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Postoperative Cognitive Dysfunction: Minding the Gaps in our Knowledge of A Common Postoperative Complication in the Elderly

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Abstract

Ever since Bedford's seminal *Lancet* case series in 1955, we have known that perioperative care is sometimes followed by significant cognitive dysfunction (1). 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 post-operative cognitive dysfunction (POCD). POCD remains a common post-operative complication associated with significant 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 papers published on this subject recently (shown in Figure 1). Recent work has also suggested surgery may be associated with cognitive improvement in some patients (2–4), termed Post-Operative Cognitive Improvement (POCI). As the number of surgeries performed worldwide approaches 250 million per year (5) (with an increasing number 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.

Keywords

Post-Operative Cognitive Dysfunction; Post-Operative Cognitive Decline; Post-Operative Cognitive Improvement; Elderly; Anesthesia; Surgery

I. A description of POCD and POCI

What is POCD?

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

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POCD cannot be diagnosed unless a patient has undergone formal neuropsychological testing before *and* after surgery, which typically doesn't happen outside a research setting. Partly as a result of this, there is no ICD-10 code for POCD, and it is not listed as a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). However, the utility of the DSM-V as a nosological 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.

Neuropsychological testing for POCD typically includes tests that assess multiple cognitive domains (see Table 1). Individual sub-test 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 exam can also detect long term post-operative cognitive changes (9). Post-operative testing is typically performed after the acute effects of surgery and the immediate post-operative period have dissipated; i.e. 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 pre-set threshold are then defined as having POCD. There is no clear agreement on how low such a POCD cutoff/threshold should be set (e.g. 1 standard deviation (SD), or 1.5, or 2 SD's) (10). There has also been disagreement over how to classify patients who drop below the pre-set 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 post-operative performance drop, because the observed post-operative performance may thus reflect both post-operative 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 pre-surgical baseline and alternate forms are used for subsequent post-operative 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 post-operative cognitive change (13). Simple change scores in performance from a patient's pre-surgical 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 pre- to post-test change in a study subject minus the average pre- to post-test change among control subjects, divided by the standard deviation of the change in pre- to post-test scores among non-surgical 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 non-surgical 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's disease (also known as mild cognitive impairment, or MCI) is often diagnosed by a less stringent measure of cognitive decline relative to normative performance expectations (e.g., 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 should be used, and how many cognitive domains must show a decline to make the diagnosis of POCD (10).

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 work force (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 may also 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 (Table 3).

How long does POCD 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 non-surgical 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 non-surgical control groups for comparison, but such study designs are non-randomized and thus potentially confounded by the fact that surgical patients may be intrinsically different than non-surgical controls. Nonetheless, several studies have compared the incidence of cognitive dysfunction in surgical patients and non-surgical 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 non-surgical 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 non-surgical controls even at 1 year after surgery (24). A retrospective study by Avidan and colleagues found no difference in the cognitive decline

trajectory between non-cardiac surgical patients and matched controls over a period of up to several years (median of 3.1 years of follow-up in surgical patients, (25)). However, the two 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 non-cardiac 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 ((28), Table 3).

After cardiac surgery Newman and colleagues found an overall cognitive trajectory of decline up to 5 years later (7). Interestingly, cognitive dysfunction in the early post-operative 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 McKann et al, 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 (8,29,30). Similarly, CAD patients who underwent off-pump CABG had similar cognitive outcomes as CAD patients 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 pre-existing 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 CAD patients treated surgically versus medically, though (33). Taken together, these data suggest that as in the case POCD after non-cardiac surgery POCD after cardiac surgery may last from weeks to several months. However, the current data does 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 5th patient in Bedford's case report was described as "an intelligent and active man- mentally normal in every way" prior to surgery, but after he was "unable to recognize his relations and remained unaware of his surroundings" even up to 18 months after surgery (1). This severe post-operative cognitive dysfunction 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 life long neurocognitive deficits. Thus, it is likely that this patient's post-operative cognitive dysfunction was caused by intraoperative hypotension, and that it lasted the rest of this patient's life. Although this is a somewhat extreme case (intraoperative periods of undetectable blood pressure lasting over 15 minutes are currently extremely rare, except in 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 non-cardiac and cardiac surgery, although it is impossible to tell how long any individual case of POCD will last. It is important to emphasize during pre-operative 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 POCI?

