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Original Research

Pre-surgical memory impairment is associated with risk of postoperative cognitive dysfunction in a large geriatric cohort

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ABSTRACT

Some patients undergoing surgical procedures display long-term post-surgery cognitive impairment (post-operative cognitive dysfunction; POCD), which may precipitate progression to dementia. We investigated whether preoperative cognitive impairment defined using specific cognitive tests (Paired-Associates Learning and Spatial-Span from the Cambridge Neuropsychological Test Automated Battery, (CANTAB) was associated with increased risk of POCD. N = 590 patients >65years and a matched control group n=114 comprised the final sample. Patients were classified as impaired if a composite memory-score derived from two tests from the CANTAB test battery (spatial working memory and paired-associate learning) scored 1 SD below norms derived from a normative database. Risk of developing POCD 3 months post-surgery was higher [odds ratio 2.048 (95% CI 1.027 – 4.087)] for those with pre-surgical cognitive impairment compared to those with no impairment. This suggests that impairment on hippocampus-based tasks spatial-span memory and paired-associates learning is associated with increased risk for POCD in older surgical patients.

1. Introduction

Patients older than 65 years, with pre-existing cognitive impairment prior to elective surgery, are at higher risk of discharge to a place other than home, have a greater likelihood of developing postoperative delirium and are more likely to have a longer hospital stay [1–3]. From a public health perspective the prevention of Postoperative Cognitive Dysfunction (POCD) and postoperative delirium (POD) through education, aimed at both healthcare providers and patients has the potential to improve post-surgical outcomes. There are a number of public health campaigns that have suggested how these might be implemented including the International Drive to Illuminate Delirium (IDID) [4], ABCDEF bundle [5] and patient-centric communication [4]. All of these campaigns refer to the importance of cognitive factors. For elderly patients undergoing planned procedures that present at outpatient anesthesia clinics for preoperative risk evaluation, there is a need for easy to apply cognitive screening methods. The increase of acute POD rates and level of care dependency may relate to the potential of anaesthesia during surgery to accelerate cognitive impairment in patients with preoperative cognitive vulnerability. Despite a large number of publications in the research field of POCD and consensus on cognitive testing in surgical cohorts since 1995 [6], there is no gold standard for the assessment of perioperative neurocognitive disorders. Furthermore, nomenclature recommendations propose to merge diagnostic criteria for POCD with the diagnostic criteria for neurocognitive disorders (NCD) in the general population. This shift of POCD from a research to a clinical diagnosis relevant to cognitive decline at the individual patient level may facilitate the implementation of specific treatment pathways for geriatric patients at risk of cognitive decline after surgery. In an analysis on the co-occurrence of POD and POCD using data from a large prospective

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observational trial from 2019 cognitive decline was detected more frequently at later follow up in patients without POD [7] suggesting POD and POCD are dissociable phenomena with different time courses. In order to address POCD specifically it is therefore important to understand measurable cognitive change in the later perioperative period in more detail.

While the pathophysiology of POCD is likely multifactorial, a number of predisposing factors have been proposed that are shared with Alzheimer's Disease such as age, ApoE status and inflammation markers [8]. While their clinical presentations differ, growing evidence highlights the critical role of neuroinflammatory processes in the pathogenesis of both Alzheimer's Disease and POCD. Surgery and associated anaesthesia trigger systemic inflammation, which can cross the blood-brain barrier (BBB) and activate neuroinflammatory cascades [9,10]. Key mediators include pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), released in response to tissue injury or surgical stress [11]. Surgery and anaesthesia activate microglia, leading to the release of cytokines, reactive oxygen species (ROS), and other pro-inflammatory agents [12]. This acute neuroinflammatory response can disrupt synaptic plasticity, impair memory consolidation, and contribute to transient or long-term cognitive dysfunction [13]. Microglial activation in Alzheimer's Disease has been suggested to be activated in response to Aβ plaques, resulting in the release of pro-inflammatory cytokines and other neurotoxic substances [12,14,15]. Over time, this inflammatory milieu has been suggested to contribute to synaptic dysfunction, neuronal death, and the progression of cognitive decline [16–18]. Astrocytes, which support neuronal health and regulate the BBB, are also implicated in AD-associated neuroinflammation. Under pathological conditions, astrocytes adopt a reactive phenotype, secreting inflammatory mediators that perpetuate neuronal damage [19,20]. Chronic neuroinflammation in AD creates a vicious cycle, where sustained immune activation exacerbates Aβ deposition and tau pathology, further fuelling disease progression [20]. Understanding the shared neuroinflammatory origins of POCD and AD opens avenues for therapeutic interventions using anti-inflammatory agents [21].

