Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Marcolongo F, Tessari G, Tropea A, et al. **Understanding postoperative cognitive dysfunction after cardiac surgery: an integrated narrative review of neuropsychological, neuroimaging, and rehabilitative perspectives**. Monaldi Arch Chest Dis doi: 10.4081/monaldi.2026.3774

Submitted: 17-10-2025
Accepted: 22-05-2026

Understanding postoperative cognitive dysfunction after cardiac surgery: an integrated narrative review of neuropsychological, neuroimaging, and rehabilitative perspectives

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Contributions: Federica Marcolongo: first author, screening and data extraction, drafting of the manuscript. Gianmarco Tessari, Alice Tropea, Silvia Faraglia: pivotal role in the study by drafting and reviewing the manuscript and providing key intellectual input. Cecilia Guariglia, Anna Pecchinenda, Anna Maria Giannini, Maurizio Volterrani: interpretation of the results and refinement of the manuscript.

Conflict of interest: the authors have no conflicts of interest to declare.

Ethics approval and consent to participate: as this study is a narrative review, it did not involve direct interaction with human participants or animals, and therefore, no ethical approval or informed consent was required. However, the study adheres to the ethical conduct policy outlined by the International Committee of Medical Journal Editors (ICMJE).

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data in study are included in this published article.

Abstract

Postoperative cognitive dysfunction (POCD) is a common and severe complication after cardiac surgery, characterized by declines in memory, attention, executive function, and processing speed. This narrative review synthesizes current evidence on POCD from neuropsychological, neuroimaging, and rehabilitative perspectives. The underlying mechanisms are multifactorial and include cerebral microembolization, systemic inflammation from cardiopulmonary bypass, hypoperfusion, and patient-specific risk factors such as advanced age and mild cognitive impairment. Neuroimaging studies have identified structural changes, such as new ischemic lesions on diffusion-weighted magnetic resonance imaging (MRI), and functional disruptions within the Default Mode Network and frontoparietal connections, which are associated with neuroinflammation as shown by positron emission tomography (PET). Neuropsychological assessment is limited by the absence of standardized diagnostic criteria and the use of diverse testing protocols, resulting in considerable variability in reported incidence rates. Although formal guidelines are lacking, cognitive rehabilitation interventions, including computerized cognitive training, multitasking exercises, and virtual reality, demonstrate potential for reducing cognitive decline, particularly when implemented before surgery. A significant gap persists in connecting these functional improvements to underlying neurobiological changes. Future research should integrate longitudinal neuropsychological, biomarker, and neuroimaging data within standardized frameworks to clarify POCD mechanisms and to develop effective, individualized prevention and rehabilitation strategies. These efforts are essential for improving long-term patient outcomes and quality of life.

Key words: postoperative cognitive dysfunction, neuropsychology, neuroimaging, cognitive rehabilitation, cardiac surgery.

Introduction

Cardiac surgery involves highly intricate procedures that can significantly influence overall physiological stability and neurological functions. Standard interventions as coronary artery bypass grafting (CABG), valve replacements, and surgeries requiring cardiopulmonary bypass (CPB) are widely utilized in clinical practice. Nonetheless, these procedures are associated with notable risks. In particular, CPB—while crucial for ensuring adequate tissue perfusion during induced cardiac arrest—has been implicated in various neurological complications, including cerebral microemboli, systemic inflammatory responses, and disruptions in cerebral blood flow regulation [1].

A wide spectrum of neurological complications following surgery has been reported, ranging from acute events, like ischemic or haemorrhagic strokes, to more frequently underrecognized conditions, as postoperative delirium and postoperative cognitive dysfunction (POCD). While stroke is typically associated with overt clinical signs and localized neurological deficits, POCD presents as a subtler deterioration in different cognitive domains—memory, attention, processing speed, and executive function—which may be transient, prolonged, or in some cases, evolve into chronic impairment [2].

In recent years, the conceptualisation of postoperative cognitive impairment has undergone a substantial revision. In 2018, the Nomenclature Consensus Working Group led by Evered et al. proposed a new framework aligned with the criteria of the DSM-5 and with recommendations from the National Institute on Aging–Alzheimer's Association [3,4]. This framework introduced the umbrella term perioperative neurocognitive disorders (PND), encompassing all cognitive impairments identified in the pre- and postoperative period.

Within this classification, several clinical entities are distinguished: pre-existing cognitive impairment (mild or major neurocognitive disorder), postoperative delirium—typically occurring within the first week after surgery or until discharge and characterized by acute and fluctuating disturbances in attention and awareness [5-7] —delayed neurocognitive recovery (dNCR), referring to cognitive decline occurring within 30 days after surgery [8], and postoperative neurocognitive disorder (previously referred to as POCD), which is identified between 30 days and 12 months after the procedure. Beyond this time window, cognitive impairment is classified according to standard neurocognitive disorder criteria with the additional specifier "postoperative," indicating a temporal, though not necessarily causal, relationship with surgery [9].

This updated framework is also consistent with the classification approach adopted in the ICD-11 [10], where postoperative cognitive dysfunction is not recognised as a distinct diagnostic entity but is subsumed under broader neurocognitive disorder categories. Despite this shift, the term POCD remains widely used in the literature, particularly in studies conducted prior to 2018 and in contexts where continuity and comparability across studies are required. Therefore, both terminologies currently coexist. In the present review, we retain the term POCD for consistency with the cited literature, while acknowledging its conceptual overlap with the more recent perioperative neurocognitive disorder framework.

