



## Review

## Surgery, neuroinflammation and cognitive impairment



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## ABSTRACT

Trauma experienced during surgery can contribute to the development of a systemic inflammatory response that can cause multi-organ dysfunction or even failure. Post-surgical neuroinflammation is a documented phenomenon that results in synaptic impairment, neuronal dysfunction and death, and impaired neurogenesis. Various pro-inflammatory cytokines, such as TNF $\alpha$ , maintain a state of chronic neuroinflammation, manifesting as post-operative cognitive dysfunction and post-operative delirium. Furthermore, elderly patients with post-operative cognitive dysfunction or delirium are three times more likely to experience permanent cognitive impairment or dementia. We conducted a narrative review, considering evidence extracted from various databases including Pubmed, MEDLINE and EMBASE, as well as journals and book reference lists. We found that further pre-clinical and well-powered clinical studies are required to delineate the precise pathogenesis of post-operative delirium and cognitive dysfunction. Despite the burden of post-operative neurological sequelae, clinical studies investigating therapeutic agents, such as dexmedetomidine, ibuprofen and statins, have yielded conflicting results. In addition, evidence supporting novel therapeutic avenues, such as nicotinic and HMGB-1 targeting and remote ischaemic pre-conditioning, is limited and necessitates further investigation.

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## Research in context

### *Evidence before this study*

Prior to undertaking this narrative review, we considered evidence extracted from databases including Pubmed, MEDLINE and EMBASE, as well as researching within high-impact journals including, but not limited to: Nature, Cell (Trend in Neuroscience), Lancet, Critical Care and Annals of Surgery. Furthermore, book reference lists were reviewed, for example: Perioperative Care of the Elderly Patient (Barnett & Neves, 2018), Anaesthesia and Neurotoxicity (Morimoto, 2017) and Perioperative Care of the Elderly (2017).

As this research is a narrative review, the only inclusion criteria were for clinical and pre-clinical papers to have been written in the last 5 years (1st January 2013 – 1st September 2018). Search terms included post-operative delirium, post-operative cognitive decline/dysfunction, systemic inflammatory response syndrome and post-surgical neuroinflammation.

### *Added value of this study*

This study summarises our current understanding of the mechanisms underlying post-operative delirium and cognitive decline, in addition to current novel therapeutic approaches to manage these conditions and promising future pathways that require further investigation.

### *Implications of all the available evidence*

With over 300 million surgical procedures performed globally and an aging population, summarising and increasing the awareness of deleterious post-surgical neurological sequelae is vital. Alarmingly, evidence suggests that post-surgical cognitive complications are not simply limited to the immediate post-surgical period but, in fact, can result in chronic cognitive decline, such as dementia. This paper has numerous implications for practice, policy and future research:

**Future research:** encourage further investigation into current novel medication associated with lower rates of post-operative delirium and cognitive decline. In addition, by highlighting promising pathways with the potential to be targeted, we aim to facilitate new pre-clinical basic scientific studies by highlighting unexplained clinical outcomes

**Policy and practice:** increasing awareness of both the short-term consequences of post-operative delirium and cognitive decline (incl. Increased length of hospitalisation and healthcare costs), as well as the long-term effects (poorer quality of life, increased morbidity and mortality). By doing so, we aim to increase funding and international awareness of the clinical, financial and socioeconomic implications of these conditions.

## 1. Introduction

Global estimates suggest that approximately 312 million major surgical procedures were performed in 2012, representing an increase of 38% over the previous 8 years [1]. Furthermore, accepted annual global estimates of the frequency of surgery in high-income countries suggest that over 11,000 surgical procedures are performed per 100,000 individuals [1,2]. With increasing lifespan and growing populations, the number of surgical procedures performed annually is likely to continue to increase. Bearing this in mind, it is critical that the peri-operative management of surgical patients is optimised to avoid deleterious sequelae, such as post-operative neurological complications. The first large prospective study in 1998 investigating post-operative cognitive decline following non-cardiac surgery estimated that 12% of patients develop symptoms of cognitive dysfunction in the post-operative period [3]. Whilst post-operative cognitive dysfunction is often self-limiting, recent concerning findings indicate that elderly patients that develop post-operative delirium or cognitive dysfunction are three times more likely to suffer from permanent cognitive impairment or dementia [4]. Despite global improvements in post-operative outcomes, our understanding of deleterious neurological sequelae in the post-operative period remains limited.

## 2. Surgical trauma and inflammation

### 2.1. Development of systemic inflammation

An uninhibited early inflammatory response results in a well-documented disorder known as Systemic Inflammatory Response Syndrome (SIRS). Studies have shown that higher surgical trauma and stress correlates with the development of SIRS and with longer hospital stay [5,6]. The proposed mechanisms underlying SIRS are summarised in Table 1. The severity of postoperative SIRS may be predicted by the increased levels of cytokines observed [7–9]. SIRS can potentially lead to multi-organ injury (Fig. 1). In this review we will focus on neuroinflammation and functional changes within the brain after surgery. In addition, it is important to note that major surgery is always accompanied with anaesthesia, which possesses its own associated pathological and functional effects within the brain which is still under investigation clinically; this is out of the scope of this review.

