

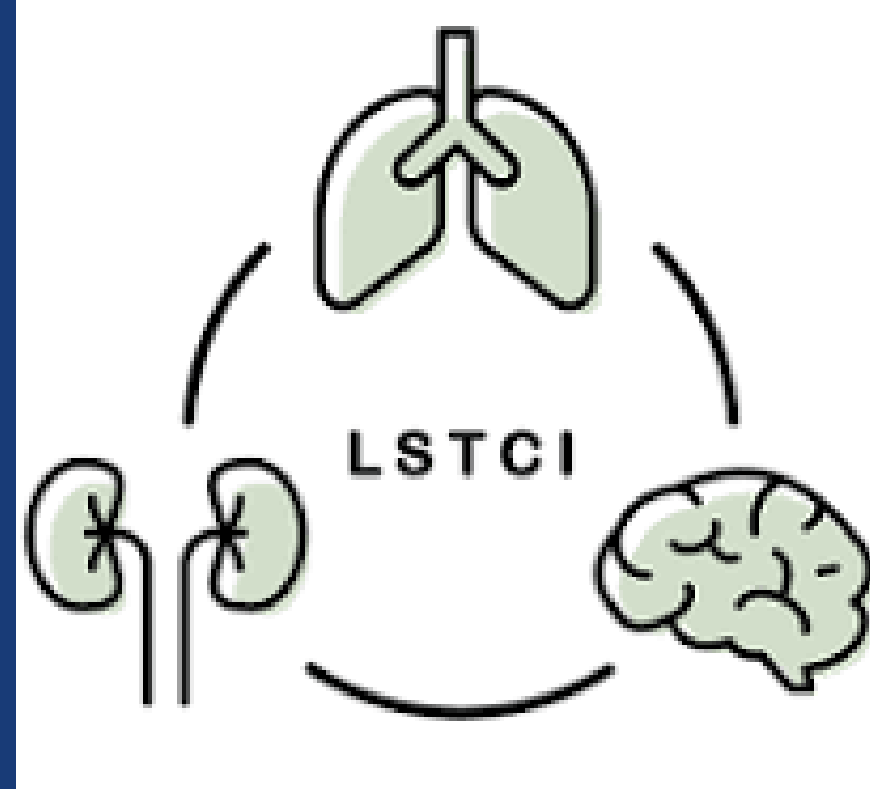


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Resilience In Youth: Sepsis Induces Neuroinflammation But Not Cognitive Deficits In Young Mice.