Although the phenomenon of postoperative cognitive decline has been extensively covered in the literature, most reviews focused on single POCD aspects, separately delving into the impact of change and risk factors [11-17], the neural correlates identified through neuroimaging [18-23], the cognitive alterations detected by neuropsychological tests with focus on the different tests used [24-28] or, more recently, restorative approaches [29-31]. However, there is currently no attempt to integrate these areas in a comprehensive view of POCD, linking its neurobiological substrates to its clinical manifestations and the possible intervention strategies. In light of these considerations, the aim of this review is to fill this gap by proposing an integrated synthesis of current knowledge on POCD. In particular, we aim to relate clinical aspects of POCD with the different neuropsychological assessments used for diagnosis, the neural correlates evidenced by neuroimaging and cognitive rehabilitation interventions.

Methods

This narrative review was conducted to analyse the current state of the art regarding the sensitive issue of POCD in the field of cardiac surgery. A bibliographic research was performed using the following databases: PubMED, WEB of Science, Google Scholar. Original articles and reviews about the subject 'cognitive functions' and ‘POCD’ published from 1996 to 2025 were sought for the following medical subject headings (MeSH): “cardiac surgery” OR “heart surgery”, “risk factor”, “POCD” OR “postoperative cognitive” OR “post-operative cognitive”, “cognitive assessment” OR “neuropsychological assessment”, “preoperative training” OR “postoperative training”.

The articles found were then analyzed and classified, firstly according to the risk factors in the development of POCD, neuropsychological assessment (the focus was on the test most commonly used) and cognitive training.

Postoperative Cognitive Dysfunction (POCD)

The concept of postoperative cognitive dysfunction has a long history in the scientific literature, dating back to the 1980s, although its definition has often been inconsistent and lacking universally accepted diagnostic criteria. Postoperative cognitive disorders encompass a range of cognitive alterations emerging after surgery, typically in the absence of identifiable acute neurological injury [9]. Clinically, POCD is defined as a measurable decline in cognitive performance relative to the patient's preoperative baseline, usually developing in a subacute manner within days to weeks following surgery and objectively assessed through standardised longitudinal neuropsychological testing [32].

The cognitive domains most frequently affected include memory, attention, executive functions, and processing speed, although visuospatial and language impairments may also occur [27]. In contrast to postoperative delirium—an acute, fluctuating neuropsychiatric condition characterised by disorientation, attentional deficits, altered levels of consciousness, and, in some cases, hallucinations—POCD does not present with overt confusion, making this distinction essential for accurate differential diagnosis [33-35].

Hypoactive delirium, a less evident but common form, is particularly relevant in cardiac surgery, although it is often underdiagnosed. In this context, the incidence of POCD varies according to the type and complexity of the surgical procedure, with cardiac surgery being associated with higher rates than those observed in other types of surgical procedures. Discrepancies in diagnostic criteria further contribute to variability of data. According to Newman et al., applying a definition based on a decline of one standard deviation from baseline, the incidence may reach 70% in the first postoperative week and approximately 40% at one year [1].

Consistent with these findings, other studies report a prevalence ranging from 25% to 70% among patients undergoing cardiac surgery [36-39]. More specifically, approximately 10%–40% of patients develop cognitive impairment within the first six weeks following surgery, although only about 45% fully recover within one year. In patients undergoing coronary artery bypass grafting with cardiopulmonary bypass (CPB), prevalence may reach 50–70% in the first postoperative week, with 10–30% exhibiting persistent deficits at six months [40].

Although often subclinical, POCD is frequently reported by patients and caregivers as a reduction in mental clarity or cognitive resilience, with functional consequences that may persist for several months [41].

Several studies have demonstrated that POCD negatively impacts patients' cognitive well-being and is associated with prolonged hospitalisation, increased healthcare costs, and reduced quality of life. In more severe cases, it may result in loss of autonomy, reduced social engagement, early retirement, and increased mortality within the first postoperative year [1,11,36-37]. Long-term evidence further indicates that cognitive impairment detected six months after surgery is significantly associated with increased long-term mortality, suggesting that its consequences may extend well beyond the immediate postoperative period [38].

Two temporal phenotypes of POCD have been proposed: a short-term form, occurring within six weeks of cardiac surgery and affecting 20% to 50% of patients, and a long-term form, defined by impairments persisting beyond six months and reported in 10% to 30% of cases [1,39].

The aetiology of POCD remains incompletely understood and is likely multifactorial. Proposed mechanisms include surgery-related factors, such as systemic inflammatory response and neuroinflammation driven by cytokine release, anaesthetic-related effects (with no clear evidence supporting a single predominant agent), and patient-related characteristics, including advanced age, lower educational attainment, and pre-existing neurodegenerative vulnerability. Postoperative increases in biomarkers of neuronal injury have also been reported, suggesting the presence of subclinical cerebral damage [9].

In this context, POCD is widely recognised as the result of multiple interacting pathophysiological mechanisms including reduced cerebral perfusion, macro- and microembolic insults, systemic inflammatory activation, and intraoperative metabolic derangements [42,43]. A central mechanism is cerebral microembolisation: during cardiac procedures, atheromatous or gaseous emboli may enter the cerebral circulation, leading to scattered ischemic lesions and subtle neuronal damages. These events may remain undetected on standard neuroimaging exams but can result in significant cognitive impairment. Concurrently, the systemic inflammatory response induced by surgical trauma and the use of cardiopulmonary bypass (CPB) plays a crucial role in pathogenesis. Contact between blood and non-endothelial surfaces triggers a cascade of pro-inflammatory mediators that may cross the blood–brain barrier and disrupt neuronal function. Furthermore, episodes of cerebral hypoperfusion or oxygen desaturation during surgery may lead to oxidative stress, energy failure, and neuronal injury, thereby contributing to the development of cognitive dysfunction [14,37,44].

