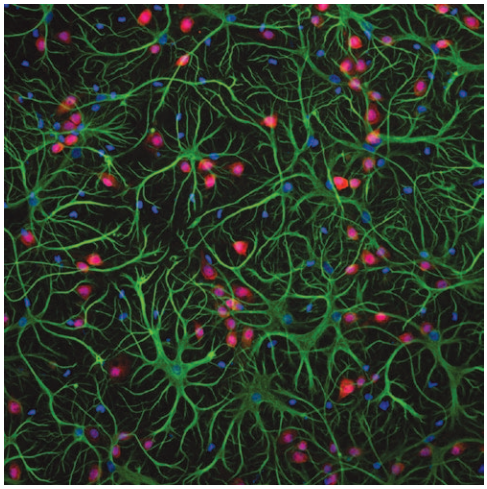
# Postoperative Cognitive Trajectories in Adults

## *The Role of Inflammatory Processes*

POSTOPERATIVE cognitive dysfunction (POCD) is a subtle decline in cognitive trajectory, which is directly attributable to a surgical, anesthetic, or adverse perioperative event. POCD is a controversial topic in perioperative medicine; unlike delirium and dementia, there is no consensus on the definition for POCD, nor is it a recognized diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*. Patients who suffer a "sentinel" perioperative event such as a stroke may experience a persistent decline in cognitive trajectory. However, many studies have found— although without determining the preoperative cognitive trajectory—that even without a clinically obvious neurological event, POCD occurs frequently in elderly patients in the first few weeks after surgery.[1,2] Interestingly, studies that have tracked cognition beyond 6 months postoperatively have generally found that, without a sentinel event, POCD tends to resolve in the majority of patients.[1,3] This does not necessarily imply that early POCD is not an important problem. Indeed, early POCD has been associated with impaired function, premature departure from the workforce, and early mortality;[4] however, it remains unclear whether early POCD is a marker or mediator of a disease process. As many studies have focused on the first 3 months postoperatively, it is likely that this has created a distorted view on the prevalence, severity, and duration of POCD. Furthermore, the research community has largely ignored the possibility that some patients might actually improve cognitively after successful surgery. A recent meta-analysis of cardiac surgery studies surprisingly found that persistent postoperative cognitive improvement (POCI) might actually be more common than POCD.[5] POCI can be defined as an improved cognitive trajectory (either cognitive improvement or deceleration of cognitive decline) relative to the preoperative trajectory that is directly attributable to a successful perioperative outcome. POCI must be differentiated from "resolved POCD" in which patients experienced a decline in their cognitive trajectory, but then recovered to their predicted preoperative cognitive course. Given that both POCD and POCI have been observed after surgery, it is important to consider what mechanisms could account for both of these processes. Insights into this intriguing question are provided in this issue of Anesthesiology by Degos *et al.*[6] Their work in a mouse model suggests a narrative in which neuroinflammation drives early POCD, and failure of neuroinflammation to resolve could promote persistent POCD. However, resolution of neuroinflammation could allow reversal of POCD or even a shift toward POCI.



***"It is certainly plausible that both cognitive dysfunction and improvement are tightly modulated by the immune response."***

Degos *et al.* show that the innate immune response may lead to short-term POCD in their mouse model of tibial surgery.[6] Equipped with a sophisticated genomic model that allows identification of infiltrating immune cells, they show that an influx of innate immune cells contributes significantly to postoperative memory impairment, which may be analogous to a "sickness behavior" in the mice.[6] They then demonstrate, with use of clodrolip to deplete phagocytic cells, that it is these cells that mediate the innate immune reaction to surgery, by contributing a host of proinflammatory cytokines. It is important to note that while the authors refer to these infiltrating phagocytic cells as macrophages, they do not formally identify them, hence it is unclear whether these cells are actually neutrophils, monocytes or macrophage. In concert with previous data,[7–9] the study intriguingly implies that perioperative manipulation of the innate immune response could improve cognitive outcomes. The findings of Degos *et al.* are paralleled by two other studies[10,11] and a linked Editorial[12] in this month's Anesthesiology, which have implicated neuroinflammation in anesthetic-induced apoptosis in the developing rodent brain. This is of particular interest as Shu *et al.* recently showed that augmenting inflammation in the neonatal rat brain with noxious stimuli

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exacerbated anesthetic-induced apoptosis.[13] It is currently unclear whether surgery exacerbates the neuroinflammatory response to anesthesia in neonatal animals, and this must be investigated expeditiously.

