Neural Decoder for Targeted Real-Time Transcranial Magnetic Stimulation

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Word Count: 4257
Number of Figures: 7
Number of Tables: 0
Number of Equations: 1
Number of Supplements: 1
Number of References: 19

Advisor Approval: Corbin W Ping, Biomedical Engineer

Date: 5/5/2025

Neural Decoder for Targeted Real-Time Transcranial Magnetic Stimulation

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Abstract

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique FDA-approved for treating neuropsychiatric disorders, particularly treatment-resistant depression, by stimulating the dorsolateral prefrontal cortex with magnetic pulses. The efficacy of TMS is often improved by utilizing individualized brain wave patterns– such as those collected by EEG– to stimulate TMS during specific brain states. A MATLAB-based, real-time neural decoding platform aims to enhance closed loop real time TMS, by integrating an additional, non-invasive brain recording technology: functional near-infrared spectroscopy (fNIRS). In this study, we combine fNIRS, electroencephalography (EEG), and TMS to enable adaptive, closed-loop brain stimulation on behavioral biomarkers not picked up by EEG alone. The platform features a graphical user interface (GUI) for real-time visualization of BOLD (blood oxygen level dependent) imaging, automated threshold detection, and manual control of stimulation parameters. The system was validated using a motor behavioral task, where participants flex their hand to induce a reliable motor cortex activation. The algorithm achieved a 77% accuracy rate in correctly triggering repetitive TMS (rTMS) pulses during task-related brain activation in a sample of 8 participants, with some variability due to signal noise and hemodynamic inconsistencies. While initial aims included implementing support vector machine algorithms, technical constraints led to a focus on developing a novel threshold detection method as the primary decoding approach. Future work will emphasize reducing system latency, testing with real-time fNIRS data during cognitive behavioral tasks, and further code optimization. Ultimately, this project aims to deliver an effective and adaptable platform that advances the precision and personalization of TMS therapy for neuropsychiatric disorders.

Keywords: Transcranial Magnetic Stimulation, electroencephalography, functional near-infrared spectroscopy, neural decoding, threshold detection

Introduction

Major depressive disorder (MDD) is one of the most prevalent mental health conditions worldwide, creating a major public health challenge. According to the World Health Organization, MDD was the third leading cause of the global disease burden in 2008 and is projected to become the leading cause by 2030.[1] Characterized by persistent low mood, loss of interest in previously enjoyed activities, and a range of cognitive and physical symptoms, depression can lead to significant functional impairment and reduced quality of life. It affects approximately 12% of individuals over their lifetimes, with women being nearly twice as likely to be diagnosed as men.[1] The causes of depression are complex involving a combination of genetic, neurochemical, hormonal, environmental, and psychosocial factors. Comorbidities such as anxiety, substance use, and chronic physical illness further complicate diagnosis and treatment, particularly among older adults and individuals in underserved areas.

Despite the availability of conventional treatments such as antidepressant medications and psychotherapy, approximately one-third of patients with MDD do not respond adequately to these interventions, a condition known as treatment-resistant depression (TRD).[16] For these individuals, the persistent symptoms of depression include profound sadness, anhedonia, disrupted sleep patterns, and suicidal ideation severely impair daily functioning and quality of life. The inadequacy of traditional treatments for this substantial patient population has driven the development of alternative therapeutic approaches, including transcranial magnetic stimulation (TMS), which offers a promising option for those who have not responded to traditional treatment options.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique that uses magnetic fields to induce electrical currents in targeted brain regions. TMS was first introduced in 1985 and it works by generating rapid electromagnetic pulses through a coil placed against the scalp, which penetrate the skull and modulate neuronal excitability within the cortex.[13] This mechanism allows for the stimulation or inhibition of specific brain areas without the need for surgical intervention. Additionally, repetitive TMS (rTMS) is used in clinical applications, involving the delivery of multiple pulses at defined frequencies to induce longer-lasting changes in cortical activity.

TMS has been FDA-approved since 2008 for the treatment of MDD, specifically for patients who do not respond to conventional therapies like antidepressant medications or psychotherapy.[6] The most common target for TMS in depression treatment is the left dorsolateral prefrontal cortex (DLPFC), a region associated with emotion regulation and executive function. Daily rTMS sessions targeting the DLPFC have been shown to improve mood and cognitive performance in patients with TRD.[4,18] TMS is also used for a number of different neuropsychiatric and neurological disorders, including PTSD, anxiety, OCD, smoking cessation, schizophrenia, chronic pain, stroke rehabilitation, and Parkinson's disease.