Importantly, patient-specific factors may significantly increase vulnerability to POCD. Advanced age represents one of the most significant risk factors: approximately 40% of elderly patients exhibit POCD at hospital discharge compared with 30% of younger individuals, with persistent impairment at three months observed in 12.7% versus 5%, respectively [45]. Additional risk factors include lower educational attainment, chronic comorbidities, and overall frailty [40,46] can exacerbate these effects.

In a comprehensive meta-analysis, Gravers et al. (2020) systematically categorised preoperative, intraoperative, and postoperative risk factors associated with POCD [47]. Significant preoperative predictors included previous stroke, depression, hypertension, diabetes, advanced age, and elevated EuroSCORE values, a tool commonly used to assess surgical risk in cardiac patients. Intraoperative factors such as prolonged surgery duration and extended mechanical ventilation were associated to higher incidence of POCD. Postoperatively, the development of delirium, arrhythmias (e.g., atrial fibrillation), and prolonged intensive care unit stays were among the strongest correlates.

A growing body of evidence also suggests that individuals with mild cognitive impairment (MCI) prior to surgery are particularly susceptible to developing POCD. Studies have reported a higher prevalence of preoperative MCI in patients who subsequently develop POCD [11], as well as postoperative attentional deficits and increased rates of early and persistent POCD [48-50]. In this context, routine preoperative cognitive screening has been advocated to identify at-risk individuals [44].

Taken together, these findings suggest that the most robust model involves the interaction between pre-existing vulnerabilities—particularly preoperative cognitive impairment—and intra- and postoperative stressors, including neuroinflammation, hypoperfusion, and delirium.

From a pathogenic perspective, a relationship between POCD and systemic and cerebral inflammation has been observed: biological markers as the S-100β protein and neuron-specific enolase (NSE) are elevated in patients developing POCD, suggesting disruption of the blood–brain barrier [51].

Scientific evidence supports the neuroinflammatory hypothesis as one of the principal pathogenic mechanisms underlying POCD, particulary following cardiac surgery involving extracorporeal circulation. Surgical trauma, ischemia-reperfusion injury and exposure to CPB induce a systemic inflammatory response characterised by increased in pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6 and TNF-α [40,52]. These mediators may cross the blood–brain barrier—whose permeability is increased by systemic and local factors—

activating resident glial cells such as microglia and astrocytes, thereby inducing central neuroinflammation and synaptic dysfunction [53,54]. This inflammatory cascade has been implicated in both acute postoperative delirium and long-term POCD.

These findings are further supported by animal model studies indicating a key role of neuroinflammation, particularly at the hippocampal level, in the development of mnemonic deficits [55].

This multifactorial perspective, grounded in both clinical and pathophysiological evidence, currently represents the most comprehensive and evidence-based explanation for the development of POCD.

Postoperative Delirium (POD)

Postoperative delirium (POD) is an acute neuropsychiatric syndrome characterized by fluctuating alterations in consciousness, attention, perception and cognition, with rapid onset and variable course over time. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [4], POD is defined as a disorder of attention and awareness, accompanied by a cognitive change that cannot be explained by a pre-existing or evolving dementia, and that develops because of a medical condition. In the surgical setting, diagnosis is frequently supported by validated tools such as the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) [56,57].

Delirium is often observed in patients undergoing cardiac surgery, with an incidence ranging from 10% to 50%, depending on the population, diagnostic criteria used and the complexity of the procedure [58,59]. Major predisposing factors include advanced age, pre-existing conditions, such as diabetes mellitus, atrial fibrillation, depression, mild cognitive disorders, sleep disturbances, reduced olfactory sensitivity and general frailty [6,60].

Although general anaesthesia has historically been implicated as a cause of delirium, recent evidence suggests that intraoperative factors—including prolonged benzodiazepine exposure, administration of inotropes or vasopressors, and sustained reductions in mean arterial pressure (MAP)—are strongly associated with the onset of delirium [7].

Emerging evidence suggests that POCD and postoperative delirium may share overlapping pathophysiological mechanisms, particularly in patients undergoing cardiac surgery. Factors such as prolonged CPB, postoperative systemic inflammation, a history of cerebrovascular disease, and cerebral microembolization have been implicated in both conditions [34]. Nevertheless, definitive causal links remain unclear. Systematic reviews and observational

studies have identified multiple independent risk factors for delirium after cardiac surgery, including older age, baseline cognitive or psychiatric impairment, prior stroke, procedural complexity, longer aortic cross-clamp times, and extended duration of mechanical ventilation [60,61]. These findings underscore a neurobiological vulnerability that predisposes some individuals to adverse neurological outcomes during the perioperative period.

Delirium is not only a short-term complication, but it is also associated with detrimental long-term outcomes. In the immediate postoperative phase, delirium has been linked to prolonged mechanical ventilation, extended stays in intensive care, delayed recovery, and increased hospitalization durations [62,63]. From a long-term perspective, persistent cognitive decline and higher one-year mortality rates have been observed, particularly among older adults with intensive care-related delirium [18,64]. Additionally, research by Martin et al. (2012) found a correlation between postoperative delirium and elevated risk of perioperative stroke as well as a greater incidence of cerebrovascular events in the decade leading up to cardiac surgery [65]. Berger et al. (2018) [14] hypothesized that POCD and delirium may represent endpoints along a shared neurobiological continuum, shaped by common mechanisms as neuroinflammation, blood-brain barrier disruption, and alterations in cerebral perfusion.

