Postoperative Cognitive Dysfunction

Minding the Gaps in Our Knowledge of a Common Postoperative Complication in the Elderly

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KEYWORDS

• Post-operative cognitive dysfunction • Post-operative cognitive decline
• Post-operative cognitive improvement • Elderly • Anesthesia • Surgery

KEY POINTS

- Postoperative cognitive dysfunction (POCD) is a syndrome of cognitive dysfunction following anesthesia and surgery, which likely has myriad causes.
- As an increasing number of elderly patients undergo surgery and anesthesia each year, optimizing postoperative cognitive function and preventing/treating POCD are major public health issues.
- POCD is associated with impaired quality of life, increased exit from the workforce, and increased mortality after surgery.
- POCD can be conceptualized as a lack of cognitive resilience in the face of perioperative stress.

Ever since Bedford's[1] seminal *Lancet* case series in 1955, we have known that perioperative care is sometimes followed by significant cognitive dysfunction. Although the safety of perioperative care has improved dramatically since 1955, the descriptions of cognitive dysfunction in that case series are eerily similar to the complaints of current patients suffering from postoperative cognitive dysfunction (POCD). POCD remains a common postoperative complication associated with significant

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.
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Anesthesiology Clin 33 (2015) 517–550
http://dx.doi.org/10.1016/j.anclin.2015.05.008 **anesthesiology.theclinics.com**
1932-2275/15/$ – see front matter

morbidity and even mortality, especially among elderly patients. There has been a great deal of interest in and controversy about POCD, from how it is measured, to how long it lasts, to its precise implications for patients. This interest and controversy is reflected partly in the increasing number of articles published on this subject (shown in Fig. 1). Recent work has also suggested surgery may be associated with cognitive improvement in some patients,[2–4] termed postoperative cognitive improvement (POCI). As the number of surgeries performed worldwide approaches 250 million per year[5] (with an increasing number in elderly patients), optimizing postoperative cognitive function and preventing/treating POCD are major public health issues. In this article, we review the literature on POCD and POCI, and discuss current research challenges in this area.

A DESCRIPTION OF POSTOPERATIVE COGNITIVE DYSFUNCTION AND POSTOPERATIVE COGNITIVE IMPROVEMENT

What Is Postoperative Cognitive Dysfunction?

POCD is a syndrome defined by a drop in cognitive performance on a set of neuropsychological tests from before to after surgery. Unlike delirium, this means that POCD cannot be diagnosed unless a patient has undergone formal neuropsychological testing before *and* after surgery, which typically does not happen outside a research setting. Partly as a result of this, there is no *International Classification of Diseases, 10th Revision* code for POCD, and it is not listed as a diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V). However, the utility of the DSM-V as a nosologic tool has been questioned recently by many, including the head of the American National Institute of Mental Health.[6] Thus, the fact that POCD is not listed in the DMS-V is of questionable import.

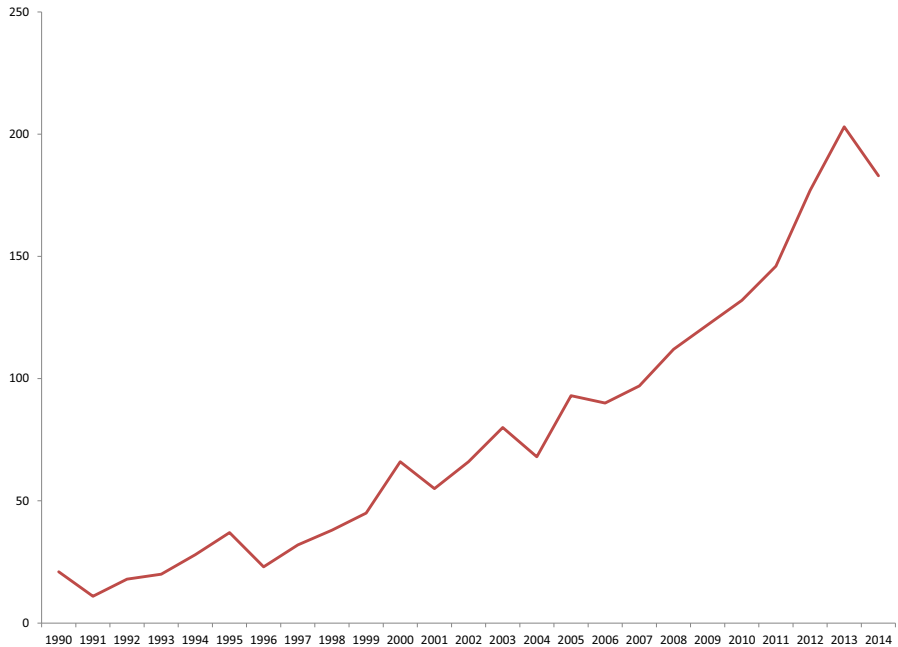

Fig. 1. POCD publications by year.

Neuropsychological testing for POCD typically includes tests that assess multiple cognitive domains (**Table 1**). Individual subtest scores are then grouped together by factor analysis or by an *a priori* understanding of which tests measure which cognitive domains (as described in **Table 1**). Depending on the study, anywhere from 4 to 8 cognitive domains have been used,[7,8] although simpler tests such as the Mini-Mental State Examination (MMSE) also can detect long-term postoperative cognitive changes.[9] Postoperative testing is typically performed after the acute effects of surgery and the immediate postoperative period have dissipated (ie, at least 1 week after surgery).[10] A threshold is typically set for either a drop in overall cognitive performance (the mean of the individual cognitive domain scores), or for a drop in performance in a single cognitive domain. Patients scoring below such a preset threshold are then defined as having POCD. There is no clear agreement on how low such a POCD cut-off/threshold should be set (eg, 1.0 SD, or 1.5, or 2.0 SDs).[10] There also has been disagreement over how to classify patients who drop below the preset threshold in one domain, but who show cognitive improvement in other domains.[11,12] Such patients may even show overall improvement in their composite cognitive index, even though they may meet POCD criteria (if POCD is defined as a drop below threshold in any individual cognitive domain).

Most patients typically improve their performance on these tests over repeated testing sessions due to a learning or practice effect, which makes a drop in performance all the more striking. However, this also makes it difficult to determine the true level of postoperative performance drop, because the observed postoperative performance may thus reflect both postoperative deficits and practice-related improvements. Practice effects can be mitigated by using cognitive tests with equivalent alternate forms, such that one form is used at presurgical baseline and alternate forms are used for subsequent postoperative evaluation (see **Table 1** for tests with available alternate forms). In addition to practice effects, each cognitive test has its own inherent test-retest variability, which can affect the interpretation of any postoperative cognitive change.[13] Simple change scores in performance from a patient's presurgical baseline do not take practice effects or other issues like test-retest reliability, floor/ceiling effects, or regression to the mean into account. Reliable change index (RCI) methods has been developed that can account for these effects.[14,15] The RCI is typically defined as the pretest to posttest change in a study subject minus the average pretest to posttest change among control subjects, divided by the SD of the change in pretest to posttest scores among nonsurgical controls.[16] The RCI method may have higher sensitivity and specificity for detecting POCD than other statistical methods.[16] However, unless there are published test-retest data over an equivalent time interval in age-matched individuals, the RCI method requires collecting data from nonsurgical controls at the same times as surgical patients.

The RCI method also allows one to define clinical significance thresholds for POCD, because the RCI method generates *z*-scores with an assumed normal distribution. An RCI score range of ± 1.645, relative to a normal distribution, means that 90% of obtained change scores would fall within this range. Outliers would thus fall either in the upper or lower 5% tails of the distribution by chance. Early Alzheimer disease (AD), also known as mild cognitive impairment (MCI), is often diagnosed by a less-stringent measure of cognitive decline relative to normative performance expectations (eg, *z*-score drop of at least 1.5[17]). Thus, the strict -1.645 RCI criterion for clinical change significance may be excessively stringent, and may miss POCD cases that are functionally relevant to patients. There is currently no consensus among neuropsychologists of statistical method (such as an RCI) and/or threshold that should be used, and how many cognitive domains must show a decline to make the diagnosis of POCD.[10]

Table 1
Recommended neuropsychological measures for the detection and characterization of postoperative cognitive dysfunction

Core Domain	Component Cognitive Process	Measure	Description	Brain Regions/Circuits Involved in Task[b]
Global	Multiple	Montreal Cognitive Assessment (MoCA)	The MoCA is a brief cognitive screening measure tapping multiple cognitive domains, including brief assessment of memory and orientation. The screening measure is freely available (www.mocatest.org) and has the advantage of multiple alternate forms, which can help in preventing overestimation of POCD recovery secondary to simple re-administration practice effects. *Administration Time*: Variable, with ~15 min average.[124,125]	Multiple tasks, n/a.
Executive function	Simple attention	Digit Span Forward Subtest from Wechsler Adult Intelligence Scale – 3rd Revision (WAIS-III)	The Digit Span Forward subtest from the WAIS-III is a simple auditory-verbal attention task, in which a participant is asked to attend to and immediately repeat a series of serially presented digits that increase in total span as the test progresses. *Administration Time*: Variable, with ~5–10 min average.	Right dorsolateral prefrontal cortex[126]
	Complex attention (working memory)	Digit Span - Backward Subtest from Wechsler Adult Intelligence Scale – 3rd Revision (WAIS-III) or Letter-Number Sequencing Subtest from WAIS-III	The Digit Span Backward (or Letter-Number Sequencing) subtest from the WAIS-III engages both simple attention and working memory skills. Participants are instructed to attend to a series of verbally presented digits of increasing total length, but rather than respond verbatim, participants are instructed to repeat the presented digits in reverse order. In the alternate Letter-Number Sequencing subtest from the WAIS-III, participants are presented with randomized series of digits and letters of the alphabet of increasing length and asked to respond to a particular series with all digits in ascending order and all letters in alphabetical order.[126,127] *Administration Time*: Variable, with ~5–10 min average.	Right dorsolateral prefrontal cortex[126]

