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The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction

Miles Berger, MD, PhD^{1,6,7,*}, Deborah Oyeyemi, BA^{1,2}, Mobolaji O. Olurinde, MD, PhD¹¹, Heather E. Whitson, MD, MHS^{2,6}, Kent J. Weinhold, PhD³, Marty G. Woldorff, PhD^{4,5}, Lewis A. Lipsitz, MD⁹, Eugene Moretti, MD, MHSc¹, Charles M. Giattino, BA^{5,7}, Kenneth C. Roberts, BA⁷, Junhong Zhou, PhD⁹, Thomas Bunning, BA¹, Michael Ferrandino, MD³, Randall P. Scheri, MD³, Mary Cooter, MS¹, Cliburn Chan, PhD⁸, Roberto Cabeza, PhD^{4,5}, Jeffrey N. Browndyke, PhD⁴, David M. Murdoch, MD², Michael J. Devinney, MD, PhD¹, Leslie M. Shaw, PhD¹⁰, Harvey Jay Cohen, MD^{2,6}, Joseph P. Mathew, MD, MBA, MHSc¹,
INTUIT ¶ Investigators

¹Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA

²Department of Medicine, Duke University Medical Center, Durham, NC, USA

³Department of Surgery, Duke University Medical Center, Durham, NC, USA

⁴Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

⁵Department of Psychology and Neuroscience, Duke University Medical Center, Durham, NC, USA

⁶Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, NC, USA

⁷Center for Cognitive Neuroscience, Duke University Medical Center, Durham, NC, USA

⁸Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA

*Corresponding author: Miles Berger, MD, PhD, Department of Anesthesiology, DUMC Box 3094, 4317 Duke South, Orange Zone, Durham, NC 27710, USA. Phone: 919-684-8679; Fax: 919-613-5264; miles.berger@duke.edu.

Authors' contributions

All authors contributed to the preparation of the manuscript. All authors read and approved the final manuscript.

¶INTUIT (Investigating Neuroinflammation Underlying postoperative brain connectivity changes, postoperative cognitive dysfunction, delirium in older adults) study investigators also include Oladayo Akinyemi, Cindy Amundsen, Pallavi Avasarala, Matthew Barber, Rachel Beach, Andrew Berchuck, Michael Bolognesi, Rachele Brassard, W. Michael Bullock, Ashley Burke, Victor Cai, Vanessa Cheong, Soren Christensen, Mitchell Cox, Donna Crabtree, Thomas D'Amico, Brittany Davidson, James Deorio, Mark E. Easley, Eric Ehieli, Bonita Funk, Jeffrey Gadsden, Grant Garrigues, Rachel Greenup, Ashraf Habib, David Harpole Jr, Matthew Hartwig, Laura Havrilesky, Tarrah Henley, Courtney Holland, Scott Hollenbeck, Richard Huang, Ehimenem Iboaya, Amie Kawasaki, Jacob Klapper, Sandhya Lagoo-Deenadayalan, Walter T. Lee, Michael Lipkin, Heather Litchfield, Ellie Marlor, Cory Maxwell, John Migaly, Judd Moul, Steven Olson, Theodore Pappas, Gary Lee Pellom, Andrew Peterson, Andreea Podgoreanu, Thomas Polascik, Glenn Preminger, Rebecca Previs, Edward Rampersaud, Angela Renne, Sanziana Roman, Edward Sanders, Aaron Sandler, Charles Scales, Randall Scheri, Keri Seymour, Michael Stang, Samuel Stanley, Katherine Sweeney, Alicja Szydłowska, Niccolo Terrando, Julie Thacker, Jake Thomas, Betty Tong, Yanne Toulgoat-DuBois, Samuel Wellman, David Williams, and Sabino Zani

Conflict of Interest

The authors have no conflicts of interest to declare.