Supporting this theory, a study by Hudetz et al. (2009) in patients undergoing cardiac surgery with CPB demonstrated that 89% of individuals who developed postoperative delirium also exhibited cognitive impairment one week after surgery [66]. By comparison, only 37% of those without delirium showed similar deficits. Patients who experienced delirium were found to be 14 times more likely to develop POCD. These findings were confirmed by Brown et al. (2018) [67], who reported significant early declines in psychomotor speed and visuospatial performance at one month among delirium patients, although these impairments largely resolved by one year—suggesting the potential for, at least partial, recovery over time.

Cumulatively, the literature indicates a strong association between delirium and postoperative cognitive deterioration in cardiac surgery patients. Delirium is not only an acute neuropsychiatric complication but also an independent predictor of subsequent cognitive impairment, with implications for long-term quality of life, functional independence, and postoperative care planning.

Given these findings, distinguishing between POCD and delirium is essential, as they differ in terms of underlying aetiology, clinical trajectory, and prognostic relevance. Early identification of at-risk individuals, especially in the cardiac surgical population, requires a comprehensive approach encompassing preoperative cognitive screening, vigilant intraoperative

management, and tailored postoperative interventions. Proactive strategies aimed at minimising modifiable risk factors may significantly reduce the incidence and severity of both conditions.

Neuropsychological assessment for POCD

One of the key barriers to advancing our understanding and clinical management of POCD lies in the significant methodological variability that characterizes current literature. This heterogeneity refers to several domains, including how POCD is defined, which neuropsychological instruments are utilized, and the timing of assessments. At present, POCD is not formally classified within major diagnostic frameworks such as the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) or the *International Classification of Diseases, Eleventh Revision* (ICD-11) [15,36,68] and this gap does not help reduce methodological variability in studying POCD. The absence of a standardized, universally accepted diagnostic definition significantly complicates efforts to determine the true incidence and prevalence of POCD. Reported rates vary widely, often due to discrepancies in the criteria used to define cognitive decline, leading to conflicting interpretations across studies [69,70]. Depending on the threshold applied for cognitive deterioration, estimates range from 30% to 50% at six weeks postoperatively, and from 20% to 40% between six months and one year following surgery [22,71].

Given the subtle and often transient nature of POCD, its accurate detection requires the use of comprehensive, domain-specific neuropsychological test batteries, administered both preoperatively and postoperatively. These assessments would allow us to capture changes across multiple cognitive domains—including memory, executive function, processing speed, attention, and concentration—and remain essential for differentiating true cognitive decline from normal postoperative fluctuations.

At a methodological level, the timing of cognitive assessments has become more harmonized in recent years. Best practices now suggest that initial postoperative testing should not occur earlier than seven days after surgery, in order to reduce the influence of confounding factors as residual anaesthesia, acute postoperative pain, sleep disruption, and environmental disorientation—factors that may transiently impair cognitive performance and distort the reliability of test results [72,73].

Despite earlier calls for methodological standardization, as those presented in a 1995 consensus statement and later reviewed by Rudolph et al. [26], who found that less than half

of the 62 cardiac surgery studies adhered to recommended neuropsychological protocols, a universally endorsed battery and scoring methodology for POCD is still lacking [22].

A recent systematic review by Glumac et al. [37] identified over 100 distinct neuropsychological tests employed to assess POCD, underscoring the extent of methodological inconsistency and its impact on comparability—even among investigations with similar designs and populations [18]. This diversity of tools and scoring thresholds contributes to the persistent variability in reported findings and limits the ability to draw robust, generalizable conclusions.

Numerous scientific studies have contributed to the identification of major affected cognitive domains in POCD using extended neuropsychological batteries and longitudinal assessments. For example, Rasmussen et al. observed that memory and attention tests were used in 90% of studies, reflecting the frequent impairment of these domains [74]. Executive functions were found to be particularly sensitive in longitudinal studies on coronary artery bypass patients, being their early decline associated with their persistent cognitive impairment up to five years after surgery [1]. In addition, the large multi-centre ISPOCD1 study confirmed the involvement of multiple cognitive domains, including memory, attention and processing speed, which remained evident months after surgery [69]. Fine motor tests as the "Grooved Pegboard" have been shown to predict the development of POCD, especially in subjects with below-average preoperative performance [75]. Other studies highlighted the involvement of visual-spatial and language skills, although less frequently assessed [74].

Based on a synthesis of existing literature, the cognitive domains most frequently affected following cardiac surgery include memory, attention, executive functioning, processing speed, visuospatial abilities, motor coordination, perception, and language [22]. However, in the absence of consensus-based, domain-specific test protocols, a consistent and comprehensive understanding of POCD remains elusive.

Table 1 provides a summary of the most commonly employed neuropsychological instruments in POCD research within the context of cardiac surgery, detailing the cognitive domains assessed and corresponding scientific references, as extracted from the studies included in this review.

Neuroimaging in POCD

Among neurological complications arising from cardiac surgical procedures, which remain a significant contributor to postoperative morbidity, mortality, and diminished quality of life,

perioperative stroke — most often of ischemic aetiology — affects approximately 3% to 9% of patients, with incidence varying according to procedural type and patient-specific risk factors [76].

In recent years, neuroimaging has emerged as a critical tool in advancing the understanding of POCD pathogenesis, especially in patients undergoing cardiothoracic procedures. Diffusion-weighted magnetic resonance imaging (DWI-MRI), in particular, has proven effective in detecting acute cerebral insults — such as silent infarcts —which often go clinically unrecognised but may play a substantial role in postoperative cognitive decline. Up to 70% of patients undergoing cardiac surgery show new DWI-detectable lesions postoperatively, although the extent to which these correlate with clinically manifest POCD remains under active investigation [77,78]. Additionally, patients presenting with POCD frequently exhibit a higher burden of preexisting infarcts on preoperative MRI, and silent infarctions—alongside baseline mild cognitive impairment (MCI) — have been independently associated with elevated POCD risk [47]. These findings support the utility of preoperative neuroimaging as a risk stratification tool.

