Aim of review: The aim of this review is to assess the different functions of various brain regions involved in cognition and how their impairment results in postoperative cognitive dysfunction (POCD).

Method: We reviewed the progress in evaluating the potential mechanisms with which they may be impaired following surgery and anaesthesia.

Recent findings: The risk of cognitive decline following surgery is a serious health concern, considering the number of surgical procedures requiring anaesthesia exceeds 230 million worldwide as well as an increasing ageing population. POCD is associated with increased mortality and a potentially devastating reduction in quality of life. POCD was suggested to be due to an inflammatory response in the brain, with the elderly population being especially vulnerable. Although the hippocampus has been heavily implicated, other brain regions and networks have not been sufficiently investigated.

Summary: A better understanding of the brain regions and their associations responsible for the cognitive functions affected in POCD, and their role in memory and cognition, could help to further clarify this potentially devastating condition.

Postoperative cognitive dysfunction (POCD) is a syndrome of prolonged impairment of cognitive function after surgery, causing deleterious effects in memory, concentration, intellectual ability and executive function (1, 2). It can last from weeks to months while the progression to dementia 3–5 years post-surgery has also been suggested in patients aged 65 or older (1, 3). However, it is distinct from delirium and dementia (1). The presentation of POCD can be very subtle, with no symptoms appearing in the first few days after surgery. Some patients and their family members will only notice a deficit when faced with new difficulties in tasks at home or work (4). These factors, along with the fact that there is no internationally agreed definition of POCD, lead to difficulty in reporting its incidence accurately. The symptoms can range from extremes of only mild memory loss, to an inability to concentrate, or plan and perform uncomplicated tasks (1). With the number of surgical procedures requiring anaesthesia exceeding 230 million worldwide and an increasing ageing population, the risks surrounding POCD could not be greater (2, 3, 5). It has been proposed that Alzheimer’s disease (AD), the most common form of dementia, may be accelerated by surgery, with also surgery itself increasing the occurrence of dementia (5). By the age of 65, 13% of people suffer from dementia and by age 85, the incidence is close to 50% (3). It is thought...
that POCD and dementia could share common pathophysiological processes (3, 6-8).

### Brain Regions

#### Hippocampus

The hippocampus, named so due to its resemblance in shape to a seahorse (9), is a crescent shaped structure formed from the inward curling of the inferomedial part of the temporal lobe (10). The hippocampus lies in the floor of the inferior horn of the lateral ventricle, deep to the parahippocampal gyrus (10). It is functionally connected to other areas of the brain which collectively form the hippocampal formation (11). These include the subiculum, presubiculum, parasubiculum and entorhinal cortex (11). The hippocampal formation receives fibres from the entorhinal cortex and projects via the fornix to the mammillary body of the hypothalamus (9).

The hippocampus is of immense importance regarding some forms of learning and memory (9, 12), functioning as our resident 'search engine', allowing us to navigate in 'mental space' when recalling memories or planning future actions (13). The knowledge of the critical role the hippocampus plays in learning and memory was first realised during studies on the famous patient HM, who had a bilateral medial temporal-lobeectomy (14). This resulted in severe anterograde amnesia and the inability to transfer new short term memories into long-term memories (15). Following on from work on HM, studies have demonstrated that the hippocampus is vital for several memory functions, including working memory, spatial memory and the process by which these new memories are consolidated into our permanent storehouse of autobiographical and factual knowledge in the neocortex (16).

A recent review analysed evidence supporting the role of the hippocampus in the temporal organisation of memory involving single hippocampal neurons, known as time cells and place cells that encode both the temporal and spatial aspects of a memory (17). These functions also allow the mental replay of spatio-temporal sequences at later points in time (16). This highlights the role of the hippocampus in episodic memory and its role for the organisation of the sequences of events within a particular episode (17). The process of replaying sequences has been hypothesised to underlie hippocampal function in both memory recollection and consolidation (16). Also, via feedback pathways with other brain areas, the hippocampus is able to support the retrieval of detailed memories that constitute strong recollective experiences in humans (16). It is this critical role of the hippocampus in memory and cognition that has made it a principle area of study in the pathogenesis and consequences of POCD.