Response inhibition	Stroop Color Word Test	A time-limited test of the ability to inhibit a pre-potent response, known to be sensitive to medial prefrontal lobe dysfunction. The Stroop Color Word Test requires participants to read a series of color words (red, green, blue), then name the color ink of a series of X characters, after which an inhibition trial is given in which the participant is asked to name the color ink of a series of color words that are in opposition to the ink color (eg, the word blue printed in red ink). The natural tendency of participants is to say the word as printed rather than the ink color; hence the sensitivity of the measure to response inhibition skills. *Administration Time*: 3–4 min.	Anterior cingulate cortex (ACC), right inferior frontal gyrus, and cerebellum[128]
Mental flexibility	Trail Making A & B Test[a]	The timed Trail Making A subtest requires participants to connect a series of numbered circles distributed on a piece of paper in ascending numerical order, whereas the Trail Making B subtest has both letters of the alphabet and numbers in circles that then must be connected in alternating ascending order (eg, 1-A-2-B-3-C…). Trail Making A & B tests should be administered in immediate succession, as the Trail Making A subtest is necessary for familiarization of general subtest B task requirements. Independent administration of Trail Making B test only may result in overestimation of POCD severity.[129,130] *Administration Time*: Variable with 5-min timed maximum for each subtest.	Medial temporal lobe[130], left-sided dorsolateral and medial frontal cortex[165]
Verbal fluency	Controlled Oral Word Association Test (COWA) from the Multilingual Aphasia Examination (MAE)[a]	A lexical verbal fluency task known to be dependent on pre-Broca area function in the language dominant brain hemisphere. This test also requires retention of task rules for proper performance. Participants say as many words as they can retrieve that start with a particular consonant with 1-min given for 3 different consonants (eg, C, F, L). Participants are asked to not use proper nouns or the same word with different endings (eg, eat, eating). *Administration Time*: 3 min.	Posterior part of the left inferior prefrontal cortex (LIPC); category fluency task activates anterior LIPC and right inferior prefrontal cortex[131,132]

(*continued on next page*)

Table 1 (*continued*)

Core Domain	Component Cognitive Process	Measure	Description	Brain Regions/Circuits Involved in Task[b]
Learning and memory	Auditory-verbal learning & memory	Hopkins Verbal Learning Test, Revised (HVLT-R)[a]	An auditory-verbal, list-learning, and memory task that involves the presentation of 12 various categorically related item words (eg, gemstones, furniture) that are then immediately recalled by the participant. Participants are given the opportunity to learn the list of words over a series of 3 repeated presentations, then after a 25-min delay, participants are assessed for delayed recall and recognition memory for the primary word list items. Scored items include total recall, delayed recall, percent retention (after delay), and recognition discrimination index. *Administration Time*: 35 min timed (includes 25-min delay).	Left ventrolateral prefrontal cortex[133]
	Visual learning & memory	Brief Visuospatial Learning Test, Revised[a]	A visuospatial learning and memory test analog to the HVLT-R. Six simple line drawings are presented in a 2 × 3 array on a single piece of paper and participants are allowed a brief period to study the figures, after which they are asked to reproduce as many figures in their proper locations as they can on a blank sheet of paper. Three learning trials of the 6 line drawings are conducted. There is a 25-min delay, after which participants are asked to recall as many figures in their locations as possible. Delayed recognition for the same line drawings is also conducted. Scored items are the same as the HVLT-R (eg, total recall, delayed recall).[134] *Administration Time*: 45 min timed (includes 25-min delay)	

Visuospatial functioning	Visuomotor integration	Digit Symbol Coding Test from the Wechsler Adult Intelligence Scale–3rd Revision (WAIS-III)	The Digit Symbol Coding Test requires participants to use a symbol/number key at the top of a printed page as a guide to determine the appropriate missing symbols for a large array of unmatched numbers below the test key. The task is timed and the scored response is the total number of correct symbol/number pairs completed by the participant within 120 s. *Administration Time*: 5 min.	Corpus callosum, internal capsule[135]; anterior cingulate gyrus, left prefrontal gyrus, and inferior parietal lobe[136]
	Complex visuospatial perception	Hooper Visual Organizational Test (HVOT)	HVOT performance is known to be dependent on bilateral parietal and temporal-occipital cortex functioning and involves participants' mental integration and naming of common objects presented in a spatially scattered puzzle piece–like format. Proper execution of the task requires participants to mentally rotate and connect partial stimuli pieces into a whole to form a perceptual gestalt. *Administration Time*: Variable, with ~10–12 min average.	Superior parietal lobules, ventral temporal-occipital cortex, and posterior visual association areas, frontal eye fields, left dorsolateral prefrontal cortex[137]
Psychomotor function	Manual dexterity & motor speed	Lafayette Grooved Pegboard Test	A manipulative dexterity and motor speed test that involves the insertion of small milled keylike pins into randomly rotated matching holes arranged in a 5 × 5 array. Each hand is evaluated separately with a score reflecting the total time to complete insertion of all 25 pegs for each hand. *Administration Time*: Variable, with ~5 min average.	Nigrostriatal dopamine function[138]

[a] Recommended measures with readily available alternate, equivalent forms.
[b] Brain regions associated with test performance by functional MRI, other brain regions may also be involved. For further discussion of the uses and limitations of fMRI technology, see Refs.[139,140]

Although POCD has been defined by the statistical results of cognitive tests, multiple investigators have found that it is also associated with impairments in quality of life,[18] increased exit from the workforce,[19] and increased mortality after surgery.[19,20] Thus, POCD can be conceptualized as a lack of resilience in the face of perioperative stress,[21] which is associated with impairments in multiple aspects of life. This conceptual model raises the question of whether POCD also may be associated with impairments in social relationships, increased physical frailty, decreased sexual interest and/or performance, and deficits in other aspects of life; these are important questions to be addressed by future studies (see **Table 4**).

How Long Does Postoperative Cognitive Dysfunction Last?

Aside from this disagreement over how POCD diagnosis is defined, it is also unclear how long it may last. This issue is difficult to address for several reasons. First, it is ethically unreasonable and practically impossible to randomize patients to surgery and anesthesia (vs placebo treatment). Without a nonsurgical control group, though, it is unclear how much of the cognitive dysfunction in surgical patients is truly due to anesthesia, surgery, and perioperative care.[22] The initial rapid drop in cognition seen in patients with POCD occurs much more rapidly than normal age-related cognitive decline.[20,23]

Matched cohort study designs can attempt to provide nonsurgical control groups for comparison, but such study designs are nonrandomized and thus potentially confounded by the fact that surgical patients may be intrinsically different from nonsurgical controls. Nonetheless, several studies have compared the incidence of cognitive dysfunction in surgical patients and nonsurgical controls.[23,24] In the International Study of Post-Operative Cognitive Dysfunction (ISPOCD), statistically significant differences in the incidence of cognitive dysfunction were found between surgical patients and nonsurgical controls at 1 week and 3 months after surgery,[23] but no difference was seen at 1 year after surgery. In a prospective matched cohort study, however, greater cognitive dysfunction was seen in surgical patients than nonsurgical controls even at 1 year after surgery.[24] A retrospective study by Avidan and colleagues[25] found no difference in the cognitive decline trajectory between noncardiac surgical patients and matched controls over a period of up to several years (median of 3.1 years of follow-up in surgical patients). However, the 2 largest studies to examine this issue both found that patients who have gone through anesthesia and surgery are at an increased risk of developing dementia years later.[26,27] Taken together, these data suggest that POCD after noncardiac surgery typically lasts months or even up to a year, but does not exclude the possibility that it may last longer in some cases. Whether perioperative care and/or POCD are linked to a long-term risk of developing dementia remains an important question for future prospective studies (see **Table 4**).[28]

After cardiac surgery, Newman and colleagues[7] found an overall cognitive trajectory of decline up to 5 years later. Interestingly, cognitive dysfunction in the early postoperative period was a predictor of cognitive decline 5 years later,[7] raising the possibility that long-term cognitive decline after cardiac surgery may be caused by insults sustained during the perioperative period. This view is challenged, however, by data from Selnes and colleagues,[8,29,30] who found no difference in the long-term cognitive trajectory (at 3 or 6 years after surgery) in patients with coronary artery disease (CAD) who underwent cardiac surgery versus control patients with CAD who did not undergo cardiac surgery. Similarly, patients with CAD who underwent off-pump coronary artery bypass grafting (CABG) had similar cognitive outcomes as patients with CAD who underwent percutaneous coronary intervention.[31] Thus, there is clearly long-term cognitive decline that occurs over years in older patients with CAD, but this long-term

decline appears to be largely due to patient factors (such as preexisting neurovascular disease) rather than procedural factors (such as cardiac surgery, cardiopulmonary bypass, or anesthesia itself[32]). This interpretation need not imply that the mechanisms of cognitive decline are identical in patients with CAD treated surgically versus medically, though.[33] Taken together, these data suggest that, as in the case of POCD after noncardiac surgery, POCD after cardiac surgery may last from weeks to several months. However, the current data do not rule out the possibility that POCD after cardiac surgery may last longer in some cases.

In asking how long POCD may last, it is important to note that POCD is a syndrome rather than a disease caused by a single underlying pathophysiologic process. In this sense, POCD is more akin to a fever than influenza. Although a recent study suggested that POCD is independent of surgical procedure or anesthetic drug choice on a population level,[34] there are likely some patients who experience POCD due to specific intraoperative or perioperative factors, and the duration of POCD likely depends on its specific etiology. For example, the fifth patient in Bedford's case report[1] was described as "an intelligent and active man—mentally normal in every way" before surgery, but after he was "unable to recognize his relations and remained unaware of his surroundings" even up to 18 months after surgery. This severe POCD was likely related to the fact that this patient's "blood pressure fell to unrecordable levels for about 15 minutes" during surgery.[1] There is considerable evidence that prolonged cerebral hypoperfusion can cause cerebral ischemic damage and result in lifelong neurocognitive deficits. Thus, it is likely that this patient's postoperative cognitive dysfunction was caused by intraoperative hypotension, and that it lasted the rest of this patient's life (this could be conceptualized as the bottom trajectory in **Fig. 2**). Although this is a somewhat extreme case (intraoperative periods of undetectable blood pressure lasting more than 15 minutes are currently extremely rare, except in

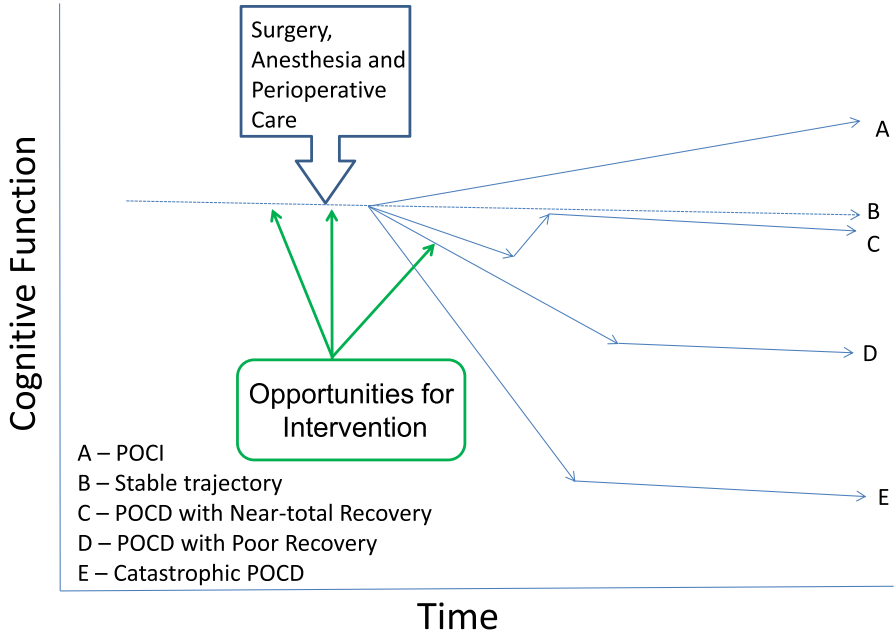

Fig. 2. Potential cognitive trajectories following surgery.

deep hypothermic circulatory arrest cases), this example makes the point that the duration of POCD depends on its etiology. This should come as no surprise. The length, severity, and outcome of any syndrome depends on its cause; a fever caused by a cold virus is likely to have a shorter duration and better outcome than one caused by gram-negative rod sepsis.