Electroencephalography

Electroencephalography (EEG) is a widely used method for recording the brain's electrical activity through electrodes placed on the scalp. It captures voltage fluctuations generated by ionic currents in neurons, particularly within the cerebral cortex, and offers millisecond-level temporal resolution, making it very effective for monitoring fast, dynamic neural processes such as oscillatory rhythms, event-related potentials, and phase shifts.[14] This allows for the detection of quick, transient brain states that may signal optimal windows for therapeutic intervention.[6] EEG has been used in advancing the understanding of cortical excitability, connectivity, and oscillatory dynamics, and it is often used with TMS to see how brain networks respond to external modulation.[18] By providing insight into the brain's electrical behavior, EEG supports the development of more responsive and individualized stimulation strategies.

Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) is an optical imaging technique that measures changes in cortical blood oxygenation to infer neural activity (Figure 1). It emits near-infrared light into the scalp and detects the amount of light absorbed by oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in the brain's blood vessels.[9] Because neural activation is accompanied by localized changes in blood flow and oxygenation, fNIRS can serve as a reliable proxy for brain activity, particularly in the prefrontal cortex and other superficial cortical regions.[5] The technique is used for continuous monitoring during behavioral tasks and is used in cognitive neuroscience, rehabilitation, and developmental research.

Figure 1: Participant is wearing the NIRx fNIRS cap during system setup. Participant is in the 32×32 optode NIRScout cap positioned on the scalp for real-time monitoring of cortical hemodynamics.

One of the main advantages of fNIRS is its portability and ease of use, making it more accessible than imaging techniques like functional magnetic resonance imaging (fMRI). It allows for flexible experimental setups and is compatible with simultaneous use of other modalities such as EEG and TMS.[10] However, fNIRS spatial resolution is lower than fMRI, and its temporal resolution is constrained by the hemodynamic response delay. Additionally, fNIRS signals are sensitive to motion artifacts and physiological noise, such as changes in heart rate or skin blood flow, which can mask true neural signals. Despite these limitations, fNIRS remains a valuable tool for assessing cortical function, especially when integrated into multimodal systems that compensate for its individual weaknesses.[6]

Integrating Neuromodulation and Neuroimaging Techniques

Integrating neuromodulation with real-time neuroimaging techniques is a promising advancement in the effort to make brain stimulation therapies like TMS more precise, adaptive, and effective. Traditional TMS protocols use fixed stimulation parameters that do not account for a patient's current neural state, often leading to inconsistent therapeutic outcomes.[11] To address this, closed-loop TMS systems are being developed that adapt stimulation in response to real-time brain signals.[17] TMS fired in synchrony with specific brain activities show heightened or lessened evoked potentials, indicating a "preferred stimulation condition" in which the brain responds differently to TMS depending on the active brain state at that moment. Traditionally, rTMS fires in synchrony with Alpha Waves– which correspond to markers of cognitive processing speed, as well as wakeful rest. In this study, we expand on that idea to investigate biomarkers from both EEG and fNIRS, allowing to obtain a more comprehensive view of neural activity and adjust stimulation timing accordingly.[3,8] This integration helps ensure that TMS pulses are delivered during optimal brain states for plasticity, ultimately supporting more personalized and effective interventions.

This project builds on that concept by developing a MATLAB-based neural decoding platform that synchronizes TMS delivery with real-time brain activity. EEG is used for detecting rapid neural changes that may indicate moments of increased excitability or responsiveness, while fNIRS provides insight into blood oxygenation and cortical metabolism over time. Together, these modalities enable a closed-loop system that goes beyond traditional open-loop TMS methods. The goal is to improve treatment outcomes for patients with TRD by tailoring stimulation not just to the individual, but to their current brain state.

