

FEATURED ARTICLE

Neurovascular and immune mechanisms that regulate postoperative delirium superimposed on dementia

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Funding information

National Institutes of Health (NIH), Grant/Award Numbers: R01AG057525, R21 AG055877-01A1, R03 AG064260-01, K76-AG057022

Abstract

Objective: The present work evaluates the relationship between postoperative immune and neurovascular changes and the pathogenesis of surgery-induced delirium superimposed on dementia.

Background and rationale: Postoperative delirium is a common complication in many older adults and in patients with dementia including Alzheimer's disease (AD). The course of delirium can be particularly debilitating, while its pathophysiology remains poorly defined.

Historical evolution: As of 2019, an estimated 5.8 million people of all ages have been diagnosed with AD, 97% of whom are >65 years of age. Each year, many of these patients require surgery. However, anesthesia and surgery can increase the risk for further cognitive decline. Surgery triggers neuroinflammation both in animal models and in humans, and a failure to resolve this inflammatory state may contribute to perioperative neurocognitive disorders as well as neurodegenerative pathology.

Updated hypothesis: We propose an immunovascular hypothesis whereby dysregulated innate immunity negatively affects the blood-brain interface, which triggers delirium and thereby exacerbates AD neuropathology.

Early experimental data: We have developed a translational model to study delirium superimposed on dementia in APPSwDI/mNos2^{-/-} AD mice (CVN-AD) after orthopedic surgery. At 12 months of age, CVN-AD showed distinct neuroimmune and vascular impairments after surgery, including acute microgliosis and amyloid- β deposition. These changes correlated with attention deficits, a core feature of delirium-like behavior.

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Future experiments and validation studies: Future research should determine the extent to which prevention of surgery-induced microgliosis and/or neurovascular unit dysfunction can prevent or ameliorate postoperative memory and attention deficits in animal models. Translational human studies should evaluate perioperative indices of innate immunity and neurovascular integrity and assess their potential link to perioperative neurocognitive disorders.

Major challenges for the hypothesis: Understanding the complex relationships between delirium and dementia will require mechanistic studies aimed at evaluating the role of postoperative neuroinflammation and blood-brain barrier changes in the setting of pre-existing neurodegenerative and/or aging-related pathology.

Linkage to other major theories: Non-resolving inflammation with vascular disease that leads to cognitive impairments and dementia is increasingly important in risk stratification for AD in the aging population. The interdependence of these factors with surgery-induced neuroinflammation and cognitive dysfunction is also becoming apparent, providing a strong platform for assessing the relationship between postoperative delirium and longer term cognitive dysfunction in older adults.

KEYWORDS

inflammation, innate immunity, neuroinflammation, neurovascular unit, surgery, vascular

1 | OBJECTIVE

Here, we propose an updated immunovascular-driven hypothesis of the mechanisms underlying delirium superimposed on dementia. We intend to: (1) use our new clinically relevant model to interrogate the pathogenesis of delirium superimposed on dementia after surgery and (2) integrate our findings with ongoing efforts, recognizing the growing awareness of neuroimmune and vascular contributions to Alzheimer's disease (AD) pathophysiology. The objective of this work is to understand the role of postoperative neuroinflammation and neurovascular dysfunction in promoting neurodegenerative disease pathology. We propose that targeted therapeutic discoveries based on selective immunoregulatory approaches to normalize postoperative blood-brain barrier (BBB) dysfunction will be efficacious for treating and, possibly, preventing postoperative delirium and ensuing long-term cognitive decline.

2 | BACKGROUND AND RATIONALE

Every year, more than 19 million Americans over age 65 undergo anesthesia and surgery. Orthopedic surgery is routinely performed in these older adults, and as many as 50% of these patients suffer from postoperative delirium.¹ Delirium is an acute and fluctuating disturbance in awareness and attention that can also manifest through other cognitive domains. Delirium occurs not only after orthopedic surgery, but also after other types of surgery and in medical, intensive, emergency, nursing, and palliative care settings.² Although some studies have described higher delirium rates after cardiac surgery (reviewed in

Marcantonio³), other studies have found similarly increased delirium rates after other types of surgery. Importantly, preexisting medical conditions can also play a role in delirium rates. For example, postoperative neurocognitive complications occur more frequently in patients with lower baseline cognitive function. However, the extent to which surgical procedures versus individual patient risk factors contribute to delirium and cognitive dysfunction remains unclear.

Studies have suggested no difference in delirium rates based on anesthesia type (ie, general anesthesia vs regional anesthesia or nerve blocks), although these findings may be confounded in part by the significant doses of intravenous sedation given to patients who received regional anesthesia.⁴ Nevertheless, because delirium has been observed following different types of major surgery and different modes of anesthesia in older adults, there may be something intrinsic to surgical trauma itself, or to perioperative care and hospitalization in general, that contributes to the risk for these perioperative neurocognitive disorders.^{3,5}

To date, the Food and Drug Administration has not approved a drug to treat delirium, which contributes an estimated \$150 billion per year to the soaring health-care costs in the United States.⁶ Although some strategies have been implemented to prevent postoperative delirium, such as unit-based targeted multifactorial intervention⁷ and proactive geriatric consultation,⁸ delirium consistently correlates with poor outcomes including a five-fold increased risk for 6-month postoperative mortality, persistent functional decline, increased nursing time per patient, increased length of hospital stay, and higher rates of nursing home placement.⁸⁻¹⁰ When postoperative delirium occurs in patients with underlying dementia, the prognosis is even worse.¹¹ In fact, patients with

dementia who suffer delirium after hip fracture surgery have a two-fold increased risk for 1-year mortality compared to hip fracture surgery patients without dementia or delirium.¹² Furthermore, a diagnosis of delirium superimposed on dementia can be challenging and elusive,¹³ and why the synergism between dementia and postoperative delirium leads to poorer outcomes and even mortality is not clear.

3 | HISTORIC EVOLUTION

Inflammation is a well-recognized hallmark of pathology in multiple disease states.¹⁴ Since Alois Alzheimer's early seminal discoveries of amyloid- β (A β) plaques and neurofibrillary tangles in the post-mortem AD brain, glial cells (the brain's first responders of the innate immune system) have been identified in close proximity to these characteristic pathologic lesions. Indeed, inflammation is now recognized as a significant contributor to AD pathogenesis as well as other neurodegenerative pathologies.¹⁵ AD is currently the sixth leading cause of death in the United States, and its inexorable debilitating course has become a global pandemic without a disease-modifying therapy.¹⁶ The impact of surgery on the vulnerable brains of patients with either clinically diagnosed dementia or preclinical AD pathology remains largely underappreciated. Indeed, with more than 16 million procedures performed each year on older Americans alone, there is a growing need to understand the impact of surgery (and hospitalization in general), especially among patients in the highest risk strata.

Systemic inflammation has been described as a key driver of neuroinflammation and delirium-like behavior. Indeed it is well known that elements of infection, such as endotoxemia, trigger behavioral changes commonly referred to as "sickness behavior." It is also appreciated that systemic inflammation causes delirium and negatively impacts a brain prone to neurodegeneration.¹⁷ In fact, lipopolysaccharide (LPS) induces acute behavioral changes via a cytokine storm that can accelerate neurodegenerative pathology.¹⁷ In a disease-prone vulnerable brain, a single systemic challenge with LPS induces microglial IL-1 β expression and contributes to subsequent neuronal death in this "immune-primed" setting.¹⁸ Importantly, blocking IL-1 β signaling pharmacologically and genetically reverses memory deficits after LPS,¹⁹ as well as surgery-induced neuroinflammation.²⁰

We have pioneered a clinically relevant tibial fracture surgery mouse model that causes systemic cytokine release, disrupts the BBB, allows macrophages to migrate into the brain, alters microglial morphology, and causes memory dysfunction. Notably, using *Cx3cr1GFP/+ x Ccr2RFP/+* mice, we have reported that orthopedic surgery promotes the acute infiltration of monocytes into the brain parenchyma, and that this is dependent in part on TNF α /NF- κ B signaling.^{21,22} Macrophage-specific deletion of IKK β , a central coordinator of TNF α activation of NF- κ B, prevents macrophage infiltration into the hippocampus following surgery. D'Mello et al.²³ have described a similar immune-to-central nervous system (CNS) communication pathway after hepatic inflammation. They also demonstrated that TNF α -stimulated microglia produce monocyte chemoattractant protein (MCP)-1/CCL2, with monocyte infiltration into the brain. One prior study in surgery

