

# OPEN Neuroinflammation and Perioperative Neurocognitive Disorders

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Neuroinflammation has become a key hallmark of neurological complications including perioperative pathologies such as postoperative delirium and longer-lasting postoperative cognitive dysfunction. Dysregulated inflammation and neuronal injury are emerging from clinical studies as key features of perioperative neurocognitive disorders. These findings are paralleled by a growing body of preclinical investigations aimed at better understanding how surgery and anesthesia affect the central nervous system and possibly contribute to cognitive decline. Herein, we review the role of postoperative neuroinflammation and underlying mechanisms in immune-to-brain signaling after peripheral surgery. (Anesth Analg 2019;128:781–8)

Perioperative neurocognitive disorders, now encompassing acute delirium and longer-lasting postoperative cognitive dysfunction, are major challenges to our rapidly growing aging population that negatively affect cognitive domains such as memory, attention, and concentration after surgery.<sup>1</sup> Patients who suffer from perioperative neurocognitive disorder are at risk for significant complications including dementia and even death.<sup>2,3</sup> Although postoperative delirium has become *the most common* complication in older adults,<sup>4</sup> the pathophysiology of these conditions remains unknown. Growing evidence suggests a possible role for neuroinflammation in this process because proinflammatory signaling molecules have been identified in both patients and animal models of perioperative neurocognitive disorder.

The aim of this review is to discuss recent evidence for the involvement of postoperative neuroinflammation in perioperative neurocognitive disorder, and to highlight possible mechanisms of relevance to perioperative neurocognitive disorder from preclinical and early clinical studies.

With continuous improvements in surgical technology and anesthesia care, increasingly sicker and older patients are exposed to often life-saving procedures. Unfortunately, many of these frail patients are left with postoperative delirium and longer-lasting cognitive decline, especially after cardiac and even noncardiac surgery. The incidence of delirium is estimated at 26%–53% and postoperative cognitive dysfunction at about 10% at 3 months.<sup>5–7</sup> Even though perioperative neurocognitive disorder is observed in patients across different age groups and undergoing different

surgical procedures, aging and operations such as cardiac and orthopedic surgery have become well-established risks factors for the development of these neurological complications.<sup>8</sup> Recent clinical studies have used different approaches to show that both cardiac and noncardiac surgery trigger neuronal injury, which we briefly summarize below.

## BIOMARKERS

A recent study by Evered et al<sup>9</sup> described a significant increase in plasma neurofilament light and tau, 2 key biomarkers classically associated with neuronal injury, as a result of exposure to general anesthesia and surgery. Several investigators have detected postoperative changes in Alzheimer's disease biomarkers, including  $\beta$ -amyloid protein and intraneuronal neurofibrillary tangles (tau), in cerebrospinal fluid (CSF). Lower CSF  $\beta$ -amyloid protein/tau ratio has been associated with patients who develop perioperative neurocognitive disorder, suggesting a possible trajectory toward dementia after exposure to anesthesia and surgery.<sup>10–12</sup> Changes in Alzheimer's disease markers and astroglial cell integrity, as well as evidence for blood-brain barrier opening were also found in the CSF of patients after hip arthroplasty,<sup>13</sup> confirming some of the earlier findings by Tang et al<sup>14</sup> for idiopathic nasal CSF leak correction after surgery. Interestingly, although surgery modifies Alzheimer's disease biomarkers and potentially accelerates their pathogenesis in some individuals, positron emission tomography imaging of  $\beta$ -amyloid protein plaque deposition has shown limited association with cognitive deficits 6 weeks after cardiac surgery.<sup>15</sup> CSF and plasma inflammatory biomarkers, cytokines, and many other immune-soluble factors have been described over the past decade in response to different surgeries.<sup>16–20</sup> Higher levels of CSF interleukin-6 were found to predict cognitive decline after coronary artery bypass surgery.<sup>21</sup> Other proinflammatory markers such as C-reactive protein and interleukin-1 $\beta$  have also been linked to cognitive decline after cardiac procedures.<sup>22</sup> Again, these changes in inflammatory markers are not limited to cardiac surgery and some of its unique aspects, for example, extracorporeal circulation and ischemia-reperfusion injury (reviewed in detail in Ref. <sup>23</sup>), but are also detected in noncardiac/nonneurological surgery. Significant amounts of pro- and anti-inflammatory markers are detectable in plasma and CSF of older adults after knee and hip replacement surgery.<sup>24,25</sup> Notably, elevation of

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inflammatory biomarkers has been noted after general anesthesia and spinal anesthesia.<sup>18</sup> Indeed, different anesthetics may modulate immune signaling pathways (reviewed in Ref. <sup>26</sup>) and perhaps cognitive outcomes.

