Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/052994nhuqqb

Changes in brain functional connectivity of patients with postoperative delirium

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Declaration of conflict of interest: None.

Received July 25, 2024; Accepted October 16, 2024; Published December 31, 2024

Highlights

- Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are compared for studying brain connectivity in POD. EEG provides high temporal resolution, while fMRI offers detailed spatial mapping. Combining these techniques can deliver a comprehensive view of brain function in POD.
- The article highlights the role of the Default Mode Network (DMN) and posterior cingulate cortex in the cognitive deficits seen in POD, noting that weakened connectivity in these areas is a key contributing factor.
- Graph theory is applied to study brain networks in POD, offering insights through metrics such as small-world structure and node degree, enhancing the understanding of POD-related connectivity changes.
- This article explores how perioperative factors (such as anesthesia, inflammation, and physiological stress) affect brain functional connectivity and their association with postoperative delirium (POD), offering important new perspectives.And this article deeply analyzes the differences in brain functional connectivity patterns caused by different surgical types and their potential association with the development of POD.
- The article advocates for combining EEG and fMRI to enable dynamic studies of brain connectivity and recommends larger, diverse samples to validate findings across various surgical types.

Abstract

Postoperative delirium (POD) is an acute cognitive disorder marked by attention deficits, fluctuating symptoms, and significant cognitive impairment. These features are closely associated with adverse outcomes, including increased mortality, prolonged hospitalization, long-term cognitive deficits, and elevated healthcare costs. Brain functional connectivity studies focus on understanding complex neuronal interactions and interregional communication within the brain. This article explores the association between POD and brain functional connectivity. It begins by summarizing the prominent features of POD as a common postoperative complication and its substantial impact on patient health, highlighting current limitations in understanding the pathophysiological mechanisms. The article then investigates the relationship between functional connectivity and cognitive function, emphasizing the role of advanced monitoring techniques, including Electroencephalography and Functional Magnetic Resonance Imaging. The advantages and limitations of these technologies in studying brain connectivity are discussed. Additionally, the article focuses on the posterior cingulate cortex and Default Mode Network, examining their roles in the development of POD and their potential connections to its pathogenesis. Finally, the application of graph theory in connectivity analysis is introduced, offering new insights into POD's pathogenesis. Based on current evidence, the article provides an outlook on future research directions and potential challenges. This study particularly emphasizes the impact of perioperative factors, such as anesthesia and postoperative inflammation, on brain functional connectivity. These changes may trigger POD by disrupting connectivity within the Default Mode Network and other key neural networks. By investigating the changes in brain functional connectivity patterns in patients undergoing different types of surgeries, this study further reveals the contribution of perioperative factors to the pathophysiological mechanisms of POD.

Keywords: Delirium, brain functional connectivity, functional magnetic resonance imaging, electroencephalography, graph theory, posterior cingulate cortex, default mode network, subcortical area

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Introduction

Postoperative delirium (POD) is a prevalent and severe acute cognitive disorder characterized by inattention, fluctuating consciousness, and significant cognitive impairment [1]. Commonly affecting critically ill patients post-surgery, POD is linked to adverse outcomes such as increased mortality, extended hospital stays, long-term cognitive deficits, and higher healthcare costs [2-5]. Despite its high incidence, the pathophysiological mechanisms behind POD remain poorly understood.

Human cognition relies on the integration of various brain regions that together support perception, memory, learning, and problem-solving. Brain functional connectivity, describing interactions among neurons and brain regions, is essential for these cognitive functions. Advanced imaging techniques, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), enable researchers to examine these brain networks and their roles in cognition.

This study explores the relationship between brain functional connectivity and postoperative delirium. By examining the benefits and limitations of fMRI and EEG, the research aims to identify reliable indicators of connectivity changes associated with POD. Additionally, it investigates the roles of specific regions, like the posterior cingulate cortex and the Default Mode Network (DMN), in POD's development. Graph theory, applied to analyze brain network structures, provides a novel framework for understanding POD's underlying mechanisms.