RESEARCH IN CONTEXT

1. Systematic review: Postoperative delirium is a common complication in many older adults and in patients with dementia, including Alzheimer's disease (AD). A growing body of evidence is highlighting the role of dysregulated innate immunity as a key driver of cognitive deficits after surgical trauma. Yet, the biologic mechanisms that contribute to delirium and neurodegeneration remain unknown and without effective therapies.
2. Interpretation: Our data in APPSwDI/mNos2^{-/-} AD mice (CVN-AD) demonstrate distinct age-dependent neuroimmune and vascular impairments after orthopedic surgery. Importantly, surgery triggered acute A β deposition accompanied by microgliosis in the hippocampus of aged CVN β AD mice. These pathologic changes correlated with postoperative inattention, one of the core features of delirium.
3. Future directions: Future research should determine the extent to which targeted interventions aimed at protecting the neurovascular unit can curtail surgery-induced A β deposition, microgliosis, and delirium-like behavior. Translational studies are needed to define the evolution of Surgical Trauma Associated Molecular Patterns (ie, STAMPs) in postoperative delirium.

patients found an association between increases in postoperative MCP-1 levels and postoperative delirium, although this study measured MCP-1 levels in peripheral serum rather than in cerebrospinal fluid (CSF).²⁴ In another prior study, preoperative CSF MCP-1 levels did not predict postoperative delirium risk, which is consistent with our hypothesis here because the investigators did not measure postoperative CSF cytokine levels, and thus did not assess the relationship between postoperative CSF MCP-1 levels and delirium status.²⁵ We and other colleagues found that postoperative CSF MCP-1 levels were increased in one patient with delirium after orthopedic surgery.²⁶ Although this finding is far from definitive as it occurred only in a single patient, it does raise the question of whether MCP-1 enters the brain from the circulation or is locally produced to chemoattract monocytes into the human brain. Although monocyte infiltration has been implicated in disease progression and neurodegeneration,²⁷⁻²⁹ bone marrow-derived macrophages also have unique reparative properties, boosting tissue recovery in ways that resident microglia cannot.^{30,31}

4 | UPDATED HYPOTHESIS

The objective is to examine the impact of systemic surgical trauma on the AD-vulnerable brain by focusing on key neurovascular and neuroinflammatory markers. Our central hypothesis is that neurovascular pathology drives the development of postoperative delirium via

surgical trauma associated molecular patterns (STAMPs) that impair the blood-brain interface, which becomes more susceptible during aging with pre-existing AD pathology. In this study, we examined immunovascular pathology leading to delirium-like behavior in 3- and 12-month-old APPSwDI/mNos2^{-/-} AD mice (CVN-AD) after orthopedic surgery. We found that aged CVN-AD mice are more susceptible to postoperative neuroinflammation due to two key age-dependent phenomena: (1) failed resolution of inflammation, thereby perpetuating a maladaptive state during aging, and (2) increased neurovascular vulnerability due to underlying AD pathology, which renders the brain more susceptible to stressors like surgery. Indeed, the compromised BBB and neurovascular unit (NVU) are critical for allowing systemic factors to impact CNS health and homeostasis. Neurovascular pathology, such as cerebral amyloid angiopathy (CAA), is a key hallmark in human AD,³² and is also an established feature in the brain of CVN-AD mice.³³ Consistent with previous work that shows BBB impairment after surgery,^{34,35} we have found a close correlation between vascular dysfunction and neurodegeneration, with a significant deposition of A β in the hippocampus in the acute postoperative period. Interestingly, these changes are exacerbated in aged CVN-AD mice, which have higher systemic pro-inflammatory cytokines with no changes in anti-inflammatory markers such as IL-10. This finding provides evidence for non-resolving inflammation as a key driver of CNS pathology, especially within the context of intrinsic brain vulnerability present during aging and neurodegeneration. Early experimental data are presented in support of this theory.

5 | EARLY EXPERIMENTAL DATA

5.1 | Increased neuroinflammation in aged CVN-AD mice after orthopedic surgery

Male and female CVN-AD mice underwent an open tibial fracture of the left hind leg with intramedullary fixation under anesthesia and analgesia (see detailed methods in the supporting information). Three-month-old and 12-month-old mice were evaluated, representing a preclinical and a pathologic AD state, respectively. Both groups exhibited a robust postoperative systemic inflammatory response (Figure 1A). Plasma levels of the pro-inflammatory cytokines G-CSF and IL-6 were increased on postoperative day 1, irrespective of age ($P = .026$ for 3-month-old mice and $P = .0022$ for 12-month-old mice; $P = .033$ for 3-month-old mice and $P = .038$ for 12-month-old mice, respectively). However, markers such as MCP-1 ($P = .03$) and IP-10 ($P = .0033$) were greatly induced in the older brain of CVN-AD mice after surgery. TNF- α and MIP-1 α showed similar trends, without reaching significance. Notably, the potent anti-inflammatory cytokine IL-10 was minimally expressed in aged mice both at baseline and postoperatively, but was detectable at baseline in 3-month-old mice ($P = .0012$).

Next, we focused on microglial activation in the hippocampus and cortex. Microglial activation was not observed in 3-month-old CVN-AD mice after surgery (Figure 1B). However, profound microgliosis, as evidenced by changes in Iba-1 immunoreactivity ($P = .0003$) and

CD68 expression in Iba-1-positive cells ($P = .0018$), was observed in 12-month-old CVN-AD mice after surgery (a 57% and 66% increase, respectively; Figure 1C-E). These changes were not limited to the hippocampus, but were also observed in cortical regions (data not shown).

Together, these findings suggest that aging and underlying neurodegeneration render the BBB/NVU more susceptible to postoperative inflammatory changes. This is evidenced by limited ability of aged CVN-AD mice to resolve inflammation, thus allowing systemic factors to enter the brain and inducing microglial activation, which are already primed in the context of established AD pathology (Figure 1F).

5.2 | Neurovascular unit and blood-brain barrier dysfunction in CVN-AD after surgery

Neurovascular dysfunction is well characterized in the CVN-AD mouse model, resulting in aging-dependent astrocytic pathology (ie, GFAP activation) and reduced expression of aquaporin 4 (AQP-4), dystrophin 1, and potassium channels. Notably, these features have also been observed in human AD tissue.³⁶ Here, we interrogated postoperative changes in the key neurovascular markers CD31, GFAP, and AQP-4. Neither aging nor surgery significantly impacted expression of CD31. However, significant postoperative changes were observed in AQP-4 and GFAP expression, which were particularly evident in 12-month-old CVN-AD mice (Figure 2A-C). Three-month-old mice retained normal expression of AQP-4, with classical tubular formations (Figure 2A). This organized cytoarchitecture was abnormal in aged mice, and was further impaired 24 hours after surgery (42% decrease, $P = .0082$). Further, astrocytic activation was evident in the dentate gyrus area of the hippocampus in the aged group, and GFAP expression was significantly exacerbated in the hippocampus after surgery (93% increase, $P = .0022$; Figure 2A, C).

Next, we evaluated BBB function using fibrinogen and 70-kDa dextran tracing. Fibrinogen deposition in the perivascular space was significantly increased after surgery in 12-month-old, but not in 3-month-old CVN-AD mice ($P = .0022$; Figure 2D-E). Interestingly, we also observed postoperative fibrinogen extravasation (Figure 2D inset), which we confirmed by evaluating dextran extravasation at 24 hours. Fluorescent dextran tracer also perfused systemically in 12-month-old CVN-AD mice. Less intravascular dextran was observed postoperatively due to more extravasation and vascular dysfunction at 24 hours ($P < .001$; Figure 2F).