Other strengths to the article by Degos *et al.* include the robust statistical approach and interaction analyses to examine how different factors modulate the immune response and subsequent cognition.[6] Nonetheless, it remains unclear how the innate immune response can be safely manipulated to reduce the burden of short-term POCD. As the authors point out, although manipulation of proinflammatory cytokines (such as tumor necrosis factor-α or interleukin-1) might reduce memory dysfunction in animal models, it may also predispose to infective complications in the perioperative period.[6–8] For similar reasons it is likely that the use of clodrolip,[6] to deplete phagocytic innate immune cells, could increase the burden of perioperative complications. As such, the authors appropriately express caution regarding the clinical translation of this therapy. The actual type of innate immune cells that infiltrate the hippocampus to provoke memory dysfunction remains unclear. It is probable that combinations of neutrophils and monocytes (the latter may locally differentiate into macrophages) typically arrive in successive waves, instituting a classical immune response. Further studies should identify the cell type responsible for the cognitive dysfunction and the chemotactic factors responsible for this influx. Other targeted immune modulatory therapies should be tested in this animal model. Nonspecific immunosuppression might be ineffective; perioperative steroids are routinely administered in many centers but no salutary effect on POCD has been demonstrated.

Neuroinflammation drives acute changes in neurotransmission, so effects on cognition seem entirely plausible. For example, tumor necrosis factor-α builds up in the brain during wakefulness, driving the need for sleep and affecting cognition.[14] Therefore, it is unsurprising that, in the short term, surgery should induce an "adaptive sickness behavior" perhaps to aid recovery and healing from the trauma of surgery (*i.e.,* patients feel the need to rest/sleep). In this context, perioperative manipulation of inflammation to reduce the adaptive sickness behavior may not actually be beneficial. However, in certain predisposed individuals, perioperative inflammation may drive severe impairment in cognition manifesting as delirium.[15,16] Hence for cognition, perioperative neuroinflammation may not be a problem unless it produces a severe deficit. Furthermore, the reduced disease burden after successful surgery, coupled with a decrease in neuroinflammation, could be expected to improve cognitive function in many subjects in the longer term. It is certainly plausible that both cognitive dysfunction and improvement are tightly modulated by the immune response.

After the initial neuroinflammation subsides, the potential for POCI is an exciting prospect after adult surgery. Successful surgical intervention may remove the cognitive burden imposed by pain, inflammation, and functional limitation. This concept is not merely theoretical; in patients suffering from chronic back pain, surgical treatment or facet joint injections led to POCI, which was associated with structural brain changes.[17] However, in situations where POCI occurs, it follows that there was a preoperative decline, and few studies have evaluated preoperative cognitive trajectories,[1,18] perhaps explaining why POCI has largely been ignored as a concept. A rising criticism of the associated preclinical work is that POCI will be hard to identify in preclinical models using healthy, young animals, where surgery is artificially induced (*i.e.*, there is no pathology driving the need for surgery). In such models, the animals are unlikely to be declining cognitively before the experimental surgery. Aging animals might provide a superior model,[19] but again the lack of pathology typical in the human surgical context (*e.g.,* major joint arthritis) remains an important limitation in animal simulations.

