The Application of Simultaneous TMS-EEG Technology in Psychological Research

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Abstract

Simultaneous transcranial magnetic stimulation-electroencephalography (TMS-EEG) is a technology that synchronously integrates transcranial magnetic stimulation with electroencephalographic recording. On the one hand, EEG can record the transient neuroelectrophysiological responses elicited by TMS pulses; on the other hand, the delivery of TMS pulses can also be implemented for state-dependent precise modulation based on recorded EEG signals. Combining these two characteristics, this article proposes and systematically reviews three primary application modes of simultaneous TMS-EEG in psychological research: neurophysiological assessment, causal investigation of neural mechanisms, and closed-loop brain modulation. Centering on these three main threads, the article distinguishes and compares differences among various modes in terms of working mechanisms, experimental protocols, and application objectives, and synthesizes relevant psychological studies from the past decade to summarize the main findings of existing research under each mode, aiming to provide a clear theoretical framework and practical guidelines for the application of simultaneous TMS-EEG technology.

Full Text

Preamble

Synchronous transcranial magnetic stimulation-electroencephalography (TMS-EEG) is a technique that integrates transcranial magnetic stimulation with simultaneous electroencephalographic recording. This approach enables the capture of instantaneous neurophysiological responses evoked by TMS pulses while also allowing for state-dependent, precisely timed brain interventions guided by real-time neural monitoring. In this review, we propose and systematically examine three primary application modes of synchronous TMS-EEG in psychological research: neurophysiological assessment, causal neural mechanism investigation, and closed-loop brain modulation. We organize our discussion around

these three themes, distinguishing and comparing their working mechanisms, experimental protocols, and application objectives. By synthesizing relevant psychological research from the past decade, we summarize key findings from each mode to provide a clear theoretical framework and practical guidance for researchers employing synchronous TMS-EEG.

Keywords: synchronous TMS-EEG, neurophysiological assessment, virtual lesion, causal neural mechanisms, closed-loop modulation

In contemporary neuroscience research, the combination of brain modulation and observation techniques is widely employed to investigate how altered activity in specific brain regions influences brain function and behavior, providing a foundation for understanding brain mechanisms and developing clinical interventions. However, many such studies focus on the aftereffects of brain modulation, assessing changes in brain activity and function only after stimulation has ceased. This approach primarily examines long-term effects and neuroplasticity induced by brain modulation (Goldenkoff et al., 2025; Heath et al., 2023; Sohn et al., 2024; Ye et al., 2022; Zhen et al., 2025) but cannot observe real-time dynamic responses during stimulation.

To address this limitation, researchers have turned to real-time synchronous integration of brain modulation and observation methods. This approach not only records instantaneous neurophysiological reactions during stimulation but also enables precise magnetic or electrical pulses to be triggered based on real-time brain signals, thereby achieving closed-loop regulation of targeted brain regions (Hernandez-Pavon et al., 2023; Ilmoniemi et al., 1997; Zrenner & Ziemann, 2024). Real-time synchronous technology provides direct evidence for revealing causal mechanisms of brain function, network dynamics, and state-dependent brain function, establishing itself as a frontier technique in modern neuroscience.

The integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) represents a key exemplar of such real-time synchronous technology. TMS is a non-invasive brain modulation technique that generates magnetic field pulses through rapidly changing currents in a coil, which penetrate the skull to induce currents that alter cortical neuronal membrane potentials (typically "depolarization") and may facilitate or hinder action potential firing, thereby changing local excitatory or inhibitory states (Barker et al., 1985; Hernandez-Pavon et al., 2023). EEG, a core brain observation technique, records electrical activity via scalp electrodes, with signals originating from field changes produced by synchronized discharges of large neuronal populations in the cerebral cortex (Ojha et al., 2024; Rossini et al., 2025). In 1997, Ilmoniemi and colleagues first achieved real-time synchronous TMS-EEG acquisition (Ilmoniemi et al., 1997), enabling scientists to immediately observe TMS-evoked neurophysiological responses (Hernandez-Pavon et al., 2023; Lefaucheur, 2019; Valero-Cabré et al., 2017).

Combining TMS with EEG offers at least three methodological advantages.

First, TMS-evoked potentials (TEPs) serve as objective indicators for assessing cortical excitability and excitation-inhibition balance in target regions (Bortoletto et al., 2015; Julkunen et al., 2022). Second, applying TMS during critical time windows of cognitive tasks can instantaneously alter neural activity in target regions while simultaneously recording task-related neural changes via EEG, revealing the temporal dynamics and information propagation pathways of brain regions during cognitive activity (Miniussi & Thut, 2010; Ziemann et al., 2015). Third, when EEG is used to monitor brain states in real time to determine TMS pulse timing, synchronous TMS-EEG enables state-dependent closed-loop modulation, greatly enhancing intervention specificity and efficacy (Ding et al., 2022; Zrenner et al., 2018).

Based on these features, we delineate three application modes. First, in neurophysiological assessment, single-pulse TMS (spTMS) or paired-pulse TMS (ppTMS) combined with EEG evaluates cortical excitation-inhibition balance and plasticity in healthy and clinical populations through TEPs, cortical oscillations, and network connectivity metrics (Cao.K et al., 2021; Dworkin et al., 2025; Farzan, 2024). Second, in causal neural mechanism studies, TMS pulses delivered during specific task phases or precise timepoints transiently alter target region activity while synchronously recording EEG and behavioral changes, revealing spatiotemporally specific causal roles of neural activity in brain function and dynamic signal propagation mechanisms (Fong et al., 2023; Hill et al., 2016; Thong et al., 2025). Third, in closed-loop brain modulation, real-time EEG activity determines optimal TMS timing to test and exploit state-dependent relationships between neural activity and function, exploring precise intervention pathways for cognitive functions or clinical symptoms (Chen.H et al., 2025; Ding et al., 2022; Poorganji et al., 2023). This framework follows a progressive logic from basic measurement to causal exploration to precise modulation, advancing from assessment of relatively "static" neurophysiological states to elucidation of dynamic causal mechanisms and ultimately to fine-grained regulation of state-dependent brain function, demonstrating the multi-level characteristics and application value of TMS-EEG technology.