Both disorders implicate hippocampal pathology. For example, animal studies have demonstrated that TNF-a-mediated dysfunction of the blood-brain-barrier (BBB) and the subsequent migration of inflammation into the hippocampus area of the brain can result in memory impairment [22].This brain area is well established for its role in memory formation and contains the largest density of inflammatory receptors, making it especially vulnerable to the detrimental effects of inflammation. Furthermore, clinical studies have demonstrated that hippocampal volume is reduced in patients experiencing a decline in cognitive function following surgery, with the reduction in hippocampal volume being proportionate to cognitive deterioration [23].

Consistent with findings of hippocampal volume change and neuroinflammation there is some evidence of an association between cognitive ability prior to surgery and risk of developing POCD. A greater proportion of patients showing pre-surgical cognitive impairment have been shown to develop POCD [24]. A simple targeted behavioural method to predict patients with a greater likelihood to develop POCD would be of significant value clinically, either alone or in conjunction with biological markers and could lead to precise evaluation of potential preventative treatments. Current tools suggested include general clinical dementia screening tools that encompass a broad range of cognitive function including memory attention and reaction time [25] but there is a lack of evidence that they can specifically predict POCD. The purpose of the current analysis project was to identify whether there are cognitive (specifically memory) related risk factors for POCD that could potentially be used to evaluate patients at higher risk of POCD prior to their surgery. Pre-surgical cognitive status (impaired or not impaired) was determined by performance on two specific cognitive tasks that involve the hippocampus, paired associates learning and spatial working memory. We calculated a composite memory score and used a normative database as reference to classify patients as impaired or not impaired prior to surgery. A control matched cohort was tested at the same timepoints. The hippocampal region of the brain is well-established for its role in memory function [26] and is particularly vulnerable to the detrimental effects of inflammation [27]. Thus, our hypothesis was that participants with an existing memory impairment on hippocampal dependent memory tasks would be more likely to develop POCD three months after surgery.

2. Methods

2.1. Study design and population

A secondary analysis investigation was performed on a subset of pseudonymized data from the BioCog project (www.biocog.eu), a prospective multicentre observational study conducted after approval of all procedures by local medical ethics committees at the Charité – University Medicine Berlin, Department of Anesthesiology and Intensive Care Medicine (EA2/092/14) and the University Medical Center Utrecht, Department of Intensive Care Medicine (14-469). The BioCog study aims to establish biomarker panels for risk and clinical outcome prediction of post-operative delirium (POD) and post-operative cognitive decline (POCD). Study registration can be found at clinicaltrials.gov under NCT02265263, and the study protocol was published [28]. Data were handled and processed in accordance with EU GDPR regulations within a collaboration agreement between Charité - Universitätsmedizin Berlin and Monument Therapeutics limited.

For this secondary analysis we included n = 933 who underwent elective surgery with an expected surgical duration greater than or equal to 60 min. Patients were ≥65 years with Mini-Mental State Examination (MMSE) scores >23, and had cognitive evaluations sampled prior to surgery (baseline), and at 3-month follow-up. A non-surgical control group of n = 144 were also included with cognitive testing completed at baseline, and at a 3-month follow-up to match the surgical sample, see Fig. 1. Cognitive tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [29] included Reaction Time (RTI), Paired Associates Learning (PAL), Spatial Span (SSP) and Verbal Recognition Memory (VRM) covering domains of simple attention, episodic memory and working memory (for details of test descriptions see Supplementary Material).

