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Closed-loop EEG-synchronized Transcranial Magnetic Stimulation: Advancing State-dependent Neuromodulation Toward Clinical Translation

Krista Casazza Ph.D[1], Slav Danev[2] and Jonathan RT Lakey Ph.D MSM[1]*

[1]*Department of Surgery and Biomedical Engineering, University of California Irvine, California, USA.*

[2]*Medeia Inc, Santa Barbara, California, USA.*

***Correspondence:**
Jonathan RT Lakey, PhD, MSM, Professor Emeritus, Department of Surgery and Biomedical Engineering, California, USA, Phone: 1-714 851 8856.

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ABSTRACT

Conventional transcranial magnetic stimulation (TMS) is delivered independent of ongoing brain activity, despite strong evidence that cortical excitability fluctuates with endogenous oscillatory dynamics. The objective of this review is to synthesize current evidence on electroencephalography (EEG)-synchronized TMS and evaluate its potential as a clinically translatable, state-dependent neuromodulation strategy. We integrate findings from experimental, technical, and early clinical studies of real-time EEG-triggered TMS, focusing on phase-specific stimulation, system latency, and closed-loop control architectures. EEG-synchronized TMS enables phase-dependent modulation of cortical excitability and plasticity, with improved consistency compared to open-loop protocols. Real-time systems require sub-100 ms latency and precise phase estimation, yet remain constrained by signal-to-noise limitations and TMS-induced artifacts. Emerging adaptive and machine learning–driven systems demonstrate feasibility for individualized neuromodulation. Closed-loop EEG-TMS represents a promising advance toward precision neuromodulation, with potential to enhance therapeutic efficacy in neuropsychiatric disorders. Standardization, artifact mitigation, and scalable system design remain critical barriers to widespread clinical adoption.

Keywords

EEG-TMS, Closed-loop neuromodulation, Brain-state dependent stimulation, Oscillatory phase, Cortical excitability, Precision psychiatry.

Introduction

Transcranial magnetic stimulation (TMS) has emerged as a central tool in both systems neuroscience and clinical neuromodulation, enabling non-invasive, causal perturbation of cortical circuits with millisecond temporal precision [1]. When combined with electroencephalography (EEG), TMS provides a powerful platform for directly assessing cortical reactivity, effective connectivity, and large-scale network dynamics *in vivo* [2,3]. TMS–EEG has therefore become an important methodological bridge between mechanistic neuroscience and translational neuropsychiatry, offering biomarkers of cortical excitability and network function across both healthy and clinical populations [4]. Despite these advances, a fundamental limitation persists in conventional TMS paradigms. To date, stimulation is delivered in an open-loop manner, without regard to the ongoing state of neural activity [5]. This approach assumes a relatively stationary brain, yet converging evidence demonstrates that cortical excitability fluctuates dynamically as a function of endogenous oscillatory activity [6].

A growing body of experimental work demonstrates that oscillatory phase is a critical determinant of TMS responsiveness [7]. In the motor system, the amplitude of motor-evoked potentials (MEPs) varies systematically with the phase of the sensorimotor μ-rhythm, with stimulation delivered at high-excitability phases producing larger and more reliable responses [8]. Similarly, phase-specific stimulation has been shown to modulate corticospinal excitability and influence plasticity induction, with evidence for differential engagement of long-term potentiation (LTP)-like and long-term depression (LTD)-like mechanisms depending on stimulation timing [9]. These findings support a model in which oscillatory phase acts as a temporal gate for external stimulation, determining the likelihood of neuronal recruitment and downstream network effects. From this perspective, delivering TMS pulses aligned to specific oscillatory phases may enhance the ability to selectively engage or disrupt functional networks, providing a mechanism for both mechanistic interrogation and targeted neuromodulation [10].

In response to these insights, there has been increasing interest in EEG-synchronized or brain-state–dependent TMS, in which stimulation is triggered in real time based on ongoing neural activity [2]. This approach represents a conceptual shift from static stimulation paradigms toward precision-timed interventions, enabling alignment of exogenous stimulation with endogenous excitability states [11]. Early proof-of-concept studies demonstrated the feasibility of phase-locked stimulation using real-time EEG processing, showing enhanced physiological responses and reduced variability relative to random-phase or open-loop stimulation [12,13]. More recent work has extended this paradigm into closed-loop systems, in which stimulation parameters are dynamically updated based on continuously evolving neural signals [14,15] However, the implementation of EEG-synchronized TMS introduces substantial technical and methodological challenges [2]. Real-time integration requires rapid signal acquisition, processing, and stimulation triggering within strict temporal constraints [16]. Effective phase-locked stimulation typically requires end-to-end latencies below ~50–100 ms, with minimal temporal jitter to preserve phase accuracy [17]. At the same time, old EEG systems has inherently noisy and non-stationary, particularly in frontal regions relevant for psychiatric applications, complicating reliable phase estimation [18]. These challenges are compounded by the presence of TMS-induced artifacts, including electromagnetic pulse artifacts, muscle activation, and auditory evoked responses, which can contaminate EEG recordings and obscure true neural signals [19].

