# The neuroinflammatory response of postoperative cognitive decline

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**Background**: Aseptic surgical trauma provokes a homeostatic neuroinflammatory response to promote healing and protect the organism from further injury. When this response is dysregulated, harmful consequences can follow, including postoperative cognitive decline.

**Sources of data**: We performed a comprehensive search on PubMed related to postoperative cognitive dysfunction (POCD).

**Areas of agreement**: Although the precise pathogenic mechanisms for POCD remain unclear, certain risk factors are known.

**Areas of controversy**: The mechanisms that lead to exaggerated and persistent neuroinflammation and the best way to counteract it are still unknown.

**Areas for developing research**: It is imperative that we identify the underlying processes that increase the risk of cognitive decline in elderly surgical patients. In this review we explore non-resolution of inflammation as an underlying cause of developing exaggerated and persistent POCD. If interventions can be developed to promote resolution of neuroinflammation, the patient's postoperative recovery will be enhanced and long-term consequences can be prevented.

*Keywords:* neuroinflammation/cognitive decline/neurodegeneration/surgery, sleep

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# Introduction

Impairment of cognition after surgery is a disturbing reality. Postoperative delirium (POD) is characterized by inattention, disorganized thinking and altered level of consciousness with acute onset and fluctuating course. While some patients develop POD, others develop a later onset form of postoperative cognitive decline known as postoperative cognitive dysfunction (POCD).

It is estimated that POCD occurs in >10% of non-cardiac surgical patients[1] over 60 years old,[2] and is independently associated with poor short-term and long-term outcomes, including an increased risk of mortality.[3,4] Although several risk factors have been identified, the exact pathophysiology that underlies POCD remains undefined.

The thesis that neuroinflammation is a possible cause of POCD has recently been tested. Data from preclinical studies support the concept that inflammation is a possible pathogenic mechanism for postoperative cognitive dysfunction.[5−9] Increased expression of interleukins in mouse hippocampus following minor surgery was associated with cognitive decline,[5,10] corroborating the view that surgery-induced neuroinflammation can result in cognitive impairment. Surgical patients exhibit elevations of pro-inflammatory cytokines in both the central nervous system and the systemic circulation, the extent of which may relate to the degree of cognitive decline.[11,12] Assuming that neuroinflammatory changes noted postoperatively in rodents also occur in humans, reasons must be sought why POCD is a relatively infrequent clinical event ($\pm 10\%$) whereas neuroinflammation always occurs. Among the possibilities include the fact that the neuroinflammatory changes are usually evanescent and do not normally cause a long-lasting consequence in animal models. Several clinical conditions can transform the self-limiting postsurgical neuroinflammatory response into one that is persistent. The persistence in neuroinflammation may be due to dysfunction in the inflammation-resolving mechanism. Alternatively, a normal neuroinflammatory response to surgery may have long-lasting detrimental effects in settings of neurological pathology, whether clinically evident or not. In a recently completed prospective study, patients who had previously suffered a stroke were more at risk of POCD even though they had no neurological sequelae from the remote stroke event.[13,14] Epidemiologic studies have suggested that neurodegenerative disorders, such as Alzheimer's disease (AD), may be accelerated by surgery[15−18] and that exacerbates dementia in AD patients[19] while increasing the occurrence of dementia[20]. However, this relationship has recently been challenged[21].

This review considers the possible role of inflammation in the development of POCD in the setting of underlying systemic and neurologic diseases; it will also discuss future research possibilities that might help identify vulnerable patients with whom interventional strategies could be invoked.

