Intracranial Recording During TMS: A Practical Guide

Preprint · February 2025

DOI: 10.31234/osf.io/eq6us_v1

8 authors, including:

Eric Tsang
University of Iowa
40 PUBLICATIONS **450** CITATIONS
SEE PROFILE

Josh Tatz
University of Iowa
16 PUBLICATIONS **147** CITATIONS
SEE PROFILE

Aaron D Boes
University of Iowa
145 PUBLICATIONS **3,198** CITATIONS
SEE PROFILE

Corey J Keller
Stanford University School of Medicine
108 PUBLICATIONS **2,810** CITATIONS
SEE PROFILE

Intracranial Recording During TMS: A Practical Guide

Running head: *TMS-iEEG*

Umair Hassan*[1,2]
Ethan Solomon*[1,2]
Eric W. Tsang[3]
Jeff Wang[2,4]
Joshua Tatz[1]
Aaron D. Boes[3,5,6,7,#]
Corey J. Keller[1,2,8,#]
Nicholas T. Trapp[3,5#]

Affiliations:
[1]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA
[2]Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA
[3]Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[4]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins, MD, USA
[5]Iowa Neuroscience Institute, University of Iowa, Iowa City, IA, USA
[6]Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[7]Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[8]Veterans Affairs Palo Alto Healthcare System, and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Palo Alto, CA, 94394, USA

*Co-first authors
[#]Co-senior authors

Abstract

Transcranial magnetic stimulation (TMS) has emerged as a powerful clinical tool for treating neuropsychiatric conditions, yet our understanding of how TMS modulates neural circuits in the human brain remains limited. While decades of research have established the therapeutic efficacy of TMS, fundamental questions persist about the spatial and temporal dynamics of TMS effects, including which brain regions are activated and modulated, how long neural changes persist, and the mechanisms underlying the antidepressant effect. Combining transcranial magnetic stimulation and intracranial electroencephalography (TMS-iEEG) can fill this gap by providing important insights into how the human brain responds to non-invasive stimulation. TMS-iEEG enables investigation of both local cortical responses and network-level propagation with millisecond temporal resolution and precise spatial localization. This chapter provides an overview for conducting TMS-iEEG experiments. We first detail phantom validation procedures for evaluating potential heating, electrode displacement, and induced currents. We then outline safety monitoring protocols for human participants, including continuous electrophysiological monitoring for epileptiform activity. Finally, we outline procedures to perform TMS-iEEG experiments – from equipment setup through data collection and analysis. When properly implemented, TMS-iEEG can reveal both immediate local effects and network-level responses to TMS that are not accessible through conventional recording approaches, providing critical insights into the mechanisms of brain stimulation.

Key Words

Transcranial magnetic stimulation, intracranial EEG, electrocorticography, stereoelectroencephalography, artifact reduction, evoked potentials, neural oscillations, cortical excitability, brain connectivity

1. Introduction

TMS combined with invasive neural monitoring in humans and nonhuman primates: existing evidence

Animal models have offered valuable insight into the neural effects of TMS. Single-unit recordings in non-human primates have revealed that TMS elicits rapid neuronal responses within 2-6 ms of stimulation, followed by prolonged inhibition lasting approximately 100 ms and subsequent rebound activation (Mueller et al., 2014; Tischler et al., 2011). These responses show clear dose-dependency, with neuronal firing only observed at suprathreshold intensities that reliably elicit motor responses (Mueller et al.,2014). The spatial specificity of these effects has been mapped, with direct neuronal responses typically confined to within 2 mm of the targeted region, though lower frequency oscillatory changes can be observed over broader spatial territories (Romero et al.,2019).

However, TMS effects further propagate through both direct and indirect pathways to influence activity in distant, functionally and anatomically connected regions. Intraoperative studies in humans with implanted electrodes have shown that motor cortex stimulation can modulate subthalamic nucleus activity through the cortico-striatal-pallidal pathway, with responses emerging around 18-20 ms post-stimulation (Strafella et al., 2004). This subcortical engagement appears to be frequency-dependent – low frequency (1 Hz) stimulation decreases beta oscillations in the motor circuit, while high frequency (10 Hz) stimulation increases high gamma power (Gaynor et al., 2008; Honda et al., 2021). These findings provide direct evidence for the differential effects of various stimulation protocols on subcortical targets, but until recently have not been elaborated beyond primate studies or intraoperative recordings in Parkinson's patients.

Beyond subcortical areas, recent work combining TMS with simultaneous recording from multiple brain regions has begun to elucidate the network-wide impact of stimulation on the neocortex. In patients with medically-intractable epilepsy, dorsolateral prefrontal cortex (dlPFC) TMS produces consistent neural responses in connected regions including the dorsal anterior cingulate cortex and insula, with response probabilities as high as 44% in some downstream regions (Wang, Hassan et al., 2024). These network effects show both anatomical and functional specificity – different stimulation sites produce distinct patterns of distributed responses that correlate with pre-existing functional connectivity measures (Wang, Hassan et al., 2024). Together, this work provides important insight into how TMS effects propagate through brain networks to influence both local and distant neural activity.

The neural effects of TMS span not only anatomical networks, but also multiple timescales. While initial responses occur within milliseconds, repetitive stimulation can induce changes lasting 30-40 minutes, particularly with protocols like theta burst stimulation (Papazachariadis et al., 2014). These sustained effects manifest as alterations in both local and network-level oscillatory activity. For example, intermittent theta burst stimulation of motor cortex in nonhuman primates induces prolonged increases in high gamma power (55-90 Hz) lasting up to 40 minutes, accompanied by concurrent decreases in theta band activity (Papazachariadis et al.,

2014). These bidirectional frequency-specific changes may reflect distinct mechanisms of local circuit activation versus large-scale network modulation.

TMS combined with intracranial EEG in humans: safety testing and new directions

Understanding how transcranial magnetic stimulation (TMS) affects neural activity in humans is critical for both basic science and clinical applications. Early work relied primarily on scalp EEG, fMRI, behavioral measures, and intraoperative recording during Parkinson's surgeries to assess TMS effects. However, recent technical advances have enabled direct measurement of neural responses through concurrent intracranial EEG (iEEG) recordings in neurosurgical patients, enabling longer-term and brainwide recordings from diverse cortical and subcortical areas. This TMS-iEEG approach provides unique advantages in both spatial and temporal resolution, enabling precise spatiotemporal characterization of local and network-level responses to stimulation. However, implementing TMS-iEEG requires extensive safety validation before any experimental studies can begin. The core challenge lies not only in recording high-fidelity neural signals in the presence of strong electromagnetic pulses, but in ensuring patient safety when delivering TMS in the presence of implanted electrodes.

