Delineating the Trajectory of Cognitive Recovery From General Anesthesia in Older Adults: Design and Rationale of the TORIE (Trajectory of Recovery in the Elderly) Project

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BACKGROUND: Mechanistic aspects of cognitive recovery after anesthesia and surgery are not yet well characterized, but may be vital to distinguishing the contributions of anesthesia and surgery in cognitive complications common in the elderly such as delirium and postoperative cognitive dysfunction. This article describes the aims and methodological approach to the ongoing study, Trajectory of Recovery in the Elderly (TORIE), which focuses on the trajectory of cognitive recovery from general anesthesia.

METHODS: The study design employs cognitive testing coupled with neuroimaging techniques such as functional magnetic resonance imaging, diffusion tensor imaging, and arterial spin labeling to characterize cognitive recovery from anesthesia and its biological correlates. Applying these techniques to a cohort of age-specified healthy volunteers 40–80 years of age, who are exposed to general anesthesia alone, in the absence of surgery, will assess cognitive and functional neural network recovery after anesthesia. Imaging data are acquired before, during, and immediately after anesthesia, as well as 1 and 7 days after. Detailed cognitive data are captured at the same time points as well as 30 days after anesthesia, and brief cognitive assessments are repeated at 6 and 12 months after anesthesia.

RESULTS: The study is underway. Our primary hypothesis is that older adults may require significantly longer to achieve cognitive recovery, measured by Postoperative Quality of Recovery Scale cognitive domain, than younger adults in the immediate postanesthesia period, but all will fully recover to baseline levels within 30 days of anesthesia exposure. Imaging data will address systems neuroscience correlates of cognitive recovery from general anesthesia.

CONCLUSIONS: The data acquired in this project will have both clinical and theoretical relevance regardless of the outcome by delineating the mechanism behind short-term recovery across the adult age lifespan, which will have major implications for our understanding of the effects of anesthetic drugs. (Anesth Analg 2017;XXX:00–00)

Brain health is a focus and priority of the American Society of Anesthesiology.[1] This year will see the advent of several patient safety and provider education initiatives to decrease postoperative delirium and raise awareness regarding postoperative cognitive dysfunction (POCD). Although anesthesia is generally considered safe, a number of central nervous system syndromes complicate the perioperative period for older patients.[2,3] It is not well understood whether these syndromes arise from anesthetics, surgery itself, illness, underlying brain frailty, or more likely some combination. Emerging literature has begun to elucidate potential mechanistic relationships between anesthetics and postoperative cognitive syndromes.[4] However, the clinical literature will always have the burden of dealing with concurrent illness and surgery and the preclinical literature will be challenged with proving the external validity of extrapolation from nonhuman systems. Understanding the role of direct and indirect effects of anesthetic drugs in the pathogenesis of POCD and delirium will focus future research. The neurophysiologic and cognitive effects of the anesthesia can be separable from those due to surgery. By studying the former in the absence of the latter, we will gain information vital to prevent and potentially treat postoperative cognitive syndromes, including POCD.

Delirium is a confusional state usually acute in nature, characterized by disorganized thinking, lack of orientation, and a fluctuating course.[5] Patients who develop delirium

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are more difficult and costly to care for, and overall have increased morbidity and mortality.[6,7] POCD, consisting of significant impairment in one or more cognitive domains, is thought to be more persistent than delirium and can occur in up to 25% of elderly patients at 1 week after surgery and persist in 10% at 3 months.[8,9] Patients who had POCD at both hospital discharge and 3 months after surgery were more likely to die in the first year after surgery.[9] Cognitive dysfunction after noncardiac surgery was associated with increased mortality, risk of leaving the labor market prematurely, and dependency on social transfer payments.[10]