Recent advances in hardware and computational methods are beginning to address these barriers. Modern EEG systems support high-density acquisition, high sampling rates, and real-time data streaming, enabling more accurate and temporally precise signal processing [16,20]. Contemporary platforms also incorporate integrated spectral analysis, connectivity metrics, and real-time visualization tools, facilitating closed-loop control architectures [21]. For example, digital EEG ecosystems such as the BrainView platform provide scalable multi-channel acquisition (up to 64 channels), high-resolution sampling, and integrated processing pipelines for spectral decomposition and brain mapping, alongside capabilities for continuous ambulatory monitoring and cloud-based data access [22]. These features are particularly relevant for EEG-TMS integration, as they enable longitudinal tracking of brain states and real-time interfacing with external stimulation devices.

Beyond technical feasibility, EEG-synchronized TMS has significant implications for clinical translation. Current repetitive TMS (rTMS) protocols (e.g., major depressive disorder (MDD), are limited by substantial inter-individual variability in treatment response [23]. One contributing factor may be the mismatch between stimulation timing and the patient’s instantaneous brain state [10]. Closed-loop EEG-TMS offers the potential to individualize stimulation delivery, targeting periods of maximal cortical excitability or network susceptibility, thereby enhancing therapeutic efficacy [24]. Furthermore, the integration of EEG monitoring with neuromodulation platforms enables the development of adaptive and learning-based control systems.

Machine learning (ML) approaches can be used to identify neural signatures associated with optimal responses and iteratively refine stimulation parameters, moving toward fully personalized neuromodulation [25]. Such strategies are particularly relevant for disorders characterized by dysregulated oscillatory dynamics, including depression, schizophrenia, epilepsy, and stroke, where abnormal network synchronization plays a central pathophysiological role [26]. Despite this promise, several barriers remain. These include the lack of standardized protocols for phase targeting and signal processing, persistent challenges in artifact mitigation, and limited large-scale clinical validation of closed-loop approaches [27]. Additionally, the complexity of real-time EEG-TMS integration raises questions regarding scalability, usability, and regulatory implementation in clinical settings [28]. In this review, we synthesize current evidence on EEG-synchronized TMS, focusing on its neurophysiological underpinnings, technical implementation, and translational potential. We further examine emerging closed-loop architectures and discuss how advances in EEG acquisition platforms may facilitate the transition from experimental paradigms to clinically viable neuromodulation strategies. Finally, we outline key challenges and future directions necessary to establish EEG-guided TMS as a foundational approach in precision brain stimulation.

Neurophysiological Rationale

Converging evidence indicates that these oscillatory dynamics critically shape the physiological response to TMS, with oscillatory phase serving as a key determinant of corticospinal output and cortical responsiveness [29]. In the human motor cortex, motor-evoked potentials (MEPs) exhibit systematic variation as a function of the phase of ongoing sensorimotor rhythms, particularly within the μ (8–12 Hz) and beta frequency bands [30]. Specifically, TMS pulses delivered during high-excitability phases, typically corresponding to depolarizing states, produce larger and more reliable MEP amplitudes compared to those delivered during inhibitory phases [8,31]. These findings provide direct empirical support for the concept that instantaneous brain state modulates the input–output function of cortical stimulation.

Oscillatory phase also appears to influence the induction of synaptic plasticity. Phase-specific TMS protocols have been shown to bias plasticity toward long-term potentiation (LTP)-like or long-term depression (LTD)-like effects depending on the temporal alignment between stimulation and endogenous oscillatory cycles [32]. Mechanistically, these observations support a model in which oscillatory phase acts as a gating variable, determining the probability that externally induced currents will recruit neuronal populations and propagate through cortical networks [33]. In this framework, stimulation delivered at optimal phases enhances neuronal recruitment efficiency and network engagement, whereas stimulation delivered at suboptimal phases may fail to produce meaningful physiological effects [34]. This phase-dependent gating is consistent with broader theoretical models of neural computation, in which oscillations regulate the temporal coordination of excitation and inhibition across distributed circuits [35].

