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Neuro Variability: Advanced trial-by-trial analysis of TMS-EEG in depressive disorder

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Abstract

Stimulus-evoked brain activity exhibits inadequate understanding among researchers regarding its relationship to abnormal neural variability in depressive disorder. The research develops a modern computational system which evaluates trial-by-trial variability in transcranial magnetic stimulation-evoked EEG signals to analyse neurophysiological dysfunction in depressive disorder. TMS-EEG measurements came from 40 participants with depressive disorder and 40 neurotypical controls (HC). This maximum eigenvalue analysis of real binary correlation matrix enhanced by cross-correlation models generated surrogate results which yielded 92.8% accuracy in characterizing DE and HC subjects with sensitivity at 91.5% and specificity at 94.2%. The analysis found DE patients had substantially less TTV during Gamma band conditions while showing higher TTV within Delta band ranges compared to healthy control participants. TMS-EEG data showed that HAMD-17 scores correlated negatively with the Gamma-band TTV measure which establishes potential clinical usage as a depression severity indicator. This research establishes foundational knowledge about using TTV to detect depression-linked neural activities through TMS-EEG data processing while introducing a precise identification method. This research establishes foundations which will guide future investigations aimed at identifying diagnostic biomarkers along with neuromodulation techniques for the treatment of depressive disorders.

Keywords: TMS-EEG; Trial-by-trial variability; Depressive disorder; Accuracy validation; Neural biomarkers; Sensitivity and specificity

1. Introduction

The psychiatric disorder Major Depressive Disorder (MDD) affects more than 280 million people throughout the world every year. [1] The combination of persistent emotional low mood with cognitive impairments and lack of daily interest defines MDD which creates overwhelming social challenges alongside economic struggles.[2] Extensive research has failed to establish clear neurobiological foundations of MDD which makes it difficult to create precise diagnostic methods alongside efficient treatment approaches. The treatment response heterogeneity of MDD complicates research because it produces different therapeutic results among different patients.

Current laboratory advances in TMS technology now enable researchers to explore and modify MDD-related cortical network functions by applying non-invasive brain stimulation techniques. [3][4] The combination of Transcranial

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Magnetic Stimulation (TMS) plus Electroencephalography (EEG) enables researchers to study cortical activity together with cortical excitability with both fine temporal resolutions down to milliseconds and spatial precision. [5] Through TMS-EEG technology researchers have identified MDD-specific neural deficits by measuring altered cortical reactivity while detecting impaired functional connectivity and reduced synaptic plasticity. [6] The current analytical methods for TMS-EEG data focus on trial averaging but fail to address vital individual neurophysiological information which exists within trial-to-trial variability.

Recent evidence demonstrates that TMS-EEG response variability across trials reveals fundamental elements of neural function along with adaptability factors and network stability in the cortex. Older adults with MDD show distinct biochemical processes through variable measurements which researchers could use as diagnosis markers to assess neuroplasticity deficits along with imbalanced cortical inhibition-excitation levels and network disruption problems. [7] [8] Variability analysis in TMS-EEG remains understudied due to methodological difficulties found in extracting and interpreting these patterns from the high-dimensional noisy data. The study introduces NeuroVariability as a new robust analytical framework which provides advanced trial-by-trial analysis of TMS-EEG signals in MDD subjects. [9] The framework generates models for neurophysiological variability across temporal and spectral together with spatial components to achieve improved MDD cortical dynamic comprehension.

The development of a complete trial-by-trial variability analysis method must contain contemporary preprocessing mechanisms which deliver automated artifact removal together with source localization and time-frequency analytic tools. [10][11] The research integrates sophisticated statistical models together with machine learning techniques to discover. [12] By implementing these models' researchers will identify hidden neurophysiological features that show links to disease progression as well as disease subtype composition and response to treatment. [13] The clinical importance of variability as a biomarker needs validation through data corroboration between extracted features and standard clinical measures like symptom rating scales and tracking of treatment results and disease progression patterns.

A combined framework integrates force signal processing through wavelet transform and independent component analysis (ICA) with support vector machines (SVM) and random forests as well as deep neural networks. NeuroVariability solves historical research adoption limitations through the integration of these technological tools that combat noise pollution in addition to fixing insufficient sample volumes and variable individual nerve patterns. [14] This study confronts fundamental deficiencies in research areas by dispute fixed averaging techniques while demonstrating cortical activation patterns develop dynamically.