#### Neocortex

The term neocortex used as most of the cortex in evolutionary terms is quite new compared to evolutionary older parts of the cortex, known as the archicortex and paleocortex (10). An area of the cortex particularly responsible for cognition and memory is the pre-frontal cortex (PFC) (16, 18). Unique to humans, the PFC is the highest level of cortical hierarchy devoted to the representation and execution of actions (19). Functionally, it is thought to integrate cortical and sub-cortical inputs to allow highly important cognitive functions such as attention, planning, working memory, reversal learning, set-shifting, response inhibition and decision making (18). Although the PFC is comprised of three regions: orbital, medial and lateral, it is the medial PFC (mPFC) that is thought to be associated with memory retrieval and consolidation. There is also new evidence to indicate that the mPFC accumulates information about the context of inter-related memories as well as controlling the specificity of memory retrieval (16). It is thought to do so through cognitive or strategic control over memory retrieval processes in other brain areas (16). A decline in the functions of the PFC has been noted with increasing age and disease; this can lead to debilitating neuropsychiatric and neurological disorders such as AD and schizophrenia (18).

#### Amygdala

The amygdala derives its name from Greek origins, meaning almond-like shape structure (20). It forms part of the limbic system and is located in the medial temporal lobe. Anatomically, it is not one single mass but it is composed of differ-
ent sub-areas or nuclei. Different nuclei of the amygdala receive inputs from the hippocampus and entorhinal cortex as well as the mPFC (20). Functionally the amygdala is associated with a variety of emotional functions, particularly fear, mediating the impact of negative emotions on memory (20, 21). It is also thought to be involved in regulation and modulation of several cognitive functions such as attention, perception and explicit (declarative) memory, a form of long term memory (20, 22). The amygdala is thought to modulate such functions via the processing of the emotional significance of external stimuli (20). As a consequence of the numerous inputs and outputs of the amygdala, it plays a crucial role in the interaction of emotion and cognition (22). Its connections with the hippocampus allow it to enhance explicit memories of emotional situations via the action of glucocorticoid hormones (20).

Other Brain Areas

Many additional brain areas contribute to the normal functioning of memory and cognition. It has been reported that brain regions that are involved in the cognitive functions decline as a result of POCD (23). Some of these areas include the cingulate and insular cortices as well as the thalamus and cerebellum (23). It is thought that the PFC could control the specificity of memory retrieval via a sub-cortical route through the thalamus, directly to the hippocampus (16). All these regions discussed above is illustrated in Figure.

Neurotransmitters

Neurotransmitters are chemicals vital to the functioning of the central nervous system (CNS). Glutamic acid (glutamate) and gamma-aminobutyric acid (GABA) are the principal CNS excitatory and inhibitory neurotransmitters, respectively (10). General anaesthetics produce their effects by interfering with their neurotransmission, either by positively modulating GABA receptors or antagonising excitatory N-methyl-D-aspartic acid (NMDA) glutamate receptors (24). Activation of the NMDA receptor is necessary for long term potentiation (LTP) and the formation of long term memories, with GABA receptors acting as the major inhibitory stimulus on memory consolidation (25). Both NMDA and GABA neurotransmitters are abundant in the hippocampus and are therefore susceptible to dysregulation by anaesthetic agents (25). Dopamine and serotonin (5-hydroxytryptamine, 5-HT) also act as neurotransmitters in the CNS, with 5-HT playing a critical role in cognitive function, short and long term memory as well as cognitive flexibility (26). Disruption of its neurotransmission has implicated it in cognitive impairment and its role in the pathophysiology of AD (26). The chief neurotransmitter of the cholinergic system, acetylcholine (ACh), plays a crucial role in memory and cognitive function (18). The depletion of ACh in the PFC is very closely linked to cognitive impairment, the development of delirium and neurodegenerative diseases such as AD (18, 27). Anaesthetics such as isoflurane and sevoflurane result in a decrease in the release of ACh (6, 8). As the depletion of ACh is associated with AD, it is thought that POCD may be an unintended consequence of the use of such agents (6) but warrants further study.

Network Dysfunction in POCD

While the hippocampus itself is critical for several aspects of memory function, it is the role of hippocampus as point of convergence for several anatomical and functional networks that makes cognition especially vulnerable to any loss of hippocampal integrity. Thus, in addition
focusing on surgery-induced changes in anatomically distinct brain regions, investigation of POCD must also consider the impact on patterns of network activity.