5.3 | Acute A β deposition in the hippocampus after surgery

Given the greater neurodegenerative pathology in 12-month-old CVN-AD mice, we evaluated the putative postoperative changes in A β levels in these mice. Compared to CVN-AD controls, we observed an acute increase in both the soluble (7.07 ± 0.80 pg/mg vs 10.36 ± 0.99 pg/mg) and insoluble (21.67 ± 3.48 pg/mg vs 36.22 ± 3.40 pg/mg) fractions of

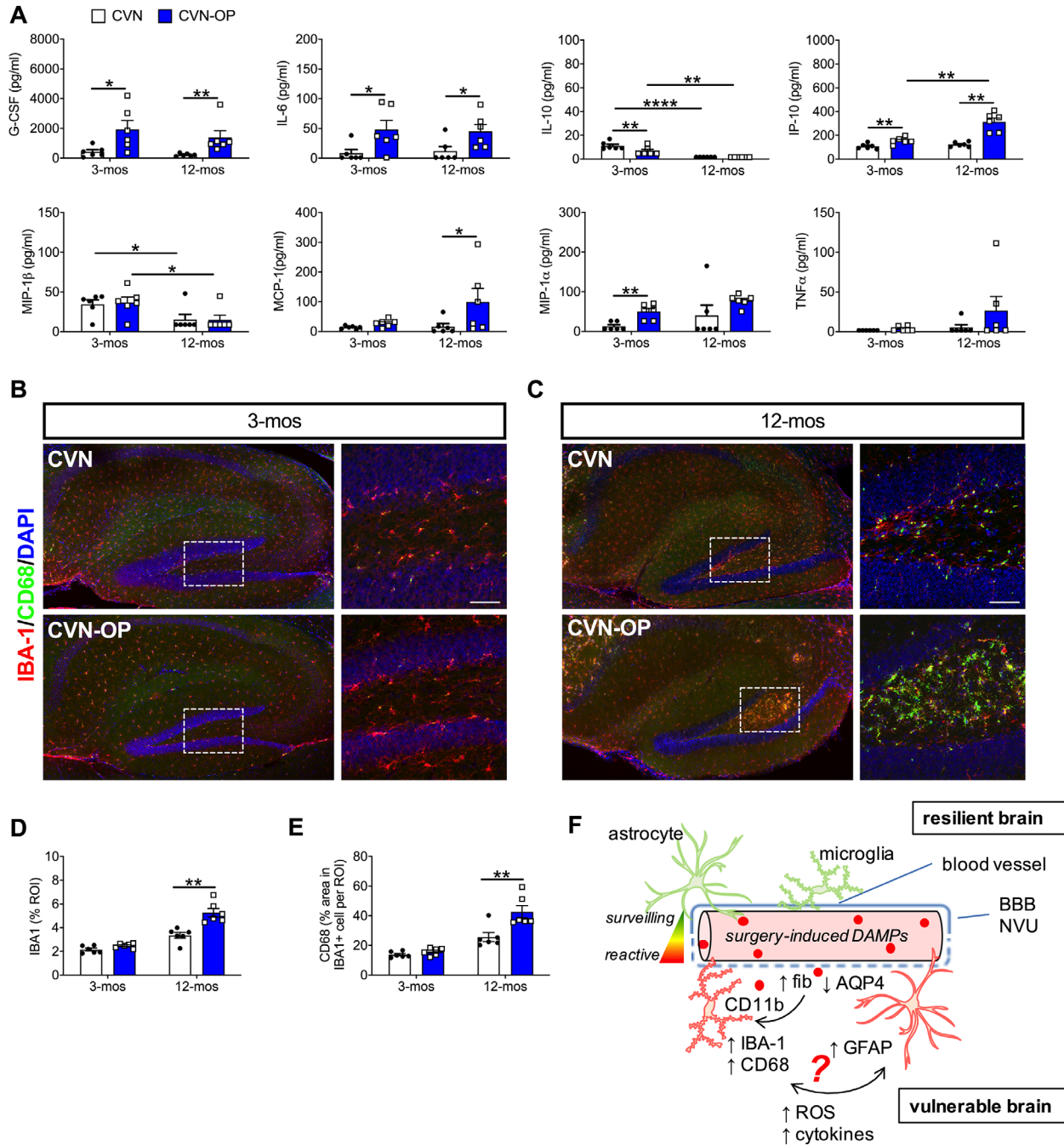


FIGURE 1 Age-dependent inflammatory changes after orthopedic surgery in CVN-AD mice. **A**, Systemic inflammatory markers in plasma from 3- and 12-month-old CVN naïve (CVN) and operated mice (CVN-OP) 24 hours after surgery. **B**, Hippocampal neuroinflammation in 3-month-old CVN-AD mice. The large field images were processed at 20× magnification and stitched. **C**, Hippocampal neuroinflammation in 12-month-old CVN-AD mice. **D-E**, Quantification of Iba-1 and CD68 immunoreactivity failed to show significant changes in microglial morphology in 12-month-old CVN-AD. *Inset* represents the dentate gyrus (DG). **F**, Schematic representation of putative mechanisms of age-dependent neuroinflammation and associated blood-brain barrier/neurovascular unit (BBB/NVU) dysfunction. In the CVN-AD adult brain the BBB is not affected by surgical trauma associated molecular patterns (STAMPs), thus resulting in no evident morphological changes in glia cells. However, older CVN-AD mice are “primed” and microglia respond greatly to STAMPs, including fibrinogen (see Figure 2), possibly inducing reactive astrocytes and initiating a vicious cycle that perpetuates neuroinflammation and neurotoxicity. Results are shown as mean ± standard error of the mean, $n = 6$ /group for both 3- and 12-month-old CVN mice. **** $P < .0001$, ** $P < .001$, * $P < .01$, $P < .05$, as measured by two-way analysis of variance with Tukey’s test for multiple comparison. Scale bar = 50 μ m