The TORIE (Trajectory of Recovery in the Elderly) study is a prospective cohort study designed to examine the effect of general anesthesia on POCD and cognitive recovery in adults across a 4-decade age span (40–80 years) in the absence of surgery or other systemic illness. Cognitive testing is administered to study participants before and after general anesthesia and we will acquire a variety of neuroimaging data before, after, and critically during anesthesia using 3 different imaging modalities: functional magnetic resonance imaging (fMRI),[11] diffusion tensor imaging (DTI),[12] and arterial spin labeling (ASL).[13] We will examine the effect of anesthetics on functional connectivity, white matter organization, and cerebral blood flow, respectively. We anticipate that older participants will have baseline differences in their brain consistent with normal healthy aging. We believe that the older participants will show marked differences in imaging measures while under anesthesia and in early recovery. Given that the preponderance of evidence suggests POCD and delirium is due to underlying medical conditions[14] and persistent inflammatory/stress response to surgery,[15,16] in the absence of illness, we expect that the oldest participants (70–80 years old) will take longer to recover cognitive function after anesthesia than younger participants. However, we expect this delay should not extend beyond several days, and that all participants regardless of age will recover to baseline cognitive performance within 30 days of anesthesia exposure.[8,9,17]

Coupling of the neuroimaging data with cognitive testing will provide a window into the alterations in neural networks that occur under anesthesia and the way in which the brain functionally recovers from anesthesia. The complementary analysis of cognitive and imaging data offers the possibility of a functional understanding of the cognitive changes observed in the postoperative period and the mechanism by which they return to baseline. This combination of cognitive testing and neuroimaging at specific time points along the perianesthetic trajectory will contribute to a more clinically relevant and scientifically informed model of brain recovery from anesthesia.

METHODS

Hypotheses

The primary aim of the TORIE study is to delineate the age-specific trajectory of recovery from general anesthesia in the absence of surgery and illness. The primary hypothesis is that the older adults exposed to general anesthesia alone will achieve complete cognitive recovery, as measured by cognitive testing, though this recovery may take longer than middle-aged adults. We expect that all participants, regardless of age, will recover to baseline cognitive performance within 30 days of anesthesia exposure.

Through the use of neuroimaging, we test 2 secondary hypotheses. First, we will observe changes in patterns of functional connectivity in the brain under anesthesia, as measured with fMRI, which will reverse after anesthesia and return to baseline. Second, functional connectivity at baseline and patterns of change under anesthesia will predict clinical outcomes including aspects of recovery such as duration until cognitive recovery. We expect both of these patterns of relationships to be modulated by age.

Study Design Overview

This study was approved by the institutional review board (IRB) of the Icahn School of Medicine at Mount Sinai (New York, NY; IRB@mssm.edu, 212-824-8200) and registered at ClinicalTrials.gov (NCT02275026, principal investigators: Joshua Mincer, Mark Baxter, and Mary Sano, registered October 23, 2014). Healthy adult volunteers 40–80 years of age undergo a battery of cognitive tests and neuroimaging before, during (imaging only), and at specific time points after exposure to general anesthesia of duration similar to typical surgical procedures (roughly 2 hours). Cognitive testing includes the Postoperative Quality of Recovery Scale (PQRS)[18,19] used for rapid assessment of short-term recovery. The cognitive component of the PQRS is the primary outcome measure. Additional neuropsychological testing covers domains of executive function and attention, episodic memory, language, processing speed, and working memory, as secondary outcomes. Instruments for this testing are the National Institutes of Health (NIH) Toolbox Cognitive Battery[20] and paper-and-pencil neuropsychological tests: Trail Making Test (parts A and B),[21] California Verbal Learning Test,[22] Logical Memory,[23] and Category Fluency.[24] These tests yield more detailed, domain-based information over longer periods of time. Details of specific timing of test administration follow.

Participant Selection

The target enrollment for this study is 76 volunteers, 19 for each decade (40–49, 50–59, 60–69, and 70–80 years of age). Our sample will consist of approximately equal numbers of men and women. Specific inclusion criteria in addition to age are otherwise essentially healthy status (American Society of Anesthesiologists physical status I or II) and no underlying cognitive dysfunction, as determined from baseline cognitive testing before general anesthesia. Specific exclusion criteria ensure safety during anesthesia and MRI, the ability to complete testing at longer-term follow-up, and the absence of pathophysiology that could predispose to POCD such as inflammatory conditions or cerebral microvascular disease. These criteria are listed in Table 1. Recent exposure to general anesthesia (within the last year) is not a specific exclusion criterion, as long as it is not associated with a comorbidity that would require exclusion.

