-γ Phase-Amplitude Coupling in the Prefrontal-Hippocampal-Medial Septal Circuit: Cross-Regional Coordination and Working Memory Regulation Mechanisms

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Abstract

As a core component of higher-order cognitive functions, working memory relies on the dynamic coordination of the prefrontal-hippocampal-medial septal neural circuit, wherein theta-gamma phase-amplitude coupling (TG-PAC) serves as a critical mechanism for inter-regional information integration. This article systematically elaborates on the core regulatory role of theta-gamma phase-amplitude coupling within the prefrontal-hippocampal-medial septal neural circuit in working memory. Research demonstrates that the prefrontal cortex maintains information representation in working memory through sustained neural activity, with its theta oscillations (4–8 Hz) forming a neural time window for cognitive control via phase modulation of gamma activity (30–80 Hz). The hippocampus, as a hub for spatial information processing, implements theta-gamma nested coding to bind spatial navigation and working memory, where the coupling strength between local gamma oscillations and theta oscillations can predict memory capacity and behavioral performance. Cross-regional coupling between prefrontal theta phase and hippocampal gamma amplitude constitutes a dynamic interactive interface between cognitive control and memory storage, ensuring precise execution of working memory tasks. The medial septum, serving as a key relay node, influences the strength and spatiotemporal characteristics of hippocampal theta-gamma phase-amplitude coupling through its cholinergic and GABAergic neurons regulating hippocampal theta oscillations, thereby modulating working memory efficacy. Furthermore, TG-PAC abnormalities are closely associated with cognitive dysfunctions such as schizophrenia and Alzheimer' s disease, suggesting its clinical value as a potential biomarker and neuromodulation target. This article innovatively integrates theta-gamma phase-amplitude coupling across the three-node prefrontal-hippocampal-medial septal circuit, and proposes that future research should combine multimodal

imaging, cell-specific manipulation, and computational modeling to advance novel strategies for cognitive disorder intervention based on neural oscillation coupling.

Full Text

Theta-Gamma Phase-Amplitude Coupling in the Prefrontal-Hippocampal-Medial Septal Circuit: Mechanisms of Cross-Regional Coordination and Working Memory Regulation

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Abstract

Working memory, as the cornerstone of higher-order cognitive functions, relies on dynamic coordination within the prefrontal-hippocampal-medial septal neural circuit, where theta-gamma phase-amplitude coupling (TG-PAC) serves as a critical mechanism for cross-regional information integration. This article systematically elucidates the central regulatory role of TG-PAC in working memory within this tripartite circuit. Research demonstrates that the prefrontal cortex sustains information representations through persistent neural activity, with its theta oscillations (4–8 Hz) modulating gamma activity (30–80 Hz) via phase coordination to form temporal windows essential for cognitive control. As the hub for spatial information processing, the hippocampus supports spatial navigation and working memory binding through theta-gamma nested coding, where the coupling strength between local gamma oscillations and theta rhythms directly predicts memory capacity and behavioral performance. Cross-regional coupling between prefrontal theta phase and hippocampal gamma amplitude establishes a dynamic interface for cognitive control and memory storage, ensuring precise execution of working memory tasks. The medial septum, acting as a crucial relay node, regulates the intensity and spatiotemporal characteristics of hippocampal TG-PAC through its cholinergic and GABAergic neurons, thereby modulating working memory efficiency. Furthermore, TG-PAC abnormalities are closely associated with cognitive impairments in schizophrenia and Alzheimer' s disease, highlighting its clinical value as a potential biomarker and neuromodulation target. This study innovatively integrates the three-node circuit coupling mechanism and proposes that future research should combine multimodal imaging, cell-specific regulation, and computational modeling to advance novel intervention strategies for cognitive disorders based on neural oscillation coupling.

Keywords: working memory, theta-gamma phase-amplitude coupling, cross-frequency coupling, prefrontal cortex, hippocampus, medial septum

Introduction

Working memory is a capacity-limited cognitive resource that temporarily stores and processes task-relevant information, serving as the core system for executing complex cognitive tasks. Successful working memory performance primarily involves successful information maintenance and effective interference suppression, which has led to the development of several classic paradigms for measuring working memory capacity. In human studies, the N-back task is most commonly used, where participants must determine whether current stimuli match information presented at specific prior positions, thereby measuring working memory updating and maintenance abilities. In animal research, spatial memory tasks are most prevalent, where animals must remember their initial choice in a Y-maze and repeat it after a brief delay, measuring working memory maintenance capacity. Both paradigms assess immediate processing and short-term maintenance of information, enabling timely correct responses to external cues, yet the underlying neural mechanisms remain incompletely understood.

Traditional perspectives posit that working memory depends on sustained, high-level firing activity in prefrontal neurons, where neural activity itself serves as the memory substrate—the "persistent firing" model (Kim et al., 2015). However, advancing research technologies and theoretical frameworks have increasingly challenged this model, as maintaining all memory items through persistent firing would impose excessive metabolic demands and vulnerability to interference. Consequently, researchers proposed the "activity-silent" model, which represents a more efficient and energy-conserving information maintenance mechanism whereby information is preserved solely through short-term synaptic strength changes, making synaptic modifications themselves the memory carriers (Rose et al., 2016). Modern perspectives suggest these two mechanisms are not mutually exclusive but rather work cooperatively to form a flexible and efficient working memory system, where persistent activity may maintain core information currently being actively manipulated, while the activity-silent mechanism preserves background information not immediately needed but potentially relevant later, with information rapidly switching between these two states during working memory processes (Adams et al., 2018).

Regarding the neural mechanisms of working memory, the classic theoretical model is Baddeley' s multicomponent framework, which proposes that working memory comprises a central executive system, visuospatial sketchpad, phonological loop, and episodic buffer. The episodic buffer serves as a critical integration interface that facilitates multimodal information fusion to form contextual memory representations by coordinating visuospatial and phonological storage modules (Baddeley, 2003). Extensive cognitive neuroscience research has primarily adopted a macroscopic perspective to elucidate the roles of different brain regions in working memory processes. For instance, neuroimaging studies demonstrate that working memory function relies on distributed neural network coordination, with core regions including the prefrontal cortex (PFC), anterior cingulate gyrus (ACC), parietal cortex (PAR), basal ganglia (BG), medial tem-

poral lobe (MTL), and midbrain dopamine systems (Chai et al., 2018). The prefrontal cortex serves as the capacity and information integration hub, maintaining memory representations through persistent neural activity (Kim et al., 2015); the anterior cingulate participates in dynamic attention allocation and cognitive control (Jimura et al., 2018); the parietal cortex dominates spatial information encoding and spatial working memory maintenance (Moore et al., 2013); and the basal ganglia enhance goal-directed signals to suppress interference information, particularly during working memory encoding phases (Murty et al., 2011). Although the specific functions of these brain regions have been systematically elucidated, working memory as a system for temporary encoding, storage, and retrieval requires coordinated activity across different brain areas, and cognitive neuroscience evidence has difficulty explaining the mechanisms of inter-regional coordination during working memory. Therefore, this article attempts to discuss different neural circuits underlying working memory from a basic neurobiological perspective, compare differences between circuits, and analyze the neurobiological mechanisms of inter-circuit connections.