We believe that the question of how long POCD lasts, as opposed to how long other types of cognitive deficits may last, is largely irrelevant for individual patients though. If a patient is suffering from cognitive decline, in most cases he or she (and family members) are unlikely to care what percentage of the cognitive decline may be attributable to perioperative care, versus what percentage may have occurred in the absence of perioperative care. Furthermore, there is no way to calculate these percentages on an individual patient basis, and even if we could calculate these percentages on an individual patient basis, it would be therapeutically irrelevant: there is currently no specific treatment for POCD that differs from that for any other age-related cognitive disorder. Nonetheless, patients may ask preoperatively what their risk of POCD is, and how long it may last. At a population level, we believe that current data suffice to tell patients that most cases of POCD resolve within months after both noncardiac and cardiac surgery, although it is impossible to tell how long any individual case of POCD will last. It is important to emphasize during preoperative counseling that POCD has more than one potential underlying cause, and if it develops, the course and prognosis will depend on its cause(s).

What Is Postoperative Cognitive Improvement?

Although much of the focus has been on patients who experience a worsening of cognitive performance after anesthesia and surgery, the same neuropsychological testing demonstrates that some patients improve their cognitive performance after their procedure. This enhancement may reflect a genuine improvement in cognitive function, or simply the slowing or reversal of a preoperative deterioration. In some cases, POCI can be directly attributed to the goals of the specific surgery itself, for example, the postoperative restoration of cerebral perfusion after carotid endarterectomy,[35] the removal of a brain lesion,[36] or the surgical treatment of obesity and metabolic syndrome.[3,4] However, even in these patients, practice effects (ie, the tendency for test performance to improve with repeat testing) may also significantly contribute to the probability of mistakenly concluding that a subject has postoperative cognitive improvement.[37]

More generally, the use of multiple sensitive tests, performed at different times, results in great measurement variability. The ISPOCD group examined this variability and uncovered cognitive improvement in 4.2% to 8.7% of patients after 1 week and in 5.0% to 7.8% after 3 months.[38] However, in the same population, these investigators found a 3 to 6 times greater incidence of POCD, leading them to conclude that the observed “improvement” merely reflected the unpredictable variability inherent in precise neuropsychological testing. Although there may be a subset of patients who improve after surgery, it appears to be a much smaller population than those who experience dysfunction.[38]

It is hard to imagine that the factors associated with anesthesia and surgery themselves (eg, fasting, stress, anesthesia, tissue damage, blood loss) would confer a cognitive benefit to patients. Thus, how do we explain patients who do appear to experience genuine cognitive improvement after anesthesia and surgery? In a meta-analysis evaluating cognitive function before and after CABG surgery, there was evidence of cognitive improvement in multiple neuropsychological tests.[39] Patients receiving CABG also demonstrate improved physical, social, and emotional function

6 months and 1 year after surgery, including less anxiety and depression.[40] It is likely that the improvement in the cognitive function of patients who received CABG stems from this generalized improvement in overall health and quality of life, especially given the known negative effects of depression on cognitive performance.[41,42] Moreover, a successful surgery sometimes enables patients to taper or discontinue cognition-clouding medications (eg, medications for pain, sleep, or anxiety) that were used preoperatively, and may thus allow patients to improve their overall functioning. In line with this idea, even among patients who had POCD at 6 weeks after surgery, increased ability to perform instrumental activities of daily living at 6 weeks after surgery was associated improved cognition at 1 year.[2]

How Long Does Postoperative Cognitive Improvement Last?

It is unclear how long cognitive improvement would last if it results from a generalized improvement in health postoperatively. The increases in performance described previously began to appear at 3 months, and continued throughout the first year after cardiac surgery.[39] In bariatric surgery, improvements were seen 2 and 3 years later.[3,4] We hypothesize that postoperative cognitive improvement will last as long as a patient's general health and quality of life remain improved after surgery, and this is an important question for future study (see **Table 4**).

A Comparison Between Postoperative Cognitive Dysfunction and Other Medically Related/Induced Cognitive Disorders

The phenomenon of POCD has a parallel in the cognitive changes associated with cancer and chemotherapy (reviewed in Ref.[43]). Although some of the classical psychological sequelae of cancer diagnosis (including depression, anxiety, fatigue) are independently associated with alterations in cognitive function, it remains difficult to untangle the pathophysiology of cancer-related cognitive impairment (CRCI) because several chemotherapeutic agents have direct neurotoxic actions (reviewed in Ref.[44]) and modulate interactions between the immune system and brain.[45] Although CRCI appears to occur more frequently than POCD, the 2 syndromes share many of the same characteristics, including demographics, biological factors, and time courses. As in the case of POCD, older patients and those with lower levels of pretreatment cognitive reserve experience the greatest reductions in performance from CRCI.[46,47] These impairments occur in multiple cognitive domains, reach a nadir shortly after cancer treatment, and then gradually return toward baseline.[48] Additionally, many of the proposed mechanisms of "chemo-brain" are the same ones proposed in the POCD literature (discussed later in this article). Patients subjectively report greater deficits than are seen in objective neuropsychological testing in both POCD and CRCI,[49,50] which suggests that the neurocognitive tests used in CRCI and POCD testing do not pick up the full intensity of the cognitive impairments that patients themselves experience. Unfortunately, many of the same methodological problems (eg, inability to randomize, variation between studies in criteria used to define cognitive impairment, practice-related effects) affect studies on both POCD and CRCI.

WHO IS AT RISK FOR DEVELOPING POSTOPERATIVE COGNITIVE DYSFUNCTION?

Modifiable Risk Factors

Several studies have examined risk factors for POCD (**Tables 2** and **3** for a list of modifiable and nonmodifiable POCD risk factors, respectively). Interestingly, several studies have found that either lighter anesthetic depth or careful anesthetic depth monitoring can lower POCD rates,[51,52] which suggests that POCD may be due to

Table 2
Potentially modifiable risk factors for POCD

Risk Factor	Effect Size	Study Design	Reference
Bispectral index (EEG) guided anesthetic care (vs routine care)	OR 0.92 (0.66–1.29) at 1 wk $P = .06$ OR 0.62 (0.39–0.97) at 3 mo $P = .02$	RCT	51
	18.1% vs 23.9% at 7 d $P = .062$ 8% vs 10.3% at 3 mo $P = .372$	RCT	52
Fentanyl dosage	Low (10 μg/kg) vs high-dose fentanyl (50 μg/kg), POCD rates 23.6% vs 13.7% at 1 wk, respectively, $P = .03$. NS at 3 and 12 mo.	RCT	141
Ketamine treatment	2 SD drop in overall cognition in 7/26 ketamine group vs 21/26 patients, $P<.001$	RCT	107
Lidocaine vs no lidocaine	POCD 18.6% vs 40%, $P = .028$	RCT	142
	Neurocognitive deficit 45.8% vs 40.7% at 10 wk $P = .577$ 35.2% vs 37.7% at 25 wk $P = .710$	RCT	143
	45.5% vs 45.7%, $P = .97$	RCT	66
Magnesium sulfate infusion	Multivariate OR for low dose 0.09 (0.02–0.50), $P = .01$; OR for high dose 0.45 (0.16–1.33), $P = .15$	RCT	144
	44.4% vs 44.9%, $P = .93$	RCT	106
Piracetam vs no piracetam	Overall cognitive function preoperative 0.06 ± 1.02 vs -0.06 ± 0.99 postoperative -0.65 ± 0.93 vs -1.38 ± 1.11, $P<.0005$	RCT	145
Intraoperative steroid treatment	No vs low-dose vs high-dose dexamethasone POCD 22.3% vs 20.6% vs 31.4%, $P = .003$	RCT	110
	RR 1.87 (0.90–3.88) at 1 mo $P = .09$ RR 1.98 (0.61–6.40) at 1 y $P = .24$	RCT	109
Postoperative delirium[a]	Multivariate OR 9.58 (4.62–19.9), $P<.001$	RCT	51
	POCD vs no POCD[b] 1.5% vs 1.1% at discharge $P = .046$ 6.7% vs 5.6% at 3 mo $P = .373$	Prospective cohort study	20
	Delirium vs no delirium MMSE scores: 24.1 vs 27.4 at 1 mo $P<.001$ 25.2 vs 27.2 at 1 y $P<.001$	Prospective cohort study	9

Postoperative infection[a]	Univariate OR 2.17 (1.50–3.15), $P = .001$	RCT	51
Postoperative respiratory complication[a]	Univariate OR 1.69 (1.01–2.89), $P = .02$	RCT	51
Metabolic syndrome[a]	POCD vs no POCD 43.3% vs 26.7%, $P<.02$	Prospective cohort study	127
Cigarette abuse	Multivariate OR 2.04 (1.11–3.74), $P = .022$ NS	RCT Prospective cohort study	146 23
Diabetes[a]	Multivariate OR 2.34 (1.22–4.51), $P = .01$ POCD vs no POCD 40% vs 19.2%, $P = .021$ Multivariate linear regression, parameter estimate 0.031 (−0.111–0.172), $P = .671$	Prospective cohort study Prospective cohort study RCT	11 104 66
Duration of anesthesia	OR 1.1 (1.0–1.3), $P = .01$ POCD vs no POCD at 3 mo 215.0 ± 92.8 vs 211.5 ± 103.2 min duration, $P = .52$ POCD vs no POCD 5.6 ± 1 .5 vs 5.0 ± 1.2, $P = .026$ POCD vs no POCD 4.6 ± 1.5 vs 3.8 ± 0.8, $P = .001$	Prospective cohort study Prospective cohort study Prospective cohort study Prospective cohort study	23 20 104 147
Benzodiazepines before surgery	OR 0.4 (0.2–1.0), $P = .03$	Prospective cohort study	23
Duration of hospital stay	POCD vs no POCD 6.6 ± 16.3 vs 4.8 ± 5.9 at discharge $P = .0003$ Multivariate OR 1.03 (1.00–1.05) at 3 mo $P = .2479$	Prospective cohort study	20
Duration of surgery	POCD vs no POCD 4.7 ± 0.9 vs 4.2 ± 1.0, $P = .01$	Prospective cohort study	104
Anesthetic type (general vs regional)	Mean Difference −0.08 (–0.17–0.01), $P = .094$ General vs nongeneral anesthesia, OR 1.34 (0.95–1.93), $P = .26$	Meta-analysis Meta-analysis	56 55