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INTRODUCTION

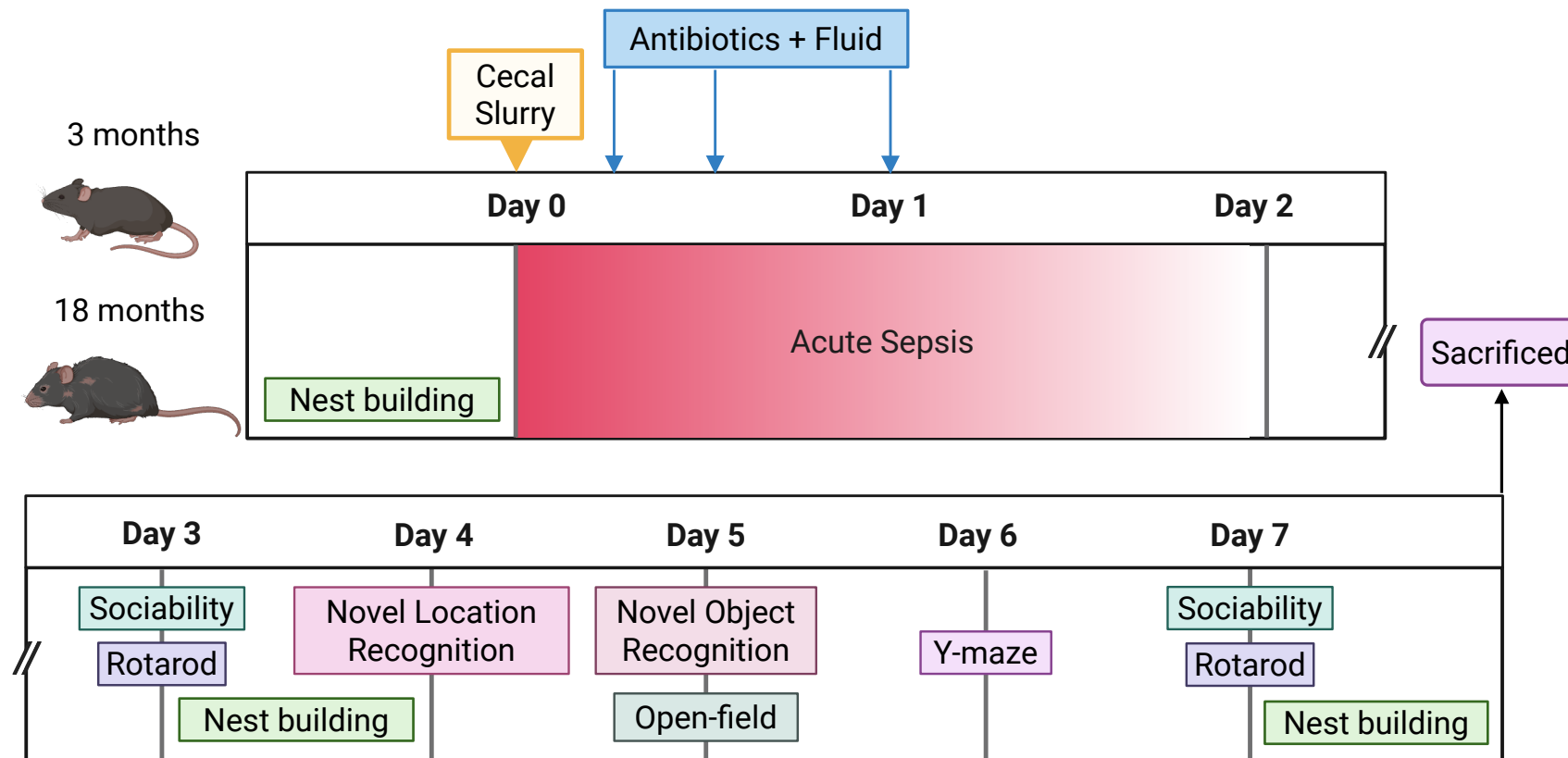
- Sepsis is often associated with both acute brain dysfunction (delirium) and chronic cognitive impairment (dementia)
- Older adults are particularly vulnerable to sepsis-associated delirium, which is linked to an increased risk of subsequent dementia
- The mechanisms underlying sepsis-induced brain dysfunction remain poorly understood