## Clinical condition

Clinical studies distinguish POD from POCD. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[22] defines the standards necessary for a diagnosis of delirium. These include disturbance of consciousness, change in cognition, inattentiveness and a fluctuating time course. Clinically, this diagnosis is often made using the confusion assessment method (CAM), a simple four-question screening tool that has a sensitivity of 94% and a specificity of 89%. A variation known as the CAM-ICU is often used in the intensive care unit (ICU) setting and is useful in sedated or intubated patients. Diagnosis of delirium in the cases of dementia can also be accomplished with the appropriate tools.[23]

There are three subtypes of delirium: hyperactive (25%), hypoactive (50%) and mixed (25%). The hypoactive subtype is the most frequently missed and may actually be associated with greater mortality than the hyperactive subtype.[24] The incidence of POD is between 10 and 55% in postoperative patients, depending on the type of procedure the patient underwent, with a higher percentage in orthopedics compared with general surgery patients.[25] Additionally, the incidence of POD is significantly higher in elderly patients. It is estimated that up to 50% of elderly patients suffer from delirium after surgery.[26] Furthermore, over 40% of hospitalized patients with delirium suffer from psychotic features, including visual hallucinations. It typically manifests itself within 24–48 h postoperatively, with exacerbation of symptoms at night, perhaps due to circadian disturbances. The implications of POD are significant. It is associated with increased morbidity and a 1-year mortality that approaches 40%.[27] The estimated healthcare-associated costs related to delirium are astronomic. They made up nearly $7 billion of Medicare expenditures in 2004.[28]

Persistent cognitive decline is predominantly seen in the elderly[29] and is termed POCD. POCD is diagnosed by the International Society of Postoperative Cognitive Dysfunction as subtle deficits in one or more discrete domains of cognition, e.g. attention, concentration, executive function, verbal memory, visuospatial abstraction and psychomotor speed.[30] This condition typically develops over weeks to months, and is long-lasting. The diagnosis requires sensitive presurgical and

postsurgical neuropsychiatric testing.[31] As a consequence of this complication, patients can lose their employment or independence, which can seriously reduce their quality of life.[4,14,32]

An international multicenter study of POCD (ISPOCD) reported memory impairments in more than a quarter of the patients 1 week after non-cardiac surgery and in 10% after 3 months in patients older than 60 years. Follow-up studies have shown similar incidences with some reports describing cognitive decline persisting for up to 1 year after surgery. Both because the number of major surgical interventions (requiring anesthesia) exceeds 230 million worldwide[33] and because of the increasing prevalence of surgical interventions in patients >65 years old, this age group will become the largest segment of surgical patients by 2020.[34] If current rates hold steady, we can expect that millions of elderly patients will run the risk of developing POCD. This possibility raises the stakes considerably: not only on an individual level, but also on a societal scale.

# Risk factors

Studies have sought to identify factors that may contribute to POCD, some of which include surgery, anesthesia and patient-related factors.

## Non-modifiable patient factors

Patient-related risk factors include: advanced age,[1,2,14,35–42] education,[1,2,14,38,40,42] genetic polymorphism (apolipoprotein E4)[43–45] and several other comorbidities.

Advanced age is associated with infirmities, many of which can be successfully treated with surgery. Unfortunately, persistent cognitive impairments can develop as a side effect of these surgical procedures.[29] An increase in the aging population and improvements in anesthesia and surgery have led to increases in the number of elderly patients undergoing surgery. Therefore, it is likely that postoperative central nervous system dysfunction will become increasingly common.

## Systemic disease: metabolic syndrome

Roughly 25% of the 45 million surgical patients in the US have metabolic syndrome (MetaS),[46] though its precise definition and diagnostic criteria continue to evolve.[47] MetaS, comprising insulin resistance, visceral obesity, hypertension and dyslipidemia, increases the risk of

postoperative complications contributing to a significant higher mortality rate.[48–51] While each of the subphenotypes that define MetaS has a strong genetic component, lifestyle factors that contribute to this cluster of conditions include sedentary behavior and a diet with a high caloric content from saturated fats and/or simple carbohydrates.[52] Many complications of MetaS (including atherosclerosis) are inflammatory in nature and the pathologic metabolism in adipose stores may be the source of pro-inflammatory adipokines.[53] Conversely, with little adiponectin to attenuate activation of the transcription factor NF-κB in macrophages, expression of genes for pro-inflammatory cytokines is increased;[54] up-regulated NF-κB activity in morbid obesity can be rectified with adiponectin.[55] Roughly a quarter of the American adult population have MetaS; 50% of cardiac surgery patients are affected with MetaS.[56] Recent evidence indicates that patients suffering from MetaS may be particularly susceptible to POCD.[50,57]