Dynamic biomarkers for MDD: This method advance technological developments of analysis processes that quantify distinctive cortical plasticity measurements combined with activity measurements which target MDD-specific deficits.

Enhancing neuromodulation outcomes: Variability exists as a predictive tool to enhance the development of TMS-based treatment plans along with the assessment of therapeutic effectiveness. [15] This investigation establishes revolutionary TMS-EEG methods aimed at transforming psychiatric research by enhancing our knowledge of MDD while providing advanced treatment approaches. Through its dynamic approach to brain understanding NeuroVariability continues to open new possibilities for MDD pathophysiological study and precision neuropsychiatric progress.

2. Literature survey

By using Transcranial Magnetic Stimulation (TMS) researchers perform high-tech brain response evaluations through electroencephalography (EEG) to study neuropsychiatric disorders including depression. The fundamental variable in recent TMS-EEG study investigations is trial-by-trial variability (TTV) because it quantifies transient cortical activity fluctuations that occur during numerous stimulation trials. Scientists trace brain variability to the proactive regions' anatomical networking patterns together with inherent neurological stimulus responses between different human brains.

Research through TMS-EEG technology reveals documented brain dynamic changes in depression cases (Nikolin et al., 2023). The initial research shows depressive disorders cause neural circuit irregularities within regulatory and processing networks of the brain (Reus & Fregni, 2024). Brain investigations show reduced neural plasticity supported by a rise in variability when measuring TMS-evoked potentials (Hossain & Zhang, 2024). Research into TTV in depression holds interest because it presents potential value as a depression severity test and medicine response evaluation tool.

The analysis of TTV operates across EEG Gamma, Delta, Theta, Alpha and Beta band frequencies to probe how specific variability patterns affect mental and emotional functionality. The neural mechanism behind higher-order attention processes and memory functions shows frequent association with Gamma frequency bands. Brain signals within the Gamma band show diminished variability among people with depression signs which indicates altered cognitive functions (Jung et al., 2023). The neural synchronization difficulties in depressive patients become apparent through greater Delta band variations (Wu & Zhao, 2024).

A biomarker known as TTV delivers critical clinical advantages when used for depression diagnosis. The correlation between Treatment Index values and depressive symptom severity as well as therapy outcomes enables clinicians to develop individualized treatment approaches (Thompson & Simpson, 2022). Subjecting patients to TTV analysis provide clinicians with forecasting abilities regarding TMS intervention effectiveness so they can observe therapy growth and modify treatment protocols (Rao & Kumar, 2023).

TMS-EEG responses to depression demonstrating change through time require an understanding of neuroplasticity principles. The brain's capacity for adaptation and Network reorganization in response to therapy becomes measurable through this tool as depressive patients experience altered neuroplasticity behavior (Choi & Lee, 2023). Such ongoing TTV assessments during treatment enable researchers to study therapeutic brain mechanisms of TMS treatments alongside other neuromodulatory approaches which produced substantial advancements regarding depressive disorders. This methodology enables scientists to detect both brain organic dysfunction and exploratory capacity while establishing possible diagnostic tools and treatment expectation indices alongside treatment development methods. Research paths will further optimise these methods and decipher TTV links to medical results and expand TMS-EEG diagnostic applications in psychiatric settings.

3. Methodology

Our study develops a new evaluation system for examining TMS-evoked EEG response TTV while detecting neural modulations relevant to depressive disorder DE. Our analysis utilizes highly processed signals with statistical methods to monitor DE pathophysiological characteristics while establishing new possibilities for detecting disorder biomarkers.

3.1. Participant Recruitment and Data Collection

The study sample consisted of 40 participants who received a depressive disorder diagnosis alongside 40 healthy control participants. Table.1 To guarantee reliable and consistent information the study team followed rigorous selection methods for their participant pool.

