10. Shahim P, Zetterberg H, Tegner Y, Blennow K. Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. *Neurology* 2017; **88**: 1788–94
11. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg* 2011; **112**: 1179–85
12. Silbert BS, Evered LA, Scott DA. Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. *Br J Anaesth* 2014; **113**: 784–91
13. Shaw PJ, Bates D, Cartlidge NE, et al. Long-term intellectual dysfunction following coronary artery bypass graft surgery: a six month follow-up study. *QJM* 1987; **62**: 259–68
14. van Dijk D, Diephuis JC, Nierich AP, Keizer AM, Kalkman CJ. Beating heart versus conventional cardiopulmonary bypass: the octopus experience: a randomized comparison of 281 patients undergoing coronary artery bypass surgery with or without cardiopulmonary bypass. *Semin Cardiothorac Vasc Anesth* 2006; **10**: 167–70
15. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. *Anesthesiology* 2018; **129**: 829–51
16. Scott DA, Evered L, Maruff P, MacIsaac A, Maher S, Silbert BS. Cognitive function before and after left heart catheterization. *JAMA* 2018; **7**, e008004
17. Berger M, Nadler JW, Friedman A, et al. The effect of propofol versus isoflurane anesthesia on human cerebrospinal fluid markers of Alzheimer's disease: results of a randomized trial. *J Alzheimers Dis* 2016; **52**: 1299–310

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Targeting microglia to mitigate perioperative neurocognitive disorders

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Perioperative neurocognitive disorders, including acute postoperative delirium and delayed neurocognitive recovery or postoperative cognitive decline (POCD), represent major health concerns for elderly patients undergoing anaesthesia and surgery.[1] These disorders are associated with poor long-term outcomes, increased healthcare costs, and increased mortality.[1,2] The lack of effective treatments place a tremendous burden on patients, their families, and our society. Thus, novel therapies are needed to prevent or treat these disorders.

In this issue of the *British Journal of Anaesthesia*, Lai and colleagues[3] postulate that Kv1.3 channels, which belong to the super-family of voltage-gated potassium (Kv) channels, are promising drug targets to mitigate POCD. The goal of their study was to determine whether inhibiting Kv1.3 channels expressed in microglia prevented POCD. The results raise interesting questions that are significant to the field of anaesthesiology, especially given the emerging role of microglia in POCD.

Microglia are the resident immune cells in the brain, where they account for about 10–15% of all cells.[4] Potassium channels, including Kv1.3, are important regulators of microglial function.[5] Previous studies in animal models have shown that microglial activation is necessary for POCD to occur[6] and also that Kv1.3 channels are required for microglial activation.[5] On the basis of these findings, Lai and colleagues[3] hypothesised that blocking Kv1.3 channels would prevent the activation of microglia and thereby mitigate POCD.

To test their hypothesis, the authors first studied the effectiveness of a small compound that inhibits Kv1.3 channels (phenoxyalkoxypsoralen-1 or PAP-1) in preventing POCD using a well-established mouse model of orthopaedic surgery. Briefly, healthy mice underwent a sham surgical procedure or repair of a tibial fracture under isoflurane general anaesthesia. Some mice were treated with PAP-1 by intraperitoneal injection before the surgery. Hippocampal-dependent memory

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performance was investigated 3 days later using a classical trace fear-conditioning paradigm. The results showed that memory performance was impaired in the surgically treated mice but not in the sham controls, as reported previously.[6,7] In contrast, memory deficits were not observed in surgically treated mice that received PAP-1.

Next, the authors studied a group of mice that had been rendered obese by eating a high-fat diet. This mouse model mimics patients with metabolic syndrome, which is a known risk factor for POCD.[6,8] Administration of PAP-1 prevented surgery-induced memory deficits in the obese mice. In addition, the authors studied genetically modified mice lacking Kv1.3 channels (*Kcna3*-/- mice), which exhibited no memory deficits after surgery. Collectively, these results suggest that activation of Kv1.3 channels is necessary for POCD in both normal and obese mice.

Previous studies have shown that both activation of microglia and neuroinflammation are necessary for POCD.[6,9] Thus, the authors next investigated whether treatment with PAP-1 reduced activation of microglia and attenuated neuroinflammation after surgery, by examining the hippocampus of obese mice 24 h after surgery. An increase in microglial size, which is a known indicator of cell activation, was observed in the hippocampal dentate gyrus region of vehicle-treated but not PAP-1-treated mice. Also, levels of the proinflammatory cytokine interleukin (IL)-6 were increased in the hippocampus after surgery in controls but not in PAP-1-treated mice. Thus, PAP-1 administered by systemic injection prevented microglial activation and the increase in IL-6.