Consent Procedures and Remuneration

Participants are recruited through local contacts and IRB–approved advertisements in local media. Potential participants are prescreened by telephone by both research staff

Table 1. Exclusion Criteria

Airway assessment as potentially difficult (Mallampati III or greater)
Allergies or hypersensitivity to drug or class
Body mass index >30
Chronic inflammatory conditions such as lupus or rheumatoid arthritis
Claustrophobia or other history suggesting inability to complete magnetic resonance imaging scanning
Current smoking
Current use of cocaine, opiates, or benzodiazepines
Diabetes mellitus
English illiteracy
History of malignant hyperthermia
Obstructive sleep apnea
Participant not expected to be able to complete the postoperative tests
Psychiatric or neurological conditions that would be expected to compromise cognitive assessments (for example, schizophrenia and major depressive disorder)
Pregnancy or nursing mother
Recent illness (within the last 2 wk)
Severe visual or auditory disorder/handicap
Significant metal implants in body
Uncontrolled hypertension

and a study anesthesiologist. Documented, informed written consent is obtained by participants signing an institutional review board–approved informed consent form in person on the first study day (ie, the day before anesthesia administration). Participants may withdraw consent at any time. Participants are compensated US $600, a level of reimbursement considered appropriate and without undue influence to participate given the nontrivial time and effort required. The study requires travel to and from the study site, approximately 1 hour of preprocedure testing on the day before anesthesia, about 6 hours on the day of anesthesia, and 2 subsequent follow-up MRI visits. There are also multiple subsequent follow-up sessions with our coordinators to complete the neuropsychological tests. Participants are reimbursed for travel or will have travel arranged for them by the study staff.

Testing Protocol and Anesthesia Exposure

The day before anesthesia ("T-1d"), after obtaining informed consent, participants undergo PQRS, cognitive testing (NIH Toolbox Cognitive Battery and paper/pencil neuropsychological tests), and a standard preoperative evaluation in-person by an anesthesiologist. On the day of anesthesia ("T0"), they return and undergo an MRI anatomical prescan that is reviewed by an on-site American Board of Radiology Certificate of Added Qualification-credentialed neuroradiologist for evidence of intracranial pathology, at which point acute pathology is excluded. Age-appropriate changes, for example, mild cortical atrophy, are not grounds for exclusion. However, pathological lesions that are not clinically evident (any mass, evidence of old infarct even without clinical signs, or cerebrovascular disease), or atrophy and/or ventriculomegaly greater than expected for age in the neuroradiologist's judgment, would be grounds for exclusion. For those with no relevant pathology, additional MRI scanning is completed, including task-based and resting-state fMRI scans. In preparation for induction of general anesthesia, a 22-gauge intravenous (IV) line is placed. After application of standard American Society of Anesthesiologists monitors and preoxygenation, anesthesia is induced in the MRI suite with propofol 2 mg/kg IV, after which, a laryngeal mask (LM) is placed. If the LM cannot be seated properly, the procedure is aborted. Anesthesia is maintained with inhaled sevoflurane at an age-adjusted depth of 1 minimum alveolar concentration. A bispectral index level of 40–60 is obtained after LM placement to aid in assessment anesthetic depth during equilibration of inhaled sevoflurane and washout of propofol, and the participant is returned to the MRI bore for scanning. Anesthetic depth is monitored by end-tidal sevoflurane concentration during scanning, along with physiological measures. Ventilation is maintained to achieve a target $Etco_2$ of 30–35 mm Hg. Resting-state fMRI, DTI, and ASL scans are obtained over the next 2 hours. During this time, appropriate bolus administration of a pressor such as ephedrine (5 mg IV or 25 mg intramuscular) or phenylephrine (100 μg IV) may be administered by the anesthesiologist to maintain mean arterial blood pressure within 20% of baseline. The participant is then removed from the MRI bore and emerged from anesthesia. The LM is removed when the participant awakens. Ondansetron (4 mg, IV) is given before emergence for antiemetic prophylaxis. No narcotics, benzodiazepines, or muscle relaxants are administered.

Once the participant is adequately emerged (generally within 15 minutes), PQRS is performed ("T + 15"). The participant is then returned to the MRI bore for task-based and resting-state scan acquisition, approximately 1 hour after emergence from anesthesia ("T + 60"), and then PQRS is repeated. Participants are then brought to the PACU where they are monitored until discharge. The participant returns to the study for follow-up cognitive testing and MRI scanning at 1 day ("T + 1 d") and 7 days ("T + 7 d") later, as well as additional cognitive testing at 30 days ("T + 30 d"). The PQRS is administered on all of these occasions, and additionally via telephone at 3 days ("T + 3 d"), 6 months ("T + 6 mo"), and 1 year ("T + 12 mo") after anesthesia. The study design is summarized in Table 2.