### NEUROIMAGING

Other recent studies have used neuroimaging techniques to visualize changes in brain structure and function after surgery. Kant et al<sup>27</sup> recently performed a systematic review of structural magnetic resonance imaging data in perioperative neurocognitive disorder and found a consistent association with neurovascular brain changes. The neurovascular unit is critically involved in neurodegenerative diseases and promoting brain health.<sup>28</sup> The role of this interface after surgery is the focus of several ongoing preclinical studies. Initial observations using gadolinium-enhanced magnetic resonance imaging show acute (<24 hours) blood–brain barrier disruption in cardiac surgery patients, and this blood–brain barrier opening seems to correlate with subsequent neurological impairments.<sup>29,30</sup> Moreover, in critically ill patients with delirium, endothelial dysfunction and impaired microvascular permeability have also been observed using peripheral artery tonometry and more recently by assessing plasma biomarkers such as S100 calcium-binding protein B, plasminogen activator inhibitor-1, and E-selectin.<sup>31,32</sup> Our capacity to image neuroinflammation in humans is limited, but second-generation positron emission tomography tracers directed to the translocator protein have been developed. Although the translocator protein is upregulated by microglia after injury, other cell types and brain vessels express great affinity for the protein (given its location on the mitochondrial membrane), and thus, the proxy of the translocator protein for inflammation may be obscured by other factors.<sup>33</sup> Using the ligand [<sup>11</sup>C]PBR28, Forsberg et al<sup>34</sup> conducted the first human imaging study to evaluate neuroinflammation during the perioperative period. Although a strong immunosuppressive response was observed acutely after surgery, microglial activation was detected in a subset of patients with cognitive deficits at 3 months. The interplay between peripheral and central inflammation is a major challenge for clinical perioperative research, and more specific markers are needed to better identify immunocompetent cells using positron emission tomography.

As clinical research in this domain intensifies, fundamental questions on “how” surgery and anesthesia affect the central nervous system (CNS) warrant detailed evaluation. Establishing and refining clinically relevant surgical models to study perioperative neurocognitive disorder are contributing to a better understanding of the pathogenesis of cognitive decline and more rigorous evaluation of contributing factors such as different anesthetics, surgical procedures, genetic susceptibilities, and comorbidities. Rodents have been the primary source of preclinical data for perioperative neurocognitive disorder, and rats and mice are most commonly used to evaluate inflammatory changes and cognition after surgery. Cardiac models of surgery, recapitulating cardiopulmonary bypass and deep hypothermic circulatory arrest, have been established to assess neurological complications and perioperative inflammation.<sup>35</sup> Notably, cardiac surgery triggers widespread

changes in cognition that differ from abdominal surgery, while both generate substantial hippocampal neuroinflammation (ie, microglial activation).<sup>36</sup> This suggests that distinct pathways may be involved in the response to injury in different organs, and further studies are needed to dissect these pathways. Abdominal and cardiac surgery were also shown to impair neuronal plasticity, as demonstrated by acute changes in hippocampal neurogenesis and brain-derived neurotrophic factor.<sup>36</sup> Importantly, these changes outlasted the neuroinflammatory profile, and remained visible for weeks after surgery. Brain-derived neurotrophic factor in particular has been involved in this response and was found to be dysregulated in several other models.<sup>37–39</sup> Yet, the role of inflammation in neuronal deficits and cognitive decline remains undefined, and further studies are needed. We have pioneered the development of a clinically relevant orthopedic model consisting of an intramedullary fixation of the mouse tibia.<sup>40–42</sup> This has been associated with hippocampal neuroinflammation and synaptic dysfunction due to proinflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and high-mobility group box 1 protein.<sup>43</sup> Models of splenectomy,<sup>44</sup> hepatectomy,<sup>45,46</sup> abdominal,<sup>47,48</sup> and vascular surgery<sup>49,50</sup> have reported hippocampal neuroinflammation and behavioral deficits. Notably, even minor surgical procedures, such as skin incisions, trigger neuroinflammation in aged animals, but not younger adults.<sup>51</sup> Because aging is a critical risk factor for perioperative neurocognitive disorder, it is paramount that future research systematically evaluates advanced age, as well as sex differences and other common susceptibilities, to ensure successful translation of preclinical data to the bedside.