## Neurologic disease

The two most common causes of dementia are vascular dementia and AD, although most cases of dementia have both types of pathology. Pre-operative cognitive impairment, such as mild cognitive impairment (possible prodrome for AD), may already exist in many elderly patients who incidentally present at surgery. Although perioperative cognitive decline and AD may share certain neuropathologic and biochemical mechanisms, there is no direct evidence linking the involvement of AD-type pathogenic mechanisms and POCD in humans and only weak epidemiological evidence associating surgery with onset of AD.[58] Epidemiological studies have suggested that neurodegenerative disorders, including AD, may be accelerated by surgery.[15] However, large retrospective studies have thus far not associated surgery or anesthesia with further dementia and AD.[21] Evidence from animal models suggests that inhaled anesthetic exposure increases pathology normally associated with AD, including increase in β-amyloid peptide and β-acting cleavage enzyme;[59] anesthesia-induced hypothermia increased tau hyperphosphorylation by decreasing phosphatase 2A activity.[60]

Symptomatic pre-operative neurologic diseases, including dementia and any disease of the central nervous system, are often considered exclusion criteria for POCD studies.[14] Interestingly, cerebral vascular accidents (without residual deficit) were associated with risk factors for POCD, suggesting for the first time that a pre-operative ischemic brain insult could influence the possibility of POCD. However, no causal link between pre-operative cerebral vascular accident and POCD has been established yet in experimental or human investigations.

Postoperative neurodegeneration, akin to AD, is observed in aged rats;[61] while inflammation-resolution mechanisms have not been investigated, it is known that these mechanisms decline with advancing age.[62,63] AD-type neurodegeneration is accelerated by neuroinflammation,[64] raising the possibility that failure to resolve neuroinflammation may provoke neurodegenerative changes that cause persistent cognitive decline. It is noteworthy that anesthesia alone, at higher concentrations and for more prolonged periods, has been reported to produce AD-like neurodegeneration although this has been challenged.[65–68]

## The anesthetized state

There are several risk factors directly related to anesthesia that may be involved in the pathogenesis of POCD. Intra-operative hypotension, hypoxia, embolism, medications and postoperative infections have all been described as risk factors for POCD. Although general anesthetics are capable of producing long-lasting cognitive dysfunction under certain circumstances,[69,70] the incidence of POCD is similar after regional and general anesthesia,[71] the reason why attention has been focused on the role of the surgical intervention itself in the genesis of this condition. Postoperative pain is a possible etiologic factor in POCD.[72] Epidural analgesia with local anesthetics and/or opioids may be better than parenteral analgesics for the control of postoperative pain and the prevention of early POCD.[73] Furthermore, patients who are prescribed postoperative oral analgesics experience less POCD compared with those receiving parenteral medication.[74] Even though studies have shown the potential benefit of intra-operative monitoring of anesthetic depth and cerebral oxygenation as a pragmatic intervention to reduce postoperative cognitive impairment,[75] this factor still remains a controversial issue as some studies have shown no relation between deeper states of anesthesia and the emergence of POCD.[76] In support of the latter position, a number of recent studies show that animals exposed to short-duration isoflurane do not develop memory impairment.[5]

## Sleep

Sleep is crucial for the repair of many types of injury and disease, especially with regard to the central nervous and immune systems; it also has anabolic, restorative properties that improve both neurocognitive and immune function. During non-rapid eye movement (NREM) sleep, slow-wave activity performs a homeostatic function

to reduce the strength of synapses that has been acquired during wakeful activity.[77] This synaptic homeostasis improves subsequent cognitive function by allowing new changes in synaptic strength. For example, both NREM and REM sleep are necessary for the consolidation of learning and memory while sleep deprivation results in cognitive dysfunction.[78]

Polysomnographic studies revealed extreme sleep disruption in ICU patients with decreases in total sleep-time, altered sleep architecture (predominance of stage 1 and 2 sleep, decreased or absent stage 3 NREM and REM sleep) and sleep fragmentation;[79,80] also, up to 50% of the total sleep-time occurred during daytime. Lack of sleep hygiene results in cognitive dysfunction,[81,82] contributes to delirium,[83] adversely affects immunity[84,85] and independently increases both morbidity and mortality.[86] Sleep disruption during hospital care has the potential to adversely impact on patients' outcome and also provides a direct financial cost with respect to the length of hospital stay and depletion of healthcare resources.

