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

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Abstract

Working memory, as the core of higher cognitive functions, relies on the dynamic coordination of the prefrontal-hippocampal-medial septal neural circuit, wherein theta-gamma phase-amplitude coupling (TG-PAC) serves as a key 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 indicates that the prefrontal cortex maintains information representation in working memory through persistent neural activity, with its theta oscillations (4~8 Hz) forming a neural time window for cognitive control by phase-modulating gamma activity (30~80 Hz). The hippocampus, as a hub for spatial information processing, achieves the binding of spatial navigation and working memory through theta-gamma nested coding, where the coupling strength between its 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, as a key relay node, employs its cholinergic and GABAergic neurons to regulate hippocampal theta oscillations, thereby influencing the strength and spatiotemporal characteristics of hippocampal theta-gamma phase-amplitude coupling and modulating working memory efficacy. Furthermore, TG-PAC abnormalities are closely associated with cognitive dysfunction in schizophrenia, Alzheimer' s disease, and other conditions, suggesting its clinical value as a potential biomarker and neuromodulation target. This article innovatively integrates theta-gamma phase-amplitude coupling across the three-node circuit of prefrontal-hippocampal-medial septum, and proposes that future research should combine multimodal imaging, cell-

specific modulation, 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 foundation of higher-order cognitive functions, relies on dynamic coordination within the prefrontal-hippocampal-medial septal neural circuit, wherein 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 circuit. Research demonstrates that the prefrontal cortex maintains information representations through persistent neural activity, with its theta oscillations (4~8 Hz) forming temporal windows for cognitive control via phase modulation of gamma activity (30~80 Hz). As a hub for spatial information processing, the hippocampus implements spatial navigation and working memory binding through theta-gamma nested coding, 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 interface for cognitive control and memory storage, ensuring precise execution of working memory tasks. The medial septum, serving as a crucial relay node, influences the intensity and spatiotemporal characteristics of hippocampal TG-PAC by regulating hippocampal theta oscillations through its cholinergic, GABAergic, and glutamatergic 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 TG-PAC across the three-node prefrontal-hippocampal-medial septal circuit 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

Working memory is a capacity-limited cognitive resource that temporarily stores and processes task-relevant information, serving as a core system for executing

complex cognitive tasks. Successful working memory performance primarily involves the successful maintenance of information and effective suppression of interference, leading to the development of several classic paradigms for measuring working memory capacity. The most commonly used paradigm in human working memory research is the N-back task, in which participants must determine whether the currently presented information matches information presented at a specific previous position. This task can be used to measure the updating and maintenance capabilities of working memory. In animal working memory research, the most commonly used paradigm is the spatial memory task, in which animals must make an initial choice in a Y-maze, then after a brief delay, make another choice to determine whether it matches the previous one. This task can be used to measure the maintenance capacity of working memory in animals. Both classic paradigms measure immediate processing and short-term maintenance of information, with humans and animals able to respond correctly to external cues in a timely manner; however, the specific neural mechanisms underlying these processes remain unknown.

The traditional view holds that working memory depends on sustained, high-level firing activity of prefrontal neurons, with neural activity itself serving as the memory substrate—the "persistent firing" model (Kim et al., 2015). However, with advances in research techniques and theory, an increasing number of researchers have questioned this model: if all memory items required persistent firing for maintenance, the brain' s energy consumption would be extremely high and vulnerable to interference. Consequently, researchers proposed the "activity-silent" model. As a more efficient and energy-conserving information maintenance mechanism, this model posits that information in working memory is maintained solely through short-term changes in synaptic strength, with synaptic modifications themselves serving as the memory substrate (Rose et al., 2016). While these two models represent competing explanations of working memory, modern perspectives suggest that these mechanisms are not mutually exclusive but rather work cooperatively to constitute a flexible and efficient working memory system. Persistent activity may maintain core information currently being actively manipulated and processed, while the activity-silent model preserves background information not immediately needed but potentially useful later, with information in working memory capable of rapid switching between these two states (Adams et al., 2018).

Regarding the neural mechanisms of working memory, the classic theoretical model is represented by Baddeley' s multicomponent framework, which proposes that working memory comprises the central executive, visuospatial sketchpad, phonological loop, and episodic buffer. The episodic buffer serves as a key integrative interface that facilitates multimodal information fusion to form contextual memory representations by coordinating visuospatial and phonological storage modules (Baddeley, 2003). Currently, extensive cognitive neuroscience research has established, from a relatively macroscopic perspective, the roles of different brain regions in working memory processes. For example, neuroimaging studies have shown that working memory function depends on coordinated

distributed neural networks, with core brain regions including the prefrontal cortex (PFC), anterior cingulate gyrus (ACC), parietal cortex (PAR), basal ganglia (BG), medial temporal lobe (MTL), and midbrain dopamine system (Chai et al., 2018). The prefrontal cortex serves as the center for working memory capacity and information integration, maintaining memory representations through persistent neural activity (Kim et al., 2015); the anterior cingulate gyrus participates in dynamic allocation of attention 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 suppress interfering information by enhancing goal-directed signals, playing a particularly critical role during the working memory encoding phase (Murty et al., 2011). Although the specific functions of each brain region have been systematically elucidated, as mentioned above, working memory—as a system for temporarily encoding, storing, and retrieving information—requires coordinated work across different brain regions, and evidence from cognitive neuroscience has difficulty explaining the mechanisms of inter-regional coordination during working memory. Therefore, this article attempts to approach from a basic neurobiological perspective to discuss the different neural circuits of working memory, compare differences between these circuits, and analyze the neurobiological mechanisms underlying their interconnections.