Although synchronous TMS-EEG shows unique potential across these three modes, systematic methodological exposition and summary remain lacking. This review aims to synthesize the basic principles, methodological considerations, and major findings of the technique across these three modes. We first elaborate on the fundamental principles and working mechanisms of each mode. We then conducted literature searches on PubMed, Web of Science, and Google Scholar using keywords including TMS-EEG, concurrent TMS-EEG, online transcranial magnetic stimulation-electroencephalography, TMS-evoked potential, virtual lesion, and closed-loop, covering the period from 2015 to July 2025. We analyzed and summarized representative applications and key findings for each mode. Finally, we discuss current challenges and propose future research directions to provide theoretical reference and practical guidance for promoting synchronous TMS-EEG in psychological research.

2.1 Neurophysiological Assessment

From a physiological perspective, TMS induces local cortical neuronal depolarization, trans-synaptic signal transmission, and propagation of neural activity across corticospinal and corticocortical pathways. Recording these neural and physiological responses following TMS application thus holds significant neurophysiological meaning. These responses not only reflect local cortical excitability and excitation-inhibition balance but also reveal information transmission and network interaction states between different brain regions, providing objective and quantifiable indicators for assessing dynamic brain function characteristics.

In this domain, an early and widely used method is the synchronous combination of TMS with electromyography (TMS-EMG), typically employed to assess primary motor cortex excitability through motor evoked potentials (MEPs). This approach has been extensively applied in diagnosing and researching neurological or psychiatric movement disorders (Che et al., 2021; Rossini et al., 2015). However, EMG primarily reflects peripheral motor output, limiting central nervous system assessment to the primary motor cortex and failing to directly capture electrophysiological activity and functional states of other brain regions. In contrast, synchronous TMS-EEG can evaluate cortical excitability across broader brain regions and reveal functional connectivity and network dynamics based on EEG oscillatory characteristics and frequency-domain parameters, offering a more comprehensive and direct perspective for exploring complex brain functional organization (Ilmoniemi & Kičić, 2010; Rogasch & Fitzgerald, 2013).

When used for neurophysiological assessment, synchronous TMS-EEG primarily measures TEPs evoked by single magnetic pulses (spTMS). TEPs represent time-locked and phase-locked neural electrical activity in response to TMS pulses, reflecting the excitatory or inhibitory state of local cortex and its functional connectivity network post-stimulation. Typical TEP components include N15, P30, N45, P60, N100, and P180, which correspond to distinct neurophysiological processes and have been widely used to assess cortical excitability (Julkunen et al., 2022; Tremblay et al., 2019). Specifically, early components N15 and P30, located near the stimulated region, reflect motor cortex excitability but often overlap with TMS artifacts, resulting in low signal-to-noise ratios (Farzan & Bortoletto, 2022). The N45 component correlates with GABA_A receptor-mediated inhibitory processes and serves as an indicator of inhibitory neurotransmission levels. The P60 component is closely linked to somatosensory input, with studies showing significant amplitude differences between conditions with and without MEP elicitation (Petrichella et al., 2017). The N100 component is often considered a marker of widespread cortical inhibition, though some research suggests that N100-P180 may relate to auditory evoked responses from the TMS coil and thus be considered part of the auditory evoked potential (Nikouline et al., 1999; Varone et al., 2021). Through analysis of these TEP components, researchers can assess neuroresponse characteristics and excitation-inhibition balance in target regions (Bortoletto et al., 2015; Chung et al., 2015).

Beyond spTMS, paired-pulse TMS (ppTMS) modes enable more precise measurement and evaluation of intracortical inhibition and facilitation states. ppTMS involves delivering two TMS pulses in short succession: a conditioning stimulus (CS) and a test stimulus (TS). The CS uses intensity below resting motor threshold (RMT) to "pre-activate" three neuronal populations: GABA_A (fast-conducting) and GABA_B (slow-conducting) mediated inhibitory neurons, and NMDA receptor-mediated excitatory neurons (intermediate conduction speed). By delivering TS (intensity above RMT) at different intervals after CS, researchers can assess CS-TS neuromodulatory effects via TS-evoked TEPs to infer functional states of the target region. Corresponding to these three neuronal populations, ppTMS modes are categorized by inter-pulse intervals: (1) short-interval intracortical inhibition (SICI) using 1-5 ms intervals to assess GABA_A-mediated fast synaptic inhibition (Di Lazzaro et al., 2007; Ziemann, 2003); (2) intracortical facilitation (ICF) using 8-30 ms intervals to evaluate NMDA-mediated glutamatergic excitatory pathways (Ferrarelli & Phillips, 2021); and (3) long-interval intracortical inhibition (LICI) using 50-200 ms intervals to assess GABA_B-mediated slow inhibitory processes (Premoli et al., 2018). Thus, SICI, ICF, and LICI provide measurement indices for both excitatory and inhibitory systems, offering important tools for comprehensive evaluation of cortical circuit states.