Cognitive Testing Protocols

The primary outcome assessment tool is the PQRS cognitive domain.[18,19,25] This generates a binary outcome (recovered/not recovered) at each time point the test is administered after baseline.[25] Secondary outcome cognitive assessment tools are the NIH Toolbox Cognitive Battery (www.nihtoolbox.org) and a battery of paper-and-pencil neuropsychological tests. There is some overlap between these instruments. The PQRS is focused on the very short term (minutes to days) while the Toolbox and neuropsychological tests are focused on a longer period (days to months). One of the primary criticisms of existing research on POCD has been the lack of a battery of tests that provide a consistent scoring approach.[26] A significant innovation of this study is the use of standardized instruments to assure comparability to future studies.

The NIH Toolbox Cognitive Battery is a validated, multidimensional computer-administered set of brief measures assessing cognitive function for ages 3–85. By using multiple constructs of each domain, the NIH Toolbox monitors neurological and behavioral function over time. This facilitates

the study of functional changes across the lifespan. This is a new battery for perioperative and anesthetic assessment, and is consistent with the cognitive domains that have been assessed in the past: executive function and attention, episodic memory, language, and processing speed. The important advantage of the NIH Toolbox is the utilization of a standard set of measures that can be used as a "common currency" across diverse study designs and settings. The NIH Toolbox has organized existing tests into a coherent package which have been extensively validated. Specific cognitive functions tested in this study (and the corresponding NIH Toolbox test) are listed in Table 3. Additional well-normed paper-and-pencil neuropsychological tests are administered at the same time points for comparison with the newer NIH Toolbox Cognition Battery tests.[27]

Practice effects are a potential concern with repeated testing on these tasks. The PQRS cognitive domain scoring accounts for a small practice effect between the first and second administrations, with stable performance on repeated administrations after the second.[25] The NIH Toolbox Cognitive Battery tests have test–retest reliability comparable to benchmark paper-and-pencil neuropsychological tests,[20,27–34] although most of these tests demonstrate practice effects. As our design does not include a comparison group of participants tested on the cognitive tasks at the same time intervals without anesthesia, we are unable to ascertain whether participants that return to baseline or better performance on these tasks might have been expected to perform at higher levels if they had not been exposed to anesthesia. Nevertheless, we are able to compare trajectories of performance in these tasks between participants across the ages of 40–80, by design, to determine whether these differ after anesthesia as a function of age.

Neuroimaging

Magnetic resonance images are acquired on a 3T scanner (Skyra, Siemens, Erlangen, Germany) with a 32-channel receiver coil. Specific neuroimaging modalities used are summarized in Table 4. Technical details related to these modalities may be found in Supplemental Digital Content, Appendix, http://links.lww.com/AA/B966.

fMRI detects localized neural activity in the brain through its signature effect on microvascular hemodynamics, modulating the blood oxygenation level–dependent endogenous contrast in MRI. Recent studies support the utility of fMRI to report on the anesthetized state and enable comparison with the awake brain to defined alterations in brain networks associated with the state of general anesthesia.[35–39] DTI and ASL are used as complementary methods to address other structural and functional effects that anesthesia may have on the brain. ASL noninvasively labels the protons of a bolus of blood passing through large arteries, which generates signal as it passes through microvasculature, enabling quantitative estimates of brain regional cerebral blood flow (rCBF). Clinically, it is useful in defining cerebrovascular disease,[40] motivating its inclusion in the imaging protocols for this study. DTI provides insight into white matter organization in the brain based on directionally weighted MRI to elucidate constrained diffusion of water molecules along white matter pathways. Alterations in white matter organization have been associated with cognitive impairments in normal aging[41] as well as in Alzheimer's disease.[42] Relevant to its use in TORIE, a recent study demonstrated a relationship between presurgical DTI abnormalities and postsurgical delirium.[43]