Preclinical studies have shown the detrimental effect of lack of sleep on cognition.[87] In addition, perioperative sleep deprivation induced significant neuroinflammatory changes.[88–90] The exact mechanism for the deleterious consequences of a 'double hit' (aseptic surgical trauma and sleep deprivation) is still poorly understood, though it has been shown to increase the expression of inflammatory cytokines in the brain.[88,89] Sedative practices have also shown to be a main causative factor for this disruption.[91,92]

Anesthetics have different action targets and ultimately different consequences. The pivotal work of the MENDs trial[92–94] indicated the benefits of a specific anesthetic agent, dexmedetomidine, in the outcome of ICU populations. α2 adrenergic agonists converge on sleep pathways within the brainstem, while those that act by modulating the $GABA_A$ receptor converge at the level of the hypothalamus. Several studies have now demonstrated the association between the use of benzodiazepine (BZD) and increased incidence[93] and duration[95] of delirium in ICU patients, although the relationship of the development and duration of delirium to sleep disruption has not yet been thoroughly ascertained. Acute withdrawal from long-term sedation with BZDs and opiate narcotics results in profound sleep disruption.[96] Thus, thoughtful attention must be paid in selecting an anesthetic agent that best mimics natural sleep in order to decrease the decline of cognitive function. These efforts have to be maintained for the entire perioperative period.

# Neuroinflammatory response to surgery

Activation of the immune system after surgery is associated with cognitive decline.[5,7] Tissue trauma releases damage-associated molecular patterns (DAMPs) that are recognized by pattern recognition receptors (PRRs), which then trigger an immune response in a manner remarkably similar to that of microbial-derived pathogen-associated molecular patterns (PAMPs).[97–99] Among PRRs, Toll-like receptors (TLRs) are of critical importance, recognizing various ligands (including PAMPs and DAMPs) and activating TLR signals along different pathways, thereby increasing the synthesis and release of pro-inflammatory mediators. Although the function of TLR4 during lipopolysaccharide (LPS) endotoxemia[100] has been deeply explored, the pathways of infection-mediated neuroinflammation and cognitive decline seem to be distinct from that of aseptic surgical trauma.[7] One of the most important DAMPs (released from dead or dying cells through non-apoptotic processes[101]) is high-mobility group box 1 (HMGB1). HMGB1 can bind and signal through a family of PRRs that are evolutionarily conserved.[102] Clinical conditions such as sepsis, arthritis and stroke all release massive amounts of HMGB1.[103] Both DAMPs and PAMPs converge on NF-κB to increase synthesis and release of pro-inflammatory cytokines,[104] including TNF-α, which disrupt blood brain barrier (BBB) integrity.[5,7,8,105] Early activation of the innate immunity through DAMPs (HMGB1 and cytokines) will introduce the initial response to surgery resulting in neuroinflammation and concomitant cognitive decline.[7]

Following injury, this 'transient' inflammation is a necessary tissue repair process that promotes healing. Macrophages are highly heterogeneous hematopoietic cells found in nearly every tissue in the body and have been defined as the sentinels of the innate immune system. They are also key players in the resolution of inflammation and are critical to tissue repair, wound healing and restoration of homeostasis.[106] In addition, macrophages are responsible for sensing, integrating and appropriately responding to a bewildering array of stimuli from its local microenvironment. Macrophage responses are mediated through two distinct and mutually exclusive activation programs, termed classical (or M1) and alternative (or M2).[107] These activation programs were initially defined by their antimicrobial activities; classical activation occurs in response to bacterial infections and results in highly inflammatory macrophages with high phagocytic and bactericidal potential.[107] In contrast, alternative activation occurs in response to parasitic infections and promotes antiparasitic functionalities as well as those involved in tissue repair and remodeling.[108] Both programs promote differentiation of neighboring macrophages to their same activation state and potently inhibit maturation of the other.