While current research has established that the neural circuit from the hippocampus to the medial prefrontal cortex (mPFC) plays a critical role in working memory information encoding, and that bidirectional connections between the thalamus and mPFC influence the maintenance and selection phases of working memory, these findings are limited to specific stages and lack a unified neural architecture to explain the coordination mechanisms across brain regions throughout the entire working memory process. Recent research has revealed the central regulatory role of Theta-Gamma Phase-Amplitude Coupling (TG-PAC) in working memory circuits. EEG recordings show that when humans perform working memory tasks, the prefrontal cortex and hippocampus achieve information interaction through nested coupling of theta (4~8 Hz) phase and gamma (30~100 Hz) amplitude (Daume et al., 2024). Moreover, the coupling strength can predict individual working memory performance (Axmacher et al., 2010). This also 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 for dissecting the coupling mechanisms of working memory circuits. Optogenetic techniques combined with multi-channel neural recordings have revealed that persistent prefrontal activity supports the maintenance of memory representations (Curtis & Sprague, 2021), while hippocampal theta oscillations participate in episodic memory encoding through a spatial navigation framework (Leutgeb et al., 2005). Notably, the medial septum (MS), as a key node in the prefrontal-hippocampal circuit, influences memory precision through GABAergic regulation of hippocampal theta oscillations (Solari & Hangya, 2018). In summary, the prefrontal-hippocampal-medial

septal neural circuit achieves working memory information integration through theta-gamma phase-amplitude coupling. Therefore, this article attempts to elucidate the neural connections between the prefrontal cortex, hippocampus, and medial septum, as well as the theta-gamma phase-amplitude coupling patterns formed by this circuit, providing a new perspective for understanding how this neural circuit participates in working memory regulation.

2. Key Neural Circuits of Working Memory

Working memory, as a system for temporarily storing and processing information, relies on close collaboration among different neural circuits within the brain to form a working memory network. Particularly critical are the ventral hippocampal-medial prefrontal circuit (Spellman et al., 2015), the medial septal-hippocampal circuit (Gemzik & Griffin, 2025), and the prefrontal-medial septal neural circuit (Bortz et al., 2023). The mechanisms of each neural circuit will be detailed below.

2.1 Prefrontal-Hippocampal Working Memory Neural Circuit

Early electrophysiological studies have shown that approximately 65% of prefrontal neurons exhibit significantly elevated firing frequency during task cue presentation and maintain persistent activation during the memory delay period (Fuster & Alexander, 1971). The Goldman-Rakic theoretical model further proposes that layer III pyramidal cells in the prefrontal cortex form local microcircuits through horizontal collaterals, with their 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 caused by hyperactivity (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 its axons to structures such as the mediodorsal thalamus, mediodorsal 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). The prefrontal cortex and hippocampus are connected through multiple pathways that enable these two regions to interact and successfully execute behavioral and cognitive tasks. In mice, excitatory monosynaptic projections originating from hippocampal CA1 directly target prefrontal regions. Additionally, CA1 efferent fibers project to the entorhinal cortex, thalamic reuniens nucleus, and mediodorsal thalamus, whose neurons in turn project to the prefrontal cortex. The prefrontal cortex also sends direct or indirect neural projections to hippocampal CA1. These functional connections provide the anatomical basis for the joint participation of

prefrontal cortex and hippocampus in working memory (Spellman et al., 2015).

The hippocampus participates in spatial information processing through environment-specific neural representations. When the environment changes, its network structure rapidly reorganizes to match new scene features (O' Keefe & Conway, 1978). This dynamic coding capability forms a functional complement with the prefrontal cortex. Animal experiments have shown that during spatial working memory tasks, ventral hippocampal gamma oscillations (30~80 Hz) precede prefrontal neuronal firing by 14~33 milliseconds, and suppressing ventral hippocampal-to-prefrontal projections during the encoding phase 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 have found that the amygdala is responsible for stimulus-specific representations during the encoding phase, while the hippocampus exhibits more stable information maintenance during the maintenance phase (Li et al., 2023). This difference may stem from neural circuit differentiation across species.

2.2 Medial Septal-Hippocampal Working Memory Neural Circuit

The medial septum, as a key node of the limbic system, exhibits remarkable heterogeneity in its neuronal populations. Quantitative analysis shows that this nucleus is primarily composed of glutamatergic neurons (52%), cholinergic neurons (32%), and GABAergic neurons (16%) (Takeuchi et al., 2021). These three neuronal types form locally interconnected, dense networks within the medial septum. Activation of medial septal cholinergic neurons leads to slow activation of glutamatergic neurons, while glutamatergic activation provides more intense and rapid activation to the other two types, with all three forming recurrent connections. Notably, GABAergic neurons in the medial septum are crucial for theta oscillation synchrony in the septal neural network (Manseau et al., 2005).

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

Interestingly, the lateral septum, as a distinct structure within the septal region, sends dense projections to the medial septum while also receiving input from the hippocampus. The medial septum, in turn, feeds information back to the

hippocampus via the fornix and fimbria, forming a closed "hippocampus-lateral septum-medial septum-hippocampus" loop (Swanson & Cowan, 1979). Bidirectional neural connections exist between the medial septum and hippocampus, whereas the lateral septum only receives hippocampal input (Tsanov, 2018). This directional connectivity further demonstrates the important role of the medial septum in the "hippocampus-lateral septum-medial septum-hippocampus" closed loop.

