Review Article

The Role of Inflammation in Postoperative Cognitive Dysfunction

Guo-Xun Xu[1,2], Ting Yang[1], and Niccolò Terrando[1]

ABSTRACT

Aim of review: Postoperative cognitive dysfunction (POCD) is a common complication following surgery, especially in the elderly population. Surgery exposes patients to extensive trauma, blood loss, and tissue injury, all of which contribute to an inflammatory response. In recent years, inflammation has been shown to be a key contributor to the pathogenesis of cognitive decline and neuroinflammatory processes, both in animal models and initial clinical observations.

Method: We review the recent literatures on the proposed mechanisms whereby peripheral trauma leads to cognitive impairments and some of the new neuroprotective strategies that may be implemented to prevent neuroinflammation and POCD.

Recent findings: Changes in pro-inflammatory cytokines, alarmins, macrophage activation and blood-brain barrier (BBB) dysfunction have been proven to be related to the pathogenesis of cognitive decline using a variety of models, reagents, and technologies. Strategies to harness these pathways through anti-inflammatory and pro-resolving strategies show remarkable effects in modulating neuronal function, synaptic plasticity, glia activity and memory processes.

Summary: Further studies are needed to better identify the patients at higher risk for cognitive decline in the postoperative period and which interventions may be suitable for translation and new clinical trials.

From the [1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; [2]Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, China.

Correspondence to Dr. Niccolò Terrando at niccolo.terrando@ki.se.

Cognitive disorders, encompassing changes in acute mental status and prolonged cognitive impairments, are often seen following hospitalization and largely contribute to functional impairment worldwide, especially with a steady increase in the geriatric population (1, 2). Much progress in the field of postoperative cognitive decline has happened over the last decade, with several studies contributing to a better understanding on the pathogenesis of this phenomenon at both the preclinical and clinical levels.

Overview on Postoperative Cognitive Dysfunctions

The initial observation that memory and learning disabilities may occur following surgery and anesthesia has long been known, as referred to as "insanity" by George Savage in 1887. We can now divide the field of postoperative cognitive decline into two main categories: postoperative delirium (POD) and longer-term postoperative cognitive dysfunction (POCD) (3). Delirium is a more evident and severe form of cognitive failure that meets defined criteria in the *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*). POD affects up to 50% of elderly patients, costing more than US $164 billion per year in the USA and over $182 billion per year in EU (4). POCD is a more subtle dysfunction affecting one or more cognitive domains following surgery and anes-

thesia, including short and long-term memory, attention, concentration, mood, language comprehension, abstract thinking, executive functioning, social integration, and orientation (5).

Despite no standardized diagnostic criteria, POCD has become an apparent complication in the perioperative care setting, especially amongst elderly patients. Both POD and POCD are associated with poorer outcome in the patients, including higher mortality, more comorbidities, increased length of hospitalization, possible permanent dementia, and severely affected overall quality of life (6).

In 1998, a seminal paper from the International multicenter study on POCD (ISPOCD) reported an incidence of cognitive impairments of 25% at 1 week and 9.9% at 3 months after noncardiac surgery (7). The study also identified risk factors, including advanced age, occurrence of postoperative infections and exposure to multiple operations as key contributors to the prolonged cognitive deficits. The association between advanced age and surgical procedure has been established by several studies thereafter, with overall incidences of POCD ranging from 12.7% (8) up to 46.1% after 1 year (9, 10).

Apart from noncardiac surgery, especially orthopedic surgery, POCD is a frequent complication of cardiac procedures (11). Long-term cognitive dysfunctions in patients after coronary artery bypass grafting (CABG) are common, with incidence up to 42% at five years after hospital discharge (12). Ablation for atrial fibrillation (AF) is also associated with a 13% to 20% prevalence of POCD in patients with AF at long-term follow-up (13). Cerebral micro-emboli caused by the cardiac procedures were initially considered to lead to brain injury and neuropsychological deficits, however, the observation from high-intensity transient signals (HITS) in transcranial Doppler recordings showed no evident correlation between cerebral micro-emboli and POCD (14, 15).

The mechanisms whereby surgical procedures and general anesthesia contribute to cognitive decline are currently poorly understood. Anesthetics may be responsible for modifications in the body that outlast their elimination, suggesting a possible role for anesthesia per se in modulating memory function (16). Anesthetics "cocktails", in-

cluding ketamine, nitrous oxide, propofol, midazolam, barbiturates, and isoflurane have been found to be associated with markers of neuro-apoptosis and long-term cognitive impairments in the developing and adult brain (17, 18). Hallmarks of neurodegenerative processes such as beta-amyloid (Aβ) aggregation and tau protein phosphorylation have been detected to be related to anesthesia exposure, suggesting that some anesthetic agents may increase the risk of Alzheimer's disease (AD) in vulnerable individuals (19, 20). Recently, markers of AD have been found to be altered after anesthesia and surgery, highlighting the possible role of cerebrospinal fluid (CSF) biomarkers in predicting POCD in different surgical settings (21-23). In a randomized study from the ISPOCD study group, no significant difference was found in the incidence of cognitive dysfunction at 3 months after either general or regional anesthesia (24). To date, the role of anesthesia and other factors contributing to POCD remain controversial due to underpowered studies with several methodological limitations (25).