While 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, post-operative cognitive improvement (POCI) can be directly attributed to the goals of the specific surgery itself, e.g. the post-operative 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 (i.e., the tendency for test performance to improve with repeat testing) may also significantly contribute to the probability of mistakenly concluding that a subject has post-operative 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 4.2–8.7% of patients after 1 week and in 5.0–7.8% after 3 months (38). However, in the same population, these investigators found a 3–6 times greater incidence of POCD, leading them to conclude that the observed “improvement” merely reflected the unpredictable variability inherent in precise neuropsychological testing. While 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 (e.g. 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 coronary artery bypass grafting (CABG) surgery, there was evidence of cognitive improvement in multiple neuropsychological tests (39). CABG patients also demonstrate improved physical, social, and emotional function six months and one year after surgery, including less anxiety and depression (40). It is likely that the improvement in the cognitive function of CABG patients 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 (e.g., 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 POCI 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 above began to appear at three months, and continued throughout the first year after cardiac surgery (39). In bariatric surgery, improvements were seen two and three 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 (Table 3).

A comparison between POCD 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 (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 CRCI since several chemotherapeutic agents have direct neurotoxic actions (reviewed in (44)) and modulate interactions between the immune system and brain (45). While cancer-related cognitive impairment (CRCI) appears to occur more frequently than POCD, the two 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 below). 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 utilized 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 (e.g. inability to randomize, variation between studies in criteria used to define cognitive impairment, practice-related effects) affect studies on both POCD and CRCI.

II. Who is at risk for developing POCD?

Modifiable risk factors

Several studies have examined risk factors for POCD (see Tables 2a and 2b for a list of modifiable and non-modifiable 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 excessive anesthetic drug exposure in some cases. In line with these findings, a prior study found an increased rate of POCD one week after general vs regional anesthesia ($p=0.06$ overall, $p=0.04$ in an as treated analysis (53)), although there was no difference in POCD rates 3 months after surgery ($p=0.93$). However, Silbert and colleagues recently found no difference in POCD rates between patients who underwent extracorporeal shock wave lithotripsy under either general or spinal anesthesia (54); if anything, there was a surprising trend towards increased POCD risk in the spinal anesthesia group ($p=0.06$, 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 above 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 Silbert et al. study (54) was nearly 4 fold smaller than the Rasmussen et al. study (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 Silbert et al. study (54). A meta-analysis performed on this subject in 2010 found a non-statistically significant trend towards an increased risk of POCD after general versus regional anesthesia (OR 1.34, 95% CI 0.93–1.95%, $p=0.26$) (55). Another meta-analysis performed in 2011 also found a slight, but non-significant trend towards a decreased risk of POCD after regional vs general anesthesia (standardized difference in means -0.08 , -0.17 to 0.01 , $p=0.094$, (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 vs regional anesthesia (Table 3).

Numerous studies have also 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 (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 one, two and three 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 vs 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 et al, who found that isoflurane use was associated with improved neurocognitive function after cardiac surgery (as compared to desflurane or sevoflurane) in a similar size pilot randomized controlled trial (61). Schoen and colleagues found that sevoflurane administration (as compared to propofol-based intravenous anesthesia) was associated with improved cognition within one week after on-pump cardiac surgery (62). In summary, the available evidence is insufficient to determine whether any specific anesthetic agent is associated with a reduced risk of POCD.

Several recent papers have also examined whether specific anesthetic drugs may be associated with less cognitive decline after surgery in patients with mild cognitive impairment (MCI, an early stage of Alzheimer's disease). One recent study found increased rates of MCI progression two years later in spine surgery patients who were randomized to receive sevoflurane vs propofol or epidural anesthesia (N=60 per group, (63)). Another study among MCI patients found no difference in POCD rates among MCI patients randomized to receive sevoflurane (N=99) vs 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 to sevoflurane anesthesia) might be associated with improved post-operative cognition in patients with MCI, but further studies are necessary to examine this issue.

Non-modifiable risk factors

One non-modifiable 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 over as in those below 60 (20). This association makes intuitive sense in the setting of the failed resilience model discussed above. 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, two other non-modifiable risk factors for POCD that have been found across multiple studies are less years of prior 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 2B). <<AU: Please check placement of Table 2B mentioned in text and revise as needed.>>

Although age itself is non-modifiable, 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 post-operative complications and/or improve post-operative 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 suggest 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 (Table 3).