2.2. Calculation of pre-surgical (baseline) memory impairment

The following memory related outcome measures were used for the calculation of a composite score to determine each participant's pre-surgical (baseline) level of memory impairment: Paired Associates Learning total errors adjusted 8 shapes (PALTEA8; episodic memory) and Spatial Span total errors (SSPTE; working memory). The baseline data for these two outcome measures were pooled across both the surgical and non-surgical control group participants, to serve as a normative data comparison against which each participant in the surgical cohort could be compared [30]. Combining baseline data across the groups (surgical and control) creates a more representative normative baseline because participants in both groups will exhibit variability in performance at baseline for various reasons. The calculation of this composite score was as follows: for each participant, a Z score for each outcome measure was created: $Z_{PALTEA8} = -(PALTEA8_{individual\ participant\ score} - PALTEA8_{normative\ mean}) / PALTEA8_{normative\ SD}$, and $Z_{SSPTE} = -(SSPTE_{individual\ participant\ score} - SSPTE_{normative\ mean}) / SSPTE_{normative\ SD}$. These scores were then calculated together to create the composite score relating to memory function: Composite score = $(Z_{PALTEA8} + Z_{SSPTE})/2$. Here, a negative score equates to an individual's performance being worse (lower) than the normative mean performance. Mild-to-moderate pre-surgical memory impairment was classified as cognitive test performance as a composite

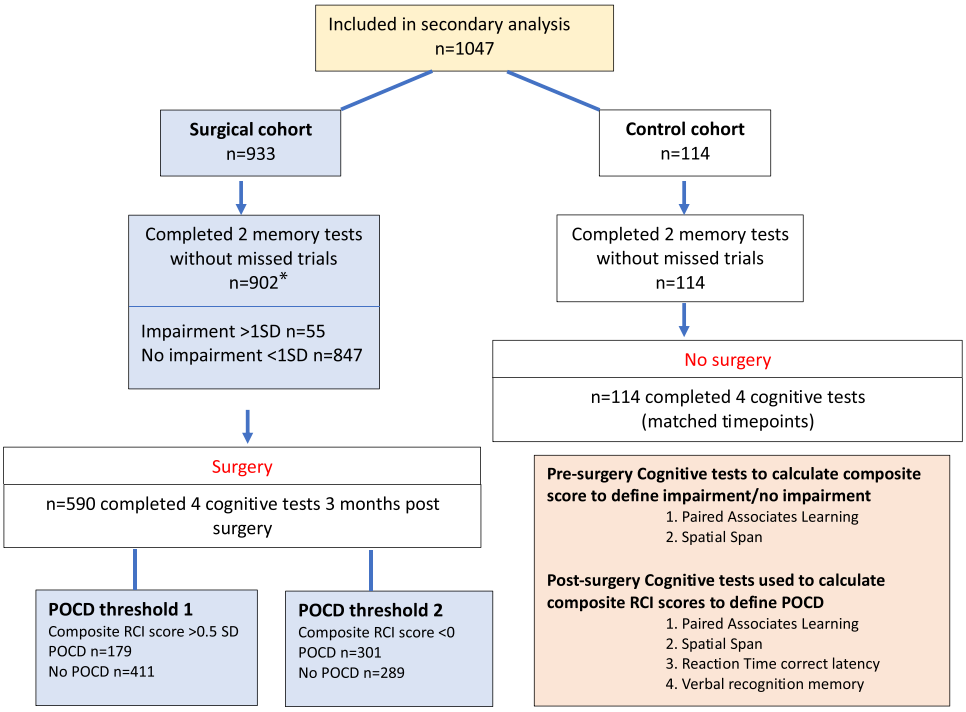

Fig. 1. Flow chart to illustrate participants included in secondary analysis of BioCog dataset. *characteristics of 31 cases that didn't complete 2 memory tasks without missed trials before surgery are detailed in the supplementary.