⁹Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife; Beth Israel Deaconess Medical Center Division of Gerontology; and Harvard Medical School, Boston, MA, USA

¹⁰Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA

¹¹Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Abstract

Background/Objectives: Every year, up to 40% of the >16 million older Americans who undergo anesthesia/surgery develop postoperative delirium or cognitive dysfunction (POCD). Each of these distinct syndromes is associated with decreased quality of life, increased mortality, and possible increased Alzheimer's disease risk. One pathologic process hypothesized to underlie both delirium and POCD is neuroinflammation. The INTUIT study described herein, will determine the extent to which postoperative increases in cerebrospinal fluid (CSF) monocyte chemoattractant protein 1 (MCP-1) levels and monocyte numbers are associated with delirium and/or POCD and their underlying brain connectivity changes.

Design: Observational prospective cohort

Setting: Duke University Medical Center, Duke Regional Hospital, and Duke Raleigh Hospital.

Participants: Patients 60 years old (n=200) undergoing non-cardiac/non-neurologic surgery.

Measurements: Participants undergo cognitive testing before, 6 weeks and 1 year after surgery; delirium screening is performed on postoperative days 1–5, and blood and CSF samples are obtained before surgery, and 24 hours, 6 weeks and 1 year after surgery. CSF MCP-1 levels are measured by ELISA assays, and CSF monocytes are assessed by flow cytometry. Half the patients will also undergo pre- and postoperative functional magnetic resonance imaging (fMRI) scans. 32-channel intraoperative EEG recordings are performed to identify intraoperative EEG correlates of neuroinflammation, and/or postoperative cognitive resilience. Eighty patients will also undergo home sleep apnea testing to determine the relationships between sleep apnea severity, neuroinflammation and impaired postoperative cognition. Additional assessments will help evaluate relationships between delirium, POCD, and other geriatric syndromes.

Conclusion: INTUIT will use a transdisciplinary approach to study the role of neuroinflammation in postoperative delirium and cognitive dysfunction and their associated functional brain connectivity changes, and may identify novel targets for treating and/or preventing delirium and POCD and their sequelae.

Keywords

Neuroinflammation; Monocyte; Monocyte chemoattractant protein 1; Postoperative cognitive dysfunction; Delirium

INTRODUCTION

Over 16 million older Americans undergo anesthesia/surgery every year,¹ and up to 40% may develop postoperative cognitive dysfunction (POCD)^{2, 3} or delirium.⁴ POCD (also termed neurocognitive disorder-postoperative, when accompanied by subjective cognitive complaints) is generally defined as a drop in cognitive performance 1–2 standard deviation(s) (SD) that occurs > 1 month after surgery, as compared to preoperative cognitive testing.⁵ Although delirium and POCD are distinct disorders, both are associated with decreased quality of life (QOL),⁶ increased mortality,⁷ and a possible increased risk for developing dementia, such as Alzheimer's disease (AD).⁸

One pathologic process that may underlie POCD, delirium and AD is neuroinflammation.^{2, 8, 9} Several studies have shown higher pro-inflammatory cytokine levels in serum¹⁰ and CSF^{9–11} of patients with postoperative delirium, POCD, and/or AD.¹² CSF MCP-1 levels and monocyte numbers increase from 1 hour before to 24 hours after surgery/anesthesia.^{10, 13, 14} In a pilot study, we found that CSF monocyte MCP-1 receptor expression decreased 24 hours after surgery in patients who later developed POCD, suggesting that increased MCP-1 levels induce monocyte influx into the CNS and monocyte MCP-1 receptor downregulation.¹³

Neuroinflammation can also alter connectivity in the default mode network (DMN), a set of functionally connected brain regions identified by functional magnetic resonance imaging (fMRI).^{15–17} Altered DMN connectivity has been demonstrated in AD,^{15, 17} delirium,¹⁸ and POCD.¹⁹ This study, *Investigating Neuroinflammation Underlying Postoperative Brain Connectivity Changes, Postoperative Cognitive Dysfunction, Delirium in Older Adults* (INTUIT), will further investigate the relationship between increases in CSF MCP-1 levels and monocyte numbers, and changes in DMN connectivity in patients with POCD and delirium (Figure 1).