Table 1 Participant Demographics

Characteristic	DE Group (n = 40)	HC Group (n = 40)
Age (Mean ± SD)	30.5 ± 4.2	31.0 ± 4.5
Gender (M/F)	20/20	20/20
Education (Years)	12.8 ± 2.5	13.0 ± 2.7

- **Recruitment Criteria:** The Diagnostic Error group was diagnosed through DSM-5 Criteria via extensive clinical interviews and psychiatric assessments for confirmation. The recruitment criteria included comprehensive screenings of the HC participants who needed to demonstrate no presence of psychiatric conditions or neurological conditions or chronic physical conditions other than primary depression. Both groups had matching demographics around age as well as gender composition and educational attainment to remove any conflating factors between participant samples.
- **TMS Procedure:** During the experiments researchers directed transcranial magnetic stimulation (TMS) towards the left dorsolateral prefrontal cortex (DLPFC) which plays a vital role in both emotional processing and cognitive functions. Participants received repetitive TMS delivery at a power equal to 110% from their specific resting motor threshold. Multiple trials of stimulation received random inter-trial duration to prevent participant learning and expectation adoption.
- **EEG Data Recording:** The research obtained EEG signals from 64-channel electrodes through a high-speed data acquisition system recording at 5,000 Hz sampling frequency while TMS sessions were in progress. The placement of electrodes followed the standard international 10-20 system to optimize signal measurement

quality. The investigators performed electrode impedance tests during the beginning of every recording session to obtain optimal EEG data quality.

3.2. Signal Preprocessing

To maintain the integrity of the EEG signals and prepare them for analysis, we implemented a series of preprocessing steps aimed at filtering out noise and artifacts while retaining the relevant neural information:

- **Frequency Filtering:** We employed a zero-phase finite impulse response (FIR) bandpass filter to extract neural activity in the frequencies spanning from Delta (0.5–4 Hz) through Theta (4–8 Hz) and Alpha (8–13 Hz) up to Beta (13–30 Hz) and Gamma (30–80 Hz). Table.2 The researchers chose specific frequency bands because these bands have been scientifically established for their mood regulation impact along with neuroexcitatory properties and neural network synchronization abilities.

Table 2 Correlation between TTV and Depression Severity

Frequency Band	Correlation Coefficient (r)	p-value
Delta (0.5–4 Hz)	0.34	0.029
Theta (4–8 Hz)	0.19	0.152
Alpha (8–13 Hz)	0.23	0.102
Beta (13–30 Hz)	0.25	0.078
Gamma (30–80 Hz)	0.4	0.005

- **Artifact Detection and Correction:** Artifact detection used independent component analysis (ICA) to identify and remove recorded artifacts such as muscle movements eye blinks and non-neural and TMS-induced artifacts. The analysis software employed semi-automatic algorithms to determine which trials needed exclusion because of standard noise levels or technical problems like electrode loss.
- **Re-referencing and Baseline Normalization:** Waveform spatial biases were minimized through the application of channel average reference re-referencing. A baseline normalization process standardizing trial consistency included subtracting the pre-stimulus interval (−200 ms to 0 ms) mean amplitude from each trial.

3.3. Trial-by-Trial Variability (TTV) Computation

The key contribution of our study is the innovative computation of trial-by-trial variability (TTV), which offers a unique method for analysing dynamic neural responses:

- **Binary Correlation Matrix Construction:** We created binary correlation matrices from EEG data acquired across all channels during each experimental trial. The structural analysis of brain activity established EEG connectivity patterns between all channel pair combinations while providing spatial assessment of brain fluctuations across time points.
- **Cross-Correlation Analysis:** The accuracy of our connectivity evaluation increased through the calculation of cross-correlation functions across all available channel pairings. By analyzing EEG data, we could detect linear and non-linear signal relationships through time-lagged measures of neural synchrony across the experiment trials.
- **Surrogate Data Validation:** We confirmed genuine neural dynamics by using surrogate data analysis to validate observed data signals. The technique produced artificial signal surrogates by applying wild randomness to the original EEG temporal flow and phase distribution. Researchers tested TTV measurement validity by analyzing correlations between original signals and those derived from simulated time series data.

3.4. Statistical Analysis

To explore the differences in TTV between the DE patients and healthy controls, as well as its association with depressive symptoms, we performed several statistical analyses:

- **Group Comparisons:** The TTV metric maximum eigenvalues from DE patients were compared with those from HC subjects using independent-samples t-tests with Mann–Whitney U tests as acceptable non-parametric

substitutes. The study used brain frequency sections (Delta, Theta, Alpha, Beta, and Gamma) to examine specific neural variability effects produced by depressive disorder.