It is well appreciated that the nervous and immune systems bidirectionally communicate with apparent implications for both health and disease.<sup>52,53</sup> Indeed, the response to peripheral surgery is able to reach the CNS via multiple pathways. Here we focus on the role of (1) systemic inflammation, (2) the neurovascular unit/blood–brain barrier, and (3) neuroinflammation after surgery.

### SYSTEMIC INFLAMMATORY RESPONSE

Systemic inflammation produces physiological and behavioral changes in humans and animals that are characterized by a decline in cognitive function, fever, decreased food intake, somnolence, hyperalgesia, and general fatigue—commonly referred to as “sickness behavior.”<sup>54</sup> Sterile inflammation activates similar innate immune pathways to other stressors, such as lipopolysaccharide, by releasing damage-associated molecular patterns, such as high-mobility group box 1 protein, and cytokines.<sup>55</sup> These soluble mediators can trigger a systemic inflammatory response via activation of pattern recognition receptors, including toll-like receptors, cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ , as well as S100 Ca<sup>2+</sup> binding proteins and oxidative stress pathways. We and others have shown a pivotal role for systemic alarmins and cytokines such as interleukin-1 $\beta$ ,<sup>40</sup> tumor necrosis factor- $\alpha$ ,<sup>41,56</sup> interleukin-6,<sup>57,58</sup> and high-mobility group box 1 protein<sup>43,46</sup> in triggering neuroinflammation after peripheral surgery in rodent models. Similar changes in biomarkers have been described in clinical samples and provide critical insights

into the temporal profile of different cytokines after surgery. This should be taken into consideration as larger datasets become available for perioperative neurocognitive disorder diagnosis and treatment.

It is important to note that inflammation is overall a protective response to injury, but the improper control of its normal resolution can become harmful and contribute to pathological hallmarks including neuroinflammation.<sup>59–61</sup> The impact of systemic inflammation on the brain can be profound. Mounting evidence indicates that blood-borne factors as well as the proinflammatory systemic milieu can negatively impact CNS function, directly affecting synaptic plasticity and cognitive function during normal aging.<sup>62,63</sup> Uniform immune signaling responses, including monocyte activation, have also been linked to surgical trauma and may serve as predictors for different recovery profiles in at-risk patients.<sup>64</sup> Peripheral cells have become attractive targets for perioperative neurocognitive disorder research because they can be easily accessed in patients and may inform subsequent changes in the CNS without accessing CSF or performing neuroimaging. Monocyte-derived macrophages migrate into the brain parenchyma after surgical trauma, and this plays a role in the pathophysiology of neurological complications including postoperative cognitive decline.<sup>43,58,65</sup> In particular, it has been proposed that elevated cerebral monocyte chemoattractant protein-1 contributes to the recruitment of monocytes to the CNS and the ensuing neuroinflammatory response.<sup>58,66</sup> Both tumor necrosis factor- $\alpha$  and high-mobility group box 1 protein have been implicated in the regulation of monocyte chemoattractant protein-1 after surgery,<sup>41,66</sup> and these may serve as targets for clinical studies. Circulating monocytes, neutrophils, and other peripheral systemic factors can contribute to changes in neuronal function, synaptic plasticity, and glial homeostasis<sup>67</sup>; however, they are also critically involved in the release of neuroprotective factors, which is crucial in the context of surgical recovery.<sup>68</sup> Overall, the contribution of other cellular factors (including T-cells and components of adaptive immunity) to perioperative neurocognitive disorder is largely understudied.