While phase represents a critical component of brain state, it is only one dimension of a broader dynamical landscape that includes oscillatory power, cross-frequency coupling, and large-scale network interactions. Closed-loop EEG-TMS paradigms extend beyond simple phase-locking by enabling stimulation to be contingent on multidimensional brain states, thereby targeting transient windows of enhanced plasticity and network susceptibility [35]. In contrast to conventional fixed-frequency rTMS, which delivers stimulation independent of endogenous activity, EEG-synchronized approaches align stimulation with intrinsic network timing, effectively embedding exogenous input within ongoing neural dynamics [35]. This alignment has several important consequences. First, it promotes temporal coherence across distributed neural populations, potentially enhancing effective connectivity and facilitating coordinated network responses [36]. Second, it may increase the efficiency of plasticity induction by delivering stimulation during periods when synaptic and neuronal systems are most responsive. Third, it offers a mechanism for reducing the substantial inter- and intra-individual variability that characterizes conventional rTMS outcomes [37].

These effects can be understood within the framework of communication-through-coherence, which posits that phase alignment between neuronal populations regulates the selective routing of information across the brain [38]. By synchronizing TMS delivery with specific oscillatory states, EEG-guided stimulation may selectively amplify or disrupt functional connectivity within targeted networks, thereby providing both mechanistic insight and therapeutic leverage [2,36].

Importantly, emerging evidence suggests that state-dependent stimulation effects extend beyond local cortical regions, influencing large-scale network dynamics and downstream connectivity patterns. TMS–EEG studies have demonstrated that stimulation-evoked responses propagate through distributed networks in a state-dependent manner, with variability in both amplitude and spatial extent linked to pre-stimulus oscillatory conditions [2,39]. These findings highlight the necessity of considering brain stimulation not merely as a local perturbation, but as an intervention embedded within a dynamically evolving network system. The ability to detect and exploit these transient brain states in real time represents a critical advancement for neuromodulation [40]. Closed-loop EEG-TMS systems enable continuous monitoring of neural activity and rapid adaptation of stimulation parameters, thereby operationalizing the concept of precision-timed, state-dependent intervention (Figure 1). As such systems continue to evolve, particularly with the integration of advanced EEG acquisition platforms and real-time analytics, they hold the potential to transform both experimental neuroscience and clinical neuromodulation by shifting from static to adaptive, individualized stimulation strategies.

Technical Implementation of EEG-Synchronized TMS

Continuous data streaming is essential, as intermittent buffering introduces delays that compromise synchronization fidelity. The acquired signals are transmitted to a real-time processing environment, where they undergo band-specific filtering, spatial referencing, and feature extraction [19,41]. The resulting features, e.g., instantaneous phase, oscillatory power, composite metrics, are evaluated against predefined or adaptive criteria to determine whether stimulation should be delivered [24]. Once a target state is detected, a trigger signal is transmitted to the TMS device, typically via a hardware-based TTL interface, initiating pulse delivery with minimal delay. Achieving reliable performance requires careful coordination across hardware and software layers. Operating system constraints, data transfer protocols, and device communication interfaces all contribute to overall system latency and variability. As a result, many implementations rely on optimized processing pipelines or dedicated real-time environments to ensure consistent timing and reproducibility [24]. More advanced approaches extend beyond single-feature detection and instead utilize multidimensional representations of brain state. These may include joint phase–power metrics, measures of cross-frequency coupling, or functional connectivity indices derived from coherence or phase-locking analyses. ML–based approaches enable a transition from simple phase-locking paradigms to more comprehensive state-space models, providing a richer framework for closed-loop control [42]

The integration of EEG with TMS is complicated by the presence of large-amplitude artifacts induced by the stimulation pulse. These artifacts arise from electromagnetic induction within the recording system, activation of cranial musculature, and auditory responses associated with coil discharge. The initial pulse artifact can saturate EEG amplifiers and obscure neural signals for several milliseconds, with additional contamination persisting beyond the immediate post-stimulation period [43]. Effective artifact mitigation is therefore essential for both real-time and offline analysis. Hardware-level solutions, such as amplifier blanking or sample-and-hold circuits, can prevent saturation during the stimulation pulse. Careful electrode placement and cable management can further reduce induction-related artifacts. In real-time applications, it is common to exclude short temporal windows immediately following stimulation to avoid contamination of subsequent processing. Offline, advanced signal processing techniques such as independent component analysis can be used to separate neural activity from artifact-related components. Despite these strategies, artifact contamination remains a significant challenge, particularly in paradigms involving repeated or high-frequency stimulation. The need to balance artifact suppression with preservation of usable neural signal represents a central constraint in system design, with implications for both detection accuracy and feedback control.