Finally, the authors studied whether PAP-1 altered the formation of bone callus at the fracture site 10 days after surgery. No differences were observed between mice treated with vehicle and those treated with PAP-1, which led the authors to conclude that PAP-1 did not impair wound healing. Notably, the assessment of 'wound healing' was limited to an assessment of the bone callus, measured only once in healthy mice. As discussed in more details below, PAP-1 inhibits Kv1.3 channels in various cell types including those that play a major role in immunological processes. The claim that the drug has no effect on wound healing requires further characterisation.

Taken together, these results highlight Kv1.3 channels as novel therapeutic targets for the prevention of POCD. The results are intriguing given that inhibition of Kv1.3 channels attenuates brain damage from other causes of injury, including radiation.[10,11] In fact, PAP-1 and other Kv1.3 channel blockers are currently used for treatment of autoimmune conditions, including multiple sclerosis, type 1 diabetes mellitus, and psoriasis.[11] The results reported by Lai and colleagues[3] suggest that these drugs might be 'repurposed' for the prevention of POCD.

While the results obtained support the authors' initial hypothesis, the experimental design and results are insufficient to discern whether PAP-1 inhibited Kv1.3 channels expressed in microglia *vs* other cell types. For example, PAP-1 administered by intraperitoneal injection would also inhibit Kv1.3 channels expressed in peripheral immune cells, including T lymphocytes, B lymphocytes, macrophages, and tissue dendritic cells, which are the peripheral sentinels of the immune system.[11,12] In addition, Kv1.3 channels are also expressed in neurones.[11,12] Indeed, inhibitors of Kv1.3 channels are effective in treating a wide variety of neurologic and non-neurologic autoimmune disorders.[11] Proinflammatory cytokines and immune cells in the periphery can cross the blood–brain barrier and stimulate the activation of microglia in the brain after surgery[7,13]; thus, inhibiting Kv1.3 channel function may prevent such changes. Experimental tools are available to determine, in future studies, whether Kv1.3 channels in the brain and, more specifically in the microglia, play a pivotal role in the actions of PAP-1. Such approaches include administration of PAP-1 or other Kv1.3 channel blockers directly into the hippocampus and use of microglia-selective conditional knockout of Kv1.3 channels.

The results reported by Lai and colleagues[3] raise three important questions about the role of glial cells in perioperative neurocognitive disorders. The first concerns whether microglia can be targeted to prevent or treat POCD. In answering this question, the complexities of various microglial 'states' must be considered. Microglia are highly heterogeneous and respond to injury through complex response 'states' that differ in terms of the cell morphology, gene expression, and release of soluble factors. The state also depends on the location in the brain and the timeline of the injury.[14,15] The exact function of microglia in various disorders, including POCD, may be highly dependent on a particular state, at a particular time.

In addition, there may be differences between microglial responses in rodents and humans. In rodent models, drug strategies aimed at curtailing microglial 'activation' have been shown to attenuate POCD.[6] However, initial evidence in humans using positron emission tomography imaging with [^{11}C]PBR28 after surgery suggests that microglia show a suppressive phenotype acutely after surgery,[16] rather than a reactive phenotype as found in rodents.[6] Thus, targeting microglial activation in humans may not improve overall cognitive outcomes. A better understanding of the functional states of microglia, the time course of development of such states after surgery, and use of more specific ligands to interrogate microglial activation in humans would substantially advance the field. Experimental strategies might also include phenotyping of microglia using single-cell RNA sequencing in animal models before and after surgery. Indeed, characterising these activation states together with the ensuing 'signalome' might help identify additional therapeutic strategies.

Microglia do not act alone. Rather, they regulate the function of the 'tripartite synapse', which includes the pre- and postsynaptic components of neurones and astrocytes.[17] The second key question therefore concerns the role of microglia in modifying the function of the tripartite synapse, and specifically their effect on neurones and behaviour. Microglia closely contact neurones and regulate their activities. They continuously survey the microenvironment and rapidly respond to changes in brain tissue homeostasis or cell injury. Given that both excitatory and inhibitory neurotransmitter receptors in hippocampal neurones are modulated by neuroinflammation,[18,19] surgery-induced microglial activation and

neuroinflammation might directly modulate neuronal and network activities leading to POCD.