HYPOTHESIS

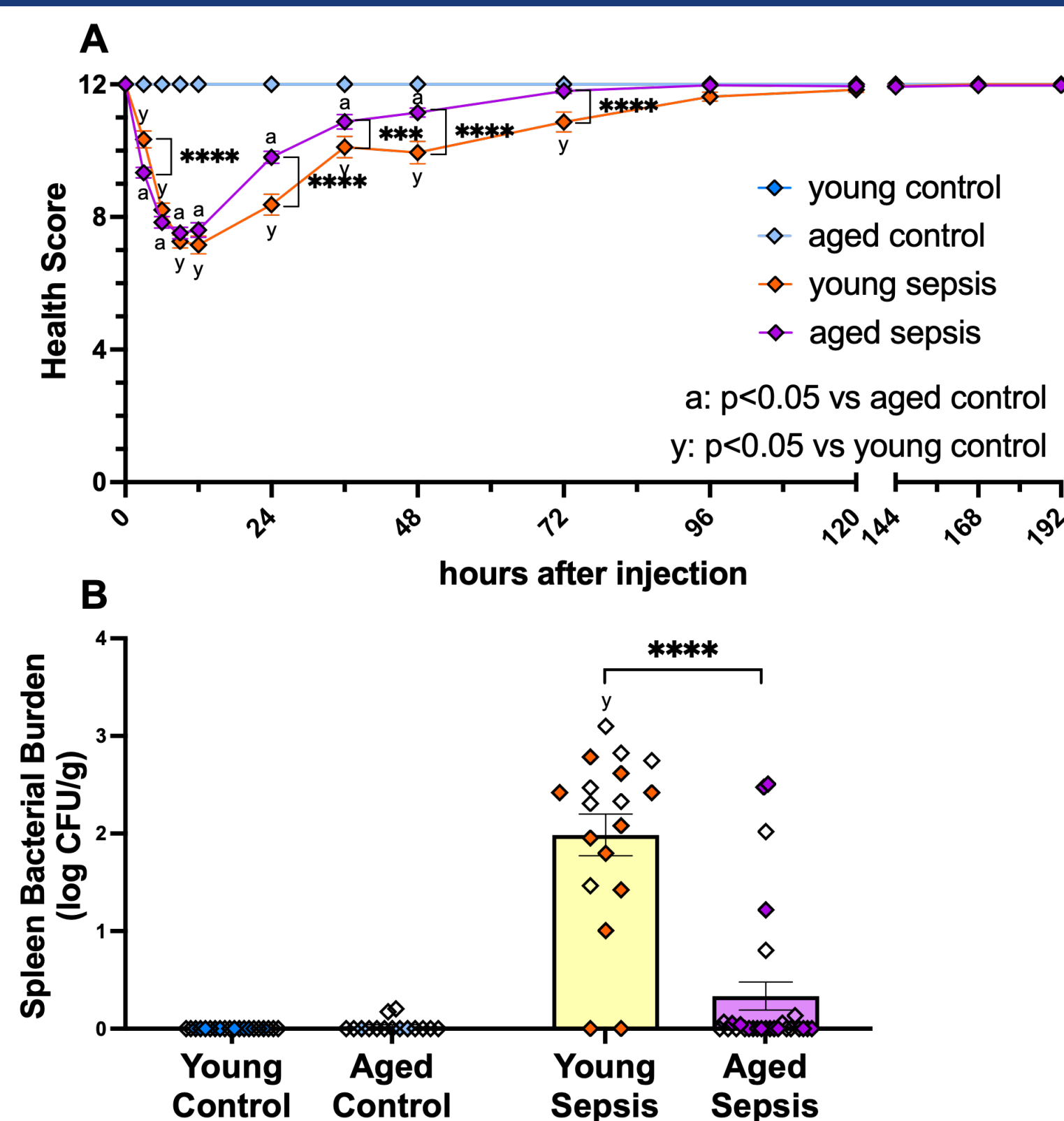
Aged mice are more likely to develop cognitive deficit upon recovering from sepsis due to augmented neuroinflammatory response and increased blood-brain barrier permeability.