Materials and Methods

Closed-Loop System

This study presents a closed-loop neural decoding system that integrates fNIRS, EEG, motor task triggering, real-time signal processing, and TMS to enable adaptive brain stimulation based on ongoing neural activity (Figure 2). Participants complete a motor task displayed through a stimulus program, which sends synchronization triggers to both the NIRScout system and Turbo Satori to ensure accurate alignment of task timing with neural data collection. Real-time brain activity is recorded using a wearable fNIRS cap connected to the NIRScout device, capturing changes in blood oxygenation levels associated with neural activation. Raw fNIRS data are transferred via NIRStar to Turbo Satori, which filters and pre-processes the signals before streaming them to a custom MATLAB-based neural decoder. When task-related activity crosses a predefined threshold, the decoder sends a signal through a parallel port to the TMS machine, prompting the coil to fire at precise, behaviorally relevant moments. This integrated setup forms a real-time, closed-loop system capable of dynamically adjusting TMS delivery based on each participant's current brain state, with the goal of enhancing stimulation precision and therapeutic efficacy.

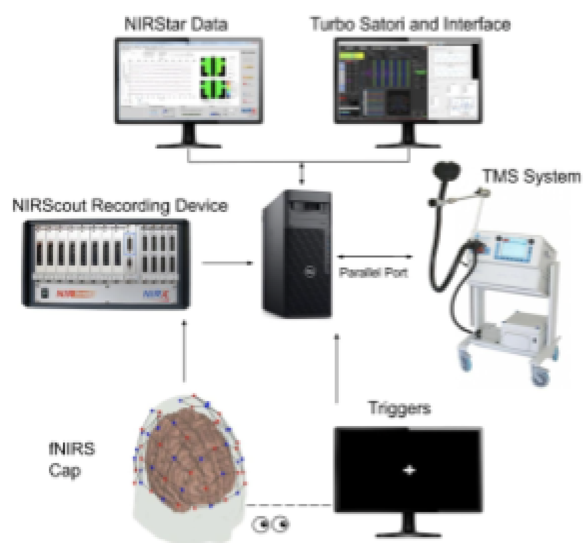

Figure 2. Experimental Setup for fNIRS-Based Neurofeedback and TMS Triggering. The NIRScout system records fNIRS signals, which are processed in real-time by Turbo-Satori via a TCP/IP connection with NIRStar. A stimulus application receives neurofeedback data and presents stimuli to the participant, while a parallel port connection enables TMS triggering based on brain activity changes.

NIRx System and NIRScout Setup

This protocol used the NIRScout system from NIRx Medical Technologies, a high-density, continuous-wave fNIRS platform designed for real-time monitoring of cortical hemodynamics. The NIRScout system captures changes in HbO and HbR hemoglobin using near-infrared light emitted and detected by optodes placed on the scalp. These changes, calculated using the modified Beer-Lambert law, serve as indirect indicators of neural activity.[5] The system was operated through NIRStar, NIRx's acquisition software, which streamed raw optical data to Turbo Satori for real-time processing and signal cleaning.[10]

Participants wore a whole-head fNIRS cap integrated with a 64-channel EEG layout (Figure 3). The fNIRS montage consisted of a 32×32 optode grid, featuring 118 channels in total, including 8 short-separation channels designed to improve signal quality by filtering out superficial physiological noise induced by blood movement in the scalp. In this layout, near infrared light sources were represented by red markers and light detectors by blue, while green dots indicated the position of EEG electrodes. The design supports compatibility with TMS, making it ideal for integrated brain stimulation.[10]

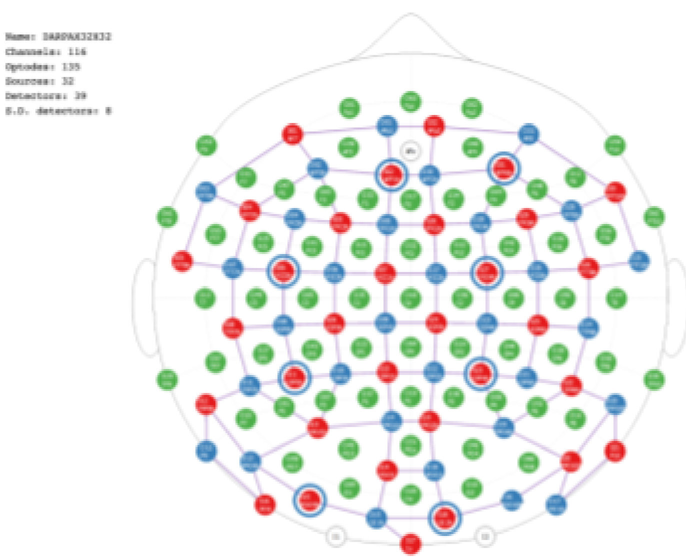

Figure 3: Whole-Head fNIRS and EEG Cap Montage for Multimodal Brain Monitoring. Diagram of the integrated 31×31 fNIRS optode grid and 32-channel EEG layout. Red and blue dots indicate fNIRS sources and detectors, while green dots mark EEG electrode positions.