III. What Causes POCD?

Animal models

Animal studies have suggested the POCD may be caused by either excessive neuroinflammation after surgery (79), a failure to resolve inflammation (80,81), blood-brain barrier/endothelial dysfunction (82–84), and/or pre-existing Alzheimer's disease pathology (reviewed in (28)). Activation of the innate immune system is increasingly appreciated as an underlying factor in several neurodegenerative conditions, including Alzheimer's disease. Using different preclinical models of non-CNS surgery, neuroinflammation has been repeatedly associated with behavioral dysfunction and memory deficits. Up-regulation of systemic proinflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukins (IL)-1, IL-6, chemokines and damage-associated molecular patterns (DAMPs) like high-mobility group box 1 (HMGB1) 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 following 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 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 (i.e. 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 post-operative memory deficits may be due to anesthetic-induced up-regulation of the $\alpha 5$ -subunit containing 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 post-operative 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 above 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, there are also no human studies that have demonstrated an association between the presence or levels of central anti-inflammatory mediators and the presence or duration of POCD. Pre-existing 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 mild cognitive impairment (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 pre-existing 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 pre-existing white matter damage (as measured by MRI) was a predictor of post-operative executive function deficits in patients who underwent knee arthroplasty (100). Neuroimaging studies have also shown that cardiac surgery in particular is associated with an increase in “silent strokes” or white matter hyperintensities seen on magnetic resonance imaging, although the total burden of white matter hyperintensities after surgery does not correlate with the presence of POCD ((101,102), reviewed in (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).

IV. How can we prevent or treat POCD?

POCD 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 (106), magnesium (107), ketamine (108), complement suppression (109), or even high dose dexamethasone (110) treatment in randomized controlled trials.

Lidocaine treatment had no effect on preventing POCD overall (106), although in a secondary analysis, lidocaine infusion appeared to have a beneficial effect on cognition in non-diabetic patients. Similarly, intraoperative magnesium treatment had no effect on preventing POCD overall, although there was a trend towards a detrimental effect of magnesium treatment on cognition in heavier patients (107). 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 (109).

Surprisingly, ketamine treatment (0.5 mg/kg) on anesthetic induction was associated with a decrease in POCD occurrence after cardiac surgery (108). Ketamine treatment was also associated with a reduction in serum CRP levels in this study (108), leading the authors to propose that ketamine decreases POCD incidence by decreasing inflammation. However, high-dose dexamethasone (i.e. 1 mg/kg on anesthetic induction) did not decrease POCD rates in patients undergoing cardiac surgery in the DECS trial (110), which was almost 4 times the size of the ketamine trial (108). Higher dose dexamethasone (0.2 mg/kg) was actually associated with increased POCD rates (as compared to 0.1 mg/kg dexamethasone or placebo treatment) in a trial of patients undergoing microvascular decompression for facial spasms (111). Taken together, these results could imply that while 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 (108) may be due to its effects on neurotransmitter receptors or other biological processes unrelated to inflammation; in addition to blocking the NMDA receptor, ketamine modulates signaling via a number of other receptors (reviewed in (112)).

While 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 over 80 billion neurons (each of which make thousands of synaptic connections to other neurons), and over 80 billion interneurons (113). The human brain also expresses more than 80% of the human genome (114), 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 multi-component 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 (115). Since remote ischemic preconditioning has a plethora of biological effects (116), this study is consistent with the idea that preventing POCD will require interventions that work more broadly than a single drug.

Similarly, Ballard et al 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 (24)

(see table 2A for statistics). However, there is mixed evidence whether bispectral (BIS) index monitoring alone can decrease POCD rates (52,117), and the authors 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 (118). 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 non-significant effect. Future studies will be necessary to examine this hypothesis by evaluating these interventions in isolation and together.

POCD 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 since most cases of POCD resolve spontaneously within months (see section I), although they would still be important given the association between POCD and decreased quality of life (18), early exit from the work force (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 (119). One randomized trial examined the use of the acetylcholinesterase inhibitor donepezil in patients who displayed cognitive decline (0.5 SD drop in at least one 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 Alzheimer's disease. However, donepezil treatment had no effect on the overall cognitive index in these patients with cognitive decline 1 year after cardiac surgery (120).