METHODS

Experimental Timeline



Sickness-Matching Model



RESULTS

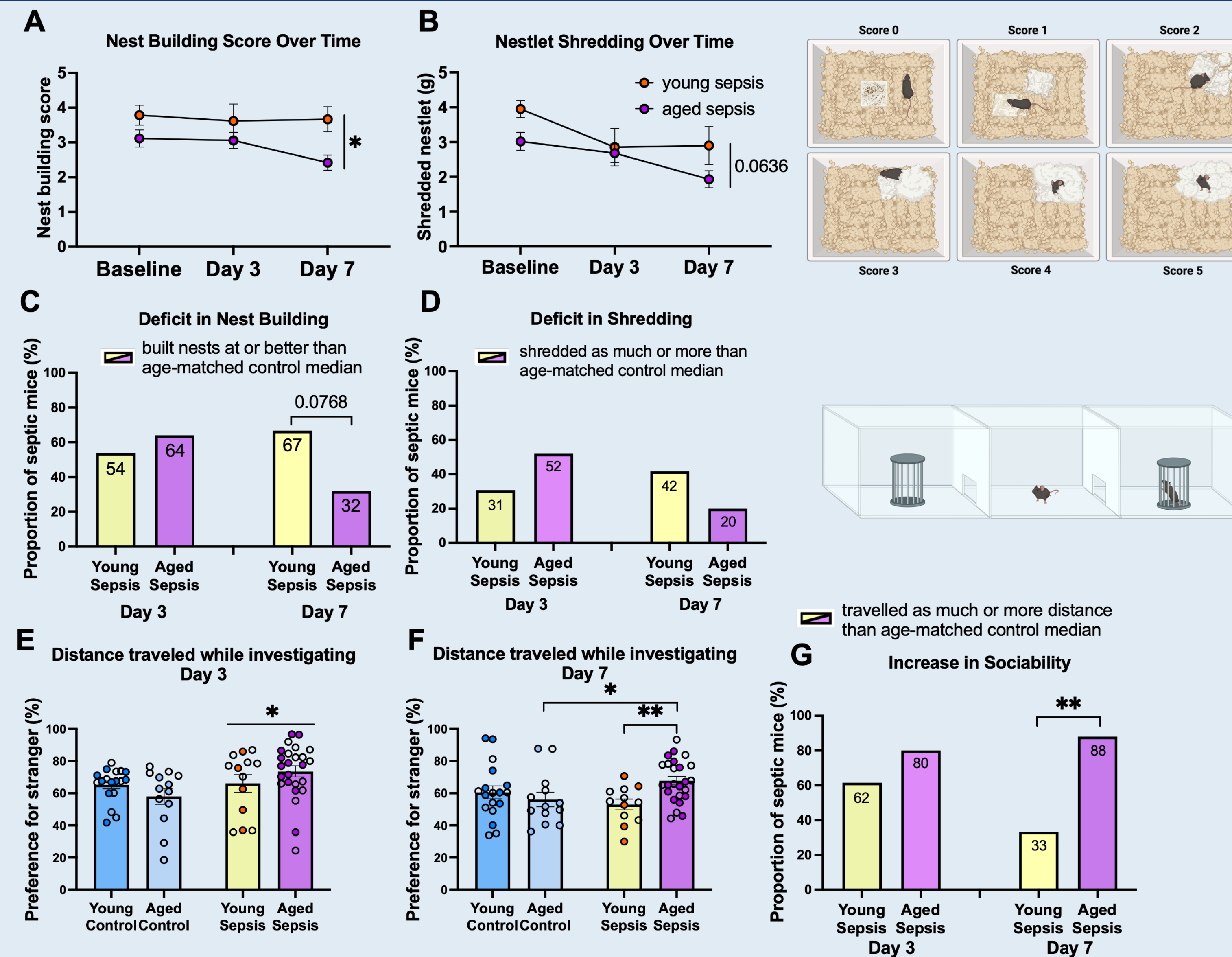


Figure 2. Aged mice showed persistent and progressive alterations in innate behavior following recovery from sepsis. (A) Aged septic mice exhibited lower nest-building scores compared to young septic mice across all time points. (B) Aged septic mice demonstrated a numerical reduction in shredded nestlet weight compared to young septic mice ($p = 0.0636$). (C, D) While young septic mice showed recovery in nest building (C) and shredding (D) between days 3 and 7 relative to young controls, aged septic mice exhibited further deterioration over the same period compared to aged controls. (E) On day 3, sepsis increased sociability independent of age. (F) By day 7, aged septic mice exhibited heightened need for sociability compared to aged controls, a response significantly more pronounced than that observed in young septic mice. (G) The transient increase in sociability observed in young septic mice on day 3 dissipated by day 7, while sociability continued to increase in aged septic mice.