Before any human TMS-iEEG studies can begin, comprehensive phantom brain or large animal testing must validate safety across the planned hardware configurations and stimulation parameters. Wang, Hassan et al. (2024) outlined critical safety concerns including electrode heating from induced currents, potential mechanical displacement of electrodes from magnetic forces, and the spatial distribution of induced voltages – all of which require systematic characterization using gel-based phantoms that approximate brain tissue properties (**Figure 1**). Once phantom testing confirms safety thresholds, human studies can proceed with rigorous ongoing monitoring protocols, including continuous real-time iEEG surveillance for epileptiform activity, regular electrode impedance testing to detect tissue changes or technical issues, and established procedures with trained personnel and medications available to respond to seizures or other adverse events. This two-stage approach – thorough phantom validation followed by comprehensive clinical safety protocols – provides the foundation for reliable data collection while ensuring patient safety throughout experimental procedures. Notably, these safety measures must be customized and assessed for each unique combination of recording setup and stimulation parameters, as variations in hardware materials, configuration or stimulation protocols could significantly impact these metrics.

This chapter provides a practical guide for implementing TMS-iEEG experiments, with specific emphasis on required safety validation prior to human studies. We begin with detailed protocols for phantom safety testing, including clear acceptance criteria that must be met before proceeding to human studies. We then outline safety protocols for human studies, followed by detailed methodological procedures for equipment setup, signal acquisition, artifact management, and signal processing. Special attention is given to methods for characterizing and minimizing artifacts and evaluation of both local and network-level intracranial effects. Throughout, we emphasize the critical importance of maintaining rigorous safety standards coupled with minimizing artifacts, yielding safe and high-quality data collection. The protocols described have been validated at one research site and should be adapted to available hardware configurations while maintaining safety standards.

2. Materials

Safety Testing Equipment

We recommend performing phantom brain testing of TMS-iEEG prior to human experimentation. Gel-based phantom brains are composed of polyacrylic acid saline gel in an 8-inch cubic container with 3/16-inch polymethyl methacrylate walls. This phantom must have conductivity matching brain tissue (approximately 0.4 S/m) and should allow for electrode placement at various depths and orientations. Temperature monitoring equipment should be non-ferromagnetic probes capable of 0.1°C resolution with multi-channel recording capability and real-time display interfaces with data logging features. Electric field measurement requires high spatial resolution probes with wide dynamic range and multiple orientation sensors, allowing for detailed mapping of induced fields throughout the phantom. A calibrated pickup coil for artifact measurement will be helpful in characterizing the temporal and spatial properties of TMS-induced signals. High resolution video recording equipment should be available to monitor movement/motion in the electrodes (**Figure 1**).

TMS Equipment

The TMS setup requires a research-grade industrially designed and developed stimulator capable of both single pulse and repetitive stimulation modes. Systems such as the MagVenture MagPro X100 or equivalent are capable of external triggering capabilities for timing synchronization, precise intensity control from 0-100% output, active coil cooling, sham stimulation capabilities including time-locked tactile sham, and appropriate safety lockout features. The stimulation coil should be a figure-8 design, although other coil types could be considered once appropriate safety testing has been performed. The coil should have integrated temperature monitoring and the ability to integrate with TMS-compatible neuronavigation equipment. Active cooling (ideally liquid cooling to avoid excess ambient noise with air cooling) is essential for extended sessions. The coil mounting system must provide multi-axis adjustment capability, quick-release safety mechanisms, and stable positioning compatible with MRI-based neuronavigation systems.

Recording Equipment

The iEEG recording system forms the core of the experimental setup. A clinical-grade amplifier system must support minimum sampling rates of at least 1000 Hz (the higher the better to capture the TMS artifact) with an input range of ±5 mV and 24-bit ADC resolution. The system should include online impedance monitoring capabilities and direct interface with TMS trigger signals. Depth electrodes for stereo-EEG and surface grid/strip electrodes for electrocorticography can be used in combination with TMS, along with appropriate reference and ground electrodes. The recording setup must include cable management systems and spare electrode sets. Real-time visualization software is essential for continuous quality monitoring.

As mentioned above, to ensure optimal data quality during TMS-iEEG experiments, the recording system should be configured ideally with a high sampling rate (preferably ≥25000 Hz) to capture rapid neuronal activity and minimize aliasing. Hardware filters should include a bandpass filter (e.g., 0.1–500 Hz) to suppress noise outside the physiological range, with additional notch filters to eliminate power line interference. The amplifier should feature high

input impedance (>10 MΩ) to maintain signal fidelity and minimize electrode polarization artifacts. Real-time visualization tools are crucial, enabling continuous monitoring of electrode impedance, signal quality, and potential TMS-induced artifacts. Furthermore, the system should support flexible triggering and synchronization capabilities to integrate seamlessly with TMS pulses, ensuring precise temporal alignment of stimulation and recording (for more details see **Table 1**).

Safety Monitoring Equipment

Safety equipment must be immediately accessible. This includes a defibrillator, vital signs monitoring equipment, oxygen supply, and seizure rescue medications. Emergency stop controls for TMS must be readily available. Real-time iEEG monitoring displays must be visible to clinical staff throughout the experiment to allow monitoring for after-discharges, ictal activity, or excessive artifact.

Patient Support Equipment

Additional equipment ensures subject comfort and safety during experiments. This includes foam head support systems, acoustic noise protection (earplugs rated for TMS noise levels) and an equipment cart with an isolation transformer for TMS power. Video monitoring systems allow constant observation of the subject, while two-way audio communication systems enable clear interaction between the subject and research team. Typically one or two research team members should remain in the room with the patient to observe behavioral changes, monitor tolerability, and adjust coil placement or patient positioning as needed (for more details see **Table 1**).

3. Methods

Required Safety Testing Protocols

Phantom Testing

Before any human experiments can begin, comprehensive phantom safety testing must be conducted. This applies even when replicating previously published configurations, as small variations in setup can affect safety parameters. For example, Wang, Hassan et al. (2024) used a MagVenture MagPro X100 230V system with a figure-of-eight liquid-cooled Cool-B65 A/P coil, testing both biphasic (290μs pulse width) and monophasic stimulation protocols at 10-40 Hz. Their phantom testing used a custom 8-inch cubic container with polyacrylic acid saline gel and 3/16-inch polymethyl methacrylate walls, containing both 32-contact grid and 8-contact depth electrodes (Ad-Tech platinum electrodes). Even when reproducing this exact configuration, independent safety validation is strongly recommended. Begin by positioning recording electrodes within the gel phantom, ensuring placements mimic expected clinical scenarios. Electrode impedances should be verified to match typical in-vivo values (0.5-5 kΩ). Specifically, Wang, Hassan et al. (2024) reported impedances of 2.82 ± 1.1 kΩ at 100 Hz and 1.44 ± 0.87 kΩ at 1000 Hz in their phantom setup. Three critical safety parameters must be evaluated: heating, mechanical forces, and induced voltages (**Figure 1**).