The perioperative period refers to the critical stages before, during, and after surgery, where patients may experience various physiological and psychological stresses. Physiological changes during the perioperative period, such as inflammatory responses, fluctuations in cerebral hemodynamics, and the neuroregulatory effects of anesthesia, may significantly affect brain functional connectivity. These changes are considered key triggers for the onset of POD. Studies suggest that different types of surgeries (e.g., cardiac, orthopedic, and abdominal surgeries) may lead to specific changes in brain functional connectivity, which in turn affect post-surgical cognitive function. This research direction not only helps to unveil the potential mechanisms of POD but also provides scientific evidence for developing personalized intervention strategies.

Ultimately, this study contributes to a deeper understanding of the neuropathological basis of POD and outlines directions for future research, particularly regarding the dynamic nature of brain connectivity.

Brain functional connectivity and cognition

Distinct brain regions support specific cognitive functions. For instance, the prefrontal cortex governs executive control and decision-making; the temporal lobe is integral to memory and language; while the parietal and occipital lobes contribute to spatial cognition and perception. To perform cognitive tasks, the brain depends on interactions across regions, where information is transmitted via synaptic connections between neurons. These functional connections form a network supporting various cognitive functions, reflecting the brain's balance of local specialization and functional integration [6, 7].

Disruptions in brain network organization can manifest in conditions such as anesthesia-induced unconsciousness and neuropsychiatric disorders, including Parkinson's disease, depression, and postoperative delirium, illustrating a "disconnection syndrome" where cognitive deficits arise from network disruptions [6-10]. Studying these abnormalities enhances our understanding of disease pathogenesis. Cognition is closely related to brain function, with brain structure and connectivity patterns directly impacting thinking, learning, memory, and other cognitive functions. Investigating this relationship provides insights into the neural basis of cognition and deepens our understanding of the neuropathological mechanisms behind POD.

Relationship between Functional and Structural Connectivity

Functional connectivity refers to the coordinated activity among different brain regions, where neurons interact and transmit signals to process and integrate information. Structural connectivity, on the other hand, denotes the physical connections between brain regions through anatomical fiber tracts. These structural connections form the foundation of neural networks, enabling functional connectivity. While structural connectivity provides the infrastructure for potential functional interactions, the strength and patterns of functional connectivity can vary with cognitive demands or pathological states [7]. For instance, in patients with postoperative delirium, although structural connections remain intact, functional connectivity—such as that between the posterior cingulate cortex within the DMN and other regions—

can significantly weaken, resulting in cognitive dysfunction [11].

EEG and traditional brain functional connectivity indicators

EEG is an electrophysiological technique that records brain electrical activity, making it useful for studying functional connectivity. Compared to other imaging techniques, EEG offers high temporal resolution, capturing real-time statistical relationships between electrical signals across electrodes or brain regions, which helps determine synchronization patterns. However, EEG's spatial resolution is limited, only localizing activity within a 1 cm³ area, making it suitable for comparing connectivity across larger brain regions or lobes.

Phase synchronization, a common measure in EEG studies, assesses functional connectivity between time series [12]. Additionally, graph theory characterizes the topological structure of functional brain networks, while coherence and Granger causality-based indicators are also widely used. Coherence describes the linear correlation between two electrodes or brain regions at a specific frequency, though it is constrained by signal amplitude and the volume conduction effect. Granger causality, a directional connectivity measure, provides insight into information flow direction. Overall, EEG is a flexible and real-time tool for studying brain functional connectivity, enhancing our understanding of cognitive processes and neurological diseases.

fMRI and brain functional connectivity

fMRI is a non-invasive imaging technique widely used to investigate brain functional connectivity by measuring blood oxygenation changes, thereby mapping functional networks within the brain. fMRI enables researchers to identify various functional networks, including the DMN, executive control network, and sensorimotor network, revealing how the brain coordinates tasks across these networks. Seed-based correlation analysis, one of the simplest methods, selects a specific brain region (the "seed") and calculates time-series correlations between this seed and other brain regions to create a connectivity map. Whole-brain, or non-seed-based, connectivity analysis assesses connectivity across the entire brain and often applies graph theory metrics, such as small-world properties and node degree. While the temporal resolution of fMRI is lower than that of EEG and only indirectly measures neural activity, its high spatial resolution (down to 2-3 mm³) allows precise analysis of connectivity between brain regions. Overall, fMRI connectivity analysis is crucial in cognitive neuroscience, neuropsychiatry, and brain disease research, advancing our understanding of the relationship between brain network structure and function.