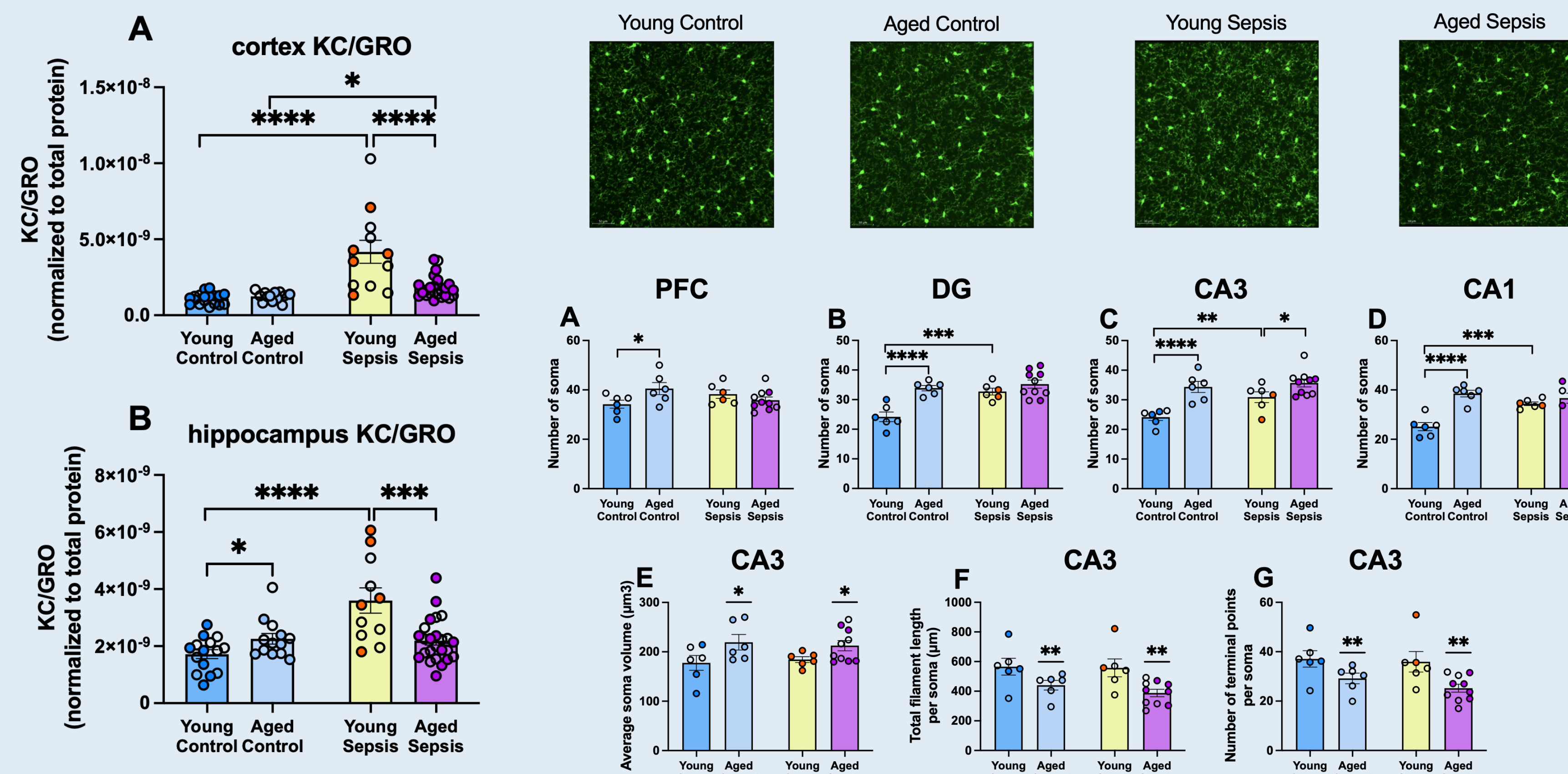


Figure 3. Young septic mice showed augmented neuroinflammation compared to aged septic mice. Cortical and hippocampal cytokine concentrations were measured 8 days post-sepsis induction. (A, B) Young septic mice showed increased levels of KC/GRO in both the cortex (A) and the hippocampus (B) that was significantly elevated relative to aged septic mice. (C-G) Young septic mice showed signs of microglial proliferation in the hippocampus. Young septic mice showed increased number of microglia in the hippocampus compared to young control mice (B-D), suggesting inflammatory milieu. Aged control mice also showed increased number of microglia compared to young control mice (A-D), indicating elevated baseline proliferation with age. Aged mice exhibited increased soma volume (E), reduced filament length (F), and decreased branching complexity (G), morphological features characteristic of reactive microglia, suggesting age-associated microglial priming.

Figure 4. Young septic mice showed signs of microglial proliferation in the hippocampus. Young septic mice showed increased number of microglia in the hippocampus compared to young control mice (B-D), suggesting inflammatory milieu. Aged control mice also showed increased number of microglia compared to young control mice (A-D), indicating elevated baseline proliferation with age. Aged mice exhibited increased soma volume (E), reduced filament length (F), and decreased branching complexity (G), morphological features characteristic of reactive microglia, suggesting age-associated microglial priming.