Statistical Analysis

Baseline characteristics of participants are summarized in terms of counts and percentages, medians and ranges, or means and standard deviations (SD), as appropriate. Cox discrete time regression, adjusted for covariates (sex, level of education, and race/ethnicity), is used to estimate the association of age to the time to recovery. The fit of all models to the data are examined using standard approaches, such as examination of residuals and the proportional hazards assumption for Cox regression. To study the time course of the cognitive measures, we use generalized linear mixed models (GLMMs)[44] that account for the covariance structure of repeated observations within participant, and test whether random intercepts and slopes for participants best fit the data. GLMMs are statistical models for data with correlations or nonconstant variability and where

Table 2. Timeline of Anesthesia, Cognitive Testing, and Neuroimaging

	T − 1 d	T0	T + 15	T + 60	T + 1 d	T + 3 d	T + 7 d	T + 30 d	T + 6 mo	T + 12 mo
Consent	X									
PQRS	X		X	X	X	X	X	X	X	X
Cognitive	X				X		X	X		
MRI		X		X	X		X			
Anesthesia		X								

Abbreviations: MRI, magnetic resonance imaging; PQRS, Postoperative Quality of Recovery Scale.

Table 3. Cognitive Testing

Function	NIH Toolbox Test	Paper/Pencil Test
Executive function and attention	Dimensional change card sort test Flanker inhibitory control and attention test	Trails A/B
Episodic memory	Picture sequence memory test	CVLT Logical memory
Language	Picture vocabulary test Oral reading recognition test	Category fluency
Processing speed	Oral symbol digit test	
Working memory	List sorting working memory test	

Abbreviations: CVLT, California verbal learning test; NIH, National Institutes of Health.

Table 4. Neuroimaging

Modality	Function
Anatomical MRI	Anatomical template for functional scans Rule out intracranial pathology before anesthesia
Task-based fMRI (N-Back)	Evoked functional activation in awake participant
Resting-state fMRI	Resting-state (not evoked) functional connectivity in awake and anesthetized participant
Diffusion tensor imaging	Structural connectivity as supported by axonal bundle formations
Arterial spin labeling	Regional cerebral blood flow

Abbreviation: fMRI, functional magnetic resonance imaging.

the response is not necessarily normally distributed. These models assume that missing data are randomly distributed; thus, participants with partial data contribute to the model estimation. We fit the appropriate distribution (eg, dichotomous, count, ordinal, normal) for each outcome.

For the cognitive primary and secondary outcomes, we use the Hochberg test to adjust for multiple comparisons[45] and maintain false discovery rate at 5%. Neuroimaging analyses also adjust multiple comparisons to maintain overall false discovery rate of 5%.

Missing Data. We expect that everyone will return to baseline cognitive function by 30 days, with most recovering earlier. Thus, even if later time points are missing, we anticipate most participants will have been observed before loss to follow-up. For intermittent missingness before returning to baseline, we truncate the observations at the time of missing observations. In a subsequent sensitivity analysis, we will assume that they are missing at random and use last observation carried forward (worst-case scenario). We will also use multiple imputation if over 5% of the outcome data are missing before returning to baseline function and varying the outcome probability of the missing data to determine the outcome event rate needed to change the estimate of age.

Cognitive Testing. The primary goal is to test whether age is associated with the time of return-to-baseline cognitive function assessed by PQRS after general anesthesia. Recovery is defined as return to baseline for the PQRS, or performance within 1 SD of baseline for secondary cognitive assessments. For the secondary cognitive tests, we will use fully-adjusted T scores for each NIH Toolbox Cognitive Battery and ascertain trajectory of function across the postanesthesia assessments. Fully-adjusted T scores take into account age, sex, level of education, and race/ethnicity so individual performance levels are scaled to the referent population. Sex, level of education, and race/ethnicity will be entered as covariates in the analyses of PQRS scores and neuroimaging measures.

