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A review on Angelica sinensis alleviates acute lung tissue injury through TLR-4/MyD88 signal pathway

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Highlights

- This review describes the main components of Angelica sinensis and their efficacy.
- Current status and basic mechanisms of the classical inflammatory signal pathways in lipopolysaccharide-in -duced acute lung injury (ALI) are discussed.
- Angelica sinensis contributes to the anti-inflammation in lipopolysaccharide-induced ALI and is expected to ex pand the application of traditional Chinese medicine in the treatment of ALI.

Abstract

Angelica sinensis (AS), commonly known as Danggui and hailed as a premier medicinal herb, holds a prominent place in traditional Chinese medicine due to its potent healing properties. It is widely used to boost blood and vital energy, promote blood flow, relieve blood stasis, regulate menstruation, and alleviate pain. With advances in medical technology, modern interest in Chinese medicine has surged, spurring more in-depth research into its pharmacological mechanisms. This review introduces the principal components of AS and its therapeutic efficacy, while also summarizing current research on fundamental mechanisms involving key inflammatory signal pathways, notably nuclear factor κB and mitogen-activated protein kinase. Z-Ligustilide, AS's primary bioactive compound, exhibits a range of pharmacological effects, including anti-inflammatory, anticancer, neuroprotective, anti-apoptotic, organ-protective, antioxidant, and analgesic properties. In addition to discuss the advancements in the treatment of acute lung injury (ALI), this review provides a detailed exploration of the main components of AS and its mechanisms for mitigating ALI induced by lipopolysaccharides, with the aim of providing a theoretical basis and inspiration for the development of drugs in Chinese medicine, with AS as a representative example. This manuscript offers a novel therapeutic method for clinical management of ALI, thereby presenting additional alternatives for pharmacological intervention.

Keywords: Angelica sinensis, ligustilide, anti-inflammation, acute lung injury, lipopolysaccharide, nuclear factor κB, mitogen-activated protein kinase, toll-like receptor 4, myeloid differentiation primary response 88

Introduction

Acute lung injury (ALI) is a common clinical complication of sepsis with high mortality rate. It is characterized by the sudden onset of respiratory insufficiency or failure, primarily triggered by non-cardiogenic factors such as severe infections, shock, trauma, and burns. At present, there are still no effective and specific therapeutic methods in treatment. Further research is required to explore specific and effective targeted inhibitors to interrupt lung injury based on different types of pathogens. Angelica sinensis (AS), known as the 'king of medicines' in traditional Chinese medicine, is a perennial herbaceous plant with its highest quality cultivation in southeastern Gansu, particularly Minxian County. The roots of AS are highly valued for

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their medicinal properties, including nourishing qi and blood, enhancing blood circulation, supporting cardiovascular health, regulating menstruation, relieving pain, moisturizing dryness, promoting gastrointestinal motility, and providing anticancer, anti-aging, hepatoprotective, neuroprotective, and immune-boosting benefits [1, 2]. Typically, the dried root of AS, harvested in late autumn, is used for medicinal purpose. This root is slightly cylindrical, with sections known as the 'head' (upper root), 'body' (primary root), and 'tail' (smaller branch roots). Its chemical composition includes volatile oils, polysaccharides, organic acids, and amino acids [2].

AS extract has demonstrated significant analgesic and anti-inflammatory effects, increasing the pain threshold in mice exposed to thermal stimuli and inhibiting the torsion response induced by acetic acid and other chemical irritants [3]. Ligustilide is a naturally occurring phthalide derivative and an active ingredient of AS, exhibits a wide range of pharmacological activities, including anti-atherosclerotic, neuroprotective, anti-cardiac hypertrophic, anti-inflammatory, and analgesic effects [4].

Major components and biological activities of AS

Angelica sinensis polysaccharide (ASP)

Recent studies have demonstrated that polysaccharides from Chinese herbs possess significant anti-tumor effects [5]. ASP, one of the principal bioactive constituents of AS. Typically obtained through aqueous alcohol extraction. ASP mainly consists of monosaccharides, such as glucose, galactose, and xylose, as well as acidic polysaccharides, including D-xylose and D-galactose. Research has revealed its immunomodulatory activity and diverse analgesic properties, such as the alleviation of uterine spasms induced by caprylyl estriol and histamine in mice [6]. Zhang's study demonstrated that ASP could reduce astrocyte apoptosis in the midbrain of mice with Parkinson's disease by inhibiting the Bax/Bcl2/Caspase-3 apoptotic signal pathway [7]. Furthermore, ASP shows therapeutic potential for osteoarthritis by inhibiting the nuclear factor κB (NF-κB) signal pathway [8]. Zhou's research found that an overdose of AS can significantly improve peripheral nerve injury in rats with diabetic neuropathy, potentially through blocking the toll-like receptor 4 (TLR-4)/myeloid differentiation primary response 88 (MyD88)/NF-κB inflammatory signal pathway [9].

AS volatile oil

The organic compounds of AS, such as its essential oil, are typically extracted using organic solvents or distillation. Due to its muscular irritability and limited stability, AS volatile oil is generally applied as a clathrate to enhance its stability in practice [10]. Z-Ligustilide, a key active component in AS volatile oil, exhibits diverse biological activities, including tumor inhibition, neuroprotection, anti-Alzheimer's effects, suppression of cardiac hypertrophy, anti-atherosclerosis, anti-inflammation, analgesic effects, cardiovascular system support, immunity enhancement, and cognitive function improvement [11]. AS volatile oil has shown significant inhibitory effects in animal models via mouse hot plate and writhing tests [3]. Additionally, Z-Ligustilide has demonstrated promising results in reducing pain responses induced by acetic acid and thermal stimuli in mice, as well as mitigating persistent pain caused by administration of complete Freund's adjuvant [4, 12].

Organic acids of AS

The primary organic acids in AS, shellacenoic acid and hesperidinic acid, have been shown to exhibit strong bacteriostatic effects against Pseudomonas aeruginosa, a pathogen predominantly affecting the respiratory system [13]. Furthermore, optimized organic acids can inhibit the expression of protein Jun NH2-terminal kinase (p-JNK) in lung tissues to various extents, underscoring their potent anti-inflammatory properties. In a rat model of lipopolysaccharides (LPS)-induced inflammatory pain, AS organic acids reduced blood levels of tumour necrosis factor alpha (TNF-α) and nitric oxide when combined with kaurenoic acid and pimaric acid in a 4:5 ratio [14]. Additionally, AS organic acids have been demonstrated to significantly alleviate inflammation in mice exposed to formalin [14].

Amino acids of AS

Amino acids, the fundamental units of proteins, are commonly present in various Chinese herbs. AS contains over 10 kinds of amino acids, with arginine, γ-aminobutyric acid and glutamic acid being the most abundant. Among different AS samples with different drying methods, total amino acids reached as high as 61.79 mg/g on average, while essential amino acids were 3.37 mg/g on average, confirming the high nutritional value of AS [15]. Wei et al. suggested that this variation may be attributed to the internal structural composition of the

medicinal material and the specific soil environment of each part [16]. Additionally, Liu et al. identified distinctive differences in amino acid content across various medicinal parts of AS [17]. For AS from different geographical origins, glutamic acid and methionine stand out as the amino acids with the most pronounced variation [18].

Other components

AS is rich in trace elements, including flavonoids, vitamins, Mn^{2+}, and other essential components vital for the body's metabolic processes [18]. **Table 1** summarizes the main bioactive components of AS and their chemical formulas.

Research on LPS-induced ALI

The etiology and pathogenesis of ALI

ALI is a common and serious complication in patients with sepsis, primarily triggered by trauma, infection, and shock, and is clinically characterized by progressive hypoxemia and dyspnea. If left untreated, ALI can progress to acute respiratory distress syndrome. Key factors in the development of ALI include apoptosis, lung fibrosis, oxidative stress, and inflammatory responses [19]. In the early phase of ALI, stimuli such as LPS prompt alveolar macrophages to produce and release numerous inflammatory factors, including IL-1, TNF-α, and NF-κB. This buildup of activated inflammatory cells and cytokines initiates an inflammatory cascade that damages lung epithelial cells, leading to the accumulation of protein-rich fluid, pulmonary edema, lymphocytic infiltration, and ultimately, lung fibrosis. Early intervention to suppress inflammatory responses and protect vascular endothelium is thus critical in ALI treatment, particularly through the inhibition of inflammatory responses and the TLR-4-mediated inflammatory signal pathway [20].