Positron emission tomography (PET) imaging has further enhanced the understanding of POCD, particularly in relation to neuroinflammatory processes. PET tracers, such as 18F-DPA-714, have been employed to visualize microglial activation, offering direct evidence of central nervous system immune responses following surgery. The FOCUS study, a key investigation in this area, demonstrated a robust link between neuroinflammation and cognitive dysfunction post-cardiac surgery, thereby highlighting the potential diagnostic and therapeutic implications of neuroimmune activation [79].

Functional MRI (fMRI) also provides valuable insights by assessing alterations in brain network connectivity rather than structural damage alone. Particular attention has been given to the Default Mode Network (DMN) and frontoparietal control networks, which govern high-order cognitive processes as working memory, attention, and executive functions. Browndyke et al. reported significantly reduced functional connectivity in the posterior cingulate cortex and right superior frontal gyrus — both DMN hubs — six weeks postoperatively in patients who had undergone cardiopulmonary bypass, and these changes were significantly correlated with reductions in global cognitive scores [80].

Corroborating this, a study published in *Annals of Surgery* showed that postoperative inflammatory states were associated with diminished connectivity between the dorsolateral prefrontal cortex (DLPFC) and superior parietal lobe, both crucial areas of the executive control

network [81]. The same study found evidence of decreased anti-correlated (negative) connectivity within the DMN, particularly affecting cognitive domains such as executive functioning and attention. These disruptions were closely linked with increased postoperative cytokine levels, suggesting that inflammatory mediators may play a causative role in network-level dysfunction.

Further evidence supporting the impact of intraoperative insults on functional brain architecture comes from task-based fMRI studies. During an N-back working memory paradigm, patients who underwent cardiac surgery demonstrated decreased activation in the prefrontal cortex in response to high cognitive load, with the reductions being the reductions proportional to the number of micro embolic events recorded intraoperatively [14]. These findings reinforce the role of cerebral microembolization in impairing cognitive performance post-surgery.

The neuroinflammatory hypothesis has also been substantiated by multimodal studies combining neuroimaging with biomarker analysis. Perioperative systemic inflammation has been shown to provoke microglial activation, which in turn disrupts intrinsic network connectivity—particularly within the DMN—thereby contributing to early postoperative cognitive deterioration [82]. This network disintegration may serve as an early biomarker for POCD, offering both prognostic insights and a target for intervention. Nevertheless, technical limitations remain, including heterogeneity in imaging protocols, inconsistency in follow-up intervals, and the lack of integrated biomarkers for comprehensive functional assessment.

Chronic cerebrovascular alterations, frequently seen in patients with cardiovascular comorbidities, further predispose individuals to ischemic brain injury preceding overt cognitive impairment [83-85]. Microvascular pathology may remain subclinical for years, particularly affecting structures such as the hippocampus—a region especially susceptible to hypoxia and ischemia [86,87]. Indeed, neuroimaging studies have shown volumetric alterations in structures such as the hippocampus and thalamus, as well as changes in cerebral perfusion in patients with POCD [21].

Frontal and parietal cortices—critical for multitasking, attention, and executive functions—reside within watershed areas of cerebral perfusion, making them vulnerable to both acute and chronic hypoperfusion during cardiac surgery [88,89]. Hypoperfusion of the left middle cerebral artery, in particular, has been linked to an increased risk of cognitive complications post-surgery [90]. Additionally, disruption of functional connectivity between the prefrontal

cortex and basal ganglia due to hypoperfusion may underlie observed impairments in working memory and attentional control [91].

Transcranial Doppler (TCD) ultrasound has been instrumental in real-time monitoring of cerebral hemodynamic during surgery. TCD studies demonstrated correlations between intraoperative cerebral hypoperfusion, embolic load, and declines in specific cognitive domains—particularly attention and short-term memory—postoperatively [92,93].

Integrating advanced neuroimaging modalities with longitudinal neuropsychological evaluations and intraoperative physiological monitoring may enhance the precision of POCD diagnostics. However, the continued absence of standardized imaging protocols, uniform diagnostic thresholds, and cohesive assessment frameworks remains a key limitation. Large-scale, multicentre studies employing harmonized methodologies are urgently needed to clarify the role of neuroimaging in the diagnosis, risk stratification, and potential intervention planning for POCD following cardiac surgery.

In conclusion, the most robust neuroimaging evidence indicates that central neuroinflammation and dysfunction of cognitive neural networks, particularly the Default Mode Network and frontoparietal connections, are the main mechanisms underlying POCD. Volumetric alterations in critical regions such as the hippocampus and changes in cerebral perfusion further contribute to cognitive impairment, with systemic and local inflammation acting as a trigger or amplifier. These data provide increasing support for the neuroinflammatory hypothesis of POCD, suggesting a possible link between intra- and post-operative events, synaptic dysfunction and alterations in brain functional connectivity.

Cognitive Training and Rehabilitation in POCD

Currently, there are no standardised guidelines for the prevention or rehabilitation of POCD following cardiac surgery, despite the substantial burden this condition imposes on patient quality of life, autonomy, and functional capacity [94-96]. The absence of clearly defined diagnostic criteria and treatment pathways has hindered the development and implementation of targeted interventions, particularly in the context of cardiac procedures where POCD is highly prevalent.