Degos *et al.* have performed another rigorous study that provides insights into how neuroinflammation might drive postsurgical memory dysfunction.[6] Although their study does not reveal a therapy for immediate clinical translation, it is an important step on the route to understanding perioperative cognitive changes. From a clinical perspective, we currently know little about the predisposing factors that may determine whether a patient will experience POCD or POCI. Therefore, it is challenging to design a clinical trial to investigate a putative therapy in a vulnerable cohort. An appropriate initial course might be to attempt to identify the patients who are at greatest risk of POCD. Patients who experience delirium after surgery probably constitute a cohort at risk of experiencing early and persistent POCD, as delirium might be a marker of vulnerability and neuroinflammation.[15,16] Once we understand how perioperative care may influence an individual's cognitive trajectory, we can study disease processes and test therapies in the subgroups that are most likely to benefit. However, premature clinical trials of immune modulatory therapies may unnecessarily treat many patients, and render them susceptible to the side effects of the therapy, including immune suppression. For the present, surgeons, anesthesiologists, and other perioperative clinicians should implement plans to limit the trauma of surgery, to treat pain effectively, to prevent postoperative complications, and to promote early mobilization and rehabilitation. When surgery is successful and general health improves, it is likely that cognition will similarly be enhanced.

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## References

1. Avidan MS, Evers AS: Review of clinical evidence for persistent cognitive decline or incident dementia attributable

to surgery or general anesthesia. J Alzheimers Dis 2011; 24:201–16

2. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351:857–61
3. Sanders RD: Persistent post-operative cognitive decline: Naked truth, invisibility cloak or the "Emperor's new clothes"? J Alzheimers Dis 2011; 24:217–20
4. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS; ISPOCD Group: Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110:548–55
5. Cormack F, Shipolini A, Awad WI, Richardson C, McCormack DJ, Colleoni L, Underwood M, Baldeweg T, Hogan AM: A meta-analysis of cognitive outcome following coronary artery bypass graft surgery. Neurosci Biobehav Rev 2012; 36:2118–29
6. Degos V, Vacas S, Han Z, van Rooijen N, Gressens P, Su H, Young WL, Maze M: Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology 2013; 118:527–36
7. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS, Maze M: Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68:360–8
8. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M: Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci USA 2010; 107:20518–22
9. Wan Y, Xu J, Meng F, Bao Y, Ge Y, Lobo N, Vizcaychipi MP, Zhang D, Gentleman SM, Maze M, Ma D: Cognitive decline following major surgery is associated with gliosis, β-amyloid accumulation, and τ phosphorylation in old mice. Crit Care Med 2010; 38:2190–8
10. Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z: Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairement. Anesthesiology 2013; 118:502–15
11. Zheng H, Dong Y, Xu Z, Crosby G, Culley DJ, Zhang Y, Xie Z: Sevoflurane anesthesia in pregnant mice induces neurotoxicity in fetal and offspring mice. Anesthesiology 2013; 118;516–26
12. Zuo Z: Postoperative cognitive effects in newborns: The role of inflammatory processes. Anesthesiology 2013; 118: 481–3
13. Shu Y, Zhou Z, Wan Y, Sanders RD, Li M, Pac-Soo CK, Maze M, Ma D: Nociceptive stimuli enhance anesthetic-induced neuroapoptosis in the rat developing brain. Neurobiol Dis 2012; 45:743–50
14. Krueger JM, Clinton JM, Winters BD, Zielinski MR, Taishi P, Jewett KA, Davis CJ: Involvement of cytokines in slow wave sleep. Prog Brain Res 2011; 193:39–47
15. Sanders RD: Hypothesis for the pathophysiology of delirium: Role of baseline brain network connectivity and changes in inhibitory tone. Med Hypotheses 2011; 77:140–3
16. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, Jackson JC, Dittus RS, Ely EW: Associations of markers of inflammation and coagulation with delirium during critical illness. Intensive Care Med 2012; 38:1965–73
17. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS: Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011; 31:7540–50
18. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology 2009; 111:964–70
19. Erickson CA, Barnes CA: The neurobiology of memory changes in normal aging. Exp Gerontol 2003; 38:61–9