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Should general anaesthesia be avoided in the elderly?

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Summary

Surgery and anaesthesia exert comparatively greater adverse effects on the elderly than on the younger brain, manifest by the higher prevalence of postoperative delirium and cognitive dysfunction. Postoperative delirium and cognitive dysfunction delay rehabilitation, and are associated with increases in morbidity and mortality among elderly surgical patients. We review the aetiology of postoperative delirium and cognitive dysfunction in the elderly with a particular focus on anaesthesia and sedation, discuss methods of diagnosing and monitoring postoperative cognitive decline, and describe the treatment strategies by which such decline may be prevented.

> Don't have a general anaesthetic once you're 50 – it'll wipe out a quarter of your brain.
>
> Barbara Cartland, novelist (died aged 98)

Concern has been growing over the last decade regarding whether anaesthesia can be harmful to the elderly brain, because elderly surgical patients frequently experience a postoperative deterioration in cognitive function, and such a decline may herald an increase in both morbidity and mortality.

In this review, we will outline some of the pertinent changes in human brain structure and function related to ageing, in order to understand the possible mechanisms behind cognitive and behavioural changes seen after surgery and anaesthesia. We will review some of the pre-clinical evidence that has given rise to the hypothesis that progressive neurodegeneration may be exacerbated by anaesthesia. Finally, we will provide clinical management insights by discussing some of the more controversial methods for monitoring the brain during anaesthesia, and outline how postoperative cognitive changes might be assessed and prevented.

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Pathophysiology of age-related neuropsychiatric decline

A number of anatomical and physiological changes manifest themselves as the human brain ages, and these may render the ageing brain more vulnerable to both reductions in cognitive reserve and the effects of surgery and anaesthesia (Table 1).

Brain volume

At approximately 45–50 years of age, a progressive decline in brain weight begins, reaching a nadir after the age of 86 years [1]. Grey matter volume increases in childhood, but then begins to decrease slowly. White matter volume increases until the age of approximately 45 years, reflecting increases in connectivity between brain regions, and thereafter starts to decrease. Decreases in whole-brain volume cannot be accounted for solely by ageing-associated losses in either white or grey matter, and seem to be multi-factorial in aetiology. For example, co-morbidities associated with ageing, such as diabetes and hypertension, can adversely affect changes in white matter tracts [2].

Blood–brain barrier

With ageing, the blood–brain barrier decreases in microvascular density and capillary lumen size, and the number of mitochondria per endothelial cell is reduced, changes that affect blood–brain barrier permeability [3]. Risk factors for acceleration of these changes include hypertension, hyperlipidaemia, diabetes mellitus and adverse drug reactions. Accumulating evidence supports the hypothesis that age-associated injury to the blood–brain barrier plays a role in the pathogenesis of white matter disease [3]. Blood–brain barrier changes may also alter the response to ischaemia, as well as drug entry to the central nervous system (CNS) [3].

Neurogenesis

In humans, neural stem cells are constitutively active in the hippocampal dentate gyrus and subventricular regions of the lateral ventricles, and proliferate into progenitors that differentiate into neurons in all age groups [4]. Neurogenesis in the dentate gyrus may cause a unique form of neural plasticity that is involved in cognitive and emotional functions. A gradual reduction in neurogenesis occurs with ageing, limiting the ability to learn and contributing to cognitive decline [4].

Inflammation

Communication between the peripheral immune system and cytokine-mediated signals within the CNS form a co-ordinated response to stress. Signals initiated in the peripheral immune system may result in CNS inflammatory responses that can manifest as changes in behaviour or cognition. Immunity in the CNS is mediated by microglia, astrocytes and CNS-associated macrophages. Microglia respond to, and propagate, inflammatory signals from the peripheral immune system. During the peri-operative period, for example, microglia might release cytokines or perform macrophage-like activities. Exaggerated or prolonged production of cytokines can occur in response to peripheral immune system stimuli as a result of impaired anti-inflammatory feedback in the aged brain [5]. An increasing body of

evidence suggests that increases in brain inflammation with ageing and systemic disease (e.g. metabolic syndrome) are associated with cognitive changes [6].