Table 1
Summary of participant characteristics for final n=590 / n=114 sample.

	CONTROL	SURGICAL	
N total	114	590	
N male	58	361	
N female	56	229	
Mean age (min-max) male	72.21 (65-92)	72.13 (65-91)	
Mean age (min-max) female	72.38 (65-90)	72.41 (65-86)	
Education (median IQR)	2.0 (2)	2.0 (1)*	*p<0.05 vs control Mann-Whitney U-test
Depression (mean sd gds)	1.54(2.2)	1.66(1.9)	
Comorbidity (mean cci (sd)	.64(.90)	1.2(1.4)**	**p<0.01 vs control T-Test
IQ (mean sd)	112.28(15)	112.18(14.2)	

[1]sd is standard deviation, IQR is interquartile range, GDS is geriatric depression scale, CCI Charlson comorbidity index.

score that was below -1, corresponding to an average cognitive test performance more than 1 SD below the baseline mean of the control group see Fig. 1.

2.3. Calculation of postoperative cognitive dysfunction

The calculation of Postoperative Cognitive Dysfunction (POCD) was based on the Reliable Change Index (RCI) diagnostic algorithm proposed by Rasmussen et al (2001) within the International Study of Postoperative Cognitive Dysfunction (ISPOCD). For each of the CANTAB tests included in the BioCog study, the key outcome measure for each test was used in the RCI calculation: Reaction Time correct latency (RTICL), PAL total errors adjusted (PALTEA), SSP span length (SSPSL) and VRM immediate free recall (VRMIFR) (for details see Supplementary Material). For each cognitive outcome measure, the corresponding RCI was calculated: $RCI = \frac{\Delta X - \Delta Xc}{SD(\Delta Xc)}$. ΔX refers to the difference in test scores after surgery compared to baseline, and ΔXc refers to the mean test score difference between the corresponding measurement time points in the non-surgical control group (to correct for learning effects and variability in repeated cognitive testing). From the single RCIs a composite RCI for each participant was calculated defined as the sum of all RCIs in relation to the standard deviation of the sum of RCIs in the control group: Composite RCI: $\frac{\sum(RCI)}{SD(\sum(RCIc))}$ [31].

Two different thresholds to define POCD were used. POCD was defined as either a negative composite RCI Z score (indicating any degree of decline from baseline performance to 3 months post-surgery), or as a >0.5SD decline from baseline performance to 3 months post-surgery (indicating cognitive performance had declined by at least half a SD after the surgery had taken place), see Fig. 1. These cut-offs for defining POCD are less conservative than the >2SD decline as proposed by Rasmussen and colleagues [31] to permit investigation of varying degrees of severity in cognitive decline from baseline to 3 months post-surgery.

2.4. Statistical Analyses

N=31 surgical cases that did not have complete data for both Spatial Span and Paired associate learning memory tests at baseline were excluded from the analysis leaving a final sample of N=902. Patient characteristic and demographic data for these excluded cases is included in supplementary table S1 and do not differ from the overall cohort. N=10 surgical cases contained missing Reaction Time (RT) correct latency trials (indicating a non-response) thereby precluding comparable RCI score calculations. These were excluded from the final analysis; cases for which data was available did not appear to differ from the analysed cohort in terms of age (mean 72.4 SD3.2, n=5) or IQ (115.6SD19.6, n=4), though numbers are too low to statistically compare. T-test with

Table 2
Descriptive statistics for individual CANTAB outcome measures by time point (baseline, 3 months) and participant group (surgical and control) for the final sample n=590. Mean (SD).