Interestingly, the antidepressant and selective serotonin reuptake inhibitor (SSRI) citalopram was used to successfully treat POCD in one case report (121). This finding is generally in line with the pleiotropic biological roles of serotonin including its ability to promote neuroplasticity (122). If POCD is a syndrome of failed resilience or a lack of neuroplasticity after perioperative care that occurs in patients with pre-existing neurovascular disease or "silent strokes", then the established efficacy of SSRI's in improving neurologic outcomes after stroke (123) suggest that they may be useful in treating POCD as well. SSRI's also have been shown to improve quality of life in depressed elderly patients (124) and improve affect and mood even in non-depressed, healthy individuals (125), which further suggests that SSRI's may be efficacious in reducing POCD-associated quality of life impairments. More work will be necessary to determine whether SSRI's improve cognition, quality of life, and other outcomes in patients with POCD (Table 3).

V. Conclusions 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 work force (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 (i.e. those with multiple risk factors listed in tables 2a and 2b, such as

elderly patients) should be counselled preoperatively about the risk of POCD, just as we counsel patients preoperatively about numerous other risks of perioperative care. This counselling 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 discussed above also mandate that we try to prevent it, and that we develop effective 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.

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Key Point Sentences

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 post-operative cognitive function and preventing/treating POCD are major public health issues.

POCD is associated with impaired quality of life, increased exit from the work force, and increased mortality after surgery.

POCD can be conceptualized as a lack of cognitive resilience in the face of perioperative stress.

Figure 1.
POCD publications by year

Figure 2.
Potential Cognitive Trajectories Following Surgery

Table 1

Recommended neuropsychological measures for the detection and characterization of POCD

Core Domain	Component Cognitive Process	Measure	Description	Brain regions/ circuits involved in task**
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 over-estimation of POCD recovery secondary to simple re-administration practice effects. <i>Administration Time</i> : Variable, with ~15 minute average. (126,127)	Multiple tasks, n/a.
Executive Function	Simple Attention	Digit Span Forward Subtest from Wechsler Adult Intelligence Scale – 3 rd 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. <i>Administration Time</i> : Variable, with ~5–10 minute average.	Right dorsolateral prefrontal cortex (128)
	Complex Attention (Working Memory)	Digit Span - Backward Subtest from Wechsler Adult Intelligence Scale – 3 rd 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.(128,129) <i>Administration Time</i> : Variable, with ~5–10 minute average.	right dorsolateral prefrontal cortex (128)
	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 (e.g.,	Anterior cingulate cortex (ACC), right inferior frontal gyrus, and cerebellum. (130)

Core Domain	Component Cognitive Process	Measure	Description	Brain regions/ circuits involved in task**
			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. <i>Administration Time:</i> 3–4 minutes.	
	Mental Flexibility	Trail Making A & B Test *	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, while the Trail Making B subtest has both letters of the alphabet and numbers in circles that then must be connected in alternating ascending order (e.g., 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 over-estimation of POCD severity. (131,132) <i>Administration Time:</i> Variable w/ 5 minute timed maximum for each subtest.	Medial Temporal Lobe (132)
	Verbal Fluency	Controlled Oral Word Association Test (COWA) from the Multilingual Aphasia Examination (MAE) *	A lexical verbal fluency task known to be dependent upon 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-minute given for three different consonants (e.g., C, F, L). Participants are asked to not use proper nouns or the same word with different endings (e.g., eat, eating). <i>Administration Time:</i> 3 minutes.	Posterior part of the left inferior prefrontal cortex (LIPC); category fluency task activates anterior left inferior prefrontal cortex and right inferior prefrontal cortex. (133,134)
<u>Learning & Memory</u>	Auditory- Verbal Learning & Memory	Hopkins Verbal Learning Test, Revised *	An auditory-verbal, list-learning and memory task that involves the presentation of 12 various categorically related item words (e.g., gemstones, furniture, etc.) that are then immediately recalled by the participant. Participants are given the opportunity to learn the list of words over a series of three repeated presentations, then after a 25- minute 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.	Left ventrolateral prefrontal cortex (135)