Current research has established that the hippocampus-to-medial prefrontal cortex (mPFC) neural circuit plays a critical role in working memory information encoding, and that bidirectional connections between the thalamus and mPFC influence working memory maintenance and selection phases. However, these findings remain limited to specific stages and lack a unified neural architecture explaining how brain regions coordinate throughout the entire working memory process. Recent studies have revealed the core regulatory role of theta-gamma phase-amplitude coupling (TG-PAC) in working memory circuits. EEG recordings show that during working memory tasks, the human prefrontal cortex and hippocampus achieve information interaction through nested coupling between theta (4–8 Hz) phase and gamma (30–100 Hz) amplitude (Daume et al., 2024), with coupling strength predicting individual working memory performance (Axmacher et al., 2010). This provides a novel perspective for integrating different working memory circuits: during working memory, different brain regions achieve information encoding, maintenance, and selection through neural oscillations.

Animal model studies provide important complementary insights into the coupling mechanisms of working memory circuits. Optogenetic technology combined with multichannel neural recordings reveals that persistent prefrontal activity supports memory representation maintenance (Curtis & Sprague, 2021), while hippocampal theta oscillations participate in episodic memory encoding through spatial navigation frameworks (Leutgeb et al., 2005). Notably, the medial septum (MS), as a key node in the prefrontal-hippocampal circuit, regulates hippocampal theta oscillations through its GABAergic neurons, directly affecting memory precision (Solari & Hangya, 2018).

In summary, the prefrontal-hippocampal-medial septal neural circuit integrates working memory information through theta-gamma phase-amplitude coupling. This article aims to elucidate the neural connections between these three brain

regions and the theta-gamma phase-amplitude coupling patterns formed by this circuit, providing a new framework for understanding how this neural circuit participates in working memory regulation.

2. Key Neural Circuits of Working Memory

Working memory, as a system for temporary information storage and processing, relies on close collaboration among different neural circuits in the brain to form a working memory network. Three circuits are particularly critical: the ventral hippocampus-medial prefrontal circuit (Spellman et al., 2015), the medial septum-hippocampus circuit (Gemzik & Griffin, 2025), and the prefrontal-medial septum circuit (Bortz et al., 2023). The mechanisms of each circuit are detailed below.

2.1 Prefrontal-Hippocampal Working Memory Circuit

Early electrophysiological studies showed that approximately 65% of prefrontal neurons exhibited significantly elevated discharge frequencies during task cue presentation and sustained activation during memory delay periods (Fuster & Alexander, 1971). The Goldman-Rakic theoretical model further proposed that layer III pyramidal cells in the prefrontal cortex form local microcircuits through horizontal collaterals, with closed-loop excitatory connections driving persistent firing during working memory maintenance. This process is regulated by synchronized inhibition from fast-spiking GABAergic interneurons (such as PV+ basket cells), which dynamically balance excitation and inhibition to prevent network destabilization from excessive activity (Constantinidis & Goldman-Rakic, 2002).

Recent studies have challenged the single prefrontal circuit hypothesis, emphasizing the necessity of cortical-subcortical pathways. The prefrontal cortex not only receives afferent projections from multiple brain regions but also extensively projects to the dorsomedial thalamus, dorsomedial striatum, basolateral amygdala, and ventral tegmental area (Cassaday et al., 2014). For example, the neural circuit formed between the prefrontal cortex and hippocampus has been repeatedly demonstrated to play an important role in working memory tasks (Schneider et al., 2017; Spellman et al., 2015; W. Zhang et al., 2022). These regions interact through multiple pathways to successfully execute behavioral and cognitive tasks. In mice, excitatory monosynaptic projections originate from hippocampal CA1 and directly target prefrontal regions, while CA1 efferent fibers also project to the entorhinal cortex, thalamic reuniens nucleus, and dorsomedial thalamus, which in turn project to the prefrontal cortex. Conversely, the prefrontal cortex sends direct or indirect projections to hippocampal CA1. These functional connections provide the anatomical basis for prefrontal-hippocampal co-participation in working memory (Spellman et al., 2015).

The hippocampus participates in spatial information processing through environment-specific neural representations. When environmental contexts

change, its network structure rapidly reorganizes to match new scene features (O' Keefe & Conway, 1978). This dynamic encoding capability functionally complements the prefrontal cortex: animal experiments show that during spatial working memory tasks, ventral hippocampal gamma oscillations (30–80 Hz) precede prefrontal neuronal discharges by 14–33 milliseconds, and suppressing ventral hippocampal-to-prefrontal projections during encoding significantly disrupts prefrontal location-selective firing and task performance, accompanied by reduced gamma synchrony, suggesting that gamma synchrony is a necessary condition for information transmission (Spellman et al., 2015). However, human intracranial recordings reveal that the amygdala is responsible for stimulus-specific representations during encoding, while the hippocampus shows more stable information maintenance during the retention phase (Li et al., 2023), a difference that may stem from species-specific neural circuit differentiation.

2.2 Medial Septum-Hippocampal Working Memory Circuit

The medial septum, as a key node in the limbic system, exhibits significant heterogeneity in its neuronal populations. Quantitative analysis shows the nucleus comprises primarily glutamatergic neurons (52%), cholinergic neurons (32%), and GABAergic neurons (16%) (Takeuchi et al., 2021). These three neuron types form dense local interconnections within the medial septum, creating a tightly woven local network where activating cholinergic neurons induces slow activation of glutamatergic neurons, while glutamatergic activation provides stronger and faster activation of the other two types, forming a recurrent connectivity pattern. Notably, medial septal GABAergic neurons are crucial for theta oscillation synchrony within the septal neural network (Manseau et al., 2005).

A major projection pathway of medial septal GABAergic, glutamatergic, and cholinergic neurons extends to the hippocampus via the fornix or fimbria fibers. Medial septal GABAergic and glutamatergic neurons primarily terminate on hippocampal GABAergic neurons, while cholinergic neurons mainly target hippocampal pyramidal neurons. Hippocampal GABAergic neurons not only receive projections from the medial septum but also project back to it, forming an interconnected long-range GABAergic circuit between the medial septum and hippocampus. Importantly, the long-range projection axons of GABAergic neurons are heavily myelinated, ensuring instantaneous synchronization of neural oscillations across remote brain regions (Müller & Remy, 2018).