LPS, a key component of Gram-negative bacterial membranes, is frequently used to model ALI due to its potent inflammatory effect. ALI models can be created via intra-airway instillation or intraperitoneal injection of LPS in mice, with experimental evidence suggesting that intra-airway delivery of LPS provides higher efficacy in modeling ALI [21].

Inflammation signal pathways of LPS-induced ALI

TLR-4/MyD88

LPS initiates an inflammatory response primarily by interacting with TLRs in mammals. The TLR family consists of 13 distinct members, each specific to certain ligands; among these, TLR-4 is specialized for recognizing LPS. The Myeloid differentiation factor 88 (MyD88) protein plays a pivotal role as a linking molecule in the TLR-4/MyD88/NF-κB inflammatory pathway. TLRs operate through two signal pathways: the MyD88-dependent pathway and the MyD88-independent pathway [22]. Initially, the MyD88 molecule binds to the TLR, subsequently associating with interleukin receptor-associated kinase, which activates inhibitor of nuclear factor kappa-B kinase (IKK). This activation leads to the degradation of the NF-κB inhibitory protein, enabling NF-κB to enter the nucleus and promote the transcription of inflammatory genes.

NF-κB

The NF-κB molecule is a dimer composed of NF-κB1 (p50) and RelA (p65). When bound to IκB, NF-κB remains inactive. In the presence of inflammatory factors, signaling molecules bind to receptors on the plasma membrane, initiating a signaling cascade that activates IKK. As a kinase for IκB, IKK induces the phosphorylation of IκB, leading to its degradation and allowing NF-κB to dissociate and activate. The active NF-κB then translocates to the nucleus, where it promotes the transcription of downstream genes and facilitates cytokine release, thereby initiating a cascade of inflammatory responses [23].

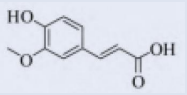
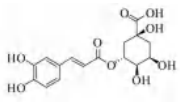
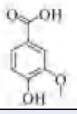
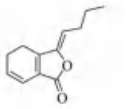
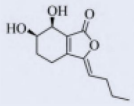
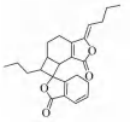
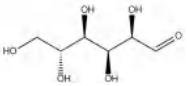
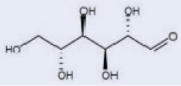
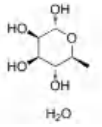
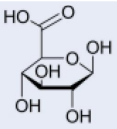
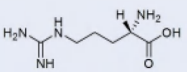
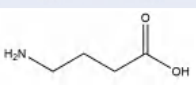
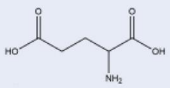
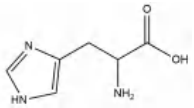
TLR-4/MyD88/NF-κB inflammation pathways

The NF-κB signal pathway is involved in inflammatory responses, oxidative stress, and apoptosis, regulates coagulation and fibrinolysis in lung tissue, and plays a crucial role in the onset and progression of ALI [24]. A study by Wang et al. demonstrated that fecal microbiota transplantation could alleviate LPS-induced ALI in rats via the TLR-4/NF-κB signal pathway. In the lung tissue of the fecal transplant group, levels of TLR-4 and NF-κB p65 were reduced, indicating that inhibiting the immune-inflammatory response can significantly aid in lung tissue recovery [25]. Additionally, TAK242 was shown to improve blood oxygen saturation in acute respiratory distress syndrome mice by inhibiting TLR-4 and NF-κB expression in lung tissues and reducing serum levels of inflammatory factors, including IL-6 and IL-18 [26].

mitogen-activated protein kinase (MAPK)/AP-1

Inflammatory factors recognize receptors

Table 1. Table of the main active ingredients of AS and its chemical structure formulas

Compound name	Chemical structure	CAS number
Organic acids		
Ferulic acid		1135-24-6
Chlorogenic acid		327-97-9
Nicotinic acid		59-67-6
Vanillic acid		121-34-6
volatile oil		
Z-Ligustilide		81944-09-4
Senkyunolide H		114586-51-5
Angelicid		92935-94-9
Polysaccharide		
Glucose		14431-43-7
Mannose		69-65-8
rhamnose monohydrate		10030-85-0
Glucuronic acid		6556-12-3
Amino acids		
L-Arginine		74-79-3
γ-aminobutyric acid (GABA)		56-12-2
L-Glutamic acid		56-86-0
L-Histidine		71-00-1

on the plasma membrane, initiating signal transmission into the cell. Through a series of cascade reactions, downstream MAPK protein kinases (MEKK) are activated, which, in turn, activate downstream MAPK kinases. This process ultimately activates p38 MAPK, extracellular signal-regulated kinase (ERK), and c-JNK, conveying signals to the nucleus to regulate gene expression. Another downstream pathway of TLR signaling involves the transcription factor AP-1 (activator protein 1), which regulates the expression of inflammatory factors [27]. Composed of c-Fos and c-Jun, AP-1 primarily mediates inflammation via the MAPK pathway. Key regulators of AP-1 transcription include p38 MAPK, JNK, and ERK, with the JNK/p38 MAPK pathway chiefly responsible for cytokine production and inflammatory responses, while the ERK pathway is primarily involved in cell proliferation, differentiation, apoptosis, and various pathological processes [28].

TLR-4/MAPK/AP-1 inflammation pathways

The MAPK inflammatory signal pathway is prevalent in lung tissue cells. Studies have shown that suppressing the p38 MAPK pathway can significantly reduce lung injury in ALI mice, likely by controlling cell apoptosis and regulating inflammation [29]. Additionally, MAPK is involved in respiratory bursts by modulating neutrophil activity [30]. Research has demonstrated that phosphorylated p38 MAPK promotes the production and release of inflammatory factors and induces overexpression of adhesion proteins, such as COX-2, thereby enhancing transcription factor activity.

In Gan's study, using an LPS-induced ALI mouse model, increased mRNA expression of p-p38 MAPK, c-fos, and c-jun were observed in the experimental group [28]. This suggests that activation of the p38 MAPK/AP-1 signal pathway may play a role in the early inflammatory response in ALI.

Therapeutic effects of AS on LPS-induced ALI

AS affects the inflammatory factors

Growing evidence indicates that inflammatory factors play significant roles in the development of LPS-induced ALI, making modulation of this pathway a promising strategy for treatment. Studies have shown that ferulic acid, an organic acid derived from AS, can effectively alleviate lung tissue edema and reduce inflammatory cells in the alveolar septum in mice with LPS-induced ALI by inhibiting the release of inflammatory mediators. Compared to the LPS model group, serum levels of TNF-α, IL-6, and IL-1β were significantly decreased in the ferulic acid treatment group [30].

In Zhu's study, ligustilide, a component of AS volatile oil, significantly reduced pulmonary interstitial inflammatory cell infiltration, interstitial pulmonary edema, and alveolar wall thickening, thus mitigating alveolar damage. Additionally, it decreased the total cell count, neutrophil ratio, total protein, as well as TNF-α and IL-1β levels in bronchoalveolar lavage fluid. Its therapeutic effect may be associated with the reduction of key pro-inflammatory cytokines in lung tissue, such as TNF-α and IL-1β [31].

AS influences NF-κB inflammatory signal pathway

Decursinol angelate, an active ingredient of AS, is a promising candidate for ALI treatment. By inhibiting the AKT/NF-κB signal pathway in LPS-induced ALI, decursinol angelate alleviates cell damage and apoptosis, reduces oxidative stress, and mitigates inflammation [32]. Treatment with decursinol angelate decreases the expression of TNF-α, IL-1β, and IL-6, while inflammation is further suppressed by reducing the phosphorylation of p65, IκBα, and AKT, thereby preventing p65 from entering the nucleus.

In Zheng's experiments, ligustilide was shown to inhibit the stimulator of interferon genes (STING)/tank-binding kinase 1/NF-κB signal pathway, and reduce lung tissue damage in a mouse model of LPS-induced ALI [33]. STING activates NF-κB, with p65 as its central component. It has been demonstrated that ligustilide specifically inhibits NF-κB activity by reducing the expression of p65 and STING, effectively alleviating lung tissue inflammation and oxidative damage.

The combination of safflower and AS improved inflammatory infiltrates in the lungs and reduced alveolar wall thickening in an LPS-induced ALI mouse model [34]. The synergy of safflower with AS effectively regulates the phosphorylation of ERK1/2 and p38, which reduces IκB depolymerization and NF-κB p65/p50 activation, limiting the nuclear transport of NF-κB p65/p50 and exerting anti-inflammatory effects. This, in turn, mitigates immune cell apoptosis and helps prevent lung damage.

ALI can progress to pulmonary fibrosis. In a pulmonary fibrosis mouse model, ligustilide treatment significantly reduced the protein expression of TLR-4, MyD88, and NF-κB p-P65/P65.