Additionally, TMS-induced EEG time-frequency characteristics, particularly TMS-related spectral perturbation (TRSP), serve as crucial diagnostic indicators for neurophysiology (Santoro et al., 2024). TRSP reflects dynamic changes in phase-locked cortical oscillatory power across different frequency bands and time points following TMS pulses, with higher power indicating greater neuronal discharge synchronization (Biondi et al., 2022; Fries, 2015). Since neurological and psychiatric disorders often accompany abnormal neuronal firing activity, EEG oscillatory features serve as commonly used biomarkers in clinical disease assessment.

Beyond evaluating single-region excitability, TMS-evoked neural activity changes propagate along structural or functional connectivity networks (Bortoletto et al., 2021; Chung et al., 2015), and synchronous TMS-EEG can effectively detect abnormal circuit connectivity in clinical diseases (Huang et al., 2025). The most common assessment approach involves stimulating a specific brain region and detecting TEP responses in distal areas such as contralateral homologous regions or subcortical structures. Researchers can infer inter-regional connection strength and information transmission speed by analyzing amplitude, latency, and duration of distal TEPs, or utilize TEP source localization to evaluate the spatial extent of TMS-evoked neural activity influence. These metrics provide scientific evidence for assessing brain functional connectivity (Bertazzoli et al., 2025; Bortoletto et al., 2021; Hallett et al., 2017).

In summary, compared to TMS-EMG limited to motor cortex assessment, synchronous TMS-EEG constructs a comprehensive evaluation system from local

physiological mechanisms to whole-brain network interactions through three complementary biomarkers: TEPs, cortical oscillations, and brain connectivity. Specifically, TEP components serve as "probes" for direct assessment of local target cortex excitability, with ppTMS-EEG further revealing excitation-inhibition balance in cortical circuits. TMS-induced cortical oscillations reflect the degree of synchronized neuronal population discharges, quantifying response states to TMS. Finally, distal TEP responses and inter-regional cortical oscillation synchrony measure and characterize the spatiotemporal propagation and integration of TMS responses across brain networks. Through synergistic analysis of TEPs in the time domain, oscillations in the frequency domain, and cross-regional signal propagation and synchronization, researchers can identify potential biomarker abnormalities in neurological and psychiatric disorders manifesting as both local physiological dysregulation and global network connectivity impairments.

2.2 Causal Neural Mechanisms

Beyond its clinical value in identifying neural response biomarkers (Section 2.1), synchronous TMS-EEG plays a crucial role in parsing causal neural mechanisms of cognitive function. By delivering transient magnetic stimulation during different time windows of cognitive tasks, researchers can temporarily disrupt normal activity in target regions, altering their functional participation in information processing. This allows investigation of when specific brain regions become involved in cognitive operations, revealing the temporal causal architecture of brain function. Synchronous EEG recording not only verifies causal links between TMS-induced neural changes and behavioral output but also captures instantaneous effects of TMS on task-evoked event-related potentials (ERPs) and neural oscillations with millisecond temporal resolution. Consequently, synchronous TMS-EEG can precisely pinpoint the time windows of brain region involvement in cognitive processing and reveal dynamic coupling relationships between neural activity and behavioral performance (Ziemann et al., 2015).

For complex cognitive processes involving multi-regional coordination, researchers can use multi-coil TMS to simultaneously or sequentially stimulate multiple functionally related brain regions at the same or different timepoints, systematically examining dynamic causal connections between brain regions through combined behavioral and EEG recordings. Specifically, if delivering a TMS pulse during a specific moment of cognitive task execution changes neural activity in a target region and produces observable behavioral changes, that brain region can be considered causally involved in that cognitive function at that moment. Furthermore, by sequentially modulating different brain regions at different timepoints and comparing their effects on task performance and EEG responses, researchers can infer the temporal sequence of brain region involvement and information propagation direction during cognitive processing (Burke et al., 2019; Miniussi & Thut, 2010). This multi-site TMS-EEG approach effectively reveals temporal causal interaction mechanisms

between brain regions and has become an important tool for parsing dynamic organizational principles of cognitive brain networks.

In addition to multi-coil TMS approaches, some researchers deliver TMS pulses to a single brain region during tasks and probe TEP signals in another region to reveal connectivity mechanisms between the two areas (Ferreri & Rossini, 2013; Massimini, 2005; Pisoni et al., 2018; Siebner et al., 2009). In such studies, the purpose of TMS delivery is not to transiently inhibit or activate a single region but to provide a temporally precise cortical perturbation event, allowing researchers to track time patterns of neural activity propagation from the stimulated region to distal regions via TEPs during cognitive processes. This reveals dynamic causal neural network mechanisms between brain regions (Lafleur et al., 2016). Notably, such studies typically use TMS intensities slightly below individual thresholds to minimize direct interference with subjective experience and behavioral performance.

It is important to note that the modulatory effects of online TMS on target brain regions remain debated. The dominant view holds that online TMS creates a "virtual lesion" (Burke et al., 2019; Pascual-Leone et al., 1999; Weissman-Fogel & Granovsky, 2019), where TMS pulses during cognitive activity briefly disrupt spontaneous cortical firing rhythms, degrade phase consistency of neural oscillations, and consequently impair behavioral performance (Chen et al., 2018; Mattavelli et al., 2016; Vernet et al., 2015). However, some researchers argue that online TMS actually enhances target region activity, manifesting as increased amplitude of specific ERP components and improved behavioral performance, suggesting that TMS may promote neuronal discharge synchrony and optimize task-related cognitive processing under certain conditions (Cespón et al., 2024; Zhou et al., 2021). A meta-analysis by Beynel et al. (2019) summarized these issues, finding that approximately 71% of online TMS studies showed interference with target region function, supporting the "virtual lesion" view, while about 13% demonstrated facilitatory effects. Some propose that heterogeneous results may relate to brain state at stimulation onset (Zrenner et al., 2018), as detailed in Section 2.3.