Neuroimaging. The secondary outcomes for neuroimaging analyses fall into 4 groups: resting-state fMRI, task-driven fMRI, diffusion imaging, and rCBF. Within the secondary outcomes, the main a priori hypotheses are for resting-state fMRI, based in part on a pilot study involving 4 participants (2 in their 20s and 2 older than 50) performed before this study was begun. This pilot study suggested differential changes in specific resting-state networks immediately after recovery from anesthesia: a clear default mode component was difficult to detect immediately after recovery in contrast to preanesthesia and T + 7 d scans, whereas a visual resting-state network was clearly identified at all 3 time points. Net amplitude on each of 10 standardized resting-state networks[46] will be determined from resting-state fMRI at each time point (ie, all scans collected at T0, T + 1 d, T + 7 d) using a dual-regression analysis on time series denoised by multi-echo independent components analysis.[47,48] The sum of amplitudes over the map will be used as a marker for total activity of each corresponding network. These values (total percent signal change) are analyzed using GLMMs adjusted for participant characteristics for associations with age. We expect that the impact of anesthesia will differ across components, and be modulated by age. fMRI analysis will consider level of task difficulty (working memory load in the N-back task), as well as time point in an overall GLMM to identify voxels with significant differences. Statistical threshold applied at the voxel level will be $P < .01$ uncorrected and $P < .05$ corrected for multiple comparisons using a permutation analysis. Permutation tests will be done using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) RANDOMISE. The threshold-free cluster enhancement mode will be used for 10,000 permutations.[49] This correction will be applied to each component map of a blood oxygenation level–dependent functional network. The cluster threshold for fMRI analyses will be $P < .05$ after applying the voxelwise threshold. Cluster significance will be determined using a Monte Carlo simulation approach.[49] Smoothness will be estimated with a nonsymmetric kernel estimator (3dFWHMx). A simulation of 10,000 iterations will be used. For the ASL analysis, an additional 5 measures for rCBF (global and right and left frontal and temporal) are generated for each of 3 time points and analyzed with GLMMs. DTI scans are analyzed by the fractional anisotropy metric (FA), an index that reflects white matter collinearity, degree of myelination, and interaxonal space structure. Whole brain FA values along all white matter tracts are determined and compared between the different time points. Diffusion tensor images are eddy-current-corrected and FA as well as mean diffusivity maps (MD) are calculated using FSL. Exploratory whole brain analysis of the diffusion parameters is performed. First, FA images are spatially normalized to the International Consortium for Brain Mapping (ICBM) template using Tract Based Spatial Statistics.[50] The procedure involves a skeletonization of the FA images to obtain centers of white matter tracts. Voxelwise statistics are performed only on the white matter skeleton to reduce the chance of type I errors due to imperfections in normalization. The parameters used to warp the FA images to ICBM template and the white matter skeleton are applied to the MD images for statistical comparison using FSL RANDOMISE to test for differences in FA and MD (separately) as a function of time point in the scanning protocol. Because all measurements are acquired on the same scanner, interscan variability that may occur when using different hardware is eliminated.

Sample Size Calculation. Sample and power for secondary outcomes were calculated with PASS12 (PASS12, Kayville, UT).[51]

Cognitive Testing: A Cox regression[52] on the time to return-to-baseline cognitive performance with an event rate of 1.0 over 30 days requires 72 participants to detect a hazard ratio of 1.03 per year for age (β = .033), assuming a SD for age of 11.26 years, 80% power, a type I error of 0.05, and adjusting for other characteristics expected to have a generalized R^2 of 0.2.[53,54] We chose Cox (proportional hazards) regression, a form of discrete time survival model, for power analysis because it allowed for the testing of the major aim (is age group related to time-to-return to preanesthetic cognitive function?) while allowing for adjustment by many covariates. The NIH Toolbox Cognitive Battery yields 7 primary fully-adjusted T scores (mean = 50, SD = 10). Although there are fewer discrete time measurements for Cox regression, the effect-size calculation is similar. Assuming 72 participants with an event rate (return to baseline) of 1.0 over 30 days and a SD for age of 11.25 years, an adjusted type 1 error rate of 0.05/7 = 0.0071, and other covariates having a generalized R^2 of 0.2 with age, a hazard ratio of 1.05 (β = .05) can be detected with 80% power.[54] Preliminary data with 4 participants had 75% return to baseline at T + 15 minutes and all by 7 days. We expect missing data to be low as the total time under observation is 30 days and all participants are expected to have returned to baseline cognitive function by 30 days. Outcomes are expected to be captured on the majority of participants even if they do not attend all follow-up visits. However, to ensure sufficient outcomes, we have increased target enrollment by 5.5% to 76, thus adding a participant to each age decade.