Temperature monitoring is an important component of safety validation. Using non-ferromagnetic temperature probes, monitor electrode temperature during repeated TMS pulses at maximum intensity (e.g., 100% stimulator output at the patterns and intensities intended for experimentation). Measurements should be taken at multiple distances from the

stimulation site. Electrodes should show minimal heating (<0.1°C change). Any observed heating above this threshold requires modification of stimulation parameters or electrode positioning to minimize heating before proceeding.

Next, mechanical electrode stability must be verified using high-speed video recording of electrode positions during stimulation. Video recordings should have sufficient resolution (minimum 0.5mm) to detect even subtle electrode movements. Monitor for any electrode movement during single pulses and repetitive stimulation protocols, including the worst-case scenario of stimulation directly adjacent to electrodes. At this resolution, no visible electrode displacement should be tolerated, as even small movements could indicate potential safety concerns. Document stability across different coil orientations and stimulation intensities.

Induced voltages must be systematically measured using high impedance recording systems across distances from 5-50 mm and multiple orientations relative to the TMS coil. Map the spatial decay of induced voltages to ensure they fall within safe limits throughout the recording volume. This corresponds to a maximum voltage gradient of 0.3 V/mm and charge density/phase below 7.2 μC/cm2 (e.g., maximum induced voltage in one published study was 5 V, see Figure 1)

Human Safety Monitoring Protocol

Following successful phantom validation, human studies require continuous safety monitoring. All studies should follow human subjects research standards, including appropriate institutional review board approval and explicit patient consent at a time when they are cognitively recovered from the initial implantation surgery and have adequate time to consider participation. Prior to any stimulation, establish clear seizure monitoring protocols and emergency response procedures. Personnel that are trained on emergency protocols should be present, along with ensuring immediate access to rescue medications. Ensure real-time iEEG monitoring with at least one neurologist continuously monitoring the iEEG throughout the session. If these procedures are conducted in patients receiving clinical epilepsy monitoring care, epilepsy monitoring unit staff should be notified of the planned experiments before starting stimulation, so this can be accounted for while performing clinical monitoring and iEEG interpretation. Document baseline activity for at least 15 minutes before beginning stimulation. The research team should communicate with the clinical team and be aware of any identified seizure foci and associated electrode contacts as they plan their stimulation protocols. Start with checking a TMS motor threshold following previously published protocols (Rossini et al., 2015, Hassan et al., 2022), and before initiating any TMS single pulse or repetitive protocol, administer brief portions of the planned pulse sequence to ensure tolerability. If tolerability is a concern, stimulation can be initiated at a lower intensity (e.g. 50% motor threshold) and gradually increased as tolerated. Monitor adverse events and patient comfort using standardized scales throughout the session.

We note that the guidelines established herein are in no way intended to replace current guidelines for general research with TMS (Rossi et al., 2021). Rather, they are intended to complement and provide additional guidance for TMS research with iEEG patients, especially insofar as intracranial electrodes and epilepsy necessitate additional safety considerations.

Perform impedance checks before stimulation, after every hour, and immediately if any signal quality changes are observed. Document all impedance values. Monitor equipment temperature

regularly, particularly the TMS coil and any equipment in contact with the patient. Maintain detailed logs of all stimulation parameters, monitoring results, amplifier settings, and any observed responses (i.e., electrophysiologic or behavioral).

Experimental Procedures

Experimental Setup

After completing all safety protocols, experimental setup can proceed. Begin with careful review of post-implantation imaging to identify TMS target and electrode locations. Use neuronavigation software to plan stimulation targets when possible. We recommend maintaining a minimum of 5mm distance from any electrode to minimize electrical artifacts. Verify the patient is back on anti-seizure medication (if applicable – all human experimentation to date has been conducted with anti-seizure medications initiated for at least one day, but this may not be necessary for low risk protocols. These low risk protocols include single pulse TMS to regions outside of the seizure onset zone and early spread regions.

Once ready for the TMS experiment, position the subject comfortably with their head supported. We have a neurosurgeon remove the head wrap prior to performing TMS. It is preferable to place the infrared tracker of the neuronavigation system on the forehead via adhesive rather than elastic strap to avoid contact with wires or sEEG anchor bolts. When positioning the TMS coil, take care to avoid direct contact with anchor bolts or other hardware from the intracranial electrode implantation. If necessary, adjust the coil angle or position to ensure stable and safe placement while maintaining the intended target. Due to the increased risk for discomfort and patient movement in this post-surgical clinical population, having a research team member hold the coil (with real-time neuronavigation target monitoring) for shorter protocols may be preferred relative to a coil holder.

Apply neuronavigation markers and verify their stability. Configure real-time iEEG monitoring with appropriate trigger synchronization between TMS and recording systems. Establish clear communication systems between control room (if applicable) and patient area (**Figure 3A**).

Data Collection

Begin experimental protocol. We recommend starting with a few single pulses of TMS at low intensity to ensure tolerability. Next, we recommend checking motor threshold, as cortical excitability can vary widely in epilepsy patients on anti-seizure medications (Theodore et al., 2003). We typically begin experiments with single-pulse TMS as it is typically better tolerated than repetitive TMS. We deliver trains of no more than 0.5 Hz and up to 120% of resting motor threshold. Jitter can be used to reduce potential plasticity effects, but also introduces a stronger saliency response (Ross et al., 2022, Ross et al., 2024). When conducting repetitive TMS protocols we typically start with a brief train of stimulation at 80% of resting motor threshold to assess tolerability, then increase to 100% and 120% as tolerated and depending on intensity goal. Continuous iEEG should be recorded at minimum 10000 Hz sampling rate with hardware lowpass (500 Hz) and highpass (0.1 Hz) filtering. Include sham and active control stimulation conditions in the experiment design. This can include auditory only (with active side of a dual active/sham TMS coil oriented away from the skull, using standard white noise developed from the sound of the TMS coil, or the newer adaptive auditory masking and experiment automation

methods (Trapp, Tsang et al., 2024, Russo et al., 2022, Hassan et al., 2022), auditory plus somatosensory (with active side of TMS coil oriented away from the skull coupled with scalp electrode stimulation mimicking the somatosensory effects of TMS), and somatosensory only. Monitor and document patient comfort throughout the session.