Interestingly, the lateral septum, as a different structure within the septal region, sends dense projections to the medial septum while also receiving input from the hippocampus, whereas the medial septum feeds information back to the hippocampus via the fornix and fimbria, forming a "hippocampus-lateral septum-medial septum-hippocampus" closed loop (Swanson & Cowan, 1979). The medial septum and hippocampus share bidirectional neural connections, while the lateral septum only receives hippocampal input (Tsanov, 2018), with

this directionality of connections further demonstrating the medial septum' s important role in the closed loop.

Pharmacological studies show that local injection of the GABA_A receptor agonist chlordiazepoxide (CDP) induces dose-dependent working memory impairments that can be completely reversed by the specific antagonist flumazenil, confirming the region-specific role of the medial septum in working memory regulation (Stackman & Walsh, 1992). Optogenetic intervention experiments further reveal the temporal specificity of medial septal regulation: selective inhibition of medial septal neurons significantly reduces behavioral accuracy only during task delay periods, suggesting the nucleus plays a critical role in information maintenance (Gemzik et al., 2021). Mechanistic studies indicate that medial septal GABAergic neurons (particularly the Teevra-labeled subpopulation) exhibit prominent theta-oscillatory firing characteristics and specifically regulate CA3 neuronal activity through fimbrial projections (Solari & Hangya, 2018). Notably, using theta stimulation—injecting AAV5-hSyn-hChR2-EYFP virus into the rat medial septum, implanting an optical fiber, and delivering blue light via 6 Hz square wave pulses to simulate theta oscillations—experiments show that medial septal activation not only enhances local hippocampal theta oscillations (4–12 Hz) but also significantly improves performance accuracy in 30-second delay tasks (Gemzik & Griffin, 2025). Further research confirms a direct causal relationship between medial septal functional inhibition and hippocampal theta power attenuation (Zutshi et al., 2018), highlighting its core position in oscillation generation.

At the molecular mechanism level, studies reveal that hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels are highly expressed in medial septal GABAergic neurons. Using the specific blocker ZD7288 disrupts hippocampal theta oscillations and impairs spatial memory task performance, indicating that HCN channels participate in theta oscillation generation by regulating neuronal excitability (Cissé et al., 2008). Additionally, cholinergic neurons are confirmed to participate in theta oscillation regulation, as their activation enhances theta oscillation amplitude while selective lesions reduce theta power (Solari & Hangya, 2018), suggesting that different neuronal subtypes cooperatively maintain hippocampal rhythmic activity.

2.3 Prefrontal-Medial Septal Working Memory Circuit

As early as 1989, using PHA-L—a plant lectin that can be taken up by neuronal somata and anterogradely transported to axon terminals—researchers discovered dense projections from the medial prefrontal cortex to the septal nuclei, most concentrated in the lateral septum, horizontal limb of the diagonal band of Broca, and lateral preoptic area, with fewer projections to the medial septum (Sesack et al., 1989). Experiments in rabbits and Japanese monkeys also demonstrated fiber connections between the medial prefrontal cortex and lateral septum (Buchanan et al., 1994; Chiba et al., 2001), partially confirming cross-species consistency of these anatomical connections. Using retrograde tracing

viruses, researchers found high expression of virus injected into the medial septum in prefrontal somata, directly proving direct neural connections between the medial prefrontal cortex and medial septum (Bortz et al., 2023). Additionally, using viral tracing combined with chemogenetic tools, direct neural projections between the lateral septum and medial prefrontal cortex have been identified (Liu et al., 2025).

Using the shock-probe defensive burying test (SPDB) to measure rodent coping strategies when facing threats, researchers found that the neuronal population projecting from the prefrontal cortex to the lateral septum was activated during SPDB testing. Selective inhibition of the prefrontal-to-lateral septum pathway significantly reduced burying behavior—an active coping response to external stress. Chronic stress (such as chronic unpredictable stress, CUS) induces a shift from active burying to passive freezing behavior, characterized by immobility, avoidance, or freezing defensive responses. Specific activation of the prefrontal-to-lateral septum pathway reverses this passive behavioral shift induced by CUS. These findings suggest that the prefrontal-lateral septum pathway constitutes the necessary neural basis for active coping behavior (Liu et al., 2025). Using strategy-shifting tests to examine cognitive flexibility—the ability to inhibit old strategies and learn new rules—researchers investigated the regulatory mechanism of the medial prefrontal-to-medial septum circuit on cognitive flexibility. Activation of the medial prefrontal-medial septum circuit significantly improved animals' strategy-shifting ability, and this pathway plays a key role in cognitive flexibility by regulating midbrain dopaminergic neuronal activity (Bortz et al., 2023). These two experiments demonstrate that both the medial and lateral septal nuclei participate in information processing about the surrounding world through close connections with the medial prefrontal cortex. In summary, the medial septum, located between the cortex and hypothalamus, can transform perceptual, memory, and emotional information into adaptive behavioral outputs, playing an important role in information processing.

Despite these important advances, individual studies remain limited to different stages of working memory and cannot form a unified framework to explain how different brain regions cooperate internally across encoding, maintenance, and retrieval phases to complete working memory tasks. Interestingly, cross-frequency coupling (CFC) of neural oscillations, as an important manifestation of synchronization mechanisms, may achieve information integration between local microcircuits and distributed neural networks by establishing dynamic phase-amplitude regulatory relationships across frequency bands. The following sections will further explain information integration during working memory tasks by combining CFC with working memory circuits.

3. Electrophysiological Mechanisms of Working Memory: The Regulatory Role of Theta-Gamma Phase-Amplitude Coupling

3.1 Information Sharing Theory (Theta-Gamma Coupling)

The multi-scale coordination mechanism of neural activity represents a frontier proposition in neuroscience, with its core challenge being to decipher how the brain achieves information integration across space and time. The temporal binding hypothesis proposes that the brain binds dispersed features into unified objects through millisecond-precise neuronal synchronization (Von Der Malsburg, 1985), a concept further substantiated by Singer' s team in cat visual cortex experiments where they first observed stimulus-dependent neuronal synchronous oscillations at the physiological level (Singer, 1993). Additionally, Malsburg proposed the "superposition catastrophe problem" —how neural systems simultaneously represent multiple information patterns within the same network without interference. He argued that temporal coding of neuronal dynamics is key to solving this problem (Von Der Malsburg, 1994). Specifically, neuronal ensembles encoding the same object form functional coupling through synchronized firing, while multiple object representations achieve information segregation through precise temporal coordination, avoiding interference.