### ENDOTHELIAL DYSFUNCTION AND NEUROVASCULAR UNIT/BLOOD–BRAIN BARRIER OPENING

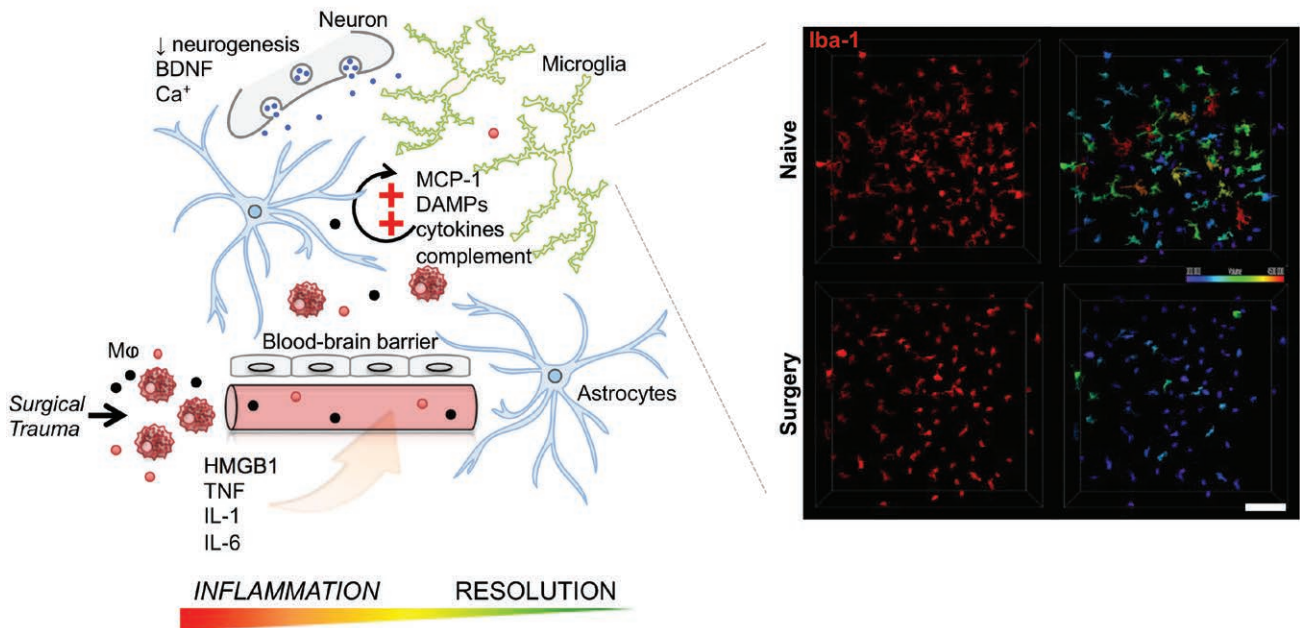
Endothelial cells, pericytes, and astrocytic end-feet are core components of the neurovascular unit.<sup>69</sup> Together with tight junction and adherent proteins of the endothelial cell layer, they ensure proper barrier formation and protection against potentially harmful peripheral molecules.<sup>70</sup> Under pathological conditions, the blood–brain barrier allows extravasation of various immune cells and systemic markers including plasma proteins, prostaglandins, cytokines, and chemokines into brain parenchyma.<sup>71</sup> Surgery triggers inflammation and pattern recognition receptors expressed at the blood–brain barrier surface can lead to endothelial inflammation and subsequent neuroinflammation.<sup>65,72–75</sup> This disruption is also found in several neurological disorders such as traumatic injury, stroke, and neurodegenerative diseases.<sup>76,77</sup> Cytokines and migration of peripheral immunocompetent cells across the blood–brain barrier have been associated with perioperative neurocognitive disorder in animal models.<sup>65</sup> After