Neuroinflammation after surgery is likely to include a pro-inflammatory phase and an anti-inflammatory phase (neural and humoral pathways mediate the switch between these two phases).[109,110] With respect to the humoral factors, resolvins, lipoxins and maresins (*ma*crophage mediators in *res*olving *in*flammation), derived from polyunsaturated fatty acids (PUFAs), are novel lipid mediators that promote the resolution of inflammation. Protective actions of D-series resolvins have been observed in both acute and chronic inflammatory diseases, such as peritonitis, ischemia/reperfusion injury and sepsis. Resolvins both limit PMN infiltration and enhance macrophage phagocytosis by transducing signaling mechanisms that originate at specific receptors on human PMN, monocytes and macrophages. Lipoxins were the first mediators recognized to have both anti-inflammatory and pro-resolving actions.[111] Maresins are newly identified macrophage mediators with the same properties.[112] They are capable of dampening the pro-inflammatory response by inhibiting macrophage NF-κB activity and polarizing macrophages into an M2 phenotype.[113–115] Dietary supplementation with PUFAs in patients with MetaS corrects many of the metabolic derangements[116] as well as the pro-inflammatory markers.[117] Regarding the resolving inflammatory state mediated by neural factors, DAMPs activate the efferent arc of the inflammatory reflex via NF-κB, termed the cholinergic anti-inflammatory pathway. At its splenic nerve terminus, vagal outflow releases adrenergic agonists (rather than the usual cholinergic neurotransmitter); these catecholamines activate $\beta_2$ adrenergic receptors on CD3 T lymphocytes that are capable of synthesizing and releasing acetylcholine needed to mediate inhibition of macrophage NF-κB activity by signaling through the α7 subtype of nicotinic acetylcholine receptors (α7 nAChR). Ultimately, it inhibits synthesis and release of pro-inflammatory cytokines from circulating immunocompetent cells.[104,118,119]

The neural cholinergic reflex is very important in resolving the inflammatory pathogenesis of several diseases including sepsis,[120] rheumatoid arthritis[121] and colitis.[122]

Furthermore, the cholinergic anti-inflammatory pathway also modulates the function of T regulatory cells,[123] which influences the production of anti-inflammatory cytokines (IL-10 and IL-4)[124] and alternative macrophage activation that promotes the resolution of inflammation.[125] IL-4 is the cytokine responsible for polarizing macrophage from the pro-inflammatory classically activating (M1) to the reparative alternatively activating (M2) phenotype. In the mouse models of type II diabetes, there is a relative lack of T regulatory cells and an imbalance of M1/M2 macrophages, which might contribute to persistent low-grade inflammation.[126] Abnormalities of the switching mechanism may cause a non-resolving chronic inflammatory state that could create the

circumstances for persistent cognitive decline. Recently, it has been shown that MetaS will contribute to exaggerated and persistent POD in a rat model of tibial fracture.[127] In addition, dysfunctional resolution of inflammation was found to be associated with behavioral deficits after surgery in metabolic syndrome rats.[128] However, the detailed mechanisms are still unclear and more research is warranted.

Studies have shown the importance of this reflex for resolving DAMP-induced neuroinflammation, pro-inflammatory cytokine release, neuroinflammation and cognitive decline; stimulating the α7 nAChR in macrophages, inhibited NF-κB activity which in the quiescent state precludes postoperative memory impairment by preventing monocyte migration into the hippocampus.[129] Drugs used clinically in the perioperative period, including anesthetics, exert anti-cholinergic activity that may translate into non-resolution of inflammation and PCD in the form of delirium.[130] Advanced age is associated with decline in cholinergic function, which may be relevant in explaining the high prevalence of POCD in elderly patients.