Increasing brain complexity demands ever-increasing loops of neuronal networks added to the basic circuit to sustain long-lasting neuronal sequences and improve prediction of more complex events. This type of network is exemplified by the hippocampus whose highly recursive matrix of local and long-distance connections is thought to function as a large ‘autoassociator’, allowing the reconstruction of entire episodes from remembered fragments (28). However, complexity comes at a price with greater risks of malfunction. Fortunately, neuronal activity in the hippocampus is itself regulated and fine-tuned by a neuromodulatory feedback network. The septo-hippocampal system is a well-characterised circuit that optimizes hippocampal firing activity by providing strong cholinergic input from the medial septal forebrain area. These projections, together with GABAergic and glutamatergic inputs, form a long-range feedback loop modulating rhythmic firing activity and synaptic plasticity in the hippocampus by maintaining a dynamic balance between excitation and inhibition (29).

In addition to classical synaptic transmission, the majority of cholinergic input to the hippocampus happens via ‘volume transmission’, occurring without identified apposite postsynaptic targets. Unlike rapid transmission at synaptic junctions, this slower diffusion mechanism is proposed to set a cholinergic “tone” by producing an extracellular ambient level of ACh (30). Basal levels of ACh are particularly susceptible to decline throughout the human lifespan in both cortical and hippocampal regions (31). This loss of cholinergic tone is strongly associated with cognitive decline and the loss of specific forms of memory, with progressive cholinergic atrophy recognized as a reliable histochemical hallmark of AD (31). Against this background, central cholinergic transmission is strongly implicated in the pathogenesis of not only postoperative delirium but also lasting POCD (32). The association between cholinergic function and delirious states is well documented, with high serum levels of cholinesterase activity or anti-cholinergic medication showing close correlation with postoperative cognitive impairment (33-35). More recently, clinical and experimental studies have indicated that cholinergic hypoactivity prior to surgery may also confer increased susceptibility to neuroinflammatory-based cognitive deficits (33, 36). This interaction between cholinergic hypofunction and a dysfunctional inflammatory response may provide insight into why acute postoperative impairments can lead to permanent cognitive decline and dementia in some patients.

In the past decade, interest in the pathophysiology of cognitive dysfunction has increasingly focused on the role of a number of higher-order cognitive ‘resting state’ networks, identified by functional magnetic resonance imaging (fMRI). These are sets of distant, but co-activating brain regions, characterised by synchronized spontaneous activity or ‘functional connectivity’ during normal wakeful resting conditions. The most widely studied of these is the cortical ‘default mode network’ (DMN), which preferentially activates when individuals engage in internal tasks such as introspection, envisioning the future and retrieving memories (37). In this respect, DMN activity is important clinically because it is associated with an individual’s level of ongoing conscious cognition. For example, degrees of consciousness impairment ranging from general anaesthesia to brain damage or coma correlate with suppression of connectivity in DMN areas (38).

Increasingly, evidence from neuroimaging studies suggests that progressive cognitive impairment may reflect the disruption of targeted networks rather than focal atrophy in specific brain regions and can progress through transneuronal spread (39, 40). The DMN appears to be especially susceptible, showing progressive age-related modifications and high vulnerability to pathophysiological processes such as the building up of amyloid-beta (Aβ), a major trigger for AD (41, 42). A possible explanation for this pattern of vulnerability was suggested by recent findings showing that Aβ appears to travel along networks in a cell-to-cell ‘infection’ like spread. This transneuronal transfer occurs prior to cellular atrophy and might be an early stress response by the cell to rid itself of aggregation-prone accumulations (43).

A growing number of experimental studies
have reported that the levels of Aβ are markedly increased in the brains of aged rodents displaying cognitive impairments following surgery and/or general anaesthesia (44, 45). It is therefore possible that among older or vulnerable surgical patients decreased clearance efficiency for Aβ may lead to network propagation of pathogenic proteins. In addition, the role of the forebrain cholinergic system may be of paramount importance. By virtue of its diffuse projections and an unusually high expression of p75 receptors, the forebrain cholinergic system is able to absorb and degrade large quantities of Aβ, thereby acting as a molecular sink for Aβ clearance in default mode areas (46), which are densely innervated by cholinergic neurons. However, a considerable topographical match between regions of cholinergic depletion and DMN areas in AD suggests that the ‘price paid’ for such a unique functional role could be greater deterioration of cholinergic projections during ageing (46). In light of these considerations, efforts to maintain central cholinergic function in the perioperative period may not only reduce the immediate risks of delirium and neuroinflammation, but may also preserve homeostatic clearance of Aβ from vulnerable networks during this at risk period.