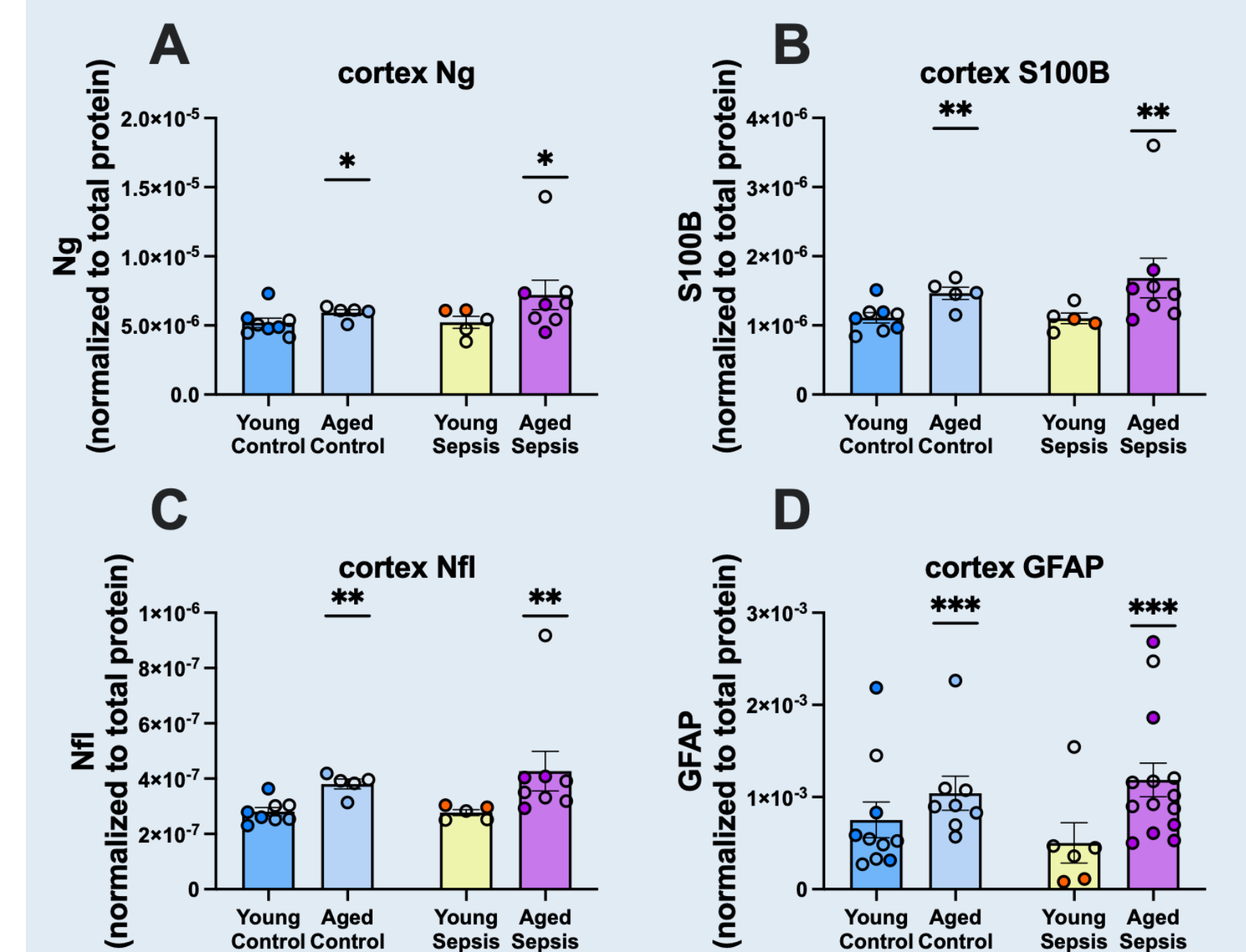


Figure 5. Aging, but not sepsis, increases markers of neuronal injury. (A-D) In the cortex, all markers of neuronal injury, including neurogranin (Ng) (A), S100 calcium-binding protein B (S100B) (B), neurofilament light chain (NfL) (C), and glial fibrillary acidic protein (GFAP) (D), significantly increased as a function of age, independent of sepsis. In the hippocampus, NfL and CRP increased significantly with age (data not shown).