Cognition

Cognition changes with age in two main ways. First, measures that reflect acquired knowledge, such as vocabulary, improve up to ~60 years of age, after which they decline. Secondly, there is a nearly linear decline from early adulthood in cross-sectional and longitudinal measures of processing speed, including reasoning, memory and spatial cognitive abilities [7]. Memory decline occurs in more than 40% of people aged over 60 and can dramatically affect the performance of daily living activities, but is not a universal finding [8].

Cognitive reserve

Cognitive reserve describes the inconsistency between anatomic and functional age-related decline, and can be classified as passive or active. Passive reserve relates to brain size or neuronal count, and is measured, for example, by brain volume, synaptic count or dendritic branching. Active reserve relates more to functional cognitive integrity, and is preserved better in people with higher socioeconomic status and educational attainment, although no 'best measure' of active reserve exists. Higher educational attainment, for example, modifies the association between post-mortem Alzheimer's disease pathology and pre-mortem cognitive function: for the same degree of brain pathology, cognitive function is better with each year of education [9]. Epidemiological evidence suggests that a patient's cognitive reserve determines their cognition, rather than their underlying neuropathology [9].

Although both biochemical and anatomical changes have been described in the ageing brain, the exact mechanisms that cause changes in functional reserve are unclear. Decreases in functional reserve are manifest as decreases in activities of daily living, increased sensitivity to anaesthetic agents, and increased risk for both postoperative delirium (POD) and postoperative cognitive dysfunction (POCD).

Cerebrovascular disease

Risk factors, including hypertension, diabetes mellitus and elevated plasma homocysteine and apolipoprotein E, are associated with age-related large vessel arteriosclerotic and small vessel angiopathic cerebrovascular disease, resulting in infarction and haemorrhage [10]. Subclinical vascular disease, manifest as white matter hyperintensities on magnetic resonance images, is associated with changes in cognition, including attention, psychomotor speed and executive function [11], although the volume of these that is necessary to cause cognitive changes is unknown.

Anaesthesia and the elderly brain

Anaesthetic agents work on a relatively small number of CNS targets, and most of these are postsynaptic ligand-gated ion channels. Some drugs act at excitatory receptors, whereas others potentiate inhibitory synaptic receptors, such as gamma-aminobutyric acid (GABA) receptors [12]. Intravenous anaesthetics may have effects on GABA (propofol, etomidate),

alpha-2 (dexmedetomidine), N-methyl-D-aspartate (ketamine), acetylcholine, adenosine and dopamine (opioids) receptors [13]. Inhalational anaesthetic agents affect multiple ion channel receptors, including GABA, glycine, acetylcholine [14], glutamate, and serotonin [15]. The variety and complexity of anaesthetic agent/ion channel interactions underlie the postoperative cognitive problems experienced by the elderly. Interactions between anaesthetic agents and the CNS cholinergic system may be of particular importance [16], due to the close relationship between acetylcholine and cognition. Age-related decline in prefrontal cholinergic neurons may render the elderly more susceptible than younger patients to anaesthesia-mediated depression of CNS cholinergic neurotransmission [17, 18].

Monitoring the elderly brain during general anaesthesia

Monitoring brain oxygenation/perfusion and depth of anaesthesia have been advocated for reducing postoperative cognitive decline in the elderly. Studies have found an association between cerebral oxygen desaturation detected by intra-operative near-infrared spectroscopy (NIRS) and poorer cognitive outcomes [19], but are limited by non-uniform definitions of desaturation and cognitive decline, as well as inadequate sample size. Randomised controlled trials designed to assess the postoperative cognitive effects of minimising intra-operative cerebral oxygen desaturation have been inconclusive [19]. The relevance of diminished age-related autoregulation of cerebral blood flow in the elderly as a contributory factor to cerebral oxygen desaturation is also unclear [20].