### Research Update of Anesthetics/Surgery Induced Cognitive Decline

#### Ageing and the Neuroinflammatory Response

Although the risk factors for POCD are multifactorial, one risk factor that is certainly clear and predominant is increasing age (47-49), but normal aging is not exclusive (12, 50). The changes observed in the hippocampus with increasing age and their effects on learning and memory highlight the correlation between the increase in incidence of POCD and increasing age. Thus it is possible that the more of these age-related hippocampal changes a patient has, the more likely they will have POCD after surgery, with increasing severity.

In the context of POCD, its pathogenesis is thought to be that of an exaggerated or prolonged neuroinflammatory response due to anaesthesia and/or surgical stress, which is more likely to occur in old age (5, 51). This is unlike the normal neuroinflammatory response seen post-surgery which is modulated and subsides after a short time period. The exact mechanism by which this exaggerated response occurs is not fully understood. Under normal circumstances, it is thought that peripheral surgical stress activates an innate immune response termed the inflammatory reflex, which then activates the cholinergic anti-inflammatory pathway (52-54). This pathway modulates the immune response, terminates excessive pro-inflammatory cytokine responses, thereby preventing immune-mediated damage (53).

The afferent arc of the inflammatory reflex can be activated by endogenous and exogenous factors which have been well documented (5, 52-59). Sterile injury as a consequence of surgical trauma to peripheral tissues causes the release of damage associated molecular patterns (DAMPs), these include cytokines, high-mobility group box 1 protein (HMGB1), heat shock proteins, hyaluronan fragments, adenosine triphosphate (ATP), uric acid, heparin sulphate. These DAMPs activate toll-like receptors (TLRs) which via intracellular signalling activate the regulatory transcription factor nuclear factor-κB (NF-κB) (5, 53, 55-57, 59). This evokes an innate immune response and the release of pro-inflammatory cytokines, including interleukin-1 (IL-1) (52-59). Pathogen associated molecular patterns (PAMPs) such as endotoxins, enterotoxins, lipopeptides, glycopeptides and nucleic acids also interact with TLRs, leading to the activation of macrophages, monocytes, dendritic cells and other early responding cells (5, 52, 53, 56, 57, 59). This also activates NF-κB and causes the release of inflammatory cytokines (53, 56).

DAMPs and PAMPs also stimulate afferent sensory neurons which propagate action potentials via the vagus nerve which relays in the brainstem (52, 53, 55, 57-59). Action potentials that fire in the brain stem then activate the efferent arc of the inflammatory reflex, known as the cholinergic anti-inflammatory pathway (52, 53, 58). Activation travels peripherally via the vagus nerve to the spleen and other lymphoid organs (53), triggering Ach release and activation of nicotinic ACh receptor subunit α7 (α7nAChR) expressed by cells of the innate immune system (53, 55, 58, 59). This in turn suppresses the activation of NF-κB and reduces the secretion of
pro-inflammatory cytokines, hence, inhibiting the innate immune response (53).

Taken together, all these inflammatory mediators being discussed above including cytokines, DAMPs and PAMPs trigger complicated biological cascades and consequently damage glial and neuronal co-interacting functions. Ultimately, the neuronal network, which is the key neurologically functional substrates of cognition, is damaged. Also, high inflammatory state in ageing brain is another risk factor. Thus, it is not surprising that cognitive dysfunction is more prevalence in elderly following surgery or trauma.

**In Vitro-Long Term Potentiation**

The majority of in vitro LTP studies have largely focused on the effect of anaesthetic volatile gases on the hippocampus. Isoflurane anaesthesia reversibly improved cognitive function and LTP in hippocampal slices via an up-regulation in NMDA receptor 2B subunit expression (60). Another study hypothesised that sevoflurane-induced changes in NMDA receptor subunit composition might cause hippocampus-dependent cognitive improvement (61). Neither cognitive performance nor LTP was impaired 24 hours after anaesthesia with sevoflurane in male C57Bl6/J mice (61). Conversely, isoflurane reversibly inhibited LTP in rat hippocampal slices. This was shown to be prevented by nicotinic ACh receptor (nAChRs) agonist nicotine and α4β2 nAChRs agonist A85380 and epibatidine (62). A comparison of the effects of isoflurane and sevoflurane on LTP in the CA1 stratum radiatum of mice hippocampi, found that both volatile gases influenced synaptic strength to a similar degree, with only high concentrations blocking hippocampal CA1 stratum radiatum LTP (63).