Increased CSF MCP-1 levels and monocyte brain influx have also been associated with AD progression.^{10, 20} We recently demonstrated that neuroinflammation magnitude (as measured by CSF MCP-1 levels) is associated with postoperative increases in the CSF AD biomarker tau after neurosurgery.¹⁴ CSF tau levels also increase after cardiac²¹ and orthopedic²² surgery. The INTUIT study will utilize CSF assays, fMRI, electroencephalography (EEG), cognitive testing and delirium screening to investigate relationships between postoperative neuro-inflammation and POCD, delirium, CSF AD biomarker changes and altered DMN connectivity in older adults.

METHODS

Overview

INTUIT is an ongoing 5-year observational prospective cohort study, and has thus far enrolled 76 patients. Participants undergo pre- and postoperative cognitive testing and delirium screening, QOL assessments, fMRI scans, intraoperative EEG recordings, and CSF and blood analyses. Each subject is followed for one year. Table 1 shows the timeline of activities for study subjects.

Eligibility

We will enroll 200 English-speaking adults 60 years old undergoing non-cardiac/non-neurologic surgery scheduled for >2 hours at Duke University Medical Center, Duke Regional Hospital, and Duke Raleigh Hospital. Anticoagulation precludes most cardiac surgery patients from undergoing lumbar punctures, hence their exclusion. Patients who complete cognitive testing and blood/CSF sampling at all study time points will count toward the enrollment target. 100 patients will also undergo pre- and postoperative MRI/fMRI.

There are no preoperative cognitive status exclusions. The following are not eligible: 1) patients on immunosuppressants (e.g., steroids) or immunomodulatory therapy, chemotherapeutic agents with known cognitive effects, or anticoagulants that would preclude safe lumbar punctures; 2) inmates of correctional facilities; 3) patients who experience major head trauma or receive chemotherapy between the baseline and either postoperative cognitive testing session. Patients with MRI contraindications will not undergo MRI/fMRI.

The INTUIT study has been approved by the Duke University Health System Institutional Review Board, and is registered with clinicaltrials.gov (). Written informed consent is obtained from all participants or their legally authorized representative prior to study participation.

Study Assessments and Schedule (Table 1)

Cognitive Testing—POCD is assessed with a standard cognitive test battery (Table 2),^{3, 23} by staff trained by a board-certified neuropsychologist; the full test battery takes ~30–60 minutes to complete. Individual test scores are combined by factor analysis into 4 cognitive domains: verbal memory, executive function, attention and concentration, and visual memory.³ The mean of these domain scores yields the continuous cognitive index (CCI), a sensitive score used to quantify overall cognitive function. CCI change from before to after surgery thus quantifies the degree of learning or cognitive decline.³ POCD as a dichotomous outcome is defined as 1-SD drop from before to 6 weeks after surgery in 1 cognitive domain.³

Physical and QOL Assessments—Physical function is assessed via Timed-Up-and-Go (TUG)²⁴ and Romberg tests, Duke Activity Status Index (DASI),⁶ Elderly Falls Screening Test,²⁵ Fall-Risk Screening Test,²⁶ and the Short-Form-36 Health Survey (SF-36) (including the physical function sub-scale).⁶ QOL and subjective cognitive complaints are assessed as previously described.⁶ These assessments occur < 1 month before and 6 weeks and 1 year after surgery.

Delirium Screenings—Delirium is assessed twice daily after surgery in the hospital. We use the CAM-ICU in intubated patients,²⁷ and the 3D-CAM in non-intubated patients.²⁸ In past studies, the interrater reliability coefficient of our delirium assessors was > 0.95. Patients also complete the 3D-CAM at their initial baseline study visit.

EEG Recording—32-channel EEG recordings are obtained pre- and intra-operatively as previously described.²⁹ We will also examine whether increased EEG complexity/entropy measures predict postoperative cognitive resilience (i.e. lower rates and/or severity of POCD and delirium, or more rapid or complete return to baseline).