Core Domain	Component Cognitive Process	Measure	Description	Brain regions/ circuits involved in task**
			<i>Administration Time</i> : 35 minutes timed (includes 25-minute delay)	
	Visual Learning & Memory	Brief Visuospatial Learning Test, Revised *	A visuospatial learning and memory test analog to the HVLTL-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 six line drawings are conducted. There is a 25-minute 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 HVLTL-R (e.g., total recall, delayed recall, etc.).(136) <i>Administration Time</i> : 45 minutes timed (includes 25-minute delay)	
<u>Visuospatial Functioning</u>	Visuomotor Integration	Digit Symbol Coding Test from the Wechsler Adult Intelligence Scale – 3 rd 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-seconds. <i>Administration Time</i> : 5 minutes.	Corpus callosum, internal capsule (137); anterior cingulate gyrus, left prefrontal gyrus and inferior parietal lobe (138)
	Complex Visuospatial Perception	Hooper Visual Organizational Test	HVOT performance is known to be dependent upon 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. <i>Administration Time</i> : Variable, with ~10–12 minute average.	Superior parietal lobules, ventral temporal- occipital cortex, and posterior visual association areas, frontal eye fields, left dorsolateral prefrontal cortex (139)
<u>Psychomotor Function</u>	Manual Dexterity & Motor Speed	Lafayette Grooved Pegboard Test	A manipulative dexterity and motor speed test that involves the insertion of small milled key-like 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. <i>Administration Time</i> : Variable, with ~5 minute average.	Nigrostriatal dopamine function (140)

* Note: Recommended measures with readily available alternate, equivalent forms are denoted with a “*” symbol.

** 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 (141) and (142).

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Table 2A

Potentially Modifiable risk factors for POCD

Risk Factor	Effect Size	Study Design	Reference
Bispectral index (EEG) guided anesthetic care (versus routine care)	Odds ratio (OR) 0.92 (0.66–1.29) at 1 week p=0.06; OR 0.62 (0.39–0.97) at 3 months p=0.02 18.1% v. 23.9% at 7 days p=0.062; 8% v. 10.3% at 3 months p=0.372	Randomized Controlled Trial (RCT) RCT	(117) (52)
Fentanyl dosage	Low (10 mcg/kg) v. High Dose Fentanyl (50 mcg/kg), POCD rates 23.6% v. 13.7% at 1 week, respectively, p= 0.03. N.S. at 3 and 12 months.	RCT	(143)
Ketamine Treatment	2 SD drop in overall cognition in 7/26 ketamine group vs 21/26 patients, P<0.001	RCT	(108)
Lidocaine v. No Lidocaine	POCD 18.6% v. 40% p=0.028 Neurocognitive Deficit 45.8% v. 40.7% at 10 weeks p=0.577; 35.2% v. 37.7% at 25 weeks p=0.710 45.5% vs 45.7%, p=0.97	RCT RCT RCT	(144) (145) (66)
Magnesium Sulfate Infusion	Multivariate OR for Low Dose 0.09 (0.02, 0.50) p=0.01; OR for High Dose 0.45 (0.16, 1.33) p=0.15 44.4% vs 44.9%, p=0.93	RCT RCT	(146) (107)
Piracetam v. No Piracetam	Overall Cognitive Function Preop 0.06±1.02 v. - 0.06±0.99 Postop -0.65±0.93 v. -1.38± 1.11 p<0.0005	RCT	(147)
Intraoperative Steroid Treatment	No v. Low v. High Dose Dexamethasone POCD 22.3% v. 20.6% v. 31.4% p=0.003 Relative Risk (RR) 1.87 (0.90–3.88) at 1 month p = 0.09; RR 1.98 (0.61–6.40) at 1 year p = 0.24	RCT RCT	(111) (110)
Post-operative delirium*	Multivariate OR 9.58 (4.62–19.9) p<0.001 POCD v. No POCD** 1.5% v. 1.1% at discharge p=0.046; 6.7% v. 5.6% at 3 months p=0.373 Delirium v. No Delirium MMSE Scores: 24.1 v. 27.4 at 1 month p<0.001; 25.2 v. 27.2 at 1 year p<0.001	RCT Prospective Cohort Study Prospective Cohort Study	(117) (20) (9)
Post-operative infection*	Univariate OR 2.17 (1.50–3.15) p=0.001	RCT	(117)
Post-operative respiratory complication*	Univariate OR 1.69 (1.01–2.89) p=0.02	RCT	(117)
Metabolic Syndrome*	POCD v. No POCD 43.3% v. 26.7% p<0.02	Prospective Cohort Study	(129)
Cigarette Abuse	Multivariate OR 2.04 (1.11–3.74) p=0.022 N.S.	RCT Prospective Cohort study	(148) (23)
Diabetes*	Multivariate OR 2.34 (1.22–4.51) p=0.01 POCD v. No POCD 40% v. 19.2% p=0.021 Multivariate linear regression, parameter estimate 0.031 (-0.111, 0.172) p=0.671	Prospective Cohort Study Prospective Cohort Study RCT	(149) (104) (66)
Duration of anesthesia	OR 1.1 (1.0–1.3), p=0.01 POCD v. No POCD at 3 months 215.0±92.8 v. 211.5±103.2 minute duration, p=0.52, POCD v. No POCD 5.6±1.5 v. 5.0±1.2 p=0.026 POCD v. No POCD 4.6±1.5 v. 3.8±0.8 p=0.001	Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study	(23) (20) (104) (150)