E-Prime Motor Task and Trigger Synchronization

A right-hand motor task was implemented using E-Prime stimulus presentation software. Participants were instructed to squeeze their right hand in response to visual cues presented on the screen. Participants squeeze their hand 20 times in a 20 second interval, separated by 30 seconds of rest in between, for a total of 7 blocks. E-Prime was configured to send digital synchronization triggers to both the NIRScout system and Turbo Satori. These triggers marked the onset of task events, ensuring precise temporal alignment of task-related brain activity with fNIRS data collection. The timestamps from these triggers were later used to define regions of interest for evaluating the hemodynamic response during task activation, and to compare with the TMS pulse timings captured during real-time stimulation.

Turbo Satori Software

Turbo Satori is a real-time signal processing platform developed by Artinis Medical Systems for fNIRS data. Turbo Satori was used to receive raw optical signals from the NIRScout system through NIRStar, filter out motion artifacts and physiological noise, and stream the cleaned data into MATLAB for further decoding. The software provides low-latency data streaming, allowing continuous monitoring of hemoglobin concentration changes during task performance.[10] Its real-time compatibility made it ideal for this project, where immediate analysis and response to brain activity were required to send time-sensitive TMS pulses. By using Turbo Satori, the system maintained synchronization across all devices and ensured accurate event alignment during closed-loop stimulation.

Parallel Port and TMS Triggering

To interface the neural decoding platform with the TMS machine, a parallel port connection was used to send digital trigger signals directly from MATLAB to the TMS device. This hardware-based triggering mechanism was chosen for its reliability and precision in timing, which is important for closed-loop applications where even minor delays can disrupt the intended alignment between brain state and stimulation.[17] The parallel port setup allowed for seamless integration with the MagVenture TMS system and supported both single-pulse and repetitive TMS modes depending on the task and protocol.

Threshold Calculator

To enable reliable and adaptive stimulation, a custom threshold calculator was developed to automatically determine when TMS should be triggered based on changes in brain activity. The calculator processes fNIRS data collected during an initial baseline task and identifies a consistent activation onset amplitude for each channel. This threshold is then used in the main closed-loop system to trigger TMS only when task-related activity exceeds a meaningful, data-driven level. By automating this process, the calculator reduces human error, speeds up experimental preparation, and allows for offline analysis.

Mathematical Approach Behind Threshold Detection

The threshold calculator operates by applying a signal smoothing filter, using a moving average, to the HbO data to reduce noise and identify distinct activation peaks. Peaks are selected based on a prominence of ≥ 0.1 and a minimum distance of 120 samples between peaks, ensuring that only strong, task-relevant activations are included. For each peak, the algorithm searches 30 samples backward to identify a local minimum, which serves as the baseline. The onset amplitude is then computed using the formula:

$$A_{target} = A_{min} + \alpha * (A_{peak} - A_{min}) \quad [1]$$

where α = 0.2, a constant selected to reflect a moderate rise from baseline toward the peak. The final threshold is calculated by averaging the onset amplitudes across all selected channels. This process enables consistent and individualized thresholding based on actual physiological responses, enhancing the temporal accuracy of TMS delivery.

Main GUI Design and Functionality

The main MATLAB-based graphical user interface (GUI) serves as the central control panel for data visualization, threshold monitoring, and TMS triggering (Figure S1). The GUI displays real-time plots of HbO and HbR signals across selected channels. A user panel allows for the input of subject information, task type, and session parameters. Users can manually select channels for monitoring, adjust stimulation thresholds, and choose between single-pulse or repetitive TMS modes via a dropdown menu with the additional option to select the frequency of the rTMS pulses in hertz. Red markers appear on the plot when a TMS pulse is triggered, providing visual confirmation of system performance. Additional GUI features include a running pulse count, real-time updates of HbO values at each firing, and the ability to start and stop recordings with a single button press. These features were designed to maximize usability while maintaining flexibility for different experimental protocols.