Advances in EEG acquisition technology have played a critical role in enabling closed-loop neuromodulation. Contemporary platforms provide high-density, high-resolution recordings alongside real-time processing capabilities, supporting the detection and tracking of dynamic brain states [44-46]. Systems such as BrainView exemplify this evolution by integrating multi-channel acquisition, real-time spectral and connectivity analysis, and scalable data management within a unified framework. From a methodological standpoint, such platforms enable continuous monitoring of neural activity across extended time scales, facilitating both within-session optimization and longitudinal assessment of brain state variability. This capability is particularly relevant for clinical applications, where fluctuations in neural dynamics across sessions may contribute to variability in treatment response. The incorporation of cloud-based data access and remote monitoring further expands the potential for distributed data collection and analysis, supporting more flexible and scalable study designs.

Equally important is the ability of these systems to interface with external stimulation devices through standardized communication protocols. Real-time integration with TMS systems requires reliable data streaming, low-latency processing, and precise synchronization between acquisition and stimulation components. As such, the performance of EEG platforms must be evaluated not only in terms of signal quality, but also with respect to latency, timing stability, and interoperability within closed-loop architectures. The convergence of these capabilities positions advanced EEG platforms as a key enabling technology for translational neuromodulation. By supporting both high-fidelity data acquisition and real-time control, such systems provide the infrastructure necessary to move EEG-synchronized TMS from laboratory-based demonstrations toward clinically viable implementations [44-46].

Toward adaptive and scalable closed-loop systems

The field is increasingly moving toward adaptive control frameworks in which stimulation parameters are continuously updated based on ongoing neural feedback. In these systems, EEG-derived features serve both as control inputs and as indicators of system performance, enabling iterative optimization of stimulation timing, intensity, and targeting. ML approaches, including reinforcement learning and state-space modeling, have shown promise in identifying neural signatures associated with optimal responses and dynamically adjusting stimulation strategies accordingly [47]. A central challenge for clinical translation lies in balancing algorithmic sophistication with robustness and usability. Real-time systems must operate reliably in heterogeneous clinical environments, where signal quality and patient state may vary substantially. Scalable implementation will therefore depend on modular system design, standardized interfaces, and integration with user-friendly EEG platforms capable of supporting both acquisition and control functions. As these technologies continue to evolve, the integration of adaptive algorithms, high-performance EEG systems, and reliable stimulation hardware will be essential for realizing the full potential of EEG-synchronized TMS as a precision neuromodulation strategy.

Closed-loop Control Strategies

The earliest implementations of EEG-synchronized TMS focused on phase-locked stimulation paradigms, in which TMS pulses were delivered at predefined phases of ongoing oscillatory activity. These approaches provided critical proof-of-concept that real-time detection of oscillatory phase is feasible and that such detection can be used to guide temporally precise stimulation. Experimental studies demonstrated that phase-locked stimulation yields enhanced and more consistent physiological responses, including increased motor-evoked potential amplitudes and reduced trial-to-trial variability compared to randomly timed stimulation [48].