TASK	*TIMEPOINT*	CONTROL	SURGICAL
Reaction Time (RTICL)	**Baseline**	329.72[305.3,354.0]	322.02[313,330]
		N=96	N=590
	3 months	320.9[301,340]	328.11[319,336]
		N=96	N=590
	Δ 3months-baseline	-9.01 [-32,-14.3]	6.05[-1.96,14.07]
Verbal Recognition memory (VRMIR)	**Baseline**	22.61[22.3,22.9]	22.92[22.6,23.2]
		N=96	N=590
	3 months	24.00 [24,24]	22.07[21.9,22.2]
		N=96	N=590
	Δ 3months-baseline	.03 [-.28,.38)	.156[-.001,- .314]
Spatial Span (Length of span)(SSPSL)	**Baseline**	5.06 [4.8,5.3]	4.82[4.7,4.9]
		N=96	N=590
	3 months	5.23[5.0,5.4]	4.90[4.8,4.9]*
		N=96	N=590
	Δ 3months-baseline	.16[-.08,.41]	.08[-.003,-.17]
Spatial Span (SSPTE)	**Baseline**	13.26[12.2,14.3]	12.21[11.8-12.6]
		N=96	N=590
	3 months	12.82[12.5,13.1]	11.11[10.7,11.4]
		N=96	N=588
	Δ 3months-baseline	-.13[-1.3,-.52]	-1.11[-1.6,-.56]
Paired Associates Learning (PALTEA)	**Baseline**	55.82[46.8,64.7]	74.78[70.8,78.7]**
		N=96	N=590
	3 months	53.08[44.2,61.9]	73.72[69.7,77.6]**
		N=96	N=590
	Δ 3months-baseline	-2.7[-10.3,4.8]	-1.05[-4.4,2.3]
Paired Associates Learning (8 shapes) (PALTEA8)	**Baseline**	37.88[31.9,43.8]	51.71[49.5,53.8]**
		N=96	590
	3 months	37.18[31.3,42.9]	48.38 [45.6,51.1]**
		N=96	408
	Δ 3months-baseline	-.69(-6.5, -5.1)	.85(-1.9,3.6)

RTICL (reaction time correct latency); VRMFR (VRM free recall); VRMIR (VRM immediate recognition); SSPSL (SSP span length); SSPTE (SSP total errors); PALTEA (PAL total errors adjusted); PALTEA8 (PAL total errors adjusted 8 shapes). See supplementary material for full test descriptions. *p<0.05 **p<0.01 Vs Control group at same time point (T-test with Bonferroni correction).

Bonferroni correction for total number of tests performed was used to compare control and surgical groups on patient characteristics and baseline and 3 month CANTAB measures. Significance levels were set at 0.05. Binary logistic regressions were performed to ascertain the effects of presurgical memory impairment (defined using Z composite memory score) on POCD at 3 months (defined using RCI). Independent variable was Z composite memory score and outcome measure was presence or absence of POCD defined 1) as a negative score or 2) >0.5 SD below normative mean. Age was controlled for in all models. Following multicollinearity assumption checks, goodness of fit was assessed by Hosmer and Lemeshow tests and models reported as odds ratios with 95%confidence intervals (CI) for developing POCD 3 months post-surgery. All analyses were performed using statistical software SPSS [IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0.1.1 [14] Armonk, NY: IBM Corp].

3. Results

3.1. Participant characteristics

Demographic information (age and sex) is shown is Table 1 for the final surgical and control group participants, similar information for the full n=902 sample are presented in the supplementary data section for information.

3.2. Overview of cognitive performance

In Table 2, pre-surgical (baseline) and post-surgical (3-month follow-up) summary descriptive statistics are described for each of the key CANTAB outcome variables, for both surgical and control participants.

Summary descriptive statistics to describe pre-surgical cognitive performance on the combined episodic and working memory composite score is provided in supplementary Table S1.

3.3. Pre-surgical memory impairment and POCD

Out of the patients examined, 6.5% had mild-to-moderate pre-surgical impairment as defined by performance >1SD below the normative comparison on the combined pre-surgical episodic + working memory composite score.