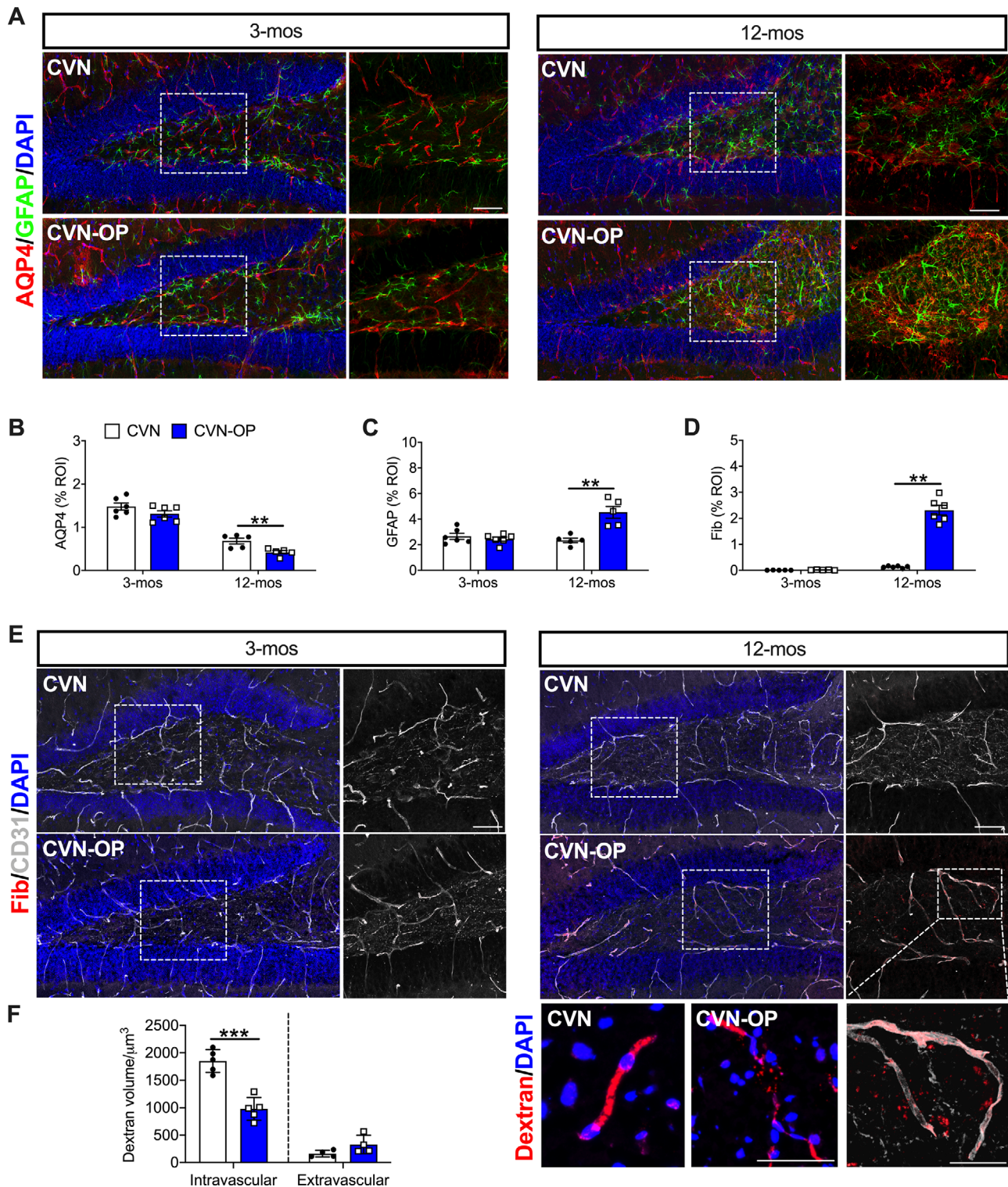


FIGURE 2 Neurovascular unit and blood-brain barrier dysfunction in CVN-AD after surgery. A-B, Age and surgery significantly impaired the expression of the water channel marker AQP-4 and increased expression of the astrocytic marker GFAP (C) in the dentate gyrus area of the hippocampus. The expression of the endothelial marker, CD31, remained constant across groups. D-E, However, 12-month-old CVN-AD mice showed increased levels of perivascular *Inset* further show extravasated fibrinogen in CVN-AD mice 24 hours after surgery. F, Dextran tracing also revealed leakiness of the blood vessels after surgery, resulting in a reduction in intravascular fluorescent dextran at 24 hours after surgery, although quantification of extravascular dextran did not reach significance. Results are shown as mean \pm standard error of the mean, $n = 5-6/\text{group}$. *** $P < .001$, ** $P < .01$, * $P < .05$, as measured by two-tailed unpaired Student t tests. Scale bar = 50 μm

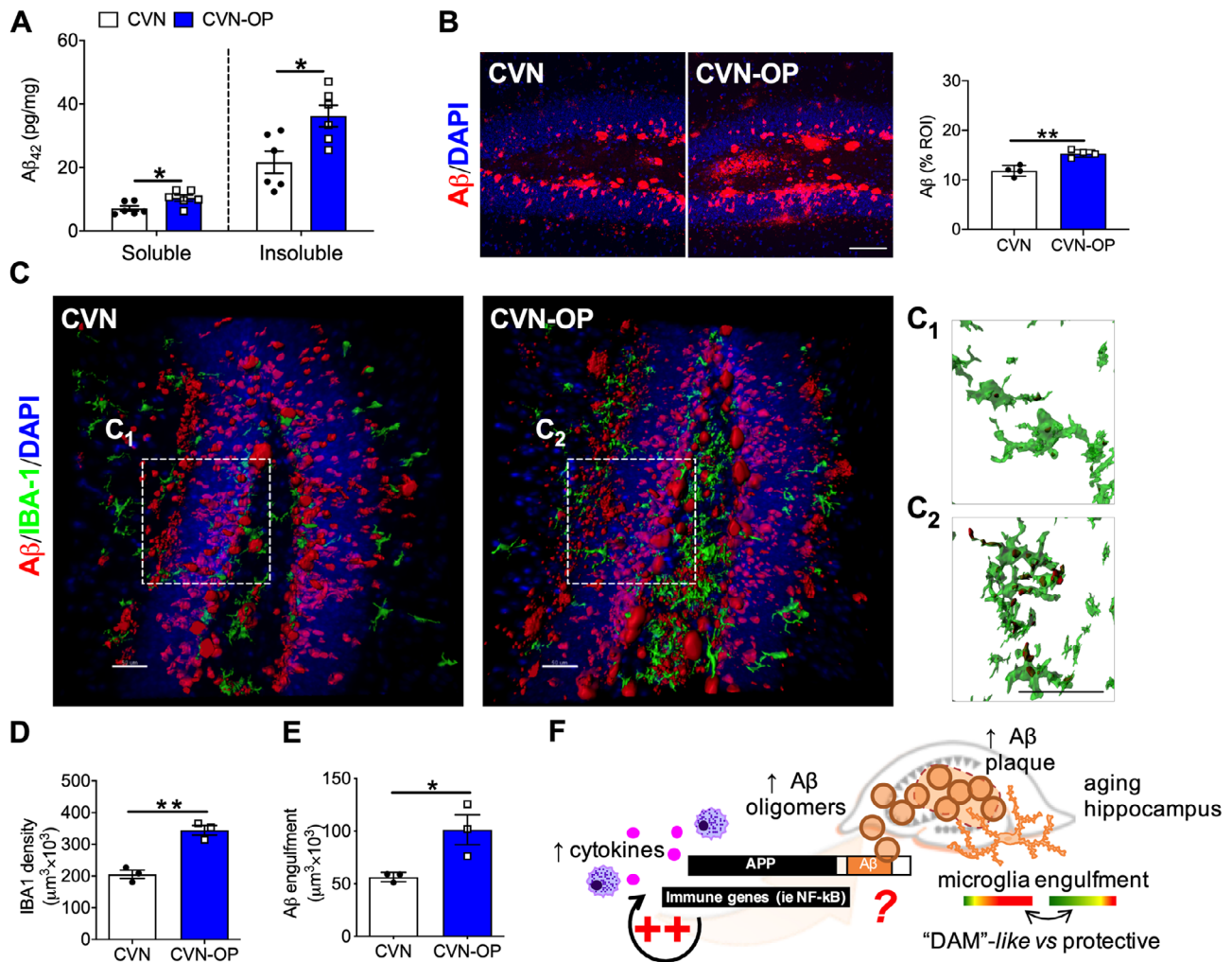


FIGURE 3 Acute amyloid- β deposition in the hippocampus after surgery in 12-month-old CVNs. **A**, Levels of soluble and insoluble A β 1-42 in hippocampal lysate were assessed using enzyme-linked immunosorbent assay. Surgery increases both fractions of A β 1-42 at 24 hours in older CVN-AD mice. **B**, Immunofluorescence and quantification of A β in the dentate gyrus area showed a rapid increase in hippocampal plaque load 24 hours after surgery compared to control mice. **C**, Tissue clarification of hippocampal slices was also performed 24 hours after orthopedic surgery using CLARITY. Three-D reconstructions of lightsheet images showed similar changes in the pan-microglial marker (Iba-1) together with amyloid β (A β) deposits after surgery. Increased A β engulfment (*inset*, renderings C1 and C2) was observed in CVN-OP mice compared to controls. **D-E**, Quantification of Iba-1 immunoreactivity and A β engulfment by microglia in tissue clarified slides. Amyloid was detected using a rabbit monoclonal anti-A β was used to visualize amyloid (D54D2, Cell Signaling Technologies). **F**, Putative model for acute postoperative A β elevation driven by immune genes like NF- κ B, thus elevating oligomers in the context of an AD-vulnerable brain. The function of microglial cells in response to surgical trauma associated molecular patterns (STAMPs)-induced A β is not yet defined and requires in-depth evaluation. Results are shown as mean \pm standard error of the mean, ** $P < .01$, * $P < .05$, as measured by two-tailed unpaired Student t test. Scale bar = 50 μ m

A β 42 in the hippocampus after surgery, as measured by enzyme-linked immunosorbent assay (ELISA; Figure 3A). This indicates the presence of the more toxic and aggregation-prone A β isoform. We corroborated these changes using standard A β immunofluorescence, and observed more plaques within 24 hours after orthopedic surgery ($P = .0139$; Figure 3B). To better evaluate and quantify changes in A β pathology and microglial dynamics, we employed tissue clarification (CLARITY)³⁷ (video 1 and 2 in supporting information). Three-D reconstruction of clarified hippocampal slices after lightsheet microscopy revealed significant changes in A β deposition at 24 hours after orthopedic surgery (22% increase; $P = .0139$; Figure 3C, D). Plaques were also

accompanied by reactive microglia as detected by Iba-1 immunostaining with CLARITY, with larger cell bodies and retracted processes indicative of a pathologic state ($P = .0026$; Figure 3C-D). Interestingly, we also found 80% greater A β engulfment by microglia after surgery ($P = .0362$; Figure 3C, E). Here, we propose an acute interaction between STAMPs and A β processing in the context of postoperative delirium superimposed on dementia. Immunity can alter AD-related transcription factors such as amyloid precursor protein (APP), which is critical in the production of A β .³⁸ The robust immune response that occurs after orthopedic surgery can rapidly elevate A β levels in the brain, thus contributing to a neurotoxic environment. Primed microglia

react to these changes; however, the function of these cells remains largely undefined, and the greater phagocytic activity described here may serve as a protective mechanism in response to the surgical stress (Figure 3F).