Equal concentrations of synaptic transmission and at subanesthetic concentration postsynaptically enhances excitatory synaptic transmission in the hippocampal CA1 region (64). It is evident that the effects of anaesthetics on LTP are still unclear, with studies reporting dissimilar results; further studies are required.

Increasing age has been associated with a substantial increased risk of POCD (65). Age-related changes in the excitability of hippocampal pyramidal neurons have been demonstrated. Specifically, a decrease in post synaptic neuronal excitability resulting from an enhanced post-burst after hyperpolarisation (AHP) (12). Voltage-clamp recordings showed that the current of the AHP most affected by aging is the sIh (12). The sIh current is critical to modulation of neuronal excitability and enhancement of this current in aging indicates the significant role it plays in the cognitive decline seen with advancing age (12). It was also noted that the sIh current is affected by many neurochemicals and all the neurotransmitter systems (12). Some of these include a loss of cholinergic neurons, changes in Ca^{2+} dynamics in aging cells and dysfunctions in the dopaminergic, noradrenergic, serotonergic, and glutamatergic systems (12).

The hippocampi of aged rats were shown to have 3 biochemical changes; a loss of synapses in the dentate gyrus and CA1, a decrease in the NMDA-receptor-mediated response at perforant path synapses onto dentate gyrus granule cells, and an alteration of Ca^{2+} regulation in the CA1 area (50). It is thought that these changes cause age-related impairments in synaptic plasticity and affect the induction and maintenance of LTP, with a reduced threshold for depotentiation and long-term depression (50). Therefore, impairing the encoding of memories and resulting in cognitive decline (50). These studies highlight the significant age related changes in the hippocampus and their possible role in cognitive decline.

**Preclinical in Vivo Studies**

Laboratory studies using rodents to model POCD have begun to shed light on how peripheral inflammation can trigger cognitive decline. Cognitive function assessed using a Y-maze was performed on splenectomised rats under an anaesthetic combination of droperidol and fentanyl (66). They found that cognitive function was temporarily impaired on day 1 and 3 post-surgery with surgery vs. non-anaesthetised rats (66). Another study compared the effects of minor surgery in adult vs aged rats on neuroinflammation and cognitive impairment. Adult rats did not show signs of neuroinflammation 24 hours after surgery, whereas, only aged mice had significantly increased levels of IL-1B mRNA in the
hippocampus post-surgery (67). The suggested reason for this finding was that the type and extent of surgery influences the severity of the neuroinflammatory response, and that the level of inflammation in the hippocampus was not severe enough to cause deficits in working memory and LTP (67). This reasoning could explain the reported variations in the severity of the effects of surgery on neuroinflammation in animal studies.

A sub-pyrogenic dose of lipopolysaccharide (LPS) administered prior to orthopaedic surgery in adult mice, exacerbated surgery-induced cognitive dysfunction. This was associated with increased levels of IL-1β in the hippocampus and plasma. It was hypothesised that a sub-clinical injection of LPS may sensitize monocytes and microglial cells to the immunological responses triggered by the subsequent orthopaedic surgery (68), providing insight into the role microglial cells may play in sustaining neuroinflammation.

The role of IL-1β and microglial cells and their involvement in the pathogenesis of POCD has been further investigated (69). Mice lacking the IL-1 receptor (IL-1R−/−) and wild type mice underwent peripheral orthopaedic surgery. Surgery caused hippocampal-dependent memory impairment that was associated with increased plasma cytokines, as well as reactive microgliosis and IL-1β transcription and expression in the hippocampus. This highlights the importance of inflammation in the pathogenesis of POCD, as well as the integral role of IL-1β (69). This was evidenced by lack of surgery-induced cognitive decline in IL-1R−/− mice, mice treated with an IL-1 receptor antagonist (IL-1β RA) and those treated with a non-specific inhibitor of inflammation, minocycline (69). Noting that when activated, they are capable of mounting macrophage-type innate immunity and secrete proinflammatory cytokines, reactive oxygen species, excitotoxins (such as glutamate), and neurotoxins such as b-amyloid precursor protein (69-71).