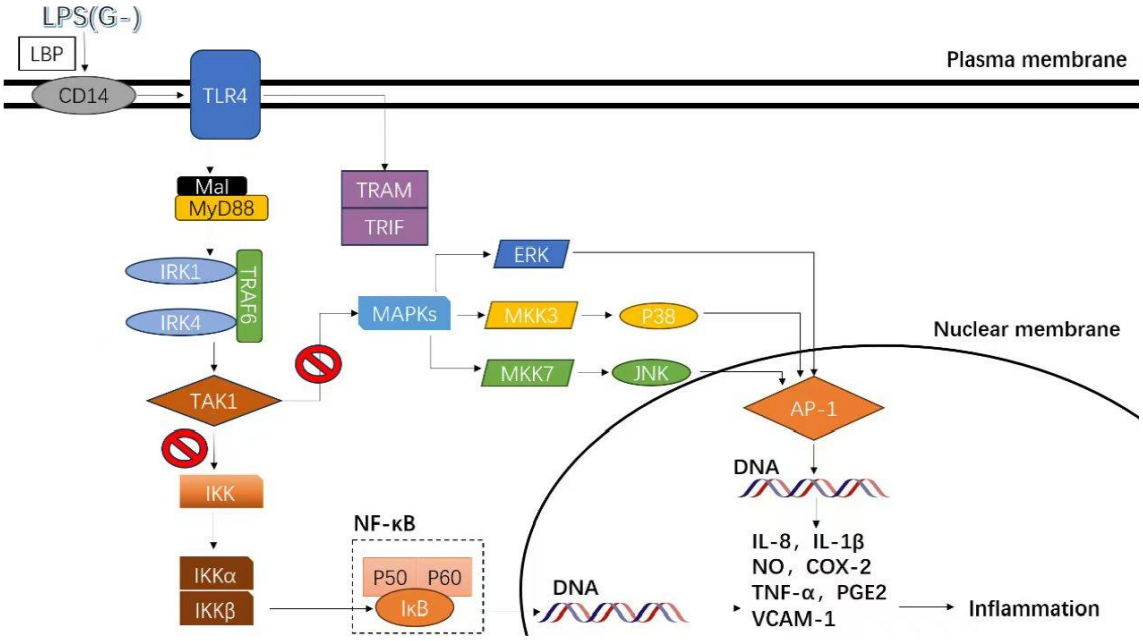


Figure 1. Diagram of the effects of Angelica sinensis on the signalling pathway.

Additionally, ligustilide demonstrated inhibition of oxidative stress and apoptosis in mice with pulmonary fibrosis [35]. These results indicate that ligustilide improves pulmonary fibrosis by enhancing ventilation, reducing fibroblast proliferation, and decreasing oxidative stress and apoptosis via the TLR4/MyD88/NF-κB P65 signal pathway. **Figure 1** reveals that ligustilide reduces the production of inflammatory factors by affecting the TLR4/NF-κB pathway.

AS regulates MAPK inflammation pathways

Traditional Chinese medicine can enhance immune function in the lungs, reduce inflammatory damage to lung tissue, and alleviate ALI symptoms by modulating macrophage activity [36]. In a study by Won et al., Z-ligustilide demonstrated anti-inflammatory effects by regulating NF-κB and MAPK signal pathways in LPS-stimulated RAW264.7 macrophages [37]. Their results showed that Z-ligustilide inhibited the phosphorylation and subsequent degradation of IκBα (an NF-κB inhibitor), as well as p38 MAPK, ERK, and JNK, in a dose-dependent manner.

The Chuanxiong Rhizome and Paeoniae Radix Rubra herbal pair (CX-CS), a traditional Chinese medicine formula for treating ALI, includes AS as one of its components. Studies indicate that CX-CS effectively suppresses LPS-induced ALI by reducing the release of TNF-α, IL-1β, and IL-6. Additionally, CX-CS inhibits the expression of p38, ERK, IκBα, p65, caspase 3, and PARP, while upregulating AKT and the Bcl-2/Bax ratio [38]. This study confirms the synergistic effect of the CX-CS herbal pair in preventing ALI by mitigating inflammation, oxidative stress, and apoptosis through the MAPK/NF-κB and PI3K/AKT signal pathways.

Figure 1 reveals that ligustilide reduces the production of inflammatory factors by affecting the TLR4/MAPK pathway.

Conclusion

The traditional Chinese medicine AS has demonstrated significant medicinal value, particularly for its antibacterial, analgesic, and anti-inflammatory properties. While AS exhibits a broad spectrum of therapeutic effects, this review focuses specifically on its anti-inflammatory role in LPS-induced ALI.

The principal components of AS include ASP, volatile oils, organic acids, and amino acids. This review introduces these key active ingredients and provides a table summarizing their chemical structures to support further research.

Apoptosis, lung fibrosis, oxidative stress, and inflammatory responses are critical factors in the progression of ALI. Therefore, early suppression of the inflammatory response and protection of the vascular endothelium are crucial for effective ALI treatment.

Growing evidence suggests that AS and its extracts can mitigate ALI by inhibiting the NF-κB inflammatory signal pathway and reducing inflammatory cytokine release. Thus, modulating

this pathway presents a promising strategy for treating LPS-induced ALI. AS and its extracts are known to alleviate inflammation by directly suppressing immune cell activity and modulating various inflammatory mediators and signaling molecules. However, the specific role of AS in ALI remains underexplored and warrants further experimental investigation. Currently, no studies have directly demonstrated that AS exerts its pharmacological effects through particular inflammatory signal pathways, such as TLR-4/MyD88/NF-κB and TLR-4/MAPK/AT-1.

This review summarizes the impact of AS and its extracts on LPS-induced ALI, suggesting that AS may inhibit inflammatory factor release by blocking the TLR-4/MyD88/NF-κB and TLR-4/MAPK/AT-1 signal pathways. Inhibiting these pathways ultimately alleviates lung epithelial cell damage, and reduces protein-rich fluid accumulation, pulmonary edema, lymphocytic infiltration, and lung fibrosis.

In the context of integrating Chinese and Western medicine, numerous scientific methodologies are available to explore the efficacy and mechanisms of Chinese medicine. This integration offers a novel perspective on traditional Chinese medical culture and opens new avenues for natural therapeutics. It is anticipated that, in the near future, new anti-inflammatory drugs incorporating AS extracts will become available for clinical use, marking a continuation of Chinese medical traditions. With advancements in modern medical technology, Chinese medicine—exemplified by AS—continues to demonstrate remarkable vitality.

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Research progress of digital therapy in pain management

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Highlights

- Analysis of collected data reveals that digital therapy offer new treatment methods and options in the field of pain management. After conducting research and analysis, it has been found that digital therapeutics offer new treatment methods and options, especially in the area of perioperative pain management.
- Multiple clinical studies indicate that digital therapy has significant effects in the treatment and relief of pain caused by various conditions.
- Domestic and international policies have positively influenced the development and progress of digital therapy.
- Ethical considerations require continuous evaluation, decision-making, and regulation, warranting ongoing re flection.
- Digital therapeutics, as an emerging intervention for pain, are propelling perioperative pain treatment towards a diversified and personalized comprehensive diagnostic and treatment model.

Abstract

Pain significantly impacts both the physical and mental well-being of individuals and imposes a substantial burden on society. Traditional pain management approaches are diverse but often fall short in adequately addressing patients' emotional and psychological experiences. In recent years, digital therapy has emerged as a rapidly developing field with significant potential in perioperative pain management. This innovative approach leverages digital technology, particularly cognitive-behavioral therapy, to alleviate pain and deliver more comprehensive, efficient, and personalized care. This study explores the applications and future directions of digital therapy in pain management, aiming to broaden understanding among healthcare professionals and patients, and to open new

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avenues for pain treatment. The text combs through the synergistic empowerment of digital therapeutics in the perioperative period, discussing its multifaceted advantages such as optimizing analgesic effects, reducing mental anxiety, and improving psychological conditions. It also analyzes current challenges including privacy protection, data security, and technological adaptation, providing a reference for future research and application directions in digital pain treatment during the perioperative period.

Keywords: Pain, digital therapy, virtual reality, pain management, cognitive-behavioral therapy

Introduction

Pain is a prevalent health concern, with chronic pain, defined as pain persisting or recurring for more than three months, posing a particularly severe societal burden [1, 2]. Managing chronic pain has long been challenging, as traditional pain treatment methods, including pharmacological, physical, and surgical interventions, are often associated with side effects or limitations. Especially during the perioperative period, which is a critical accompaniment to surgical treatment, there are higher demands on the medical team. If pain management during the perioperative period is inadequate, it can lead to numerous complications for patients, increasing medical costs and the difficulty of recovery. In this context, digital therapy has garnered increasing attention as an innovative therapeutic option.