Pharmacological studies have shown that local injection of the GABAA receptor agonist chlordiazepoxide (CDP) induces dose-dependent working memory impairments, an effect 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 have further revealed the temporal specificity of medial septal regulation. Selective inhibition of medial septal neurons significantly reduces behavioral accuracy only during the task delay period, suggesting that this nucleus plays a critical role in the information maintenance phase (Gemzik et al., 2021). Mechanistic studies have shown 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 and implanting an optical fiber to deliver blue light at 6 Hz square wave pulses to simulate theta oscillations—experimental results show that medial septal activation not only enhances local hippocampal theta oscillations (4~12 Hz) but also significantly improves performance accuracy in a 30-second delay task (Gemzik & Griffin, 2025). Further research has confirmed a direct causal relationship between medial septal functional inhibition and hippocampal theta power attenuation (Zutshi et al., 2018), highlighting its central role in oscillation generation.

At the molecular mechanism level, studies have found 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 have been shown to participate in theta oscillation regulation, with their activation enhancing theta amplitude and selective lesions causing theta power reduction (Solari & Hangya, 2018), suggesting that different neuronal subtypes work cooperatively to maintain hippocampal rhythmic activity.

2.3 Prefrontal-Medial Septal Working Memory Neural Circuit

As early as 1989, using PHA-L—a plant lectin that can be taken up by neuronal somata and anterogradely transported to synaptic terminals—researchers discovered that the medial prefrontal cortex sends dense projections 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 have also demonstrated fiber connections between the medial prefrontal cortex and lateral septum (Buchanan et al., 1994; Chiba et al., 2001), providing some evidence for cross-species consistency in these anatomical connections. Using retrograde tracing viruses, researchers found that virus injected into the medial septum was highly expressed in somata of the medial prefrontal cortex, directly demonstrating a direct neural connection between the medial prefrontal cortex and medial septum (Bortz et al. 2023). Simultaneously, using viral tracing techniques combined with chemogenetic tools, direct neural projections between the lateral septum and medial prefrontal cortex have been discovered (Liu et al., 2025).

Using the Shock-Probe Defensive Burying test (SPDB test) to measure coping strategies in rodents facing threats, researchers found that neuronal populations projecting from the prefrontal cortex to the lateral septum were activated during the SPDB test. Selective inhibition of the prefrontal-to-lateral septum pathway significantly reduced animals' burying behavior—a measure of active coping responses to external stressors. Chronic stress (such as chronic unpredictable stress, CUS) induces a shift from active burying behavior to passive freezing behavior, manifested as immobility, avoidance, or freezing defensive responses. Specific activation of the prefrontal-to-lateral septum pathway reverses the passive behavior induced by CUS. These findings suggest that the prefrontal-lateral septum pathway is a necessary neural substrate for active coping behavior in animals (Liu et al., 2025). Using strategy-shifting tests to examine cognitive flexibility—the ability to suppress old strategies and learn new rules—to investigate the regulatory mechanism of medial prefrontal-to-medial septum projections on cognitive flexibility, researchers found that activation of the medial prefrontal-medial septal neural circuit significantly improves 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 validate that both the medial and lateral septum, through close connections with the medial prefrontal cortex, participate in information processing about the external world. In summary, the medial septum, situated 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, each study is limited to different stages of working memory, making it difficult to form a unified framework to explain how different brain regions coordinate with each other across working memory stages (encoding, maintenance, and retrieval) 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. Next, we will further elaborate on information integration during work-

ing 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 is 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 posits that the brain binds distributed features into the same object through millisecond-precision neuronal synchronization (Von Der Malsburg, 1985). This hypothesis was further confirmed in Singer' s team' s research, where they first observed stimulus-dependent neuronal synchronous oscillations at the physiological level in cat visual cortex experiments (Singer, 1993). Additionally, Malsburg proposed the "superposition problem" —how the nervous system can simultaneously represent multiple information patterns in the same network while avoiding mutual 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 information interference.

Cross-frequency coupling (CFC) of neural oscillations, as an important manifestation of synchronization mechanisms, reveals the hierarchical interaction of neural electrical activity across different timescales. Current theoretical models propose that high-frequency oscillations (such as gamma oscillations, 30~40 Hz) typically represent rapid information processing in local neural ensembles, while low-frequency oscillations (such as theta oscillations, 3~7 Hz) mediate long-range information communication across brain regions through phase coding 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 primarily in three forms: phase-phase coupling (PPC), amplitude-amplitude coupling (AAC), and phase-amplitude coupling (PAC).

PPC refers to high-frequency oscillation phases being locked to specific phases of several low-frequency oscillations. Phase synchronization in PPC is also called n:m phase synchronization, where n cycles of low-frequency rhythms contain m cycles of high-frequency rhythms. PPC primarily provides precise timing for information communication (Figure 1 [Figure 1: see original paper]A). AAC refers to high-frequency oscillation amplitude (energy) changes being modulated by low-frequency oscillation amplitude (energy), also called

energy-energy coupling (Figure 1B). PAC, the most widely studied form, specifically refers to high-frequency oscillation amplitude (energy) (such as gamma oscillations, 30~140 Hz) being locked to the phase of low-frequency rhythms and modulated by low-frequency oscillation phase (such as theta oscillations, 3~7 Hz). This cross-frequency modulation is considered the interface between local information processing and global cognitive control (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 Lixin et al., 2017).

Figure 1. Schematic diagram of cross-frequency coupling of neural oscillations. (A) Phase-phase coupling (PPC); (B) Amplitude-amplitude coupling (AAC); (C) Phase-amplitude coupling (PAC).

