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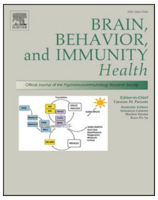

Exploring the gut microbiome-Postoperative Cognitive Dysfunction connection: Mechanisms, clinical implications, and future directions

Yan Yang [a], Zhipeng Xu [b], Jianrong Guo [c], Zhiqiang Xiong [d], Baoji Hu [b,c,*]

[a] *Department of Anesthesiology, Xuzhou Renci Hospital, Xuzhou, 221000, Jiangsu Province, China*
[b] *Department of Anesthesiology, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, 2800 Gongwei Road, Pudong, Shanghai, 201399, China*
[c] *School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology, Shanghai, 200093, China*
[d] *Shanghai Engineering Research Center of Food Microbiology, School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, 200093, China*

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ABSTRACT

Postoperative Cognitive Dysfunction (POCD) is a common yet poorly understood complication of surgery that can lead to long-term cognitive decline. The gut-brain axis, a bidirectional communication system between the central nervous system and the gut microbiota, plays a significant role in maintaining cognitive health. The potential for anesthetic agents and perioperative medications to modulate the gut microbiota and influence the trajectory of POCD suggests the need for a more integrated approach in perioperative care. Perioperative medications, including opioids and antibiotics, further compound these disruptions, leading to dysbiosis and consequent systemic and neuroinflammation implicated in cognitive impairment. Understanding how surgical interventions and associated treatments affect this relationship is crucial for developing strategies to reduce the incidence of POCD. Strategies to preserve and promote a healthy gut microbiome may mitigate the risk and severity of POCD. Future research should aim to clarify the mechanisms linking gut flora alterations to cognitive outcomes and explore targeted interventions, such as probiotic supplementation and microbiota-friendly prescription practices, to safeguard cognitive function postoperatively.

1. Introduction

Postoperative Cognitive Dysfunction (POCD) is a subtle yet often debilitating outcome observed in a fraction of patients following surgical procedures. Historically overshadowed by more immediate and life-threatening complications, POCD has emerged as a significant postoperative challenge, manifesting as impairments in memory, concentration, and overall cognitive functioning(Yang et al., 2022). Despite its transient nature in some patients, POCD can persist for weeks to months, profoundly impacting quality of life and the ability to resume daily activities and work(Silbert et al., 2015). The etiology of POCD is multifactorial, encompassing elements of surgical stress, systemic inflammation, anesthesia, and individual patient vulnerability(Li et al., 2022; Yang et al., 2022). Research increasingly implicates the intestinal flora, commonly known as the gut microbiota, as a potential contributor to this complex syndrome(Jiang et al., 2019). The gut microbiota comprises a vast ecosystem of microorganisms, inhabiting the human gastrointestinal tract and exerting significant influence on the host's metabolism, immunity, and even neurological function through the well-characterized gut-brain axis(Agirman et al., 2021). The gut-brain axis represents the bidirectional communication network between the central nervous system and the enteric nervous system(Agirman et al., 2021). Emerging evidence has shed light on the relevance of this axis in the context of surgical stress, where alterations in gut permeability, dysbiosis, and subsequent immune activation may play a role in the neuropsychological outcomes observed postoperatively(Custers et al., 2023; Lukovic et al., 2019).

Remarkably, recent findings also suggest that the composition and

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Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; FMT, Fecal Microbiota Transplantation; GA, general anesthesia; GABA, gamma-aminobutyric acid; GALT, gut-associated lymphoid tissue; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; LPS, lipopolysaccharide; POCD, Postoperative Cognitive Dysfunction; SCFAs, short-chain fatty acids.

* Corresponding author. Department of Anesthesiology, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, 2800 Gongwei Road, Pudong, Shanghai, 201399, China.

E-mail address: selfconfidence2005@sina.com (B. Hu).

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diversity of the gut microbiome could influence the risk and severity of POCD. For instance, perioperative interventions, including administration of antibiotics and anesthetics, are known to impact the microbial equilibrium. This disruption may precipitate systemic inflammatory responses or neural inflammation that predispose patients to cognitive disturbances(Pellegrini et al., 2018; Skvarc et al., 2018).

Considering the vast array of microbes residing within the gut, the potential for the gut microbiota to influence postoperative outcomes, including cognitive function, represents an exciting frontier in perioperative medicine and neuroscience. This review seeks to untangle the complex interplay between the gut microbiome and POCD, elucidating potential mechanisms (displayed in Fig. 1), implications for clinical practice, and directions for future research.