Cross-frequency coupling (CFC) of neural oscillations, as an important manifestation of synchronization mechanisms, reveals hierarchical interactions of neural electrical activity across different temporal scales. Current theoretical models propose that high-frequency oscillations (such as gamma, 30–40 Hz) typically represent rapid information processing in local neural clusters, while low-frequency oscillations (such as theta, 3–7 Hz) mediate long-distance interregional information exchange through phase-encoding mechanisms (Lisman & Buzsáki, 2008). CFC may achieve information integration between local microcircuits and distributed neural networks by establishing dynamic phase-amplitude regulatory relationships across frequency bands, a mechanism considered the neural basis for spatiotemporal information coupling in cognitive processes. CFC manifests in three forms: phase-phase coupling (PPC), amplitude-amplitude coupling (AAC), and phase-amplitude coupling (PAC). First, PPC refers to high-frequency oscillation phases being locked to specific phases of low-frequency oscillations, also known as n:m phase synchronization where n low-frequency cycles contain m high-frequency cycles, primarily providing precise timing for information communication (Figure 1 [Figure 1: see original paper]A). Second, AAC refers to high-frequency oscillation amplitude (power) being modulated by low-frequency oscillation amplitude, also called power-power coupling (Figure 1B). Third, PAC, the most extensively studied form, specifically refers to high-frequency oscillation amplitude (such as gamma, 30–140 Hz) being locked to low-frequency rhythm phase, modulated by low-frequency oscillation (such as theta, 3–7 Hz) phase. This cross-frequency modulation is considered the interface between local information processing and global cognitive regulation (Figure 1C) (Jensen & Colgin, 2007). Experimental evidence shows that cross-

frequency coupling phenomena widely exist in rodent hippocampus, primate auditory cortex, and human neocortex, suggesting its potential as a universal mechanism for neural information processing (Zhang et al., 2017).

Theta-gamma phase-amplitude coupling (TG-PAC), as a typical paradigm of cross-frequency coupling, refers to the coupling relationship between low-frequency theta oscillation (4–8 Hz) phase and high-frequency gamma oscillation (30–100 Hz) amplitude. As a neural coding mechanism, TG-PAC may facilitate information transmission and play an important role in working memory by coordinating neural activity across different brain regions or different locations within the same region (Lisman & Jensen, 2013). TG-PAC can participate in working memory regulation because it provides a precise spatiotemporal coding framework that integrates neuronal firing activity, information storage, and cross-regional communication into a highly coordinated rhythmic system. This cross-frequency coupling mechanism is essentially a dynamic process that optimizes information encoding and retrieval efficiency across different temporal scales through time compression and phase separation strategies (Zhang et al., 2017). The frequency ratio of TG-PAC determines working memory capacity. According to Lisman' s theoretical model, working memory capacity is determined by the number of gamma cycles nested within one theta cycle. For example, if theta frequency is 5 Hz (200 ms period) and gamma is 40 Hz (25 ms period), each theta cycle can accommodate 8 gamma subcycles, approximating classic memory capacity limits. Moreover, as memory load increases, gamma power and theta-gamma coupling strength increase until saturation (Lisman & Idiart, 1995). Each theta cycle serves as a basic temporal window that segments working memory information into discrete time periods, with multiple gamma cycles (25–50 ms) nested within each theta cycle (100–200 ms), where each gamma cycle represents an independent memory item (such as digits or object features) and forms an ordered sequence (Lisman & Jensen, 2013). Therefore, during working memory tasks when individuals need to make decisions, information is replayed in the form of gamma oscillations within theta cycles, where TG-PAC coupling strength can predict individual working memory task performance (Axmacher et al., 2010).

Within gamma oscillation cycles, dynamic inhibitory neural networks critically influence working memory capacity and precision. According to the E%-MAX theory—a neural computational mechanism based on dynamic inhibitory networks—the core principle is that within each gamma cycle, only neurons whose excitatory (E) input reaches a certain percentage (E%) of the current cycle' s maximum excitatory input (Emax) will fire. As shown in Figure 2 [Figure 2: see original paper], Emax is monitored and determined in real-time by inhibitory interneurons, while E% reflects neuronal activation thresholds determined by two factors: the delay time d of feedback inhibition (the time for inhibitory signals to return after excitatory neurons trigger interneurons) and the decay time constant tau of inhibitory postsynaptic potentials (De Almeida et al., 2009).

During working memory gamma oscillation cycles, inhibitory interneurons peri-

odically release GABAergic inhibitory signals. As GABA inhibition gradually decays, the most excitable neurons in the network first reach firing threshold and discharge, simultaneously triggering global feedback inhibition onto less excitable neurons, thereby regulating the synchrony and selectivity of neural activity (Lisman & Jensen, 2013). Through this dynamic inhibitory competition, the E% threshold is dynamically regulated. When the E% threshold is high, inhibitory effects are stronger and appear earlier, more effectively suppressing neuronal ensembles representing other items with weaker excitability, thus preventing cross-interference between different memory items and improving information processing accuracy. Conversely, when the E% threshold is lower, more neurons can participate in the information encoding network, which may increase working memory capacity but reduce information processing precision (De Almeida et al., 2009). The dynamic regulation of neuronal activation E% by inhibitory networks allows the brain to balance information precision and capacity according to different cognitive demands.

In summary, during working memory processes, TG-PAC integrates temporal coding and content coding through phase-dependent gain control—a phenomenon where neuronal response magnitude (gain) to input signals dynamically changes with local field potential oscillation phase. Theta oscillations determine the sequence of processing different information, while gamma oscillations determine which information is processed. Gamma oscillations nested within theta cycles explain why working memory possesses both temporal accuracy and content stability. The following sections will further parse the mechanisms of TG-PAC involvement in working memory in relation to specific brain regions and neural circuits.

3.2.1 Hippocampal Theta-Gamma Coupling Mechanisms in Working Memory Regulation Hippocampal gamma oscillations play critical roles in memory encoding, retrieval, and integration. The hippocampus contains two major gamma oscillation generators—neural circuits that can independently produce gamma oscillations. One appears in CA3 and propagates to CA1, while the other is located in the dentate gyrus and primarily depends on neural input from the entorhinal cortex (Colgin et al., 2009). These two gamma oscillation generators are typically independent and may produce different frequency gamma oscillations in CA1: slow gamma oscillations (25–50 Hz) generated by CA3 and transmitted via the CA3-CA1 pathway, whose synchronization enhancement correlates with memory retrieval task performance; and fast gamma oscillations (65–140 Hz) generated by the entorhinal cortex and transmitted via the entorhinal cortex-dentate gyrus pathway, responsible for transmitting current environmental information and primarily participating in memory encoding (Colgin & Moser, 2010). Notably, fast and slow gamma oscillations appear at different phases of the theta cycle and are regulated by theta oscillations.