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Table 2
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Risk Factor	Effect Size	Study Design	Reference
Bispectral index and cerebral oxygenation monitoring	1 wk mild Fisher's exact test $P = .018$ 1 wk moderate, Pearson $P = .037$ 1 wk severe, Fisher exact test $P = .12$ 12 wk mild χ^2 test $P = .02$ 12 wk moderate χ^2 test $P = .85$ 12 wk severe χ^2 test $P = .65$ 1 y mild χ^2 test $P = .015$ 1 y moderate χ^2 test $P = .02$ 1 y severe Fisher exact test $P = .36$	RCT	24
Postoperative copeptin levels[a]	OR 28.814 (7.131–116.425), $P<.001$	Prospective cohort study	104
Peripheral inflammatory markers[a]	S-100β standardized mean difference 1.377 (0.423–2.331), $P = .005$ IL-6 standardized mean difference 1.614 (0.603–2.624), $P = .002$	Meta-analysis	148
Off-pump vs on-pump cardiac surgery	Standardized cognitive change score 0.19 vs 0.13 at 3 mo $P = .03$ 0.19 vs 0.12 at 1 y $P = .09$	RCT	149
	Off-pump vs on-pump vs nonsurgical cardiac comparison vs healthy heart comparison MMSE 27.7 ± 2.0 vs 27.6 ± 2.4 vs 27.9 ± 2.0 vs 28.5 ± 1.9 at baseline $P<.01$ 28.5 ± 1.8 vs 27.4 ± 2.5 vs 28.0 ± 2.3 vs 28.6 ± 1.7 at 6 y $P<.01$	Prospective longitudinal study	8
	62% vs 53% at postoperative day 4, $P = .50$; 39% vs 14% at 3 mo $P = .04$	RCT	150
Perfusion pressure (in cardiac surgery)	MMSE score drop 48 h after surgery, in low pressure vs high pressure: 3.9 ± 6.5 vs 1.1 ± 1.9, $P = .012$	RCT	151
$r^{S_{O_2}}$ Desaturation score >3000	Multivariate OR 2.22 (1.11–4.45), $P = .024$	RCT	146
Hemodilution (in CPB cases)	Age × hemodilution interaction, $P = .03$	RCT, stopped early	152

Hyperglycemia (ie, glucose >200 mg/dL at any point during CPB cases)	Associated with POCD in nondiabetic patients, N = 380, OR = 1.85 (95% CI 1.12–3.04), P = .017; NS (P = .81) in diabetic patients, n = 145	Retrospective analysis of pooled data from multiple previous prospective studies	[153]
Slow rewarming vs normal rewarming (in CPB cases)	Multivariate linear regression variable estimate 0.35, P = .047 (favoring slow rewarming)	RCT	[154]
Continuous cell saver use (in CPB cases)	6% vs 15% in controls, P = .038	RCT	[155]
	16.7% vs 15.9% in controls, relative risk: 1.05, 95% CI 0.58–1.90 at 3 mo.	RCT	[156]
Embolic load (in CPB cases)	No correlation between embolic load measured by transcranial Doppler ultrasound and POCD at 1 wk (P = .617) or at 3 mo (P = .110), n = 356 patients.	Pooled analysis of data from 2 other RCTs	[102]
Alpha stat vs pH stat blood gas management (in CPB cases)	27% vs 44%, P = .047	RCT	[157]
Hypothermia vs normothermia (in CPB cases)	Multivariate odds ratio 1.15 (95% CI 1.01−1.31), P = .042, for POCD at hospital discharge after intraoperative normothermia vs mild hypothermia.	Retrospective analysis of pooled data from 2 previous trials	[158]
	NS difference for POCD at 6 wk after surgery.	RCT	[159]
	Hypothermia vs normothermia, relative risk for POCD at 1 wk after surgery = 0.77, P = .048.	RCT	[160]
	Hypothermia vs normothermia, relative risk for POCD at 5 y after surgery = 0.66, P = .16.	RCT	[161]

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; EEG, electroencephalogram; MMSE, Mini-Mental State Examination; NS, not significant; OR, odds ratio; POCD, postoperative cognitive dysfunction; RCT, randomized controlled trial; RR, relative risk.

[a] Partially modifiable risk factor.

[b] Delirium during hospital stay.

Table 3
Nonmodifiable risk factors for POCD

Risk Factor	POCD vs No POCD	Study Design	Reference
Age	Multivariate OR 1.04 (1.01–1.08), $P = .01$	RCT	51
	Multivariate OR 1.03 (0.99–1.06), $P = .1$	Prospective observational study	11
	Age of patients with POCD 51.9 ± 17.3 vs no POCD 49.4 ± 16.5, measured at discharge $P = .027$	Prospective cohort study	20
	OR 1.03 (1.01–1.06), $P = .013$	Prospective cohort study	67
	OR 1.151 (1.030–1.285), $P = .003$	Prospective cohort study	104
	Multivariate OR 1.34 (1.01–1.78), $P = .043$	Prospective cohort study	147
	Multivariate OR 0.95 (0.71–1.26), $P = .70$	RCT	146
	Multivariate linear regression parameter estimate (for continuous cognitive change score) −0.009 (−0.012 to −0.005), $P<.001$	RCT	66
Educational level	Multivariate OR 0.98 (0.91–1.07), $P = .67$	Prospective cohort study	11
	Multivariate OR 0.84 (0.76–0.93) at 3 mo $P = .0031$	Prospective cohort study	20
	OR 0.9 (0.83–0.98), $P = .021$	Prospective cohort study	67
	Multivariable linear regression model, parameter estimate: 0.012 (−0.002–0.027), $P = .098$	RCT	66
Type of surgery	Minimally invasive 4% vs 34%, intra-abdominal/thoracic 21% vs 14%, orthopedic 11% vs 16% at discharge $P = .001$	Prospective cohort study	20
	Congenital disease 10 vs 42 Valvular disease 32% vs 54% Aorta disease 14% vs 20% Tumor 2% vs 2%; $P = .051$ overall	Prospective cohort study	147
	NS	Prospective cohort study	23

Genetic risk alleles	*CRP* 1059G/C SNP OR 0.37 (0.16–0.78), $P = .013$ *SELP* 1087G/A SNP OR 0.51 (0.30–0.85), $P = .011$	Prospective cohort study	67
Left hippocampal volume	POCD vs no POCD 2.26 ± 0.21 vs 2.45 ± 0.15, $P<.01$	Prospective cohort study	162
Right hippocampal volume	POCD vs no POCD 2.49 ± 0.11 vs 2.62 ± 0.20, $P<.05$	Prospective cohort study	162
MCA velocity	Left MCA POCD vs no POCD 42.5 ± 5.5 vs 54.3 ± 4.4, $P<.1$ Left vs Right MCA POCD 42.5 ± 5.5 vs 56.3 ± 4.5, $P<.05$[a]	Prospective cohort study	163
Preoperative renal insufficiency	Multivariate OR 0.18 (0.04–0.75), $P = .019$	RCT	146
Previous stroke	Multivariate OR 0.30 (0.11–0.84), $P = .02$	RCT	144

Abbreviations: CRP, C-reactive protein; MCA, middle cerebral artery; NS, not significant; OR, odds ratio; POCD, postoperative cognitive dysfunction; RCT, randomized controlled trial; SELP, P-selectin; SNP, single nucleotide polymorphism.

[a] Values estimated from the bar graph in Fig. 1.

excessive anesthetic drug exposure in some cases. In line with these findings, a previous study found an increased rate of POCD 1 week after general versus regional anesthesia ($P = .06$ overall, $P = .04$ in an as treated analysis[53]), although there was no difference in POCD rates 3 months after surgery ($P = .93$). However, Silbert and colleagues[54] recently found no difference in POCD rates between patients who underwent extracorporeal shock wave lithotripsy under either general or spinal anesthesia; if anything, there was a surprising trend toward increased POCD risk in the spinal anesthesia group ($P = .06$, and the trial was stopped early). This suggests that general anesthesia does not increase POCD risk. These findings are particularly difficult to reconcile with those discussed previously because more than 90% of the patients in the spinal anesthesia group did not receive any intravenous sedation,[54] in contrast to many other studies in which patients randomized to receive regional anesthesia also received large doses of intravenous sedation.[53] However, the study by Silbert and colleagues[54] was nearly fourfold smaller than the study by Rasmussen and colleagues.[53] Further, the patients in the spinal anesthesia group were also 3 years older on average than those in the general anesthesia group in the study by Silbert and colleagues.[54] A meta-analysis performed on this subject in 2010 found a nonstatistically significant trend toward an increased risk of POCD after general versus regional anesthesia (odds ratio 1.34, 95% confidence interval 0.93%–1.95%, $P = .26$).[55] Another meta-analysis performed in 2011 also found a slight, but nonsignificant trend toward a decreased risk of POCD after regional versus general anesthesia (standardized difference in means −0.08, −0.17–0.01, $P = .094$,[56]). Future studies will be necessary to better understand whether there is a relationship between general anesthesia and POCD risk, and whether certain subgroups of patients (such as older patients, those with more cerebrovascular disease, or those with less cognitive reserve for other reasons) are at higher risk of developing POCD after general versus regional anesthesia (**Table 4**).

Numerous studies also have examined whether specific anesthetic drugs are tied to POCD risk. Although basic science studies have suggested differential neurotoxicity between inhaled/volatile anesthetics versus intravenous agents (reviewed in Ref.[28]), there is a paucity of well-controlled clinical studies examining this issue. For example, higher rates of cognitive decline (as measured by the MMSE) were found on 1, 2, and 3 days after surgery among 2000 patients randomized to receive inhaled versus intravenous anesthesia.[57] However, there was no MMSE test score difference between groups by 10 days after surgery in this study, there was no attempt made to ensure equivalent anesthetic depth in both groups, and patients in the inhaled group likely received a significant anesthetic overdose.[58] There was no difference in POCD rates between patients randomized to sevoflurane versus desflurane in another study, although patients who received desflurane awakened faster and had higher satisfaction scores.[59] Patients who received spinal anesthesia and isoflurane had a higher incidence of POCD than patients who received spinal anesthesia alone or spinal anesthesia plus desflurane in a pilot study.[60] It is somewhat unusual to use spinal and inhaled anesthesia together in the United States, though, which makes it hard to apply these findings to typical clinical practice. These findings are also challenged by the results of Kanbak and colleagues,[61] who found that isoflurane use was associated with improved neurocognitive function after cardiac surgery (as compared with desflurane or sevoflurane) in a similar size pilot randomized controlled trial. Schoen and colleagues[62] found that sevoflurane administration (as compared with propofol-based intravenous anesthesia) was associated with improved cognition within 1 week after on-pump cardiac surgery. In summary, the available evidence is insufficient to determine whether any specific anesthetic agent is associated with a reduced risk of POCD.