### 2.2. Severe SIRS and pathological changes in the brain

#### 2.2.1. Disruption of BBB – The hallmark of neuroinflammation

Following surgical trauma, the innate immune system is activated in a nuclear factor- $\kappa$ B (NF- $\kappa$ B)-dependent manner. This results in the release of a variety of pro-inflammatory mediators, such as TNF $\alpha$ , which ultimately causes blood-brain barrier (BBB) compromise and promotes monocyte-derived migration of macrophages into brain parenchyma [10]. In turn, intensification of CD11b immunoreactivity occurs, which has been identified in the surgical phenotype [11]. In addition, a murine study demonstrated that surgery and anaesthesia both play a role in reducing the levels of tight junction proteins including claudin, occludin and ZO-1 [12]. This reduction of tight junction proteins may be caused

by an increase of IL-6, which is essential in the metabolism of  $\beta$ -catenin resulting in a reduction of tight junction proteins [12]. The mechanisms underlying the development of BBB dysfunction and neuroinflammation are highlighted in Fig. 2

Surprisingly, mast cells can also be found in the brain and appear to contribute to the disruption of the BBB following surgery. An increased number of mast cells is seen in the hippocampus in mice following tibial fracture surgery, which is associated with increased permeability of the BBB [13]. Although it is not yet fully understood, mast cells are shown to play a role in reducing the levels of tight junction proteins, including occludin and claudin-5 [13]. Mast cells may also indirectly disrupt the BBB by upregulating MMP-2 and 9, which subsequently break down the basal lamina and tight junction proteins of the BBB upon the release of serine protease trypsin and chymase.

### 2.2.2. The role of microglia and astrocytes

Both microglia and astrocytes have shown to play a key role in neuroinflammation. The release of pro-inflammatory cytokines during surgery-induced neuroinflammation results in the transformation of inactivated microglia to an activated, phagocytic state. Studies have demonstrated that the inhibition of microglia can lead to a reduction of proinflammatory cytokines including TNF $\alpha$  and IL-1 $\beta$ , as well as chemokines such as MCP-1, which are all important factors in causing neuroinflammation [14]. Evidence has shown that astrocytes and microglia can communicate with each other upon surgical trauma, resulting in a pro-inflammatory state. It appears that CCL2, a chemokine also known as MCP-1, is released by astrocytes following surgery, which binds to its receptor CCR2 in microglia causing activation of microglia and transformation into M1 phenotype [15]. Ultimately, there is an increased production of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ , causing neuroinflammation and neuronal apoptosis [15]. Astrocytes may also contribute to neuroinflammation and neuronal damage by producing amyloid proteins following surgery. IL-17A is a cytokine that is upregulated in multiple inflammatory diseases, including neuroinflammation following surgery [16,17]. It has been demonstrated that IL-17A causes an increased production of A $\beta_{1-42}$  via the TGF $\beta$ /Smad signalling pathway inside the astrocyte, a mechanism that is also observed in Alzheimer's disease [18]. It is also important to note that the production of reactive oxygen species (ROS) in microglia is increased following surgery, contributing to neuroinflammation [19].

### 2.2.3. The role of DAMPs

Following surgical trauma, danger-associated molecular patterns (DAMPs) are released, which adhere to pattern recognition receptors (PRRs). PRRs are present within the BBB endothelium, and macrophages, whilst interaction between DAMPs and PRRs results in further activation of pro-inflammatory pathways. S100A8 is a cytosolic protein that acts as a DAMP and is upregulated following surgical trauma, associated with microgliosis and macrophage migration into the brain via the TLR4/MyD88 signalling pathway [20]. Interestingly, S100A8 expression is reduced in TLR4 knock-out (TLR4 $^{-/-}$ ) mice, suggesting a loop relationship between activation of the TLR4/MyD88 pathway and the ligand S100A8.

Other DAMPs, including the high-mobility group box 1 protein (HMGB-1), are also increased after surgery and cause neuroinflammation, particularly within the perivascular space and brain parenchyma [21]. It has been shown that HMGB1 can lead to microglial activation, which is a crucial step in neuroinflammation, ultimately resulting in cognitive dysfunction [22]. Furthermore, circulating HMGB-1 from a distant site can also be found in the brain [23]. These findings suggest that HMGB-1 may enter the disrupted BBB following surgery and cause neuroinflammation.