To overcome some of these problems, animal models have been introduced in order to better understand the multifactorial origin of cognitive decline following surgery, anesthesia and comorbidities. This review will focus on the growing evidence highlighting a role of inflammation, as caused by surgical trauma, in the pathogenesis of cognitive decline. In this setting, we will discuss the mechanisms whereby pro-inflammatory mediators affect the brain and how novel neuroprotective strategies may be implemented in the clinic to possibly limit the occurrence of postoperative cognitive complications.

Surgery, Neuroinflammation and POCD

Inflammation is an evolutionary conserved critical response to any type of injury, for example infection or trauma, and is necessary to restore function in a tissue or organ (26). Release of soluble mediators, including pro-inflammatory cytokines, chemokines and oxidative stress may however impact on remote organs including the central nervous system (CNS) overall contributing to "sickness behaviour", whose symptoms include fever, decreased food intake, somnolence, hyperalgesia, and general fatigue (27). Accumu-

lating evidence from animal models and clinical studies suggests a key role of surgical trauma in modulating the brain and CNS function, leading to cognitive decline, neuroinflammation and neurodegeneration (28-34). Some of the most recent proposed mechanisms in the pathogenesis of POCD are discussed herein:

Systemic Cytokines and Immune-to-Brain Signaling

Surgical procedures expose the patients to significant damages (i.e. blood loss, tissue trauma, bone reamings, device implanting, ischemia-reperfusion injury etc.) that contribute to inflammation. This ensuing sterile inflammatory response is clinically similar to sepsis, even though not mediated by infective agents (35). Sterile inflammation may actually activate similar downstream signaling pathways as pathogens, for example through release of damage-associated molecular patterns (DAMPs) and cytokines. These soluble mediators trigger a systemic inflammatory response through the activation of different pattern recognition receptors (PRRs), including toll-like receptors (TLRs), cytokine receptors interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α and oxidative stress pathways (36).

Animal models of perioperative cognitive decline have been studied to assess the causal relationship between soluble mediators including TNF-α (29), IL-1β (28, 32, 37), IL-6 (38), high mobility group box-1 (HMGB-1) (39, 40) and memory dysfunction after surgery and critical illness. In a recent meta-analysis, Peng et al. showed that POCD was correlated with the concentrations of systemic inflammatory markers, with IL-6 and S-100β as highly predictive biomarkers (41). Notably, changes in systemic pro-inflammatory cytokines are also found in human samples and some of these soluble mediators may serve as novel biomarkers to predict poor cognitive outcome in patients at risk (42-44).

Peripheral immune signals may reach the brain and cause neuroinflammation by activating a neuronal, cellular and humoral response (Figure 1) (45).

Nerve conduction, for example via afferent vagal projections to the brainstem, represents a fast processor that sense peripheral inflammatory molecules and conveys information directly
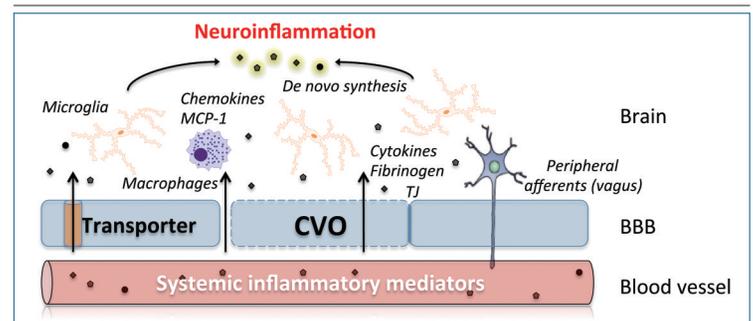

Figure 1. Immune-to-Brain Signaling after Surgery.
Surgery induces changes in brain cytokines, including transcription and translation in selective regions such as hippocampus. From the periphery, cytokines and other pro-inflammatory mediators can penetrate the brain via the circumventricular organs (CVOs) and choroid plexus, which lack a patent BBB. Cytokines, chemokines and matrix metalloproteinases (MMPs) can directly disrupt the barrier by affecting tight junctions (TJs) integrity and allowing blood-derived molecules like fibrinogen and monocytes-derived macrophages to enter the brain parenchyma. Through more regulated processes, cytokines can be actively transported across the brain endothelium, thus gaining access to the CNS and contributing to microglia activation and de-novo synthesis of other cytokines. At last, peripheral afferents such as the vagus nerve bypass the BBB interface and signal to brain physiological and inflammatory changes due to systemic injury.