Data Saving and BIDS Compliance

All recorded data, including subject metadata, HbO and HbR time series, trigger timestamps, stimulation parameters, and threshold values are saved in an output CSV file formatted according to the Brain Imaging Data Structure (BIDS) standard. The filename structure follows the BIDS convention, including fields such as subject ID, session number, task name, and run number, ensuring that data are well-organized and easily accessible for downstream analysis. When a recording session ends, the GUI prompts the user to save the session data, which are automatically compiled into a BIDS-compliant spreadsheet for later analysis. This approach improves reproducibility, promotes data sharing, and aligns the system with best practices in neuroimaging research.

Results

Automatic Threshold Calculator Validation

To evaluate the performance of the MATLAB-based neural decoding platform, a series of validation tests were conducted using pre recorded motor task datasets. The focus of these tests was to determine the accuracy and responsiveness of the threshold detection algorithm, assess the usability and output of the custom GUI, and quantify the precision of TMS pulse delivery in a closed-loop framework. The goal was to ensure that TMS pulses were triggered only when task-related neural activity crossed the threshold, calculated automatically from fNIRS data.

The automatic threshold calculator was validated using pre recorded motor task datasets. As shown in Figure 4, the calculator successfully smoothed the HbO signal, identified key peaks and local minima, and computed the threshold value of 0.221 based on the specified onset formula. These calculated thresholds were then used to drive TMS pulse decisions in both rTMS and single-pulse modes. The algorithm handled variability in peak height and baseline drift effectively, and its performance remained consistent despite some noise. Additionally, the parameters that dictate peak prominence, threshold α-value, and cooldown time are all easily adjustable in the code, allowing future users to adjust system sensitivity to specific experimental protocols.

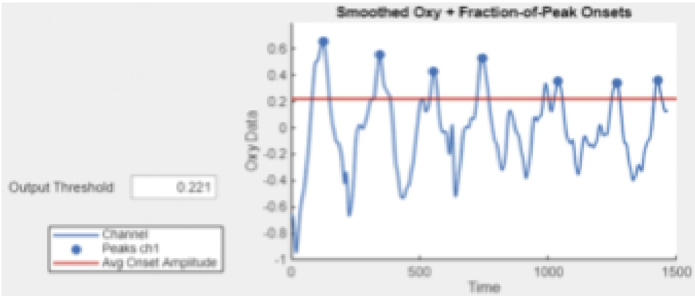

Figure 4: Output of Automatic Threshold Calculator on a Right Hand Motor Task. Graphical output of the threshold calculator showing detected peaks in the HbO signal and the final calculated threshold of 0.221 (red line).

Real-Time GUI Performance

The custom MATLAB GUI was evaluated for its ability to monitor fNIRS signals in real time and trigger TMS pulses after crossing the threshold. During test sessions, the GUI successfully displayed live HbO traces for selected channels, marked TMS pulses with red indicators, and updated firing information dynamically. Users were able to input subject data, select pulse modes (single or rTMS), adjust thresholds manually, and view total pulse count and timing. No major bugs were encountered during testing, and the GUI operated without lag. The system's responsiveness and visual clarity confirmed that the interface met the project's goals for functionality and user control in a closed-loop setting.

System accuracy was measured by comparing TMS pulse timing to the expected onset of motor task-related hemodynamic responses. As shown in Figures 5 and 6, which display the output of the calculated threshold of 0.221 from figure 4 for rTMS and single-pulse modes, the majority of firings occurred within the correct activation window– when the hemodynamic response is at its peak. These results highlight the precision of both the threshold calculator and the hardware-based pulse triggering via the parallel port.