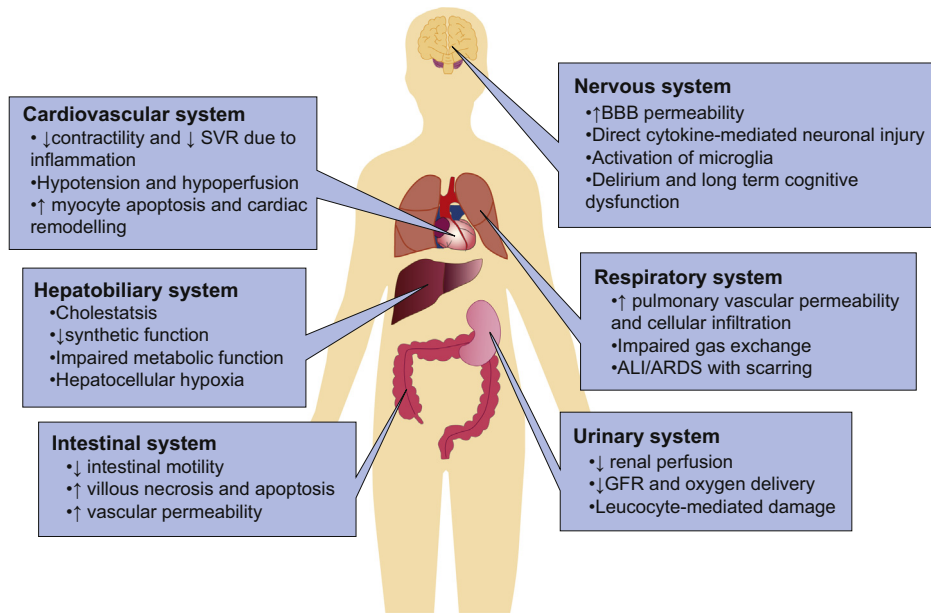
### 2.2.4. The role of BDNF

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neurogenesis, synaptogenesis and regulating neural

**Table 1**

Pathogenesis of the systemic inflammatory response following surgical trauma and other disease conditions *per se*.

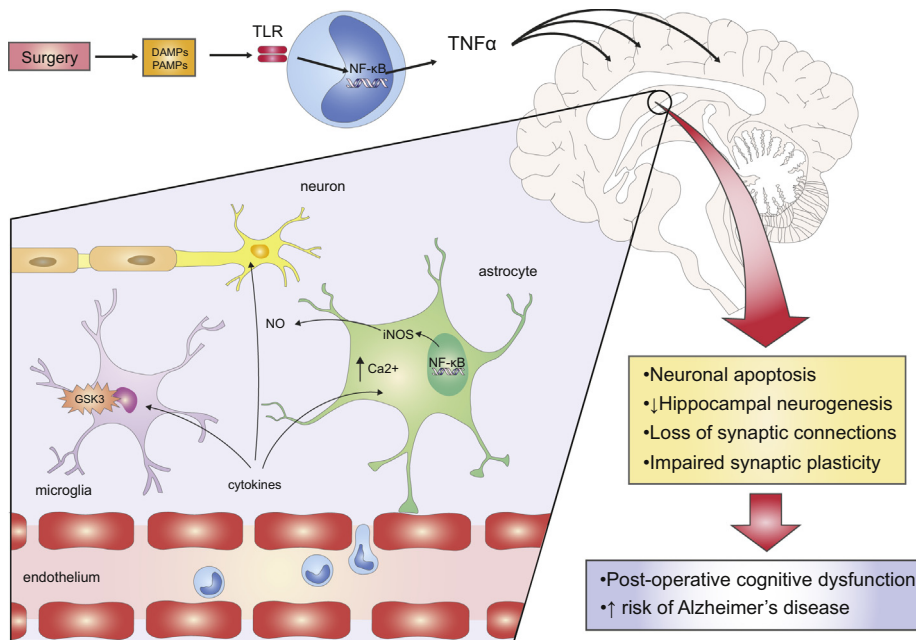
Stage	Response	Result
I	Initial localised inflammation to limit further injury and promote site healing following surgical trauma, infection, burns and various other conditions.	There is initiation of a local inflammatory reaction via activation of the innate immune system and recruitment of immune cells, such as macrophages and neutrophils, to the site of injury.
II	Activation of the early compensatory anti-inflammatory response (CARS) aims to restore immunologic balance.	CARS results in various physiological alterations including the reduction of lymphocytes via apoptosis, a dampened monocytic response to cytokine stimulation and cutaneous energy. In addition, CARS causes a decrease in human leukocyte antigen (HLA) antigen-presenting receptors on monocytes, as well as an increased production of specific cytokines, such as IL-10, that act to suppress TNF expression. Ultimately, there are two potential outcomes for patients in stage II: <ol style="list-style-type: none"> <li>Restoration of immunologic balance and dampening of the pro-inflammatory response</li> <li>An overactive systemic inflammatory response prevails over CARS.</li> </ol>
III	The overactive pro-inflammatory SIRS reaction predominates over the anti-inflammatory response.	SIRS causes endothelial dysfunction, increased microvascular permeability, profound vasodilation and activation of the coagulation system. The uninhibited action of NF- $\kappa$ B results in the release of pro-inflammatory cytokines, including TNF $\alpha$ and IL-1. Other cytokines, particularly IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP), whilst activation of the complement cascade, particularly via C3a and C5a, promotes vasodilation and increased vascular permeability.
IV	The anti-inflammatory response is upregulated in order to compensate for the vigour of the systemic pro-inflammatory state.	The CARS eventually becomes excessive, resulting in profound immunosuppression or immune paralysis. This predisposes the individual to nosocomial or secondary infections, re-initiating the vicious cycle of systemic inflammation.
V	Prolonged dysregulation of the SIRS and CARS response.	This stage is termed immunologic dissonance. The prolonged action of pro-inflammatory cytokines, such as TNF $\alpha$ and IL-1, directly alters endothelial surfaces, resulting in the increased expression of tissue factor (TF). TF initiates the production of thrombin, promoting coagulation and also acting as a pro-inflammatory mediator itself. TNF $\alpha$ and IL-1 promote the production of plasminogen activator inhibitor-1, inhibiting the process of fibrinolysis. The pro-coagulant state is further upregulated via the activation of the complement cascade, which disrupts the action of anti-thrombin and activated protein-C. Persistence of the pro-coagulant state results in various complications of microvascular thrombosis, ultimately resulting in multiple organ dysfunction or failure and, in the most severe cases, death.