Commercially available means of monitoring anaesthetic depth include electroencephalogram (EEG, processed or raw) and auditory evoked potentials. The most common EEG device in clinical use is the bispectral index (BIS) monitor. The association between depth of anaesthesia and postoperative cognition remains uncertain, with some studies concluding that ‘lighter’ levels of general anaesthesia guided by either the BIS monitor or auditory evoked potentials improve postoperative cognitive outcomes [21, 22], whereas others have reported no association or the opposite [23, 24]. Studies utilising both BIS and NIRS suggest that reducing both cerebral oxygen desaturation and the duration and depth of anaesthesia may be of benefit in reducing POCD [25].

The elderly patient and sedation

The sedation of elderly patients is a commonly employed, but under-researched, adjunct to regional anaesthesia, often for orthopaedic procedures. Dosage and method of administration are invariably extrapolated from clinical trials involving younger patients, and fail to take into account the altered pharmacokinetics and pharmacodynamics of elderly patients, resulting in relative overdosage and peri-operative cognitive alteration [26]. Patient-controlled sedation may avoid over-sedation, and has been used safely during cataract surgery with a high level of patient satisfaction [27], although use of this technique requires validation in other elderly populations, and may be limited to patients without pre-morbid cognitive dysfunction.

Evidence suggests that depth of sedation monitoring is important for elderly surgical patients. In a randomised double-blind study of 114 patients aged 65 years or over

administered spinal anaesthesia for hip fracture repair, patients who received deep sedation (BIS ~50) had a significantly higher prevalence of POD than those patients who received light sedation (BIS ~ 80) (40% vs 19%, p = 0.02) [28]. The type of sedation monitor used appears less important than the fact that the depth of sedation should always be monitored; indeed, BIS monitoring correlates poorly with clinical sedation scale scores [29].

POD and POCD – an update on classification, assessment and prevention

The most common types of deterioration in cognitive function are POD and POCD. Both are associated with significant morbidity and mortality, reinforcing the importance of their peri-operative assessment.

Classification

Postoperative delirium—Postoperative delirium is an acute organic brain syndrome that usually develops within the first few days after an operation. Postoperative delirium exhibits a fluctuating course and is often accompanied by abnormal circadian rhythm. The core symptom is inattention, but other cognitive changes are also common, including memory deficit and disorientation. Changes in psychomotor behaviour define whether delirium is classified hypoactive, hyperactive or mixed variation [30]. The hypoactive form is associated with relatively higher mortality, but is underdiagnosed because patients are quiet and relatively motionless, or misdiagnosed as symptomatic manifestations of dementia and/or depression [31]. Following a lucid interval, POD symptoms tend to appear 24–72 h after surgery, and are distinct from cognitive ‘emergence phenomena’ that occur during the transition from anaesthesia to wakefulness [32]. ‘Subsyndromal delirium’ has been suggested as a diagnosis for elderly patients who display one or more symptoms of, but do not meet defined diagnostic criteria for, delirium [33].

Approximately 10% of elderly surgical patients develop POD, rising to 30–65% after certain types of surgery, such as hip fracture, cardiac and emergency surgery [34, 35]. Patient-specific factors including advanced age, cognitive impairment, lower educational level and pre-existing medical conditions predispose to POD, as do potentially reversible risk factors such as pre-morbid CNS co-medication, infection, malnutrition, electrolyte imbalance, dehydration, environmental disturbances and substance withdrawal (alcohol, medication). Severe pain and inadequate analgesia increase the risk of POD in cognitively intact patients [36].

The pathogenesis of POD is still to be elucidated, but is generally thought to be multifactorial. Normal brain function relies on numerous well-functioning hormonal and neuromodulatory systems. Disturbances in CNS acetylcholine, dopamine and melatonin levels have been associated with POD [37]. It has been proposed that the high prevalence of POD after major surgery is related to the inflammatory component of the stress response to surgery. However, although a variety of inflammatory biomarkers have been investigated, postoperative elevations of only a few cytokines have been linked (weakly) to POD [38, 39]. It is of interest that microglial cytokine responses to peripheral immune system stimuli in vitro differ depending on whether cultures are exposed to isoflurane, sevoflurane or propofol [40].