It is important to implement real-time quality monitoring of raw signal quality, stimulation artifact characteristics, and basic physiological markers. Visually-apparent features of raw signal quality include the presence of large-scale noise (high-amplitude, high-frequency signal across many electrodes which may indicate disrupted connections, excessive movement of cabling or the patient, or the presence of electronic interference if noisy signals are oscillatory). Stimulation artifact will usually cause an unavoidable amplifier saturation in many electrodes, particularly those electrode contacts close to the coil; this is usually followed by a slower decay period before the iEEG reaches the pre-stimulation baseline. Care should be taken to try to minimize this artifact saturation. Notable physiologic markers to monitor may include stimulation afterdischarges (polymorphic, but often exhibit sharp spikes), brief inter-ictal discharges, or highly synchronous activity across numerous leads (which may be an early marker of precipitated seizure activity or the patient falling asleep; correlate with changes in patient behavior). Perform regular impedance checks and signal-to-noise ratio verification throughout data collection; increases in impedance may indicate poor connections or broken leads.

Signal Processing

Offline signal processing begins with robust artifact management using a three-step approach: identify the stimulation pulse artifact window using automated amplitude thresholding, replace the pulse artifact period with synthesized data matching pre-stimulus signal characteristics (Cline et al., 2021), and verify pulse artifact removal through visual inspection and spectral analysis. Following artifact removal, implement a processing pipeline including downsampling after appropriate anti-aliasing filtering (**Figure 2, 3B**)

To avoid discontinuities in the data that complicate analysis and visualization, we recommend replacing the artifact period with synthesized data (e.g., interpolation or model-based reconstruction). However, it is important to note that the artifact period itself remains un-analyzable, and this approach is solely intended to improve the interpretability of the post-stimulation period.

When evaluating the post-stimulation time period, care should be taken to assess data quality and the potential for residual artifact. While the immediate artifact typically resolves within 50ms, there may be a decay period where signal quality remains compromised, particularly in spectral analyses. For example, high-frequency activity may be disproportionately affected by residual artifact, and this should be considered when interpreting results. To mitigate these concerns, researchers may employ detailed spectral methods that are less sensitive to overlapping artifact, such as continuous Morlet wavelets, which provide better time-frequency resolution compared to windowed analyses. An additional advantage of using Morlet wavelets for time-frequency decomposition is that the wavelet cycle length can be scaled logarithmically, which can be important when considering the wide-frequency range typical of local-field potential analyses. However, each method has tradeoffs, and the choice of analysis should be guided by the specific research question and the characteristics of the artifact in the dataset.

Network analyses should examine both amplitude and timing of responses across recording sites to characterize the neural propagation patterns of TMS. To separate evoked (oscillations phase-locked to stimulation) from induced responses (oscillations with variable phase relationship to stimulation), combine phase-locking analyses with trial-by-trial assessment of oscillatory power changes (Solomon et al., 2024) (**Figure 3B**). Include quality metrics such as signal-to-noise ratio calculations and verification of artifact rejection success. Statistical significance should be assessed using appropriate corrections for multiple comparisons across channels and time points.

Re-reference depth electrodes using a bipolar montage to capture local field potentials while minimizing volume conduction effects. For surface electrodes, multiple referencing approaches may be appropriate depending on the scientific questions being addressed: common average referencing can help reduce global noise but may blur focal effects, while bipolar referencing of adjacent surface contacts or laplacian re-referencing can highlight local activity gradients. The choice of reference scheme should be explicitly justified based on the experimental goals and validated through careful evaluation of the resulting signals. Apply notch filters at line noise frequencies using frequency-domain regression techniques. Alternatively, to preserve activity near line noise frequencies, consider using time-frequency decomposition techniques capable of demodulating such signals (Kovach & Gander, 2016). For analysis of evoked responses, band-pass filtering between 1-35 Hz using zero-phase FIR filters is a reasonable approach. Advanced processing should employ multitaper spectral estimation with frequency-dependent time windows (**Figure 2**).

Analysis should address three key domains: local responses near the stimulation site, network-level effects at distant regions, and separation of evoked from induced spectral responses. For example, one can compare spectral power in 500 ms windows before and after TMS pulses, excluding the immediate artifact period (0-50 ms) (Solomon et al., 2024) (**Figure 3B**). The specific parameters of spectral analysis depend on the experimenter's unique goals.

4. Notes

Critical Safety Considerations

Safety monitoring during phantom brain TMS-iEEG requires vigilance at multiple levels. Temperature monitoring deserves particular attention during initial phantom brain testing – if electrode heating exceeds 0.1°C, immediately check coil positioning and distance. The relationship between induced heating and distance from the coil follows an exponential decay, meaning small adjustments in coil position can significantly reduce heating while maintaining effective stimulation. Regular monitoring of electrode impedances throughout the session provides early warning of potential tissue heating or contact problems.

During human experiments, continuous iEEG monitoring for epileptiform activity is essential. While most participants tolerate the procedure well, any increase in epileptiform discharges should trigger immediate protocol adjustment or session termination. A trained epileptologist should be readily available for consultation. Establish clear thresholds for stopping criteria, such as the appearance of repetitive pathological spikes or high-frequency oscillations that deviate from the patient's baseline.

Technical Challenges and Solutions

Most TMS-iEEG implementation challenges fall into three categories: stimulation pulse artifact contamination, amplifier saturation, and signal noise issues. Amplifier saturation during TMS pulses presents a common challenge, especially in clinical-grade iEEG systems (and not research-grade TMS-compatible systems that have a high dynamic range). If saturation occurs in more than 10% of channels, first verify proper grounding and cable routing. All cables should run perpendicular to the TMS coil orientation when possible. If problems persist, consider using diodes to prevent amplifier saturation or reducing stimulation intensity (Mueller et al., 2014). Note that some signal loss or distortion in the immediate post-stimulus period (0-15ms) is expected and acceptable if later responses can be reliably recorded. However, signal distortion (rather than outright loss) may extend beyond this period, particularly in higher-frequency bands or in channels closer to the stimulation site. Investigators should carefully evaluate their data to determine an appropriate time threshold for excluding potentially contaminated signals. This threshold may vary depending on the research question, the stimulation parameters, and the tolerance for artifact-related signal quality issues. For example, studies focusing on early evoked responses may adopt a more conservative threshold (e.g., 50ms), while those examining later network dynamics may extend the exclusion period to 100ms or more. Ultimately, the choice of artifact duration should be justified and reported transparently to ensure reproducibility.