orthopedic surgery, we found opening of the blood–brain barrier with parenchymal fibrinogen deposition in the hippocampus.<sup>65</sup> Using *Cx3cr1<sup>GFP/+</sup>Ccr2<sup>RFP/+</sup>* transgenic mice, we described acute infiltration of monocytes C-C chemokine receptor type 2 into the brain parenchyma via processes partly mediated by tumor necrosis factor- $\alpha$ /nuclear factor kappa-light-chain-enhancer of activated B cells signaling in monocytes.<sup>58,65</sup> Macrophage-specific deletion of I $\kappa$ B kinase, a central coordinator of tumor necrosis factor- $\alpha$  activation of nuclear factor kappa-light-chain-enhancer of activated B cells, prevented subsequent infiltration into the hippocampus after surgery. D'Mello et al<sup>66</sup> described a similar immune-to-brain communication pathway after hepatic inflammation, and also demonstrated that tumor necrosis factor- $\alpha$ -stimulated microglia produce monocyte chemoattractant protein-1, which subsequently causes monocyte infiltration into the brain. Monocyte chemoattractant protein-1 is elevated in the CSF of a limited subset of patients with delirium after orthopedic surgery,<sup>24</sup> suggesting that similar mechanisms may occur in humans. Other preclinical surgical models have found similar changes in blood–brain barrier ultrastructure, with infiltration of exogenous tracers into the brain parenchyma, as well as astrocyte pathology.<sup>72,78</sup> Cardiac surgery was shown to impair expression of tight junctions in rats.<sup>79</sup> Laparotomy, especially in aged mice, triggers changes in several markers including claudins, occludins, and adhesion molecules, leading to blood–brain barrier opening and cognitive decline in a process dependent on interleukin-6 signaling.<sup>74</sup> Notably, other studies have shown that administration of interleukin-6 monoclonal antibody and targeting of tumor necrosis factor- $\alpha$  (upstream from interleukin-1 and interleukin-6 signaling) prevent perioperative neurocognitive disorder.<sup>41,73</sup> Surgery was shown to upregulate enzymes that break down extracellular matrix, such as matrix metalloproteinase 9, and lead to blood–brain barrier opening and neuroinflammation.<sup>75</sup> Importantly, different concentrations of sevoflurane anesthesia differentially regulate matrix metalloproteinase 9 and 2,<sup>80</sup> suggesting that anesthesia per se contributes to these changes in the aging brain. Significantly more work is needed to define the role of different anesthetics in blood–brain barrier/neurovascular unit perioperative changes. Many of these pathological features, including blood–brain barrier opening, neurovascular unit dysfunction, and cell infiltration into the CNS, have been implicated in many neurological disorders.<sup>81–83</sup> Yet in some cases, the infiltration of blood-derived cells, such as macrophages, is necessary to boost tissue recovery in unique ways that resident microglia, astrocytes, and oligodendrocytes cannot.<sup>84,85</sup> Therefore, the role and timing of blood–brain barrier/neurovascular unit opening after surgery require further investigation to possibly develop strategies to effectively limit neuroinflammation in the perioperative period.

### NEUROINFLAMMATION

Neuroinflammation has become a key feature of virtually every neurological complication.<sup>86,87</sup> Microglial activation plays a critical role in CNS dyshomeostasis.<sup>88</sup> Microglia, the resident immune cells of the CNS, are highly motile cells that continuously survey the brain microenvironment, facilitating synaptic activity, pruning, and remodeling.<sup>89,90</sup>

**Neuroinflammation & PND**



**Figure.** Schematic overview of mechanisms involved in postoperative neuroinflammation. Surgery activates the innate immune system resulting in release of proinflammatory mediators (cytokines, chemokines, alarmins, eicosanoids, etc) and activation of systemic immunocompetent cells. These processes negatively affect the blood–brain barrier, resulting in endothelial dysfunction and infiltration of peripheral cells/factors into the brain parenchyma. Within the central nervous system, astrocytes and microglia shift from their resting state and contribute to overall neuronal dysfunction and memory function. Harnessing resolution programs as early as the inflammatory response begins may translate into neuroprotective strategies for PND. An example of microglial activation after surgery using CLARITY is provided on the right panel. Scale bar: 150  $\mu$ m. BDNF indicates brain-derived neurotrophic factor; Ca<sup>+</sup>, calcium; DAMP, damage-associated molecular pattern; HMGB1, high-mobility group box 1 protein; IL, interleukin; M $\phi$ , macrophage; MCP, monocyte chemoattractant protein; PND, perioperative neurocognitive disorder; TNF, tumor necrosis factor.

Under normal conditions, microglia display highly complex and morphologies with small nuclei and slender processes.<sup>91</sup> Upon injury, these cells can shift to a “reactive” phenotype, losing their ramified morphology to become enlarged and stumpy. Activated microglia have been implicated as the primary source of the CNS pro- and anti-inflammatory milieu.<sup>92</sup> Activated microglia secrete proinflammatory factors such as cytokines, eicosanoids, complement factors, excitatory amino acids, reactive oxygen radicals, and nitric oxide.<sup>93</sup> While dysregulation of these factors can lead to pathology, microglial activation is also responsible for jump-starting reparative processes and releasing neuroprotective factors. For example, in Alzheimer’s disease, microglia contribute to the clearing of amyloid deposits, and support synaptic remodeling by releasing growth factors.<sup>94</sup> However, microglia also contribute to pathological features in the Alzheimer’s disease brain, including hyperphosphorylation of tau and neuronal loss via cytokine release.<sup>95</sup> Thus, microglia display both defensive and protective functions, making their role in neurological conditions paradoxical and poorly understood. Microglial activation has been described in several rodent models after peripheral surgery and recently, in human subjects, and is associated with longer-lasting cognitive impairments.<sup>34</sup> Conventional histology is still the most common strategy for evaluating microglia in the CNS. Ionized calcium-binding adaptor molecule 1, a protein found on microglia and macrophages,<sup>96</sup> is a classic marker for morphological evaluation that has often been used in