2.3 Closed-loop Modulation

In the first two application modes, EEG primarily serves as a passive recording tool for capturing and evaluating TMS-evoked neural responses and their temporal and network propagation characteristics. This open-loop stimulation mode heavily relies on researcher-selected TMS timing based on a priori assumptions, which cannot guarantee consistent brain states across stimulation events, leading to substantial variability in TMS effects across participants and studies. In closed-loop modulation mode, EEG signals serve as active control sources, with current brain states (such as instantaneous oscillatory phase or power) acting as TMS trigger conditions to achieve individualized, state-dependent precise neuromodulation. For example, when neural oscillations in a target region reach a preset phase in a specific frequency band (e.g., alpha, theta), the system imme-

diately delivers spTMS or repetitive TMS (rTMS) to that region (Ding et al., 2022; Zrenner & Ziemann, 2024).

This brain activity-driven closed-loop approach enables more precise manipulation of neuronal population excitability states, enhancing stimulation timeliness and biological efficacy while allowing precise examination of causal relationships between specific brain states and cognitive function. Research indicates that compared to conventional open-loop stimulation, closed-loop TMS can induce stronger synaptic-like plasticity effects at specific oscillatory phases, including enhanced cortical responses or prolonged plasticity maintenance (Zrenner et al., 2018). This characteristic significantly improves therapeutic efficacy for psychiatric and neurological conditions such as epilepsy (Faller et al., 2022; George et al., 2023; Zrenner et al., 2020) and provides new empirical techniques for understanding cognitive mechanisms across different brain states. summarizes the mechanistic comparisons across the three TMS-EEG modes.

3.1 Neurophysiological Assessment

In auxiliary diagnosis of neurological or psychiatric disorders, synchronous TMS-EEG provides important diagnostic indicators through abnormalities in TEP characteristics, cortical oscillations, and brain connectivity. This section organizes relevant biomarkers into three categories: TEP components reflecting cortical excitation-inhibition imbalance, cortical oscillations representing pathological rhythmic dysregulation, and brain connectivity revealing abnormal network transmission. Below we elaborate on clinical applications of these three indicators to advance the construction of a TMS-EEG neurophysiological assessment framework.

3.1.1 TEP Characteristics

Compared to TMS-EMG integration, synchronous TMS-EEG extends cortical activity detection to broader brain regions. Its key indicator, TEP, directly reflects cortical excitability and has become an important biomarker for clinical disease diagnosis, widely applied in auxiliary diagnosis of major depressive disorder, schizophrenia, and attention deficit hyperactivity disorder (Cao.K et al., 2021; Farzan, 2024; Hadas et al., 2021; Kallioniemi et al., 2022; Noda, 2020). Studies have found that in major depressive disorder patients undergoing spTMS examination, the dorsolateral prefrontal cortex (DLPFC) shows abnormal markers with significantly larger N45 and N100 amplitudes than healthy controls, and N45 amplitude significantly predicts depressive symptoms, suggesting that DLPFC excitation-inhibition imbalance may constitute a biological basis for depression (Voineskos et al., 2019). This view of N45 as a biomarker for cortical excitation-inhibition balance has been validated in other neurofunctional disorders. An rTMS study of patients with cerebellar inhibition dysfunction found that baseline N45 amplitude was significantly lower than healthy controls but increased after rTMS treatment, with the degree of increase significantly correlating with symptom relief, highlighting its potential as a transdiagnostic

biomarker (Chen.Y et al., 2025). Similarly, when stimulating DLPFC, cognitive impairment patients show longer N100 latency and larger amplitude compared to healthy populations, with pattern recognition results indicating that N100 features provide optimal symptom prediction (Zhang et al., 2021). In schizophrenia diagnosis, given impaired prefrontal GABAergic systems (Nakazawa et al., 2012), spTMS applied to DLPFC reveals shortened early component latency and prolonged late component latency compared to healthy individuals, reflecting baseline hyperactivity and local inhibition deficits (Mijancos-Martínez et al., 2025). Beyond spTMS, ppTMS also serves as a common diagnostic tool, with TEP component amplitudes reflecting intracortical circuit properties. For example, at a 2 ms CS-TS interval, schizophrenia patients show significantly reduced SICI effects on P60, with SICI modulation of P60 significantly correlating with working memory performance; at 10 ms intervals, ICF facilitation effects on P60 and N100 are significantly reduced, with ICF modulation of N100 significantly correlating with symptom severity (Noda et al., 2017).

3.1.2 Cortical Oscillations

Cortical oscillation indices provided by synchronous TMS-EEG constitute another important basis for brain disease assessment. Under spTMS, studies have found reduced power changes in early delta, theta, and gamma bands in schizophrenia patients, i.e., reduced TRSP. Reduced delta and theta TRSP may reflect decreased neuronal firing, while reduced gamma TRSP relates to impaired GABAergic inhibitory circuit system function (Santoro et al., 2024), particularly reduced synaptic connectivity resulting from abnormal activity of GABAergic interneurons (Daskalakis et al., 2002; Hou et al., 2021). Research indicates that gamma oscillations depend on normal activity of inhibitory interneurons, whose fast inhibitory output forms the physiological basis for synchronized rhythms (Gonzalez-Burgos & Lewis, 2008). Therefore, when patients (e.g., with Alzheimer' s disease or bipolar disorder) exhibit cortical inhibition deficits due to impaired interneuron function, they show lower frontal gamma oscillation power in TMS responses (Canali et al., 2017; Casula et al., 2022; Palmisano et al., 2024). Beyond gamma oscillations, theta oscillations also serve as reliable indicators for mental disorders. For example, in consciousness disorder patients assessed with TMS-EEG, those in minimally conscious and unconscious states show shorter response times, lower reactivity, and smaller theta cumulative power across 4-40 Hz compared to healthy individuals. The study also found that theta oscillation reactivity evoked by parietal and frontal TMS reliably distinguishes consciousness disorder patients from healthy controls and differentiates minimally conscious from unconscious states (Bai et al., 2024). The value of such oscillatory features as biomarkers extends to treatment monitoring. Research shows that after spinal cord stimulation treatment for consciousness disorders, minimally conscious patients exhibit significantly increased TMS-EEG oscillation frequencies (5-12 Hz), with change magnitude positively correlating with consciousness improvement (Wang et al., 2023), demonstrating that abnormal brain oscillations can serve as biomarkers for therapeutic

monitoring.