to the brain (46). Activation of the inflammatory reflex limits ongoing systemic inflammatory processes by modulation of alpha7 nicotinic acetylcholine receptor (nAChR) signaling and suppression of nuclear factor (NF)-κB in bone marrow-derived cells (47). A key role of cholinergic signaling has been proposed in POD (48) and recent evidence from animal models suggests an involvement of neuronal signaling and the inflammatory reflex in preventing neuroinflammation and cognitive decline (30, 49).

The brain has been historically considered an immuno-privileged organ given the presence of the blood brain barrier (BBB) but the systemic pro-inflammatory milieu can negatively impair its function by direct proteolytic actions on the tight junctions (TJs), thus allowing more of these molecules and peripheral cells to enter the brain (50). It is now established that peripheral injury increases levels of cytokines including TNF-α, IL-1β, IL-6, S-100β and these molecules can exert effects on the BBB, alone or in combination. TNF-α is rapidly released after orthopedic surgery and is a strong inducer of endothelia dysfunction and BBB opening (29). IL-1β exposure induces endo-

thelial barrier dysfunction through activation of protein kinase C (PKC), phosphorylation of zona-occludens (ZO)-1, and downregulation of claudins (51, 52). Peripheral cytokines, including alarmins like HMGB-1, mediate and facilitate the migration of macrophages into the brain parenchyma through activation of TNF-α/NF-κB signaling pathway and impairing BBB function, which may consequently affect memory and cognitive function (30, 53). HMGB-1 has recently been shown to be associated with BBB dysfunction after abdominal surgery and its effect on macrophages have been proven to be related to the processes of surgery-induced cognitive decline and long-term neurocognitive function after sepsis (39, 40, 54). Aside from a direct effect of pro-inflammatory cytokines on the endothelium, comorbidities including advanced age, systemic diseases, and infections can further impact on the BBB integrity and permeability (55). Drugs, including anesthetic agents, and toxins accumulation due to decreased efflux through permeability glycoprotein (P-gp), basement membrane disruption, and decreased nutrient transport may also contribute to BBB damage (55).

Overall, impairments to the neurovascular unit result in disrupted CNS microenvironment, with systemic molecules including fibrinogen, cytokines, and alarmins contributing to neuronal damage and neuroinflammation (56). Yet, the crosstalk between systemic inflammation, endothelial function and neuroinflammation remains unclear and further studies are needed to understand how immune-to-brain signaling can be effectively modulated after surgery.

Neuroinflammation and CNS Function

The transduction of peripheral inflammation into the brain results in neuroinflammation, a process that affects glia function and overall neuronal homeostasis (57). Microglia activation is a hallmark of brain pathology. These cells are responsible to actively sense changes in brain homeostasis, for example the presence of inflammatory molecules, becoming reactive and mounting macrophage-type innate immunity within the CNS (58). Microglia have been referred to as a "double-edged sword": they can not only exert protective function by releasing neurotrophic and anti-inflammatory molecules

but also contribute to a pro-inflammatory milieu, de novo cytokine production, and neurodegenerative processes once activated (59). It is well established that several substances can activate microglial cells, for instance, lipopolysaccharide (LPS), Aβ, interferon (IFN)-γ, ATP and some pro-inflammatory cytokines (60). Centrally released cytokines, including TNF-α, IL-1β, and IL-6, have also been implicated in processes of synaptic formation and scaling, long-term potentiation (LTP), and neurogenesis (61). Recent studies have highlighted some of the possible mechanisms whereby surgery and the ensuing inflammatory response contribute to cognitive decline, including changes in synaptic plasticity (62, 63), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking (64), and N-methyl-D-aspartate receptor (NMDA) subtype 2B (NR2B) expression (65).

Although many studies reported microglia activation after surgery and anesthesia exposure, especially in older animals, the exact role of microglia in the pathogenesis of POCD remains elusive and no evidence of neuroinflammation in humans exists. Recently, monocytes and macrophages have been found in the brain parenchyma after peripheral surgery, suggesting a possible role for these cells in mediating the neuroinflammatory response (30, 53). Similar neuropathology with macrophage infiltration and defective phagocytosis has been highlighted in the brain of AD patients (66) and this may be mediated by changes in BBB permeability during the neurodegenerative process (67). Changes in BBB permeability and function have been reported in several models of surgery-induced cognitive decline, including orthopedic (30), cardiac (68) and abdominal (54) surgery-induced cognitive decline, suggesting a role of endothelial and other glia cells contributing to cognitive decline.

