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Untangling anaesthesia and amyloid

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The burden of Alzheimer's disease is enormous: it has been estimated to be as high as the third leading cause of death and carries with it tremendous societal costs.[1] There are no effective treatments to delay the progression of Alzheimer's disease, and thus, prevention efforts are paramount.

The potential contribution of anaesthesia and surgery to the development of Alzheimer's disease is not clear. However, a growing body of literature suggests that older adults commonly experience cognitive changes after surgery, including delirium and longer-term cognitive decline.[2] Fortunately, many acute cognitive changes resolve, but there is likely a subset of vulnerable patients who suffer long-term cognitive sequelae. As more older adults undergo surgery, the importance of defining the perioperative contribution to postoperative cognitive decline is paramount.

A hallmark of Alzheimer's disease pathology is accumulation of amyloid beta (Aβ) in the brain. A leading conceptual model suggests that accumulation of Aβ is a very early event, starting decades before symptom onset. This is followed by appearance of neurofibrillary tangles, consisting largely of the protein tau, and neurodegeneration reflected by cortical thinning. Symptoms of memory impairment make their appearance at this stage.[3] Preclinical research has shown that surgery and anaesthesia contribute to the accumulation of Aβ, neuroinflammation, and functional impairment, but it is unclear if these processes occur in humans and are clinically relevant. Additionally, although enormous scientific effort has focused on the prevention of Aβ accumulation, the results of anti-amyloid therapies in clinical trials focused on cognitive loss have been almost entirely negative, suggesting either poor timing of the therapy or that other mechanistic pathways are better targets for therapy.

In this issue of the *British Journal of Anaesthesia*, Sprung and colleagues[4] report a study that examined the association between exposure to surgery/general anaesthesia (GA) and Aβ deposition in a group of 585 older adults (70–91 yr old) in the Mayo Clinic Study of Aging (MCSA). The authors measured brain Aβ using Pittsburgh compound B (PiB) positron emission tomography (PET), and used data from the Rochester Epidemiology Project medical records linkage system to identify surgery/GA in 84% of participants retrospectively (n=493). The authors used multiple approaches to characterise surgery/GA exposure, including as a yes/no dichotomous variable, by the number of anaesthetic exposures, and by the duration of anaesthesia exposure. Parallel analyses were conducted examining two different windows for surgery/GA exposure: within the prior 20 yr and since age 40.

Regardless of how surgery/GA was defined and the time window used to define the exposure, the authors found no association between exposure to surgery/GA and elevated brain Aβ deposition in later life. The authors also examined how prior surgery/GA related to two neuroimaging-defined markers of neurodegeneration: MRI-defined cortical thickness and 18-fluorodeoxyglucose (FDG) PET, a measure of glucose metabolism that typically shows region-specific abnormalities years before onset of clinically defined Alzheimer's disease. Whilst the authors did find evidence for an association between past surgery/GA exposure and reduced cortical thickness in brain regions known to be vulnerable to atrophic changes in the context of Alzheimer's disease, no association was found with FDG PET.

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Contextualisation of results

The authors should be commended for conducting this study and a series of other studies that address important questions relevant to preserving brain health in older adults. Longitudinal cohort studies, such as the MCSA and others, are particularly suited to research questions focused on brain health and often require long-term follow-up or expensive imaging. As with all studies, there are important limitations, including a geographically distinct and predominantly Caucasian sample, complicated selection biases for patients included in the study sample, and lack of imaging before surgery.

Thus far, studies that have examined the putative associations between surgery/GA and dementia in older adults have yielded mixed results.[5] Whereas a recent study provided evidence for a modest increase in dementia risk associated with surgical hospitalisation,[6] other studies, including a nested case-control study conducted within the MCSA cohort, found no such association.[7] However, using data from nearly 2000 participants in the MCSA cohort, this group did show that surgery/GA exposure in the prior 20 yr was associated with a steeper rate of cognitive decline, particularly in domains of attention/executive function and memory.[8]