2. The human gut microbiome

The human gut microbiota is a complex ecosystem, predominantly composed of bacteria, but also includes archaea, viruses, fungi, and protozoa(Pellegrini et al., 2018). The richness and diversity of this microbial community are paramount for the host's physiological well-being. It is regulated by genetics, age, diet, lifestyle, and various environmental factors. Bacterial phyla, such as Firmicutes and Bacteroidetes, are major occupants, followed by Actinobacteria, Proteobacteria, and Verrucomicrobia, creating a dense and diverse microbial landscape(Rodriguez et al., 2015). Each individual's microbiota is unique, evolving throughout their life, and contributes to their metabolic and immunological profiles.

The gut microbiota plays an indispensable role in human health, transcending beyond digestive functions. Metabolic activities include the fermentation of indigestible dietary fibers, resulting in the production of short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. These SCFAs are vital for maintaining the integrity of the gut barrier, modulating metabolism, and immune regulation(Canfora et al., 2019).Immunologically, the gut microbiota is essential for the development of the host's immune system. It educates immune cells, promotes the maturation of lymphoid tissues and influences the balance between pro-inflammatory and anti-inflammatory actions(Wong and Yu, 2023). The symbiotic relationship helps in defending against pathogen overgrowth, a phenomenon termed "colonization resistance".

Moreover, the gut microbiota is recognized for influencing the gut-brain axis. Through metabolic products, such as neurotransmitters, it can communicate with the central nervous system, affecting mood, stress responses and pain perception(Wang et al., 2023). This interaction is so integral that the gut microbiota has been referred to as the "second brain".

Dysbiosis, an imbalance in the gut microbial community, can disrupt this harmonious interaction and has been implicated in a multitude of diseases, including inflammatory bowel disease, obesity, type 2 diabetes, and even neurological disorders like Alzheimer's disease(Carranza-Naval et al., 2021) and Parkinson's disease(Li et al., 2023). The mechanisms underpinning these associations range from inflammatory processes to metabolic disruptions and immune dysregulation. In the surgical context, dysbiosis has been observed in response to stress, antibiotics, and other perioperative factors. Such alterations can potentially weaken the mucosal barrier, contribute to systemic inflammation, trigger neuroinflammation and thereby emerge as a critical factor influencing postoperative outcomes, including cognitive functions (Jiang et al., 2019). Recent studies have shown that gut microbiota plays a key role in iron metabolism, which involved in the production of myelin and neurotransmitter synthesis in the central nervous system (Arnoriaga-Rodriguez et al., 2020; Rosell-Diaz et al., 2023).

As we consider the impact of the gut microbiome on human health and disease, understanding its perturbation in the face of surgery will be indispensable. The following sections will delve into the intricate relationship between the altered gut microbiota and POCD, evaluating the strength of current evidence and pondering future research avenues and therapeutic strategies.

3. Postoperative cognitive dysfunction and the potential role of the gut microbiome

POCD is characterized by impairments in cognitive faculties such as memory, attention, executive function, and psychomotor ability following surgery(Geng et al., 2023). Clinically, POCD may manifest with symptoms ranging from subtle concentration difficulties to more pronounced disorientation, memory loss, and an inability to perform complex tasks. These changes are often more apparent to family members than health professionals, and symptoms may go unrecognized within standard postoperative care.

Assessment of POCD is usually performed using neuropsychological testing, comparing pre-operative and post-operative cognitive performance(Evered et al., 2018). Diagnostic criteria for POCD are not standardized, and the condition's onset can be acute, surfacing immediately post-surgery, or subacute, developing over weeks to months