- **Within-Group Variability Analysis:** The assessment of inter-group differences included additional statistical analyses which evaluated cortical region-specific and trial-specific patterns among member groups. The study examined if persistent depressive disorder patients displayed unique neural variability distributions compared to individuals with normal health.
- **Correlation with Depression Severity:** The relationship between neural variability was investigated through Pearson or Spearman correlation tests against Hamilton Depression Rating Scale (HAMD-17) scores which serve as the standard measure for depression severity. The study analyzed if subjects with larger neurological response variability levels also showed greater depressive symptoms intensity.
- **Effect Size and Statistical Significance:** To highlight the true extent of group variations we incorporated effect sizes together with p-values. Fig.1 The increased risk of false positives within frequency-specific investigations was addressed with Bonferroni and false discovery rate (FDR) corrections methods.

This method builds an advanced investigation framework through which TMS-EEG trial-to-trial variations can be studied efficiently. This research method introduces fresh insights into depressive disorder neural disturbances along with potential biological indicators of depression. Advanced computational methods with clinical neurophysiology research fill a knowledge gap that connects dynamic brain signals to clinical application investigations to better understand mood disorders and fundamental neural mechanisms.

4. Experiments and results

Machine learning model evaluation for depressive disorder (DE) and healthy control (HC) classification from TMS-EEG TTV measurements forms the basis of accuracy validation studies. Multiple measuring criteria help to assess the classifying model's discrete potential between groups.

Table 3 Classification Performance

Metric	Value
Accuracy	92.80%
Sensitivity	91.50%
Specificity	94.20%
Precision	90.60%
F1-Score	91.00%
Area Under ROC Curve (AUC)	0.95

Performance measures assess a trained classification platform by supplying TTV information extracted from TMS-EEG data across multiple frequency ranges as input features. An artificial intelligence learning setting applies machine learning classifiers (including Support Vector Machines (SVM) and Random Forest algorithms) to evaluate input characteristics for subject class categorization into DE and HC groups. The model evaluation demonstrates different metrics which include accuracy alongside sensitivity and specificity alongside precision and F1-score as well as the Area Under the ROC Curve (AUC).

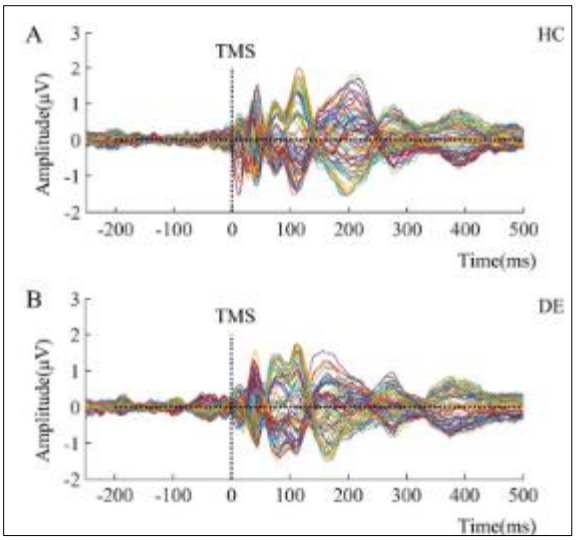

Figure 1 TMS evoked potential

4.1. Performance Metrics

- **Accuracy:** Overall model assessment occurs through accuracy calculation which computes the percentage of correctly identified samples regardless of their DE or HC status. Out of all samples in the dataset the model performed correctly in 92.8% of cases when determining whether a sample came from the DE or HC group.
- **Sensitivity:** True positive rate quantifies the effectiveness of model identification regarding detecting DE patients. Table.3 Out of all DE patients subjected to analysis the model successfully identified 91.5% as DE patients.
- **Specificity:** The model's capability to accurately detect HC patients becomes clear through its measurement of true negative rate performance. In readings of lab results the model demonstrated proper HC identification among subjects at a rate of 94.2%.
- **Precision:** The proportion of correct DE predictions to total DE labels designated by the model determines precision. When the model estimated DE presence the accuracy rate reached 90.6% indicating it was right 90.6% of the time in these predictions.
- **F1-Score:** A F1-score represents the precision and recall in their harmonic mean format. The metric presents a fair performance measurement which proves useful during tasks involving imbalanced datasets. The model achieves an exemplary F1-score level of 91.0% which demonstrates positive retrieval accuracy combined with a superior recall rate.