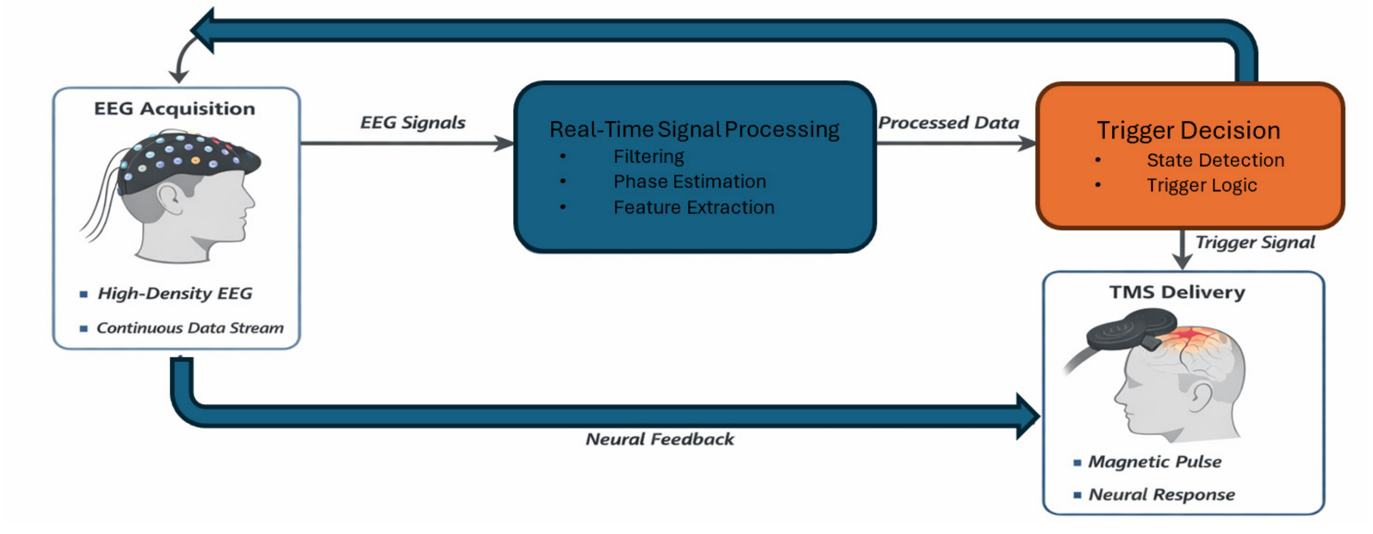

Figure 1: Schematic of a closed-loop EEG-synchronized TMS system. EEG signals are continuously acquired and processed in real time to detect targeted brain stress, triggering TMS delivery in a phase-specific manner.

These findings established that aligning stimulation with specific phases of endogenous rhythms can modulate cortical excitability in a predictable manner, thereby validating the fundamental premise of state-dependent neuromodulation. Importantly, phase-locked approaches also enabled controlled testing of causal relationships between oscillatory dynamics and stimulation outcomes, providing a mechanistic bridge between electrophysiological theory and intervention.

However, fixed-phase stimulation strategies are inherently limited by their reliance on a priori assumptions regarding optimal phase targets. Oscillatory dynamics vary substantially across individuals, cortical regions, and behavioral contexts, and the phase associated with maximal excitability is not universally consistent [49]. Moreover, oscillatory phase interacts with other dimensions of brain state, including power and network configuration, which are not captured by phase alone. As a result, fixed-phase approaches may fail to generalize across subjects or conditions, limiting their translational applicability. To address these limitations, recent work has shifted toward adaptive closed-loop systems that dynamically adjust stimulation parameters based on ongoing neural activity. In contrast to static phase-targeting, these systems incorporate real-time feedback to refine stimulation timing, intensity, and targeting in a subject-specific manner. EEG-derived features serve as control variables, allowing the system to respond to fluctuations in brain state and optimize stimulation delivery accordingly.

While early EEG-TMS paradigms focused primarily on single cortical targets, emerging approaches are increasingly oriented toward network-level modulation. This shift reflects a growing recognition that both normal brain function and neuropsychiatric disorders are fundamentally organized at the level of distributed circuits rather than isolated regions [50].

Closed-loop systems are now being developed to incorporate functional connectivity metrics derived from EEG, such as coherence or phase-locking values, to guide stimulation. These measures provide insight into the dynamic coupling between brain regions and can be used to identify network states associated with pathological or optimal function. By targeting stimulation to specific network configurations, rather than single-site activity, these approaches aim to modulate large-scale circuit dynamics more effectively.

In parallel, advances in stimulation technology have enabled multi-locus TMS, allowing coordinated stimulation of multiple cortical sites. When combined with EEG-based feedback, such systems offer the possibility of synchronizing stimulation across distributed nodes, thereby influencing network-level oscillatory patterns and connectivity. This approach is particularly relevant for disorders characterized by dysregulated network synchronization, including depression, schizophrenia, and epilepsy [51-55]. Closed-loop modulation of distributed circuits represents a conceptual extension of phase-locked stimulation, moving from local excitability control toward dynamic regulation of network states. This paradigm aligns with contemporary models of brain function that emphasize the role of oscillatory coordination in shaping cognition and behavior, and it provides a framework for developing more targeted and effective neuromodulation strategies.