Table 4
Important questions for future research, suggestions, and challenges

Research Question	Suggested Study Design and Methods[a]	Issues/Challenges
What aspects of aging are most closely tied to POCD risk?	Cohort design, with cognitive testing and geriatric evaluations	Important to have involvement of geriatricians.
Are certain patients (ie, the elderly, or those with less cognitive reserve) at higher risk for POCD after general vs regional anesthesia?	RCT of general vs regional anesthesia with cognitive testing, stratified by age group and/or other variables	Patient recruitment, importance of minimizing sedation in the regional arm to allow for a true comparison of general vs regional anesthesia.
Is POCD associated with an increased long-term risk of dementia?	Prospective cohort with long-term follow-up, cognitive and MCI/AD/dementia screening	Need to enroll patients who may already have MCI or other baseline cognitive deficits. Large sample sizes needed to obtain sufficient power for clinically relevant effects; see Refs.[28,164] for discussion of this issue.
What is the relationship between central neuroinflammation, cerebrovascular white matter disease, AD pathology (and/or perioperative changes in these pathologic processes) and POCD?	Cohort design, cognitive testing, neuroimaging, and CSF AD and inflammatory biomarker studies	Patient recruitment.
Is POCD associated with altered functional brain connectivity?	Cohort design, cognitive testing and functional MRI scans	Patient recruitment, MRI safety issues may exclude some elderly patients with pacemakers/AICDs, metal joint replacements, and so forth.
Are there CSF biomarkers of POCD?	Cohort design, cognitive testing and CSF sampling	Patient recruitment.
Would SSRI treatment prevent POCD; improve cognitive trajectory, affect, and mood; and/or improve quality of life in patients with POCD?	RCT, cognitive testing, quality-of-life measurement, depression/anxiety and affect rating scales	Possible side effects from treatment.

(*continued on next page*)

Table 4
(*continued*)

Research Question	Suggested Study Design and Methods[a]	Issues/Challenges
Would preconditioning with ischemia or anesthetic agents help prevent POCD?	RCT	Patient recruitment.
Would physical and/or cognitive prehabilitation reduce the incidence or severity of POCD, and/or improve quality of life after surgery in the elderly?	RCT	Blinding difficult if not impossible; need to ensure patient participation in prehabilitation interventions.
How long does POCI last? Does it depend on surgery type? To what extent does POCI reflect surgically induced improvements in underlying disease processes, quality of life, and/or mental health?	Cohort design	Careful statistical analysis required to separate true POCI from test practice effects.

Abbreviations: AICD, automatic implantable cardioverter defibrillator; AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; POCD, postoperative cognitive dysfunction; POCI, postoperative cognitive improvement; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

[a] For prospective study designs, it is important that all testing be completed both before and after surgery.

Several recent articles also have examined whether specific anesthetic drugs may be associated with less cognitive decline after surgery in patients with MCI (an early stage of AD). One recent study found increased rates of MCI progression 2 years later in patients who received spine surgery who were randomized to receive sevoflurane versus propofol or epidural anesthesia (n = 60 per group,[63]). Another study among patients with MCI found no difference in POCD rates among patients with MCI randomized to receive sevoflurane (n = 99) versus propofol anesthesia (n = 101) for radical rectal resection, although there was an increased rate of severe POCD in the sevoflurane-treated patients.[64] Taken together, these studies raise the possibility that propofol anesthesia (as compared with sevoflurane anesthesia) might be associated with improved postoperative cognition in patients with MCI, but further studies are necessary to examine this issue.

Nonmodifiable Risk Factors

One nonmodifiable risk factor for POCD consistently found in multiple studies is increased age[7,20,23,51,54]; POCD was present in one study more than twice as often in patients age 60 and older as in those younger than 60.[20] This association makes intuitive sense in the setting of the failed resilience model discussed previously. Older patients often have more neurovascular disease risk factors, more cerebral white matter damage, and less cognitive reserve,[65] which may place them at a higher risk of cognitive dysfunction after the stress of surgery, anesthesia, and perioperative care. Aside from age, 2 other nonmodifiable risk factors for POCD that have been found across multiple studies are fewer years of previous education and lower preoperative cognitive test scores,[20,66,67] which also fits with the idea that patients with less cognitive reserve are at higher risk of developing POCD (see **Table 3**).

Although age itself is nonmodifiable, age is also frequently associated with frailty, which is at least partly modifiable.[68–71] Numerous studies in recent years have focused on physical "prehabilitation" to decrease postoperative complications and/or improve postoperative physical function,[72–75] but to the best of our knowledge no study has evaluated whether physical and/or cognitive prehabilitation might decrease the risk of POCD. The plasticity of the human brain in response to both physical[76] and cognitive[77] exercise suggests that such interventions may help prevent and/or treat POCD. The degree to which an aging brain possesses the plasticity to benefit from such interventions is unclear, though,[78] making this is an important area for future research (see **Table 4**).

WHAT CAUSES POSTOPERATIVE COGNITIVE DYSFUNCTION?

Animal Models

Animal studies have suggested the POCD may be caused be either excessive neuroinflammation after surgery,[79] a failure to resolve inflammation,[80,81] blood-brain barrier/endothelial dysfunction,[82–84] and/or preexisting AD pathology (reviewed in Ref.[28]). Activation of the innate immune system is increasingly appreciated as an underlying factor in several neurodegenerative conditions, including AD. Using different preclinical models of non–central nervous system surgery, neuroinflammation has been repeatedly associated with behavioral dysfunction and memory deficits. Upregulation of systemic proinflammatory cytokines, including tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, chemokines, and damage-associated molecular patterns, like high-mobility group box 1, have been shown to activate bone-marrow derived macrophages and contribute to the overall brain pathology after aseptic trauma.[80,81,85,86] Several mechanisms, including humoral, cellular, and neuronal pathways, have been proposed in this bidirectional communication between the immune system and the brain after surgery.

Notably, strategies aimed at mitigating the excessive inflammatory milieu have been promising in limiting surgery-induced cognitive decline in several rodent models and may offer novel insights for future interventional studies in humans.

Ongoing clinical studies are starting to uncover a potential role for blood and cerebrospinal fluid (CSF) inflammatory biomarkers in the pathophysiology of POCD, and this represents a burgeoning area of research for the field. However, it remains unclear to what extent the findings in animal models translate to human patients. Although mice are useful for modeling spatial memory deficits after anesthesia and surgery, mice lack the ability to perform more complex human cognitive functions, such as executive function. Thus, mouse models may be useful for understanding some of the memory deficits seen in human POCD, but they cannot recapitulate the full spectrum of cognitive deficits seen in our patients. Also, it is challenging to model the temporal course of human POCD in rodents: preclinical studies often report acute cognitive changes in hippocampal-dependent cognitive tasks but provide limited evidence for longer-lasting neurocognitive dysfunction. Combining anesthesia/surgical trauma with known risk factors for POCD (ie, aging, infection, metabolic syndrome) in rodents may provide a more relevant model of human POCD.[87–89] Further, given the significant differences between the mouse and human immune systems and inflammatory mechanisms,[90] it is unclear to what extent the neuroinflammatory mechanisms seen in mouse models are involved in human POCD.

One recent animal study also suggested that postoperative memory deficits may be due to anesthetic-induced upregulation of alpha-5 subunit containing gamma-aminobutyric acid (GABA)-A receptors in the hippocampus.[91] These alpha-5–containing GABA receptors inhibit long-term potentiation (LTP, a cellular correlate of learning and memory). Thus, upregulation of these receptors would be predicted to cause learning and memory deficits, which could play a role in contributing to human POCD and/or postoperative delirium. However, it is unclear whether anesthetic drugs and/or inflammatory mediators that impinge on LTP function also cause a sustained upregulation of alpha-5 GABA-A receptors in humans.

Human Studies

The mouse studies described previously provide useful hypotheses about what might cause POCD, which can then be investigated in human studies. Indeed, surgery is associated with a central neuroinflammatory response in humans.[92–96] It remains unclear, though, whether this central neuroinflammatory response is associated with POCD. To the best of our knowledge, no human studies have demonstrated an association between the presence or levels of central inflammatory mediators and the presence or duration of POCD. Preexisting AD pathology (as measured by CSF biomarkers) has been associated with increased perioperative decline in some cognitive tests but not in others,[97] and patients with MCI, a prodromal stage of AD, have larger cognitive deficits in some tests after perioperative care than surgical patients without MCI.[98,99] These studies suggest that preexisting AD pathology may be associated with POCD, but the full extent of this relationship remains to be elucidated. One recent pilot study also found that the extent of preexisting white matter damage (as measured by MRI) was a predictor of postoperative executive function deficits in patients who underwent knee arthroplasty.[100] Neuroimaging studies also have shown that cardiac surgery in particular is associated with an increase in “silent strokes” or white matter hyperintensities seen on MRI, although the total burden of white matter hyperintensities after surgery does not correlate with the presence of POCD[101,102] (reviewed in Ref.[32]). Clearly, understanding the relationship between central neuroinflammation, cerebrovascular white matter disease, AD pathology

(and/or perioperative changes in these processes) and POCD is a major question in the field.

Numerous human studies have failed to find plasma biomarkers associated with POCD,[11,103] although one recent study found that higher plasma levels of copeptin (a peptide co-released with arginine vasopressin from the hypothalamus) were associated with increased risk of both postoperative delirium and POCD.[104] Remarkably, plasma copeptin levels were a better predictor of POCD risk than age in this study[104]; it will be important to replicate these results. The failure of numerous other studies to find plasma biomarkers of POCD may be due to differential protein and cytokine expression between the cerebrospinal fluid and plasma.[94] Future human studies combining CSF biomarker measurements, cognitive testing, and functional neuroimaging both before and after perioperative care will be necessary to further elucidate the pathophysiology of POCD, and to fully ascertain whether anesthesia and surgery are associated with an acceleration of AD pathology.[28,105]

HOW CAN WE PREVENT OR TREAT POSTOPERATIVE COGNITIVE DYSFUNCTION?