With the rapid development of digital technology, digital therapeutics have demonstrated numerous advantages such as personalization, convenience, and remote monitoring, as well as unique potential in pain treatment. However, the application of digital therapeutics in pain treatment is still in a phase of continuous exploration and development, and further in-depth research is needed in terms of efficacy, safety, and reliability. Therefore, a comprehensive review of the research progress of digital therapeutics in pain treatment is presented, along with a graphical summary (see **Figure 1**). It is hoped that through this visual presentation, medical practitioners and researchers can quickly understand the cutting-edge dynamics in this field, providing new ideas for future research and clinical application in the field of pain treatment.

Current status of pain management

Statistics show that approximately 20% of patients globally experience pain, with chronic pain accounting for about 50% of these cases [3]. Chronic pain, characterized by its long-term and persistent nature, inflicts significant physical and psychological harm on patients. In China, the number of chronic pain patients exceeds 300 million and is rapidly increasing, with a trend towards younger patients [4]. This trend is expected to worsen as the population ages. Despite the widespread and detrimental nature of pain, there remains a lack of focus on pain management across various specialties, and current clinical pain treatments have yet to fully satisfy both patients and healthcare providers.

According to guidelines and consensus from the Pain Society of the Chinese Medical Association, pain management begins with preventive strategies, lifestyle modifications, and rehabilitation as initial treatments [5]. Pharmacological treatments, including nonsteroidal anti-inflammatory drugs, opioid analgesics, ion channel blockers, and antidepressants, are commonly used for pain management [6, 7]. However, long-term use of medications inherently carries risks and potential dependency. When medications fail to alleviate pain or cause adverse effects, minimally invasive interventional pain techniques are available as alternatives [8]. Research indicates that 64% of chronic pain patients are dissatisfied with the pain relief achieved through various treatments, with complete relief rates of less than 20% [9].

The absence of objective measures for pain introduces significant variability in causes, tolerance levels, and treatment responses, presenting challenges for accurate diagnosis and treatment. Furthermore, the establishment of pain management departments in China is relatively recent, having developed only within the past decade, leading to limited awareness of pain management among both medical professionals and the public. Given these obstacles, pain management faces pressing questions: What specific problems and challenges does it confront? Should alternative methods be explored to improve treatment outcomes? There is an urgent need to explore new treatment options, with digital therapy emerging as a promising, effective approach for pain management.

Overview of digital therapy

Definition of digital therapy

Digital therapy (DTx) is a novel concept in the field of medical technology, driven by software programs and grounded in evidence-based

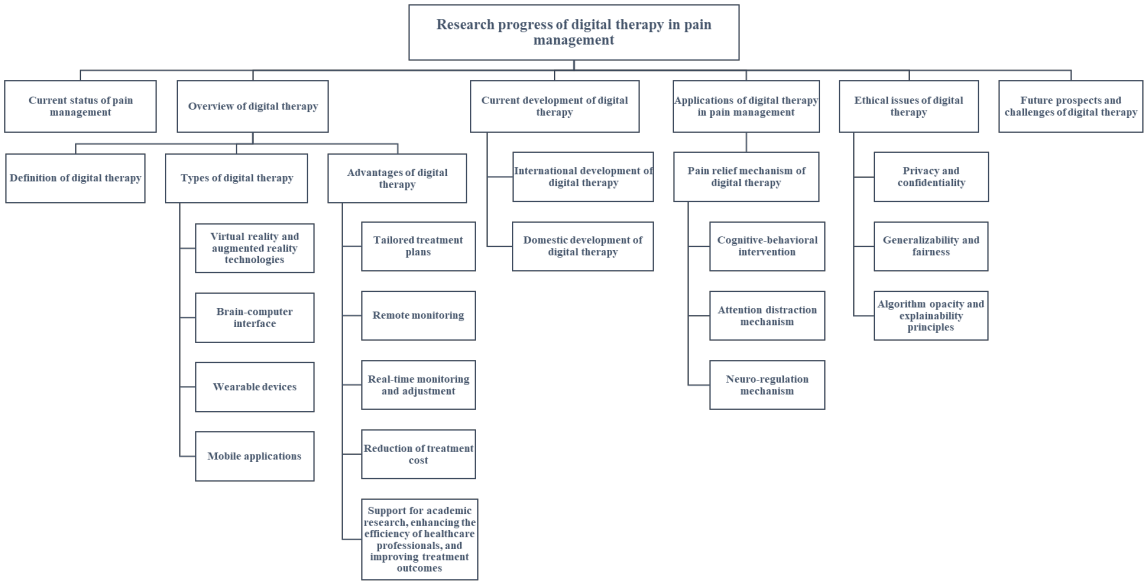

Figure 1. Digital therapeutics in pain treatment research progress analysis chart.

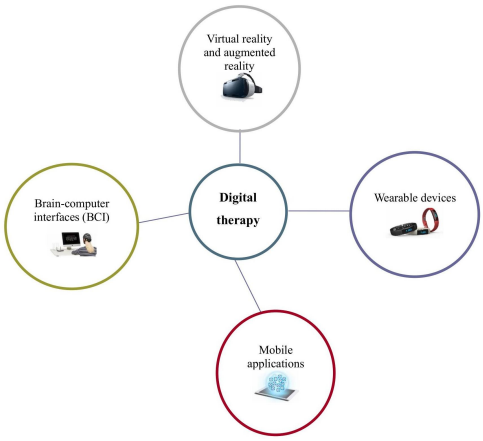

Figure 2. The main types of digital therapy.

medicine. It involves intervention schemes designed to treat, manage, or prevent diseases [10]. In terms of product form, the core of digital therapy is computer software that can be used independently or in conjunction with other medications. Diseases characterized by long management cycles, multiple intervention measures, poor patient adherence, low levels of patient self-management, and clear clinical guidelines are particularly suitable for the treatment with digital therapeutic products [11]. These are the primary application areas for digital therapy.

Types of digital therapy

At present, the main types of DTx include Virtual Reality (VR) and Augmented Reality Technologies, Brain-Computer Interfaces, Wearable Devices, and Mobile Applications (**Figure 2**). Since DTx covers a broad range, its main types include but are not limited to the descriptions mentioned above, and also encompass sub-branches under the main types or other types that have not been explicitly classified.

1. VR and Augmented Reality Technologies [12]: VR is used in psychological therapy or rehabilitation training by immersing patients in therapeutic scenarios, thereby enhancing treatment efficacy. By leveraging big data and artificial intelligence, VR and Augmented Reality technologies can provide customized treatment plans based on individual patient characteristics and specific conditions.

2. Brain-Computer Interfaces [13]: This technology establishes a direct connection between the brain and external devices, allowing users to control external devices through conscious thought or brain signals. This “dialogue” between the brain and machines facilitates the acquisition of external information.

3. Wearable Devices [14]: Essential to digital therapy, wearable devices include smart wristbands, electrocardiogram monitors, and physiological trackers for sleep, heart rate, and blood pressure monitoring. They enable continuous health data recording and management, with features like vibration feedback supporting remote treatment by healthcare providers.

4. Mobile Applications [15]: These applications support mental health and disease management, promoting patient-centered care and autonomy in managing health conditions.

Advantages of digital therapy

Digital therapy leverages virtual reality technology and other digital tools, transforming real medical principles into software-driven interventions. They represent an innovative approach that extends beyond traditional treatment limiations and serve as a complement and optimization of conventional therapies [16].

VR technology is a novel alternative for pain management and has shown significant effectiveness in various acute pain treatments [17]. Despite the complex pathophysiology that drives the transition from acute to chronic pain, VR technology has also demonstrated benefits in managing chronic pain [18]. For instance, Sam et al. conducted a study on VR-based pain relief [19]. They recruited 15 volunteers, applied capsaicin to induce a pain model on their legs, and simulated chronic pain with electric shocks. Volunteers used VR to either experience an Arctic adventure or view static images to alleviate pain. The results showed that immersive VR reduced both pain and sensitivity, supporting the hypothesis that "immersive VR reduces pain by distracting attention."

Compared to traditional therapies, digital therapy offer several advantages:

1. Targeted Treatment Plans: Provides targeted therapeutic options based on individual patient conditions.

2. Remote Monitoring: Enables disease intervention at home, making treatment more accessible and convenient.

3. Real-Time Monitoring and Adjustment: Facilitates timely interventions and adjustments through real-time data monitoring and recording.