Theta-gamma phase-amplitude coupling (TG-PAC), as a typical paradigm of cross-frequency coupling, refers to the coupling relationship between the phase of low-frequency theta oscillations (4~8 Hz) and the amplitude of high-frequency gamma oscillations (30~100 Hz). As a neural coding mechanism, TG-PAC may facilitate information transmission by coordinating neural activity across different brain regions or different locations within the same region, thereby playing an important role in working memory (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 timescales through temporal compression and phase segregation strategies (Zhang Lixin 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 (cycle 200 ms) and gamma is 40 Hz (cycle 25 ms), each theta cycle can accommodate 8 gamma subcycles, approximating classical memory capacity. Moreover, as memory load increases, gamma power and theta-gamma coupling strength increase accordingly until reaching saturation (Lisman & Idiart, 1995). Each cycle of theta oscillation serves as a basic temporal window that segments information in working memory into discrete time periods. Each theta cycle (100~200 ms) nests multiple gamma cycles (25~50 ms), with each gamma cycle representing an independent memory item (such as digits, object features) and forming 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, and TG-PAC coupling strength can predict individual working memory task performance (Axmacher et al., 2010).

In gamma oscillation cycles, dynamic inhibitory neural networks have impor-

tant influences on the breadth and precision of working memory. According to the E%-MAX theory—a neural computational mechanism based on dynamic inhibitory networks—the core of this mechanism is that within each gamma cycle, only neurons whose excitatory (E) input reaches a certain percentage (E%) of the maximum excitatory input (Emax) in that cycle 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 the activation threshold of neurons. The E% value is jointly determined by two factors: the delay time of feedback inhibition (d) (the time for inhibitory signals to return after excitatory neurons trigger interneurons), and the decay time constant of inhibitory postsynaptic potentials (tau) (De Almeida et al., 2009).

Figure 2. How global inhibition in gamma oscillation cycles determines which neurons fire. The three lines with different grayscale shades in the image represent three types of neurons with excitability ranging from strong to weak within a gamma cycle: light gray represents the most excitable neurons, medium gray represents moderately excitable neurons, and black represents weakly excitable neurons. In a gamma cycle, as inhibition from interneurons to surrounding neurons decays (determined by the time constant tau of inhibitory postsynaptic potentials), the most excitable neurons fire first. Once a neuron fires, it triggers global feedback inhibition through fast inhibitory interneurons, preventing other neurons from continuing to fire. However, due to the delay in feedback inhibition transmission (d), during this delay window, other neurons with excitability slightly lower than the most excitable neurons (moderately excitable neurons) also have the opportunity to fire.

Within working memory gamma oscillation cycles, inhibitory interneurons periodically 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 of slightly 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 occur earlier, more effectively suppressing neuronal ensembles representing other items with weaker excitability, thereby preventing cross-interference between different memory items and enhancing information processing accuracy. Conversely, when the E% threshold is low, 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 inhibitory network dynamically regulates the E% of neuronal activation, enabling the brain to achieve a balance between information precision and breadth to adapt to different cognitive demands.

In summary, during working memory processes, through phase-dependent gain control—the phenomenon where neuronal response magnitude (gain) to input signals dynamically changes with local field potential oscillation phase—TG-PAC integrates temporal coding and content coding in working memory. Theta os-

cillations determine the sequence of processing different information, gamma oscillations determine which information is processed, and the nesting of gamma within theta oscillations explains why working memory possesses both temporal accuracy and content stability. Next, we will further dissect the mechanisms by which TG-PAC participates in working memory by combining specific brain regions and neural circuits.

3.2.1 Neural Mechanisms of Hippocampal Theta-Gamma Coupling in Working Memory Regulation

Hippocampal gamma oscillations play a critical role in memory encoding, retrieval, and integration. The hippocampus contains two main gamma oscillation generators—neural circuits capable of independently generating gamma oscillations. One appears in CA3 and propagates to CA1; 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. Specifically, slow gamma oscillations (25~50 Hz) generated by hippocampal CA3 and transmitted via the CA3-CA1 pathway have enhanced synchronization correlated with memory retrieval task performance. In contrast, fast gamma oscillations (65~140 Hz) generated by the entorhinal cortex and transmitted via the entorhinal-dentate gyrus pathway are responsible for conveying current environmental information to CA1 and primarily participate in memory encoding (Colgin & Moser, 2010). Notably, fast and slow gamma appear at different phases of the theta oscillation cycle and are regulated by theta oscillations.

Hippocampal theta primarily exists in two types: atropine-sensitive theta and atropine-resistant theta. Atropine-sensitive theta is mainly generated by cholinergic input from the medial septum. Medial septal cholinergic neurons project via the fornix to all hippocampal regions (CA1, CA3, and dentate gyrus), releasing acetylcholine to enhance the excitability of hippocampal pyramidal cells and interneurons, generating hippocampal atropine-sensitive theta, which is characterized by lower frequencies and may function in information encoding or environmental monitoring. In contrast, 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, which enhances excitatory input from entorhinal cortex to hippocampal CA1, generating hippocampal atropine-resistant theta characterized by higher frequencies and potentially related to motor control and behavioral execution mechanisms (Kramis et al., 1975; Leung, 1998). Interestingly, both the raphe nucleus and entorhinal cortex are regulated by the medial septum, with medial septal GABAergic neurons potentially coordinating their activities to ensure spatiotemporal synchronization of theta oscillations. This article focuses primarily on atropine-sensitive theta activity and proposes that it plays a critical role in working memory information encoding. In addition to theta oscillations from other brain regions, the hippocampal CA3 region

can also independently generate theta oscillations. CA3 pyramidal neurons form strong feedback connections through excitatory synapses, constituting a self-oscillating system. Moreover, pyramidal neurons typically drive inhibitory interneurons, forming feedback inhibitory loops that generate rhythmic theta activity (Buzsáki, 2002).