Recently, there has been a growing interest in rehabilitation interventions, including cognitive training, structured physical activity, neuromodulation (for example, DC transcranial stimulation) and the use of immersive technologies as virtual reality. However, the available evidence is fragmentary and rarely linked to underlying neurophysiological mechanisms.

One of the few exceptions is the recent review by Zhang and colleagues [29], who explore the potential of POCD rehabilitation interventions, without systematically investigating the relationship between cognitive recovery and induced brain modifications.

Cognitive training (CT) has recently gained attention as a non-pharmacological, scalable, and safe therapeutic option for mitigating cognitive decline associated with anaesthesia and surgery [97,98]. However, its integration into clinical practice remains limited, especially within cardiac populations, due to the ongoing ambiguity surrounding the clinical characterization of POCD [99].

CT can be administered through a variety of modalities—including traditional face-to-face sessions with paper-and-pencil exercises, computer-based programs for home use, and tablet-delivered applications—with increasing evidence supporting the efficacy of digital platforms [97]. In a recent study, Greaves et al. utilized a computer-based cognitive training (CCT) protocol via the HappyNeuron Pro platform, involving sessions of 45–60 minutes delivered every other day preoperatively and three times per week postoperatively over a 12-week period [100]. The intervention included weekly in-person or remote supervision, reinforced by regular telephone follow-up to maintain engagement and adherence. Significant improvements were observed in psychomotor speed, attention, memory, and executive functioning—domains commonly impaired in cardiac surgery patients.

Evidence also supports the efficacy of shorter CCT interventions (6–9 hours on 2–3 weeks), especially when delivered in the preoperative phase, demonstrating their beneficial effects on memory, attention, and mood, with reductions in anxiety and depressive symptoms [101-104]. Some studies reported reductions in the incidence of early postoperative delirium and cognitive deterioration—particularly within the first postoperative week—when CT was delivered through structured and supervised programs [105]. Conversely, trials with smaller sample sizes or less structured interventions failed to demonstrate significant cognitive benefits, suggesting that factors as supervision frequency and intervention structure may modulate efficacy [97,101].

Beyond purely cognitive interventions, multidimensional approaches combining cognitive and physical exercises are gaining attention. Specifically, multitasking training—which involves simultaneous motor and cognitive tasks—appears promising for cardiac surgery patients, since it engages attentional, executive, and motor functions concurrently [106-108]. While the effectiveness of multitasking has been established in neurological populations (e.g.,

Parkinson's and Alzheimer's diseases) and fall prevention in older adults [109,110], evidence in rehabilitation after cardiac surgery remains scarce.

In a recent study Tarasova et al. initiated multitasking training within 3–4 days post–coronary artery bypass grafting (CABG), delivering one session per day over a 5–7-day period [88]. Improvements were observed in psychomotor speed, attention, and figural memory, although no significant reduction in POCD incidence was achieved, with rates remaining at 60–65%. These results highlight the potential of early intervention to support initial recovery, albeit with limited effect in the absence of sustained training. This aligns with broader evidence suggesting the need for extended and comprehensive intervention protocols [111,112].

Emerging technologies as virtual reality (VR) are increasingly being investigated for their rehabilitative potential. VR enables dynamic modulation of task complexity and offers immersive, engaging environments for cognitive stimulation [95]. Adapting multitasking protocols to VR platforms may enhance the rehabilitation of memory, attention, and executive function, especially when personalized to patient capacity.

Mobile-based interventions have also been shown to be promising. Jiang et al. implemented a smartphone application—*The Light of Future*—designed to train six cognitive domains through gamified exercises [113]. Despite a prescribed training duration of 10 hours, improvements were noted after an average of only 6 hours. Notably, patient engagement was higher preoperatively than postoperatively, reflecting common postoperative barriers such as fatigue, pain, and logistical limitations [97,113].

A critical concept gaining traction in this field is cognitive reserve, which refers to the brain's resilience against neuropathological damage and functional decline. Traditionally viewed as the cumulative result of lifelong cognitive engagement, recent studies indicate that cognitive reserve can also be enhanced in the short term through intensive cognitive interventions [14,114]. Interventions totalling 10–20 hours showed durable improvements in processing speed and attention—domains frequently affected in POCD. As with physical prehabilitation, boosting cognitive reserve prior to surgery may reduce the cognitive impact of perioperative brain insults [115].

POCD is thought to be the result of a complex interaction between several factors, including neuroinflammation, microembolic events, alterations in the blood-brain barrier, neurotoxicity from anaesthetics and reduced cerebral perfusion [14]. As reported before, these mechanisms affect some cognitive functions, namely attention, executive functions and processing speed, justifying rehabilitation interventions specifically oriented towards these functions.

Indeed, cognitive training and multitasking protocols often focus on enhancing attention, executive functions, and working memory-typically compromised functions in POCD. Interventions targeting these domains resulted in specific improvements (for example in psychomotor speed or working memory), suggesting a partial consistency with the pathophysiological hypotheses. However, more general or multidimensional interventions - especially those integrating physical activity or immersive environments - may offer broader cognitive and functional benefits by promoting neuroplasticity, cardiovascular health and greater motivational engagement.