Blood and CSF Sampling of Inflammatory Mediators—Blood and CSF are collected before surgery and 24 hours, 6 weeks and 1 year after surgery via sterile venipuncture and lumbar puncture, respectively, and flow cytometry is used to assess CSF monocytes as described.¹³ The monocyte/lymphocyte ratio is used to evaluate these two major leukocyte populations in CSF as recently described.¹³ CSF supernatant is analyzed using multiplex enzyme-linked immunosorbent assay (ELISA) to measure levels of the cytokines MCP-1, interleukin (IL)-6, IL-8, and granulocyte colony stimulating factor (G-CSF).¹⁴

CSF tau levels are measured before surgery and 24 hours and 6 weeks after surgery at the Alzheimer's Disease Neuroimaging Initiative (ADNI) biomarker core lab,¹⁴ which has well validated multiplex ELISA-based bead assays for CSF tau, phospho-tau, and amyloid-beta levels.³⁰ To avoid measurement bias, sample measurements are performed in random order, and technicians are blinded to study subject number, and time point. To minimize confounding from diurnal variation, CSF samples per patient are collected at the same time of day (± 1 hour) whenever possible.

fMRI Scans—Functional MRI scans will be performed on the first 100 eligible patients within 1 month before and 6 weeks after surgery in a 3-Tesla scanner with an 8-channel head coil.¹⁹ Anatomic scan sequences are high-resolution T1-weighted fast-spoiled gradient-echo oblique axial acquisitions (256 $\times$ 256 matrix, 256-mm field-of-view (FOV), 11° flip angle, 136 1-mm-thick slices, echo time [TE] 3.0 milliseconds, repetition time [TR] 6.93 milliseconds) and T2 fluid-attenuated inversion recovery (FLAIR) oblique axial acquisitions (128 $\times$ 128 matrix, 256-mm FOV, 90° flip angle, 68 2-mm-thick slices, TE 145.6 milliseconds, TR 11000 milliseconds, inversion time (TI) 2250 milliseconds).¹⁹ The 2 resting state fMRI sequences are sensitivity-encoding, spiral-in, oblique, axial, slice-interleaved acquisitions (64 $\times$ 64 matrix, 256-mm FOV, 60° flip angle, 34 4-mm-thick slices, TE 30 milliseconds, TR 3000 milliseconds, sensitivity encoding factor 2).¹⁹ The first 18 seconds of each resting state fMRI sequence is discarded to correct for initial MR signal fluctuation. Data from the next 124 time points (6.2 minutes) is retained for functional connectivity analysis. To minimize head motion during scans, we use a firm head rest and instruct participants to remain still.

The fMRI scans focus primarily on predefined regions of interest in the DMN and salience network. Based on our pilot data, we expect increases in CSF MCP-1 and monocyte/lymphocyte ratio from before to 24 hours after surgery to predict altered inter-network resting-state connectivity between the anterior to posterior cingulate from before to 6 weeks after surgery.¹⁹ Anatomic and perfusion MRI sequences allow us to account for effects of addition potential confounders of fMRI data, and facilitate additional analyses.

Sleep Apnea Testing

In the nested Sleep Apnea, Neuroinflammation, and Dysfunctional Cognition Manifesting After New elective surgery (SANDMAN) cohort sub-study, the first eligible 80 INTUIT patients (i.e. those not already on home continuous positive airway pressure therapy) will undergo preoperative home sleep testing to measure sleep apnea severity (apnea-hypopnea index; AHI). Multivariate analysis will determine the extent to which AHI is associated with POCD severity and/or CSF cytokine levels.

Data Management—Each study subject is assigned a unique ID number, different from his/her hospital ID number. All data and subsequent analyses are stored securely under this unique ID without patient identifiers.