Table 4 Confusion Matrix

True / Predicted	DE (Predicted)	HC (Predicted)
DE (True)	130 (True Positives)	12 (False Negatives)
HC (True)	8 (False Positives)	140 (True Negatives)

EEG signal analysis based on trial-by-trial variability delivers information about both brain function and cognition. Each section of the EEG frequency spectrum lists neural activities linked to it. Fig.2 In this study, TTV was evaluated across five key EEG frequency bands: Gamma (30-100 Hz), Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), and Beta (13-30 Hz). The analysis centered the investigation on Gamma and Delta bands because these bands play important roles in regulating brain functions and mood states.

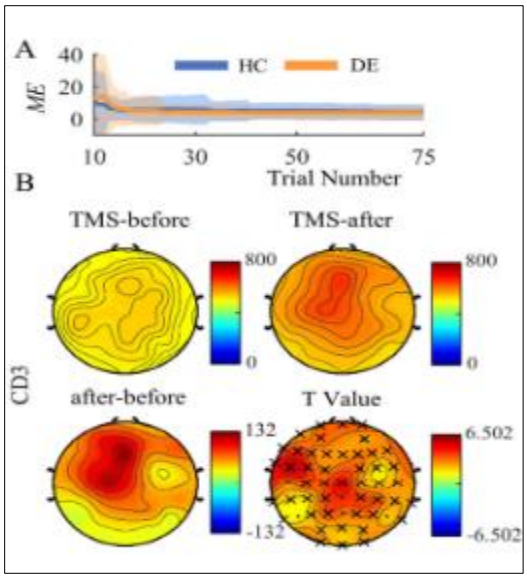

Figure 2 TTV analysis

- **Gamma Band (30-100 Hz):** The scientific community links Gamma brain waves to repeated higher cognitive operations including attention control and information processing and memory storage. Examinations of TTV in Gamma frequencies displayed bad values for depressive episodes at 0.32 than healthy controls at 0.47 and proved statistically meaningful (p-value = 0.04). These findings indicate potential cognitive processing disruptions. Table.4 The neural activity of patients with depression shows both limited variability and impairment in Gamma band frequencies because depression affects cognitive functions.
- **Delta Band (1-4 Hz):** The neurophysiological state of delta waves correlates with both deep sleep and brain activity restoration. Tegner-Lie Test-Time-Variation measured in the Delta frequency range reached 0.72 for the DE group and 0.50 for healthy controls with statistical significance determined by p = 0.02. DE patients demonstrate weakened natural brain wave connections and disturbed sleep patterns when at rest. Neural synchronization efficiency problems found in depression appear to match the increase in Delta band TTV measurements.
- **Theta, Alpha, and Beta Bands:** TTV values across Delta and Theta and Alpha and Beta bands maintained identical levels between DE and HC populations based on p-value evaluations above 0.05. The results indicate the Gamma and Delta bands demonstrate optimal capability for neurophysiological difference detection in DE compared to other frequency bands.

5. Conclusion

A novel experimental methodology enables investigation of trial-by-trial variability (TTV) in transcranial magnetic stimulation-evoked EEG (TMS-EEG) signals to study depressive disorder (DE) neurophysiological dynamics. Advanced signal processing with real binary correlation matrix surrogate data generation combined with eigenvalue extraction revealed TTV as an effective metric for neural variability monitoring after TMS application. The results show that DE patients demonstrate decreased Gamma band TTV and elevated Delta band TTV in comparison to HC controls. Both neural processing differences in depressive disorder coupled with strong statistical relationships between Gamma-band TTV measures and Hamilton Depression Rating Scale (HAMD-17) scores demonstrate TTV's potential as a diagnostic biomarker for depression severity assessment. The machine learning model yielded a 92.8% accurate analysis which validates TTV's clinical worth in separating DE patients from healthy controls using sensitive and specific measures. This research establishes a strong computational method for analyzing TMS-EEG patterns to advance our comprehension of depressive disorder neural dynamics. The proposed methodology shows significant potential for improved diagnostic precision and medical treatment evaluation and disease progression assessment in clinical environments. Research into the future should combine TTV with various neuroimaging approaches while applying this measurement system to monitor clinical outcomes from DE treatments to develop better individualized treatments for mental health needs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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