**Fig. 1.** End organ effects of postoperative systemic inflammatory response syndrome (SIRS). Surgical dissection and its associated trauma cause cell death which, in turn, results in the release of intracellular components into the extracellular space. These include immunogenic compounds such as RNA and DAMPs (HMGB-1, ATP and Histone) which bind to and activate specific toll-like receptors (TLRs), driving the NF- $\kappa$ B mediated transcription of pro-inflammatory cytokines. Furthermore, activated T cells release pro-inflammatory mediators and can cause direct cytotoxicity. These processes result in tissue injury, oedema and inflammation and ultimately damage organs. ALI, acute lung injury. ARDS, acute respiratory distress syndrome. BBB, blood brain barrier. GFR, glomerular filtration rate. SVR, systemic vascular resistance.

plasticity, as well as learning and memory. Reduction of BDNF is seen in many neurodegenerative diseases including Alzheimer's disease and Parkinson's disease [24,25]. Interestingly, a decreased level of BDNF is also observed in parallel with neuroinflammation following surgery [26,27]. It is likely that surgery causes neuroinflammation

and further downregulates both BDNF and its receptor TrkB, leading to a reduction of p-TrkB and inhibition of its downstream signalling pathway, which is important for learning and memory [28,29]. BDNF reduction may be mediated by phosphorylation of the glucocorticoid receptor GR [26].



**Fig. 2.** Mechanism of post-operative neuroinflammation. DAMPs and PAMPs activate the downstream pathway involved in inducing the production of TNF $\alpha$ , as well as other pro-inflammatory mediators via NF- $\kappa$ B. This causes the loss of blood-brain barrier (BBB) integrity, due to endothelial dysfunction occurs and increased permeability of the BBB. As a result, there is a recruitment of circulating lymphocytes into the neuronal tissue, and microglia and astrocytes are activated. Cytokines induce the synthesis and release of NO via inducible nitric oxide synthase from the activated microglia and astrocytes. Also, cytokines cause an increase in intracellular Ca<sup>2+</sup>. In addition, GSK-3 dysfunction occurs in neuroinflammation, which potentiates microglial activation and migration and stimulates cells to produce NO and TNF $\alpha$  via NF- $\kappa$ B activation. Subsequently, neuroinflammation leads to neuronal apoptosis, reduced hippocampal neurogenesis, impaired synaptic plasticity and a loss of synaptic connections. All of this, in turn, leads to neurodegenerative conditions such as post-operative cognitive dysfunction and increased risk of Alzheimer's disease. BBB, blood brain barrier. DAMP, danger associated molecular pattern. GSK-3, Glycogen synthase kinase-3. iNOS, inducible nitric oxide synthase. NO, nitric oxide. TLR, toll like receptor.



### 2.3. Iron accumulation

Iron is necessary to ensure a normally-functioning CNS, as it is involved in DNA and RNA synthesis, myelin formation, and serves as a co-factor for multiple reactions [30]. As the brain ages there is also an accumulation of iron, and this has been associated with neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease [31,32]. Iron accumulation may also be a result of surgical trauma, in which oxidative stress may contribute to POCD in rodents [34]. Peripheral surgical trauma has been shown to cause changes in hippocampal iron homeostasis, resulting in post-surgical neuroinflammation and cognitive decline, which is attenuated with the administration of deferoxamine [35]. Deferoxamine is thought to reduce the effects of post-surgical hippocampal iron accumulation by ameliorating oxidative stress, microglial activation and neuronal apoptosis, thus potentially reducing the incidence of POCD [36]. Clinical studies are required to determine if there is a significant relationship between iron accumulation and post-operative neurological disease in humans.

### 2.4. Surgical stress response and the cholinergic anti-inflammatory pathway

As discussed, direct traumatic injury results in the activation of local inflammatory processes, whilst unregulated stress responses may lead to SIRS and multi-organ failure. It is important to note that the stress response to surgical trauma is comprised of a sequence of physiological processes involving biochemical alterations and changes to the metabolic, cardiovascular, endocrine and immune systems.

Local tissue injury acts as an afferent stimulus which causes activation of autonomic and somatic responses. This results in stimulation of the sympathetic nervous system and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Following activation of the hypothalamus, there is an increase in adrenocorticotrophic hormone (ACTH) release from the anterior pituitary and a subsequent increase in cortisol release from the adrenal medulla. Cortisol, in humans, and corticosterone, in rodents, are the primary glucocorticoid hormones responsible for the stress response. Overall, the release of cortisol causes an increase in blood glucose levels due to significant changes in protein, fat and carbohydrate metabolism. Furthermore, activation of the HPA axis also causes an increased synthesis of adrenaline and noradrenaline within the adrenal medulla, resulting in hypertension and tachycardia. Other hormonal changes include an increase in glucagon, anti-diuretic hormone and growth hormone, as well as activation of the renin-angiotensin-aldosterone system.