In patients with postoperative delirium, structural connectivity refers to anatomical links between brain regions, whereas functional connectivity captures the synchronous activity of these regions during tasks. Research shows that disruptions in structural connectivity can result in abnormal functional connectivity, impacting cognitive and emotional regulation—effects particularly prominent in delirium [7, 11, 13]. Thus, exploring these relationships can illuminate delirium mechanisms and inform treatment strategies.

Brain Connectivity Changes in Postoperative Delirium: From DMN to Cognitive Impairment

DMN comprises brain areas more active at rest than during attention-based tasks, including the posterior and anterior medial cortices and the temporoparietal junction [14-16]. As a highly coherent and distinct circuit, the DMN dynamically interacts to regulate sensory, motor, and cognitive functions such as consciousness, memory, and attention [17-21]. In states of severely impaired consciousness, such as vegetative states or coma, DMN connectivity proportionally diminishes [22]. Abnormal DMN activity is also observed in conditions like Alzheimer's disease [23]. Within the DMN, the posterior medial cortex, particularly the posterior cingulate cortex, is a focal area for studies on cognition, attention, and consciousness [24-27]. Given that cognitive and consciousness impairments are hallmarks of delirium, disrupted connectivity between the posterior cingulate cortex and DMN may be a core dysfunction source in delirium patients. Choi et al. proposed that the loss of independence between the DMN and the task-positive network suggests a mechanism related to upregulated inhibitory tension, contributing to diminished or lost consciousness [11].

This finding aligns with the clinical profile of delirium, characterized by inattention, inability to complete simple tasks, confusion, and apathy—symptoms that are present at rest and during tasks. Although the improvement in delirium scores may signal a reduction in clinical symptoms, normal connectivity between functional networks may not fully restore, a phenomenon observed in patients recovering from propofol-induced coma as well [9]. Understanding whether recovery of functional connectivity timing could serve as a prognostic indicator is an intriguing future direction, given that even clinically recovered patients may face risks of poor long-term outcomes or dementia [28, 29].

The Key Role of Subcortical Areas in Postoperative Delirium: Neurotransmitter Abnormalities and Functional Connectivity

Subcortical regions, particularly those related to acetylcholine and dopamine, play a significant role in the pathogenesis of delirium, a condition hypothesized to stem from neurochemical abnormalities [30, 31]. The cholinergic neurotransmitter system, which influences sleep, attention, arousal, and memory, has garnered attention due to the impact of acetylcholine deficiency [32, 33]. Additionally, excess dopamine may contribute by regulating acetylcholine release [11, 34]. Resting-state functional connectivity between brain regions that produce or utilize acetylcholine and dopamine may thus offer insight into delirium's pathophysiology. Building on the hypothesis by Gaudreau and Gagnon, which highlights the importance of the thalamus and the interactions between acetylcholine- and dopamine-related neurons, several subcortical areas (including the thalamic plate nuclei, midbrain cingulate, Meynert's basal nucleus, ventral tegmental area, caudate nucleus, and putamen) emerge as key target regions [34].

In a study by Choi et al. 22 patients underwent resting-state fMRI scans during delirium onset [11]. Using the posterior cingulate gyrus as a seed region, the authors assessed functional connectivity in cortical and subcortical regions related to acetylcholine and dopamine across 20 initial and 13 follow-up scans. Results showed that the interaction between the dorsolateral frontal cortex and the posterior cingulate cortex was disrupted, with a reversible decrease in subcortical functional connectivity, suggesting a pathophysiological basis for delirium [11]. Moreover, enhancing information integration in the posterior medial cortex could facilitate rapid recovery from delirium [11]. Similar findings were observed in EEG-derived functional connectivity studies, where postoperative delirium patients exhibited increased alpha-band excitation, linked to attention deficits [35-37].