Overall, current evidence supports the feasibility and potential effectiveness of structured, personalized cognitive rehabilitation programs—particularly when started preoperatively and continued into the postoperative period. Interventions combining cognitive and physical elements, delivered through flexible and engaging formats such as VR or mobile applications, may offer enhanced benefits. However, key challenges related to patient motivation, adherence, and resource allocation must be addressed through rigorously designed, large-scale trials to determine the most effective strategies for preventing and mitigating POCD in cardiac surgery populations. At present, there is no conclusive evidence to show the superiority of targeted over general interventions. An increasing number of studies suggest that individualized approaches, calibrated on the patient's cognitive profile, past conditions and perioperative risk factors, can lead to better outcomes [116]. Customised training programmes, in which intensity, content and mode of administration can be modulated, could provide a bridge between enteropathogenic models and rehabilitative strategies applicable in clinical practice, even if further studies are needed to validate this hypothesis.

Discussion

This review highlights POCD as a common and clinically impactful neurological complication following cardiac surgery, carrying significant implications for patients' long-term cognitive health, autonomy, and clinical outcomes. A growing body of literature consistently identifies memory, attention, executive function, and processing speed as the most vulnerable cognitive domains affected by POCD. It is noteworthy to underline that these cognitive domains play a key role in functional autonomy in daily life and that their impairments significantly reduce individuals' ability in maintain previous levels in working, social and familiar activates.

POCD is a multifactorial condition, driven by several underlying mechanisms such as cerebral microembolization, systemic inflammation from cardiopulmonary bypass, hypoperfusion, and

patient-specific risk factors such as advanced age and mild cognitive impairment. Therefore, this narrative review aims to collect current evidence on POCD from neuroimaging, neuropsychological, and rehabilitative perspectives to map and encompass the most salient factors in the understanding of the disorder. In particular, findings show that several neuroimaging studies have identified structural changes, such as new ischemic lesions on diffusion-weighted magnetic resonance imaging (MRI), and functional disruptions within the Default Mode Network and frontoparietal connections, which are associated with neuroinflammation as shown by positron emission tomography (PET). Despite these insights, the relationship between observed neurofunctional alterations and clinical cognitive recovery remains poorly explored and needing further investigation. Indeed, neuropsychological examination is limited by the of the absence of a universally accepted clinical definition for POCD, which determines variability in neuropsychological test batteries and timing of cognitive assessments, standardized diagnostic pathways resulting in considerable variability in reported incidence rates. Moreover, the majority of existing research relies primarily on behavioural outcomes, with minimal integration of neuroimaging biomarkers to validate or contextualize cognitive changes. Despite the lack of formal guidelines in the neuropsychological assessment, cognitive rehabilitation interventions by digital platforms, including mobile applications and virtual reality (VR)-based environments, are showing growing potential in enhancing engagement, accessibility, and adaptability, particularly for high-risk cardiac surgery patients, particularly when implemented before surgery.

From a clinical standpoint, the early identification of patients susceptible to POCD through comprehensive preoperative assessments, including both neuropsychological testing and neuroimaging, is critical. This proactive strategy enables the development of targeted, multimodal interventions aimed at prevention and recovery. Multidimensional rehabilitation approaches—especially those combining cognitive and physical elements or leveraging immersive technologies—represent promising non-pharmacological ways to mitigate POCD and promote neuroplasticity.

Nonetheless, current literature is limited by substantial methodological heterogeneity. The absence of a universally accepted clinical definition for POCD, alongside variations in neuropsychological test batteries and timing of cognitive assessments, significantly reduce the comparability and reproducibility of findings across studies. Moreover, the majority of existing research relies primarily on behavioural outcomes, with minimal integration of neuroimaging biomarkers to validate or contextualize cognitive changes.

Despite advances in understanding the pathophysiology of POCD, a review of the literature reveals significant inconsistencies that limit its clinical translation. First, reported incidence rates vary widely. This variability reflects not so much actual epidemiological differences as the absence of standardized diagnostic criteria and heterogeneity in neuropsychological assessment protocols and timing. Second, although the domains of memory, attention, and executive functions are frequently reported as impaired, there are conflicting findings regarding the specificity and persistence of these deficits, with some studies reporting a predominant involvement of psychomotor speed and others highlighting visuospatial or language impairments, often due to the differing sensitivity of the tests used. Finally, the results of rehabilitation interventions appear inconsistent: while some trials demonstrate significant benefits of early or computerized cognitive training, others do not detect significant reductions in the incidence of POCD, suggesting that efficacy depends critically on factors such as duration, supervision, personalization, and the timing of intervention administration.
These contradictions highlight the urgent need to adopt harmonized protocols and to integrate behavioral data, neuroimaging, and biomarkers in order to overcome the current fragmentation of knowledge and develop truly effective strategies.

~~A~~ Notable gap in the evidence base is the lack of longitudinal studies investigating the neurofunctional effects of cognitive rehabilitation in cardiac surgery populations. Most trials report behavioural improvements without evaluating whether these are paralleled by structural or functional changes in the brain. Addressing this limitation through the integration of neuroimaging modalities into intervention studies could provide critical insights into the mechanisms driving POCD and ultimately enhance the precision and effectiveness of therapeutic strategies.

Conclusions

Postoperative cognitive dysfunction (POCD) continues to represent a multifaceted and insufficiently elucidated complication of cardiac surgery. This review provides a comprehensive and updated synthesis of the existing literature, emphasizing the necessity of adopting multidimensional frameworks for both the assessment and management of POCD. In particular, the integration of detailed neuropsychological evaluation with advanced functional neuroimaging techniques offers significant potential for enhancing early detection and informing the design of targeted cognitive rehabilitation strategies.

While accumulating evidence supports the efficacy of cognitive training in improving postoperative cognitive outcomes, a critical shortcoming in the current research landscape is the paucity of studies investigating the neurobiological substrates underlying these functional gains. Addressing this limitation will require future research to adopt longitudinal designs involving large, well-characterized patient cohorts and extended follow-up periods. The development and use of standardized intervention protocols—alongside the concurrent evaluation of cognitive performance, inflammatory biomarkers, and neuroimaging parameters—will be essential to ensure methodological rigor and comparability across studies.