Hippocampal theta oscillations consist of two types: atropine-sensitive theta and atropine-resistant theta. Atropine-sensitive theta is primarily generated by

cholinergic input from the medial septum, where cholinergic neurons project via the fornix to all hippocampal regions (CA1, CA3, and dentate gyrus), releasing acetylcholine to enhance excitability of hippocampal pyramidal cells and interneurons, producing atropine-sensitive theta characterized by lower frequencies that may function in information encoding or environmental monitoring. Atropine-resistant theta is generated by serotonergic input from the raphe nucleus, which directly projects serotonergic fibers to the entorhinal cortex, inhibiting entorhinal interneurons and thereby disinhibiting entorhinal principal cells, enhancing entorhinal-to-hippocampal CA1 excitatory input to produce atropine-resistant theta characterized by higher frequencies potentially related to motor control and behavioral execution (Kramis et al., 1975; Leung, 1998). Interestingly, both the raphe nucleus and entorhinal cortex are regulated by the medial septum, whose GABAergic neurons may coordinate their activities to ensure spatiotemporal synchrony of theta oscillations. This article focuses primarily on atropine-sensitive theta activity and its critical role in working memory information encoding. In addition to theta oscillations from other brain regions, the hippocampal CA3 region can independently generate theta oscillations through strong feedback excitatory connections between CA3 pyramidal neurons, forming a self-exciting oscillatory system where pyramidal neurons typically drive inhibitory interneurons to create feedback inhibition loops that generate rhythmic theta activity (Buzsáki, 2002).

Single-neuron activity and local field potential recordings in epilepsy patients show that hippocampal theta oscillation (3–7 Hz) coupling strength with gamma oscillations correlates with memory load. Under high memory load, hippocampal TG-PAC weakens, gamma oscillations become more dispersed, and theta rhythm regulation efficiency decreases. Conversely, under low memory load, TG-PAC is stronger and theta regulation efficiency is higher. Stronger TG-PAC also correlates with faster response speeds (Daume et al., 2024). This suggests that when memory load is low, the hippocampus alone can complete working memory information encoding, storage, and retrieval, and hippocampal TG-PAC can serve as a key indicator for predicting individual working memory performance. However, high memory load may require coordination with higher-level brain regions. Indeed, under high memory load, prefrontal theta oscillation synchrony with hippocampal PAC neurons (neurons whose firing is regulated by TG-PAC) is enhanced, and prefrontal-hippocampal theta synchrony can predict individual behavioral performance, indicating that the prefrontal cortex regulates hippocampal information maintenance through theta oscillations (Daume et al., 2024). Notably, hippocampal TG-PAC power does not significantly change with memory load, suggesting it may be locally generated—either by hippocampal CA3 or driven by the medial septum—and regulated by the prefrontal cortex.

The functional characteristics of hippocampal TG-PAC in working memory have been validated across different research paradigms. In T-maze tasks, local field potential (LFP) recordings in rats show that theta-gamma coupling strength dynamically changes across task phases, displaying a three-phase pattern of "no

coupling–strong coupling–decoupling" that temporally corresponds to memory encoding, maintenance, and decision-making processes (Tort et al., 2008). In a low-frequency electromagnetic field exposure model of working memory impairment, prolonged exposure significantly attenuates hippocampal theta and gamma power as well as theta-gamma coupling strength (Y. Zhang et al., 2017). Human intracranial EEG studies confirm that in epilepsy patients performing Sternberg tasks, theta-gamma phase coupling strength peaks during working memory maintenance, forming cross-species correspondence with animal experimental conclusions (Chaieb et al., 2015). These findings demonstrate that hippocampal theta-gamma phase-amplitude coupling is a key electrophysiological signature of dynamic working memory regulation.

The regulatory mechanisms of hippocampal interneurons on theta-gamma coupling have received extensive attention. Selectively removing synaptic inhibition from parvalbumin-positive (PV+) interneurons significantly reduces CA1 theta oscillations and disrupts characteristic theta-gamma coupling patterns (Wulff et al., 2009). NMDA receptor antagonist MK801 intervention experiments show that while the drug enhances gamma oscillations, it simultaneously disrupts theta-gamma coupling during working memory (Abad-Perez et al., 2023). These studies indicate that hippocampal interneurons regulate local network oscillations through GABAergic inhibition, while glutamatergic receptor-mediated excitation/inhibition balance forms the neurochemical basis for maintaining theta-gamma coupling homeostasis. These findings not only deepen understanding of theta-gamma coupling mechanisms but also provide potential targets for cognitive dysfunction interventions.

3.2.2 Prefrontal Theta-Gamma Coupling Mechanisms in Working Memory Regulation During attention or working memory tasks, recording prefrontal local field potentials can independently detect prefrontal gamma oscillations (Gregoriou et al., 2009), demonstrating that the prefrontal cortex can independently generate gamma oscillations that may function in working memory information processing. The prefrontal cortex possesses abundant inhibitory interneurons and pyramidal neurons, providing the anatomical basis for gamma oscillation generation (Fries, 2015). Prefrontal gamma oscillations are generated through two primary mechanisms: first, excitatory drive from pyramidal neurons activates interneurons, which then provide feedback through GABAergic inhibition to form rhythmic activity; second, mutual inhibition among inhibitory interneurons alone can generate oscillations. In addition to internal generation, prefrontal gamma oscillations are also modulated by theta oscillations from sensory cortices (such as visual area V4) and the hippocampus (Benchenane et al., 2011).

The prefrontal cortex generally has weak intrinsic theta oscillation generation capacity, with its theta activity primarily driven by external inputs (especially from the hippocampus), which can transmit theta oscillations to the prefrontal cortex directly or indirectly via the thalamus or entorhinal cortex (Benchenane

et al., 2011). Prefrontal neuronal firing phases are modulated by hippocampal theta rhythms, mediating inhibitory regulation of pyramidal cells by prefrontal interneurons to form synchronized cell ensembles that discharge synchronously at hippocampal theta troughs, enhancing information transmission efficiency (Benchenane et al., 2010). When the hippocampal-to-prefrontal pathway is inhibited, the prefrontal cortex retains partial theta activity, further demonstrating its relative independence from hippocampal theta activity (O' Neill et al., 2013).

By recording local field potentials from both hippocampus and prefrontal cortex, researchers analyzed theta-band coherence between the two regions—a metric measuring inter-regional neural oscillation synchrony where higher coherence typically indicates better information transmission efficiency. During decision-making phases, hippocampal-prefrontal theta coherence significantly increases, and trials with higher coherence show greater accuracy. During high coherence periods, prefrontal pyramidal neuronal firing shifts from theta peaks to troughs, while interneurons synchronize prefrontal neurons through pyramidal cell inhibition, forming functional ensembles that ensure the prefrontal cortex processes and receives information from the hippocampus at the correct time (Benchenane et al., 2010). Thus, the hippocampus modulates prefrontal neuronal firing patterns through theta oscillations, influencing working memory information consolidation.