Age-specific changes in microglia may also explain the difference in hippocampal dependent cognitive deficits in young vs aged subjects (72). In a healthy adult brain, innate immune glial cells (astrocytes and microglia) usually exhibit a quiescent phenotype (73). However, due to age-dependent impairments in immune function and an increased inflammatory profile in the aging brain, glial cells can become primed (73). In their primed state, cells exhibit increase expression of GFAP, S100β and major histocompatibility complex-II (73). Therefore, in the event of a peripherally induced stress response, primed glial cells become hyper-responsive to secondary stimuli and can produce an exaggerated and prolonged neuroinflammatory response (72, 73).

Further evidence for the role of the CNS and microglial activation in response to surgically induced neuroinflammation has been shown following the failure of a peripherally injected IL-1β antagonist (IL-1β RA) to show any protective effect (47). In contrast, an intracisternal injection of an IL-1β RA prevented both hippocampal memory impairment and any neuroinflammatory response (47), suggesting that the cognitive deficits are a result of a centrally produced IL-1β. In contrast to these findings, the effect of acetylcholinesterase inhibitors on neuroinflammation and degeneration in the cortex and hippocampus was investigated on adult wistar rats undergoing surgery (51). Surgery accompanied by LPS-treatment led to increased IL-1β gene and protein upregulation in the cortex and hippocampus but was significantly reduced by physostigmine and neostigmine (51). This supports the idea that a peripherally induced stress response is able to mediate and cause prolonged central neuroinflammation. This could also provide potential therapeutic strategies for reducing neuroinflammation postoperatively in at risk individuals.

Mice undergoing surgery, pretreated with atorvastatin, had significant protection from hippocampal IL-1β production, but not systemic IL-1β production, accompanied by a marked reduction in hippocampal inflammation including endothelial COX-2, NF-κB activation and decreased microglial reactivity (13). This highlights the role of atorvastatin as a potential therapeutic strategy in the treatment of POCD.

Surgery resulted in a postoperative elevation in brain β-amyloid (Aβ) levels and cognitive impairment in aging and AD transgenic mice (74). Peripheral surgery was able to induce cognitive impairment independent of general anaesthesia, and that the combination of peripheral surgery with aging- or Alzheimer gene mutation-associated Aβ accumulation was needed for the POCD.
to occur (74), although general anesthesia itself also caused cognitive impairment (75). This study could provide some evidence as to the reason why surgery may accelerate AD. As well as hippocampal changes with age, it is also affected by other insults such as trauma, hypoxia and neuroinflammation. The hippocampus is vulnerable to inflammation through a number of routes, namely; vascular; through the CSF (ventricles); or possibly from the periphery via inputs from the vagal nerve (69). The cause of the inflammation is still under scrutiny, whether it is the effect of surgery or anaesthesia alone, or a combination of the two is still unclear. However, there appears to be no difference in the incidence of POCD between general and regional anaesthesia (76). Hence, current studies have focused on the effects of peripheral surgical stress and the neuroinflammatory response that follows (51, 68, 77-79).

The release of inflammatory cytokines, particularly, IL-1β as a result of surgical stress and its role in the pathogenesis of POCD has been explored in many studies (47, 51, 69, 72). Other proinflammatory cytokines such as HMGB1 and the receptor for advanced glycation end products (RAGE) have been stated as being central mediators of surgery-induced cognitive decline, and may contribute to changes in BBB permeability after peripheral surgical trauma (78). Further studies are needed to better understand the pathophysiology of POCD.

**Human Studies**

An international multicentre study (the International Study of Postoperative Cognitive Dysfunction [ISPOCD1]) observed the effects of anaesthesia and surgery on 1218 people (65). They found that POCD was present in 25.8% of patients 1 week post-surgery and in 9.9% 3 months post-surgery, concluding that the risk of long term POCD is unequivocally increased with age (65). A subset of 336 elderly patients from this study was followed up 1-2 years post-surgery. Of the 336, 10% had cognitive dysfunction and only 0.9% had POCD (80). The authors concluded that POCD is a reversible condition in the majority of patients but can persist in approximately 1% (80). A further cohort follow up study of the ISPOCD1 study concluded that POCD was not significantly associated with registered dementia over a median 11 year follow up period (81). However, there is some degree of bias in the patient cohorts of these studies, with those considered to be high risk for developing POCD, withdrawing from the study.