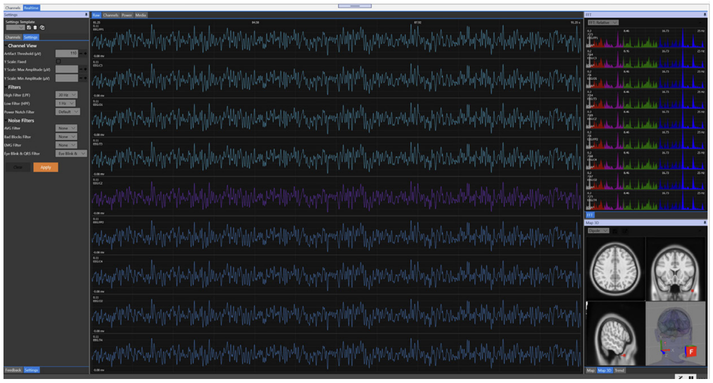

Figure 2: Representative interface illustrating simultaneous visualization of raw multichannel EEG, quantitative trends, automated detection overlays, and hemispheric amplitude-integrated EEG (aEEG) summaries. Multichannel EEG is displayed in standard longitudinal bipolar montage with preserved signal fidelity, demonstrating organized posterior-dominant alpha rhythm across bilateral channels without electrographic seizure activity. Automated annotations identify rhythmic activity and flagged events in real time. Quantitative trend panels include hemispheric aEEG traces, spike-detection heat maps, signal quality indicators, and time-aligned event markers. Color-coded density mapping reflects spatial distribution of detected activity over time. This integrated display exemplifies the capacity to combine rapid acquisition, real-time analytics, and remote-ready interpretation within a unified workflow, supporting both clinical decision-making and neuromodulation targeting.

Clinical Applications

The translational promise of EEG-synchronized TMS lies in its ability to move beyond fixed stimulation paradigms toward state-dependent, individualized neuromodulation, with the potential to improve both efficacy and reliability of clinical interventions. While conventional rTMS has demonstrated efficacy across several neuropsychiatric conditions, clinical outcomes remain variable, with response rates often limited by inter-individual differences in neurophysiology and network dynamics [56]. State-dependent stimulation addresses this limitation by aligning intervention with ongoing neural dynamics.

Major depressive disorder (MDD) represents the most established clinical application of TMS, yet treatment response remains heterogeneous [56]. Standard protocols targeting the left dorsolateral prefrontal cortex (DLPFC) are delivered according to fixed schedules, without consideration of ongoing neural activity [56]. This approach may result in stimulation being applied during suboptimal states of cortical excitability or network engagement. EEG-synchronized TMS introduces the possibility of targeting stimulation to periods of maximal network susceptibility, potentially enhancing engagement of fronto-limbic circuits implicated in mood regulation [57]. Prefrontal oscillatory activity, particularly within the theta and alpha bands, has been associated with treatment response and may serve as a biomarker for guiding stimulation timing [58]. Early-stage clinical investigations, (e.g., NCT03421808), have begun to explore the feasibility and therapeutic impact of EEG-triggered stimulation in depression. These studies aim to determine whether aligning TMS pulses with specific oscillatory states can improve antidepressant efficacy relative to conventional open-loop protocols. Although large-scale randomized controlled trials remain limited, preliminary findings suggest that state-dependent stimulation may reduce variability in treatment response and enhance clinical outcomes, particularly in patients with treatment-resistant depression. Importantly, EEG-guided approaches also offer the potential to identify patient-specific biomarkers of response, enabling stratification and personalization of treatment protocols.

Schizophrenia and related disorders are characterized by profound disruptions in neural oscillations, particularly within the gamma and theta frequency ranges, which are thought to underlie deficits in perception, cognition, and working memory [44,59]. These abnormalities reflect impaired synchronization across cortical networks, suggesting that interventions targeting oscillatory coordination may have therapeutic benefit. EEG-synchronized TMS provides a means to modulate pathological oscillatory patterns in a phase- and state-specific manner, potentially restoring network synchrony. For example, stimulation aligned with endogenous oscillatory rhythms may enhance coherence within frontoparietal networks or normalize aberrant gamma activity [60]. While clinical evidence remains in early stages, the mechanistic alignment between oscillatory dysfunction and state-dependent stimulation provides a strong rationale for further investigation in this population.

In the context of stroke, recovery is critically dependent on activity-dependent plasticity within peri-lesional and contralesional networks. Conventional TMS protocols have been used to facilitate motor recovery by modulating cortical excitability; however, outcomes are variable and often modest [61]. Closed-loop EEG-TMS offers a strategy to target stimulation during optimal windows of plasticity, such as periods of increased sensorimotor rhythm desynchronization associated with motor intention or execution. By aligning stimulation with these endogenous states, it may be possible to enhance synaptic efficacy and promote functional reorganization more effectively than fixed-schedule stimulation. In addition, EEG-based monitoring enables real-time assessment of network recovery, providing a potential biomarker for tracking treatment progress and adapting intervention strategies over time.