Furthermore, using transcranial alternating current stimulation (tACS) that superimposes continuous theta oscillations (4–8 Hz) with high-frequency gamma bursts (80 Hz) over the prefrontal cortex successfully simulates physiological theta-gamma coupling patterns (Alekseichuk et al., 2016). This experimental design overcomes traditional limitations of extracorporeal electrical stimulation frequency restrictions, enabling precise regulation of gamma burst phase and theta peak time windows. Results show that working memory performance improves most significantly when 80 Hz gamma bursts are phase-locked to theta peaks, revealing the critical role of phase-specific theta-gamma coupling in working memory encoding efficiency. This extracorporeal intervention paradigm not only validates the neural coding hypothesis that theta oscillations serve as temporal frameworks while gamma activity acts as information carriers but also provides important experimental evidence for developing cognitive enhancement technologies.

Transcranial direct current stimulation (tDCS) studies further expand understanding of prefrontal theta-gamma coupling functions. Anodal tDCS enhancing prefrontal activity reveals a positive correlation between theta-gamma coupling strength and working memory performance (Jones et al., 2020), suggesting that prefrontal theta-gamma coupling may optimize working memory dynamic maintenance mechanisms by regulating neural network temporal synchrony. Notably, during high-load tasks, the enhancement magnitude of prefrontal theta activity shows linear correlation with memory capacity, while theta phase modulation of posterior cortical beta (13–30 Hz) and gamma (>30 Hz) amplitudes reflects

cooperative mechanisms of the prefrontal-parieto-occipital network (Fernández et al., 2021). Specifically, enhanced occipital beta oscillations may relate to sustained activation of visual representations, while enhanced parietal gamma activity may reflect dynamic allocation of spatial attention resources.

These studies reveal the core role of prefrontal theta-gamma coupling in multi-level cognitive regulation: theta oscillations provide temporal frameworks for working memory through phase-resetting mechanisms, while gamma activity achieves precision regulation of information representations through amplitude modulation. This cross-frequency coupling mechanism not only supports dynamic maintenance of working memory but also enables cooperative regulation of attention resources and sensory representations through prefrontal-parieto-occipital network interactions. These findings provide important theoretical support and technical insights for developing cognitive intervention strategies based on neural oscillation regulation.

3.2.3 Hippocampal-Prefrontal Theta-Gamma Phase-Amplitude Coupling and Working Memory The functional coupling mechanism of neural circuits in cross-regional cognitive coordination has always been a frontier proposition in neuroscience, with low-frequency oscillations (such as theta) facilitating cross-regional synchronization control of gamma oscillations (Bonnefond et al., 2017). As shown in Figure 3 [Figure 3: see original paper], cross-regional neural communication relies on theta oscillation phase synchronization, which provides a global temporal reference framework for distributed neural networks. Within this framework, gamma oscillations serve as local information organization units nested within theta cycles, packaging discrete information units into specific phase windows of theta cycles. Specifically, sending and receiving brain regions first achieve synchronization through high theta oscillation consistency. The sending region then bursts gamma activity at a specific theta phase, carrying particular information. Due to synchronized theta oscillations, the receiving region becomes most sensitive to information input during the same theta phase segment, thereby most effectively receiving and decoding gamma information from the sending region.

As the core hub of the limbic system, the hippocampus' s coupling mechanisms with multiple brain regions remain a research focus. Among these, the functional specificity of the hippocampal-prefrontal circuit in the working memory network has been systematically elucidated. Specifically, the hippocampal CA1 subregion directly targets the prefrontal cortex through monosynaptic projections that show specific activation patterns during the encoding phase of spatial working memory. The prefrontal cortex also directly projects to hippocampal CA1 via ventral pathways, with some neurons terminating on hippocampal inhibitory interneurons. Intervention studies show that selective inhibition of hippocampal CA1-to-prefrontal glutamatergic projections causes significant deficits in cognitive representations during encoding without affecting memory maintenance or retrieval (Spellman et al., 2015), providing anatomical evidence

for bidirectional communication between hippocampus and medial prefrontal cortex.

Neurophysiological studies indicate that oscillatory coupling in the hippocampal-prefrontal circuit exhibits dynamic regulatory characteristics. Hippocampal CA1 theta oscillations conduct to the prefrontal cortex through monosynaptic projections, driving prefrontal theta synchronization. During hippocampal-prefrontal theta synchrony, prefrontal pyramidal cells undergo inhibitory regulation by interneurons, forming synchronized cell ensembles that facilitate information transmission (Benchenane et al., 2010). Subsequently, prefrontal theta oscillations top-down regulate hippocampal local gamma activity through long-range phase synchronization, forming theta-gamma phase-amplitude coupling (TG-PAC). Through PAC neurons (neurons whose firing is regulated by both theta phase and gamma amplitude), this mechanism transforms long-range rhythmic control signals (prefrontal theta) into local, structured regulatory information, thereby refining hippocampal population coding efficiency for information processing and ultimately improving behavioral output quality (Daume et al., 2024). This cross-frequency coupling achieves functional integration of prefrontal control signals (theta) and hippocampal content representation signals (gamma). Notably, during working memory encoding, the ventral hippocampus drives prefrontal neuronal action potential firing through gamma oscillations (30–80 Hz), with the temporal locking characteristics of these high-frequency oscillations positively correlating with behavioral performance (Fernández et al., 2021). Additionally, analyzing gamma oscillation phase differences between prefrontal cortex and hippocampus during working memory tasks reveals that during the choice phase of DNMTS tasks requiring working memory, prefrontal gamma oscillation phase leads ventral CA1, suggesting that while the hippocampus provides information to the prefrontal cortex via gamma oscillations during encoding, the prefrontal cortex may send executive control signals back to the hippocampus through gamma oscillations during decision-making and response output phases (De Mooij-van Malsen et al., 2023).

At the cellular mechanism level, electrophysiological feature analysis shows that hippocampal PAC neurons (hippocampal neurons whose firing is simultaneously modulated by low-frequency theta oscillation phase and high-frequency gamma oscillation amplitude) primarily exhibit narrow action potentials, a characteristic consistent with inhibitory interneurons (such as PV+ cells). Hippocampal PAC neurons optimize neural information processing through two key mechanisms: first, achieving temporal desynchronization through local inhibition, enabling different neuronal ensembles to activate independently at specific theta phases, thereby supporting multi-item working memory encoding (György, 2006); second, selectively enhancing pyramidal cell response sensitivity to prefrontal control signals through shunting inhibition and threshold regulation, while simultaneously reducing spontaneous activity in non-target neurons through broad inhibition (such as SST+ neurons), effectively improving signal-to-noise ratio (Pouille & Scanziani, 2001). Specifically, prefrontal theta input may preferentially activate hippocampal PV+ neurons, thereby selectively en-

hancing gain of gamma neuronal clusters associated with specific memory items while suppressing competitive neural representations.