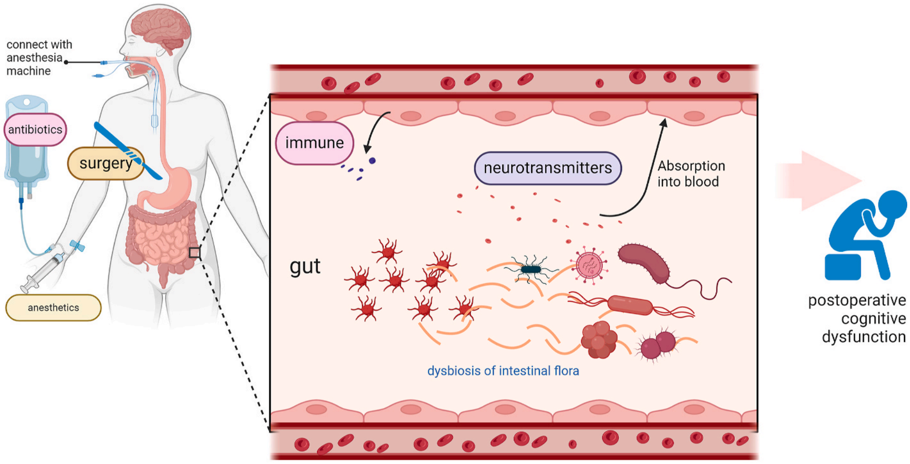

Fig. 1. The dysbiosis of intestinal flora induced postoperative cognitive dysfunction. Multiple neuro-transmitters/modulators were synthesized by intestinal flora, absorbed into the blood and cross the BBB, which modulate the activity of glial cells and neurons. Dysbiosis of intestinal flora affect the levels of these neurotransmitters within the CNS, influencing cognition. The impacr factors include but not limited surgery procedure, antibiotics, anesthetics, hemodynamic instability and hyoxemia during the operation, which induce the dysbiosis of intestinal flora and lead to the postoperative cognitive dysfunction. The figure was Created with BioRender.com.

post-discharge. The duration of POCD can be temporary or extend for longer periods, potentially leading to long-term deficits(Yang et al., 2022). The pathophysiological mechanisms underlying POCD are complex and multi-dimensional, involving inflammatory pathways, neuroinflammation, blood-brain barrier disruption, cerebral microemboli, neuronal apoptosis, and neurotransmitter imbalances. The stress of surgery and anesthesia can provoke a systemic inflammatory response, releasing cytokines and inflammatory mediators that potentially propagate to the central nervous system, contributing to cognitive impairment(Danielson et al., 2020). Another contributor is the anesthesia itself, which may lead to alterations in cerebral blood flow, impaired synaptic function, and neurotransmitter disruption. The use of specific anesthetic agents, oxygen deprivation, and fluctuations in blood pressure during surgery have also been investigated for their roles in POCD's pathogenesis. Furthermore, the individual patient's genetics, pre-existing health conditions, age, and the type and duration of surgery are significant risk factors for developing POCD(Jia et al., 2020; Yang et al., 2022).

The management of POCD requires a multi-disciplinary approach, as no specific treatment exists. Preventive strategies are centered on risk mitigation, including the selection of less invasive surgical techniques (Stessel et al., 2020), minimizing exposure to anesthetics(Shortal et al., 2019), optimizing pain management(Wang et al., 2007), maintaining hemodynamic stability(Berger et al., 2018), and ensuring adequate oxygenation perioperativlly(Zhang et al., 2019b). Postoperatively, cognitive rehabilitation therapies may support recovery. Strategies span from cognitive exercises to functional activities that engage the patient cognitively and physically(Butz et al., 2022). Patient education preoperatively is also crucial to set realistic expectations and foster strategies for coping with potential postoperative changes(Butz et al., 2022; O'Gara et al., 2020). Patients with POCD may experience a slower recovery from surgery and a delayed return to daily activities or work. Long-term POCD can significantly affect life quality and has been associated with an increased risk of leaving the workforce earlier, long-term cognitive decline, and even increased mortality. It is therefore of great importance to identify at-risk patients, optimize surgical and anesthetic techniques, and provide postoperative support to mitigate the potential negative outcomes associated with POCD.

Understanding the intricate connection between the gut microbiome and POCD may also offer new preventive and therapeutic avenues. Tailoring perioperative care to the needs of the microbiome, such as the judicious use of antibiotics and dietary interventions, represents a promising field of research with the potential to reduce the incidence and severity of POCD.

4. The gut-brain axis

The gut-brain axis is a bidirectional communication network that links the central and enteric nervous systems. This axis incorporates endocrine, immune, and neural pathways, allowing the gut microbiota to influence brain function and behavior(Agirman et al., 2021). Herein we explore the mechanisms and pathways through which the gut-brain axis could contribute to the development of POCD. The gut microbiota synthesizes a vast array of metabolites, some of which are neuroactive compounds including SCFAs, such as butyrate, acetate, and propionate. These metabolites can cross the blood-brain barrier (BBB) and modulate the activity of glial cells and neurons, influencing neuroinflammation, neurogenesis, and neurotransmission(Erny et al., 2015).Additionally, gut bacteria produce neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which can signal the nervous system directly or via the modulation of the host's neurotransmitter synthesis(Deczkowska et al., 2018). An imbalance in the production of these substances due to dysbiosis has been proposed to alter cognitive functions, potentially laying the groundwork for POCD(Zhao et al., 2019). The gut microbiome also influences the systemic immune system. Microbiota dysbiosis can promote the translocation of bacteria or bacterial components (such as lipopolysaccharide, LPS) across the gut barrier, triggering immune responses. Perioperative stress and interventions can exacerbate this process, leading to a heightened inflammatory state. Cytokines such as IFN-γ, IL-1β, IL-6, and TNF-α and other inflammatory mediators can access the central nervous system and contribute to neuroinflammation, which has been implicated in the pathogenesis of POCD(Parker et al., 2020).