3.1.3 Brain Connectivity

Synchronous TMS-EEG is also used to examine abnormal brain connectivity in neurological or psychiatric disorders. Alzheimer' s disease, characterized by episodic memory impairment, shows altered frontal connectivity in neuroimaging studies (Zhang et al., 2016). Delivering TMS pulses to frontal regions reveals that right parietal P30 amplitude inversely correlates with cognitive ability, particularly memory performance, suggesting enhanced frontoparietal effective connectivity relates to disease severity (Bagattini et al., 2019). Other studies show that Alzheimer' s disease patients exhibit smaller TEP response propagation range and longer duration under spTMS examination, indicating reduced brain connectivity and local response reverberation (Ferreri et al., 2016). In adolescent depression research, spTMS applied to DLPFC followed by source analysis reveals significantly higher N100 and P200 amplitudes in cingulate cortex and angular gyrus (core nodes of the default mode network) compared to healthy populations, indicating abnormal functional connectivity between DLPFC and the default mode network (Dhami et al., 2020), a finding validated in adult patients (Hadas et al., 2019). Both studies provide new evidence for abnormal neural circuit mechanisms in depression. Attention deficit hyperactivity disorder, characterized primarily by attention impairment, shows abnormal interhemispheric connectivity. A right frontal spTMS-EEG study found lower left hemisphere TEP amplitude in patients versus healthy controls, indicating weakened interhemispheric propagation mechanisms (Avnit et al., 2023). Similar interhemispheric connectivity assessment reveals imbalanced interhemispheric inhibition in stroke patients: spTMS applied to the unaffected primary motor cortex induces contralateral TEP inhibition, while stimulation of the affected hemisphere lacks this effect, indicating preserved inhibition from unaffected to affected hemisphere but deficient reverse inhibition (Casula et al., 2021). Similarly, multiple sclerosis, a neurological disease with impaired interhemispheric signal transmission due to corpus callosum damage, shows significantly higher contralateral N280 amplitude after unilateral motor cortex spTMS compared to healthy controls, suggesting compensatory network reorganization and hyperexcitability of interhemispheric circuits after callosal damage (Zipser et al., 2018). summarizes the main methods and results of these TMS-EEG neurophysiological assessment studies.

3.2 Causal Neural Mechanisms

This section reviews the causal role of synchronous TMS-EEG in revealing cognitive neural mechanisms across three levels: temporal characteristics of brain regions, functional coordination among multiple brain regions, and dynamic information flow transmission. First, at the temporal level, TMS-EEG reveals the timing and functional stages of specific brain region involvement in cognitive processing by delivering instantaneous perturbations during critical task

time windows, clarifying "when" a region exerts causal influence on cognitive function. Second, at the multi-regional level, dual- or multi-site TMS-EEG examines causal interaction patterns and network integration features among different brain regions, further elucidating the dynamic network architecture underlying complex cognitive functions. Finally, at the information flow level, analyzing propagation pathways of TMS-evoked activity across cortical regions tracks dynamic information flow between brain regions, revealing causal information transmission mechanisms of cognitive processing.

3.2.1 Temporal Windows of Brain Region Involvement in Specific Cognitive Processes

By applying spTMS at precise timepoints to transiently disrupt target brain region activity, researchers can reveal dynamic patterns of stage-specific involvement across cognitive functions. Below we examine temporal characteristics of different brain regions following a progression from basic to higher-order cognitive activities.

In motion perception, to investigate visual cortex involvement timing and optimal spTMS parameters, researchers delivered spTMS to visual area V5 at different intensities (0%, 80%, 100%, 120% RMT) either 30 ms before visual stimulus presentation or at individual ERP component N2 latency (approximately 154 ms, associated with spatial attention). Results showed that spTMS delivered at N2 onset significantly improved motion direction discrimination accuracy compared to pre-stimulus delivery, with the strongest effect at 80% RMT intensity. Additionally, 120% RMT spTMS at N2 peak onset induced larger central-parietal P3 amplitude (reflecting attention allocation), indicating that visual cortex directly mediates motion perception within the N2 time window after visual presentation and that TMS effects are intensity-dependent (Gamboa Arana et al., 2020).