Because our primary hypothesis was based on cognitive measures, power analyses and target sample size were determined purely based on those measures. We did not perform additional power analyses for other imaging measures, based on specified effects (activation patterns in task fMRI, for example), given that we would not recruit additional participants to increase the sample size beyond what was required to address our primary end points. Our pilot study, with 4 participants, suggested that different resting-state networks (in fMRI) were differentially affected by anesthesia, as described above. Analyses of these data will be based on the entire complete sample. The same Cox regression model used for cognitive scores applies for analysis of return-to-baseline on the measures of resting-state network activity (the sum of amplitudes over the map for each corresponding network), rCBF from ASL scans, and whole brain FA from DTI scans. These analyses will also be corrected for multiple comparisons (the total number of components analyzed) to a false discovery rate of 0.05.

Data and Safety Monitoring Board

Due to potential risk associated with exposing older adult volunteers to general anesthesia, the funding agency (National Institute on Aging) recommended the formation of a Data and Safety Monitoring Board (DSMB) for the TORIE study. The DSMB is charged with evaluating the study data after the first 10 participants (all between 70 and 80 years old) undergo their 30-day follow-up testing, as well as at 6-month intervals thereafter. The DSMB has the authority to stop the study or recommend protocol modifications based on cognitive outcomes after the first 10 participants, or adverse events that take place at any point during the study. The DSMB consists of 5 members, including experts in geriatrics, anesthesiology, and biostatistics, as well as the NIA program officer responsible for the award who serves as a sixth ex officio member. DSMB members were selected by Dr Jeffrey Silverstein and the National Institute on Aging program officer.

DISCUSSION

Expected Results

The primary product of this research study will be a delineation of the trajectory of cognitive recovery from general anesthesia alone in otherwise healthy human participants aged 40–80 years old, at short and long time points before and after exposure to general anesthesia. This will yield a rich dataset enabling detailed analysis of return of specific aspects of cognitive function.

Alongside the cognitive data, we will collect a wealth of neuroimaging data on these participants, including resting-state and task-based fMRI, DTI, and ASL. These data will yield insight into the effects of anesthesia on functional brain connectivity and dynamics during and after anesthesia exposure, and the extent to which these effects vary with age. Analysis will elucidate the functional brain dynamics underlying cognitive recovery from anesthesia. Additionally, we will explore the possibility that either baseline brain dynamics or changes during anesthesia may constitute imaging-based biomarkers predictive of individual or age-based variation in cognitive recovery. The TORIE imaging protocol was created to address structural and functional effects that anesthesia alone may have on the brain in the absence of a surgical procedure, including differential changes in specific resting-state networks immediately after recovery from anesthesia. Resting-state networks have been associated recently with postoperative cognitive function in surgical patients.[55] This imaging protocol, and the use of healthy participants, is distinct from numerous studies on surgical patients which have focused on changes or damage to the brain which are a result of surgical phenomena or vascular compromise such as silent strokes as a result of surgery (plus anesthesia or medical illness).[56] These include injury due to embolism[57] and pre-existing leukoaraiosis and lacunae volumes, suggestive of demylination and hyalinosis, in patients undergoing total knee arthroplasty.[58] MRI has also been utilized to examine functional connectivity during delirium in medical patients.[59] These studies in surgical patients underscore the value of acquiring multimodal imaging data in the TORIE study, to characterize the peri- and immediate postanesthesia period at a systems neuroscience level, in conjunction with detailed neurocognitive measures at the same time points.

Limitations

The results are intended to represent a primary exploration, and our data cannot completely elucidate age-related differences in participants and conditions associated with clinical indications for surgery. The study focuses on the main effect of anesthesia on cognitive recovery but cannot

address the possibility that administration of anesthesia interacts in some way with what happens due to the surgery itself. Moreover, there are multiple anesthetics in current use. This proposal includes a standard combination of anesthetic agents that would be typical for general surgical procedures in an adult population. Variations in duration of anesthesia, comparison of different agents, or additional agents (eg, narcotics, benzodiazepines) cannot be accommodated in this study design. The current design is focused on safety. The inclusion and exclusion criteria are designed to ensure an optimally healthy group of participants, and moreover ensure that comparisons in age groups will be minimally contaminated by overall differences in physical health between younger and older participants. At the same time, this issue is even more relevant for an otherwise healthy group of older adults that may have to weigh the risk of potential cognitive impairments that could follow elective surgery. However, it is a potential limitation of the study that the participants in this study are healthier than many elderly individuals that would be seen by surgeons and anesthesiologists in general practice. Nevertheless, this is the starting point for future research needed to understand the impact of other common conditions (eg, comorbidities common in elderly populations) as well as variations in anesthesia protocols that may affect these outcomes.