The third question regards the contribution of astrocytes to microglia-dependent changes in brain function. Microglia interact with astrocytes, which are the most abundant cells in the brain. Astrocytes are known to play a key role in POCD.[20,21] They form direct contacts with neurones as they regulate synaptic structure, neurotransmission, and network function. They release soluble factors, including gliotransmitters and neurotrophins such as brain-derived neurotrophic factor, which attenuate behavioural deficits after general anaesthesia.[22] Surgery-induced microglial activation might directly or indirectly modulate astrocyte function, leading to neuronal dysfunction and ensuing POCD. Such cross-talk between astrocytes and neurones, which involves a subtype of γ-aminobutyric acid type A ($GABA_A$) receptors that may play a pivotal role in POCD, has been shown.[20]

In summary, Lai and colleagues[3] have provided the first evidence that Kv1.3 channels are promising drug targets for mitigation of POCD. Whether the drug used in their study inhibited Kv1.3 channels in microglia remains unresolved. Importantly, the long-lasting impact of surgery on cognition is unlikely to be as a result of a single protein or cell type. Rather, it is more probable that multiple factors and cells act in concert to impair cognitive performance. It is of great interest to decipher the dynamic and reciprocal interactions among microglia, neurones, and astrocytes. Results from such studies will not only advance our understanding of perioperative neurocognitive disorders, but also inform a variety of disorders associated with cognitive decline, including neurodegenerative diseases such as dementia and Alzheimer's disease.

Authors' contributions

Concept and design of manuscript: all authors
Drafting and revising of the manuscript: all authors
Final approval: all authors
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Declarations of interest

DSW and NT have no conflicts of interest to declare. BAO is an inventor named on a Canadian patent (2 852 978), a US patent (9 517 265), and a pending US patent (62/268 137).

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References

1. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth* 2018; **121**: 1005–12
2. Steinmetz J, Christensen KB, Lund T, et al. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009; **110**: 548–55
3. Lai IK, Valdearcos M, Morioka K, et al. Blocking the Kv1.3 potassium channel prevents postoperative neuroinflammation and cognitive decline without impairing wound healing. *Br J Anaesth* 2020. https://doi.org/10.1016/j.bja.2020.05.018
4. Lawson LJ, Perry VH, Gordon S. Turnover of resident microglia in the normal adult mouse brain. *Neuroscience* 1992; **48**: 405–15
5. Di Lucente J, Nguyen HM, Wulff H, et al. The voltage-gated potassium channel Kv1.3 is required for microglial pro-inflammatory activation *in vivo*. *Glia* 2018; **66**: 1881–95
6. Feng X, Valdearcos M, Uchida Y, et al. Microglia mediate postoperative hippocampal inflammation and cognitive decline in mice. *JCI Insight* 2017; **2**, e91229
7. Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011; **70**: 986–95
8. Feng X, Degos V, Koch LG, et al. Surgery results in exaggerated and persistent cognitive decline in a rat model of the metabolic syndrome. *Anesthesiology* 2013; **118**: 1098–105
9. Eckenhoff RG, Maze M, Xie Z, et al. Perioperative neurocognitive disorder: state of the preclinical science. *Anesthesiology* 2020; **132**: 55–68
10. Peng Y, Lu K, Li Z, et al. Blockade of Kv1.3 channels ameliorates radiation-induced brain injury. *Neuro Oncol* 2014; **16**: 528–39
11. Wulff H, Castle NA, Pardo LA. Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* 2009; **8**: 982–1001
12. Feske S, Wulff H, Skolnik EY. Ion channels in innate and adaptive immunity. *Annu Rev Immunol* 2015; **33**: 291–353
13. Wang P, Velagapudi R, Kong C, et al. Neurovascular and immune mechanisms that regulate postoperative delirium superimposed on dementia. *Alzheimers Dement* 2020; **16**: 734–49
14. Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? *Nat Neurosci* 2016; **19**: 987–91
15. Tan YL, Yuan Y, Tian L. Microglial regional heterogeneity and its role in the brain. *Mol Psychiatry* 2020; **25**: 351–67
16. Forsberg A, Cervenka S, Jonsson Fagerlund M, et al. The immune response of the human brain to abdominal surgery. *Ann Neurol* 2017; **81**: 572–82
17. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci* 2009; **32**: 421–31
18. Wang DS, Zurek AA, Lecker I, et al. Memory deficits induced by inflammation are regulated by α5-subunit-containing $GABA_A$ receptors. *Cell Rep* 2012; **2**: 488–96
19. Haroon E, Miller AH, Sanacora G. Inflammation, glutamate, and glia: a trio of trouble in mood disorders. *Neuropsychopharmacology* 2017; **42**: 193–215
20. Zurek AA, Yu J, Wang DS, et al. Sustained increase in α5$GABA_A$ receptor function impairs memory after anesthesia. *J Clin Invest* 2014; **124**: 5437–41

21. Terrando N, Gomez-Galan M, Yang T, et al. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. *FASEB J* 2013; **27**: 3564–71

22. Wang DS, Kaneshwaran K, Lei G, et al. Dexmedetomidine prevents excessive γ-aminobutyric acid type A receptor function after anesthesia. *Anesthesiology* 2018; **129**: 477–89

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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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