Binary logistic regression indicates that >1SD baseline deficit on the pre-surgery episodic + working memory composite score is trending as a significant predictor of POCD (defined as a negative RCI score), when controlling for age: Wald=2.947, P=.086. The odds ratio for the composite is 1.857 (95% CI .916 – 3.765), indicating that the odds of having POCD defined as a negative RCI score at 3 months are 85% higher for those with a >1SD baseline deficit on the composite than those with no baseline deficit.

Binary logistic regression indicates that >1SD baseline deficit on the baseline episodic + working memory composite is a significant predictor of POCD (defined as *RCI score ≥0.5SD*), when controlling for age: Wald=4.141, P=.042. The odds ratio for the composite is 2.048 (95% CI 1.027 – 4.087), indicating that the odds of having POCD defined as an RCI score >0.5SD at 3 months are 105% higher for those with a >1SD baseline deficit on the composite than those with no baseline deficit. The percentage of participants meeting POCD as defined by RCI score >0.5SD decline from baseline was 30%.

4. Discussion

This secondary analysis of a large European dataset identified episodic and working memory impairment as potential cognitive risk

factors for POCD. The risk of developing POCD 3 months post-surgery was higher for those with a pre-surgical cognitive impairment defined by scores on a combination of two computerized neurocognitive tests (Paired Associates Learning and Spatial Span from the Cambridge Neuropsychological Test Automated Battery, CANTAB) compared to those with no deficit prior to surgery taking place.

We aimed to investigate preoperative memory impairment for several reasons. Difficulties with memory function are frequently the first complaints of patients and their proxies who are concerned about deteriorating cognitive abilities. Everyday functioning of patients with memory deficits may be preserved by adaptations in the patient‘s environment, e.g. writing notes, practicing routines and intensifying support by families and carers. Many of these compensation strategies rely on executive function and may be lost during hospitalization for surgery. This loss of compensation strategies may be aggravated by direct effects of anesthesia and surgery on reference memory that have been described in an animal model investigating the role of m-TOR-regulated autophagy in synaptic plasticity. Analyses of imaging data from the same cohort as our analysis sample (BioCog-study) revealed an association of larger preoperative thalamus volume with reduced odds of POD [32]. A better or worse performance in cognitive testing of spatial and episodic memory may reflect higher reserve or more severe vulnerability of the thalamo-hippocampal system and be accessible more easily during preoperative risk assessment than neuroimaging with MRI.

Strengths of our analysis are a large analysis sample, moderate loss to follow up (33%), and the inclusion of a non-operated comparison group to control for natural variability and learning effects in repeated cognitive testing. We previously published results on the test-retest-reliability of the cognitive tests applied in the BioCog neuropsychological test battery [33]. All of them showed moderate to excellent test-retest reliability during 3-month intervals (ICC range 0.60 to 0.92; all $p < 0.01$).

Yet our results need careful interpretation based on limitations to the applied nomenclature and definition of POCD. In a systematic review on measuring postoperative cognitive dysfunction our working group showed large heterogeneity of diagnostic rules to calculate POCD incidence from raw cognitive data [13]. For our sub-analysis we chose a relatively liberal cut-off (any negative RCI value and 0.5 SD RCI deterioration) that does not necessarily reflect the clinical significance of cognitive decline on the individual patient level [34]. We applied a POCD definition that differs from the main BioCog study [28] and our previously described POCD algorithm (accessible on https://github.com/Wiebachj/POCDr) that uses the same cut-off (RCI -1.96) as reported in the ISPOCD study. While the BioCog neuropsychological test battery included two additional non-computerized tests (Trailmaking Test and Grooved Pegboard) we used data from computerized tests only. We chose this approach, because we intended to evaluate the feasibility of computerized testing with the Cambridge Neuropsychological Test Automated Battery (CANTAB) in research on perioperative neurocognitive disorders. Our composite outcome therefore contains reaction time (RT) as a single non-memory test to assess for processing speed. More complex executive functioning is not included in our definition. As shown in Table 2 RT was stable on 3 months follow up in the surgical cohort as compared to baseline testing. The focus of our analysis is therefore on perioperative memory change. As loss of executive function abilities may be characteristic for POCD and distinguish POCD from other types of progressive memory loss future analyses should include computerized cognitive tests that reflect non-memory cognitive domains. Our results show that memory function changes perioperatively and that patients who are more severely impaired in memory function prior to surgery are at higher risk of further decline in memory function post-operatively. We cannot conclude from our results if complex executive function is affected in POCD and contributes to aggravation of memory dysfunction. Further research is merited to understand whether executive functioning (e.g. strategic planning, multi-tasking) may be suited as target for cognitive prehabilitation and non-pharmacologic prevention strategies during hospital treatment and neuropsychological follow up and support after hospital discharge.