Since the ISPOCD1 study there have been a number of studies investigating POCD in humans. A meta-analysis (17 studies) of POCD after total joint arthroplasty (TJA) in the elderly found small declines in reaction time and general cognition pre-discharge, but no evidence of decline 3-6 months post-surgery (82). However, their control data was severely limited and further research may be needed (82). A meta-analysis of 13 studies that measured the concentrations of peripheral inflammatory markers, in patients with and without POCD, found that POCD was correlated with increased concentrations of peripheral inflammatory markers (83). Particularly IL-6 and S-100β, but not of neuron specific enolase, IL-1β or tumor necrosis factor-α (TNF-α) (83). This is in stark contrast to numerous animal studies and the authors commented that it was possible their findings could not be interpreted as truly negative due to small sample sizes and significant heterogeneity between studies (83). Further studies, with larger patient cohorts and control groups are needed to clarify these contrasting reports.

Another study investigated the effect of intraoperative magnesium administration to improve neurocognitive function after cardiac surgery in 389 patients (magnesium: N=198; placebo: N=191) which concluded that it had no effect in reducing POCD (84). However, a qualitative review of 25 randomised clinical trials (RCTs) which investigated perioperative pharmacological neuroprotection found that atorvastatin and magnesium sulphate reduced the incidence of neurological deficit, and that all other agents remained controversial in their role (85). The other agents that were tested included: lidocaine, thio- pental, S(+)-ketamine, propofol, nimodipine, GM1 ganglioside, glutamate/aspartate and xenon remacemide, erythropoietin, piracetam, rivastigmine, pegorgotein, and 17b-estradiol (85).

A randomised double-blind study investigated whether postoperative ondansetron administration had a favourable effect on postoperative de-
lirium and 30th day cognitive function and pain in 106 patients (aged >40 years old) undergoing surgery with general anaesthesia due to femoral or hip fracture (86). Interestingly, postoperative administration of ondansetron was followed by a lower incidence and duration of postoperative delirium and improved postoperative neurocognitive function on the 30th postoperative day, regardless of age or history of stroke. Ondansetron seemed to improve cognitive function and have neuroprotective effects following surgery under general anaesthesia (86). From the human studies that have utilised a pharmacological intervention to attenuate cognitive decline, only ondansetron, magnesium sulphate and atorvastatin have been reported to be of benefit. Animal models can be used to further evaluate their mechanism of action in ameliorating POCD.

A deep level of anaesthesia measured by the bispectral index (BIS) has been found to improve processing speed as one aspect of cognitive function after surgery (87). The effect of the level of anaesthesia on POCD in 70 patients (aged >60 years old), assessed before and 1 week post-surgery, was unable to detect a link between the depth of anaesthesia and POCD (87). However, a randomised single blinded study found that the use of the BIS monitor was associated with a lower incidence of delirium, but not POCD (88). The lower incidence of delirium was suggested to be a result of avoiding extremely low BIS values intraoperatively (88). This provides some evidence that use of the BIS monitor could prevent a precipitating factor contributing to delirium in high risk patients.

Furthermore, a prospective cohort study with a nested randomised, controlled intervention trial examined the effectiveness of an intra-operative anaesthetic intervention in reducing POCD in adults (aged over 60 years old) undergoing elective orthopaedic or abdominal surgery (89). BIS monitors and cerebral oxygen saturation (rSO2) monitoring were used to optimise the depth of anaesthesia and rSO2 respectively (89). The 52 week cohort study (192 surgical patients, 138 controls) showed a significantly higher proportion of mild, moderate and severe POCD in surgical patients, than aged matched controls (89). The nested RCT also showed that mild and moderate POCD was reduced in the interventional group. S-100B levels were found to be correlated with both duration of surgery and number of minutes outside of optimal BIS index range (89). The study concluded that monitoring the depth of anaesthesia and cerebral oxygenation are beneficial interventions to reduce POCD (89). Further studies could build on this evidence, perhaps providing a framework for future guidelines in the use of BIS monitoring and cerebral oxygen monitors in at risk patients.