Pharmacological intervention studies provide causal evidence for this mechanism. Selective application of NMDA receptor antagonist MK-801 to dorsal CA1 and medial prefrontal cortex results in abnormal enhancement of hippocampal gamma power accompanied by theta-gamma coupling disruption, while the prefrontal cortex exhibits biphasic changes in theta and gamma oscillation power and abnormal emergence of high-frequency oscillations (155–185 Hz) (Abad-Perez et al., 2023). Behavioral analysis shows that Y-maze working memory task performance significantly correlates with theta-gamma frequency-domain energy coupling strength in the hippocampal-prefrontal circuit, suggesting that MK-801 may cause working memory dysfunction by disrupting excitation-inhibition balance maintained by inhibitory interneurons.

In summary, theta rhythms from the hippocampus drive prefrontal theta synchronization, enhancing the prefrontal cortex' s ability to receive hippocampal information. Subsequently, prefrontal theta can couple with hippocampal gamma activity and regulate local circuits through PAC neurons to optimize working memory information storage and retrieval. Hippocampal gamma oscillations represent neural coding of environmental information, and their regulatory biological basis may involve specific prefrontal projections to hippocampal inhibitory interneurons. Through temporal desynchronization and spatial gain regulation, inhibitory neurons optimize information transmission efficiency between prefrontal cortex and hippocampus, supporting high-fidelity encoding and stable maintenance of information during working memory processes.

3.2.4 Hippocampal-Medial Septal Theta-Gamma Phase-Amplitude Coupling and Working Memory The medial septum exerts precise control over hippocampal neural oscillation dynamic patterns through diverse projections of cholinergic, GABAergic, and glutamatergic neurons. Among these, medial septal PV+ interneurons directly target hippocampal GABAergic interneurons, forming feedforward inhibitory regulatory loops that modulate hippocampal pyramidal cell excitatory output (Unal et al., 2015).

Functional inactivation experiments reveal the necessity of the medial septum-hippocampal circuit for working memory: local injection of muscimol (a GABA_A receptor agonist) into the medial septum to inhibit neuronal excitability results in significant spatial memory impairments in experimental rats compared to saline controls, accompanied by sharp declines in hippocampal theta oscillation power. Although theta oscillation amplitude itself cannot directly predict single-trial memory performance, hippocampal theta-gamma cross-frequency coupling strength shows significant positive correlation with episodic memory success. Control animals exhibit high theta-gamma coupling with good memory performance, while medial septum-inhibited groups show both decreased coupling strength and increased behavioral error rates (Shirvalkar et al., 2010).

Medial septal neuronal firing not only couples with hippocampal theta oscillation phases but also specifically couples with different beta or gamma oscillations, playing multi-timescale coordinating roles in memory encoding and retrieval. In hippocampal CA1 local field potentials, higher-frequency oscillations nested within theta cycles are called theta-nested spectral components, including beta/gamma frequency bands, abbreviated as tSCs. The medial septum influences hippocampal tSCs through direct and indirect pathways. The direct pathway involves medial septal GABAergic neurons directly projecting to hippocampal interneurons, disinhibiting CA1 pyramidal neurons to promote gamma oscillations, with medial septal neuronal gamma-frequency firing synchronizing with CA1 local field potential gamma phases. The indirect pathway involves medial septal orchid cells projecting to CA1 via the entorhinal cortex to regulate tSC3/tSC4 and influence information encoding, while tevra cells project to CA1 via CA3 to regulate memory retrieval processes. Simultaneously, the hippocampus directly projects to the medial septum through SOM+ interneurons, particularly targeting medial septal PV+ "pacemaker" neurons to form inhibitory feedback loops that dynamically inhibit medial septal drive strength on tSCs. Optogenetic activation of medial septal PV+ neurons can induce artificial tSCs with laminar distributions highly similar to physiological states, providing direct evidence for medial septal GABAergic network regulation of hippocampal theta activity (Király et al., 2023).

In summary, the medial septum and hippocampus form an efficient inhibitory feedback loop through bidirectional neural connections. The medial septum serves as a multi-frequency integration center for the hippocampus, achieving cross-frequency coupling with the hippocampus through direct and indirect loops to participate in memory encoding and retrieval, while hippocampal-to-medial septal GABAergic inhibitory feedback dynamically regulates medial septal PV+ neuron activity to ensure tSCs appear at the correct time and frequency, preventing excessive neuronal population synchronization that could damage memory encoding.

Additionally, neurotransmitter system interaction studies reveal the complexity of medial septal regulation: specific activation of medial septal cholinergic neurons significantly increases hippocampal acetylcholine concentration, accompanied by enhanced theta/gamma power, yet impairs working memory performance (Y. Zhang et al., 2021). This paradoxical phenomenon suggests the cholinergic system may have an inverted U-shaped dose-response effect or interacts with the GABAergic system. Studies show that medial septal GABAergic neurons mediate spatial memory effects by regulating hippocampal acetylcholine release (Roland et al., 2014), indicating that these two neuronal populations form functional microcircuits that jointly maintain cognitive homeostasis. Serotonergic system studies further support this view: medial septal serotonin depletion reduces low-frequency theta activity while causing compensatory enhancement of high-frequency theta, accompanied by decreased working memory error rates (López-Vázquez et al., 2014), whereas activation of serotonin 2A receptors significantly improves memory performance (Li et al., 2015), highlighting the

multidimensional role of the medial septum as a neurotransmitter integration center in cognitive regulation.

3.3 Theta-Gamma Phase-Amplitude Coupling Abnormalities in Psychiatric Disorders

Theta-gamma phase-amplitude coupling is not only closely related to normal cognitive function but also plays an important role in the pathological mechanisms of psychiatric disorders. Clinical studies show that patients with mild cognitive impairment exhibit significantly reduced theta-gamma coupling strength in the hippocampal-cortical circuit (Van Den Berg et al., 2023), while depression model rats show abnormal theta-gamma phase-amplitude modulation in the right auditory cortex (He et al., 2023), suggesting this neurophysiological indicator has translational value as a potential biomarker for depression. Notably, in Alzheimer' s disease transgenic models (APP-KO mice), hippocampal theta-gamma cross-frequency coupling shows significant attenuation that negatively correlates with reduced amyloid-beta deposition (X. Zhang et al., 2016), indicating that theta-gamma coupling strength can serve as a functional monitor of Alzheimer' s disease pathological progression.

Intervention studies further support the cognitive regulatory role of theta-gamma coupling: in Alzheimer' s disease patients receiving hippocampal-targeted transcranial alternating current stimulation (tACS), enhanced theta-gamma coupling shows significant positive correlation with cognitive function improvement (Tang et al., 2024), suggesting that theta-gamma oscillation-based neuromodulation may become a novel therapeutic strategy for Alzheimer' s disease. In schizophrenia research, theta-gamma coupling abnormalities are directly associated with working memory deficits. Under 3-Back task paradigms, schizophrenia patients show decreased theta-gamma coupling strength synchronized with reduced task accuracy, while healthy controls show significant positive correlation between theta-gamma coupling and behavioral performance (Barr et al., 2017). These findings not only reveal the core role of theta-gamma coupling in schizophrenia pathological mechanisms but also suggest its potential predictive validity as an objective disease assessment indicator.