The outcome of this analysis provides support for further research and future development of a prediction tool to measure key cognitive factors associated with risk for POCD, which would potentially provide major medical advancement to this field. The identification of patients with cognitive vulnerability would enable clinicians to focus limited resources on specific treatment pathways for those at highest risk within an increasing number of patients aged ≥65 years scheduled for elective surgery [35]. Knowledge about specific cognitive domains would allow for cognitive training before the operation which has shown reduction of postoperative delirium rates in a single-blinded RCT investigating the effect of an electronic, tablet-based preoperative cognitive exercise program targeting memory, speed, attention, flexibility, and problem-solving functions. Prevention strategies based on individualized patient risks may not only reduce catastrophic consequences for patients and their families/carers but also reduce the economic burden of POCD with approximately 1.6 billion EUR annual cost in long-term care insurance [36]. Such tests could readily be adapted for integration into current practice. Incorporating preoperative vulnerability assessments to identify at-risk patients. including neuropsychological testing has been highlighted as of particular importance in the field for e.g. in IDID [4]. In current practice clinicians in the area of perioperative care are aware of cognitive vulnerability as a key risk factor for postoperative cognitive delirium and long-term cognitive decline [37]. Consequently, neurocognitive screening has been implemented in routine preoperative assessment, mainly using short screens such as Mini-Cog © (https://mini-cog.com/) and been integrated into comprehensive geriatric assessment alongside screening for clinical frailty. Yet the focus in clinical routine remains mainly on short term in hospital complications including postoperative delirium [1,38]. A European Clinical guideline on the prevention and treatment of postoperative delirium has been updated in 2024, and as part of a clinical trial at Charité Universitätsmedizin Berlin, we are currently evaluating effects of the implementation of these guidelines [39,40].

Implementation of a specialized treatment path for patients who are screened positively for cognitive vulnerability prior to surgery (preoperative cognitive impairment) and/or develop postoperative delirium may reduce long-term cognitive decline. Yet there are methodological challenges to detect long-term perioperative cognitive change and to align research outcomes like POCD with the clinical diagnosis of mild/major NCD or MCI/Dementia [41].

As resources for diagnosing neurocognitive disorders are sparse, perioperative computerized cognitive testing may help to detect those patients at highest risk for long-term cognitive decline who might benefit most from timely referral to a memory clinic for further clinical evaluation and early treatment.

Conclusion: Assessment of memory impairment prior to surgery may be useful to assist with identifying POCD propensity in older surgical patients. Given the relatively advanced understanding of the neural substrate of memory it suggests that it may be possible to identify patients at higher risk of POCD using specific memory tests, thereby facilitating the clinical evaluation of both pharmacological and behavioral therapeutic interventions.

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Disclosures

KTG, SC, JHB are employees of Monument Therapeutics Ltd. PMM is scientific consultant for Monument Therapeutics Ltd.

Declaration of competing interest

None

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Not applicable

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jarlif.2025.100002.

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