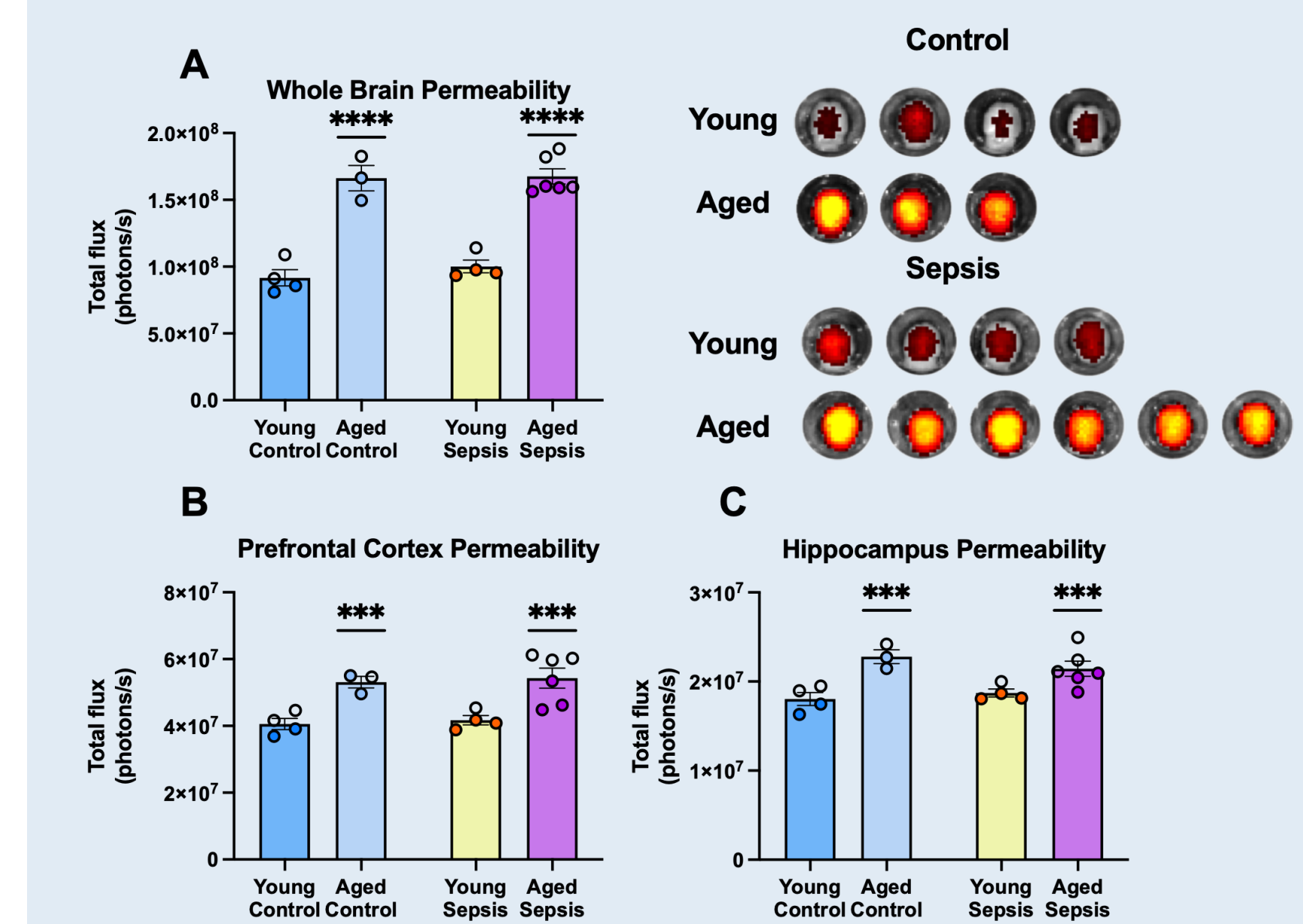


Figure 6. Aging, but not sepsis, increases brain permeability. Blood-brain barrier (BBB) integrity was assessed via endothelial permeability 8 days post-sepsis induction. (A) Whole brain permeability significantly increased as a function of age, independent of sepsis. (B, C) Endothelial permeability in both the prefrontal cortex (PFC) (B) and the hippocampus (C) increased significantly with age, irrespective of treatment.

SUMMARY

- Aged mice exhibited persistent and progressive behavioral alterations despite resolution of neuroinflammation.
- Young mice demonstrated behavioral resilience despite sustained neuroinflammatory profiles.
- Such dichotomy suggests that sepsis-induced cognitive vulnerability in aging is driven by cumulative neurodegeneration and structural alterations that persist independently of active inflammation, not by inflammation itself.

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