The gut-brain axis is also mediated by neural pathways, particularly the vagus nerve, which conveys sensory information from the gut to the brain(Tan et al., 2022a). Surgical stress and anesthesia can disrupt vagal tone, potentially affecting the gut-brain communication and altering the brain's response to stimuli, mood, and cognition. Hence, the perioperative modulation of vagal activity represents a possible intervention point for attenuating POCD risk(Furness, 2012; Gacias et al., 2016). Moreover, the enteric nervous system can send signals to the brain through the activation of the enteric neurons due to changes in the gut luminal environment influenced by the microbiota. Altered enteric signaling could affect central nervous system function and contribute to cognitive decline post-surgery(Cryan et al., 2019). The BBB maintains the brain microenvironment's homeostasis, and its disruption is associated with numerous neurological disorders. Neuroinflammation driven by gut dysbiosis, as well as direct effects of microbial metabolites on the BBB, could contribute to an increased permeability, facilitating the influx of neurotoxic agents and inflammation into the brain parenchyma, leading to neuronal damage and cognitive impairments observed in POCD(Paik et al., 2022).

These communication pathways highlight potential targets for preventive and therapeutic strategies against POCD. Prebiotic and probiotic supplementation, dietary modifications to promote a healthy microbiota, and management of perioperative stress and inflammation could be employed to fortify the gut-brain axis and mitigate the risk of developing POCD. Clinical trials targeting these mechanisms could elucidate the effectiveness of such interventions in the perioperative period.

5. The influence of intestinal flora on the central nervous system

The gut microbiota synthesizes a range of neurotransmitters and neuromodulators that mirror those found in the central nervous system (CNS), including serotonin, dopamine, and GABA. Remarkably, it is estimated that up to 95% of the body's serotonin, a neurotransmitter crucial for mood and cognitive function, is produced in the gut(Chen et al., 2021). Gut bacteria can affect the levels of these neurotransmitters not only within the gut but also within the CNS, influencing mood, anxiety, and cognition. The gut microbiome plays a pivotal role in the development and modulation of the host's immune system(Furusawa et al., 2013). Microbial antigens can prime immune cells in the gut-associated lymphoid tissue (GALT)(Morbe et al., 2021), which can travel to the CNS and participate in immune surveillance. Dysbiosis may disrupt this interaction, leading to an inflammatory state that can promote neuroinflammation and contribute to neuropsychiatric conditions and cognitive decline(Hoffman et al., 2023). Gut bacteria produce various metabolites that can influence brain health. SCFAs, like butyrate, are not only a primary energy source for colonocytes but also modulate the blood-brain barrier's integrity, have anti-inflammatory properties, and modulate neuronal gene expression and neuroplasticity(Hoffman et al., 2023). These actions potentially impact cognitive functions and the vulnerability to POCD. The gut microbiota can influence the CNS by modulating visceral sensory information. The vagus nerve is a primary conduit for this information, transmitting signals from the gut to the brain. Vagus nerve stimulation has been shown to have therapeutic effects on depression and epilepsy, suggesting that it might also play a role in modulating the influence of the gut microbiota on the brain(Tan et al., 2022b).

The hypothalamic-pituitary-adrenal (HPA) axis, which governs the stress response, is modulated by the gut microbiota. Exposure to stress, especially during early life or critical developmental windows, can alter both the composition of the gut microbiota and the reactivity of the HPA axis(Chidambaram et al., 2022). This dysregulated response can, in turn, affect cognitive function and potentially contribute to the development of disorders such as POCD.

Understanding how the gut microbiota influences the brain opens up possibilities for novel therapeutic strategies, such as the use of prebiotics or probiotics to ameliorate stress-related conditions and cognitive decline. Interventional studies that manipulate the microbiota may provide insights into developing treatments for preventing or mitigating the effects of POCD and other cognition-related disorders(Hoffman et al., 2023).