Postoperative Cognitive Dysfunction Prevention Studies

Although we are likely only in the infancy of understanding the etiologies of POCD, its detrimental impact on patients mandate that clinicians do everything in their power to prevent patients from developing POCD and to treat POCD once it does develop. Numerous investigators have attempted to prevent POCD with interventions ranging from intraoperative lidocaine,[66] magnesium,[106] ketamine,[107] complement suppression,[108] or even high-dose dexamethasone[109] treatment in randomized controlled trials. Lidocaine treatment had no effect on preventing POCD overall,[66] although in a secondary analysis, lidocaine infusion appeared to have a beneficial effect on cognition in nondiabetic patients. Similarly, intraoperative magnesium treatment had no effect on preventing POCD overall, although there was a trend toward a detrimental effect of magnesium treatment on cognition in heavier patients.[106] Complement suppression with the monoclonal antibody pexelizumab (which inhibits complement factor C5) also had no effect on the rate of POCD, although it was associated with improved visuospatial cognition.[108]

Surprisingly, ketamine treatment (0.5 mg/kg) on anesthetic induction was associated with a decrease in POCD occurrence after cardiac surgery.[107] Ketamine treatment also was associated with a reduction in serum C-reactive protein levels in this study,[107] leading the investigators to propose that ketamine decreases POCD incidence by decreasing inflammation. However, high-dose dexamethasone (ie, 1 mg/kg on anesthetic induction) did not decrease POCD rates in patients undergoing cardiac surgery in the Dexamethasone for Cardiac Surgery (DECS) trial,[109] which was almost 4 times the size of the ketamine trial.[107] Higher-dose dexamethasone (0.2 mg/kg) was actually associated with increased POCD rates (as compared with 0.1 mg/kg dexamethasone or placebo treatment) in a trial of patients undergoing microvascular decompression for facial spasms.[110] Taken together, these results could imply that although inflammation may play a role in POCD, not all drugs with anti-inflammatory activity have the same effects on POCD. Alternatively, the efficacy of ketamine in reducing POCD[107] may be due to its effects on neurotransmitter receptors or other biological processes unrelated to inflammation; in addition to blocking the N-methyl-D-aspartate receptor, ketamine modulates signaling via a number of other receptors (reviewed in Ref.[111]).

Although the failure of numerous single-drug therapies for POCD prevention are disappointing, these failures are not surprising if POCD is viewed as a syndrome of

brain dysfunction caused by diverse factors rather than a single disease caused by a specific etiology. Further, the complexity of the human brain itself is staggering: it contains more than 80 billion neurons (each of which make thousands of synaptic connections to other neurons), and more than 80 billion interneurons.[112] The human brain also expresses more than 80% of the human genome,[113] a higher percentage than any other organ. Considering the complexity of the human brain, and the diverse factors that may contribute to POCD, it is less surprising that several single-drug interventions failed to reduce the incidence of POCD.

Preventing POCD may thus require a multicomponent intervention that addresses the diverse factors that contribute to its genesis. A recent pilot study suggested that remote ischemic preconditioning may decrease cognitive deficits after cardiac surgery.[114] Because remote ischemic preconditioning has a plethora of biological effects,[115] this study is consistent with the idea that preventing POCD will require interventions that work more broadly than a single drug.

Similarly, Ballard and colleagues[24] examined the effect of a combined intervention to decrease POCD rates, which included intraoperative bispectral index monitoring (to optimally titrate anesthetic depth) and cerebral oxygen saturation monitoring (to titrate cerebral oxygen delivery). This combined intervention reduced POCD incidence at multiple time points (see **Table 2** for statistics). However, there is mixed evidence whether bispectral (BIS) index monitoring alone can decrease POCD rates,[51,52] and the investigators of a systematic review also concluded that there is insufficient evidence to recommend the use of cerebral oximetry monitoring on its own to decrease POCD rates after cardiac surgery.[116] Taken together, these studies may mean that the combined use of BIS and cerebral oximetry monitoring may help decrease POCD rates, but that either monitor alone may have a lesser or nonsignificant effect. Future studies will be necessary to examine this hypothesis by evaluating these interventions in isolation and together.

Postoperative Cognitive Dysfunction Treatment Studies

Very few randomized controlled studies have examined whether any intervention can treat or improve POCD once it has already occurred. Such studies are challenging to conduct, as most cases of POCD resolve spontaneously within months (see the section "A description of postoperative cognitive dysfunction and postoperative cognitive improvement"), although they would still be important given the association between POCD and decreased quality of life,[18] early exit from the workforce,[19] and premature mortality.[19,20] However, these studies would be neither unprecedented nor impossible; a similar challenge occurs in depression treatment trials, in which there is a high response even among patients receiving placebo within weeks to months.[117] One randomized trial examined the use of the acetylcholinesterase inhibitor donepezil in patients who displayed cognitive decline (0.5 SD drop in at least 1 cognitive domain) 1 year after cardiac surgery. Donepezil improved some aspects of memory performance in these patients, which is consistent with the role of acetylcholinesterase inhibitors in improving memory in patients with early-stage AD. However, donepezil treatment had no effect on the overall cognitive index in these patients with cognitive decline 1 year after cardiac surgery.[118]

Interestingly, the antidepressant and selective serotonin reuptake inhibitor (SSRI) citalopram was used to successfully treat POCD in one case report.[119] This finding is generally in line with the pleiotropic biological roles of serotonin, including its ability to promote neuroplasticity.[120] If POCD is a syndrome of failed resilience or a lack of neuroplasticity after perioperative care that occurs in patients with preexisting neurovascular disease or "silent strokes," then the established efficacy of SSRIs in

improving neurologic outcomes after stroke[121] suggests that they may be useful in treating POCD as well. SSRIs also have been shown to improve quality of life in depressed elderly patients[122] and improve affect and mood even in nondepressed, healthy individuals,[123] which further suggests that SSRIs may be efficacious in reducing POCD-associated quality-of-life impairments. More work will be necessary to determine whether SSRIs improve cognition, quality of life, and other outcomes in patients with POCD (see **Table 4**).

SUMMARY AND FUTURE DIRECTIONS

POCD is a syndrome that occurs more frequently in patients age 60 and older, and is associated with early exit from the workforce,[19] decreased quality of life,[18] and premature mortality.[19,20] It typically lasts for weeks to months,[23] although rare cases may last considerably longer.[1] Based on this understanding, we believe that patients at high risk for POCD (ie, those with multiple risk factors listed in **Tables 2** and **3**, such as elderly patients) should be counseled preoperatively about the risk of POCD, just as we counsel patients preoperatively about numerous other risks of perioperative care. This counseling could allow patients to make cognitively demanding decisions before surgery/anesthesia, and/or to ensure that they will have loved ones or others to help them with cognitively demanding tasks for the first weeks to months after surgery/anesthesia. Additional help and assistance may help these patients recover better from surgery in general; after all, patients with POCD who may not be able to remember what they ate for breakfast that morning are also unlikely to be able to remember whether they took their medicine that morning.

The long-term sequelae of POCD also mandates that we try to prevent it, and that we develop effect treatments for it once it has occurred. The failure of numerous intervention trials to prevent POCD, and our general lack of understanding of what causes POCD, argue that developing a better understanding of the etiology of POCD may be essential for developing strategies to prevent it. We have conceptualized POCD as a failure of resilience in the face of perioperative stress, which suggests that strategies to improve physical and cognitive resilience in the elderly may help prevent POCD and improve overall recovery after surgery.

ACKNOWLEDGEMENTS

Dr M. Berger acknowledges grant funding from the International Anesthesia Research Society (Mentored Research Award) and the National Institute of Health (T32 #GM08600). Dr J. Browndyke acknowledges funding from the following grants: NIA R01-AG042599, NHLBI R01-HL109219, and NHLBI R21-HL109971. Dr H. Whitson acknowledges funding from the following grants: NIH R01AG043438, NIH R24AG045050, Alzheimer's Association NIRG-13-282202, and VA I21 RX001721-01. Dr Whitson's and Cohen's contributions are supported by Duke Pepper Center (P30AG028716). Dr J. Mathew acknowledges support from NIH grants HL096978, HL108280, and HL109971.

REFERENCES

1. Bedford PD. Adverse cerebral effects of anaesthesia on old people. Lancet 1955;269:259–63.
2. Fontes MT, Swift RC, Phillips-Bute B, et al, Neurologic Outcome Research Group of the Duke Heart Center. Predictors of cognitive recovery after cardiac surgery. Anesth Analg 2013;116:435–42.

3. Alosco ML, Galioto R, Spitznagel MB, et al. Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery. Am J Surg 2014;207:870–6.
4. Alosco ML, Spitznagel MB, Strain G, et al. Improved memory function two years after bariatric surgery. Obesity (Silver Spring) 2014;22:32–8.
5. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372:139–44.
6. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry 2012;17:1174–9.
7. 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.
8. Selnes OA, Grega MA, Bailey MM, et al. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? Ann Thorac Surg 2009;88:445–54.
9. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012;367:30–9.
10. Funder KS, Steinmetz J, Rasmussen LS. Methodological issues of postoperative cognitive dysfunction research. Semin Cardiothorac Vasc Anesth 2010;14:119–22.
11. McDonagh DL, Mathew JP, White WD, et al. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010;112:852–9.
12. Avidan MS, Xiong C, Evers AS. Postoperative cognitive decline: the unsubstantiated phenotype. Anesthesiology 2010;113:1246–8 [author reply: 1248–50].
13. Levine AJ, Miller EN, Becker JT, et al. Normative data for determining significance of test-retest differences on eight common neuropsychological instruments. Clin Neuropsychol 2004;18:373–84.
14. Duff K. Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. Arch Clin Neuropsychol 2012;27:248–61.
15. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991;59:12–9.
16. Lewis MS, Maruff P, Silbert BS, et al. The sensitivity and specificity of three common statistical rules for the classification of post-operative cognitive dysfunction following coronary artery bypass graft surgery. Acta Anaesthesiol Scand 2006;50:50–7.
17. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.
18. Phillips-Bute B, Mathew JP, Blumenthal JA, et al. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006;68:369–75.
19. Steinmetz J, Christensen KB, Lund T, et al. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009;110:548–55.
20. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18–30.
21. Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. Br J Anaesth 2014;112:440–51.