Epilepsy is characterized by abnormal hypersynchronization of neural activity, often manifesting as paroxysmal oscillatory events [62]. EEG-triggered TMS has been proposed as a potential intervention for disrupting pathological synchronization in real time, either by delivering stimulation contingent on pre-ictal signatures or by modulating network excitability to reduce seizure likelihood [63]. Although this application remains largely experimental, the ability to detect and respond to specific electrophysiological patterns in real time positions closed-loop EEG-TMS as a promising approach for seizure modulation. Integration with continuous EEG monitoring systems may further enable long-duration or ambulatory implementations, expanding the potential clinical utility of this approach.

Across these clinical domains, a unifying theme is the transition from standardized treatment protocols toward precision neuromodulation, in which stimulation is tailored to the individual's neurophysiological state. EEG-synchronized TMS provides a framework for this transition by enabling the identification and targeting of brain states associated with optimal responsiveness.

Advances in EEG acquisition platforms, including scalable systems capable of continuous monitoring and real-time analysis, further support this paradigm by enabling longitudinal characterization of neural dynamics. Such capabilities are essential for understanding intra-individual variability across sessions and for implementing adaptive stimulation strategies that evolve over the course of treatment. However, significant challenges remain before EEG-guided TMS can be widely adopted in clinical practice. These include the need for standardized biomarkers, validation in large-scale randomized trials, and demonstration of superiority or added value relative to existing protocols. Additionally, practical considerations such as system complexity, cost, and integration into clinical workflows must be addressed. Despite these challenges, the convergence of mechanistic insight, technological innovation, and early clinical evidence suggests that EEG-synchronized TMS has the potential to transform neuromodulation from a static intervention into a dynamic, feedback-driven therapeutic modality, with broad applicability across neuropsychiatric and neurological disorders.

Beyond acute and interventional settings, the clinical utility of EEG-based platforms extends into translational and outpatient domains where objective neurophysiologic biomarkers remain limited. Across neurology, psychiatry, rehabilitation medicine, and cognitive neuroscience, a persistent challenge is the reliance on subjective symptom reporting and coarse behavioral measures to characterize disorders that are increasingly understood as network-level dysfunctions. EEG and ERP methodologies address this limitation by providing direct, temporally precise measures of neural oscillations, functional connectivity, and task-evoked processing that are not captured by structural imaging or standard clinical assessments. Scalable EEG platforms enable longitudinal characterization of these dynamics, facilitating the identification of biomarkers associated with disease state, treatment response, and recovery trajectories. Within this context, systems capable of rapid deployment and continuous monitoring support a shift toward neurophysiologically informed clinical decision-making, in which diagnosis, stratification, and treatment optimization are guided by objective measures of brain function. This paradigm is particularly relevant for EEG-synchronized TMS, where longitudinal tracking of brain state may inform adaptive stimulation strategies across treatment sessions. The integration of real-time electrophysiology with neuromodulation thus provides a pathway toward precision medicine frameworks grounded in dynamic, patient-specific neural signatures.

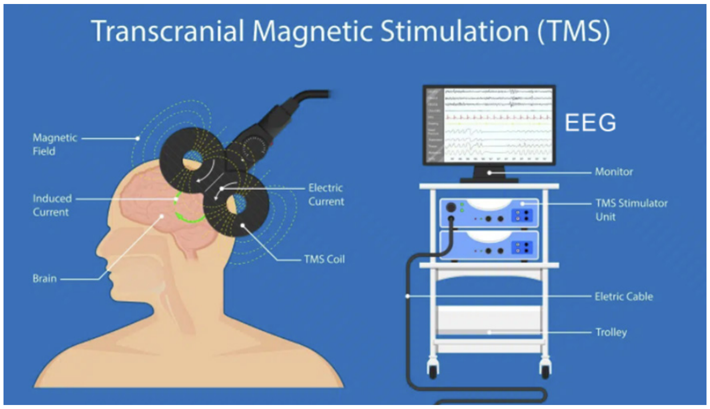

Figure 3: Illustration depicting rapid bedside application of a simplified EEG headband in a supine patient undergoing neurophysiologic monitoring. The electrode array is secured using a streamlined frontal montage designed for expedited placement by trained non-specialist personnel. EEG signals are transmitted in real time to a portable interface displaying multichannel tracings with time-locked waveform activity. This schematic highlights the operational model of point-of-care EEG, characterized by minimal setup time, reduced dependency on specialized technologists, and immediate access to interpretable neurophysiologic data. Such deployment supports early seizure detection or exclusion, triage decisions, and initiation of time-sensitive interventions across emergency, critical care, and resource-limited environments.