When inflammation does not subside, it can contribute to the pathogenesis of diseases.[106] Through a permeable BBB, CCR2-expressing bone marrow-derived macrophages (BM-DM) are attracted, by the newly expressed chemokine, MCP-1, into the brain parenchyma. The macrophages synthesize and release a variety of pro-inflammatory cytokines that interfere with processes required for memory. Macrophage-specific Ikappa B kinase (IKK)$\beta$ coordinates activation of NF-κB; when it is deleted, it prevents BBB disruption and BM-DM infiltration into the hippocampus following surgery.[129] Transgenic mice that overexpress Hsp72 and inhibit NF-κB activity have attenuation of postoperative neuroinflammation and cognitive decline.[131,132]

Learning and memory processes rely on the hippocampus, a region of the brain that contains a large number of pro-inflammatory cytokine receptors.[133,134] The hippocampus has the highest density of IL-1 receptors, and although IL-1$\beta$ is required for normal learning and memory processes, higher levels can also produce diminished cognitive function.[135,136] Recent studies have suggested a role for cytokines such as interleukins-1 and -6 in the genesis of POCD. The relative prevalence of the TNF-$\alpha$ receptor, as well as other PRR, on the endothelium of this brain region may account for its vulnerability to systemic pro-inflammatory cytokines.[137]

Surgical trauma in animal models is associated with the persistent activation of macrophages in the CNS that are capable of maintaning elevated levels of IL-1$\beta$, and other pro-inflammatory cytokines, such as TNF-$\alpha$ and IL-65. These changes are correlated with cognitive dysfunction seen in animal models (contextual fear memory,[5,7,9] spatial learning[99,138] or reversal learning[98]). IL-1 is released in response to a wide

range of infectious, inflammatory or toxic insults, IL-1.[99,139] Sub-clinical inflammation following administration of LPS substantially increases IL1-$\beta$ levels and cognitive deterioration after surgery.[8] In addition, several studies suggest that the marked and sustained expression of inflammation-related enzymes, such as cyclooxygenase- 2, plays an important role in secondary events that amplify cerebral injury after ischemia.[140] Patients also exhibit a robust neuroinflammatory response to peripheral surgery with an initial rise in pro-inflammatory cytokines in the CSF[12,141] as well as release of reactive oxygen species and endothelins.[102,142,143]

## Can we identify vulnerable patients pre-operatively?

We believe that non-resolution of inflammation is a factor that contributes to the pathogenesis of POCD, which in turn significantly increases morbidity and mortality in surgical patients. We might be witnessing a perfect and unfortunate storm of factors with regard to POCD: to put it another way, given the rise in surgeries and increasing number of elderly patients worldwide, the stakes could not be higher.

Vulnerable patients need to be identified and risk/benefit should be considered before contemplating the efficacy of surgical intervention. Advanced age, MetaS, patients prone to AD and poor selection of sedative agents may each result in an exaggerated and persistent neuroinflammatory response to surgery. Further studies are needed to understand which patients will suffer from exacerbated inflammation with the aim of developing a biomarker that is quick to assay for clinicians and easy to comprehend for patients and their families. Concurrently, clinical interventions need to be further developed to promote the resolution of neuroinflammation in postoperative patient populations. Following both tracks, we anticipate that postoperative recovery for vulnerable patients will be greatly enhanced and possible long-term consequences, such as postoperative neurodegeneration, can be significantly reduced.

## Conclusions

In the majority of patients, postoperative neuroinflammation is part of the normal protective mechanism to peripheral trauma and resolves properly with no residual cognitive consequences. Indeed, it is also possible that surgery for a chronic inflammatory disease may result in cognitive improvement by eliminating disease-inducing cognitive impairment that may be associated with chronic inflammatory disease. That

said, some risk factors, such as MetaS, patients prone to AD and poor selection of sedative agents, may each promote the intractable persistence of neuroinflammatory response to surgery. For an increasing number of patients with advanced age, POCD is alarmingly common, making postoperative central nervous system dysfunction a looming public health crisis, given the world's rising elderly population.

Additional study is essential to elucidate the risk factors, preventative strategies and the underlying pathophysiology of this disorder. If these studies can succeed in identifying patients prospectively, or early enough in the advent of persistent inflammation, interventions can be judiciously and appropriately launched.

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