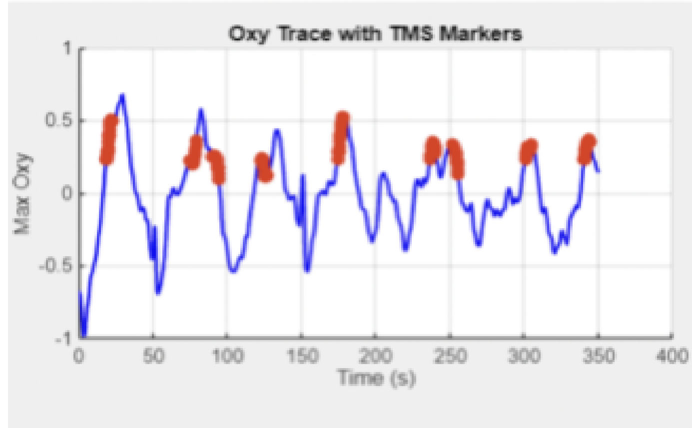

Figure 5: Output of rTMS Using Previously Calculated Threshold. Graph showing rTMS pulses (red dots) triggered in real time when the HbO signal exceeded the threshold of 0.221.

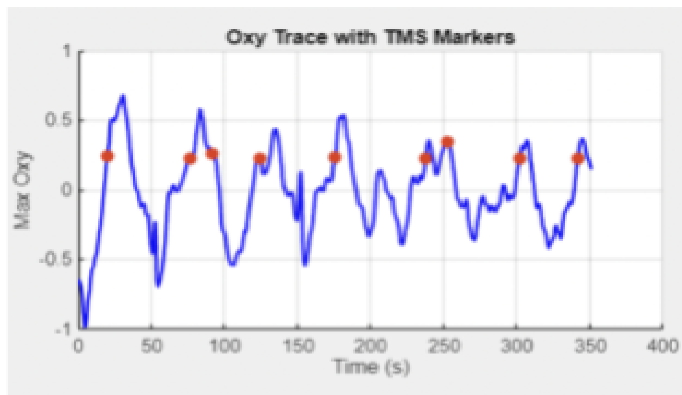

Figure 6: Output of Single Pulse TMS Using Previously Calculated Threshold. Graph showing TMS pulses (red dots) triggered in real time when the HbO signal exceeded the threshold of 0.221.

Accuracy Visualization and Interpretation

To quantify the performance of the closed-loop TMS triggering mechanism, a summary graph was generated to visualize the accuracy of pulse firings across all test events. This graph (Figure 7) categorizes each event into one of three outcomes: success (TMS Fires during behavior), false positive (TMS fires outside behavior), or false negative (TMS does not fire during behavior). Out of 78 total trials, 60 events were correctly identified as activation-related, resulting in a 77% overall success rate. The remaining outcomes included 12 false positives, where a pulse was fired without corresponding activation, and 6 false negatives, where the system missed a task-related response. The false positives and false negatives observed in the results were primarily due to the artifacts in the pre recorded fNIRS dataset. This variability was a result of small peaks or baseline drift that either triggered the system prematurely or masked real activations. Additionally, several trials had inconsistent signal quality, caused by issues such as hair impeding the signal quality, which occasionally led to threshold crossings that did not correspond to true task-related responses. The accuracy graph effectively illustrates the reliability of the system while also identifying opportunities for further refinement.

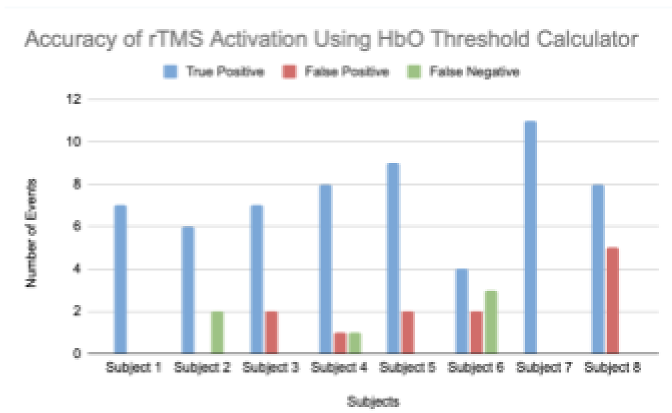

Figure 7:**Accuracy of TMS Pulse Triggering.** Bar graph categorizing all 78 test events into successes, false positives, and false negatives, illustrating the system's 77% accuracy in identifying task-related brain activation.