4. Cost Reduction: Reduces treatment costs and lessens the economic burden on patients.

5. Support for Academic Research [16]: Enhances the of healthcare professionals' efficiency, and improves treatment outcomes.

Current development of digital therapy

International development of digital therapy

With rapid advancements in science and technology, a new technological revolution, led by artificial intelligence, is driving a global innovation, including the integration of advanced technologies into healthcare. This integration aims to improve the current medical environment and has spurred the concept of digital therapy. DTx, introduced by Joseph Kvedar, provides effective, evidence-based medical interventions driven by high-quality software [10, 20]. The approval of digital therapy prescription products by the U.S. Food and Drug Administration, such as the BlueStar® diabetes management platform depression treatment platforms, and treatments for substance abuse, marks the entry of digital therapy into clinical practice as an effective complement to traditional therapies [21-23].

Government support has significantly accelerated the progress of digital therapy. However, only a few countries have implemented related policies for the practical execution of digital therapy. The United States has a relatively mature registration and approval process for digital therapy products, having introduced the Digital Health Pre-Certification Program in 2017 and initiated pilot projects for digital health and certification [24]. In 2019, Germany proposed public access to digital therapeutic products free of charge, incorporating them in the health insurance reimbursement scope, while Belgium approved similar reimbursement schemes [25, 26]. In 2020, South Korea released approval guidelines, paving the way of digital therapy regulation [27]. Currently, digital therapies are widely used abroad in areas such as chronic diseases, mental health, neurological disorders, and other conditions, with national approval systems taking shape.

Additionally, countries like the UK, France, and Australia have adopted effective measures to ensure the legality and compliance of digital therapy, even without fully developed regulatory frameworks [28].

Domestic development of digital therapy

Compared to international advancements, digital therapy in China began later and remains in the early stages, with few mature solutions currently established. Globally, definitions and regulations for digital therapy are still evolving, and China has yet to adopt a clear official definition. In February 2017, the National Medical Products Administration categorized digital therapy as conventional medical devices in the "Guiding Principles for Technical Review of Mobile Medical Devices" [29].

Approval systems, clinical trial results, business models, and insurance reimbursement for digital therapy are still under exploration. However, with ongoing policy improvements and increasing market demand, digital therapy has gained attention, and prospects for development in

China appear promising.

Following the outbreak of COVID-19 in early 2020, digital technologies rapidly advanced in the healthcare field. That year, a digital therapy product in China received one of the first National Medical Products Administration approvals, permitting direct doctor prescriptions. Subsequently, the government initiatives like the "Healthy China 2030" Planning Outline and the "14th Five-Year Plan" for Bioeconomic Development, have emphasized the construction and application of innovative therapies, supporting the development and innovation of digital healthcare technologies [30]. With policy guidance and expert advice, domestic digital therapy companies have made progress in areas such as pain management. For instance, in 2023, Suzhou Reacool Medical Technology Co., Ltd. obtained the first national approval for a digital pain relief rehabilitation product [31].

Digital therapy not only reduces treatment costs but also facilitates the transformation of treatment methods, complementing or even substituting traditional therapies. According to ClinicalTrials.gov, as of July 2022, there were 5,291 clinical studies on digital therapy globally, with approximately 300 studies in China [32]. The shift toward clinical-oriented medical innovation and the integration of medicine and engineering is expected to drive the widespread adoption of digital therapy. As an emerging force in pain management, digital therapy is poised to gain prominence.

Application of digital therapy in pain management

According to the latest survey by Managed Markets Insight & Technology, LLC., a primary barrier to digital therapy is the perceived lack of "clinical value" [33]. As digital therapy evolves from concept to practice, stakeholders increasingly recognize that clinical trials play a crucial role in maturing digital therapy.

As of October 2021, data from E-Capital shows that there were 417 clinical trials related to digital therapy worldwide [33]. The number of trials grew over fivefold, from 16 in 2016 to 98 in 2020. In China, data from the Clinical Trial Registration Center indicates 60 trials involving "digital therapy," "software," and "virtual reality" between January 2021 and March 2023 [34]. Further analysis reveals that only 13 were conducted in 2021, while 37 were conducted in 2022, indicating a nearly threefold increase in clinical trials and a significant rapid growth trend [34].

Digital therapy is characterized by its evidence-based foundation, which necessitates high-quality clinical trials to demonstrate their safety and effectiveness in medical interventions. One randomized controlled trial showed that a digital program could serve as a viable model for alleviating chronic shoulder pain [35]. The study observed high acceptance, satisfaction, and adherence rates across groups, with significant clinical improvements. This trial highlighted the potential of digital therapy in alleviating chronic shoulder pain and considered its scalability and effectiveness. Another study also confirmed that combining virtual reality technology with local anesthesia and anxiety interventions provided additional analgesic effects [36]. This non-pharmacological intervention shows promise as an effective adjunct to pain management, reducing surgical pain and anxiety during procedures without serious complications.

Currently, VR is used in the treatment of various pain conditions, including burn pain, dental pain, ischemic pain, cancer pain, and chronic headaches [37-41]. It not only alleviates pain perception but also improves psychological well-being. Research confirms VR's effectiveness in relieving various types of pain, such as acute pain from surgical procedures and chronic pain from other causes [42-47]. A study on the efficacy of VR in reducing pain sensitivity in patients with lower back pain revealed that immersive VR effectively alleviated pain by distracting attention [48]. Moreover, VR's application extends to pediatric pain management. Wong et al. conducted a randomized controlled trial with children undergoing intravenous cannulation, showing that VR significantly improved pain and anxiety in these patients [49]. In digital health psychological intervention, adolescent pain management showed significant improvements over time, with participants reporting greater improvement post-treatment and during follow-up [50]. However, further research is needed to understand how digital health interventions can enhance treatment engagement and optimize implementation, ensuring the safety and reliability of digital therapy.

Digital therapy represents the empowerment of current medical methods through information technology and artificial intelligence, using innovative treatment methods to alleviate pain and modulate pain perception. The pain relief mechanisms of digital therapy include:

1. Cognitive Behavioral Intervention: Alters patients' negative perceptions and coping strat-

egies regarding pain, fostering a positive and optimistic mindset, thus breaking the "pain → negative emotion → pain" vicious cycle, and aiding in pain relief [51].

2. Attention Diversion Mechanism [52]: Uses virtual environments to attract patients' attention, reducing their cognitive awareness of pain, thereby decreasing pain intensity and discomfort.

3. Neuroregulation Mechanism: Utilizes techniques such as electrical and magnetic stimulation to directly influence neural system activity and alleviate pain. Early research by Hoffman et al. on functional magnetic resonance imaging showed that VR technology could significantly reduce patients' subjective pain perception and decrease brain activity in five pain-related brain regions [53]. However, the specific mechanisms by which VR alleviates chronic pain remain unclear and require further study.

Ethical issues in digital therapy

In the past 20 years, the digital transformation of healthcare has relied on deep learning and simulation computing, primarily applied to medical diagnostics, remote care, and data monitoring, aiming to provide more convenient and adaptable care models for the public [54]. However, with the rapid development of digital medical technology, certain ethical risks and challenges have emerged. Addressing these ethical concerns requires intervention and management not only from a legal perspective but also from an ethical standpoint [55].

Privacy and confidentiality

Compared to traditional patient-doctor interactions, digital therapy platforms introduce new risks related to patient information leakage. Training digital intervention models requires collecting large amounts of patient data, and the instability and vulnerability of networks may exacerbate the risk of data breaches. If privacy protection systems are flawed, there is a potential for violating individuals' property rights, personal rights, or leading to intellectual property disputes [56]. As more personal information appears in large online databases, data aggregation and analysis raise the risk of re-identification, making complete privacy protection challenging. Thus, data security and privacy are fundamental and crucial ethical issues in digital therapy.

When collecting, using, and storing data, strict adherence to laws, regulations, and ethical standards is essential. Privacy issues should be addressed through rigorous scientific research and ethical design, with sensitive data subjected to appropriate de-identification or encryption to prevent unauthorized access or misuse. Patients' rights to informed consent and choice must be fully protected, and data should be collected and used only within the minimum necessary scope [57]. Comprehensive data privacy protection measures and security standards must be established to effectively safeguard the development of digital therapy.

Generalizability and fairness

While digitalization brings convenience to daily life, it also creates a "digital divide" disproportionately affects populations with limited information technology skills, such as the elderly [58]. Older adults are a high-risk group for diseases, with declining physical functions, weakened immune systems, and frequent medication use. They often recover more slowly and have greater healthcare needs. However, the "digital divide" poses significant barriers to their access to healthcare. Additionally, factors such as educational levels and economic conditions in remote areas may affect their ability to benefit from digital health services.