5.4 | Delirium-like behavior in CVN-AD mice

Impaired attention is key feature for delirium. We used the 5-choice serial-reaction time task (5-CSRTT), a validated procedure for the assessment of attention in mice³⁹ to characterize attention in age-matched 12-month-old C57BL/6J (C57) and CVN-AD mice. During a trial, a nose poke funnel is illuminated for 1.5 seconds followed by a 5-second response phase with extinguished nose funnels. The training and testing protocols are described in detail in the supporting information. All mice sustained at least an 80% response rate out of 40 daily trials throughout testing (Figure 4A). Within the responded trials, the correct responses were more than 90% in both C57 and CVN-AD mice across the baseline 3 days prior to tibial fracture (Figure 4B). However, on post-surgery day 1 and 2, CVN-AD mice showed significant increases for incorrect responses compared to baseline (average of 3 days prior to surgery, $P = .004$ and 0.045 respectively, Figure 4B). Although the incidence of incorrect responses also increased in C57 mice after surgery, no statistical difference was observed compared to baseline. The percentage of incorrect responses on post-surgery day 1 was also significantly higher in CVN-AD mice ($40\% \pm 8\%$) compared to C57 ($23\% \pm 6\%$, $P = .043$; Figure 4B). In addition, the increase of incorrect responses from average baseline to post-surgery day 1 (Δ incorrect responses) was significantly higher for CVN-AD mice compared to C57 ($15\% \pm 6\%$ vs $35\% \pm 8\%$, $P = .0497$; Figure 4C). Because the overall behavioral response ratio in 40 trials, whether correct or incorrect, remained stable in both groups after surgery compared to baseline (Figure 4A), the reduction in accuracy of behavior responses is most likely caused by incorrect choices. Therefore, our data suggest that compared to C57 mice, the CVN-AD mice experience more profound attention impairment following surgery.

In a separate cohort, we assessed neuronal markers at 24 hours after surgery, the peak of the attention deficit. Immunostaining showed that the number of MAP2+ neurons in 12-month-old CVN-AD mice was decreased although it did not reach significance from age-matched C57BL/6J mice (Figure 4E). After surgery, neurites were significantly impaired in both C57 and CVN-AD mice, although more significantly in the latter (25% reduction, $P = .0147$; and 42% reduction, $P = .0032$, respectively; Figure 4D and F).

6 | FUTURE EXPERIMENTS AND VALIDATION STUDIES

Future experiments should focus on defining the causal link between STAMPs and specific behavioral deficits. Based on our early experimental data, we propose to focus future work on the following two key areas.

6.1 | BBB and neurodegenerative hallmarks

We used the CVN-AD mouse model to specifically address the increased vulnerability of the NVU, part of the CAA pathology that these mice develop by 12 months of age.⁴⁰ Indeed, many limitations are intrinsic to the use of rodent models to address complex human diseases, especially to represent the more common, late-onset, form of AD.⁴⁰ The generation of reliable sporadic AD models will likely have a larger impact on delirium and aging-associated neurological disorders. In addition, models of other risk factors common to dementia and delirium, for example, metabolic syndrome and diabetes, should also be tested. Because AD pathology develops over decades before becoming clinically manifest,⁴¹ it remains crucial to determine how surgery may impact cognitive trajectories in animal models that attempt to recapitulate preclinical and mild cognitive impairment states. Additional experiments should evaluate relationships between trauma-induced factors and BBB/NVU dysfunction, and between BBB permeability and AD pathologic hallmarks such as $A\beta$, tau, and other proteinopathies.

Studies are under way to evaluate BBB dysfunction as a risk factor for postoperative delirium. In cardiac surgery the BBB can become compromised and this may have implications for postoperative delirium.⁴² Moreover, biomarkers of oxidative stress and neuronal injury are elevated in this surgical population, and are amplified in patients with BBB dysfunction, as detected by plasma levels of S100 calcium-binding protein B, which is usually released by astrocytes.⁴³ Endothelial dysfunction involving the BBB is also a feature of delirium in critically ill patients,⁴⁴ and studies in several animal models suggest changes in BBB permeability in perioperative neurocognitive disorders.^{35,45}

Future studies must also evaluate the kinetics of BBB opening after surgery, and determine whether specific biomarkers may help to identify patients at risk for developing delirium. One such biomarker is fibrinogen. For example, we found fibrinogen extravasated after orthopedic surgery in adult wild-type^{34,46} and CVN-AD mice (Figure 2). Fibrinogen can bind to the CD11b receptor expressed on microglia, which is associated with dendritic and spine loss in AD-like mice,^{47,48} and can additionally interact with $A\beta$ ⁴⁹ (Figure 5). In addition, $A\beta$ can interact with other inflammatory genes, such as NF- κ B, which is upregulated via pro-inflammatory cytokines during surgery; thus, NF- κ B can interact directly with APPs to transcribe oligomeric $A\beta$ 1-42.³⁸ As an acute-phase response to surgical trauma, this "immunocentric" function of $A\beta$ must be further assessed.

Inflammation is likely an influential event in the pathophysiology of AD.⁵⁰ Delirium can acutely accelerate existing neurodegeneration; however, such pathologic changes in the vulnerable brain may be unique to delirium superimposed on dementia. In fact, delirium in non-demented patients does not induce long-term changes in $A\beta$ load, according to positron emission tomography (PET) imaging,^{51,52} and similar findings are described when measuring CSF $A\beta$ biomarkers.^{53,54}

However, more detailed evaluation of vascular $A\beta$ pathology is required to determine if this is a *protective* response to acute trauma or a *pathogenic* hallmark of delirium superimposed on dementia, possibly