22. 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.
23. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998;351:857–61.
24. Ballard C, Jones E, Gauge N, et al. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. PLoS One 2012;7:e37410.
25. Avidan MS, Searleman AC, Storandt M, et al. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology 2009;111:964–70.
26. Chen PL, Yang CW, Tseng YK, et al. Risk of dementia after anaesthesia and surgery. Br J Psychiatry 2014;204:188–93.
27. Chen CW, Lin CC, Chen KB, et al. Increased risk of dementia in people with previous exposure to general anesthesia: a nationwide population-based case-control study. Alzheimers Dement 2014;10:196–204.
28. Berger M, Burke J, Eckenhoff R, et al. Alzheimer's disease, anesthesia, and surgery: a clinically focused review. J Cardiothorac Vasc Anesth 2014;28:1609–23.
29. Selnes OA, Grega MA, Bailey MM, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. Ann Neurol 2008;63:581–90.
30. Selnes OA, Grega MA, Bailey MM, et al. Neurocognitive outcomes 3 years after coronary artery bypass graft surgery: a controlled study. Ann Thorac Surg 2007;84:1885–96.
31. Sauer AM, Nathoe HM, Hendrikse J, et al, Octopus Study Group. Cognitive outcomes 7.5 years after angioplasty compared with off-pump coronary bypass surgery. Ann Thorac Surg 2013;96:1294–300.
32. McDonagh DL, Berger M, Mathew JP, et al. Neurological complications of cardiac surgery. Lancet Neurol 2014;13:490–502.
33. Bartels K, McDonagh DL, Newman MF, et al. Neurocognitive outcomes after cardiac surgery. Curr Opin Anaesthesiol 2013;26:91–7.
34. Evered L, Scott DA, Silbert B, et al. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg 2011;112:1179–85.
35. Hemmingsen R, Mejsholm B, Vorstrup S, et al. Carotid surgery, cognitive function, and cerebral blood flow in patients with transient ischemic attacks. Ann Neurol 1986;20:13–9.
36. Raeder MB, Helland CA, Hugdahl K, et al. Arachnoid cysts cause cognitive deficits that improve after surgery. Neurology 2005;64:160–2.
37. Casey JE, Ferguson GG, Kimura D, et al. Neuropsychological improvement versus practice effect following unilateral carotid endarterectomy in patients without stroke. J Clin Exp Neuropsychol 1989;11:461–70.
38. Rasmussen LS, Siersma VD, Ispocd G. Postoperative cognitive dysfunction: true deterioration versus random variation. Acta Anaesthesiol Scand 2004;48:1137–43.
39. Cormack F, Shipolini A, Awad WI, et al. A meta-analysis of cognitive outcome following coronary artery bypass graft surgery. Neurosci Biobehav Rev 2012;36:2118–29.
40. Lindquist R, Dupuis G, Terrin ML, et al, POST CABG Biobehavioral Study Investigators. Comparison of health-related quality-of-life outcomes of men and women after coronary artery bypass surgery through 1 year: findings from the POST CABG Biobehavioral Study. Am Heart J 2003;146:1038–44.

41. Rabbitt P, Donlan C, Watson P, et al. Unique and interactive effects of depression, age, socioeconomic advantage, and gender on cognitive performance of normal healthy older people. Psychol Aging 1995;10:307–13.
42. Norman S, Troster AI, Fields JA, et al. Effects of depression and Parkinson's disease on cognitive functioning. J Neuropsychiatry Clin Neurosci 2002;14:31–6.
43. Janelsins MC, Kesler SR, Ahles TA, et al. Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int Rev Psychiatry 2014;26:102–13.
44. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry 2003;8:201–16.
45. Maier SF, Watkins LR. Immune-to-central nervous system communication and its role in modulating pain and cognition: implications for cancer and cancer treatment. Brain Behav Immun 2003;17(Suppl 1):S125–31.
46. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol 2010;28:4434–40.
47. Schilder CM, Seynaeve C, Beex LV, et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. J Clin Oncol 2010;28:1294–300.
48. Falleti MG, Sanfilippo A, Maruff P, et al. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. Brain Cogn 2005;59:60–70.
49. Johnson T, Monk T, Rasmussen LS, et al, ISPOCD2 Investigators. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 2002;96:1351–7.
50. Correa DD, Hess LM. Cognitive function and quality of life in ovarian cancer. Gynecol Oncol 2012;124:404–9.
51. Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25:33–42.
52. Radtke FM, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013;110(Suppl 1):i98–105.
53. Rasmussen LS, Johnson T, Kuipers HM, et al, ISPOCD2 Investigators. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47:260–6.
54. Silbert BS, Evered LA, Scott DA. Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. Br J Anaesth 2014;113:784–91.
55. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 2010;22(Suppl 3):67–79.
56. Guay J. General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: a meta-analysis. Indian J Anaesth 2011;55:358–63.
57. Cai Y, Hu H, Liu P, et al. Association between the apolipoprotein E4 and postoperative cognitive dysfunction in elderly patients undergoing intravenous anesthesia and inhalation anesthesia. Anesthesiology 2012;116:84–93.
58. Deiner S, Baxter MG. Cognitive dysfunction after inhalation versus intravenous anesthesia in elderly patients. Anesthesiology 2012;117:676–8 [author reply: 8].

59. Rortgen D, Kloos J, Fries M, et al. Comparison of early cognitive function and recovery after desflurane or sevoflurane anaesthesia in the elderly: a double-blinded randomized controlled trial. Br J Anaesth 2010;104:167–74.
60. Zhang B, Tian M, Zhen Y, et al. The effects of isoflurane and desflurane on cognitive function in humans. Anesth Analg 2012;114:410–5.
61. Kanbak M, Saricaoglu F, Akinci SB, et al. The effects of isoflurane, sevoflurane, and desflurane anesthesia on neurocognitive outcome after cardiac surgery: a pilot study. Heart Surg Forum 2007;10:E36–41.
62. Schoen J, Husemann L, Tiemeyer C, et al. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. Br J Anaesth 2011;106:840–50.
63. Liu Y, Pan N, Ma Y, et al. Inhaled sevoflurane may promote progression of amnestic mild cognitive impairment: a prospective, randomized parallel-group study. Am J Med Sci 2013;345:355–60.
64. Tang N, Ou C, Liu Y, et al. Effect of inhalational anaesthetic on postoperative cognitive dysfunction following radical rectal resection in elderly patients with mild cognitive impairment. J Int Med Res 2014;42:1252–61.
65. Griebe M, Amann M, Hirsch JG, et al. Reduced functional reserve in patients with age-related white matter changes: a preliminary FMRI study of working memory. PLoS One 2014;9:e103359.
66. Mathew JP, Mackensen GB, Phillips-Bute B, et al, Neurologic Outcome Research Group of the Duke Heart Center. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 2009;40:880–7.
67. Mathew JP, Podgoreanu MV, Grocott HP, et al, PEGASUS Investigative Team. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. J Am Coll Cardiol 2007;49:1934–42.
68. Brown M, Sinacore DR, Ehsani AA, et al. Low-intensity exercise as a modifier of physical frailty in older adults. Arch Phys Med Rehabil 2000;81:960–5.
69. Binder EF, Schechtman KB, Ehsani AA, et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. J Am Geriatr Soc 2002;50:1921–8.
70. Mohandas A, Reifsnyder J, Jacobs M, et al. Current and future directions in frailty research. Popul Health Manag 2011;14:277–83.
71. Cameron ID, Fairhall N, Langron C, et al. A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. BMC Med 2013;11:65.
72. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 2014;121:937–47.
73. Jaggers JR, Simpson CD, Frost KL, et al. Prehabilitation before knee arthroplasty increases postsurgical function: a case study. J Strength Cond Res 2007;21:632–4.
74. Nielsen PR, Andreasen J, Asmussen M, et al. Costs and quality of life for prehabilitation and early rehabilitation after surgery of the lumbar spine. BMC Health Serv Res 2008;8:209.
75. Furze G, Dumville JC, Miles JN, et al. “Prehabilitation” prior to CABG surgery improves physical functioning and depression. Int J Cardiol 2009;132:51–8.
76. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108:3017–22.

77. Maguire EA, Gadian DG, Johnsrude IS, et al. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci U S A 2000;97:4398–403.
78. Burke SN, Barnes CA. Neural plasticity in the ageing brain. Nat Rev Neurosci 2006;7:30–40.
79. Terrando N, Monaco C, Ma D, et al. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A 2010;107:20518–22.
80. Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol 2011;70:986–95.
81. Su X, Feng X, Terrando N, et al. Dysfunction of inflammation-resolving pathways is associated with exaggerated postoperative cognitive decline in a rat model of the metabolic syndrome. Mol Med 2012;18:1481–90.
82. Bartels K, Ma Q, Venkatraman TN, et al. Effects of deep hypothermic circulatory arrest on the blood brain barrier in a cardiopulmonary bypass model–a pilot study. Heart Lung Circ 2014;23:981–4.
83. Hu N, Guo D, Wang H, et al. Involvement of the blood-brain barrier opening in cognitive decline in aged rats following orthopedic surgery and high concentration of sevoflurane inhalation. Brain Res 2014;1551:13–24.
84. He HJ, Wang Y, Le Y, et al. Surgery upregulates high mobility group box-1 and disrupts the blood-brain barrier causing cognitive dysfunction in aged rats. CNS Neurosci Ther 2012;18:994–1002.
85. Degos V, Vacas S, Han Z, et al. Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology 2013;118:527–36.
86. Vacas S, Degos V, Tracey KJ, et al. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. Anesthesiology 2014;120:1160–7.
87. Rosczyk HA, Sparkman NL, Johnson RW. Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol 2008;43:840–6.
88. Terrando N, Yang T, Ryu JK, et al. Stimulation of the alpha 7 nicotinic acetylcholine receptor protects against neuroinflammation after tibia fracture and endotoxemia in mice. Mol Med 2015;20(1):667–75.
89. Feng X, Degos V, Koch LG, et al. Surgery results in exaggerated and persistent cognitive decline in a rat model of the metabolic syndrome. Anesthesiology 2013;118:1098–105.
90. Zschaler J, Schlorke D, Arnhold J. Differences in innate immune response between man and mouse. Crit Rev Immunol 2014;34:433–54.
91. Zurek AA, Yu J, Wang DS, et al. Sustained increase in alpha5GABAA receptor function impairs memory after anesthesia. J Clin Invest 2014;124:5437–41.
92. Yeager MP, Lunt P, Arruda J, et al. Cerebrospinal fluid cytokine levels after surgery with spinal or general anesthesia. Reg Anesth Pain Med 1999;24:557–62.
93. Tang JX, Baranov D, Hammond M, et al. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology 2011;115:727–32.
94. Buvanendran A, Kroin JS, Berger RA, et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology 2006;104:403–10.
95. Reis HJ, Teixeira AL, Kalman J, et al. Different inflammatory biomarker patterns in the cerebro-spinal fluid following heart surgery and major non-cardiac operations. Curr Drug Metab 2007;8:639–42.