Single-unit activity and local field potential recordings from epilepsy patients have shown that the coupling strength between hippocampal theta oscillations (3~7 Hz) and gamma oscillations is related to memory load. Under high memory load, hippocampal TG-PAC weakens, gamma oscillations become more dispersed, and the regulatory efficiency of theta rhythms decreases. Conversely, under low memory load, TG-PAC is stronger and theta regulatory efficiency is higher. The study also found that stronger TG-PAC is associated with faster response speeds in subjects (Daume et al., 2024). This suggests that under low memory load, 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, under high memory load, coordination with higher-order brain regions may be required to complete working memory information processing. Indeed, experimental results show that under high memory load, prefrontal theta oscillations and hippocampal PAC neurons (neurons whose firing activity is regulated by TG-PAC) show enhanced synchrony. In this condition, 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, in experiments, hippocampal TG-PAC power did not change significantly with memory load, suggesting that it may depend on local generation—either produced 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 from rat hippocampus show that theta-gamma coupling strength dynamically changes with task phases, exhibiting 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 working memory impairment model induced by low-frequency electromagnetic field exposure, hippocampal theta power, gamma power, and theta-gamma coupling strength all significantly attenuate with prolonged exposure time (Y. Zhang et al., 2017). Human intracranial EEG studies have confirmed that when epilepsy patients perform Sternberg tasks, theta-gamma phase coupling strength peaks during the working memory maintenance phase, forming cross-species correspondence with animal experimental conclusions (Chaieb et al., 2015). These findings indicate 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 cou-

pling have received extensive attention. Selective removal of synaptic inhibition from parvalbumin-positive (PV+) interneurons leads to significant reduction of theta oscillations in CA1 and disruption of characteristic theta-gamma coupling patterns (Wulff et al., 2009). Intervention experiments with the NMDA receptor antagonist MK801 show that the drug enhances gamma oscillations while disrupting theta-gamma coupling during working memory (Abad-Perez et al., 2023). These studies indicate that hippocampal interneurons regulate local network oscillations through GABAergic inhibitory systems, while glutamate receptor-mediated excitation/inhibition balance constitutes the neurochemical basis for maintaining theta-gamma coupling homeostasis. These findings not only deepen our understanding of the neural mechanisms of theta-gamma coupling but also provide potential targets for interventions in cognitive dysfunction.

3.2.2 Neural Mechanisms of Prefrontal Theta-Gamma Coupling in Working Memory Regulation

During attention or working memory tasks, recording local field potentials from the prefrontal cortex can independently detect prefrontal gamma oscillations (Gregoriou et al., 2009). This experiment demonstrates that the prefrontal cortex can independently generate gamma oscillations and that gamma oscillations may function in working memory information processing. The prefrontal cortex possesses abundant inhibitory interneurons and pyramidal neurons, providing the anatomical basis for generating gamma oscillations (Fries, 2015). Gamma oscillations are generated internally through two main mechanisms: the first involves excitatory drive from pyramidal neurons, with interneurons activated and providing feedback through GABAergic inhibition to form rhythmic activity; the second depends solely on mutual inhibition between inhibitory interneurons. In addition to internally generated gamma oscillations, prefrontal gamma oscillations are also modulated by input from sensory cortices (such as visual cortex V4) and hippocampal theta oscillations (Benchenane et al., 2011).

The prefrontal cortex's ability to generate theta oscillations intrinsically is generally weak, and its theta activity mainly depends on external input (particularly from the hippocampus). The hippocampus can transmit theta oscillations to the prefrontal cortex through direct or indirect projections (via thalamus or entorhinal cortex) (Benchenane et al., 2011). The firing phase of prefrontal neurons is modulated by hippocampal theta rhythms, mediating inhibitory control of pyramidal cells by prefrontal interneurons, thereby forming synchronized cell ensembles that fire synchronously at the troughs of hippocampal theta, enhancing information transmission efficiency (Benchenane et al., 2010). When the hippocampal-to-prefrontal pathway is inhibited, the prefrontal cortex still retains some theta activity, further demonstrating the relative independence of prefrontal theta activity from the hippocampus (O' Neill et al., 2013).

By recording local field potentials from the hippocampus and prefrontal cortex, researchers have analyzed theta-band coherence between them—a metric used

to measure neural oscillation synchrony across brain regions, with higher coherence generally indicating better information transmission efficiency. Studies have found that during decision-making phases, hippocampal-prefrontal theta coherence is significantly enhanced, and trials with higher coherence also show higher accuracy. Moreover, during high coherence periods, prefrontal pyramidal neuron firing shifts from theta peaks to troughs, while interneurons synchronize prefrontal neurons through inhibition of pyramidal cells, forming functional ensembles that ensure the prefrontal cortex processes and receives information from the hippocampus at the correct time (Benchenane et al., 2010). That is, the hippocampus synchronously modulates prefrontal neuronal firing patterns through theta oscillations, thereby influencing the information consolidation process in working memory.

Additionally, using cross-frequency transcranial alternating current stimulation (tACS) paradigms—superimposing continuous theta oscillations (4~8 Hz) with high-frequency gamma pulses (80 Hz) in the prefrontal cortex—has successfully simulated physiological theta-gamma coupling patterns (Alekseichuk et al., 2016). This experimental design breaks through the frequency limitations of traditional in vitro electrical stimulation, achieving precise control over gamma pulse phase and theta peak time windows. Results show that when 80 Hz gamma pulses are phase-locked to theta peaks, working memory performance exhibits the most significant enhancement, revealing the critical role of phase specificity in theta-gamma coupling for working memory encoding efficiency. This in vitro intervention paradigm not only validates the neural coding hypothesis that theta oscillations serve as temporal frameworks and gamma activity as information carriers, but also provides important experimental evidence for developing cognitive enhancement technologies.