Implications

Perioperative geriatrics desperately needs data regarding how patients are expected to recover. Neither accepting that older patients recover more slowly nor denying the existence of POCD, whether transient or persistent, advances our understanding or gives direction as to how to enhance recovery. The data acquired in this project will have both clinical and theoretical relevance regardless of whether our hypotheses are correct. Information regarding cognitive recovery will be important for a patient population at risk for postoperative cognitive alteration who are frequently sent home on the day of surgery with instructions for self-care. At least some portion of readmission rates to hospitals in the days after ambulatory surgery may be due to poor comprehension of these discharge instructions. The trajectory at which various patients recover from anesthesia is perhaps the most unappreciated confounding factor in the debate on the direct and indirect effects of anesthetic drugs. Furthermore, significant health care concerns arising from the controversy over the persistent cognitive effects of anesthetics may impact the willingness of patients to engage with surgeons, preventing them from accessing appropriate life-enhancing therapies. By studying the effects of anesthesia, we hope to reassure patients, as well as improve our understanding of cognitive alterations after anesthesia.

Ethics

We have seriously considered the ethical implications of exposing participants to possible risk in this volunteer study where participants derive no direct benefit. The most significant risks involve exposure to general anesthesia and, in the case of the older participants, the possibility of cardiopulmonary disease or collapse. Successful mitigation of risk from general anesthesia has improved the safety profile dramatically over recent decades. Before the early 1970s, the risk of mortality from general anesthesia was 357 per million, but since then the mortality frequency has declined 10-fold, such that the risk today is about 0.0034%.[60] In this study, we follow the same protocols regarding anesthetic administration and postanesthetic care as with any ambulatory procedure at our institution. Consequently, we feel the risk in this study is extremely low.

Regarding the possibility of cognitive alteration after the anesthetic, especially in the older participants, we note again that the preponderance of evidence suggests that delirium and POCD likely are a consequence of an underlying illness or the generalized inflammatory response to surgery rather than due to the pharmacodynamics of the anesthetics themselves. Such evidence provides support for clinical equipoise[61] by specifically supporting the null hypothesis that general anesthesia alone has no long-term effects on cognition in older adults. At the same time, this has yet to be definitively shown, and can only be demonstrated by separating the anesthesia from the surgical insult.

We have incorporated various safety measures into the study to minimize the risk of cognitive alteration. Candidates suspected during prescreening of having a baseline cognitive deficit are excluded, even in the absence of a definitive diagnosis. Similarly, an anatomical MRI scan is obtained on each participant and read by a clinical neuroradiologist before proceeding with anesthesia to exclude candidates with occult central nervous system pathology before anesthesia, who may also be at greater risk of postanesthesia cognitive impairments. Additional measures are meant to identify, as early as possible, any factors that would break the clinical equipoise underlying the study. Initial enrollment of the first 10 participants is focused on the oldest group (aged 70–80) to support an early safety assessment in the group most at risk. Furthermore, we have included an external DSMB to review all data after enrollment of these first 10 participants and at intervals of 6 months thereafter. Finally, strict discharge criteria identical to those used for ambulatory surgery at our institution are used in this study to minimize risk to participants' safety once they have left our monitored setting.

CONCLUSIONS

The TORIE study aims to test the hypothesis that exposure to general anesthesia alone (in the absence of surgery) will not engender long-term cognitive impairment in older adults, though they may take longer than younger adults to recover cognitive function in the immediate postoperative period. It is the first and only study to date that addresses the trajectory of cognitive recovery in older adults in the context of general anesthesia alone. As such, it is the only study to date that has the capacity to definitively demonstrate the safety of general anesthetics (vis-a-vis cognitive recovery) in older adults. Regardless of the outcome, the combination of cognitive testing and neuroimaging (both awake and anesthetized) offers the possibility of elucidating a more complete model of how the brain recovers from anesthesia that is both clinically relevant and scientifically informed. Other planned and ongoing studies examining the pattern of cognitive recovery after anesthesia in younger

subjects[62] will complement our study and provide a fuller picture of long-term effects of general anesthesia on brain and cognition across the lifespan.

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DISCLOSURES

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