Barriers to Clinical Translation, Future Directions, and Conclusions

Despite rapid advances in EEG-synchronized TMS, several critical barriers currently limit its translation from experimental paradigms to routine clinical practice. These challenges span methodological, technical, biological, and regulatory domains, and must be addressed systematically to realize the full potential of state-dependent neuromodulation. A central limitation is the lack of standardization across key methodological dimensions. There is currently no consensus regarding optimal oscillatory targets, phase selection strategies, or stimulation timing criteria. While sensorimotor rhythms have been extensively studied in motor cortex paradigms, the generalizability of these findings to association cortices remains uncertain. Furthermore, outcome measures vary widely across studies, ranging from motor-evoked potentials to behavioral or clinical endpoints, complicating cross-study comparisons and meta-analytic synthesis. The absence of standardized protocols and benchmarks hinders reproducibility and slows the accumulation of clinically actionable evidence. Technical constraints represent an additional major barrier. Interoperability across EEG and TMS platforms is also limited, with many systems relying on custom integration solutions that are not easily scalable or transferable across sites. In addition, real-time signal processing imposes significant computational demands, particularly when incorporating advanced feature extraction. Signal quality and reliability further complicate clinical implementation. EEG recordings, particularly from prefrontal regions, are characterized by relatively low signal-to-noise ratios, susceptibility to motion and muscle artifacts, and variability across sessions and individuals. Accurate phase estimation under these conditions remains challenging, and errors in feature detection can directly impact stimulation fidelity. Moreover, brain states themselves exhibit substantial intra-individual variability across time, raising questions about the stability and reproducibility of targeted stimulation conditions. Addressing these issues will require advances in both acquisition technology and signal processing methodologies, as well as improved characterization of biologically meaningful brain-state features.

Regulatory and scalability considerations present additional challenges. Closed-loop neuromodulation systems are inherently more complex than conventional open-loop devices, incorporating multiple interacting components and adaptive control algorithms. This complexity raises important questions regarding safety, validation, and regulatory approval pathways. At the same time, widespread clinical adoption will depend on the development of robust, user-friendly platforms that can be deployed in real-world settings without requiring extensive technical expertise. Integration with scalable EEG systems capable of reliable, continuous monitoring will be essential for bridging the gap between laboratory feasibility and clinical practicality.

Addressing these barriers will require coordinated efforts across the field, supported by several key directions for future research. First, there is a pressing need for standardization and benchmarking, including the development of shared protocols, open datasets, and consensus definitions of relevant brain-state features. Cross-site reproducibility studies will be critical for establishing the reliability of EEG-synchronized TMS and identifying sources of variability across populations and experimental conditions. Second, the integration of artificial intelligence and data-driven modeling is likely to play a central role in advancing closed-loop neuromodulation. Predictive models of brain state can improve the timing and targeting of stimulation, while reinforcement learning approaches enable adaptive optimization of stimulation parameters based on ongoing feedback. These methods offer a pathway toward fully individualized neuromodulation, in which stimulation strategies are continuously refined based on patient-specific neural dynamics. Third, multimodal integration represents a promising avenue for improving both targeting precision and mechanistic understanding. Finally, large-scale randomized controlled trials are essential to establish the clinical efficacy of EEG-synchronized TMS relative to standard open-loop protocols. These studies should incorporate well-defined biomarkers, standardized outcome measures, and stratification strategies to identify patient populations most likely to benefit from state-dependent stimulation. The identification of reliable predictors of treatment response will be critical for translating EEG-guided neuromodulation into precision medicine frameworks.

In conclusion, EEG-synchronized TMS represents a significant conceptual and technological advance in neuromodulation, enabling precise alignment of stimulation with endogenous brain dynamics. By leveraging real-time electrophysiological feedback, this approach offers a pathway toward more effective, reliable, and individualized interventions across a range of neurological and psychiatric conditions. Achieving meaningful clinical impact, however, will depend on continued progress in system reliability, methodological standardization, and scalable implementation. In this context, emerging integrated EEG platforms such as BrainView illustrate how gaps between experimental capability and clinical deployment may be addressed, particularly through improvements in rapid acquisition, real-time analytics, and accessible workflow design. Such systems align closely with the core technical requirements of EEG-synchronized TMS, including low-latency signal processing, robust feature detection, and longitudinal brain-state tracking. As these capabilities converge, closed-loop EEG-TMS is positioned to transition from a promising experimental paradigm to a clinically viable, precision-guided neuromodulation strategy.

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