The development of digital therapy should consider broad applicability and respect for special groups and cultural differences. Recognizing that older populations may have limited familiarity, learning capacity, and acceptance of new technologies, digital therapeutic products should incorporate age-friendly services [59]. Simple and intuitive interface design, user-friendly digital therapeutic platforms, and tools should be prioritized to improve the overall health status of diverse populations.

Algorithm opacity and explainability principles

Digital therapeutic technologies are software-based, and due to algorithm opacity or technical and commercial confidentiality, their reliability and safety undergo testing in a "black box" manner. This "black box" characteristic is one of the main obstacles to the application of digital therapy in the medical field [58]. For various digital therapeutic domains, validating product safety and reliability depends on the source of research evidence and must be scientifically rigorous. When developing digital therapeutic systems, ethical issues must be carefully considered to ensure that artificial intelligence products meet corresponding ethical requirements during clinical trials. For example, ChatGPT is programmed with source code to

adhere to OpenAI's ethical and moral standards, avoiding actions that could result in adverse outcomes when responding to abnormal instructions [60].

As digital medical technologies become increasingly crucial for public health and personalized healthcare, their global adoption is accelerating. The healthcare sector's digital transformation, often referred to as "Health 4.0," signifies a shift into a new era where digital healthcare will face unique challenges and opportunities.

Future prospects and challenges of digital therapy

According to the latest report by Markets and Markets, the global artificial intelligence market is expected to reach USD 11.03 billion in 2023 and USD 51.8 billion by 2028, with a compound annual growth rate of 35.6% [61]. FORTUNE BUSINESS INSIGHTS predicts that the digital health market size will reach $1,965.3 billion by 2030, with a compound annual growth rate of 23.3% from 2023 to 2030 [62]. Insider Intelligence forecasts that digital therapy will become a USD 56 billion global opportunity by 2025 [28]. Between December 1, 2022 and December 22, 2023, Chinese central government issued 66 policies related to digital health [61]. The alignment of global market trends with supportive local policies is expected to refine the digital therapy framework, establishing a solid foundation for the industry's healthy development. Moreover, the latest report by the Peterson Health Technology Institute indicates that digitally guided therapy programs offer cost-effective solutions, providing outcomes to face-to-face therapy at lower costs. For patients with commercial insurance, virtual or remote digital solutions can save at least USD 737 to 1,306 in medical expenses annually [63].

Digital therapy is rapidly evolving, with ongoing developments in disease management and regulatory approvals, holding immense potential. Although recent investment data have been less than ideal, with overall decline in market investment, reflecting a normal fluctuation cycle [63]. The domestic prospects for digital therapy are broad, but the industry remains in its infancy and faces several challenges. First, ensuring the safety and efficacy of digital therapy in China requires rigorous clinical trials and robust regulatory mechanisms to better support these trials. Given the potential technical differences among various digital therapeutic products, there is an urgent need to establish unified standardized protocols for digital therapy. Additionally, patient data privacy and security must be prioritized, as safeguarding personal information and data security is crucial. Despite the advantages of digital therapy over traditional methods, achieving comprehensive solutions remains challenging. The promotion of digital therapy may involve issues related to medical costs and the willingness of doctors and patients to adopt new technologies, which could hinder widespread adoption. Therefore, exploring suitable payment models and increasing awareness and acceptance among healthcare professionals and patients are essential.

The challenges extend beyond clinical trials and regulatory issues, as further development is also needed in areas such as mechanism exploration and delivery technology. While some well-known international digital therapeutic companies, such as Pear in the U.S. and Babylon in the U.K., have encountered financial difficulties and even bankruptcy, the outlook for digital therapy in China remains optimistic. Local governments, particularly in Hainan, have shown strong support for digital therapy industry, issuing the first policy documents to facilitate its growth and conducting pilot projects to accelerate digital health transformation in Hainan Province [64]. Strengthening international collaboration and incorporating innovative practices from other countries can help shape a digital therapeutic model suitable for China's unique healthcare needs and national conditions.

Conclusion

Amid rapid technological advancements, digital therapy is playing an increasing prominent role in modern medical diagnosis and treatment. Many countries and regions have introduced policies and regulations to encourage the innovation and application of digital therapy. Alongside a favorable policy environment, substantial research and clinical trials have proven the effectiveness and safety of digital therapy, providing scientific evidence for their application value.

Digital therapeutic interventions for pain management offer significant clinical and social values. Given the limitations of traditional treatment methods in meeting the needs of pain patients, digital therapy emerges as a promising solution. Future research and development will further drive the application and innovation of digital therapy in the field of pain management. While our current understanding continues to evolve, the outlook for digital therapy is promising, with significant potential to transform pain management in the years ahead.

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Chunhui Qin: Leading the conception of the research direction and the overall framework, and putting forward innovative research ideas.
Shuya Wang: Responsible for the main writing of the manuscript, literature review, manuscript revision and submission.
Zhaohui Xie: Conducting the final review of the full text of the manuscript to ensure the accuracy of the research content, logical rigor and reasonable conclusions.
Liyun Kong: Carefully revising and polishing the language expression, logical structure and grammatical errors of the manuscript.
Lili Zhong: The corresponding author of this article, the person in charge of the industry-university-research cooperation project, and responsible for the medical scientific review.
Hong Wang: Discovering research topics, sorting out the academic context, and putting forward the core arguments.
Yun Cai: Proofreading details, supplementing domestic and foreign references, and improving the scientific nature of the paper.
Guohua Jiao: Participating in the design of the article's content and structure, and putting forward key suggestions and improvement opinions.
Zhenwei Wang: The corresponding author of this article, the person in charge of the industry-university-research cooperation project, and responsible for the medical scientific review.
Qiwen Zhu: Translating and proofreading the full text of the manuscript.
Ruoyu Tang: Translating and proofreading the full text of the manuscript.

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Pain biomarkers based on electroencephalogram: Current status and prospect

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Highlights

- During the perioperative period, electroencephalography (EEG) has significant advantages as a tool for pain as sessment. The applications of indicators such as the pain threshold index (PTI) and γ wave activity in preopera tive, intraoperative, and postoperative pain assessment have been validated, contributing to the optimization of perioperative analgesic strategies.
- CEEG showed that pain intensity was negatively correlated with α wave activity and positively correlated with γ wave activity.
- Analysis of the characteristics of EEG in pain state is helpful for the diagnosis and treatment of pain, and to prevent the transformation of chronic pain.
- Comparing different EEG pain biomarkers can enhance the understanding of brain activity in pain state and im prove the accuracy of data.

Abstract

Pain is a subjective and complex symptom, making its prediction, management, and treatment a significant challenge in clinical research. To address these challenges, the search for reliable and objective pain biomarkers has become a focal point in pain studies. Electroencephalography (EEG), a non-invasive clinical tool, has emerged as the most widely used method for assessing brain regions associated with pain due to its temporal resolution, accuracy, and comprehensive nature. Multichannel EEG is now a primary technique in the study of pain biomarkers. This review discusses the current status and future prospects of EEG biomarkers in pain research, synthesizing evidence on the potential of EEG recordings as reliable biomarkers for pain perception. This will contribute to establishing a more solid foundation for the prediction, diagnosis, and intervention of pain in future research and management.

Keywords: Pain, electroencephalography, biomarker

Introduction

Pain, an unpleasant sensory and emotional experience, varies greatly among individuals and is a common complication following surgical procedures [1]. Studies have revealed that over 60% of surgical patients experience moderate to severe acute postoperative pain [2]. Recently, the quest for objective measures to enhance pain assessment and treatment has garnered increasing attention [2]. Despite this, the identification of uniform and reliable pain biomarkers remains elusive, with different biomarkers serving various functions such as diagnosis, monitoring, and treatment. The recognition of changes in brain structure and function has led to a growing interest in developing brain-based pain biomarkers using neuroimaging

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and electrophysiological methods. Compared to other brain imaging techniques like functional magnetic resonance imaging (fMRI), electroencephalography (EEG) offers advantages such as portability, convenience, and high temporal resolution, making it a widely used tool in assessing brain function [3, 4].