Prolonged duration and increased severity of POD increase postoperative mortality [41]. Postoperative delirium is independently associated with prolonged hospital stay, short- and long-term risk of death and higher rates of institutionalisation after discharge, leading to a cumulative increase in healthcare expenses [41].

Postoperative cognitive dysfunction—Postoperative cognitive dysfunction is a syndrome of prolonged impairment of cognitive function after surgery, with limitations in memory, intellectual ability and executive function that usually last for weeks or months, but is distinct from delirium and dementia. It is a subtle condition; some patients only have minor symptoms, such as mild memory loss, whereas others are severely affected with pronounced inability to concentrate, process information or execute formerly uncomplicated tasks. Subjective symptoms or behavioural changes observed before and after surgery may arouse suspicion, but formal neuropsychological testing is necessary to diagnose POCD. Mild cases can easily be overlooked or dismissed as just normal signs of ageing, and often the patients or their relatives are the only ones to notice that deterioration has occurred.

To date, no formal diagnostic criteria have been established for POCD, which makes it difficult to evaluate in daily clinical practice. Nevertheless, recognition is essential, as POCD has been associated with increased mortality, risk of prematurely leaving the work market and dependence on socio-economic support [42, 43].

The incidence of POCD varies according to the definitions used in various studies [44]. Higher incidences are demonstrated in populations of elderly patients undergoing major surgery. For example, following coronary artery bypass grafting, the quoted prevalence of POCD varies between 10 and 80% early after the procedure and is thought to be associated with emboli, atherosclerosis and intra-operative ischaemia [45]. Postoperative cognitive dysfunction does not appear to be related to the use of cardiopulmonary bypass circuits [46], or intra-operative hypoxaemia or hypotension [47].

Similar to POD, several hypotheses regarding the aetiology of POCD have been suggested, including surgical stress-associated systemic or localised inflammatory reactions, alterations in hormonal homeostasis, and direct anaesthetic agent toxicity [48, 49]. Patterns of diurnal salivary cortisol excretion, for example, are significantly related to the development of POCD [48]. Intriguingly, serum levels of S-100B protein, a biomarker of cerebral damage, are significantly elevated in abdominal and vascular surgery patients who develop POCD, when compared with those patients who do not develop POCD [50] and after hip fracture in patients who develop POD [51]. Experimental studies in rats have shown that inhaled anaesthetics (in the absence of surgical stress) have sustained effects on memory formation, and are capable of inducing neurodegenerative changes on a cellular level [52]. Hippocampal damage correlates with cognitive impairment in rats [53], and reduction in hippocampal volume in humans measured by MRI may be valuable in predicting POCD [54, 55]. Despite intensive investigation, the pathogenesis of POCD remains poorly elucidated. It is still to be established to what extent postoperative decline in cognitive function is attributable specifically to either surgical or anaesthetic management, as distinct from patient-related risk factors such as extensive co-morbid cerebrovascular and systemic

vascular disease, or undiagnosed mild cognitive dysfunction, which may be of greater aetiological importance (Table 2) [56, 57].

Recent research interest has focused on whether POCD and POD are prodromal forms of Alzheimer's disease. The cerebral accumulation of β-amyloid and tau proteins are pathognomonic features of Alzheimer's disease, and anaesthetic agents appear to enhance this process, as well as potentiating the cytotoxicity of β-amyloid proteins, and tau phosphorylation and aggregation [58, 59], although evidence remains inconclusive. Surgery may have an independent effect on these processes [60], and one study suggested that elevation of β-amyloid concentrations might simply reflect synaptic activity [61]. The apolipoprotein E genotype is strongly associated with Alzheimer's disease and vascular dementia, but has not been shown to be associated with POCD [62–64]. Although it is methodologically difficult to establish any correlation between POD and POCD, a recent prospective study suggested that POD and POCD might represent a trajectory of postoperative cognitive impairment [65], perhaps as a progression of unrecognised pre-operative mild cognitive impairment [66].