An association between past surgery/GA exposure and increased brain amyloid would provide support for the hypothesis that surgery or anaesthesia exposure increases risk for cognitive decline by promoting Alzheimer's-specific processes within the brain. Indeed, numerous preclinical studies have shown an association between exposure to surgery/anaesthetics and increased oligomerisation[9] and accumulation[10] of brain amyloid. Whilst human studies have also been conducted to address this hypothesis, these studies have been small and have generally relied on CSF measurements. One study that measured CSF the day before and 24 h after open-heart surgery reported increases in $A\beta_{1-42}$ after surgery in a group of 10 patients. More striking, however, were the increases in CSF measures of inflammation, including tumour necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-8.[11] Another study of CSF samples from 11 patients undergoing idiopathic nasal CSF correction found no increases in postoperative $A\beta_{1-42}$ within 48 h, but did find longitudinal increases in CSF measures of neuronal and glial injury (total tau, phosphorylated tau, and S100beta) and inflammation (IL-10, IL-6, and TNF-α).[12] Despite evidence that surgery may not affect brain amyloid concentrations, several studies suggest that patients with elevated brain amyloid at the time of surgery may be at greater risk for adverse postoperative neurocognitive outcomes. For example, low $A\beta_{1-42}$ in the CSF and plasma (suggestive of higher concentrations of brain amyloid) has been associated with increased risk for postoperative delirium[13] and cognitive decline,[14] respectively.

With the increasing availability of PET tracers for Aβ, investigators have been able to test hypotheses about Alzheimer's disease-specific neurobiological mediators of postoperative cognitive decline in large cohorts. The results of the current analysis do not support an association between surgery or GA and increased deposition of Aβ. These findings are largely consistent with recently published results from the Atherosclerosis Risk in Communities study, which showed that exposure to surgical hospitalisation within the prior two decades was not associated with elevated concentrations of PET-defined brain Aβ in a group of 300 non-demented older adults.[15]

An important contribution of the current study was the use of a multimodal imaging approach to provide insight about the relative contributions of surgery/GA to changes in discrete neurobiological pathways associated with cognitive decline and dementia. Although past surgery/GA was not associated with cortical Aβ or cerebral metabolism, the association between surgery/GA and lower cortical thickness in brain regions vulnerable to Alzheimer's disease[16] is supportive of the notion that exposure to surgery/GA may promote regional neurodegenerative processes that occur independent of amyloidogenic processes or metabolic disruption. Taken as a whole, these findings suggest that surgery and anaesthetic exposure may cause neuronal damage in a process that is independent of brain Aβ deposition, but observable via CSF in the days immediately after surgery and measurable via MRI many years later.

Theoretical outlook

Whilst studies suggest that there may be a modest association between surgery/anaesthesia and neurodegenerative brain changes, acute or long-term cognitive decline, or dementia risk, the biological pathways connecting these events have yet to be fully elucidated. The results of the current study suggest important directions of future research, but also need to be interpreted in the context of the current understanding of the timeline of amyloid deposition.

First, amyloid deposition is an early event in the development of Alzheimer's disease, with a requirement for subsequent tau deposition for disease progression. It is now clear that amyloid alone is poorly correlated with neurodegeneration and cognitive loss, whilst tau accumulation and spreading are. In this regard, it should be recalled that several clinical studies now have shown large increases in CSF tau in the days after surgery, and it is conceivable that this reflects alterations in tau accumulation or spreading in the brain. Thus, information on tau deposition, using currently available tau PET tracers, may be more informative than amyloid. Finally, patients in this study were at least 70 yr old at the time of their PET scan and the prevalence of abnormal PiB was >50%, so it is conceivable that any alteration in amyloid accumulation trajectory as a result of surgery and anaesthesia decades earlier may no longer be apparent as amyloidosis tends to plateau.

Second, there are many other mechanisms for cognitive changes after surgery that need investigation. Human CSF studies, such as those described previously, and animal models[17 18] strongly suggest a role for inflammatory signalling. It is hypothesised that damage-associated molecular patterns distributed throughout the body as a result of surgery-induced tissue injury act as peripheral inflammatory triggers, which can, through neural or humoral routes, propagate a neuroinflammatory response. Indeed, increased pro-inflammatory signalling has been shown to occur after surgery in animal and human studies.[17–20] These inflammatory mediators have enhanced access to the CNS in the older adult because of both age and any ongoing pathologies. Moreover, these same individuals may have impaired ability to resolve inflammation; these pathways are currently an area of intense interest. A central role for inflammation is further emphasised by reports showing that hospitalisation alone, especially for acute infections and critical illness (both potent inflammatory triggers), is consistently associated with subsequent dementia risk and neurodegenerative changes.[21–24] If immune pathways define the link between surgery and adverse neurocognitive outcomes, then individual differences in the immunogenic response to tissue injury and anaesthesia exposure may be an important determinant of postoperative neurocognitive outcomes.