Transcranial direct current stimulation (tDCS) studies have further expanded our understanding of prefrontal theta-gamma coupling functions. By enhancing prefrontal activity with anodal tDCS, a positive correlation between theta-gamma coupling strength and working memory performance was observed (Jones et al., 2020). This study suggests that prefrontal theta-gamma coupling may optimize the dynamic maintenance mechanism of working memory by regulating temporal synchrony in neural networks. Notably, in high-load tasks, the enhancement magnitude of prefrontal theta activity shows a linear correlation with memory capacity, while the modulation of posterior cortical beta (13~30 Hz) and gamma (>30 Hz) amplitude by theta phase reflects the cooperative working mechanism of the prefrontal-parieto-occipital network (Fernández et al., 2021). Specifically, enhanced occipital beta oscillations may be related to sustained activation of visual representations, while enhanced parietal gamma activity may reflect dynamic allocation of spatial attention resources.

These studies reveal the central role of prefrontal theta-gamma coupling in multi-level cognitive regulation: theta oscillations provide temporal frameworks for working memory through phase reset mechanisms, while gamma activity

achieves precision regulation of information representation through amplitude modulation. This cross-frequency coupling mechanism not only supports dynamic maintenance of working memory but also achieves coordinated 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 role of functional neural circuit coupling mechanisms in cross-regional cognitive coordination has always been a frontier proposition in neuroscience, with low-frequency oscillations (such as theta) facilitating cross-regional synchronous control of gamma oscillations (Bonnefond et al., 2017). As shown in Figure 3 [Figure 3: see original paper], cross-regional neural communication depends on phase synchronization of theta oscillations, 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. That is, information-sending and information-receiving brain regions first synchronize through high coherence of theta oscillations. Then, the information-sending brain region bursts gamma activity at a specific theta phase. This gamma activity carries specific information. The receiving brain region, because its theta oscillations are synchronized with the sending region, is most sensitive to information input during the same theta phase segment, thereby most effectively receiving and decoding gamma information from the sending region.

Figure 3. Coupling between low-frequency oscillation (such as theta) phase and gamma power can promote inter-regional information coordination at the same frequency. (A) When neurons in brain regions A and C communicate, they engage in coherent same-frequency oscillations through low-frequency bands (such as theta), with gamma oscillations typically nested within theta oscillations, i.e., TG-PAC. Therefore, gamma activity in region A can be transmitted to neurons in region C, and gamma oscillations in A and C will maintain the same frequency. Brain region B serves as an important external driver of low-frequency oscillations for region C, indirectly influencing TG-PAC between regions A and C. (B) In the diagram, triangles, circles, and squares represent glutamatergic, GABAergic, and cholinergic neurons, respectively. The diagram shows neural connections among the prefrontal cortex, medial septum, and hippocampus. Within the medial septum, the three neuron types form locally interconnected dense networks. Medial septal GABAergic and glutamatergic neurons primarily terminate on GABAergic neurons in hippocampal CA1. Hippocampal CA1 glutamatergic neurons project to prefrontal regions. The prefrontal cortex has synaptic connections with both medial and lateral septum. Theta-gamma phase-

amplitude coupling between prefrontal cortex and hippocampus, and between medial septum and hippocampus, is also indicated by waveforms across the three brain regions.

As a core hub of the limbic system, the coupling mechanisms between the hippocampus and multiple brain regions have always been a research hotspot. Among these, the functional specificity of the hippocampal-prefrontal circuit in working memory networks has been systematically elucidated. Specifically, hippocampal CA1 subfield directly targets the prefrontal cortex through monosynaptic projections, and this anatomical pathway shows 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 have shown that selective inhibition of hippocampal CA1-to-prefrontal glutamatergic projections leads to significant deficits in cognitive representations during the encoding phase, with no significant effects on memory maintenance and retrieval processes (Spellman et al., 2015). This anatomical evidence demonstrates bidirectional communication between the hippocampus and medial prefrontal cortex.

Neuroelectrophysiological studies have shown that oscillatory coupling in the hippocampal-prefrontal circuit has dynamic regulatory characteristics. Theta oscillations in hippocampal CA1 are transmitted to the prefrontal cortex via monosynaptic projections, driving prefrontal theta synchronization. During hippocampal-prefrontal theta synchronization, prefrontal pyramidal cells are under inhibitory control from interneurons, forming synchronized cell ensembles that facilitate information transmission (Benchenane et al., 2010). Furthermore, prefrontal theta oscillations exert top-down regulation on local hippocampal gamma activity through long-range phase synchronization, forming theta-gamma phase-amplitude coupling (TG-PAC). Through PAC neurons (Phase-Amplitude coupling neurons)—neurons whose firing activity is simultaneously regulated by theta phase and gamma amplitude—long-range, rhythmic control signals (prefrontal theta) are transformed into local, structured regulatory information, thereby finely tuning the population coding efficiency of hippocampal 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), and the temporal locking characteristics of these high-frequency oscillations positively correlate with behavioral performance (Fernández et al., 2021). Additionally, by analyzing gamma oscillation phase differences between prefrontal cortex and hippocampus during working memory tasks, researchers found that when mice perform DNMTS tasks requiring working memory and are in the selection phase, prefrontal gamma oscillation phase leads vCA1. This suggests that during working memory information encoding, the hippocampus provides information to the prefrontal cortex via gamma oscilla-

tions, but during the selection phase requiring decision-making and response output, there may be a neural mechanism where the prefrontal cortex sends executive control signals to the hippocampus through gamma oscillations (De Mooij-van Malsen et al., 2023).