As key cellular components of the BBB, astrocytes have been found to be related to several neurological conditions. Astrogliosis is characterized by cellular hypertrophy and hyperplasticity, accompanying an elevation of expression of markers like glial fibrillary acidic protein (GFAP) and S100β (69). Disrupted BBB can affect astrocytes function leading to astrogliosis and perturbing neuronal homeostasis (70). Furthermore, mitochondria in astrocytes directly

participates in the metabolic changes associated with astrogliosis and neuroinflammation via iN-OS-mediated NO production and subsequent dynamin-related protein 1 (Drp1) activation (71). TNF-α, IL-1, IL-6, IFN-γ, bone morphogenetic proteins (BMPs) and Notch signaling molecules are all potent activators of astrogliosis and activated astrocytes subsequently release comprehensive cytokine and chemokine secretome [e.g., IL-1β, TNF-α, monocyte chemotactic protein-1 (MCP1)], which closely link to NF-κB activation and might affect short-term memory processes at the synapses (72-74). Overall, it is evident that POCD is a classic multifactorial condition with many factors contributing to the memory dysfunction and several targets being affected both systemically and centrally (Figure 2).

Neuroprotective Strategies and Future Directions

Neuroinflammation has become the hallmark of cognitive decline and several neurodegenerative processes (75). Significant efforts have been devoted to define strategies to limit, and possibly prevent, neuroinflammation and ensuing cognitive decline after trauma. Anti-inflammatory therapies have shown promising effects in limiting memory decline after surgery in several preclinical models. Targeting of the systemic pro-inflammatory milieu with selective antibody strategies or general anti-inflammatories has provided insights on how trauma contributes to POCD pathophysiology.

Release of pro-inflammatory cytokines and alarmins is a timely event with defined kinetic and resolution indices (76). Pre-emptive targeting of early-released cytokines like TNF-α, HMGB-1, and IL-1β limit the perpetuation of the inflammatory cascade and protect the CNS from neuroinflammation and cognitive decline (28-30, 39). Administration of broadly used anti-inflammatory agents including minocycline (77), non-steroidal anti-inflammatory drugs (NSAIDs) and more selective cyclooxygenase (COX) inhibitors (78, 79) have shown beneficial effects in preventing microglia activation and memory decline. Antioxidants may also attenuate some of the processes associated with cognitive decline (80), including tissue damage and apoptosis resulting from ischemia-reperfusion injury (81). It
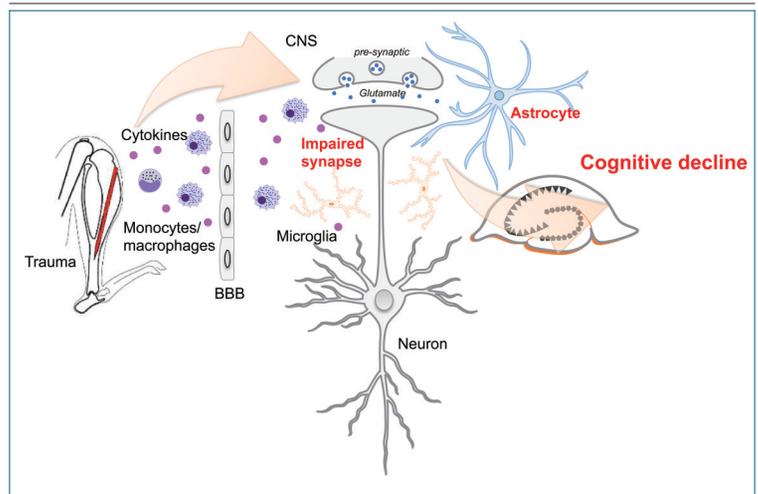

Figure 2. Proposed Mechanisms for Neuroinflammation and POCD.
Surgery has been shown to engage the innate immune system and activate a cascade of pro-inflammatory mediators, including alarmins, cytokines and eicosanoids. These molecules exert effects on the humoral and neuronal signaling overall contributing to the neuroinflammatory response. These processes are mediated not only by activation of resident microglia but also by infiltration of peripheral cells into the brain parenchyma via a disrupted BBB. This pro-inflammatory milieu and glia dysfunction impair neuronal activity and synaptic plasticity, impinging on processes of long-term potentiation, neurotransmission, and receptor function at the synapse. In combination, these pathological hallmarks contribute to learning and memory impairments following surgical trauma.

has become apparent that cytokines are necessary and sufficient for disease pathogenesis (82) and inflammation in POCD has gained more attention both from preclinical mechanistic studies and clinical researches. Endogenous control of inflammatory process is therefore of considerable interest to modulate cognitive dysfunction and unresolved inflammation (83).