Fluctuations in melatonin secretion perioperatively have been used to predict the occurrence and detect POCD (90). This was based on the established knowledge that abnormal fluctuations of melatonin secretion occurs during postoperative delirium (POD) in elderly patients (90). The major melatonin metabolite, 6-sulfatoxymelatonin (6-SMT), was measured in urinary samples of 97 patients (aged 96-80 years old) on the day of surgery and on days 1, 2 and 7 after surgery (90). The incidence of POCD in patients with 6-SMT fluctuation was significantly higher (p < 0.01) (90). POCD occurred in a significant number of people in the first week post non-cardiac surgery (31.6% of patients) and this was linked to fluctuations in endogenous melatonin levels (90). The study concluded that measuring urinary 6-SMT during the perioperative period could assist in the diagnosis of POCD (90). Conversely, another method of detecting POCD was investigated using MRI to measure hippocampal volume in 41 patients (aged >65 years old) undergoing open gastrointestinal tract surgery (91). It was reported that 36% of these patients had POCD on postoperative day 4, with hippocampal volume significantly smaller in the POCD vs non-POCD group (91), suggesting that MRI of hippocampal volume could be a valuable predictor of POCD in the elderly. More studies evaluating new and existing reported predictors of POCD are necessary, potentially providing a useful tool in evaluating high risk patients.

### Co-risk Factors

Increasing age has been unequivocally identified as one of the biggest risk factors for long term POCD (65). Many other risk factors have also been identified. These include surgery related
risk factors such as: cardiac surgery, major and invasive surgery, long operation duration and postoperative complications (48).

Patient related risk factors can be categorised into cerebral, systemic and social risks (1). Cerebral factors refer to structural changes, namely: decreased whole-brain volume; changes in the blood brain barrier; a reduction in neurogenesis; hippocampal changes and amyloid and tau accumulation (1). Indeed, studies have shown that AD patients have reduced volumes of both the hippocampus and the amygdala (92). Other non structural cerebral changes associated with an increased risk are: brain inflammation; cerebrovascular disease; dysregulation of neurotransmitter levels; preoperative cognitive impairment (e.g. AD and mild cognitive impairment [MCI]) and a reduction in cognitive reserve (1).

Systemic risk factors such as vascular disease are usually associated with a range of comorbidities such as hypertension, diabetes mellitus and hyperlipidaemia (1). Pre-existing and postoperative infections present significant risks, priming microglia and exacerbating the neuroinflammatory response (65, 70). Lower educational level and a history of alcohol abuse have been identified as social risk factors (1, 48). Disturbances in sleep, inadequate analgesia and the genetic polymorphism (apolipoprotein E4) have also been stated as potential risks (5, 48).

Clinical Significance

Although there are various clinical trials that are currently investigating potential therapeutic interventions to prevent POCD, no definitive treatment has yet been identified. The clinical implications of POCD are potentially grave. The long-term consequences of POCD have been associated with increased mortality, increased risk of leaving the labour market prematurely and a higher prevalence of time receiving social support payments (93). With an increasingly elderly population that undergoes 25-30% of all surgical procedures, this can result in huge economic implications, longer hospital stays and increased placement into long-term care homes (2). Indeed, POCD has the potential to bare significant health, economic and social consequences.

Future Study

Cognitive function is governed by multiple brain regions. Hence preclinical studies should reflect this by investigating more brain areas and their impact on network function, not exclusively the hippocampus (23). The majority of pre-clinical studies analyse evidence 1 week post-surgery, this should be extended to reflect the greater time length it takes POCD to present, as shown in clinical studies (23). Further studies are required to elucidate the pathophysiology of POCD with the hope to identify vulnerable patients and find suitable preventive/therapeutic interventions to prevent the occurrence of POCD.

Conclusions

In conclusion, with an ageing population and increase in demand for surgical procedures, the need for investigating POCD could not be greater. An internationally agreed definition and battery of neuropsychological tests with formal diagnostic criteria to detect cognitive decline will help to provide greater understanding and homogeneity within the scientific community. Further study of the brain areas that govern the cognitive functions which decline in POCD could provide useful platforms and models for investigating its pathophysiology and devastating effects.

The work was supported by an Alzheimer’s Society- BUPA foundation project grant London, UK.

The authors have no potential conflicts of interest for this work.

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