Artifact contamination beyond 20 ms post-stimulation requires careful investigation. To achieve this, it is critical to record with a high sampling rate (>10 kHz at minimum, though ideally 25 kHz or higher) to accurately capture the biphasic pulse shape of the TMS artifact without ripples, which aids in its subsequent removal. Avoid using antialiasing filters, as higher sampling rates inherently minimize their need, and record in DC mode instead of AC to prevent aggressive filtering that can introduce ripples. Additionally, ensure a solid subject ground connection to reduce electromagnetic noise and carefully manage bipolar channels, as they can carry higher charges and prolong artifacts if not isolated properly. Cable routing, shielding, and the physical arrangement of equipment in the room also play crucial roles in minimizing electromagnetic coupling between the TMS system and recording equipment. Consistency in setup, including mitigating electrical interference from electronic beds, cell phones, and hospital monitoring equipment, is essential for maintaining an optimal artifact profile. These considerations collectively enhance the fidelity of the recorded data and improve the accuracy of artifact removal. Check for potential sources of electromagnetic coupling between the TMS system and recording equipment. Cable routing and shielding often play crucial roles. The physical arrangement of equipment in the room can significantly impact artifact profiles – maintain consistent arrangements once an optimal setup is achieved, including special attention to electrical interference from electronic beds, cell phones, hospital monitoring equipment, and other appliances.

Subdural grid/stim recordings should employ careful common average referencing with exclusion of noisy or artifact-contaminated channels. When using common average referencing, it is critical to exclude channels with excessive noise, artifacts, or pathological activity (e.g., epileptiform discharges) to avoid biasing the reference. Additionally, investigators should consider the spatial distribution of the remaining channels to ensure the reference is

representative of the overall signal. For example, excluding too many channels from one region may skew the reference and introduce artificial connectivity patterns.

Analytically, investigators can assess for zero-lag phase differences between recording contacts to evaluate the potential presence of volume-conducted signals. Alternatively, they can adopt specific connectivity metrics (e.g., the weighted phase lag index; wPLI) that attempt to account for volume conduction by removing zero-lag components of the signal in connectivity computations. Other advanced methods, such as current source density (CSD) analysis or Laplacian filtering, may also be employed to further mitigate volume conduction effects and improve spatial specificity.

Protocol Optimization

The basic protocol can be adapted for various research applications while maintaining core safety principles. For higher temporal precision, sampling rates up to 50k Hz can be used, though this increases storage requirements and processing time. When targeting deep structures, consider using electrical stimulation through implanted electrodes near the superficial targeted site to validate network responses observed with TMS.

Real-time data quality optimization often requires adjustment of multiple parameters. The TMS coil orientation significantly affects both artifact characteristics and neural responses. Systematic testing of different orientations, while maintaining the intended stimulation target, can help optimize the trade-off between signal quality and stimulation effectiveness. Online artifact detection algorithms provide immediate feedback on recording quality, allowing real-time adjustment of stimulation parameters.

Quality Control Indicators

Several key indicators help ensure data quality throughout experiments. Verify that sham stimulation produces minimal pulse artifacts in most channels – significant responses during sham conditions may indicate inadequate artifact suppression. The auditory cortex response to TMS clicks provides a useful positive control, as consistent auditory evoked potentials should be observable with appropriate latency, and suppressed with proper auditory masking. Motor cortex stimulation should produce expected cortico-spinal responses when targeting relevant areas.

Signal preprocessing requires careful consideration of filter choices. While high-pass filtering above 1 Hz can remove slow drift, it may also distort low-frequency components of the TMS-evoked response and induce ringing of higher frequency stimulation artifact. Similarly, notch filters for line noise removal should employ narrow bands to minimize distortion of physiological signals. Consider using alternative approaches such as spectrum interpolation for noise reduction.

Future Directions

Areas for future development include experimental minimization of TMS artifacts through hardware optimization. This includes investigating modified amplifier designs, implementing advanced hardware filters, and exploring novel shielding techniques. Systematic investigation of wire orientation and optimal lead routing could substantially reduce artifact contamination at the source. Leveraging the spatiotemporal resolution of TMS-iEEG, it may also be possible to

identify the neural bases of peripheral artifacts and inform artifact suppression (for a report on TMS-iEEG auditory-evoked responses, see Trapp, Tsang et al., 2024).

Emerging applications include closed-loop stimulation systems, which trigger TMS pulses based on real-time EEG features or update stimulation parameters based on specific behaviors or neural changes observed. Integration with simultaneous fMRI may provide complementary information about stimulation effects, though this requires careful validation of timing precision, additional safety testing, modified echo-planar image sequencing Mizutani-Tiebel et al., 2022), and removal of MR-related artifacts from the iEEG (namely gradient and ballistocardiographic artifacts). These advanced applications require careful validation and should be implemented only after mastering the basic protocol described here.

Comprehensive dose-response curves need to be established across different brain regions and stimulation parameters. The field would benefit from detailed characterization of how inter-stimulus intervals, stimulation intensity, brain state, and temporal parameters affect intracranial evoked responses, particularly given the known variability in noninvasive evoked responses (Kop et al., 2024, Hassan et al., 2024). In turn, such dose-response curves could inform the adequacy of current dosing strategies, including motor-based thresholding and E-field modeling based on individual anatomy (Numssen et al., 2024; Lueckel et al., 2023). Understanding these relationships will be crucial for optimizing therapeutic protocols and advancing mechanistic insights into TMS effects.

iEEG offers a rich space to compare effects within and across neuromodulation techniques. Notably, comparisons between TMS-provoked effects and similar intracranial electrical stimulation delivered at the same target site could provide mechanistic insight into how TMS neuromodulation differs from more focal perturbations. Comparisons to transcranial electrical stimulation and low-intensity transcranial focused ultrasound also represent promising avenues, although rigorous safety testing would be necessary for each technique. Several informative comparisons are also possible within the TMS space. For instance, TMS-iEEG could inform whether targeting a given region directly, upstream, or even downstream (i.e., through antidromic propagations) optimizes a given neural outcome. Likewise, comparing various sequences (e.g., rTMS, iTBS, cTBS) could identify sequence-specific neural effects and inform artifact suppression strategies. Finally, TMS can be combined with intracranial recordings during behavioral or cognitive tasks to determine how specific cognitive domains influence neural activity. Some exciting applications could include using single-pulse TMS to probe local, task-based excitatory or suppressive influences that might not be detectable with task-based iEEG recordings alone (e.g., below baseline activity).