EEG biomarkers of pain typically focus on specific brain regions associated with nociception, such as the somatosensory cortex and the anterior cingulate cortex. Activity patterns in these regions can be distinguished from those related to non-nociceptive sensations, such as touch or thermal perception [5]. For instance, pain is often linked to higher frequency EEG activity, like gamma band oscillations, whereas other sensations may elicit activity at different frequencies. Although emotional states can also influence EEG signals, these effects are generally reflected in brain regions related to emotional processing, such as the prefrontal cortex and amygdala, rather than in core pain processing regions [6]. Pain-related EEG features, such as decreased alpha waves and increased gamma waves, show significant differences compared to EEG changes induced by emotional states, thereby enhancing the specificity of EEG in distinguishing between pain and emotional states.

This article aims to illustrate the reliability of EEG signals as predictive biomarkers for pain by synthesizing evidence from relevant literature and exploring the potential of quantifying pain through EEG measurements. This will significantly enhance clinical pain management and contribute to the development of new therapeutic approaches.

EEG

EEG signals, generated by neuronal discharges from the pyramidal cells of the cerebral cortex, reflect the physiological processes of neurons in the brain and contain rich information about brain activities [7-9]. This technology has achieved significant advancements in clinical practice, including the assessment of cognitive function, diagnosis of epilepsy, and monitoring of anesthesia depth. The EEG acquisition system, based on a high-precision analog-to-digital converter, captures minute signal changes emitted by electrodes on the scalp surface. The acquired pain signals are then decoded through time-frequency domain analysis and other EEG techniques, revealing cortical loops involved in pain processing and analysis. Quantifying the correlation between the somatosensory cortex and pain from different topographic maps and waveform features deepens our understanding of pain-related EEG signals, making it a valuable tool for pain prediction, diagnosis, and treatment in clinical settings [4, 8, 10]. However, in practical applications, EEG data collection is inevitably subject to noise and artifacts due to external environmental interference. Some artifacts can be effectively removed during data preprocessing, and preventive measures can also be taken to avoid artifacts caused by unnecessary movements.

In recent years, studies have focused on quantifying pain through algorithmic analysis of EEG data characteristics, resulting in various derivative indices. The clinical application of these indices has been effectively demonstrated, with EEG also being used to study changes in brain oscillatory activity and functional connectivity across different frequencies. Pain-related EEG rhythms primarily involve changes induced by oscillations in the gamma-band (30-100 Hz), theta-band (4-7 Hz), and alpha-band (8-13 Hz) [11, 12]. Among these, gamma-band oscillations are considered one of the most promising biomarkers for pain perception, while the peak alpha frequency (PAF) is a significant biomarker for predicting pain sensitivity [13, 14]. Finally, literature suggests that microstate analysis of EEG is capable of quantifying resting-state EEG recordings into sequences of a finite number of microstates to explain changes in brain function in patients with chronic pain [15].

EEG biomarkers of pain states

Electroencephalogram derivative index

The EEG-derived indices are generated from raw EEG features and converted into dimensionless values through algorithmic analysis, reflecting changes in brain activity. Clinically, one of the most commonly used EEG-derived indices is the Bispectral Index, which is employed to assess sedation levels and monitor the depth of anesthesia. Recent studies have demonstrated that EEG-derived indices can also serve as biomarkers for pain, helping to predict and quantify pain responses [16]. Commonly used pain indices include the Pain Threshold Index, the Surgical Pleth Index, and the Wavelet Index. These indices aid physicians in monitoring patients' responses to nociceptive stimuli during general anesthesia and guide postoperative pain management, particularly in predicting postoperative pain in both adults and children [17]. Among them, Pain Threshold Index, through the use of wavelet algorithms, achieves temporal and spatial resolution coordination of EEG signals and extracts objective quantitative features related to pain. It provides

a reliable basis for predicting postoperative pain and hemodynamic responses. In recent years, studies have confirmed the significant advantages of Pain Threshold Index in predicting acute postoperative pain in both pediatric and adult populations and its effectiveness in guiding opioid dosage [18-20].

However, some studies have indicated that certain EEG indices, such as quantium nociception index, are not effective in predicting acute postoperative pain, possibly because they assess the depth of anesthesia rather than pain itself [21]. Furthermore, these EEG-derived indices are mostly measured under general anesthesia and are not applicable in awake states, as their values significantly increase during arousal and are prone to interference from medications and medical conditions. The accuracy of these indices may be affected by the influence of anesthetics and analgesics, limiting their utility in preoperative and postoperative pain assessments. In contrast, raw EEG neural oscillations, used as pain biomarkers, can compensate for these limitations, providing more objective assessments of pain, better predictive value, and aiding in the development of new pain management approaches.

α waves

To date, oscillatory activity in EEG frequencies has been repeatedly shown to play a significant role in experiments involving pain stimulation in healthy subjects. Recent studies have indicated that neuronal responses related to pain are primarily concentrated in α-frequency, γ-induced responses, and θ-evoked responses, further supporting the feasibility of EEG as a tool for predicting pain and analgesic responses [11]. In the resting state, changes in α-wave activity are the most commonly observed. When the body is subjected to pain stimuli, α-frequency in the frontal and parieto-occipital regions is considered an important biomarker. Clinical data have shown that in healthy individuals, α-frequency increases in response to acute pain stimulation, while in chronic pain patients, α-frequency tends to decrease [11, 22].

In the past decade, the mainstream method for pain-related EEG research has been using experimental pain paradigms (e.g., laser or thermal pain stimulation) to assess evoked potentials in response to brief nociceptive stimuli [23]. Time-frequency analysis has further expanded the scope of evoked potential studies, with most experiments converting the time-domain data of pain EEG signals into the frequency domain, yielding the PAF as a key measurement. Furman et al. used a "capsaicin-heat pain" model to simulate the transition from a pain-free state to persistent pain in healthy subjects, demonstrating that PAF is negatively correlated with postoperative pain intensity in both pain-free and persistent pain states [22]. Subsequently, De Martino et al. investigated muscle pain through intramuscular injection of nerve growth factor, finding that PAF significantly slowed during muscle contraction and in the state of prolonged muscle pain [24]. These findings are consistent with previous experimental pain studies, which showed that during sustained skin pain, the amplitude or peak frequency of α-oscillations decreased, suggesting that PAF slowing could serve as a potential biomarker for pain sensitivity and provide insights into the transition from acute to chronic pain. Although PAF has been demonstrated as a biomarker for pain, its reliability remains a subject of debate. Previous studies have shown that PAF can remain stable over time, but fluctuations in α-wave energy induced by pain may affect its predictive accuracy [25, 26]. A recent study explored the effects of frequency window selection, EEG recording time, and peak identification methods on PAF stability, showing minimal impact from these factors and confirming the reliability of PAF in predicting pain sensitivity [26]. However, most studies have been conducted on healthy individuals in response to experimental pain, and the relationship between α-frequency and clinical pain in patients still requires further investigation.

In recent years, although EEG technology has become increasingly sophisticated in pain research, evidence linking EEG with postoperative pain remains limited. A study conducted in lung cancer patients with no or mild pain found that PAF, measured in the preoperative awake state, demonstrated high sensitivity and specificity in predicting postoperative acute pain [14]. PAF could be used as a clinical tool for stratifying pain-sensitive patients and predicting postoperative acute pain, with preoperative PAF negatively correlated with postoperative pain intensity. This finding contrasts with the increase in α-frequency observed in response to acute pain stimulation in healthy individuals, possibly due to the fact that pain induced by external nociceptive stimuli does not fully represent acute pain but rather reflects a transition from acute to chronic pain. Additionally, a study by de Vries et al. in patients with chronic pancreatitis showed that the longer the duration of pain, the greater the reduction in PAF, as assessed through comparisons of PAF and power amplitude in specific regions of interest during the awake state [27]. Thus, PAF may also serve

as a marker of the progression from acute to chronic pain.

In summary, whether in experimental or clinical pain research, these findings provide important insights into the prediction of acute pain and the diagnosis and treatment of patients with chronic pain. The reduction of PAF is associated with persistent abdominal pain caused by chronic pancreatitis, neuropathic pain resulting from spinal cord injury, and acute pain following postoperative trauma. PAF shows significant potential as a reliable clinical biomarker for predicting pain intensity in preoperative pain-free patients or those experiencing mild pain.

γ waves

In the field of neuroscience, gamma oscillations are considered an important characteristic of cortical activity, not only closely related to cognitive functions such as learning, attention, and memory, but also significantly associated with subjective pain ratings, stimulus intensity, and pain perception [12]. Evidence suggests that gamma-band oscillations measured through scalp EEG are one of the most selective biomarkers for reflecting both stimulus-evoked and spontaneous pain perception intensity [13].

