages of convenience, being real-time and non-invasive, and are closely related to cognitive function. Therefore, it is practical to add these neurological monitoring methods to studies of PND. In clinical practice, to reduce cost, the use of EEG and/or fNIRS can be considered as first-line modalities to identify vulnerable patients and facilitate the optimization of relevant intraoperative variables; fMRI and/or PET can be considered when a patient's condition warrants their use. Possible mechanisms need to be further explored to understand the link between PND and cerebral FC changes. This will allow greater understanding of PND both acutely and over the longer term.Evaluating risk factors for PND and further elucidating FC of the brain will provide humanity with greater insights into links between neuronal systems and temporal, spatial, physiological, and cognitive functions. However, all brain monitoring techniques and their use in PND research discussed here are in the early stages and, therefore, whether the current body of literature, as summarized here, informs future research on the mechanisms underlying cognitive changes after surgery and potentially guides the development of interventions to mitigate postoperative cognitive decline in elderly individuals needs to be explored further. ■

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