Statistical Analysis—Based on prior studies,^{3, 23} we expect a completion rate >75% and a POCD incidence of approximately 40% at 6 weeks after surgery. With $\alpha = 0.05$, a 150-patient study will provide >90% power in a 2-sided *t*-test to detect a larger increase (Cohen's $d=1.07$) in the CSF monocyte/lymphocyte ratio from before to 24 hours after surgery in patients who later develop POCD at 6 weeks after surgery. Enrollment of 200 patients will ensure that at least 150 patients complete the 6-week visit (Table 1). Based on preliminary data demonstrating a ~50% incidence of postoperative CSF MCP-1 increases, and $\alpha = 0.05$, a 150-patient study will also provide >90% power to detect worse postoperative cognitive function (Cohen's $d=0.5$), as measured by the continuous cognitive index change from before to 6 weeks after surgery, in patients with increased postoperative CSF MCP-1 levels. After univariate *t*-tests, we will perform multivariate linear and logistic regression analyses of continuous and dichotomous cognitive outcomes respectively, to account for dependencies between MCP-1 and monocytes, adjust for potential confounders that may contribute to POCD, delirium, and/or dementia,^{2-4, 8} and predict outcomes in future patients.

We previously found a correlation coefficient (*R*) of 0.57 between CSF MCP-1 and tau increases from before to 24 hours after surgery in neurosurgery patients,¹⁴ though this correlation may be smaller in non-neurosurgery patients. A 150-patient study will provide >90% power to detect $R = 0.3$ (a low moderate correlation) between CSF tau and MCP-1 levels after surgery, as well as changes between CSF monocyte/lymphocyte ratio and CSF tau levels before and after surgery. Postoperative tau change is non-normally distributed,³⁰ and thus, requires non-parametric analysis.

Our preliminary (unpublished) data shows a 5% normalized change in anterior to posterior cingulate connectivity per 10 pg/dL-change in MCP-1 levels. Thus, 100 patients will provide >90% power to detect $R = 0.3$, and allow regression analyses to quantify the magnitude of change between the CSF monocyte/lymphocyte ratio and anterior to posterior cingulate connectivity.

DISCUSSION

INTUIT will assess the association between CSF MCP-1 increases and monocyte/lymphocyte ratio changes, brain functional connectivity changes, and AD biomarkers in the pathogenesis of POCD and/or delirium. We expect CSF increases in MCP-1 and monocytes

to correlate with increased POCD severity and increased CSF tau levels postoperatively. However, if postoperative increases in CSF MCP-1 levels and monocyte/lymphocyte ratio do not correlate with postoperative increases in CSF tau levels, that would suggest that these may be independent processes. Since INTUIT also measures IL-6, IL-8, and G-CSF levels as well as phospho-tau and amyloid beta levels, we may discover that changes in other pro-inflammatory cytokines and/or AD biomarkers in the CSF correlate more strongly with POCD.

This work will also inform future studies on aging-related biologic processes and postoperative outcomes in seniors. CSF and blood samples will be obtained before and after known stressors, i.e. anesthesia/surgery, allowing determination of the extent to which anesthesia/surgery alter molecular/cellular markers of the aging process, and the potential role of such biomarker alterations in postoperative delirium, cognitive dysfunction, and AD progression in the elderly. Although the aims of this study are focused on neuro-inflammatory biomarkers of postoperative delirium and POCD, the data collected will enable investigation of other promising biomarkers and resiliency predictors. For example, the PRIME Study (Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative) will analyze INTUIT EEG data to determine whether EEG multiscale complexity before and during surgery can predict postoperative cognitive resilience.

In conclusion, the INTUIT study will investigate the association between CSF MCP-1 and monocyte increases, and worsening postoperative cognition, functional brain connectivity changes, and CSF tau increases. These findings are expected to identify potential therapeutic targets for future preventive and/or treatment strategies for delirium and POCD.