4. Future Perspectives and Conclusions

This article systematically elucidates the central regulatory role of theta-gamma phase-amplitude coupling in the prefrontal-hippocampal-medial septal circuit for working memory. As a higher-order cognitive function, effective working memory implementation relies on coordinated activity within the distributed neural network composed of prefrontal cortex, hippocampus, and medial septum, while the three-node theta-gamma phase-amplitude coupling mechanism provides a critical neural coding mechanism for cross-regional information integration.

The prefrontal cortex maintains information representations in working memory through persistent neural activity, with its theta oscillations (4–8 Hz) modulating gamma activity (30–80 Hz) via phase coordination to form temporal windows for cognitive control. As the hub for spatial information processing, the hippocampus achieves spatial navigation and working memory binding through theta-gamma nested coding—a conceptual superordinate to theta-gamma phase-amplitude coupling quantified by PAC—where the coupling strength between local gamma activity and theta oscillations directly determines memory capacity and behavioral performance. Cross-regional coupling between prefrontal theta phase and hippocampal gamma amplitude constitutes a dynamic interface for cognitive control and memory storage, ensuring precise execution of working memory tasks. The medial septum, as a crucial relay node, forms extensive neural connections with prefrontal neurons that influence animal cognitive activity, while its cholinergic and GABAergic neurons regulate hippocampal theta oscillations to influence the intensity and spatiotemporal characteristics of hippocampal theta-gamma phase-amplitude coupling, thereby modulating working memory efficiency. Notably, medial septal GABAergic neurons (especially the Teevra-labeled subpopulation) exhibit prominent theta-oscillatory firing characteristics and are considered hippocampal theta oscillation pacemakers (Solari & Hangya, 2018). Based on these findings, we propose the prefrontal-medial septal-hippocampal circuit as an ideal model for in-depth investigation of working memory mechanisms. This circuit integrates three core components of the working memory system: prefrontal cortex (cognitive control center), medial septum (rhythm generator), and hippocampus (information processing center). The medial septum provides temporal organizational frameworks for information temporary storage through theta oscillations while achieving top-down regulation of hippocampal information processing, forming a functionally complete system.

Neuropsychiatric disease research further highlights the clinical relevance of this mechanism. Schizophrenia patients show abnormal theta-gamma phase-amplitude coupling in the prefrontal-hippocampal circuit accompanied by working memory deficits, while Alzheimer' s disease models demonstrate negative correlation between hippocampal theta-gamma coupling strength and amyloid-beta deposition. These findings not only reveal the pathological significance of theta-gamma phase-amplitude coupling in cognitive dysfunction but also suggest its potential value as a therapeutic target.

Elucidating the theta-gamma phase-amplitude coupling mechanism in the prefrontal-hippocampal-medial septal circuit not only deepens our understanding of working memory neural foundations but also opens innovative avenues for neuropsychiatric disease treatment. However, translational applications in this field still face key challenges, with current research limitations and future directions including:

1. **Cross-species validation**: Existing medial septum studies primarily rely on animal models lacking human brain imaging evidence. Future

research should combine invasive neural recordings (such as stereoelectroencephalography) with non-invasive imaging techniques (such as fMRI-EEG integrated scanning) to explore the regulatory mechanisms of the prefrontal-hippocampal-medial septal circuit on working memory.

2. **Cellular mechanism resolution**: Future studies should utilize transgenic animal models combined with optogenetics to parse how different neuronal subtypes in the medial septum (PV+, ChAT+, etc.) targetedly regulate the hippocampal-prefrontal circuit and their dynamic contributions during working memory encoding, maintenance, and retrieval phases.
3. **Clinical translation needs**: Develop neuromodulation paradigms based on theta-gamma phase-amplitude coupling, such as transcranial alternating current stimulation (tACS) targeting enhanced theta-gamma coupling, to evaluate its efficacy in improving cognitive impairments in schizophrenia patients with negative symptoms and mild cognitive impairment patients.
4. **Computational model construction**: Build computational models incorporating biophysical mechanisms to reveal information flow integration rules of theta-gamma phase-amplitude coupling in distributed neural networks, providing theoretical frameworks for developing closed-loop neurofeedback systems.

In domestic and international research, most studies focus on hippocampal local oscillations or bidirectional coupling between hippocampal-prefrontal circuits in working memory processes. Although theta-gamma phase-amplitude coupling in hippocampal-prefrontal and hippocampal-medial septal circuits has been extensively reported, technical limitations have resulted in fewer studies on functional connectivity between prefrontal cortex and medial septum. Current research has confirmed direct neural connections between prefrontal cortex and medial septum (Bortz et al., 2023), and future studies could combine optogenetics with multichannel recordings to verify the regulatory role of the prefrontal-to-medial septum circuit in working memory. Of particular interest is whether temporal differences exist between prefrontal neuronal firing and medial septal theta oscillations, and the differences and relationships between prefrontal and medial septal theta oscillations warrant further investigation. Future research must integrate multimodal neuroimaging, cell-resolution recordings, and precise neuromodulation techniques to reveal the causal role of theta-gamma phase-amplitude coupling between prefrontal cortex and medial septum in cognitive dysfunction and promote clinical translation of rhythm-based interventions. Additionally, local prefrontal dopamine injection while simultaneously recording hippocampal and prefrontal field potentials shows that post-injection hippocampal-prefrontal theta coherence significantly increases and positively correlates with task accuracy, inducing phase alignment of prefrontal pyramidal neurons. This finding suggests that dopamine, as a reward prediction signal, may trigger inter-regional synchrony during information encoding to mark important information (Benchenane et al., 2010).

This article begins with theta oscillations generated by the medial septum, analyzes neural connections between medial septum and hippocampus, proposes that the medial septum may play a critical role in working memory information processing, and for the first time integrates the three-node circuit coupling mechanism of prefrontal-hippocampal-medial septum, further refining the working memory neural circuit. Future research should combine multimodal neuroimaging techniques (such as fMRI-EEG integrated recording) with interventional regulation methods (such as optogenetics and transcranial alternating current stimulation) to systematically parse the dynamic coding mechanisms of this circuit across different cognitive phases and explore the application potential of theta-gamma coupling-based neuromodulation paradigms in treating cognitive dysfunction. These studies will deepen understanding of working memory neural foundations and provide innovative biomarkers and therapeutic targets for neuropsychiatric disease diagnosis and treatment.

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Note: Figure translations are in progress. See original paper for figures.