Conclusions. TMS-iEEG represents a powerful approach for understanding how non-invasive brain stimulation affects neural circuits, offering unique advantages in both spatial and temporal resolution that are not accessible through conventional recording methods. While implementing TMS-iEEG requires extensive safety validation and careful technical considerations, when properly executed, it enables precise characterization of both local and network-level neural responses to stimulation, from immediate effects to sustained changes in brain dynamics. This method has opened new avenues for investigating brain connectivity, cognitive processes, and

therapeutic mechanisms, while also providing a platform for comparing different neuromodulation approaches and developing more targeted, effective treatments.

Figures

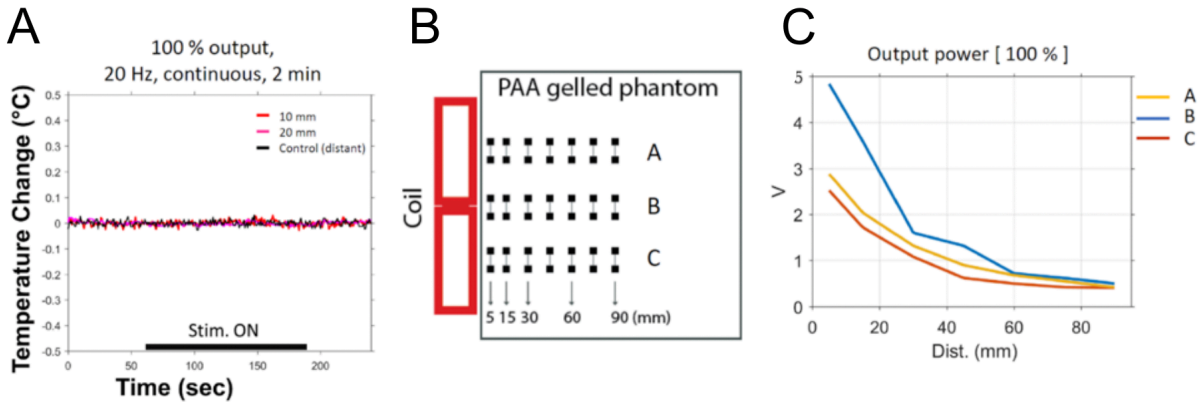

Figure 1. In vitro safety testing of thermal and electrical effects of TMS on intracranial electrodes using a phantom brain model. (A) Thermometry traces showing temperature changes in intracranial electrodes during TMS exposure. (B) Schematic representation of the phantom setup used to study TMS-induced voltage in intracranial electrodes. Electrodes were positioned in a gel phantom along three parallel lines: one at the center of the figure-of-8 TMS coil and two additional lines each 17.5 mm from the center, aligned with the axis of stimulus delivery. (C) Voltage traces over time, demonstrating the exponential decay of induced voltage as a function of distance from the TMS coil, both orthogonal and parallel to the stimulation axis. *Adapted from Wang, Hassan et al., 2024, Molecular Psychiatry*.