Resolution of inflammation is now regarded as an active process involving a class of specialized pro-resolving lipid mediators (SPM), which exert potent stereoselective actions during acute inflammation and restore homeostasis (84, 85). Resolvins, protectins and maresins are three families of SPM biosynthesized from omega-3 essential eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that display evident anti-inflammatory and pro-resolving effects (86). Omega-3 supplementation has been shown to increase SPM production in the blood (87, 88), demonstrating the presence of these mediators in human samples. Recently, resolvins like AT-

RvD1 have been tested in POCD with remarkable neuroprotective effects on synaptic plasticity, memory function and neuroinflammation when administered systemically at very low doses (62). Neuroprotective strategies using SPM have also been established in different neurological models ranging from stroke (89), neurodegenerative processes (90), inflammatory pain (91), infection-mediated neuroinflammation (92) to spinal cord injury (93). Thus endogenous lipid mediators are likely to play key roles in modulating innate inflammatory response and may provide novel insights in developing effective strategies in preventing and treating POCD.

Different agents of relevance to the perioperative care setting and ageing population may also be used to effectively jumpstart resolution. Atorvastatin and pitavastatin reduce the levels of oxidative stress and activation of cytokines in the CNS (94). These drugs also protect synaptic networks and prevent subsequent worsening of cognitive function (95-97). Statins may also redirect microglial activation and promote an anti-inflammatory phenotype, thereby reducing the clinical occurrence of delirium and attenuating neuroinflammation (98). In line with these mechanisms, preoperative administration of statins has been associated with the reduced risk of postoperative delirium after cardiac surgery with cardiopulmonary bypass, and ongoing statin therapy is associated with a lower daily risk of delirium in critically ill patients (99, 100). Although some clinical evidence supports the use of statins in reducing cognitive impairment, double-blind randomized placebo-controlled clinical trials are required to validate these findings.

Recently, a crosstalk between SPM and the in-flammatory reflex has been shown (101) and stimulation of the cholinergic anti-inflammatory pathway through activation of alpha7 nAChR significantly attenuated macrophage infiltration in the CNS after surgery, increasing production of anti-inflammatory cytokines like IL-10 (30). To modify the pro/anti-inflammatory balance, anesthetic agents including isoflurane may contribute to resolution of inflammation (102) and noble gases like xenon effectively prevented surgery-induced memory dysfunction by modulating heat shock protein 72 (HSP72) expression in the hippocampus (97).

Overall, modulation of pro-resolving processes after surgery may offer a safe and effective treatment to prevent postoperative cognitive dysfunctions in our patients, but it remains of paramount importance to further develop better tools to predict POCD in patients at risk, including validated blood/CSF biomarkers, neuroimaging (fMRI, PET) and omic-tools (lipidomic, metabolomic) to add on standardized neuropsychological assessment. These approaches are becoming more mature amongst the neurodegenerative field, with blood tests acquiring more validity in detecting preclinical AD in patients (103). Similarly, in the perioperative care it will be necessary to spearhead novel preclinical investigations and large multicenter clinical studies in order to better understand and treat postoperative cognitive disorders.

References

1. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA 2010; 303: 763-70.
2. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012; 367: 30-9.
3. Terrando N, Brzezinski M, Degos V, Eriksson LI, Kramer JH, Leung JM, et al. Perioperative cognitive decline in the ageing population. Mayo Clin Proc 2011; 86: 885-93.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014; 383: 911-22.
5. Monk TG, Price CC. Postoperative cognitive disorders. Curr Opin Crit Care 2011; 17: 376-81.
6. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110: 548-55.
7. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351: 857-61.
8. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108: 18-30.
9. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010; 112: 852-9.
10. Scott JE, Mathias JL, Kneebone AC. Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: a meta-analysis. J Arthroplasty 2014; 29: 261-7.e1.
11. McDonagh DL, Berger M, Mathew JP, Graffagnino C, Milano CA, Newman MF. Neurological complications of cardiac surgery. Lancet Neurol 2014; 13: 490-502.
12. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344: 395-402.
13. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol 2013; 62: 531-9.
14. Rodriguez RA, Rubens FD, Wozny D, Nathan HJ. Cerebral emboli detected by transcranial Doppler during cardiopulmonary bypass are not correlated with postoperative cognitive deficits. Stroke 2010; 41: 2229-35.
15. Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, et al. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesth Analg 2009; 109: 1013-22.
16. Culley DJ, Baxter MG, Yukhananov R, Crosby G. Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. Anesthesiology 2004; 100(2): 309-14.
17. Stratmann G. Review article: Neurotoxicity of anesthetic drugs in the developing brain. Anesth Analg 2011; 113: 1170-9.
18. Xie Z, Tanzi RE. Alzheimer's disease and post-operative