5.1. *Intestinal flora and surgery*

Anesthetic agents are known to have a significant impact on the body's physiological processes, and recent evidence suggests that they can also affect the composition and function of the gut microbiota(Guo et al., 2021; Han et al., 2021). The administration of general anesthetics can lead to alterations in gut motility, reduced blood flow to intestinal organs, and changes in the immune responses within the gut(Minerbi and Shen, 2022), all of which can foster dysbiosis. For instance, volatile anesthetics may depress peristalsis and alter the gut mucosal barrier, potentially allowing translocation of bacteria and their metabolites into the systemic circulation. These disturbances can trigger an immune response, increasing the levels of cytokines and chemokines that may contribute to neuroinflammation and subsequently, POCD.

Beyond anesthetics, other medications commonly used in the perioperative setting, such as opioids for pain management, can influence gut microbiota. Opioids are notorious for causing constipation by reducing gut motility, potentially leading to an overgrowth of certain bacterial populations and a decrease in microbial diversity(Brown et al., 2021; Lee et al., 2018). A disturbed microbial environment could exacerbate the neuroinflammatory pathways associated with POCD. Antibiotics used perioperatively to prevent or treat infections can have a profound and sometimes long-lasting impact on gut microbiota. While necessary for managing bacterial infections, antibiotics can non-selectively reduce microbial populations and diversity, including commensals and beneficial bacteria, which play a role in maintaining cognitive health via the gut-brain axis, potentially increasing the risk of POCD(Liang et al., 2018; Zhang et al., 2019a).

The effects of anesthetics on neuroinflammation and neurocognitive outcomes are areas of active investigation. Research in animal model suggests that some anesthetic agents can lead to increased levels of amyloid-beta and tau proteins in the brain(Xu et al., 2021), hallmarks associated with neurodegenerative diseases, and cognitive decline. However, a multicenter study found exposure to surgery/GA was not associated with increases in cortical amyloid deposition(Sprung et al., 2020). These findings raise concerns about the potential exacerbation of these mechanisms in the development of POCD in humans.

To mitigate the potential impact of anesthesia and medication on gut microbiota and POCD, several strategies are being explored. These include the use of short-acting anesthetic agents, minimizing opioid use via multimodal pain management, and the careful selection and dosing of antibiotics. Limiting the use of broad-spectrum antibiotics and employing regional anesthesia where possible may also help preserve microbiome integrity and reduce the incidence or severity of POCD. Moreover, the timing of antibiotic administration and the use of narrow-spectrum antibiotics can help preserve gut microbial diversity.

Prophylactic use of probiotics to maintain gut homeostasis and the careful management of postoperative pain and constipation are additional strategies that may prove beneficial in reducing the risk of POCD. It is also essential for clinicians to consider a patient's existing microbiota health when formulating anesthetic and perioperative medication plans. Future research should focus on delineating the mechanisms by which these pharmacological agents affect the microbiome, with the goal of developing targeted interventions that reduce the cognitive sequelae following surgery.

The stress of surgery, combined with anesthesia, postoperative pain management, and antibiotic administration, can disrupt the delicate equilibrium of the gut microbiota(Lin et al., 2020). This disruption can lead to a state of dysbiosis, characterized by a reduction in microbial diversity and alterations in the composition of the microbial community. These disturbances can subsequently influence the occurrence and severity of POCD by various mechanisms involving the microbiome-gut-brain axis. Surgery and the associated stress response can increase intestinal permeability, often colloquially referred to as "leaky gut"(Lai et al., 2021). This increased permeability allows bacteria and their metabolites, including inflammatory mediators, to enter the circulation more readily, potentially reaching the central nervous system and influencing cognitive function.

A shift towards a pro-inflammatory microbial profile may contribute to systemic inflammation, a key player in the pathogenesis of POCD. Potentially pathogenic bacteria can proliferate when the balance is disturbed, increasing the production of LPS and peptidoglycans, which can stimulate the innate immune system and promote inflammation (Kesika et al., 2021). This systemic inflammatory response can cross the blood-brain barrier, exacerbating neuroinflammation and contributing to cognitive decline.