Graph Theory and Connectivity: Unveiling Delirium's Neural Dysregulation

Graph theory metrics enable the study of brain network topology, offering insights into the brain's functional segregation and integration. Since the 19th century, it has been recognized that neurons form an intricate structural network, considered essential for information processing and mental representation [38-42]. Graph theory provides a mathematical framework to represent this complex network, with nodes representing brain regions and edges representing anatomical, functional, or effective connections between them.

Graph theory introduces a quantitative approach to analyzing brain connectivity, with recent studies highlighting the "small-world" structure—a network characterized by high clustering and short path lengths—that supports efficient information processing in the brain [13, 43-45]. Various graph theory metrics quantitatively describe the topological structure of the brain network. However, the optimal measures for analyzing brain networks in delirium are yet to be determined.

1. Node Degree [46]: Node degree refers to the number of nodes directly connected to a specific node, or the number of edges connected to it. It is a fundamental network metric, with many other metrics ultimately related to node degree. Node degree measures the importance of a single node within the network.

2. Degree Distribution [47]: Degree distribution describes the distribution of node degrees across all nodes in a network, providing an important measure of network structure and resilience.

3. Assortativity [48]: Assortativity reflects the tendency of nodes to connect to others with similar degrees. Higher assortativity indicates that high-degree nodes are more likely to connect with each other.

4. Clustering Coefficient and Network Motifs [46, 49]: When a node and its closest neighbors are directly connected, they form a cluster. The clustering coefficient is the ratio of actual connections between a node and its neighbors to the maximum possible connections [46]. Network motifs quantify the local connection patterns within the network.

5. Characteristic Path Length (CPL) [46]: CPL is the average shortest path length between all node pairs in a network, commonly used to assess functional integration.

6. Paths, path lengths, and efficiency are based on the shortest path length [46, 50]; a shorter path suggests greater integration potential. Effi-

ciency is inversely related to path length, facilitating the measurement of topological distance between nodes in a non-connected graph.

7. Hubs, centrality, and robustness [47, 51, 52]: Hubs are nodes with high node degree or high centrality crucial for efficient communication as they are part of many shortest paths within the network [51]. The impact of removing a high-centrality node on network efficiency can help evaluate its importance. Robustness refers to the network's structural resilience after node or edge removal, indicating its stability against local or global disturbances.

8. Modular Structure [53]: Complex metrics describe not only the presence of tightly interconnected groups but also their size and composition, forming the network's modular structure. This division into distinct, non-overlapping groups (modules) maximizes connections within groups while minimizing connections between groups.

9. Small-world Property [46]: The small-world property indicates whether a network exhibits small-world characteristics, measured by the metric $\sigma = \gamma/\lambda$, where γ (standardized clustering coefficient) is Creal/Crandom, and λ (standardized shortest path length) is Lreal/Lrandom. A small-world coefficient (σ) greater than 1 suggests the network has small-world characteristics; less than 1 indicates otherwise.

In the study by Van Dellen et al., graph theory was applied to compare the topological maps of functional brain networks between patients with and without postoperative delirium [35]. Results showed that the standardized path length (λ) of the α-band was significantly lower in delirium patients than in non-delirium patients, correlating with the average Phase Lag Index of the α-band [35]. No significant differences were observed in the standardized clustering coefficient (γ) or small-world index between the α-bands of the two groups. However, among delusional patients with hallucinations, the α-band γ was significantly reduced, while λ remained unchanged. The small-world index of the α-band was also significantly lower in patients with hallucinations than those without. This study is the first to use graph theory to characterize the functional network in delusion, demonstrating the valuable role of graph theory analysis in understanding the pathophysiological basis of postoperative delirium [35].

Potential functional connections in the development of postoperative delirium

Recent studies have emphasized the critical role of brain functional connectivity alterations in the development of POD. Specifically, disruptions in key neural networks, such as the DMN, frontoparietal network, and salience network, are associated with POD onset [54]. Functional connectivity within these networks is essential for maintaining cognitive processes like attention, memory, and executive function, which are significantly impaired during delirium [55, 56]. For instance, decreased DMN connectivity, particularly in the posterior cingulate cortex, has been linked to cognitive disturbances in POD patients [54, 57]. Abnormal connectivity in the frontoparietal network may contribute to attentional deficits characteristic of delirium, while changes in the salience network may impair the brain's ability to appropriately filter and respond to environmental stimuli [55]. Understanding these connectivity changes is crucial for developing targeted interventions to prevent or alleviate POD.