In selective attention, the superior frontal gyrus (SFG) is considered critical for attentional control, information integration, and top-down information transmission (Bichot & Schall, 1999; Heinen et al., 2014; Kammer, 2008). To reveal SFG' s specific temporal involvement, researchers applied spTMS to suppress SFG activity at 0, 50, 100, 150, and 200 ms after visual stimulus presentation during color or motion direction selection tasks. Only SFG suppression at 100 ms post-stimulus slowed reaction times, identifying this as the temporal window for SFG' s role in attentional selection and allocation. Source analysis of early TEPs under the 100 ms condition showed that SFG regulated fusiform gyrus (for color judgment) or temporoparietal junction (for motion direction judgment) depending on attentional attribute, revealing SFG' s attribute-specific attentional control (Chen et al., 2018). Another study using a dot-probe task (Torriero et al., 2019) required participants to respond to probes following 500-ms presentations of threat-related face and neutral house pairs. Excitatory spTMS applied to right SFG at 140 ms after pair onset enhanced face-evoked occipitotemporal N170 (reflecting facial structural encoding) and frontal N2 (conflict

control) amplitudes, indicating that SFG promotes early threat face perception through top-down mechanisms during the 140 ms post-cue window. Behaviorally, however, SFG modulation prolonged reaction times in congruent trials (probe on same side as threat face), possibly because participants employed situation modification strategies similar to emotion regulation to avoid subsequent threat processing and reduce negative emotional interference. The superior temporal sulcus (STS) also participates in selective attention (Bogadhi et al., 2019; Stemmann & Freiwald, 2019). To examine STS' s temporal window in attentional processing, researchers used a delayed match-to-sample task requiring participants to judge whether target stimulus features (shape or color) matched preceding cue features, applying excitatory spTMS to STS 300 ms before target presentation. Results showed that STS priming facilitated reaction speed and enhanced parieto-occipital P1 amplitude (reflecting early visual processing) while reducing parietal N2 amplitude. Time-varying network analysis further revealed that STS priming significantly enhanced frontoparietal network connectivity, indicating that STS begins early attentional system regulation 300 ms before stimulation and promotes attentional processing by increasing prefrontal information flow (Zhou et al., 2021).

In emotion regulation, different prefrontal subsystems collaborate, potentially operating in distinct temporal windows (Cao.D et al., 2021, 2022; Cheng et al., 2024; Li et al., 2023). The DLPFC serves as a key node in the frontoparietal attention network, supporting cognitive control and working memory functions, while the ventrolateral prefrontal cortex (VLPFC), particularly the left region near Broca' s area, primarily mediates semantic processing and alternative interpretation (Morawetz et al., 2016; Silvers et al., 2019). Studies applying spTMS to disrupt DLPFC or VLPFC activity during negative picture presentation found that interfering with DLPFC at 0 ms and 600 ms post-picture or with VLPFC at 400 ms post-picture intensified negative emotion experience (Cheng et al., 2024). These results suggest that during emotion processing time courses, DLPFC first participates in selective attention processes, VLPFC subsequently performs semantic processing, and DLPFC finally updates current emotional context evaluations to memory and assumes cognitive control functions (Zhang et al., 2022; Zhao et al., 2021). Other spTMS studies indicate VLPFC involvement in emotion regulation begins approximately 300 ms post-stimulus (Cao.D et al., 2021, 2022; Li et al., 2023). Specifically, Li et al. (2023) combined spTMS with EEG to facilitate VLPFC activity 300 ms after picture onset during emotion regulation tasks, finding that this manipulation significantly enhanced early and mid-stage parietal LPP amplitudes (reflecting cognitive control), with early LPP amplitude negatively correlating with emotional arousal ratings.

3.2.2 Multi-Region Coordination

Complex cognitive functions depend on dynamic coordination among multiple brain regions. Using multi-target TMS combined with EEG observation, researchers have causally revealed multi-region collaborative neural mechanisms

in perception and language domains.

Ambiguous perception involves dynamic alternation between stable perception and alternative interpretations, with neural mechanisms primarily involving the frontoparietal attention network centered on the intraparietal sulcus (IPS) and DLPFC (Britz et al., 2009; de Graaf et al., 2011; Zaretskaya et al., 2010). To examine this network' s coordination mechanism, researchers designed two experiments: one applying spTMS to suppress IPS 70 ms before the second presentation of ambiguous figures; another suppressing IPS and then DLPFC 10 ms later. Results showed that IPS suppression alone reduced perceptual stability compared to controls, with parietal TEP amplitude differences (141-208 ms) trending with behavioral differences. However, under dual-pulse conditions, DLPFC suppression reduced the IPS suppression effect, eliminating significant differences between real TMS and control conditions in perceptual stability and TEP-behavior correlations. These findings indicate that IPS maintains early perceptual stability while DLPFC mediates perceptual switching, with both coordinating to regulate ambiguous perception balance (Vernet et al., 2015). Given functional differentiation between anterior and posterior parietal cortex in ambiguous perception—anterior regions involved in top-down regulation and posterior regions processing bottom-up perceptual error signals (Kanai et al., 2011)—researchers examined their coordination mechanism using a task requiring judgment of ambiguous rotating sphere motion direction, applying spTMS to anterior or posterior parietal regions every 3 seconds. Results showed TEP amplitude at 25 ms was larger for anterior than posterior stimulation, while at 105 ms the pattern reversed, revealing dynamic coordination mechanisms between anterior and posterior parietal regions in ambiguous perception at the temporal scale (Schauer et al., 2016).

Sentence comprehension depends on dynamic collaboration of the frontotemporal network centered on the inferior frontal gyrus (IFG) and STS (Obleser & Kotz, 2010). Kroczek et al. (2019) applied 10 Hz 3-pulse TMS to IFG or STS at verb onset during auditory sentence comprehension tasks, with participants performing lexical decisions on final nouns while receiving TMS. TEP results showed that during 0-200 ms after verb onset, only IFG suppression produced more positive frontal TEPs for high- versus low-predictability verbs, while during 200-400 ms, only STS suppression produced more negative parietal TEPs for high-predictability verbs, suggesting temporal functional differentiation between the two regions in verb processing. However, neither TMS manipulation affected subsequent noun processing, as evidenced by non-significant differences in N400 amplitude (semantic violation effect) between TMS and control conditions, suggesting that other language-related regions such as the angular gyrus may have compensated for TMS interference. In follow-up studies, researchers first suppressed angular gyrus function with rTMS, then applied 3-pulse TMS to IFG or STS at 0, 150, or 300 ms after verb onset. Results showed that suppressing STS in early (0-200 ms) and late (300-500 ms) windows, or suppressing IFG in middle (150-350 ms) windows, all significantly reduced noun-evoked N400 effects, indicating that sentence comprehension depends on bidirectional

dynamic interactions following a "temporal → frontal → temporal" pattern (Schroën et al., 2023). These TMS-EEG studies collectively demonstrate that IFG and STS collaboratively participate in semantic integration through temporally complementary mechanisms, providing causal evidence for multi-region dynamic coordination underlying sentence comprehension.