Literature indicates that gamma oscillations in the primary somatosensory cortex induced by pain are significantly correlated with subjective pain experiences [11, 12, 28]. Since the amplitude of gamma band oscillation (GBO) is directly related to subjective pain intensity, studies suggest that these oscillations reflect cortical activity directly linked to pain perception. In pain-free patients or those with mild pain, gamma oscillations recorded in the awake state before surgery can encode individual pain sensitivity and predict postoperative changes in subjective pain intensity [29]. Most studies on gamma activity during pain stimulation have shown a significant increase in energy [30]. A preoperative measurement of gamma frequency to predict acute postoperative pain found that patients in the moderate-to-severe pain group had significantly higher gamma frequencies than those in the low-pain group, indicating that preoperative EEG data could effectively identify patients at high risk of postoperative pain [31]. However, due to the high frequency of gamma waves, they are susceptible to external environmental interference during signal acquisition, and when using high-pass filters for data processing, gamma waves may be mistakenly removed as noise artifacts. Therefore, although gamma oscillations have the potential to be a biomarker for pain prediction, many challenges still exist in clinical trials. The effective elimination of such interference remains a critical issue for future research to address.

Other frequency bands of EEG activity

Resting-state EEG studies have shown that changes in α-frequency and θ-band power, as well as increases in β-band power during pain, occur in the frontal, parietal, temporal, and occipital cortices [27]. In normal brains, θ waves are associated with functions such as intuition, creativity, and imagination; δ waves increase significantly during deep sleep or coma; low-frequency β waves are related to focused attention, while high-frequency β waves are linked to alertness and agitation [32]. As research progresses, the relationship between these brainwave activities and pain is becoming clearer, and they all have the potential to serve as clinically useful biomarkers for pain. Clinical data suggest that the relationship between θ wave activity and pain is somewhat contradictory. Some studies have found that θ wave power increases in response to brief pain stimulation, chronic pain, or neuropathic pain [11, 33-35]; other studies, however, have indicated that pain stimulation leads to reduced θ activity [36, 37]. Additionally, research has shown an increase in θ power in cold pain stimulation models [38, 39]. Despite these discrepancies, most studies agree that pain stimulation elicits increased δ and β wave activity, although some literature has presented differing views [38, 39]. While these relationships between various EEG frequency bands and pain have been observed, whether they can serve as convincing and clinically useful biomarkers for pain remains to be further validated. Given the complexity of pain, along with the differences in its types, intensity, duration, and location, EEG changes induced by pain vary greatly. Future studies will need to conduct in-depth analyses of the changes in different EEG frequency bands and explore their relationships with patients' clinical symptoms.

An increasing body of evidence suggests that oscillatory patterns in different brain regions, as well as their synchronization, play a critical role in both acute and chronic pain [40]. The study and development of biomarkers are considered key steps in the prediction and treatment of pain. To further develop the potential of EEG signals as biomarkers for pain, distinguish between biomarker types, and assess their specificity, this review also introduces an additional EEG analysis method, microstate analysis. As shown in **Table 1**.

Table 1. The relationship between EEG frequency and pain

EEG Rhythm	Frequency Range	Relation to pain
Delta	0.5-4 Hz	Increased in deep sleep or unconscious states; not directly related to pian but can be elevated in chronic pain conditions [32, 38].
Theta	4-8 Hz	Often increased during pain anticipation and chronic pain; related to emotional processing and attention [33-35].
Alpha	8-13 Hz	Decreased in response to acute pain; associated with relaxation and inhibitory processes [11, 22].
Beta	13-30 Hz	Increased during states of alertness and cognitive processing; can be elevated in anticipation of pain [32].
Gamma	30-100 Hz	Increased during acute pain; associated with the perception of pain and processing of nociceptive information [28-30].

Note: EEG, Electroencephalography.

Microstate analysis of pain monitored by EEG

Microstates are brief, patterned brain topographies observed in resting-state EEG recordings, representing functional brain networks. Microstates remain stable before rapidly transitioning to another functional network and can reflect pain perception and the temporal dynamics of the brain [15, 41]. As such, EEG microstates are considered valuable tools for assessing brain function, offering important insights into pain perception by capturing momentary changes in brain activity.

A study utilizing closed-eye resting-state EEG microstate analysis to evaluate chronic pain showed that, compared to healthy individuals, microstate D was reduced in chronic pain patients, while no significant microstate changes were observed in patients with chronic widespread pain [39]. Another study found that, in patients with chronic widespread pain, the occurrence and time coverage of microstate C were lower in resting-state EEG recordings with open eyes [42]. This discrepancy may stem from differences in methodology and sample size or reflect that the brain activity changes revealed by microstate analysis are specific to certain types of pain. These findings support the use of EEG microstates as biomarkers of chronic pain and in analyzing brain function changes and potential pathological dynamics. However, further research is needed to better elucidate the specificity of microstate changes in different chronic pain populations. Additionally, Li et al. performed clustering and time-feature analysis on resting-state EEG microstates in breast cancer patients during the preoperative awake state, finding that patients prone to postoperative pain exhibited higher occurrence and coverage of microstate C, which was positively correlated with scores of the numeric rating scale [43].

In summary, these studies support the novel idea that EEG microstates can serve as windows into specific differences in brain networks related to pain and may be used as brain biomarkers of pain. Although current research suggests a link between EEG microstates and pain sensitivity, the nature of this relationship is inherently complex, and many brain mechanisms associated with pain sensitivity remain to be discovered.

Discussion

This review summarizes the evidence supporting EEG as a biomarker for pain and highlights the differences between potential biomarker types. Although the use of EEG-derived indices has some limitations, and the correlation between certain oscillatory activities and pain remains controversial, numerous studies have validated that pain intensity is negatively correlated with alpha-band activity and positively correlated with gamma-band activity. Additionally, EEG microstate analysis has opened new perspectives in the study of EEG pain biomarkers, demonstrating that EEG technology can provide objective and reliable biomarkers to complement patients' subjective reports of pain intensity.

In clinical practice, the use of EEG requires placing multiple electrodes on the scalp or wearing an electrode cap, and using conductive gel or saline solution to maintain good conductivity. Compared to devices such as magnetoencephalography or fMRI, EEG has a relatively lower signal-to-noise ratio, necessitating complex data analysis and large sample sizes to extract useful information from EEG data. Therefore, some studies have combined EEG with other techniques to improve the accuracy of pain detection [44, 45]. EEG has high temporal resolution, while fMRI offers high spatial resolution. Combining the two can more accurately predict

the subjective experience of pain and better identify brain regions associated with pain [44]. Near-Infrared Spectroscopy is a technique that evaluates neural activity by measuring oxygen levels in the brain. Studies have shown that combining EEG and Near-Infrared Spectroscopy can enhance the detection accuracy of pain responses, particularly in clinical settings such as during surgery or monitoring of chronic pain patients [45].

The advancement of EEG has allowed researchers to investigate functional connectivity in different brain regions during pain states, contributing to the construction of EEG-based pain prediction models. While clinical monitoring of pain biomarkers includes various techniques such as Bispectral Index, Surgical Pleth Index, EEG, Magnetoencephalography, and fMRI, integrating EEG-based pain monitoring into clinical practice remains a crucial step forward. Therefore, anesthesiologists should enhance their understanding of EEG-based pain monitoring techniques and actively apply them in clinical settings. Currently, several tools and software packages for EEG data acquisition and analysis are available, such as Brain Vision Recorder, Matrix Laboratory (MATLAB), and the EEGLAB (Electrical and Elastic Glass Brain Analysis Lab) toolbox. Anesthesiologists need to become proficient in using these tools, including how to acquire EEG signals and perform data analysis and processing. Developing new therapeutic techniques based on EEG technology, which target specific symptoms, reduce side effects, and improve patient compliance, is a key direction for future pain research. Identifying the EEG rhythms that should be modulated to achieve optimal analgesia is crucial to the success of these therapeutic strategies.

Conclusion

This review summarizes the potential of EEG as an objective biomarker for pain assessment and management. By analyzing EEG features such as α-wave suppression, γ-wave enhancement, and EEG-derived indices, it provides valuable insights into pain perception, sensitivity, and the transition from acute to chronic pain. Particularly during the perioperative period, EEG demonstrates significant value in predicting postoperative pain, optimizing analgesic strategies, and guiding personalized pain management. Despite challenges such as signal noise, environmental interference, and the effects of anesthetics, the integration of advanced techniques like microstate analysis and combination with fMRI and Near-Infrared Spectroscopy offers improved precision in pain assessment. Future research should focus on addressing these limitations to promote the widespread clinical application of EEG biomarkers, thereby enhancing patient outcomes.

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Changes in brain functional connectivity of patients with postoperative delirium

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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) af fect 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 recom mends 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 cm^3 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 mm^3) 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 neurosci-

ence 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.

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