Assessment

Postoperative delirium—Diagnostic criteria are defined in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Table 3), the former including more specific criteria than the latter, and proving more useful in establishing the diagnosis of POD (after cardiac surgery) [67].

Other diagnostic tools have been developed and validated to diagnose POD. The confusion assessment method (CAM) is easy to perform and sensitive, specific and reliable across populations [68], but is unable to stratify delirium according to severity; delirium is diagnosed by patient inattention of acute onset and fluctuating course, accompanied by either/or altered consciousness and disorganised thinking (Table 3). Subsequently, a CAM-ICU non-verbal screening tool was developed to diagnose delirium in intubated and critically ill patients [68].

Other scoring systems stratify POD severity, but are less sensitive in diagnosing delirium, and should only be employed once a diagnosis of POD is established. Repeated testing is important as POD exhibits a fluctuating time course, which is often overlooked in studies of POD [69]. Developing composite risk scores may enhance the prediction of delirium.

Postoperative cognitive dysfunction—There are no generally agreed criteria for the assessment of POCD, and the diagnosis is not yet described in either ICD-10 or DSM-IV. There are considerable inconsistencies between the multiple studies that have investigated POCD, which makes it difficult to formulate diagnostic criteria. No single test can adequately measure cognitive function with acceptable sensitivity. Instead, a battery of neuropsychological tests is required to assess individual cognitive domains, such as verbal skills and memory. When testing a new diagnostic screening tool, baseline tests must have been obtained pre-operatively and specific definitions of what constitutes a decline in cognitive function must be pre-defined [70], but there is no agreed definition of what

constitutes a significant decline, even though most studies are powered to detect a cognitive decline of one standard deviation from pre-operative levels.

In addition, the constituent tests of the battery administered vary between studies, and the intervals between testing are inconsistent [71]. Timing is crucial, as factors such as postoperative pain, opioid use and sleep disturbances all influence cognitive deterioration early after surgery. Furthermore, composite cognitive testing is associated with low sensitivity and specificity, and floor/ceiling effects (the test is too easy or too difficult, reducing discrimination between individuals scoring near the highest/lowest possible values), and may not always reflect specific patient symptoms. Finally, many studies fail to use an appropriate control group, invalidating inter-individual and intra-individual comparisons over time.

Prevention of POD and POCD—Treatment of POD is directed towards the correction of contributing factors after diagnosis, but prevention can reduce prevalence and improve outcome, and the same probably applies for POCD. Postoperative delirium may be predictable pre-operatively and therefore preventable to a degree [72], but attempts to create universal risk scales have failed, due to wide variation in surgical, patient and anaesthetic factors [73]. A systematic review suggested avoidance of opioids, benzodiazepines, dihydropyridines and histamine H_1-receptor antagonists in patients at risk of POD [74].

The multifactorial aetiology of POD appears amenable to improvement by using multi-domain interventions, including BIS-guided depth of anaesthesia monitoring combined with cerebral oxygen saturation monitoring [25], and proactive, multidisciplinary assessment, goal-directed optimisation of oxygen delivery, blood volume and serum electrolytes, and non-pharmacological support, including early mobilisation and sleep facilitation [75, 76]. Hypothetically, long-term cognitive outcomes might be improved by pre-operative diet, exercise and drug modification of underlying, undiagnosed systemic and cerebrovascular disease [57].