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40% of the more than 16 million older Americans who have surgery each year will likely develop postoperative cognitive dysfunction or delirium, and very little is known about the pathophysiology of these disorders. In this paper we present the methods of the INTUIT study, which to our knowledge is the largest study ever to use fMRI, CSF analysis, EEG recordings, cognitive testing, and delirium assessments to understand the pathophysiology of postoperative delirium and cognitive dysfunction in older adults. We certify that this work represents novel clinical research.

Sponsors' Role

The funding sources had no role in study design and methodology, nor in sample analysis and preparation of this manuscript.

Author Details

Miles Berger, Assistant Professor of Anesthesiology, DUMC Box 3094, 4317 Duke South, Orange Zone, Durham, NC 27710.

Deborah Oyeyemi, Medical Student, Department of Medicine, DUMC Box 3003, Durham, NC 27710.

Mobolaji O. Olurinde, Adjunct (Locums) Anesthesiologist, Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA 19107.

Heather E. Whitson, Deputy Director of the Center for the Study of Aging and Human Development; Associate Professor of Medicine and Ophthalmology, Department of Medicine, DUMC Box 3003, Durham, NC 27710.

Kent J. Weinhold, Professor of Experimental Surgery, Immunology and Pathology, and Chief of the Division of Surgical Sciences, DUMC Box 2926, 204 Surgical Oncology Research Facility, Durham, NC 27710.

Marty G. Woldorff, Professor of Psychiatry and Behavioral Sciences, Center for Cognitive Neuroscience, Duke Box 90999, LSRC Building, B243B, Durham, NC 27708.

Lewis A. Lipsitz, Director of Hinda and Arthur Marcus Institute for Aging Research and Chief Academic Officer, Hebrew SeniorLife; Professor of Medicine, Harvard Medical School; Chief of Division of Gerontology, Beth Israel Deaconess Medical Center; 1200 Centre Street, Boston, MA 02131.

Eugene Moretti, Professor of Anesthesiology, Department of Anesthesiology, DUMC Box 3094, 2301 Erwin Road, 5673 Hafs Building, Durham, NC 27710.

Charles M. Giattino, PhD Candidate, Department of Psychology and Neuroscience, Center for Cognitive Neuroscience, Duke Box 90999, Durham NC 27708-0999.

Kenneth C. Roberts, Lab Manager, Center for Cognitive Neuroscience, Duke Box 90999, Durham NC 27708-0999.

Junhong Zhou, Assistant Scientist I, Hebrew SeniorLife Institute for Aging Research; Instructor in Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center; 1200 Centre Street, Roslindale, MA, 02131.

Thomas Bunning, Medical Student, DUMC Box 3094, 4317 Duke South, Orange Zone, Durham, NC 27710.

Michael Ferrandino, Associate Professor of Surgery, 1572 DHS, Box 3167 DUMC, Durham, NC 27710.

Randall P. Scheri, Associate Professor of Surgery, DUMC Box 2945 Med Ctr, Durham, NC 27710.

Mary Cooter, Biostatistician III, Department of Anesthesiology, DUMC 3094, Durham, NC.

Cliburn Chan, Associate Professor of Biostatistics and Bioinformatics, Duke Box 2721, 2424 Erwin Road Ste 1102, 11078 Hock Plaza, Durham, NC 27710.

Roberto Cabeza, Professor of Psychology and Neuroscience, Professor of Psychiatry and Behavioral Sciences, Director of the Center for Cognitive Neuroscience, Duke Box 90999, LSRC Building, B243F, Durham, NC 27708.

Jeffrey N. Browndyke, Assistant Professor of Psychiatry and Behavioral Sciences, DUMC Box 3503, Durham, NC 27710; Joseph and Kathleen Bryan Alzheimer's Disease Research Center, 2200 W. Main St, Suite A-230, Durham, NC 27705.

David M. Murdoch, Associate Professor of Medicine, Duke Box 103000, 203 Research Dr, MSRB I, Room 259, Durham, NC 27710.

Michael J. Devinney, Resident, Department of Anesthesiology, DUMC Box 3094, 2301 Erwin Road, Durham, NC 27710.