3.2.3 Dynamic Information Flow Between Brain Regions

Synchronous TMS-EEG also tracks propagation characteristics of TMS-evoked electrophysiological responses in brain networks, providing causal evidence for dynamic information transmission between brain regions during specific cognitive activities. This technique has been applied to study tactile, motor, and speech processing, gradually mapping dynamic mechanisms of brain network operations.

In tactile empathy research, observing others being touched activates the observer's primary somatosensory cortex (Rizzolatti & Sinigaglia, 2016). To reveal inter-regional information transmission patterns, researchers delivered spTMS "probes" to primary somatosensory cortex at 50 or 150 ms after tactile events (real touch, observed touch, observed object touch). TEP analysis showed that spTMS at 50 ms evoked higher P60 and N90 amplitudes than at 150 ms in both real and observed touch conditions, confirming enhanced early excitability in primary somatosensory cortex. Further analysis of TMS-triggered network responses using weighted phase lag index (WPLI) revealed that perturbing primary somatosensory cortex at 50 ms activated frontoparietal effective connectivity networks in the beta band during both real and observed touch conditions, indicating that frontoparietal networks transmitting information via beta oscillations constitute the neural simulation basis of tactile empathy. Additionally, only real touch condition spTMS activated extra frontoparietal connectivity in the alpha band, suggesting that alpha-band synchronization in frontoparietal networks may serve as a neural marker for distinguishing self versus others' tactile experiences (Pisoni et al., 2018).

Synchronous TMS-EEG has also revealed information flow mechanisms during action preparation. Traditional views hold that the readiness potential (bereitschaftspotential, BP) before action execution primarily reflects enhanced supplementary motor area (SMA) excitability (Di Russo et al., 2017; Lu et al., 2012). Researchers combined TMS-EEG to analyze network information transmission processes underlying BP using a Go/No-go task, applying spTMS to SMA at BP onset (700 ms before stimulus) or peak (300 ms before stimulus). TEP source analysis showed higher SMA excitability at BP peak than onset, accompanied by enhanced left occipital responses and gradually weakened right inferior frontal gyrus (IFG) responses in late stages, indicating that action preparation depends not only on enhanced SMA excitability but also involves sensory pathway pre-activation and reduced information flow between SMA and IFG to support motor preparation by releasing prefrontal active inhibition (Bianco et al., 2023). In motor control, IFG coordinates with distal brain regions to regu-

late action execution (Borra & Luppino, 2017; Fox & Raichle, 2007). To reveal its information transmission mechanism, researchers required finger movements based on cues and applied spTMS to IFG 1.5-2.5 seconds after cue presentation. Results showed increased frontoparietal TEP amplitude at 60 ms windows while left posterior sensory cortex (FT7, T7, TP7, CP5) TEP amplitude decreased, and right default mode network (T8, CP6) TEP amplitude increased at 80 ms windows. This indicates that IFG early enhances connectivity with frontoparietal action networks to generate motor commands while reducing connectivity with posterior sensory cortex to suppress sensory input, and later enhances default mode network connectivity to suppress task-irrelevant brain activity, revealing dynamic network regulation mechanisms during motor execution (Zanon et al., 2018).

Significant progress has also been made in exploring dynamic information flow in speech comprehension networks using synchronous TMS-EEG. The ventral occipito-temporal cortex (vOT), a key hub for visual and language processing, exhibits extensive functional connectivity with multiple brain regions during speech comprehension (Chen et al., 2019; Dehaene & Cohen, 2011; Stevens et al., 2017). In a Go/No-go paradigm requiring symbolic or semantic judgment, researchers applied spTMS to left vOT 100 ms after probe stimulus presentation. Consistent TEP and source localization results showed lower TEP amplitudes in right visual cortex, superior parietal lobule, and anterior temporal lobe during semantic versus symbolic detection tasks, indicating that vOT suppresses neural transmission to these regions during semantic processing. Time-series correlation analysis of TMS-induced current source density (CSD) further showed significantly higher correlation of activity within left hemisphere language networks than right hemisphere during semantic tasks. This study demonstrates at the causal intervention level that language processing supports functional lateralization by suppressing left vOT to right hemisphere propagation while promoting intra-hemispheric language network collaboration (Planton et al., 2022). summarizes main methods and parameter settings of current TMS-EEG causal neural mechanism studies.