96. Reinsfelt B, Westerlind A, Blennow K, et al. Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid beta. Acta Anaesthesiol Scand 2013;57:82–8.
97. Xie Z, McAuliffe S, Swain CA, et al. Cerebrospinal fluid: a beta to tau ratio and postoperative cognitive change. Ann Surg 2013;258:364–9.
98. Kline RP, Pirraglia E, Cheng H, et al. Surgery and brain atrophy in cognitively normal elderly subjects and subjects diagnosed with mild cognitive impairment. Anesthesiology 2012;116:603–12.
99. Bekker A, Lee C, de Santi S, et al. Does mild cognitive impairment increase the risk of developing postoperative cognitive dysfunction? Am J Surg 2010;199:782–8.
100. Price CC, Tanner JJ, Schmalfuss I, et al. A pilot study evaluating presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. Anesthesiology 2014;120:601–13.
101. Cook DJ, Huston J 3rd, Trenerry MR, et al. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. Ann Thorac Surg 2007;83:1389–95.
102. Rodriguez RA, Rubens FD, Wozny D, et al. Cerebral emboli detected by transcranial Doppler during cardiopulmonary bypass are not correlated with postoperative cognitive deficits. Stroke 2010;41:2229–35.
103. Gerriets T, Schwarz N, Bachmann G, et al. Evaluation of methods to predict early long-term neurobehavioral outcome after coronary artery bypass grafting. Am J Cardiol 2010;105:1095–101.
104. Dong S, Li CL, Liang WD, et al. Postoperative plasma copeptin levels independently predict delirium and cognitive dysfunction after coronary artery bypass graft surgery. Peptides 2014;59:70–4.
105. Terrando N, Eriksson LI, Eckenhoff RG. Perioperative neurotoxicity in the elderly: summary of the 4th international workshop. Anesth Analg 2015;120:649–52.
106. Mathew JP, White WD, Schinderle DB, et al, Neurologic Outcome Research Group of the Duke Heart Center. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. Stroke 2013;44:3407–13.
107. Hudetz JA, Iqbal Z, Gandhi SD, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand 2009;53:864–72.
108. Mathew JP, Shernan SK, White WD, et al. Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery. Stroke 2004;35:2335–9.
109. Ottens TH, Dieleman JM, Sauer AM, et al, DExamethasone for Cardiac Surgery (DECS) Study Group. Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. Anesthesiology 2014;121:492–500.
110. Fang Q, Qian X, An J, et al. Higher dose dexamethasone increases early postoperative cognitive dysfunction. J Neurosurg Anesthesiol 2014;26:220–5.
111. Potter DE, Choudhury M. Ketamine: repurposing and redefining a multifaceted drug. Drug Discov Today 2014;19:1848–54.
112. Azevedo FA, Carvalho LR, Grinberg LT, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol 2009;513:532–41.
113. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, et al. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 2012;489:391–9.
114. Hudetz JA, Patterson KM, Iqbal Z, et al. Remote ischemic preconditioning prevents deterioration of short-term postoperative cognitive function after cardiac

surgery using cardiopulmonary bypass: results of a pilot investigation. J Cardiothorac Vasc Anesth 2015;29(2):382–8.
115. Gill R, Kuriakose R, Gertz ZM, et al. Remote ischemic preconditioning for myocardial protection: update on mechanisms and clinical relevance. Mol Cell Biochem 2015;402(1–2):41–9.
116. Zheng F, Sheinberg R, Yee MS, et al. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesth Analg 2013;116:663–76.
117. Keller M, Montgomery S, Ball W, et al. Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. Biol Psychiatry 2006;59:216–23.
118. Doraiswamy PM, Babyak MA, Hennig T, et al. Donepezil for cognitive decline following coronary artery bypass surgery: a pilot randomized controlled trial. Psychopharmacol Bull 2007;40:54–62.
119. Yap KK, Joyner P. Post-operative cognitive dysfunction after knee arthroplasty: a diagnostic dilemma. Oxf Med Case Reports 2014;3:60–2.
120. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med 2009;60:355–66.
121. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol 2011;10:123–30.
122. Heiligenstein JH, Ware JE Jr, Beusterien KM, et al. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. Int Psychogeriatr 1995;7(Suppl):125–37.
123. Knutson B, Wolkowitz OM, Cole SW, et al. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry 1998;155:373–9.
124. Hewitt J, Williams M, Pearce L, et al. The prevalence of cognitive impairment in emergency general surgery. Int J Surg 2014;12:1031–5.
125. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
126. Aleman A, van't Wout M. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex disrupts digit span task performance. Neuropsychobiology 2008;57:44–8.
127. Hudetz JA, Patterson KM, Amole O, et al. Postoperative cognitive dysfunction after noncardiac surgery: effects of metabolic syndrome. J Anesth 2011;25:337–44.
128. Takeuchi H, Taki Y, Sassa Y, et al. Regional gray and white matter volume associated with Stroop interference: evidence from voxel-based morphometry. Neuroimage 2012;59:2899–907.
129. Vazzana R, Bandinelli S, Lauretani F, et al. Trail making test predicts physical impairment and mortality in older persons. J Am Geriatr Soc 2010;58:719–23.
130. Oosterman JM, Vogels RL, van Harten B, et al. Assessing mental flexibility: neuroanatomical and neuropsychological correlates of the trail making test in elderly people. Clin Neuropsychol 2010;24:203–19.
131. Audenaert K, Brans B, Van Laere K, et al. Verbal fluency as a prefrontal activation probe: a validation study using 99mTc-ECD brain SPET. Eur J Nucl Med 2000;27:1800–8.
132. Wood AG, Saling MM, Abbott DF, et al. A neurocognitive account of frontal lobe involvement in orthographic lexical retrieval: an fMRI study. Neuroimage 2001;14:162–9.

133. Strangman GE, O'Neil-Pirozzi TM, Goldstein R, et al. Prediction of memory rehabilitation outcomes in traumatic brain injury by using functional magnetic resonance imaging. Arch Phys Med Rehabil 2008;89:974–81.
134. Kane KD, Yochim BP. Construct validity and extended normative data for older adults for the brief visuospatial memory test, revised. Am J Alzheimers Dis Other Demen 2014;29:601–6.
135. Gawryluk JR, Mazerolle EL, Beyea SD, et al. Functional MRI activation in white matter during the symbol digit modalities test. Front Hum Neurosci 2014;8:589.
136. Forn C, Rocca MA, Bosca I, et al. Analysis of "task-positive" and "task-negative" functional networks during the performance of the symbol digit modalities test in patients at presentation with clinically isolated syndrome suggestive of multiple sclerosis. Exp Brain Res 2013;225:399–407.
137. Moritz CH, Johnson SC, McMillan KM, et al. Functional MRI neuroanatomic correlates of the Hooper Visual Organization Test. J Int Neuropsychol Soc 2004;10:939–47.
138. Bohnen NI, Kuwabara H, Constantine GM, et al. Grooved pegboard test as a biomarker of nigrostriatal denervation in Parkinson's disease. Neurosci Lett 2007;424:185–9.
139. Logothetis NK. What we can do and what we cannot do with fMRI. Nature 2008;453:869–78.
140. Ropper AH. Cogito ergo sum by MRI. N Engl J Med 2010;362:648–9.
141. Silbert BS, Scott DA, Evered LA, et al. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. Anesthesiology 2006;104:1137–45.
142. Wang D, Wu X, Li J, et al. The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. Anesth Analg 2002;95:1134–41 [Table of contents].
143. Mitchell SJ, Merry AF, Frampton C, et al. Cerebral protection by lidocaine during cardiac operations: a follow-up study. Ann Thorac Surg 2009;87:820–5.
144. Mack WJ, Kellner CP, Sahlein DH, et al. Intraoperative magnesium infusion during carotid endarterectomy: a double-blind placebo-controlled trial. J Neurosurg 2009;110:961–7.
145. Holinski S, Claus B, Alaaraj N, et al. Cerebroprotective effect of piracetam in patients undergoing coronary bypass surgery. Med Sci Monit 2008;14:PI53–7.
146. Slater JP, Guarino T, Stack J, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009;87:36–44 [discussion: 44–5].
147. Xu T, Bo L, Wang J, et al. Risk factors for early postoperative cognitive dysfunction after non-coronary bypass surgery in Chinese population. J Cardiothorac Surg 2013;8:204.
148. Peng LY, Xu LW, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. PLoS One 2013;8:e79624.
149. Van Dijk D, Jansen EW, Hijman R, et al, Octopus Study Group. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 2002;287:1405–12.
150. Kok WF, van Harten AE, Koene BM, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass. Anaesthesia 2014;69:613–22.

151. Siepe M, Pfeiffer T, Gieringer A, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. Eur J Cardiothorac Surg 2011;40:200–7.
152. Mathew JP, Mackensen GB, Phillips-Bute B, et al, Neurologic Outcome Research Group of the Duke Heart Center. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. Anesthesiology 2007; 107:577–84.
153. Puskas F, Grocott HP, White WD, et al. Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg 2007;84:1467–73.
154. Grigore AM, Grocott HP, Mathew JP, et al, Neurologic Outcome Research Group of the Duke Heart Center. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. Anesth Analg 2002;94:4–10 [Table of contents].
155. Djaiani G, Fedorko L, Borger MA, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. Circulation 2007;116:1888–95.
156. Rubens FD, Boodhwani M, Mesana T, et al. The cardiotomy trial: a randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. Circulation 2007;116:I89–97.
157. Murkin JM, Martzke JS, Buchan AM, et al. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. J Thorac Cardiovasc Surg 1995;110:349–62.
158. Boodhwani M, Rubens FD, Wozny D, et al. Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery. Circulation 2006;114:I461–6.
159. Grigore AM, Mathew J, Grocott HP, et al, Neurological Outcome Research Group, CARE Investigators of the Duke Heart Center, Cardiothoracic Anesthesia Research Endeavors. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. Anesthesiology 2001;95:1110–9.
160. Nathan HJ, Wells GA, Munson JL, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. Circulation 2001;104:I85–91.
161. Nathan HJ, Rodriguez R, Wozny D, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. J Thorac Cardiovasc Surg 2007;133:1206–11.
162. Chen MH, Liao Y, Rong PF, et al. Hippocampal volume reduction in elderly patients at risk for postoperative cognitive dysfunction. J Anesth 2013;27:487–92.
163. Messerotti Benvenuti S, Zanatta P, Valfre C, et al. Preliminary evidence for reduced preoperative cerebral blood flow velocity as a risk factor for cognitive decline three months after cardiac surgery: an extension study. Perfusion 2012; 27:486–92.
164. Steinmetz J, Siersma V, Kessing LV, et al, ISPOCD Group. Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study. Br J Anaesth 2013;110(Suppl 1):i92–7.
165. Zakzanis KK, Mraz R, Graham SJ. An fMRI Study of the Trail Making Test. Neuropsychologia 2005;43(13):1878–86.