cognitive dysfunction. Exp Gerontol 2006; 41: 346-59.
19. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, et al. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. Ann Neurol 2008; 64: 618-27.
20. Whittington RA, Virág L, Marcouiller F, Papon MA, El Khoury NB, Julien C, et al. Propofol directly increases tau phosphorylation. PLoS One 2011; 6: e16648.
21. Xie Z, Swain CA, Ward SA, Zheng H, Dong Y, Sunder N, et al. Preoperative cerebrospinal fluid β-Amyloid/Tau ratio and postoperative delirium. Ann Clin Transl Neurol 2014; 1: 319-28.
22. Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology 2011; 115: 727-32.
23. Xie Z, McAuliffe S, Swain CA, Ward SA, Crosby CA, Zheng H, et al. Cerebrospinal fluid abeta to tau ratio and postoperative cognitive change. Ann Surg 2013; 258(2): 364-9.
24. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47: 260-6.
25. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology 2007; 106: 572-90.
26. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454: 428-35.
27. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008; 9: 46-56.
28. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68: 360-8.
29. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A 2010; 107: 20518-22.
30. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol 2011; 70: 986-95.
31. Rosczyk HA, Sparkman NL, Johnson RW. Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol 2008; 43: 840-6.
32. Barrientos RM, Hein AM, Frank MG, Watkins LR, Maier SF. Intracisternal interleukin-1 receptor antagonist prevents postoperative cognitive decline and neuroinflammatory response in aged rats. J Neurosci 2012; 32: 14641-8.
33. Xu Z, Dong Y, Wang H, Culley DJ, Marcantonio ER, Crosby G, et al. Peripheral surgical wounding and age-dependent neuroinflammation in mice. PLoS One 2014; 9: e96752.
34. Tang JX, Mardini F, Janik LS, Garrity ST, Li RQ, Bachlani G, et al. Modulation of murine Alzheimer pathogenesis and behavior by surgery. Ann Surg 2013; 257: 439-48.
35. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464: 104-7.
36. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol 1994; 12: 991-1045.
37. Terrando N, Rei Fidalgo A, Vizcaychipi M, Cibelli M, Ma D, Monaco C, et al. The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. Crit Care 2010; 14: R88.
38. Yang J, Xin X, Zhang J, Zhang L, Dong Y, Zhang Y, et al. Inflammatory pain may induce cognitive impairment through an interleukin-6-dependent and postsynaptic density-95-associated mechanism. Anesth Analg 2014; 119: 471-80.
39. Vacas S, Degos V, Tracey KJ, Maze M. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. Anesthesiology 2014; 120: 1160-7.
40. Chavan SS, Huerta PT, Robbiati S, Valdes-Ferrer SI, Ochani M, Dancho M, et al. HMGB1 mediates cognitive impairment in sepsis survivors. Mol Med 2012; 18: 930-7.
41. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. PLoS One 2013; 8: e79624.
42. Lin GX, Wang T, Chen MH, Hu ZH, Ouyang W. Serum high-mobility group box 1 protein correlates with cognitive decline after gastrointestinal surgery. Acta Anaesthesiol Scand 2014; 58: 668-74.
43. Ji MH, Yuan HM, Zhang GF, Li XM, Dong L, Li WY, et al. Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery. J Anesth 2013; 27: 236-42.
44. Li YC, Xi CH, An YF, Dong WH, Zhou M. Perioperative inflammatory response and protein S-100beta concentrations-relationship with post-operative cognitive dysfunction in elderly patients. Acta Anaesthesiol Scand 2012; 56: 595-600.
45. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther 2011; 130: 226-38.
46. Tracey KJ. Reflex control of immunity. Nat Rev Immunol 2009; 9: 418-28.
47. Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. J Exp Med 2012; 209: 1057-68.

48. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 2010; 375: 773-5.
49. Kalb A, von Haefen C, Sifringer M, Tegethoff A, Paeschke N, Kostova M, et al. Acetylcholinesterase inhibitors reduce neuroinflammation and -degeneration in the cortex and hippocampus of a surgery stress rat model. PLoS One 2013; 8: e62679.
50. Daneman R. The blood-brain barrier in health and disease. Ann Neurol 2012; 72: 648-72.
51. Rigor RR, Beard RS Jr, Litovka OP, Yuan SY. Interleukin-1beta-induced barrier dysfunction is signaled through PKC-theta in human brain microvascular endothelium. Am J Physiol Cell Physiol 2012; 302: C1513-22.
52. Beard RS Jr, Haines RJ, Wu KY, Reynolds JJ, Davis SM, Elliott JE, et al. Non-muscle Mlck is required for beta-catenin- and FoxO1-dependent downregulation of Cldn5 in IL-1beta-mediated barrier dysfunction in brain endothelial cells. J Cell Sci 2014; 127: 1840-53.
53. Degos V, Vacas S, Han Z, van Rooijen N, Gressens P, Su H, et al. Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology 2013; 118: 527-36.
54. He HJ, Wang Y, Le Y, Duan KM, Yan XB, Liao Q, et al. Surgery upregulates high mobility group box-1 and disrupts the blood-brain barrier causing cognitive dysfunction in aged rats. CNS Neurosci Ther 2012; 18: 994-1002.
55. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA. The blood-brain barrier: geriatric relevance of a critical brain-body interface. J Am Geriatr Soc 2010; 58: 1749-57.
56. Ryu JK, Davalos D, Akassoglou K. Fibrinogen signal transduction in the nervous system. J Thromb Haemost 2009; 7 Suppl 1: 151-4.
57. Aloisi F, Ambrosini E, Columba-Cabezas S, Magliozzi R, Serafini B. Intracerebral regulation of immune responses. Ann Med 2001; 33: 510-5.
58. van Rossum D, Hanisch UK. Microglia. Metab Brain Dis 2004; 19: 393-411.
59. Mosher KI, Wyss-Coray T. Microglial dysfunction in brain aging and Alzheimer's disease. Biochem Pharmacol 2014; 88: 594-604.
60. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiol Rev 2011; 91: 461-553.
61. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. Front Behav Neurosci 2009; 3: 14.
62. Terrando N, Gómez-Galán M, Yang T, Carlström M, Gustavsson D, Harding RE, et al. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. FASEB J 2013; 27: 3564-71.
63. Vizcaychipi MP, Watts HR, O'Dea KP, Lloyd DG, Penn JW, Wan Y, et al. The therapeutic potential of atorvastatin in a mouse model of postoperative cognitive decline. Ann Surg 2014; 259: 1235-44.
64. Tan H, Cao J, Zhang J, Zuo Z. Critical role of inflammatory cytokines in impairing biochemical processes for learning and memory after surgery in rats. J Neuroinflammation 2014; 11: 93.
65. Zhang X, Xin X, Dong Y, Zhang Y, Yu B, Mao J, et al. Surgical incision-induced nociception causes cognitive impairment and reduction in synaptic NMDA receptor 2B in mice. J Neurosci 2013; 33: 17737-48.
66. Fiala M, Lin J, Ringman J, Kermani-Arab V, Tsao G, Patel A, et al. Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease patients. J Alzheimers Dis 2005; 7: 221-32.
67. Fiala M, Liu QN, Sayre J, Pop V, Brahmandam V, Graves MC, et al. Cyclooxygenase-2-positive macrophages infiltrate the Alzheimer's disease brain and damage the blood-brain barrier. Eur J Clin Invest 2002; 32: 360-71.
68. Bartels K, Ma Q, N Venkatraman T, R Campos C, Smith L, E Cannon R, et al. Effects of deep hypothermic circulatory arrest on the blood brain barrier in a cardiopulmonary bypass model - a pilot study. Heart Lung Circ 2014; 23: 981-4.
69. Alvarez JI, Katayama T, Prat A. Glial influence on the blood-brain barrier. Glia 2013; 61: 1939-58.
70. Zhang D, Hu X, Qian L, O'Callaghan JP, Hong JS. Astrogliosis in CNS pathologies: is there a role for microglia. Mol Neurobiol 2010; 41: 232-41.
71. Motori E, Puyal J, Toni N, Ghanem A, Angeloni C, Malaguti M, et al. Inflammation-induced alteration of astrocyte mitochondrial dynamics requires autophagy for mitochondrial network maintenance. Cell Metab 2013; 18: 844-59.
72. Gibbs ME, Hutchinson D, Hertz L. Astrocytic involvement in learning and memory consolidation. Neurosci Biobehav Rev 2008; 32: 927-44.
73. Choi SS, Lee HJ, Lim I, Satoh J, Kim SU. Human astrocytes: secretome profiles of cytokines and chemokines. PLoS One 2014; 9: e92325.
74. Hostenbach S, Cambron M, D'haeseleer M, Kooijman R, De Keyser J. Astrocyte loss and astrogliosis in neuroinflammatory disorders. Neurosci Lett 2014; 565: 39-41.
75. Eckenhoff RG, Laudansky KF. Anesthesia, surgery, illness and Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2013; 47: 162-6.
76. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008; 8: 349-61.