At the cellular mechanism level, electrophysiological feature analysis shows that hippocampal PAC neurons (neurons in the hippocampus whose firing activity is simultaneously modulated by low-frequency theta oscillation phase and high-frequency gamma oscillation amplitude) primarily exhibit narrow action potentials, a characteristic consistent with electrophysiological properties of inhibitory interneurons (such as PV+ cells). Hippocampal PAC neurons optimize neural information processing through two key mechanisms: first, through local inhibition achieving temporal desynchronization, enabling different neuronal populations to be independently activated at specific phases of theta cycles, thereby supporting encoding of multi-item working memory (György, 2006); second, through shunting inhibition and threshold regulation, selectively enhancing pyramidal cell response sensitivity to prefrontal control signals, while simultaneously reducing spontaneous activity of 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 enhancing the gain of gamma clusters related to specific memory items while suppressing competing neural representations.

Pharmacological intervention studies provide causal evidence for this mechanism. When the NMDA receptor antagonist MK-801 selectively acts on dorsal CA1 and medial prefrontal cortex, abnormal enhancement of hippocampal gamma power accompanied by theta-gamma coupling disruption can be observed, 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 is significantly correlated with theta-gamma frequency-domain energy coupling strength in the hippocampal-prefrontal circuit, suggesting that MK-801 may cause working memory dysfunction by disrupting the 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 regulate local circuits and optimize working memory information storage and retrieval by coupling with hippocampal gamma activity through PAC neurons. Hippocampal gamma oscillations represent the neural encoding of environmental information, and the biological basis of their regulation may involve specific prefrontal projections to hippocampal inhibitory interneurons. Inhibitory neurons optimize information transmission efficiency between prefrontal cortex and hippocampus through temporal desynchronization and spatial gain regulation. This refined neural mechanism supports 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 fine 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 a feedforward inhibitory regulatory loop that modulates hippocampal pyramidal cell excitatory output (Unal et al., 2015).

Functional inactivation experiments have revealed the necessity of the medial septal-hippocampal circuit for working memory. Local injection of muscimol (a GABAA receptor agonist) into the medial septum to suppress neuronal excitability resulted in significant spatial memory impairments in experimental rats compared to saline controls, accompanied by a sharp decrease 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 a significant positive correlation with episodic memory success rate. Control animals showed high theta-gamma coupling and good memory performance, while the medial septal inhibition group exhibited dual deficits of decreased coupling strength and increased behavioral error rates (Shirvalkar et al., 2010).

Medial septal neuronal firing not only couples to hippocampal theta oscillation phase but also specifically couples to different beta or gamma oscillations, playing a multi-timescale coordinating role in memory encoding and retrieval. In hippocampal CA1 local field potentials, higher-frequency oscillations nested within theta oscillations are called theta-nested spectral components, including beta/gamma frequency bands, abbreviated as tSCs. The medial septum influences hippocampal tSCs through direct or indirect pathways. Its direct pathway involves medial septal GABAergic neurons directly projecting to hippocampal interneurons, promoting gamma oscillations through disinhibition of CA1 pyramidal neurons, and medial septal neuronal gamma-frequency firing synchronizes with gamma phase of CA1 local field potentials. Its indirect pathways include medial septal orchid cells projecting to CA1 via the entorhinal cortex, regulating tSC3/tSC4 and influencing information encoding processes; additionally, medial septal tevra cells project to CA1 via CA3, regulating memory retrieval processes. Meanwhile, the hippocampus directly projects to the medial septum through SOM+ interneurons, particularly targeting medial septal PV+ "pacemaker"neurons, forming an inhibitory feedback loop that dynamically suppresses the driving strength of medial septal control over 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 or indirect loops to participate in memory encoding and retrieval. Meanwhile, hippocampal-to-medial septal GABAergic inhibitory feedback dynamically regulates medial septal PV-positive neuronal activity, ensuring that tSCs appear at the correct time and frequency to prevent excessive neuronal population synchronization from damaging memory encoding.

Furthermore, studies on neurotransmitter system interactions have revealed the complexity of medial septal regulation. Specific activation of medial septal cholinergic neurons significantly enhances hippocampal acetylcholine concentration, accompanied by increased theta/gamma power, yet leads to impaired working memory performance (Y. Zhang et al., 2021). This paradoxical phenomenon suggests that the cholinergic system may have an inverted U-shaped dose-response effect, or there may be interactive regulation with the GABAergic system. Research shows that medial septal GABAergic neurons mediate spatial memory effects through the mechanism of regulating hippocampal acetylcholine release (Roland et al., 2014), indicating that the two neuronal populations form functional microcircuits that jointly maintain cognitive function homeostasis. Serotonergic system studies further support this view: medial septal serotonin depletion leads to reduced hippocampal low-frequency theta activity and compensatory enhancement of high-frequency theta activity, accompanied by decreased working memory error rates (López-Vázquez et al., 2014); while 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 phenomena are not only closely related to normal cognitive function but also play an important role in the pathological mechanisms of psychiatric disorders. Clinical studies have shown that patients with mild cognitive impairment exhibit significantly reduced theta-gamma coupling strength in hippocampal-cortical circuits (Van Den Berg et al., 2023), while depression model rats show theta-gamma phase-amplitude modulation abnormalities in the right auditory cortex (He et al., 2023), suggesting that this neuroelectrophysiological 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 (CFC) shows significant attenuation, and this electrophysiological change is negatively correlated with reduced amyloid protein deposition in the brain (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: after implementing hippocampal-targeted transcranial alternating current stimulation (tACS) in Alzheimer' s disease patients, enhanced theta-gamma coupling shows significant positive correlation with cognitive function improvement (Tang et al., 2024), suggesting that neural modulation based on theta-gamma oscillations may become a new therapeutic strategy for Alzheimer' s disease. In schizophrenia research, theta-gamma coupling abnormalities show direct associations with working memory deficits. Under the 3-Back task paradigm, schizophrenia patients show synchronized decreases in theta-gamma coupling strength and task accuracy, while healthy controls exhibit significant positive correlation between theta-gamma coupling and behavioral performance (Barr et al., 2017). These findings not only reveal the central role of theta-gamma coupling in the pathological mechanisms of schizophrenia but also suggest its predictive validity as an objective indicator for disease assessment.