6. Therapeutic interventions and future directions

The burgeoning recognition of the gut-brain axis and its modulation by the gut microbiota in the development of POCD heralds a new domain of therapeutic interventions. These interventions aim to protect or restore the integrity of the gut microbiome throughout the perioperative period. The administration of probiotics, live beneficial bacteria, could help maintain a healthy balance of the gut microbiome(Cao et al., 2023), potentially reducing the risk of developing POCD. Lactobacillus and Bifidobacterium, common ingredients in probiotics, have been shown to secrete metabolites that support the gut barrier and have anti-inflammatory effects(Dalile et al., 2019). Prebiotics, the non-digestible fibers that act as food for beneficial bacteria, can also be valuable. They help to increase populations of beneficial bacteria and the production of SCFAs, which have neuroprotective roles(Hall et al., 2023). Both probiotics and prebiotics are being studied for their potential to reduce systemic and neuro-inflammation associated with POCD(Novotny et al., 2019). Nutrition plays a pivotal role in modulating the gut microbiome. Dietary interventions aimed at increasing the intake of fibers, as well as nutrient-dense plant-based foods, could promote a diverse and resilient microbial population(Dammavalam et al., 2023). Such dietary patterns might also enhance recovery times and cognitive outcomes post-surgery. Fecal Microbiota Transplantation (FMT) is a more radical approach to recolonizing the gut with a healthy microbiome(Dini-Andreote and Custer, 2023). While FMT has been utilized mainly for treating recurrent Clostridioides difficile infection (Baunwall et al., 2022), its potential for restoring microbiome balance in the context of POCD presents an intriguing yet underexplored research area.

Targeting the inflammatory response elicited by microbiota dysbiosis through the use of anti-inflammatory drugs might offer another path to mitigating POCD. Selective targeting of pro-inflammatory cytokine signaling pathways or the use of specific BBB protectants are areas worth exploring.

Prospective studies are needed to identify the precise microbial changes associated with POCD and to discern their temporal relationship with cognitive outcomes. Randomized controlled trials assessing the efficacy of prebiotics, probiotics, dietary interventions, or FMT in preventing or reducing POCD are necessary to advance clinical practice.

Multidisciplinary research integrating microbiology, anesthesiology, neurology, and nutrition science could uncover novel biomarkers for predicting POCD and deepen our understanding of the underlying pathophysiological mechanisms. Likewise, uncovering the interactions between lifestyle factors, genetics, and the microbiome may allow for personalized therapeutic strategies.

Investigations into therapeutic modulation of the gut microbiome hold promise for preventing and managing POCD. As research in this area evolves, it is anticipated that approaches focusing on the preservation and restoration of gut microbial health will become more refined and integrated into standard perioperative care practices, with the hope of mitigating the burden of cognitive complications after surgery.

7. Conclusion

The research dissected herein supports a model in which the richness and diversity of the gut microbiota are essential for maintaining cognitive health, particularly in the context of perioperative care. The potential of strategies aimed at preserving and restoring the microbiome's integrity, such as probiotic and prebiotic administration, dietary interventions, and even fecal microbiota transplantation, opens new avenues for mitigating the onset or severity of POCD.

Clinicians must recognize the gut microbiota's role in patient recovery following surgery. Incorporating strategies to monitor and manage gut health before and after surgery may become an integral component of perioperative care. Although the evidence for specific interventions is still evolving, there is a growing appreciation of the need to avoid unnecessary disruption of the microbiome and to maintain a broad spectrum of microbial diversity. For researchers, the gut microbiome presents fertile ground for investigating POCD's pathophysiology, biomarkers, and treatment. The identification of specific microbial signatures associated with POCD risk or resilience could pave the way for personalized medicine approaches. Moreover, exploring the efficacy of various microbiota-targeted therapies will likely be a focus of future clinical trials. Continued interdisciplinary collaborations across microbiology, neuroscience, anesthesiology, and other related fields will be essential for advancing our understanding of the microbiome's contribution to POCD and for translating these findings into effective interventions.

In conclusion, acknowledging the gut microbiota's influence on brain health signifies a shift towards a more integrative and holistic view of patient care. As we endeavor to enhance surgical outcomes and foster better recovery processes, attention to gut microbial health holds significant promise. The road ahead is one of discovery and translation, as ongoing and future research endeavors aim to fill the current knowledge gaps and provide evidence-based strategies to counteract the challenge of POCD.

CRediT authorship contribution statement

Yan Yang: Writing – review & editing, Conceptualization. **Zhipeng Xu:** Funding acquisition, Data curation. **Jianrong Guo:** Methodology, Funding acquisition. **Zhiqiang Xiong:** Supervision, Project administration. **Baoji Hu:** Writing – original draft, Visualization, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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