Finally, there may be a smaller subset of individuals who have particularly poor long-term neuropsychiatric outcomes who are masked in group-level analyses. Stated differently, some brains may be particularly vulnerable to acute stressors, including peripheral immune challenges, such as that which comes with tissue injury or exposure to GA. As an example, age-related immunological changes (i.e. immunosenescence) and the deposition of proteinaceous aggregates, such as Aβ, may prime or sensitise microglia, the brain's resident immune cells, so that they respond abnormally in the context of stressors, such as surgery or anaesthesia exposure.[25,26] Sensitised microglia can propagate a prolonged and potentially harmful neuroinflammatory response that may promote neurodegeneration through tau-mediated or alternative pathways with little to no effect on amyloid processing. Consistent with this notion, human and non-human studies have shown a reliable link between neuroinflammation and tau deposition.[27,28] Thus, a seminal challenge is to identify specific biomarkers of the vulnerable or sensitised brain. Such biomarkers will be important in future studies to determine whether the association between surgery/GA and neurodegeneration/cognitive decline is stronger in individuals with brain vulnerabilities because of age, genetics, or pre-existing morbidities. They will also allow us to appropriately risk stratify, and to inform, our older patients.

Understanding the mechanisms of postoperative delirium and longer-term cognitive changes and dementia is critically important for the growing number of older adults undergoing surgery. This study provides mechanistic insights using an epidemiologic approach and demonstrates the value of this type of study design. It is our hope that integrating details of surgical hospitalisations with novel biomarkers, brain imaging, and long-term cognitive and dementia assessments in this and other cohorts will provide important information to develop and optimise strategies to preserve brain health after surgery.

Authors' contributions

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Drafting of article: KAW
Revision for critical content: all authors
All authors approved the article and agree to be accountable

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Declarations of interest

CHB has had a data share and consulted for Medtronic in areas unrelated to this article. The other authors have no conflicts of interest to declare.

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Advances in precision anaesthesia may be found by testing our resistance to change

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Anaesthetic depth changes spontaneously over the course of an anaesthetic for pharmacological and physiological reasons. Traditional methods for determining the efficacy of anaesthetic agents in individuals rely on population statistics, which limits progress towards precision anaesthesia for each individual. The laboratories of Proekt and Kelz have begun to quantify this variability in anaesthesia in mice, both at the level of the individual mouse[1,2], and also regarding differences between specific anaesthetic agents.[2] In a study from their groups published by Wasilczuk and colleagues[2] in this issue of *British Journal of Anaesthesia*, three volatile anaesthetics (isoflurane, sevoflurane, and halothane) were quantitatively assessed with regard to stability over time of the loss of righting reflex, a surrogate measure of loss of consciousness in rodents.[3] Steady-state concentrations at the minimum alveolar concentration dose for each agent were administered, and the ability to right was determined at 3-min intervals in each mouse over 2 h. Although the responses of the population of mice resulted in a calculable half maximal effective concentration (EC_{50}) for each anaesthetic, the response dynamics of each individual mouse were highly variable. Over the 2-h measurement period, some mice exhibited the righting reflex on a majority of trials, while other mice failed to right on a majority of trials. The majority of the mice, however, exhibited seemingly random fluctuations between responsiveness and unresponsiveness during anaesthetic administration. The authors quantified this as a *resistance to state transitions* (R_{st}) using models of stochastic processes (Fig. 1).

Interestingly, different volatile agents exhibited differing degrees of R_{st}. Halothane produced the most stable behavioural responses during anaesthesia (highest R_{st}), whereas sevoflurane, and more so isoflurane, produced lower resistances (i.e. higher fluctuations between response and no-response trials). Wasilczuk and colleagues[2] argue that pharmacokinetic factors could not have played a role since animals were held at fixed inhaled concentrations for more than 2 h before behavioural measures commenced. Thirty minutes

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