3.3 Closed-loop Modulation

Multiple studies have confirmed that neuromodulation efficacy depends on real-time brain state. Closed-loop modulation achieves state-dependent precise regulation by continuously monitoring and decoding brain activity states to deliver magnetic pulses at exact timepoints. Zrenner et al. (2018) first applied closed-loop modulation in human subjects, demonstrating that real-time phase of brain oscillatory rhythms modulates corticospinal excitability. Using real-time EEG signal processing with Hjorth filtering and autoregressive prediction algorithms, the study precisely locked onto positive and negative peak phases of individual sensorimotor mu rhythm and delivered spTMS at corresponding phases. MEP results showed higher corticospinal excitability at negative peak phases and lower excitability at positive peaks. Subsequent rTMS experiments found that

only stimulation at negative peaks induced long-term potentiation-like plasticity changes, manifested as higher MEPs up to 30 minutes post-intervention, while positive peak stimulation showed no significant effects. This finding provides crucial evidence for phase-specific closed-loop TMS modulation. Follow-up studies extended closed-loop TMS to cortical levels. Research applying spTMS at different intensities to primary motor cortex at specific mu rhythm phases found that suprathreshold TMS at negative peaks evoked significantly larger P70 and N100 amplitudes than at positive peaks, with phase modulation effects on N100 persisting even at subthreshold stimulation, confirming phase-dependence of instantaneous cortical excitability from a TEP perspective (Desideri et al., 2019). Recent research extended to beta rhythms (Perera et al., 2024), revealing that early TEP components in primary motor cortex are modulated by both mu and beta rhythm phases, while late components are modulated only by mu rhythm. Furthermore, mu and beta power predicted early TEP responses, while only mu power predicted late responses, indicating that rhythm phase and power constitute dual regulatory mechanisms of cortical state. These findings reveal brain state-dependent dynamic mechanisms through corticospinal and cortical electrophysiological indices, laying foundations for developing precise clinical modulation strategies.

Beyond basic research, studies have focused on closed-loop modulation of pathological neural oscillations. Given that enhanced prefrontal alpha activity correlates with depression severity (Monni et al., 2022; Xie et al., 2023), researchers applied rTMS to left DLPFC at alpha rhythm negative peaks in patients, significantly reducing frontal alpha power and enhancing TMS-evoked beta oscillations, providing a potential new therapeutic avenue for depression (Zrenner et al., 2020).

After confirming closed-loop modulation effects on cortical excitability, researchers began investigating its cognitive enhancement effects. Animal studies show that rTMS delivered at specific oscillatory phases induces synaptic plasticity and improves behavioral performance (Hyman et al., 2003; Siegle et al., 2014). Given theta rhythm' s close relationship with working memory (Cruzat et al., 2021; Sun & Bao, 2025), research applied 100 Hz 3-pulse rTMS to dorsomedial prefrontal cortex locked to theta positive peaks, negative peaks, or random phases to examine effects on subsequent working memory performance. Results showed that negative peak stimulation increased theta power and shortened working memory reaction times, while positive peak stimulation decreased theta power without affecting working memory performance, demonstrating that closed-loop TMS can bidirectionally modulate neural oscillations and alter working memory performance in a phase-specific manner (Gordon et al., 2022). Recently, Jovellar et al. (2025) innovatively combined closed-loop modulation with cortical paired associative stimulation (cPAS) to implement theta-phase-locked cPAS on working memory-related frontoparietal networks, finding that theta positive peak-synchronized cPAS significantly improved working memory performance, demonstrating the potential of closed-loop dual-target TMS for spatiotemporally precise cognitive

network modulation. summarizes main methods and parameter settings of these TMS-EEG closed-loop modulation studies.

4 Summary and Outlook

As one of the most promising neural techniques combining brain modulation and observation, synchronous TMS-EEG has demonstrated important value in psychological and clinical research. This review synthesized three major application modes, including advantages in clinical diagnostic biomarkers, roles in revealing cognitive neural mechanisms, and the value of closed-loop modulation in real-time phase-locked neural regulation. Although the technique has achieved progress in multiple aspects, it remains in early development stages and faces challenges in broader applications and standardized practice. To advance psychological and cognitive neuroscience research, future synchronous TMS-EEG technology should focus on several directions:

First, determining inter-regional information transmission duration based on TEP latency differences. Current studies largely rely on a priori assumptions, delivering single-region TMS pulses at hypothesized timepoints—for example, inferring brain region involvement periods based on ERP latencies (Schroën et al., 2023) or setting multiple timepoints for exhaustive investigation (Chen et al., 2018; Cheng et al., 2024) to indirectly infer multi-region temporal sequences, lacking direct, accurate evidence for sequential multi-region operation. Since TEP latency directly reflects inter-regional conduction speed (Bortoletto et al., 2015), recent proposals suggest using TMS to stimulate region A and observing TEP differences in region B between suprathreshold and sham conditions, employing the peak latency of difference waves as the neural transmission duration from A to B (Borgomaneri et al., 2023). Applying this method to set inter-stimulus intervals for sequential multi-target modulation could potentially parse temporal sequences of different brain regions at more precise timescales.

Second, employing closed-loop TMS-EEG online modulation to examine brain state effects on cognitive activity. The state-dependency hypothesis of TMS posits that modulation effects heavily depend on instantaneous brain excitability states at stimulation onset (Pitcher et al., 2021), which may account for current heterogeneity in TMS effects. To precisely reveal causal effects of specific brain states on cognitive function requires continuous detection of target neural states during task execution through closed-loop computational analysis (Kahilakoski et al., 2025) to trigger TMS promptly. For example, since enhanced theta oscillation power correlates with successful emotion regulation (Zouaoui et al., 2023), automatically triggering TMS pulses when EEG monitoring detects theta power below threshold could efficiently enhance theta neural activity. Therefore, researchers have recently focused on real-time processing algorithms during data acquisition. For instance, an integrated SOUND filtering and independent component analysis real-time correction scheme can efficiently remove extracranial noise such as TMS-evoked muscle activity and electrode artifacts (Makkonen et al., 2021). Other studies have achieved real-time TMS artifact minimization

and TEP signal-to-noise ratio maximization through single-trial TEP waveform-based TMS parameter adjustment (Parmigiani et al., 2019; Varone et al., 2021). Future work must continue exploring more efficient real-time artifact correction methods to expand the technique' s application prospects.

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