Pharmacological intervention is rarely of benefit in treating POD/POCD. Haloperidol can be used in cases of severe agitation, and may decrease the incidence of delirium [77] and reduce the severity and duration of POD [77–79], but evidence is inconclusive. Pharmacological modification of circadian disturbance using diazepam, flunitrazepam and pethidine reduced POD in a small randomised controlled trial (RCT) of 40 elderly patients after laparotomy [80], but this contradicts more recent evidence proscribing benzodiazepine administration [74]. Peri-operative dexmedetomidine infusion may be useful in reducing the prevalence of POD if patients require intensive care postoperatively [81]. A recent meta-analysis of 38 RCTs comparing prevention strategies for POD concluded that trials showed great inconsistencies in definition, incidence, severity and duration of POD, but supported the effectiveness of dexmedetomidine sedation (compared with propofol or benzodiazepine sedation), multicomponent interventions and antipsychotics in preventing POD, without finding any benefit relating to type of anaesthesia (general/spinal) or analgesia (nerve block) or use of anticholinesterase inhibitors (donepezil/rivastigmine) [82]. Other studies have found the risk of both POD and POCD to be similar after both regional and general anaesthesia [83, 84], but may be confounded by concomitant use of sedation with regional

anaesthesia. It is not yet clear whether the choice of general anaesthesia agent is important, but recent studies suggest that volatile anaesthetic agents (isoflurane, sevoflurane) are associated with a lower prevalence of POD than propofol [85, 86].

Is anaesthesia harmful for elderly patients? It is difficult to attribute cognitive changes to anaesthetic drugs per se. Even though some experimental research indicates such a correlation, evidence is conflicting and may not be significant in clinical practice. Surgical trauma or underlying pathology may be of greater importance, although their causal contributions to the pathogenesis of postoperative cognitive decline are yet to be determined. Neurophysiological and anatomical changes are relevant to the understanding of post-anaesthetic cognitive dysfunction in the ageing brain, but numerous other factors are involved, including surgical stress, inflammation, pain, co-morbidities and the phenotypic trajectory of a patient's cognitive decline with age. Further studies of postoperative cognitive decline need to employ assessment methods that are reliable and reasonably applicable in daily clinical practice, and these require further development alongside well-designed clinical trials that aim to investigate (multimodal) interventions that reduce the prevalence of this most distressing of postoperative complications.

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Table 1

Predisposing factors and possible mechanisms for the development of postoperative delirium/cognitive deterioration in elderly patients.

Predisposing factors		
Cerebral	Structural changes	
		• decreased whole-brain volume
		• blood–brain barrier damage
		• reduction of neurogenesis
		• hippocampal changes
		• amyloid or tau accumulation
	Brain inflammation	
	Cerebrovascular disease	
	Disturbances in levels of neurotransmitters	
	Pre-operative cognitive impairment	
	Reduction in cognitive reserve	
Systemic	Advanced age	
		• increased frailty
		• increased incidence of pre-existing illness
		• increased incidence of polypharmacy
	Systemic vascular disease	
Social	Lower educational level	
Potential mechanisms		
Neurohumoral inflammatory surgical stress response		
Thromboembolism		
Direct anaesthetic agent toxicity		
Ischaemia (hypoperfusion, hypoxaemia)		
Polypharmacy		
Hospital environment		

Table 2

Diagnostic criteria for postoperative delirium (POD).

DSM-IV [87]	
A.	Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
B.	A change in cognition (e.g. memory deficit, disorientation, language disturbance)
C.	Development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
D.	Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
E.	There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition
ICD-10 [88]	
An aetiologically non-specific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep – wake schedule. The duration is variable and the degree of severity ranges from mild to very severe	
Includes:	
•	brain syndrome
•	confusional state (non-alcoholic)
•	infective psychosis
•	organic reaction
•	psycho-organic syndrome
Excludes:	
•	delirium tremens, alcohol-induced or unspecified

Table 3

The confusion assessment method (CAM) diagnostic algorithm adapted from Inouye et al. [89].

Feature 1	**Acute onset and fluctuating course**
	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: is there evidence of acute change in mental status from the patient's baseline? Did the (abnormal) behaviour fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2	**Inattention**
	This feature is shown by a positive response to the following question: did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3	**Disorganised thinking**
	This feature is shown by a positive response to the following question: was the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4	**Altered level of consciousness**
	This feature is shown by any answer other than 'alert' to the following question: overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant (hyperalert), lethargic [drowsy, easily aroused], stupor [difficult to rouse] or coma [unrousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4