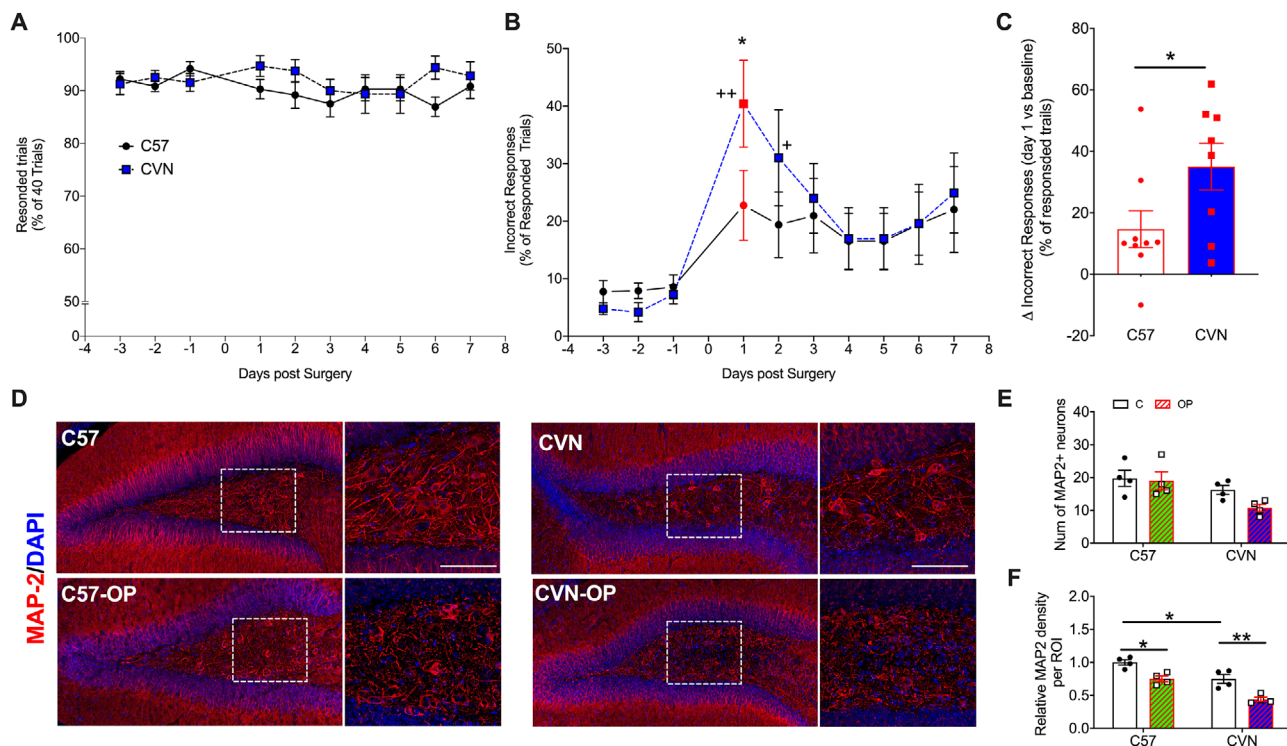


FIGURE 4 Orthopedic surgery triggers deficits in attention processes in CVN-AD mice and impairs neuronal markers. Attention was assessed using the 5-choice serial reaction time task (5-CSRTT) in 12-month-old C57 and CVN-AD mice. **A**, All the mice had over 80% responses (including correct and incorrect responses) in 40 daily trials throughout the testing days. **B**, On postoperative day 1 and 2, CVN-AD mice showed significantly higher incidence of incorrect responses compared to baseline. Furthermore, the incorrect response ratio on postoperative day 1 was significantly higher in CVN-AD mice compared to C57. **C**, The increase of incorrect response from baseline (average of results of 3 days prior to surgery) to postoperative day 1 was higher in CVN-AD mice compared to C57. **D–F**, Neuronal cytoarchitecture in the dentate gyrus (DG) area of the hippocampus. The expression of MAP2 was reduced in the DG of operated 12-month-old C57 as well as CVN-AD mice, although the number of neurons were not significantly affected. Results are shown as mean \pm standard error of the mean, $n = 8–9$ /group (behavior) and $n = 4$ /group (histology). ** $P < .01$, * $P < .05$, as determined by repeated measures analysis of variance (ANOVA) with Bonferroni corrections for 5-CSRTT and as measured by two-way ANOVA with Tukey's test for multiple comparison for histology. Scale bar = 50 μ m

predictable in the context of elective surgery. This is especially relevant in the context of $A\beta$ -directed therapies as many have failed in recent clinical trials for mild to moderate AD, with a remaining hope for efficacy in early “preclinical AD.”⁵⁵ Thus, targeting $A\beta$ within the context of a predictable injury, that is, surgery, will require careful validation in patients at risk for postoperative delirium.

6.2 | Neuroinflammation and delirium-like behavior

Dysregulated innate immunity is regarded as a key hallmark of many neurologic diseases including AD.⁵⁶ Further work is needed to define the signaling mechanisms involved in the transduction of systemic inflammation to the CNS, including defining if specific STAMPs are causally related to delirium onset. In this regard, using models of isochronic and heterochronic parabiosis, pioneering studies from Wyss-Coray et al. have demonstrated the important contribution of hematogenous factors to aging-related cognitive decline.⁵⁷ Because peripheral inflammatory stimuli are sufficient to disrupt synaptic communication and functional brain connectivity, it will be important to determine the extent to which perioperative increases in neuroinflam-

mation, for example, PET scan ligands, or cytokines in CSF, are associated with changes in brain activity/connectivity as measured by electroencephalogram (EEG [or functional magnetic resonance imaging (fMRI)]).

Multiple surgical models and clinical trials have been used in rodents and humans, respectively, to study perioperative neurocognitive disorders. These range from minimally invasive abdominal procedures to more invasive procedures such as cardiac, orthopedic, and vascular surgery (for a recent review of the preclinical field, see Eckenhoff et al.⁵⁸). Although the contribution of different immune factors and damage-associated molecular patterns (DAMPs) may vary depending on the procedure, neuroinflammation has been reported as a common overarching phenomenon that may presage delirium. Surgery activates glia, including microglia and astrocytes, which contribute to neuronal impairment and behavioral deficits. In our own work, we have found virtually no evidence that brief isoflurane anesthesia causes neuroinflammation or behavioral deficits, suggesting that the immune response to trauma is the main driver of cognitive deficits.^{20,59} Further, others have described inattention with acute changes in α -synuclein 24 hours after abdominal surgery with isoflurane anesthesia.⁶⁰ Also, anesthesia with surgery, but not anesthesia alone, caused long-term cog-

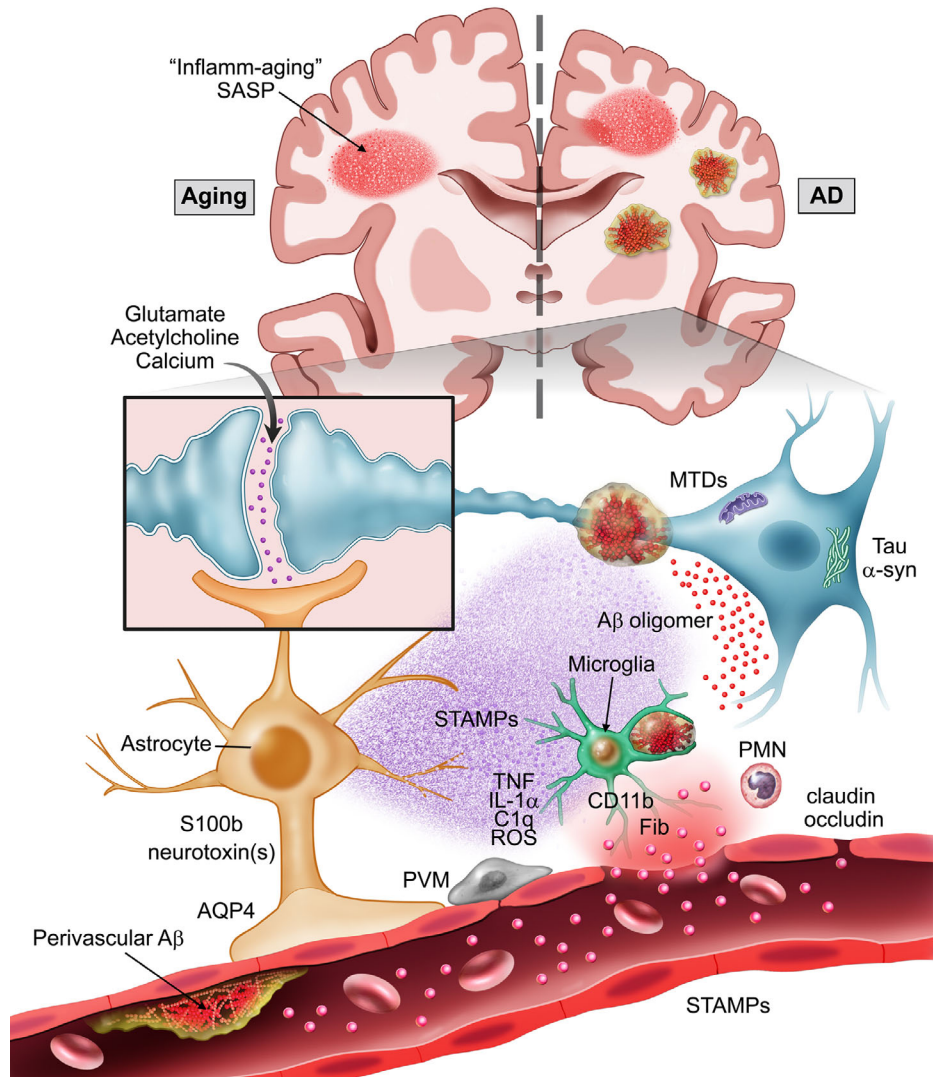


FIGURE 5 Visual abstract of putative mechanisms involved in the pathogenesis of postoperative delirium. Aging and dementia are the most significant risk factors for delirium. Both states are characterized by chronic inflammation (including inflamm-aging) as well as upregulation of senescent cells (SASP). The Alzheimer's disease (AD) brain has additional hallmarks of vulnerability, herein we focus on pre-existing amyloid β ($A\beta$) pathology. Together with the classical plaques and tangles, vascular pathology (including perivascular $A\beta$ /cerebral amyloid angiopathy) are commonly found in the AD brain. This ongoing pathology compromises the blood-brain barrier/neurovascular unit (BBB/NVU), which becomes more susceptible to additional stressors like surgery. Surgical trauma associated molecular patterns (STAMPs) can disrupt the BBB and preexisting BBB pathology amplifies delirium risk in patients. Detailed characterization of STAMPs (including cytokines, damage-associated molecular patterns [DAMPs], resolvins, etc) is needed. A putative factor, fibrinogen, enters the brain parenchyma and activates microglia via CD11b signaling. The time course of postoperative glial activation needs significant investigation. "A1" mediators like TNF, IL-1 α , and C1q can activate astrocytes contributing to neuronal loss. A similar process may explain postoperative delirium; however, astrocytes may also be an earlier responder in settings in which the BBB is already compromised. Markers like S100b are detectable at baseline in patients with perioperative neurocognitive disorders, thus STAMPs affecting astrocytic-end feet, water channels (like AQP-4) and tight junctions (claudin, occludin, etc) may in turn trigger microglial activation. Whether astrocytes directly release specific neurotoxins after surgery that compromise surrounding neurons is unknown. Thus, STAMPs may directly disrupt synaptic plasticity and/or by upregulating other factors like neurotoxic $A\beta$. These can impair calcium signaling, neurotransmitter release, and induce oxidative stress. Finally, peripheral immune cells may further contribute to this pathology and selective therapies to prevent infiltration may reduce delirium incidence in the vulnerable brain. Additional abbreviations: MTDs, mitochondrial damage associated molecular patterns; PMN, polymorphonuclear leukocytes; ROS, reactive oxygen species; PVM, perivascular macrophage

nitive deficits with signs of microglial activation, amyloidopathy, and tauopathy in 3xTgAD mice.⁶¹ Thus, anesthesia combined with surgery leads to a cascade of immune events, although anesthesia per se may influence inflammatory and neurodegenerative pathologic hallmarks, for example.^{62,63}