77. Kong F, Chen S, Cheng Y, Ma L, Lu H, Zhang H, et al. Minocycline attenuates cognitive impairment induced by isoflurane anesthesia in aged rats. PLoS One 2013; 8: e61385.
78. Griffin EW, Skelly DT, Murray CL, Cunningham C. Cyclooxygenase-1-dependent prostaglandins mediate susceptibility to systemic inflammation-induced acute cognitive dysfunction. J Neurosci 2013; 33: 15248-58.
79. Kamer AR, Galoyan SM, Haile M, Kline R, Boutajangout A, Li YS, et al. Meloxicam improves object recognition memory and modulates glial activation after splenectomy in mice. Eur J Anaesthesiol 2012; 29: 332-7.
80. Liu Y, Ni C, Tang Y, Tian X, Zhou Y, Qian M, et al. Melatonin attenuates isoflurane-induced acute memory impairments in aged rats. Basic Clin Pharmacol Toxicol 2013; 113: 215-20.
81. Xie W, Yang Y, Gu X, Zheng Y, Sun YE, Liang Y, et al. Senegenin attenuates hepatic ischemia-reperfusion induced cognitive dysfunction by increasing hippocampal NR2B expression in rats. PLoS One 2012;7: e45575.
82. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007; 117: 289-96.
83. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. Nat Rev Immunol 2013; 13: 59-66.
84. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014; 510: 92-101.
85. Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: agonists of resolution. Curr Opin Pharmacol 2013; 13: 632-40.
86. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, Mirick G, et al. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med 2002; 196: 1025-37.
87. Mas E, Croft KD, Zahra P, Barden A, Mori TA. Resolvins D1, D2, and other mediators of self-limited resolution of inflammation in human blood following n-3 fatty acid supplementation. Clin Chem 2012; 58: 1476-84.
88. Colas RA, Shinohara M, Dalli J, Chiang N, Serhan CN. Identification and signature profiles for pro-resolving and inflammatory lipid mediators in human tissue. Am J Physiol Cell Physiol 2014; 307: C39-54.
89. Marcheselli VL, Hong S, Lukiw WJ, Tian XH, Gronert K, Musto A, et al. Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J Biol Chem 2003; 278: 43807-17.
90. Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, et al. 1α,25-dihydroxyvitamin D3 and resolvin D1 retune the balance between amyloid-β phagocytosis and inflammation in Alzheimer's disease patients. J Alzheimers Dis 2013; 34: 155-70.
91. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, et al. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. Nat Med 2010; 16: 592-7.
92. Orr SK, Palumbo S, Bosetti F, Mount HT, Kang JX, Greenwood CE, et al. Unesterified docosahexaenoic acid is protective in neuroinflammation. J Neurochem 2013; 127: 378-93.
93. Lim SN, Gladman SJ, Dyall SC, Patel U, Virani N, Kang JX, et al. Transgenic mice with high endogenous omega-3 fatty acids are protected from spinal cord injury. Neurobiol Dis 2013; 51: 104-12.
94. Kurata T, Miyazaki K, Morimoto N, Kawai H, Ohta Y, Ikeda Y, et al. Atorvastatin and pitavastatin reduce oxidative stress and improve IR/LDL-R signals in Alzheimer's disease. Neurol Res 2013; 35: 193-205.
95. Kozuki M, Kurata T, Miyazaki K, Morimoto N, Ohta Y, Ikeda Y, et al. Atorvastatin and pitavastatin protect cerebellar Purkinje cells in AD model mice and preserve the cytokines MCP-1 and TNF-alpha. Brain Res 2011; 1388: 32-8.
96. Kurata T, Miyazaki K, Kozuki M, Panin VL, Morimoto N, Ohta Y, et al. Atorvastatin and pitavastatin improve cognitive function and reduce senile plaque and phosphorylated tau in aged APP mice. Brain Res 2011; 1371: 161-70.
97. Vizcaychipi MP, Lloyd DG, Wan Y, Palazzo MG, Maze M, Ma D. Xenon pretreatment may prevent early memory decline after isoflurane anesthesia and surgery in mice. PLoS One 2011; 6: e26394.
98. Morandi A, Hughes CG, Girard TD, McAuley DF, Ely EW, Pandharipande PP. Statins and brain dysfunction: a hypothesis to reduce the burden of cognitive impairment in patients who are critically ill. Chest 2011; 140: 580-5.
99. Page VJ, Davis D, Zhao XB, Norton S, Casarin A, Brown T, et al. Statin use and risk of delirium in the critically ill. Am J Respir Crit Care Med 2014; 189: 666-73.
100. Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, et al. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology 2009; 110: 67-73.
101. Mirakaj V, Dalli J, Granja T, Rosenberger P, Serhan CN. Vagus nerve controls resolution and pro-resolving mediators of inflammation. J Exp Med 2014; 211: 1037-48.
102. Chiang N, Schwab JM, Fredman G, Kasuga K, Gelman S, Serhan CN. Anesthetics impact the resolution of inflammation. PLoS One 2008; 3: e1879.
103. Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH, et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med 2014; 20: 415-8.