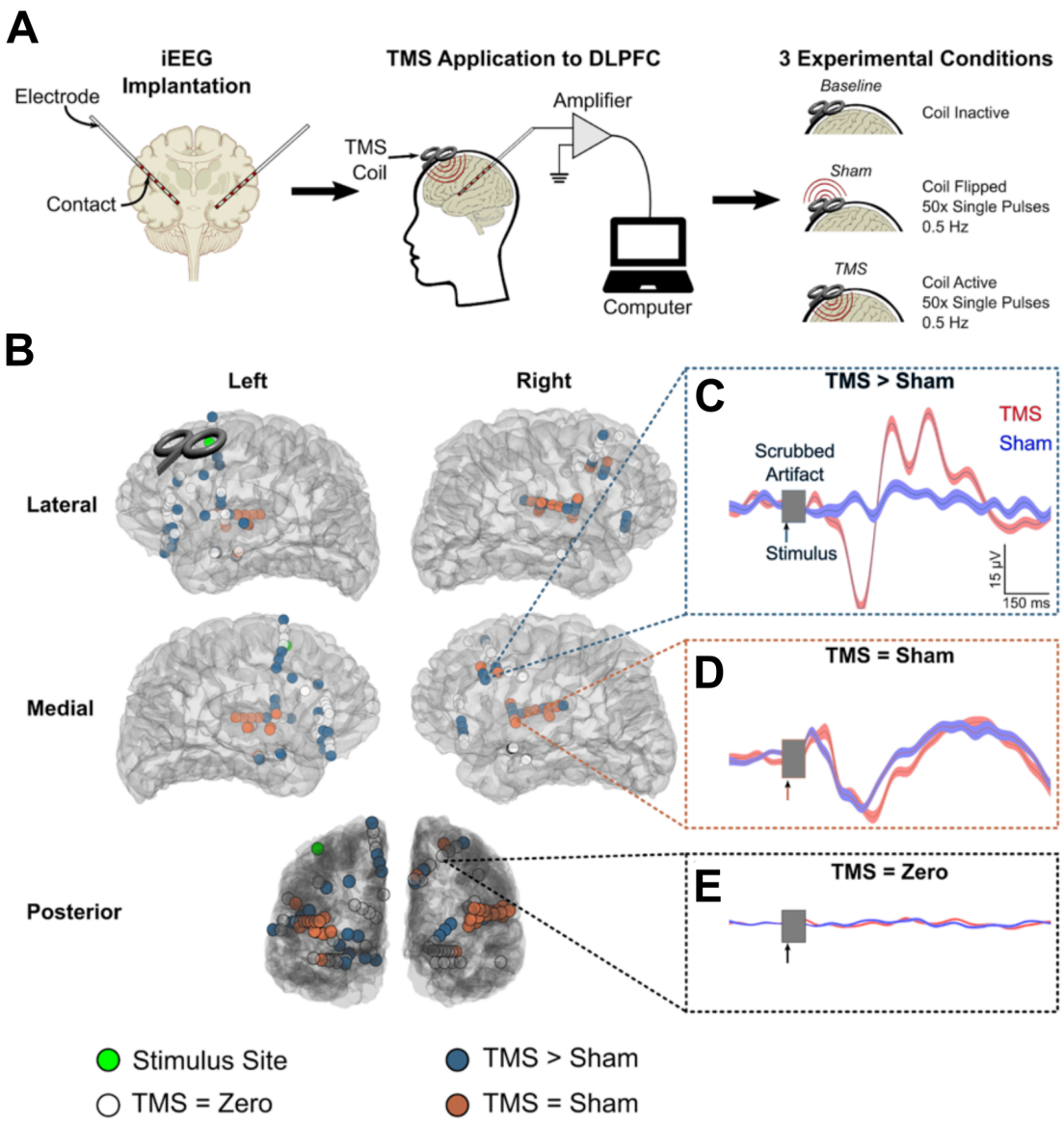

Figure 2. TMS-iEEG experimental setup and Intracranial TMS-Evoked Potentials (iTEPs) in Humans. (A) Schematic of the experimental setup. After surgical implantation of intracranial electroencephalography (iEEG) electrodes, subjects received single pulses of TMS while simultaneous recordings were taken from iEEG contacts. Two conditions were tested: a sham condition with the TMS coil flipped away from the scalp and a TMS condition with the coil correctly oriented. (B) Representative brain of Subject 483, showing the location of implanted iEEG contacts (circles). (C) Representative TMS-evoked intracranial potential (iTEP) significantly greater in the TMS condition compared to sham. The gray region around time zero indicates the period where the TMS artifact was removed, and the vertical arrow marks the time of TMS pulse delivery. Shaded regions represent ±1 standard error of the mean (SEM). (D) Representative neural evoked response with no significant difference between TMS and sham conditions. e) Example of an electrode showing no neural response in either TMS or sham conditions. *Adapted from Wang, Hassan et al., 2024, Molecular Psychiatry*.

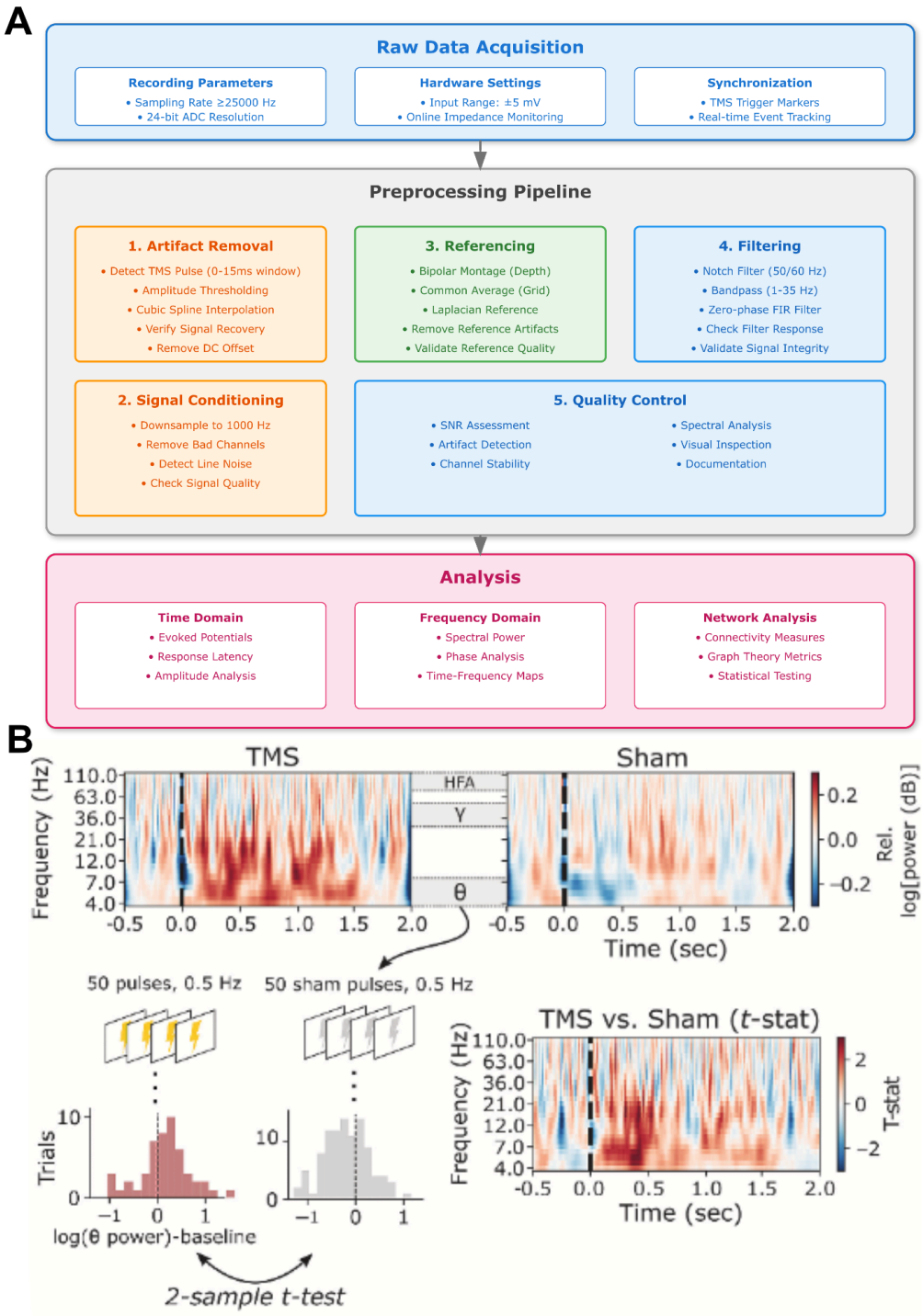

Figure 3. Analysis pipeline for TMS-iEEG data. (A) Flow diagram of signal processing steps from raw data acquisition through final analysis. Critical preprocessing stages include artifact removal, referencing, and filtering. (B) Example time-frequency analysis showing TMS-provoked neural responses: early evoked activity (0-500ms) and later induced oscillations (>500ms) and statistical approach for separating true neural responses from sham-related artifacts and noise. *(B) adapted from Solomon et al., 2024, Brain Stimulation*.

Tables

Table 1: Equipment requirements for TMS-iEEG experiments including phantom testing, stimulation, recording, safety monitoring, and patient support systems. All equipment must meet relevant safety standards and be compatible with the hospital/research environment's electrical and physical requirements.