More detailed definitions of neuroinflammation that specifically focus on the function of microglial and astrocyte modulation by anesthesia and surgery are urgently needed in the perioperative field. Comprehensive transcriptomic studies are helping to define molecular signatures of highly heterogeneous immune cells in health and

disease.⁶⁴ Approaches that use single-cell RNA sequencing are identifying novel clusters with functional implications, such as disease-associated microglia (DAM),⁶⁵ that strongly associate with pathologic immunity in AD and other neurodegenerative disease. Future work should define and compare markers of perioperative immunity, including immune-metabolic signatures, with established datasets of rodent and human biofluids. Such cross-species comparisons are critical to validating the rodent models and to understanding similarities and differences in pathologic processes that accompany delirium and neurodegenerative disease. Current human data can be accessed via large programs such as Accelerating Alzheimer's Research and Drug Development (AMP-AD), which is supported by the National Institutes of Health (NIH) with multiple stakeholders in industry, academia, and non-profit agencies.⁶⁶

Finally, efforts should be devoted to safely targeting perioperative immunity with new therapeutic approaches. Therapies aimed at dampening the immune response, for example, with non-steroidal anti-inflammatory drugs or glucocorticoids, have shown limited or no efficacy in treating dementia (INTREPAD trial⁶⁷) or perioperative neurocognitive disorders (DECS trial⁶⁸). These drugs may also interfere with wound healing. Thus, more specific approaches may be required, especially in the context of a predictable stressor like an elective surgical procedure. Such approaches should focus on *selective* strategies that safely and effectively *regulate* perioperative immune responses (and/or specific STAMPs) without inappropriately activating or prolonging their effects. To ensure safety and selectivity, promising strategies may involve administration of specialized pro-resolving mediators, for example, resolvins, lipoxins, and maresins, or stimulation of neuronal pathways such as the vagus nerve, to regulate innate immunity.^{69,70} Finally, one of the most promising interventions to reset homeostasis between a compromised BBB, pathologic microgliosis and synaptic dysfunction is a "broad-spectrum" brain-penetrant small molecule inhibitor to mixed lineage kinases, URM-099.⁷¹ We have recently demonstrated its efficacy in preventing delirium and safety with respect to bone healing in our orthopedic model of hip fracture.⁷² The utility of this agent is further strengthened by its ability to reverse neuroinflammatory and synaptic damage in the APP/PS-1 model of AD.⁷³

7 | MAJOR CHALLENGES FOR THE HYPOTHESIS

Delirium is an emerging challenge in neuropsychiatry, gerontology, and perioperative medicine. Aging and dementia are the strongest risk factors for postoperative delirium. According to the network hypothesis of aging, "inflamm-aging" has been proposed as a critical driver of senescence via continuous low-level exposure to antigenic load and stress⁷⁴ (Figure 5). Surgery, especially in older frail adults, is associated with a potent antigenic load capable of inducing sterile inflammation through the release of DAMPs and cytokines. In vulnerable systems, DAMPs and cytokines can trigger postoperative complications such as delirium. In fact, older adults who develop delirium have significantly

elevated levels of pro-inflammatory cytokines in the CSF and plasma.²⁶ IL-6, a classic biomarker of inflammation, can induce pleiotropic effects both in health and disease by modulating the NF- κ B transcription factor.⁷⁵ Indeed, plasma IL-6 and C-reactive protein are the most powerful predictors of morbidity and mortality as well as postoperative delirium in older adults.^{76,77} In our study, we found similar changes in pro-inflammatory systemic markers, including IL-6 and the monocytic chemoattractant proteins MCP-1, MIP, and G-CSF. A key question remains: Does the increased incidence of postoperative delirium in older adults reflect a greater CNS inflammatory response with aging, or are older adults more cognitively sensitive to a similar magnitude of postoperative neuroinflammatory response? Although identifying more specific biomarkers may help to predict risk for developing delirium, deep immunophenotyping of elderly surgical candidate has the potential to provide further insights in this area.

Delirium and dementia are complex multifactorial disorders with multiple risk factors that can influence each other. Indeed, dementia is a strong predictor of delirium; however, many of the genes that are known to increase risk for AD are not clearly linked to delirium.⁷⁸ The apolipoprotein E (APOE) genotype is perhaps the most studied of these genes, given its predominant role in late onset AD. In the Successful AGing after Elective Surgery (SAGES) cohort of 560 patients aged ≥ 70 years who did not have recognized dementia or a history of delirium, APOE $\epsilon 4$ was not associated with higher delirium incidence, nor was $\epsilon 2$ carrier status, which is associated with decreased AD risk and with lower delirium incidence.⁷⁹ Similarly, in older adults undergoing elective primary hip or knee arthroplasty, APOE genotype and postoperative delirium were not associated.⁸⁰ However, Ely et al. found that the APOE $\epsilon 4$ genotype is the strongest predictor of delirium duration in critically ill patients.⁸¹ This finding is consistent with a large retrospective analysis of $\epsilon 4$ carriers undergoing general anesthesia and surgery, which showed that these patients experienced worse long-term cognitive outcome and an accelerated rate of decline.⁸²

APOE $\epsilon 4$ negatively affects tau pathology and tau-mediated neurodegeneration independently of A β ,⁸³ thereby providing a possible bridge between neurodegeneration and inflammation, especially in the context of glial activation and A β plaque phagocytosis.^{84,85} Thus, baseline immune status and/or immune cell-specific susceptibilities may underlie the different outcomes reported in the clinical studies above. Although host inflammatory responses are well conserved and ubiquitous following critical illness, trauma, or surgery, immune signatures may be unique to each patient. For example, a specific peripheral CD14+ monocyte subset was shown to predict postoperative clinical outcomes in hip surgery patients.⁸⁶ This finding suggests that more in-depth immunophenotyping of individual patients pre-/post-surgery is necessary to assign immune risk scores that may predict cognitive changes over time.

Interactions between delirium and dementia are becoming apparent; yet, the factors that contribute to progression are not known. Some studies have identified hospitalization as a strong risk factor for subsequent dementia.^{87,88} Based on our immunocentric model of delirium, it is plausible that early stressors impact brain function and accelerate individual predisposition to neurodegeneration. Indeed,

several aspects of the innate immune response are evolutionarily conserved, and thus our surgical model has important translational implications. In fact, we previously demonstrated that BBB opening allows macrophage migration into the brain parenchyma, and promotes changes in microglial activity, which is associated with deficits in declarative memory and hippocampal neuroplasticity.^{20,22,59,89,90} The interplay between glial cells and a potentially protective role of microglia and astrocytes is largely unexplored in perioperative medicine. Reactive "A1" astrocytes are present in several neurologic conditions including aging and AD, and have been observed after peripheral surgery.^{89,91,92} Liddel et al.⁹¹ demonstrated that microglia activate A1 astrocytes via cytokines and complement factors (Figure 5). Surgery triggers similar immunologic changes that are often transient and self-resolving; however, these changes may become maladaptive in co-morbid states such as advanced age, metabolic syndrome, and neurodegeneration.