Risk Factor	Effect Size	Study Design	Reference
Benzodiazepines before surgery	OR 0.4 (0.2–1.0) p=0.03	Prospective Cohort Study	(23)
Duration of hospital stay	POCD v. No POCD 6.6±16.3 v. 4.8±5.9 at discharge p=0.0003; Multivariate OR 1.03 (1.00–1.05) at 3 months p=0.2479	Prospective Cohort Study	(20)
Duration of Surgery	POCD v. No POCD 4.7±0.9 v. 4.2±1.0 p=0.01	Prospective Cohort Study	(104)
Anesthetic Type (general vs regional)	Mean Difference –0.08 (–0.17–0.01) p=0.094 General vs. non-general anesthesia, OR 1.34 (0.95– 1.93), p=0.26	Meta-Analysis Meta-analysis	(56) (55)
Bispectral Index and Cerebral Oxygenation	1 week Mild Fisher's exact test p=0.018 1 week Moderate, Pearson's p=0.037 1 week Severe, Fisher's exact test p=0.12	RCT	(24)
Monitoring	12 week Mild Chi Square Test p=0.02 12 week Moderate Chi Square Test p=0.85 12 week Severe Chi Square Test p=0.65 1 Year Mild Chi Square Test p=0.015 1 Year Moderate Chi Square Test p=0.02 1 Year Severe Fisher's Exact Test p=0.36		
Postoperative Copeptin Levels *	OR 28.814 (7.131–116.425) p<0.001	Prospective Cohort Study	(104)
Peripheral Inflammatory Markers *	S-100β Standardized Mean Difference 1.377 (0.423–2.331) p=0.005; IL-6 Standardized Mean Difference 1.614 (0.603– 2.624) p=0.002	Meta-Analysis	(151)
Off pump v. On pump Cardiac Surgery	Standardized Cognitive Change Score 0.19 v. 0.13 at 3 months p=0.03; 0.19 v. 0.12 at 1 year p=0.09 Off Pump v. On Pump v. Non-Surgical Cardiac Comparison v. Healthy Heart Comparison MMSE 27.7±2.0 v. 27.6±2.4 v. 27.9±2.0 v. 28.5±1.9 at baseline p<0.01 28.5±1.8 v. 27.4±2.5 v. 28.0±2.3 v. 28.6±1.7 at 6 years p<0.01 62% vs 53% at post op day 4, p=0.50; 39% v. 14% at 3 months p=0.04	RCT Prospective longitudinal study RCT	(152) (8) (153)
Perfusion Pressure (in Cardiac Surgery)	MMSE Score drop 48 h after surgery, in Low Pressure v. High Pressure: 3.9±6.5 v. 1.1±1.9 p = 0.012	RCT	(154)
rS ₀₂ Desaturation Score >3000	Multivariate OR 2.22 (1.11–4.45) p=0.024	RCT	(148)
Hemodilution (in CPB cases)	Age x hemodilution interaction, p=0.03	RCT, stopped early	(155)
Hyperglycemia (i.e. glucose >200 mg/dL at any point during CPB cases)	Associated with POCD in non-diabetic patients, N=380, OR=1.85 [95% CI 1.12–3.04], p=0.017; N.S. (p=0.81) in diabetic patients, N=145	Retrospective analysis of pooled data from multiple prior prospective studies	(156)
Slow rewarming vs normal rewarming (in CPB cases)	Multivariate linear regression variable estimate 0.35, p=0.047 (favoring slow rewarming)	RCT	(157)
Continuous Cell Saver use (in CPB cases)	6% vs 15% in controls, p=0.038 16.7% vs 15.9% in controls, relative risk: 1.05, 95% CI: 0.58 to 1.90 at 3 months).	RCT RCT	(158) (159)
Embolus Load (in CPB cases)	No correlation between embolic load measured by transcranial doppler ultrasound and POCD at 1 week (P=0.617) or at 3 months (P=0.110), N=356 patients.	Pooled analysis of data from 2 other RCTs.	(102)
Alpha stat vs pH stat blood gas management (in CPB cases)	27% versus 44%, p = 0.047	RCT	(160)