The concept of cognitive reserve, proposed as a potential moderator of vulnerability and responsiveness to intervention, also merits further exploration in this clinical context. Its role may prove instrumental in identifying individuals most likely to benefit from early preoperation and postoperation rehabilitative efforts.

In conclusion, meaningful progress in POCD understanding and treatment will depend on the integration of clinical, cognitive, and neuroimaging data into cohesive investigative and therapeutic frameworks. Such an interdisciplinary approach is critical to elucidate the complex pathophysiological mechanisms driving POCD and to support the development of personalized, evidence-based interventions tailored to the cognitive profiles and risk factors of cardiac surgery patients.

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Table 1. Commonly used neuropsychological tests for the assessment of postoperative cognitive dysfunction following cardiac surgery, categorized by cognitive domain and supported by relevant literature.

Cognitive Domain	References
Verbal memory	
Rey Auditory Verbal Learning Test (RAVLT)	Newman et al., 2001; Peters van TonfiAM,et al.2021; Stessel B, et al 2020; Lewis et al. 2022; Butz M, et al. 2023
Free and Cued Selective Reminding Test (FCSRT)	Florido-Santiago M., et al., 2020
Digit Span (WAIS-IV)	Vedel et al., 2019; Yazit NAA et al.,2024; Peters van TonfiAM,et al.2021; Stessel B, et al 2020; Santiago Garcia et al 2020; Rahman SH et al. 2024
Hopkins Verbal Learning Test (HVLT)	Oldham et al 2015
Verbaler Lern- und Merkfähigkeitstest (VLMT)	Butz M, et al. 2023
Attention	
Trail Making Test Part A (TMT-A)	Rasmussen et al., 2001; Florido-Santiago M., et al., 2020; Oldham et al 2015; Naito Y. Et al., 2022; Yazit NAA et al.,2024; Peters van TonfiAM,et al.2021; Stessel B, et al 2020; Santiago Garcia et al 2020; Lewis et al. 2022; Rahman SH et al. 2024; Butz M, et al. 2023
Trail Making Test Part B (TMT-B)	Evered et al., 2011; Florido-Santiago M., et al., 2020; Naito Y. Et al., 2022; Yazit NAA et al.,2024; Peters van TonfiAM,et al.2021; Stessel B, et al 2020; Oldham et al 2015; Santiago Garcia et al 2020; Lewis et al. 2022; Rahman SH et al. 2024; Butz M, et al. 2023
Letter Digit Substitution Test (LDST)	Peters van TonfiAM,et al.2021; Oldham et al 2015 Stessel B, et al 2020
WAIS-III Symbol Coding	Oldham et al 2015; Lewis et al. 2022; Rahman SH et al. 2024
Symbol Digit Modalities Test	
Executive function	
Stroop Color-Word Inference Test (SCWIT)	Glumac et al., 2019; Florido-Santiago M., et al., 2020; Peters van TonfiAM,et al.2021
Clock Drawing Test (CDT)	Yazit NAA et al.,2024
Language	
Boston Naming Test (BNT)	Bowden et al., 2022
Semantic and Phonological Tests (SVFT and PVFT)	Florido-Santiago M., et al., 2020
Letter Fluency Test (LFT)	Peters van TonfiAM,et al.2021; Oldham et al 2015; Santiago Garcia et al 2020
Token Test (short form)	Peters van TonfiAM,et al.2021
Controlled Oral Word Association Test	Lewis et al. 2022
Regensburger Wortflüssigkeits-Test (RWT)	Butz M, et al. 2023

Global memory	
Rivermead Behavioural Memory Test-3 (RBMT-3)	Peters van Tonfi AM,et al.2021
Wechsler Memory Scale, Fourth Edition (WMS-IV)	Oldham et al 2015
Non-Verbal Learning Test (NVLT)	Butz M, et al. 2023
German Syndrom- Kurztest (SKT)	Butz M, et al. 2023
Visual-spatial memory	
Rey Complex Figure Test	Kastaun et al., 2016; Lewis et al. 2022; Peters van Tonfi AM,et al.2021
Block-Tapping Test	Butz M, et al. 2023
Visualspatial perception	
Judgment of Line Orientation Test (JLOT)	Florido-Santiago M., et al., 2020
Symbolic Picture Processing	
The Symbolverarbeitungstes' (SVT)	Butz M, et al. 2023
Global cognitive	
Montreal Cognitive Assessment (MoCA)	Oyoshi et al., 2023; Naito Y. Et al., 2022; Santiago Garcia et al 2020; Rahman SH et al. 2024; van Zuylen et al 2023; Jiang Y et al., 2024; Zhao et al. 2025
MiniMental State Examination (MMSE)	Naito Y. Et al., 2022; Yazit NAA et al.,2024; Oldham et al 2015
The Repeatable Battery for the Assessment of Neuropsychological Status Effort Scale (RBANS)	Yuhe K., et al., 2020
Neuropsychological Assessment Battery (NAB)	Oldham et al 2015
Modified Telephone Interview for Cognitive Status	van Zuylen et al 2023; Jiang Y et al., 2024
MATRIX test battery	Butz M, et al. 2023
Addenbrookes Cognitive Examination (ACE-III)	Greaves D. et al., 2023
Cambridge Neuropsychological Test Automated Battery (CANTAB)	Greaves D. et al., 2023
Premorbid intelligence (descriptive)	
National Adult Reading Test-IQ	Peters van Tonfi AM,et al.2021