According to this theory, an early stressor can predispose the individual to subsequent changes in neuroimmune functions, thus eliciting such phenomena as microglial priming.⁹³ Indeed, the blood-derived protein fibrinogen, which has been detected in the brain after postoperative decline (Terrando et al.²¹ and this study), promotes microglial activation, peripheral macrophage recruitment, and synapse loss.^{48,94} The mechanism by which systemic inflammation drives postoperative neuroinflammation remains unclear. Does it simply involve passive flux across the permeable BBB,⁴² or are cytokines produced in situ within the brain itself, perhaps due to a neural relay from the peripheral trauma site into the brain?⁹⁵ The latter model is supported by at least one study that reports higher levels of inflammatory cytokines in the CSF than in the peripheral serum after non-neurologic surgery.⁹⁶ In the CVN-AD mouse model, we detected high levels of systemic cytokines and chemokines after surgery, which may indicate an important role for the peripheral milieu in driving subsequent neuroinflammatory changes in the brain. In either case, the extent to which acute postoperative neuroinflammation contributes to long-term cognitive decline or even dementia after postoperative delirium remains unanswered. Work by Davis et al. demonstrated that *baseline* neurodegeneration increases the risk, severity, and duration of delirium in mice and humans.⁹⁷ However, the impact of one, or multiple, episodes of delirium on a nervous system without evidence of neurodegeneration will require further studies. For example, the differential impact of delirium on dementia subtypes or other neurodegenerative conditions such as tauopathies and Parkinson's and Lewy body diseases, is poorly described in the current literature.

Importantly, a recent analysis of autopsy and Medicare records that included cognitive outcomes data on >500 older adults showed higher rates of cognitive decline after hospitalization in subjects with tau tangles and neocortical Lewy bodies.⁹⁸

Finally, we do not yet know definitively how surgery affects select areas of the brain. CVN-AD mice exhibit postoperative age-dependent pathologic changes in the NVU, which are associated with changes in astrocytes and pericytes.³⁷ Surgery selectively impairs the hippocampal vasculature, which in turn can impact $A\beta$ distribution and CAA pathology.⁹⁹ However, hippocampal capillary damage is also

observed in patients with early cognitive decline, suggesting that this damage may occur before dementia onset.^{100,101} Indeed, these pathologic changes correlate with memory and cognitive impairments. Inattention, one feature of delirium, is largely attributed to impaired frontoparietal and frontostriatal networks in humans but is somewhat difficult to define in rodents. Thus, there is a critical need to study the effect of postoperative neuroinflammation on networks in the human brain that are related to dementia and delirium. Using fMRI and other brain imaging modalities will allow us to map postoperative changes in these networks and to identify other brain regions of interest.

8 | TRANSLATIONAL POTENTIAL

Postoperative delirium provides a unique clinical setting because we know exactly when inflammatory processes begin as the elective surgical procedures are typically scheduled weeks to months in advance. Therefore, therapeutic strategies (including those that have failed in AD) may find repurposing for conditions like delirium or for delirium superimposed on dementia.

Ongoing clinical studies are examining whether postoperative neuroinflammation leads to postoperative delirium with an attempt at identifying putative biomarkers for prevention. For example, advanced proteomic analyses comparing pre- and postoperative markers have identified plasma C-reactive protein as a perioperative marker of delirium.¹⁰² The application of blood-based biomarkers is attractive compared to CSF, which is more invasive and carries some risks. With the advances in blood-based biomarkers that accurately reflect AD pathology,¹⁰³ there are newer opportunities to detect autoantibodies, exosomes, and microRNAs that may readily identify high-risk patients for delirium.¹⁰⁴ Intraoperative markers of oxidative stress, including F2-isoprostanes and isofurans, were recently correlated with postoperative ubiquitin carboxyl-terminal hydrolase isozyme L1 in patients with delirium after cardiac surgery. This change was exacerbated in subjects with elevated S100 calcium-binding protein B, suggesting a vulnerable BBB hastens delirium.⁴³ PET imaging and dynamic contrast-enhanced magnetic resonance imaging are providing more selective approaches for interrogating changes in glial activity and NVU/BBB opening in older adults following surgery¹⁰⁵ and for those with neurodegeneration.¹⁰⁰ Ongoing studies like RISE (Role of Inflammation after Surgery for Elders)¹⁰⁶ and ASCRIBED (the impact of Acute Systematic inflammation upon CSF and blood Biomarkers of brain inflammation and injury in dementia)¹⁰⁷ will provide large cohort data on immune biomarkers in orthopedic patients during aging and ongoing neurodegeneration. These combined approaches are likely to contribute to a better understanding of delirium and AD pathology to refine therapeutic targets.

9 | LINKS TO OTHER MAJOR THEORIES

Evidence of impaired neurovascular function and neuroinflammation are increasingly recognized in the AD field.¹⁰⁸ The cerebral

vasculature plays a pivotal role in regulating the blood supply to the brain and the BBB interface. Changes in the cerebral vasculature can lead to neuronal dysfunction, and have been implicated in aging-related cognitive impairment including AD.^{109,110} Epidemiologic studies have shown that midlife vascular risk factors such as metabolic disorders and hypertension are associated with increased risk for dementia¹¹¹ and cerebral amyloid deposition later in life.¹¹² A separate population-based study revealed that demented patients are two times more likely to develop cerebral vascular pathology, for example, infarcts, atherosclerosis, and small vascular diseases, than are non-demented patients. In addition, patients who have vascular pathology plus AD-type lesions, that is, neurofibrillary tangles and A β plaques, have nearly twice the incremental risk for dementia compared to patients with only AD-type lesions.¹¹³ Thus, vascular dysfunction plays a critical role in the pathogenesis and development of dementias, and is one of the research priorities presented at the 2019 Alzheimer's Disease-Related Dementia Summit held at the NIH.

Dysregulated calcium signaling has been implicated in processes of neurodegeneration and associated cognitive loss, including AD.¹¹⁴ Indeed, A β plaques can alter calcium levels and overload synaptodendritic signaling;¹¹⁵ this in turn activates calcineurin that initiates long-term depression and decreases synaptic efficacy.¹¹⁶ Impaired calcium signaling also contributes to neurotoxic effects, including oxidative stress, mitochondrial damage, and neuroapoptosis by promoting opening of the ryanodine and inositol 1,4,5-trisphosphate receptors.¹¹⁷ Importantly, these receptors can be activated by anesthetics such as isoflurane, thus contributing to further toxicity in the vulnerable brain¹¹⁸ and synergize with the immune system¹¹⁹ (Figure 5).

Finally, aging itself is characterized by a low-grade, chronic, inflammatory state that can be exacerbated by multiple factors including co-morbidities; infection; trauma; and in some cases, surgery. Failed resolution of inflammation has been implicated in several pathologies and inhibits the return to homeostasis necessary for premonitory health.¹²⁰⁻¹²³ As our aging population increases in number, surgical procedures increase as well to maintain quality of life. Thus, strategies to prevent pathologic activation of innate immune responses in the aging brain become even more important to insure brain health.

ACKNOWLEDGMENTS

Supported by the National Institutes of Health (NIH) grants R01AG057525 (NT), R21 AG055877-01A1 (NT), R03 AG064260-01 (NT), K76-AG057022 (MB); additional support from the Duke Claude D. Pepper Older American Independence Center (P30AG028716); the Duke Anesthesiology Department (NT and MB); the Alzheimer's Association (NT). The equipment for the attention test was purchased with a grant from the North Carolina Biotechnology Center (to WCW). The Zeiss light sheet was purchased with a NIH S10 grant 1S10OD020010-01A1 (Dr. Lisa Cameron). Biomarker profiling was performed under the management of Dr. Andrew N. Macintyre and direction of Dr. Gregory D. Sempowski in the Immunology Unit of the Duke Regional Biocontainment Laboratory, which received partial support for construction from the NIH, National Institute of Allergy and Infectious Diseases (UC6-AI058607). We thank Stuart Sundseth

(Colton Lab, Duke University Medical Center) for assistance with the MSD assays; Benjamin Carlson, PhD (Light Microscopy Core Facility, Duke University) for guidance on imaging analyses; Kathy Gage, BS (Duke University Medical Center) for editorial assistance; and Katerina Akassoglou, PhD (Gladstone Institutes, UCSF) for discussions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Wang P, Velagapudi R, Kong C, et al. Neurovascular and immune mechanisms that regulate postoperative delirium superimposed on dementia. *Alzheimer's Dement*. 2020;16:734-749. <https://doi.org/10.1002/alz.12064>