perioperative neurocognitive disorder models. However, recent advancements in technology are revolutionizing our understanding of neuroinflammation in health and disease. Cell sequencing and multiomics approaches are now revealing unique phenotypes and functions of these cells during normal aging and neurodegeneration that go beyond morphological changes and immunostaining.<sup>97–99</sup> Evaluation of microglia across discrete brain regions in mice has revealed selective regional sensitivity to neuroinflammation.<sup>100</sup> Further, microglia isolated from different brain regions respond differently to challenges, possibly the reason that neurological disorders affect specific areas and cell populations.<sup>101,102</sup> To date, a large number of studies interrogating perioperative neurocognitive disorder in rodent models have focused on the hippocampus, given its essential role in learning and memory. Within this larger framework, studies that evaluate multiple brain regions may reveal different response profiles for microglia, and possibly other cell types, related to surgery and anesthesia. Other technologies have been implemented with direct implications to neuroimmunology. Tissue clarification allows investigators to evaluate complex structures in intact specimens, including the brain.<sup>103,104</sup> CLARITY is offering novel insights into 3D imaging.<sup>105–107</sup> This pioneering technique preserves cellular integrity while rendering tissues visually transparent for deeper optical imaging. Our own work using CLARITY is providing ways to evaluate changes in microglial morphology after surgery and to further evaluate their relationship

with other cell types including endothelial cells, neurons, and astrocytes. Indeed, microglia can induce astrocyte activation, which leads to neuronal death and toxicity.<sup>108</sup> Astrocytes are also activated postoperatively in perioperative neurocognitive disorder models of major surgery (eg, liver surgery).<sup>109</sup> Tibial fracture induces morphological and functional changes in astrocytes<sup>110,111</sup> that contribute to the disruption of neuroglial metabolic coupling and subsequent neuronal dysfunction. Complement activation, in particular C3 and C3R, is increased in microglia and astrocytes after orthopedic surgery thereby contributing to synaptic loss and hippocampal inflammation.<sup>112</sup> Similar mechanisms involved in synaptic pruning during development were described by Stevens et al,<sup>113</sup> and were found to be hijacked in Alzheimer's disease.<sup>114</sup> Defining the role of complement signaling and mechanisms of communication between glia and neurons in perioperative neurocognitive disorder will require extensive studies.

The role of inflammation in perioperative brain function is becoming apparent (Figure). Although this is a necessary response to tissue trauma, defective resolution and nonresolving inflammation are now appreciated as key contributors to chronic and maladaptive states.<sup>61</sup> In perioperative neurocognitive disorder, we are beginning to understand that "fine-tuning" of immune signaling may be a way forward to limit secondary CNS damage. Broad approaches that block inflammation, for example, treating with dexamethasone or statins, yield limited results in clinical trials.<sup>115,116</sup> Harnessing endogenous pathways and mediators, such as cholinergic signaling and lipids biosynthesized from omega-3 fatty acids, may provide unique opportunities to curtail inflammation after surgery without causing unwanted side effects.<sup>117</sup> In particular, omega-3 fatty acids are important catalysts in the synthesis of potent specialized proresolving mediators,<sup>61</sup> which can exert proresolving and anti-inflammatory actions after surgery and several other conditions (reviewed in Ref. <sup>118</sup>).<sup>110,119</sup> Alternative approaches to regulate immunity at a neuronal level are also under development. The cholinergic anti-inflammatory reflex is one of the exemplary circuits that can regulate inflammation by stimulating the vagus nerve.<sup>53,120,121</sup> The establishment of bioelectronic approaches is already able to reduce inflammation in rheumatoid arthritis patients,<sup>122</sup> and may be effective in treating neuroinflammation although further research is needed.

The human brain is the source of all human thought, and also the target of many neurological disorders. These disorders can cause disturbances in behavior, cognition, and emotions that can sometimes even interfere with the essence of who we are as human beings. We have an opportunity to protect our brain, at least within the perioperative space, and preserve its fundamental functions including our capacity to reason. René Descartes' classic line from 1637 could not be more relevant for today's research in neuroprotection: *Cogito, ergo sum*. ■■

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#### DISCLOSURES

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