Brain functional connectivity in patients with different surgical types

Different surgeries may influence brain function in unique ways; for instance, cardiac, orthopedic, and abdominal surgeries can trigger varying inflammatory responses, hypoxia, or other physiological stressors, potentially altering brain functional connectivity patterns [56, 58, 59]. However, some studies suggest that despite differences in surgical type, patients with POD may exhibit similar connectivity changes, especially reduced connectivity within the DMN and frontoparietal network [58, 59]. The common underlying mechanisms associated with POD—such as neuroinflammation, blood-brain barrier disruption, and neurotransmitter imbalances—are likely to impact brain functional connectivity across different surgical types [60]. Consequently, POD patients may exhibit certain connectivity patterns regardless of surgery type.

Both EEG and fMRI have inherent limitations in practical applications, due to their low spatial and temporal resolutions, respectively. Despite this, this review demonstrates that using both EEG and fMRI can produce reliable findings. To overcome these limitations, future research could combine EEG and fMRI, allowing for the collection of data with both high temporal and spatial resolutions to enhance the analysis of brain functional connectivity.

Additionally, traditional brain functional connectivity measures and graph theory each have unique advantages and limitations in neuroscience research. Traditional measures provide an intuitive spatial distribution of brain activity but may be limited by technical constraints and interpretive complexity. In contrast, graph theory offers an abstract, mathematical approach, describing network topology and node relationships and allowing a comprehensive network structure analysis. However, it may lack the intuitive neurobiological details essential for interpreting specific mechanisms. Therefore, combining these methods often yields more complete insights in neuroscience research.

Research on changes in brain functional connectivity in POD patients remains limited, typically focusing on a single type of surgery. Larger sample sizes are necessary to validate current findings, and it remains uncertain whether these findings can be generalized to monitor delirium in patients undergoing other surgeries. Future studies should gather data from patients across various surgical types, stratify them, and analyze postoperative connectivity changes to extend these findings to broader populations.

From an informational perspective, brain information processing is dynamic, encompassing perception, transmission, coordination, storage, and generation of information. Even in stable environments, the brain functions as a dynamic information-processing system. Current measures of functional connectivity—both traditional and graph theory-based—are generally static, potentially limiting their capacity to capture the brain's dynamic state changes. Therefore, applying sliding time-window analysis techniques could be advantageous for tracking the dynamics of brain functional connectivity. This approach may offer valuable insights into the fundamental properties of brain networks and the temporal dynamics of brain function, representing a promising direction for future research.

Conclusion

In summary, this article explores the intricate relationship between POD and changes in brain functional connectivity. Various types of surgeries, including cardiac, orthopedic, and abdominal surgeries, contribute to distinct physiological stressors, such as inflammation and hypoxia, which can lead to disruptions in neural communication and connectivity patterns within critical brain networks like the DMN and executive networks. These disruptions play a central role in the cognitive impairments observed in POD.

Advances in neuroimaging techniques, such as fMRI and EEG, have provided valuable insights into the dynamic changes in brain connectivity associated with POD. By applying tools like graph theory to study the organization of brain networks, researchers have identified key areas of dysfunction, including the posterior cingulate cortex and regions within the DMN, which are vital for cognition, attention, and consciousness.

Future research should focus on understanding how different surgical interventions impact brain functional connectivity and how these effects may vary across patients, especially considering factors such as age, pre-existing cognitive conditions, and surgical complexity. Moreover, integrating EEG and fMRI data, along with the application of advanced computational techniques, will enable more accurate and dynamic monitoring of brain connectivity in POD patients. As we continue to explore the neurophysiological mechanisms underlying POD, these findings have the potential to guide more effective interventions and preventive strategies for improving patient outcomes following surgery.

Author contributions: Tuo Deng drafted the manuscript. Changkuan Tan and Guangkuo Ma provided suggestions for revising the paper. Meiyan Zhou and Liwei Wang polished the paper.

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