Activation of the cholinergic anti-inflammatory pathway is a vital response in dampening the effects of the sympathetic nervous system following surgical trauma. Cholinergic inhibition is mediated via the vagus reflex, whereby afferent vagus nerve fibres sense peripheral inflammatory mediators and convey these signals to the dorsal motor nucleus, subsequently inducing an efferent signal and acetylcholine release which acts on nicotinic  $\alpha$ -7 receptors of macrophages and pro-inflammatory cells. Vagal activation therefore suppresses local and systemic inflammation by inhibiting the release of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-18 and TNF- $\alpha$  [37]. Following surgical trauma, the body needs to maintain an intricate balance between an inflammatory state, which is required for physiological processes such as wound healing, and the cholinergic anti-inflammatory response, which is important in preventing SIRS and its associated complications [38].

## 3. Consequences of neuroinflammation

Post-surgical neuroinflammation causes a variety of deleterious structural and functional alterations within the brain, ultimately resulting in neurological impairment.

### 3.1. Synaptic dysfunction

Whilst synaptic impairment has classically been considered a characteristic feature of late stage neurodegeneration, it has more recently been heralded as an early indicator of dementia progression [39]. Surgical trauma results in the pathological activation of astrocytes, thus causing the release of pro-inflammatory cytokines and subsequent synaptic dysfunction [40]. The release of pro-inflammatory mediators triggers a vicious cycle whereby cytokines cause a reduction in glutamate-induced  $\text{Ca}^{2+}$  increase in astrocytes, thus resulting in a detrimental effect on astrocyte reactivity, and subsequent synaptic dysfunction [41]. Synaptic dysfunction has been shown to precede the development of irreversible neurodegenerative pathology, such as tauopathies [42].

### 3.2. Neuronal death

The process of post-surgical neuroinflammation involves several pro-apoptotic pathways. Activation of the TNF receptor-1 (TNFR1) signalling pathway results in the promotion of neuronal apoptosis, whilst increased levels of TNF $\alpha$  correlate with increased hippocampal neuron apoptosis [43]. In addition to cytokines, the release of NO from activated microglia and astrocytes further promotes the inflammatory response, thus resulting in neuronal apoptosis.

Zhang et al. showed that activated mast cells following surgery can induce microglial activation via MAPK signalling pathway, resulting in neuronal apoptosis [44]. In addition, activated mast cells are also directly involved in neuronal apoptosis, as indicated by increased levels of proapoptotic factors Bax/Bcl-2 and caspase-3 following surgery [44].

Recent studies have identified that peripheral surgery causes a reduction in cerebral acetylcholine, thus triggering a complex neuroinflammatory response [45], as well as subsequent degeneration of cholinergic neurons. Plaschke et al. have demonstrated that cholinergic signalling mediates the secretion of pro-inflammatory markers, such as IL-1 $\beta$ , following surgical stress [45], whilst decreases in cerebral acetylcholine results in an increased secretion of numerous pro-inflammatory cytokines [46]. Furthermore, increasing acetylcholine levels by inhibiting acetylcholinesterase causes a sustained anti-inflammatory effect, which may be a therapeutic option in reducing post-surgical neuroinflammation [47].

### 3.3. Neurogenesis impairment

Neurogenesis describes the maturation and differentiation of neural progenitor cells (NPCs) to neurons. The process of neurogenesis is confined to subventricular zone on the walls of the lateral ventricles, and the subgranular zone of the dentate gyrus within the hippocampus. Pro-inflammatory cytokines can inhibit neurogenesis by causing the death of NPCs and limiting neuronal differentiation. It has been proposed that an age-related decline in hippocampal neurogenesis may contribute, at least partially, to the cognitive deficits observed in neurodegenerative diseases. This may potentially indicate a relationship between neuroinflammation and the cognitive deficits observed in conditions such as dementia [48].

### 3.4. GSK3 dysregulation

Glycogen synthase kinase-3 (GSK3) is a serine/threonine protein kinase, which possesses significant pro-inflammatory effects within the brain [49]. GSK3 potentiates the activation and migration of microglia, and stimulates cells to produce pro-inflammatory mediators, including nitric oxide and TNF $\alpha$ , via the activation of NF $\kappa$ B-mediated pathways. In addition, a positive correlation between GSK3 concentration and BBB permeability has also been demonstrated [50], whilst GSK3 also facilitates the migration of leukocytes across the BBB. Inhibition of GSK3 is associated with an upregulation of IL-10 mediated anti-inflammatory

pathways, as well as a decrease in pro-inflammatory markers [49]. As GSK3 has demonstrated a role in the pathophysiology of neuroinflammation, it has been reasoned that it may possess a role in the development of neurodegenerative pathology, whilst its inhibition may be a novel therapeutic option to potentially dampen the neuroinflammatory response associated with surgical trauma.

#### 4. Post-surgical neuroinflammation related neuro-disorders

##### 4.1. Post-operative delirium (POD)

Delirium is an acute confusional state that is characterised by its fluctuating nature and reversibility, associated dysfunctional mental state and inattention, and typical time course. A diagnosis is usually made when the patient conveys differentiating perceptions. POD has an incidence of 37–46%, which differs depending on the type of surgical-procedure carried out, with reports as high as 51% [51]. Adverse events are also common; these include increased length of hospital stay and associated healthcare costs, and increased mortality. Whilst anaesthesia has classically been considered the major contributor to post-operative delirium, animal studies indicate that surgery-induced inflammation may be a significant cause of POD-associated neurological impairment [45,47].