Category	Equipment	Specifications
Safety Testing Equipment	Gel-based phantom brain	8-inch cubic container 3/16-inch polymethyl methacrylate walls Polyacrylic acid saline gel Conductivity ~0.4 S/m
	Temperature probes	Non-ferromagnetic 0.1°C resolution
	Temperature recording system	Multi-channel Real-time display
	Video recording equipment	High resolution
	Electric field measurement probes	Multiple orientation sensors
	Calibrated pickup coil	For artifact measurement
	Impedance measurement system	Verify 0.5-5 kΩ range
TMS Equipment	TMS stimulator	Research-grade (e.g.,MagVenture MagPro X100) External triggering capabilities 0-100% intensity control Active cooling system
	TMS coil	Figure-8 design Integrated temperature monitoring Active/Placebo version for sham
	Neuronavigation system	MR-based TMS-compatible
	Coil mounting system	Multi-axis adjustment Quick-release mechanisms
	Power supply	With isolation transformer
iEEG Recording Equipment	iEEG amplifier system	Research/Clinical grade ≥ 25000 Hz sampling rate ≥ ±10 mV input range ≥ 24-bit ADC resolution Online impedance monitoring Events trigger markers interface
	Electrodes	Depth electrodes (stereo-EEG) Surface grid/strip electrodes

		Reference/ground electrodes Spare sets
	Cable management system	For organized circuit routing
	Visualization software	Real-time monitoring capability
Safety Monitoring	Emergency equipment	Defibrillator Vital signs monitor Oxygen supply Seizure rescue medications
	Control systems	Emergency stop controls Real-time iEEG/Epileptic spike monitoring
Patient Support	Positioning equipment	Foam head support Adjustable bed/chair
	Audio equipment	TMS-rated earplugs Noise masking ear molds Two-way communication system
	Monitoring systems	Audio/Video monitoring setup
Data Processing	Computer system	Sufficient computational processing power (50khz x 300 channels x 5-10 hours per patient) Data acquisition software Analysis packages (Python/Matlab) Storage with backup (> 20 TB)
	Display setup	Multiple monitors for real-time monitoring various montages
Additional Supplies	Contact materials	Electrode gel/solution Skin preparation supplies
	Tools	Basic adjustment tools Marking tools for neuronavigation
	Emergency supplies	Backup kit for critical components

REFERENCES

Cline CC, Lucas MV, Sun Y, Menezes M, Etkin A. Advanced artifact removal for automated TMS-EEG data processing. In2021 10th International IEEE/EMBS Conference on Neural Engineering (NER) 2021 May 4 (pp. 1039-1042). IEEE.

Gaynor LM, et al. Suppression of beta oscillations in the subthalamic nucleus following cortical stimulation in humans. Eur J Neurosci. 2008;28:1686-95.

Hassan U, Pillen S, Zrenner C, Bergmann TO. The brain electrophysiological recording & stimulation (BEST) toolbox. Brain Stimulation. 2022 Jan 1;15(1):109-15.

Hassan U, Okyere P, Masouleh MA, Zrenner C, Ziemann U, Bergmann TO. Pulsed inhibition of corticospinal excitability by the thalamocortical sleep spindle. bioRxiv. 2024 Jul 24:2024-07.

Honda Y, et al. Changes in beta and high-gamma power in resting-state electrocorticogram induced by repetitive transcranial magnetic stimulation of primary motor cortex in unanesthetized macaque monkeys. Neurosci Res. 2021;171:41-8.

Kop BR, Oghli YS, Grippe TC, Nandi T, Lefkes J, Meijer SW, Farboud S, Engels M, Hamani M, Null M, Radetz A. Auditory confounds can drive online effects of transcranial ultrasonic stimulation in humans. Elife. 2024 Aug 27;12:RP88762.

Kovach CK, Gander PE. The demodulated band transform. Journal of neuroscience methods. 2016 Mar 1;261:135-54.

Lueckel M, Radetz A, Hassan U, Yuen K, Mueller-Dahlhaus F, Kalisch R, Bergmann TO. Functional connectivity-and E-field-optimized TMS targeting: method development and concurrent TMS-fMRI validation. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2023 Jan 1;16(1):189.

Mizutani-Tiebel Y, Tik M, Chang KY, Padberg F, Soldini A, Wilkinson Z, Voon CC, Bulubas L, Windischberger C, Keeser D. Concurrent TMS-fMRI: technical challenges, developments, and overview of previous studies. Frontiers in Psychiatry. 2022 Apr 21;13:825205.

Mueller JK, et al. Simultaneous transcranial magnetic stimulation and single-neuron recording in alert non-human primates. Nat Neurosci. 2014;17:1130-6.

Numssen O, Kuhnke P, Weise K, Hartwigsen G. Electric-field-based dosing for TMS. Imaging Neuroscience. 2024 Mar 11;2:1-2.

Papazachariadis O, et al. iTBS-induced LTP-like plasticity parallels oscillatory activity changes in the primary sensory and motor areas of macaque monkeys. PLoS One. 2014;9:e112504.

Romero MC, et al. Neural effects of transcranial magnetic stimulation at the single-cell level. Nat Commun. 2019;10:2642.

Ross JM, Forman L, Gogulski JD, Hassan U, Cline CC, Parmigiani S, Truong J, Hartford JW, Chen NF, Fujioka T, Makeig S. Sensory Entrained TMS (seTMS) enhances motor cortex excitability. bioRxiv. 2024:2024-11.

Ross JM, Sarkar M, Keller CJ. Experimental suppression of transcranial magnetic stimulation‐electroencephalography sensory potentials. Human Brain Mapping. 2022 Dec 1;43(17):5141-53.

Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, Carpenter LL, Cincotta M, Chen R, Daskalakis JD, Di Lazzaro V. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology. 2021 Jan 1;132(1):269-306.

Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine

clinical and research application. An updated report from an IFCN Committee. Clinical neurophysiology. 2015 Jun 1;126(6):1071-107.

Russo S, Sarasso S, Puglisi GE, Dal Palù D, Pigorini A, Casarotto S, D'Ambrosio S, Astolfi A, Massimini M, Rosanova M, Fecchio M. TAAC-TMS Adaptable Auditory Control: A universal tool to mask TMS clicks. Journal of neuroscience methods. 2022 Mar 15;370:109491.

Solomon EA, et al. TMS provokes target-dependent intracranial rhythms across human cortical and subcortical sites. Brain Stimul. 2024;17:698-712.

Strafella AP, et al. Transcranial magnetic stimulation of the human motor cortex influences the neuronal activity of subthalamic nucleus. Eur J Neurosci. 2004;20:2245-9.

Theodore WH. Transcranial Magnetic Stimulation in Epilepsy. Epilepsy Curr. 2003 Nov;3(6):191-197. doi: 10.1046/j.1535-7597.2003.03607.x. PMID: 15346149; PMCID: PMC321221.

Tischler H, et al. Mini-coil for magnetic stimulation in the behaving primate. J Neurosci Methods. 2011;194:242-51.

Trapp NT, Tsang EW, Bruss J, Russo S, Gander PE, Berger JI, Nourski KV, Rosanova M, Keller CJ, Oya H, Howard MA. TMS-associated auditory evoked potentials can be effectively masked: Evidence from intracranial EEG. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2024 May 1;17(3):616-8.

Wang JB, et al. Effects of transcranial magnetic stimulation on the human brain recorded with intracranial electrocorticography. Mol Psychiatry. 2024.