Risk Factor	Effect Size	Study Design	Reference
Hypothermia vs normothermia (in CPB cases)	Multivariate odds ratio 1.15 [95% Confidence Interval, 1.01, 1.31] p=0.042, for POCD at hospital discharge after intraoperative normothermia vs mild hypothermia. N.S. difference for POCD at 6 weeks after surgery. Hypothermia vs normothermia, relative risk for POCD at 1 week after surgery = 0.77, P=0.048. Hypothermia vs normothermia, relative risk for POCD at 5 years after surgery =0.66, p=0.16	Retrospective analysis of pooled data from 2 prior trials. RCT RCT RCT	(161) (162) (163) (164)

* Partially modifiable risk factor.

** Delirium during hospital stay.

N.S. = Not Significant, CPB= Cardiopulmonary Bypass.

Table 2B

Non-Modifiable risk factors for POCD

Risk Factor	POCD vs no POCD	Study Design	Reference
Age	Multivariate Odds Ratio (OR) 1.04 (1.01–1.08), p=0.01 Multivariate OR 1.03 (0.99–1.06) p=0.1 Age of patients with POCD 51.9±17.3 v. no POCD 49.4±16.5, measured at discharge p=0.027 OR 1.03 (1.01–1.06) p=0.013 OR 1.151 (1.030–1.285) p=0.003 Multivariate OR 1.34 (1.01–1.78) p=0.043 Multivariate OR 0.95 (0.71–1.26) p=0.70 Multivariate linear regression parameter estimate (for continuous cognitive change score) - 0.009 (–0.012, –0.005) p<0.001	Randomized Controlled Trial (RCT) Prospective Observational Study Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study RCT RCT	(117) (149) (20) (67) (104) (150) (148) (66)
Educational Level	Multivariate OR 0.98 (0.91–1.07) p=0.67 Multivariate OR 0.84 (0.76–0.93) at 3 months p=0.0031 OR 0.9 (0.83–0.98) p=0.021 Multivariable linear regression model, parameter estimate: 0.012 (–0.002, 0.027) p=0.098	Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study RCT	(149) (20) (67) (66)
Type of surgery	Minimally invasive 4% v. 34%, Intraabdominal/thoracic 21% v. 14%, Orthopedic 11% v. 16% at discharge p=0.001 Congenital disease 10 v. 42 Valvular disease 32% v. 54% Aorta disease 14% v. 20% Tumor 2% v. 2%; p=0.051 overall N.S.	Prospective Cohort Study Prospective Cohort Study Prospective Cohort Study	(20) (150) (23)
Genetic risk alleles	<i>CRP</i> 1059G/C SNP OR 0.37 (0.16–0.78) p=0.013; <i>SELP</i> 1087G/A SNP OR 0.51 (0.30–0.85) p=0.011	Prospective Cohort Study	(67)
Left Hippocampal Volume	POCD v. No POCD 2.26±0.21 v. 2.45±0.15 p<0.01	Prospective Cohort Study	(165)
Right Hippocampal Volume	POCD v. No POCD 2.49±0.11 v. 2.62±0.20 p<0.05	Prospective Cohort Study	(165)
Middle Cerebral Artery Velocity	Left MCA POCD v. No POCD 42.5±5.5 v. 54.3±4.4 p<0.1; Left v. Right MCA POCD 42.5±5.5 v. 56.3±4.5 p<0.05**	Prospective Cohort Study	(166)
Preoperative Renal Insufficiency	Multivariate OR 0.18 (0.04–0.75) p=0.019	RCT	(148)
Prior Stroke	Multivariate OR 0.30 (0.11, 0.84) p=0.02	RCT	(146)

** Values estimated from the bar graph in Fig. 1 of the paper

Table 3**Important Questions for Future Research, Suggestions and Challenges**

Research Question	Suggested Study Design and Methods*	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 samples sizes needed to obtain sufficient power for clinically relevant effects; see (167) and (28) 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, etc.
-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
-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.

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