The peripheral inflammatory response affects the brain, underlying the pathogenesis of POD. Cytokines, especially IL-1 $\beta$ , TNF- $\alpha$  and IL-6, are believed to interact with the brain. The mechanism by which peripheral cytokines make their way to the brain is either via vagal afferents, via the blood-brain barrier, or through the circumventricular region [52]. These peripheral cytokines cause microglial-induced cytokine synthesis and result in a cycle of neuroinflammation. A recent meta-analysis of human observational studies demonstrated that an increase in the concentration of peripheral and cerebrospinal fluid (CSF) inflammatory markers, such as CRP and IL-6, has demonstrated an association with both POD and POCD [53]. Furthermore, an increase in central and peripheral levels of S-100 $\beta$  and IL-8 levels has been shown to be significantly associated with POD, rather than POCD.

Further clinical evidence is required to understand these underlying mechanisms in humans.

##### 4.2. Post-operative cognitive dysfunction (POCD)

Due to the surgery-induced systemic inflammatory response, patients may suffer 'post-operative cognitive dysfunction' (POCD). POCD is characteristically observed in the immediate post-operative period and manifests as a transient disturbance in cognition. This disturbance presents as a spectrum, from lethargy to social withdrawal and reduced concentration, to severe cognitive dysfunction. POCD may also result in fluctuating consciousness and sleep-wake-cycle irregularities.

Elderly patients have the highest incidence of POCD. Amongst hospitalized post-operative patients aged 60 years and older, rates as high as 40% have been observed [55]. Whilst a transient fluctuation in cognition within the post-operative period is often not considered to be particularly concerning, it is important to note that POCD has been shown to predict the onset of dementia in the future and may contribute to chronic neurodegeneration, particularly with repeated surgical procedures [4,56].

An increase in pro-inflammatory cytokines intra-operatively potentiates short-term cognitive impairment [57]. In addition, reports from animal studies have suggested that TNF $\alpha$ -mediated dysfunction of the BBB, and the subsequent migration of leukocytes into the hippocampus, has the ability to cause memory impairment [58].

POCD is more common following major surgery and in the presence of postoperative complications. Although POCD is traditionally considered a complication that occurs following cardiac surgery, epidemiological evidence suggests that the condition is also prevalent following various other surgical procedures, including abdominal surgery [59].

Both surgical trauma and neurodegenerative disorders are associated with increased cytokine release, resulting in numerous preliminary studies that have suggested that patients with Alzheimer's disease may be prone to the development of post-operative cognitive decline [60,61]. Furthermore, this relationship is thought to be due to a peripheral inflammatory stress response that promotes a neuroinflammatory process that results in cognitive dysfunction [62,63]. Increased levels of CRP and IL-6 have been noted in both POCD and POD, whilst increased levels of neuron-specific enolase (NSE) centrally and peripherally in patients with POCD specifically has been reported [53].

##### 4.3. Other neurodegenerative conditions

Alzheimer's disease (AD) is a chronic neurodegenerative condition and is the most frequently diagnosed dementia. Both POCD and AD share the common feature of increased microglial activity, which ultimately results in profound neuroinflammation, cholinergic dysfunction and synaptic impairment. It is important to consider the fact that these inflammatory processes are not resolved as efficiently in elderly patients, in comparison to the younger population. It is hypothesized that this is due to a process known as microglial priming, whereby the accumulation of abnormally folded proteins and neurodegenerative changes result in abnormal microglial activation and multiplication [64]. Furthermore, this may explain why retrospective studies have suggested that the rates of POCD and post-operative dementia are high in older patients. For instance, Vanderweyde et al. (2010) states that 1/3 of patients aged 65 and over develop POCD, with 70% of these patients developing dementia 3 to 5 years later [65].

As discussed previously, GSK3 dysregulation has been hypothesized to play a role in post-surgical neuroinflammation due to its ability to control cellular proliferation and migration, inflammation, apoptosis and immune modulation. However, GSK-3 dysregulation has also been described as a hallmark of Alzheimer's disease [66,67], thus suggesting a common pathogenesis between stress-induced neuroinflammation and neurodegenerative disorders. Despite this, there have been limited studies investigating the direct impact of surgical trauma on the development of dementia. Evidence is predominantly limited to animal studies [68], whilst a retrospective cohort study demonstrated an increased 5-year risk of developing AD after coronary artery bypass grafting compared to patients who underwent transluminal coronary angioplasty [69]. This is corroborated in other surgeries, including dermatological, musculoskeletal, genitourinary, ophthalmological, and ENT, where there is almost a reported two-fold increase in dementia within 3–7 years [70].

## 5. Therapeutic options for post-operative neurological complications

A summary of the potential drugs that may be effective in treating POCD, as well as their proposed mechanisms, are summarised in Table 2.

### 5.1. Novel use of existing licenced medications

#### 5.1.1. Anti-inflammatory drugs

Due to the close association between neuroinflammation and post-operative neurological complications, several studies have investigated the effect of both steroids and non-steroid anti-inflammatory drugs.

The therapeutic value of peri-operative corticosteroids is conflicted in the current literature. Several randomised control trials of peri-operative methylprednisolone administration failed to show any improvement in post-operative cognitive function [71,72]. However, more recent studies using high dose intra-operative Dexamethasone (8 mg to 1 mg/kg) have reported a significantly lower rate of POD and POCD [73,74].