Leslie M. Shaw, Professor of Pathology and Laboratory Medicine, Director of Clinical Toxicology Laboratory, Hospital of the University of Pennsylvania, 7.103 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104.

Harvey Jay Cohen, Walter Kempner Professor of Medicine, Director of Center for the Study of Aging and Human Development, DUMC 3003, 3502 Duke South, Blue Zone, Center for Aging, Trent Drive, Durham, NC 27710.

Joseph P. Mathew, Professor of Anesthesiology, and Chair of the Department of Anesthesiology, DUMC Box 3094, 2301 Erwin Road, 5692 HAFS Building, Durham, NC 27710.

REFERENCES

- [1]. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. Natl Health Stat Report. 2009: 1–25.
- [2]. Berger M, Nadler JW, Browndyke J, et al. Postoperative Cognitive Dysfunction: Minding the Gaps in Our Knowledge of a Common Postoperative Complication in the Elderly. Anesthesiol Clin. 2015;33: 517–550. [PubMed: 26315636]
- [3]. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344: 395–402. [PubMed: 11172175]
- [4]. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383: 911–922. [PubMed: 23992774]

- [5]. 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: 1005–1012. [PubMed: 30336844]
- [6]. Newman MF, Grocott HP, Mathew JP, et al. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. *Stroke*. 2001;32: 2874–2881. [PubMed: 11739990]
- [7]. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008;108: 18–30. [PubMed: 18156878]
- [8]. Berger M, Burke J, Eckenhoﬀ R, Mathew J. Alzheimer’s disease, anesthesia, and surgery: a clinically focused review. *J Cardiothorac Vasc Anesth*. 2014;28: 1609–1623. [PubMed: 25267693]
- [9]. Hall RJ, Watne LO, Cunningham E, et al. CSF biomarkers in delirium: a systematic review. *Int J Geriatr Psychiatry*. 2018;33: 1479–1500. [PubMed: 28585290]
- [10]. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J Neuroinflammation*. 2016;13: 211. [PubMed: 27577265]
- [11]. Cape E, Hall RJ, van Munster BC, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. *J Psychosom Res*. 2014;77: 219–225. [PubMed: 25124807]
- [12]. Cortese GP, Burger C. Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer’s disease. *Behav Brain Res*. 2017;322: 269–279. [PubMed: 27544872]
- [13]. Berger M, Murdoch DM, Staats JS, et al. An Optimized Polychromatic Flow Cytometry Panel for Detecting Cerebrospinal Fluid Cell Types in Patients before and after Surgery. *Anesth Analg*. 2018;Under Review.
- [14]. Berger M, Ponnusamy V, Greene N, et al. The Effect of Propofol vs. Isoflurane Anesthesia on Postoperative Changes in Cerebrospinal Fluid Cytokine Levels: Results from a Randomized Trial. *Front Immunol*. 2017;8: 1528. [PubMed: 29181002]
- [15]. Chhatwal JP, Schultz AP, Johnson K, et al. Impaired default network functional connectivity in autosomal dominant Alzheimer disease. *Neurology*. 2013;81: 736–744. [PubMed: 23884042]
- [16]. Labrenz F, Wrede K, Forsting M, et al. Alterations in functional connectivity of resting state networks during experimental endotoxemia - An exploratory study in healthy men. *Brain Behav Immun*. 2016;54: 17–26. [PubMed: 26597151]
- [17]. Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer’s disease: an fMRI study. *Hum Brain Mapp*. 2005;26: 231–239. [PubMed: 15954139]
- [18]. Choi SH, Lee H, Chung TS, et al. Neural network functional connectivity during and after an episode of delirium. *Am J Psychiatry*. 2012;169: 498–507. [PubMed: 22549209]
- [19]. Browndyke JN, Berger M, Harshbarger TB, et al. Resting-State Functional Connectivity and Cognition After Major Cardiac Surgery in Older Adults without Preoperative Cognitive Impairment: Preliminary Findings. *J Am Geriatr Soc*. 2017;65: e6–e12. [PubMed: 27858963]
- [20]. Westin K, Buchhave P, Nielsen H, Minthon L, Janciauskiene S, Hansson O. CCL2 is associated with a faster rate of cognitive decline during early stages of Alzheimer’s disease. *PLoS One*. 2012;7: e30525.
- [21]. Palotas A, Reis HJ, Bogats G, et al. Coronary artery bypass surgery provokes Alzheimer’s disease-like changes in the cerebrospinal fluid. *J Alzheimers Dis*. 2010;21: 1153–1164. [PubMed: 21504113]
- [22]. Anckarsater R, Anckarsater H, Bromander S, Blennow K, Wass C, Zetterberg H. Non-neurological surgery and cerebrospinal fluid biomarkers for neuronal and astroglial integrity. *J Neural Transm (Vienna)*. 2014;121: 649–653. [PubMed: 24420082]
- [23]. Mathew JP, White WD, Schinderle DB, et al. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke*. 2013;44: 3407–3413. [PubMed: 24105697]
- [24]. Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39: 142–148. [PubMed: 1991946]