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 neural circuit in working memory. Working memory, as a higher-order cognitive function, depends on the coordinated action of distributed neural networks composed of the prefrontal cortex, hippocampus, and medial septum. The three-node theta-gamma phase-amplitude coupling mechanism of the prefrontal-hippocampal-medial septal circuit provides a crucial 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) forming temporal windows for cognitive control via phase modulation of gamma activity (30~80 Hz). As a hub for spatial information processing, the hippocampus implements spatial navigation and working memory binding through theta-gamma nested coding (referring to high-frequency gamma oscillations nested at specific phases of low-frequency theta oscillations, a broader concept encompassing theta-gamma phase-amplitude coupling, where PAC can quantify theta phase modulation of gamma amplitude). 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 and influences animal cognitive activity. Simultaneously, medial septal cholinergic and GABAergic neurons regulate hippocampal theta-gamma phase-amplitude coupling intensity and spatiotemporal characteristics by modulating hippocampal theta oscillations, thereby regulating working memory efficiency. Particularly noteworthy is that medial sep-

tal GABAergic neurons (especially the Teevra-labeled subpopulation) exhibit prominent theta-oscillatory firing characteristics and are considered pacemakers of hippocampal theta oscillations (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: the prefrontal cortex (cognitive control center), medial septum (rhythm generator), and hippocampus (information processing center). Among them, the medial septum provides a temporal organizational framework for information temporary storage through theta oscillations while simultaneously implementing top-down regulation of hippocampal information processing, forming a functionally complete system.

Studies of neuropsychiatric disorders further highlight the clinical relevance of this mechanism. Schizophrenia patients exhibit abnormal theta-gamma phase-amplitude coupling in the prefrontal-hippocampal circuit accompanied by working memory deficits; Alzheimer' s disease models show that hippocampal theta-gamma coupling strength is negatively correlated with amyloid protein 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.

The dissection of theta-gamma phase-amplitude coupling mechanisms in the prefrontal-hippocampal-medial septal circuit not only deepens our understanding of the neural basis of working memory but also opens innovative pathways for treating neuropsychiatric disorders. However, translational applications in this field still face critical challenges. Specifically, there are several limitations in current research and directions for future expansion:

(1) **Cross-species validation:** Current medial septum research primarily relies 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 combined scanning) to explore the regulatory mechanisms of the prefrontal-hippocampal-medial septal circuit on working memory.

(2) **Cellular mechanism dissection:** Future studies should utilize transgenic animal models combined with optogenetics to dissect the targeted regulatory pathways of different medial septal neuronal subtypes (PV+, ChAT+, etc.) on the hippocampal-prefrontal circuit and their dynamic contributions during working memory encoding, maintenance, and retrieval phases.

(3) **Clinical translation needs:** Develop neural modulation paradigms based on theta-gamma phase-amplitude coupling, such as tACS targeting enhancement of theta-gamma coupling, to evaluate its improvement effects on 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 a theoretical framework for developing closed-loop neural feedback systems.

In domestic and international research, most studies have focused on hippocampal local oscillations or bidirectional coupling between hippocampal-prefrontal circuits in working memory processes. Although there have been numerous reports on theta-gamma phase-amplitude coupling in hippocampal-prefrontal and hippocampal-medial septal circuits, functional connectivity between prefrontal cortex and medial septum has been less studied due to technical limitations. Current research has demonstrated direct neural connections between prefrontal cortex and medial septum (Bortz et al., 2023). Future studies could combine optogenetics with multi-channel recordings to verify the regulatory role of the prefrontal-to-medial septum neural circuit in working memory. Particularly noteworthy is whether there exists a certain temporal difference between prefrontal neuronal firing and medial septal theta oscillations, and the differences and connections between prefrontal theta oscillations and medial septal theta oscillations warrant further investigation. Future research needs to integrate multimodal neuroimaging, cell-resolution recordings, and precise neuromodulation technologies to reveal the causal role of theta-gamma phase-amplitude coupling between prefrontal cortex and medial septum in cognitive dysfunction, promoting clinical translation of rhythm-based interventions.

Additionally, simultaneous recording of hippocampal and prefrontal field potentials after local dopamine injection into the prefrontal cortex revealed that dopamine injection significantly increases theta coherence between hippocampus and prefrontal cortex, positively correlates with task accuracy, and induces 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, starting from theta oscillations generated by the medial septum and analyzing neural connections between medial septum and hippocampus, proposes that the medial septum may play a critical role in working memory information processing. It is also the first to integrate the coupling mechanism of the three-node prefrontal-hippocampal-medial septal circuit, further refining the neural circuitry of working memory. Future research should combine multimodal neuroimaging techniques (such as fMRI-EEG combined recordings) with interventional modulation methods (such as optogenetics and transcranial alternating current stimulation) to systematically dissect the dynamic coding mechanisms of this circuit across different cognitive stages and explore the application potential of theta-gamma coupling-based neural modulation paradigms in treating cognitive dysfunction. These studies will deepen our understanding of the neural basis of working memory and provide innovative biomarkers and

therapeutic targets for diagnosing and treating neuropsychiatric disorders.

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