Discussion

Steps Toward Personalized, Behaviorally Responsive TMS

The present work demonstrates the feasibility of a MATLAB-based, closed-loop neural decoding platform capable of triggering TMS in response to real-time brain activity measured with fNIRS. The system achieved a 77% success rate in correctly triggering TMS during simulated task-related activation, with flexibility to adjust parameters like signal smoothing, peak detection thresholds, and pulse cooldown times. These findings build on research that emphasizes the need for personalized neuromodulation protocols, especially in disorders like TRD, where individual variability in brain structure and state can reduce the efficacy of standard fixed-parameter TMS.[11,15]

Traditional rTMS operates as an open-loop system, delivering pulses at set frequencies regardless of the patient's current neural state. However, emerging studies in behaviorally contingent TMS have demonstrated that aligning stimulation with task performance or internal cognitive states can enhance therapeutic effects and plasticity outcomes.[19] The system developed in this project takes a critical step in this direction, enabling dynamic, individualized intervention by pairing stimulation to physiologically grounded markers of cortical activation.

Implications for Cognitive and Behavioral Modulation

Beyond clinical treatment of depression, closed-loop TMS systems like the one proposed here have broader implications for shaping cognitive and behavioral processes. TMS has already been explored as a tool for disrupting or reinforcing thought patterns, with applications in addiction, obsessive-compulsive disorder, and maladaptive rumination.[13] By targeting areas involved in executive function, like the DLPFC during moments of cognitive vulnerability or heightened plasticity, TMS may be used to reinforce adaptive responses or disrupt maladaptive ones.[7] In the future, this system could be extended to detect internal brain states associated with certain thoughts or behaviors, such as cravings or anxiety, and deliver timely stimulation to interrupt or modulate these patterns.

This approach aligns with growing evidence that the effects of TMS can vary depending on the brain's internal state at the moment the stimulation is applied.[2] For instance, eyes-open versus eyes-closed resting states can result in significantly different patterns of brain connectivity and responsiveness to stimulation.[12] Real-time decoding systems make it possible to tailor stimulation not just to outward behavior, but also to what's happening internally in the brain, adding an important layer of precision to neuromodulation research and therapy.

Technical Contributions and Flexibility

The structure of this decoding platform also addresses practical challenges in implementing real-time TMS. The automatic threshold calculator allowed consistent and repeatable identification of task-related hemodynamic changes, and its adjustable parameters allowed customizable sensitivity for different signal qualities. The GUI supports real-time signal monitoring, user-defined control of TMS modes, and automated BIDS-compliant data saving, all of which are essential for reproducible research and future clinical use. Hardware-level triggering through the parallel port enabled precise and low-latency pulse delivery, and the accuracy graph confirms that the majority of pulses occurred within expected activation windows.

Although this system was validated using pre-recorded data, it is structured for seamless real-time integration with EEG and live fNIRS recordings. EEG could allow for even more precise detection of cortical excitability, while fNIRS provides the spatial localization needed for targeted TMS. The next phase of development will involve utilizing this newly designed platform in human pilot testing using cognitive-behavioral tasks and EEG-fNIRS data to assess feasibility and accuracy in more complex protocols beyond simple motor tasks.

Limitations and Future Directions

While the system performed well in pre-recorded trials, there are a few important limitations. First, the validation relied on pre-recorded datasets, and performance in real-world conditions that are subject to motion artifacts, physiological noise, and individual variability, could lead to greater inconsistencies. Second, while a 77% accuracy rate is promising, higher precision will be needed for clinical applications. These issues can be addressed through further real-time optimization, such as adaptive filtering, dynamic thresholding based on ongoing baseline shifts, and machine learning algorithms for pattern recognition. This neural decoder offers a customizable, dynamic and multimodal approach for targeting neural states in real time. With future improvements, systems like this could help change how we treat not just depression, but a wide range of neuropsychiatric and cognitive disorders.

End Matter

Author Contributions and Notes

E.G.S. wrote software, C.W.P., J.K.D. and L.M.M. advised; and G.J.D., J.M.E. and A.B.W. collected DARPA data.

The authors declare no conflict of interest.

Acknowledgments

The authors did not receive funding from any organization for the submitted work.

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Supplemental Material

Fig.S1: *Main GUI of the Neural Decoder for Real-Time TMS.* The interface displays real-time HbO fNIRS data with marked TMS triggers. Users can see selected channels, subject information, HbO and HbR data stress and select trigger method.