Parecoxib is a cyclooxygenase (COX)-2 selective NSAID thought to have good CNS distribution. Animal models of post-operative SIRS have reported that parecoxib administration results in significantly lower IL-1 $\beta$  and TNF- $\alpha$  expression, as well as lower Prostaglandin E levels in the hippocampus [75]. This is associated with better-preserved cognitive performance. In clinical trials, both single-dose parecoxib during anaesthesia and regular parecoxib in the post-operative period are associated with significantly lower rates of POD and POCD [76,77].

Paracetamol is a centrally acting antipyretic and analgesic thought to act through inhibition of the COX enzyme in the central nervous system. A recent animal study by Zhao et al. reported significantly reduced hippocampal IL-1 $\beta$ , IL-6, TNF- $\alpha$ , as well as better cognitive performance associated with paracetamol administration [78]. However, this has not yet been confirmed in human studies.

Ibuprofen works by inhibiting both COX-1 and COX-2. Its inhibition of COX-1 may be responsible for its unwanted gastrointestinal effects [79]. Conversely, the inhibition of COX-2 provides ibuprofen with its analgesic, antipyretic, and anti-inflammatory properties. Research on mice by Huang et al. [80], has demonstrated improved cognitive performance, reduced systemic inflammation and glial activation upon the utilisation of ibuprofen perioperatively. Pre-operative administration of IV ibuprofen has been shown to improve post-operative cognitive function in the clinical setting, where the level of cytokines, cortisol, and catecholamines were reduced [81].

### 5.1.2. Dexmedetomidine

Dexmedetomidine is a  $\alpha_2$  adrenoceptor agonist first licenced for clinical use in 1999 by FDA, with an initial use for sedation. In animal models of SIRS and surgical insult, dexmedetomidine has been shown to reduce the severity of neuroinflammation and neuroapoptosis [82–86]. Dexmedetomidine administration is associated with reduced hippocampal expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$  and TLR-4, as well as reduced astrocyte and microglial activities [83,87].

Dexmedetomidine has demonstrated promising therapeutic benefits in clinical trials. A randomised control trial by Su et al. reported a 60% reduced rate of post-operative delirium after an infusion of dexmedetomidine [88]. Furthermore, a recent randomised controlled trial discovered improved cognitive function and quality of life in 3-year survivors, as well as increasing survival up to 2-years after a low-dose dexmedetomidine infusion in non-cardiac surgery [89]. In a meta-analysis of 13 studies with over 1300 patients, Zhou et al. estimated an effect size of 40% reduction in the risk of POCD [90]. In conjunction with these findings, a meta-analysis of 18 human studies has also demonstrated a significantly reduced POD risk after an administration of dexmedetomidine [91].

**Table 2**

Potential drugs that may be effective in treating POCD and their proposed effects.

Drugs	Proposed effects	References
Dexamethasone		71, 72
Parocoxib	Reduction in IL-1 $\beta$ , TNF- $\alpha$ , prostaglandin E	73, 74, 75
Paracetamol	Reduction in IL-1 $\beta$ , TNF- $\alpha$ , IL-6	76
Ibuprofen	COX-2 inhibition and a reduction in peripheral cytokines, cortisol, and catecholamines	77, 78, 79
Dexmedetomidine	Reduction in IL-1 $\beta$ , TNF- $\alpha$ , IL-6, TLR-4	80–85
Statins	Upregulation of $\alpha$ -secretase non-amyloidogenic pathway of APP processing	92–97
Ulinastatin	Reduction of inflammatory mediators and blood brain barrier permeability	102, 103
Nicotinic stimulation	Reduction of TNF- $\alpha$	36, 44, 46, 104
HMGB-1	Reduction of inflammatory mediators	22, 105, 106
Hydrogen sulphide donor		107, 108, 109
Nt-p65-TMD	Inhibition of NF- $\kappa$ B p65	110

Whilst dexmedetomidine has demonstrated promising results, due to concerns over its potential side effects on cardiopulmonary system [92,93], its use needs to be further optimised in various clinical settings.

### 5.1.3. Statins

Statins, as shown through experimental models, have demonstrated a reduction in the production of A $\beta$  plaques. This is achieved by down-regulating neuroinflammation secondary to an interrupted secretase enzyme function. The  $\alpha$ -secretase non-amyloidogenic pathway of amyloid precursor protein (APP) processing is upregulated by statins, in addition to  $\beta$ -secretase dimerization's inhibition by statins [94–97]. As such, statins in epidemiological studies have demonstrated a reduction in AD incidence and POCD development [98,99]. Despite this, it is important to note that the association between statins and AD in humans varies across different properties of statins, patient gender and ethnicity [100]. Furthermore, evidence from both observational and randomised trials have produced conflicting results, with no well-powered high-quality data indicating a significant reduction in dementia with statin use, including the Medical Research Council (MRC) and British Heart Foundation (BHF) Heart Protection Study [101], pravastatin in elderly individuals at risk of vascular disease trial (PROSPER) [102] and Cochrane review and analysis [103]. Whilst these studies are dated, they provide the most robust and well-powered evidence regarding the relationship between statins and cognitive impairment.

### 5.2. Novel therapeutic targets

Ulinastatin is associated with reduced circulating inflammatory mediators and reduced blood brain barrier permeability in animal models of SIRS [106]. A recent meta-analysis of 5 studies and over 450 patients has reported a 60% reduction in the rate of POCD [107].