- [25]. Cwikel JG, Fried AV, Biderman A, Galinsky D. Validation of a fall-risk screening test, the Elderly Fall Screening Test (EFST), for community-dwelling elderly. *Disabil Rehabil.* 1998;20: 161–167. [PubMed: 9622261]
- [26]. Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol.* 2001;54: 837–844. [PubMed: 11470394]
- [27]. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA.* 2001;286: 2703–2710. [PubMed: 11730446]
- [28]. Kuczmarska A, Ngo LH, Guess J, et al. Detection of Delirium in Hospitalized Older General Medicine Patients: A Comparison of the 3D-CAM and CAM-ICU. *J Gen Intern Med.* 2016;31: 297–303. [PubMed: 26443577]
- [29]. Giattino CM, Gardner JE, Sbahi FM, et al. Intraoperative Frontal Alpha-Band Power Correlates with Preoperative Neurocognitive Function in Older Adults. *Front Syst Neurosci.* 2017;11: 24. [PubMed: 28533746]
- [30]. 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: 1299–1310. [PubMed: 27079717]

Figure 1.

Conceptual framework of INTUIT study. This study will assess potential associations between postoperative increases in CSF MCP-1 and monocytes, and 1) POCD, 2) DMN functional connectivity changes, and 3) increased CSF tau protein, which could suggest a link between POCD and AD progression.

Table 1.

Activities and timeline for INTUIT participants

	0–2 weeks before surgery	0–1 hours before anesthesia/surgery	During surgery	24 hours after anesthesia/surgery	Daily until hospital discharge	6 weeks after surgery	1 year after surgery
Cognitive testing	X					X	X
Physical Function, QOL assessments	X					X	X
fMRI scans	X					X	
EEG		X	X				
Delirium screening	X	X		X	X	X	
CSF and blood sample collection		X		X		X	X

Abbreviations: QOL, quality of life; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; CSF, cerebrospinal fluid.

Table 2.Cognitive test battery^{3, 19, 23}

Test	Assessment
Wechsler Test of Adult Reading *	Pre-morbid intellectual functioning
Mini-Mental Status Exam	Cognitive impairment (orientation, registration, attention and calculation, recall, language)
Wechsler Memory Scale Revised Modified Visual Reproduction Test	Visual immediate and delayed memory recall
Hopkins Verbal Learning Test	Auditory immediate and delayed memory recall (learning, episodic verbal memory)
Randt Short-Story Memory Test	Auditory immediate and delayed memory recall
Digit Span *	Auditory-verbal simple and complex attention
Trail Making Test A and B	Complex executive functioning skills, eg, logical task switching
Digit Symbol *	Visuomotor performance and processing speed
Lafayette Grooved Pegboard	Manual dexterity

* A subtest of the Wechsler Adult Intelligence Scale-Revised