Nicotinic stimulation, in the form of a selective  $\alpha 7$  nicotinic acetylcholine receptor agonist, has demonstrated improved hippocampal-associated memory deficits and neuroinflammation. The proposed mechanism involves the modulation of nuclear factor-kappa B (NF- $\kappa$ B) activity in monocytes, as well as the attenuation of oxidative stress responses by downregulating nicotinamide adenine dinucleotide phosphate's (NADPH) signalling [108], and the eventual inhibition of TNF- $\alpha$  [37]. Furthermore, it has been suggested that utilising procholinergic drugs, such as physostigmine, may also be therapeutic options in downregulating SIRS and neuroinflammation [45,47].

High mobility group box 1 (HMGB-1) is a DAMP that interacts with TLR-4 to induce the expression of NF $\kappa$ B and other inflammatory mediators, as well as being involved in the recruitment of bone marrow derived macrophages. In animal studies, administration of HMGB-1 has been shown to lead to memory impairment [109], whilst inhibition of HMGB-1 production and administration of anti-HMGB-1 antibodies are both associated with reduced neuroinflammation and better cognitive function [22,110].

Although hydrogen sulphide donors are toxic at high concentrations, research in recent years suggests that at smaller doses they may have possesscytoprotective effects [111,112]. Several animal studies have demonstrated that pre-treatment with sodium hydrosulphide is associated with significantly reduced SIRS-induced neuroinflammation and cognitive impairment [113].

Inhibition of NF- $\kappa$ B p65 activation using the cell-penetrating fusion protein, nt-p65-TMD, regulates and attenuates post-surgical systemic inflammation [114]. These preliminary results indicate that NF- $\kappa$ B p65 inhibition may be a potential future therapeutic option in the prevention of POCD.

### 5.3. Other novel approaches

Remote ischaemic preconditioning (rIPC), a technique whereby blood flow to a limb is repeatedly impaired, has shown promising neuroprotective results. Rat studies have demonstrated that the rIPC is



neuroprotective against cerebral ischaemia by altering peripheral immune responses [115]. Clinical studies indicate that implementing rIPC in colon and cardiac surgery results in improved post-operative cognitive function [116,117]. Improved cerebral blood flow is believed to play a part in this neuroprotection, as mediated by circulating nitrite and its associated nitrosylation of complex I [118]. In addition, clinical studies also suggest that rIPC prevents the deterioration of short-term post-operative cognitive function in cardiac surgery patients [117], as well as reduces post-operative ischaemic tissue damage in brain tumour surgery [119]. However, the role of rIPC in neuroprotection has produced conflicting results, with findings from the multicentre, randomised RIPHeart (Remote Ischaemic Preconditioning for Heart Surgery) study demonstrating no effect on neurocognitive function or long-term outcomes in cardiac surgery patients [120].

The term human 'microbiota' refers to the microbes, including bacteria, fungi, archaea and viruses, found within a specific environment, whilst the microbiome refers to their respective genomes. It has been suggested that microbiota is critically involved in normal brain development [121,122], whilst changes in gastrointestinal microbiota may contribute to memory decline and cognitive dysfunction in elderly patients [121,123]. Furthermore, significant differences in microbiota have been found between healthy, cognitively intact individuals and patients with depression, autism and neurodegenerative disorders [121,123–126]. In fact, administration of a combination of antimicrobials, including ampicillin, meropenem, vancomycin, neomycin and bacitracin, causes a reduction of gut microbiota and subsequently impairs novel object recognition memory [127]. In addition, the systemic use of ceftazolin, an antibiotic commonly used in the peri-operative period, causes changes in gut microbiota resulting in increased inflammation in the brain and gut, as well as learning impairment and cognitive dysfunction [128]. Studies exploring specific microbiomic patterns that may predispose to post-operative cognitive delirium and dysfunction may allow the therapeutic use of microbiome interference to reduce unwanted post-operative neurological sequelae. Furthermore, avoiding specific combinations of anti-microbial agents may also provide benefit in reducing post-operative cognitive dysfunction. However, further pre-clinical and clinical studies are warranted.

## 6. Concluding remarks and future perspectives

Studies have shown that surgery results in a systemic inflammatory response, which may potentiate neuroinflammation and, in turn, trigger deleterious neurological sequelae in some patients. Evidence suggests that post-surgical neuroinflammation may result in delirium and cognitive dysfunction, as well as long-term, irreversible disorders such as dementia per se.

Various therapeutic agents have been investigated for their neuroprotective effects, including dexmedetomidine and statins, as well as other novel agents targeting nicotinic and HMGB-1 pathways. Unfortunately, clinical studies investigating the utility of these agents are currently limited by number and quality, with dexmedetomidine demonstrating significant promise in recent studies. In addition, further investigation of other therapeutic avenues, including remote ischaemic pre-conditioning and microbiome interference, is required.

Overall, further pre-clinical and well-powered clinical studies are required to further investigate the precise pathogenesis underlying the relationship between surgery, neuroinflammation and the development of neurological disorders, as well as the efficacy and safety profile of therapeutic agents in ameliorating these post-surgical complications.

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## Declarations of interests

All authors declare no conflicts of interest.

## Author's contribution

All authors contributed equally.

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