Prediction of TMS-evoked Potentials from Prestimulus Spectral Features: A Machine Learning Approach

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Background

Brain Criticality

A state near a phase transition in which neural networks achieve optimal adaptability and computational efficiency [1].

TMS-EEG

Transcranial Magnetic Stimulation (TMS) combined with electroencephalography (EEG) provides a non-invasive method to study neural dynamics through TMS-evoked potentials (TEPs) [2, 3].

TEPs

Reflect cortical excitability and connectivity.

Frequency Bands in Brain Function:

- **Delta (1–3 Hz):** Linked to deep sleep and unconscious processes.
- **Theta (4–7 Hz):** Involved in memory encoding and cognitive control.
- **Alpha (8–13 Hz):** Associated with inhibition, sensory gating, and readiness states.
- **Beta (14–30 Hz):** Reflects motor preparation and top-down control.
- **Gamma (31–90 Hz):** Related to local processing, excitability, and cortical responsiveness.

Goal

To examine the predictive relationship between pre-stimulus TEP features and post-stimulus TEP variability.

Methods

Dataset:

- A publicly available TMS-EEG dataset of 20 right-handed healthy volunteers (age: 24.50 ± 4.86 years; 14 females). Available at: https://github.com/BMHLab/TEPs-PEPs
- Recorded with a 62-channel EEG system at 1 kHz.
- EEG pre-processing was performed using the **EEGLAB** and **TESA** toolboxes.

Features Extraction:

- Each trial was segmented into 2000 samples (1000 pre-stimulus, 1000 post-stimulus).
- Focused on channel C3, where TMS was applied.
- Morlet wavelet transform (constant=7) was applied to pre-stimulus window (from −800 to −200 ms).
- Power Spectral Density (PSD) was computed to the five frequency bands

Targets Variables:

- **Area**: Total area under the absolute post-stimulus signal (global response magnitude).
- **Peak**: The maximum amplitude of the post-stimulus signal (the most prominent response).

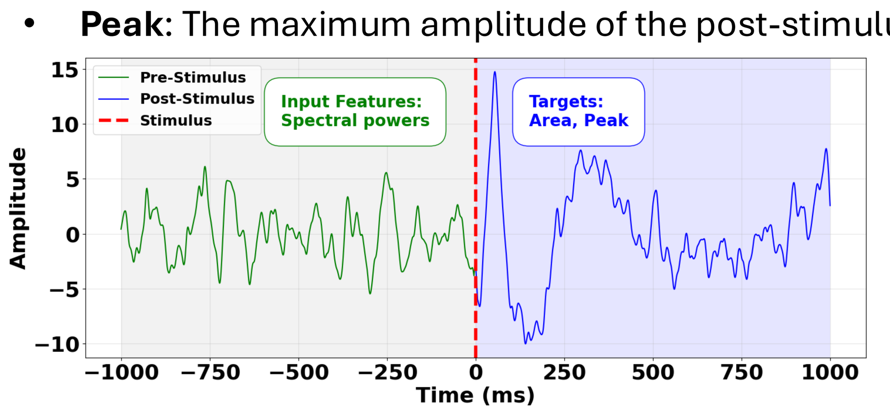

Fig1. Pre- and post-stimulus from a single trial TEP, with pre-stimulus features predicting post-stimulus targets, separated by the stimulus onset.

Machine Learning Pipeline

Train-Test split: 5-fold stratified cross-validation (CV) was applied at the **subject level** to ensure that the training and test sets contained data from **non-overlapping subjects**.
In each fold:
- 16 subjects → training
- 4 subjects → testing
- 3-fold cross-validation was used for

Machine learning model: A **Random Forest Regressor** was used to predict post-stimulus targets (Area and Peak) from pre-stimulus spectral features.

hyperparameter tuning: Input features were optimized via grid search with 3 folds cv.

Model Evaluation Metrics:

- **Normalized Mean Squared Error (nMSE):** This quantifies prediction error relative to variance. Values below 1 indicate better-than-mean prediction.
- **Spearman's ρ:** This measures how well the predicted rankings match actual trial order.
  ρ > 0.7 = strong
  0.5–0.7 = moderate
  < 0.3 = weak

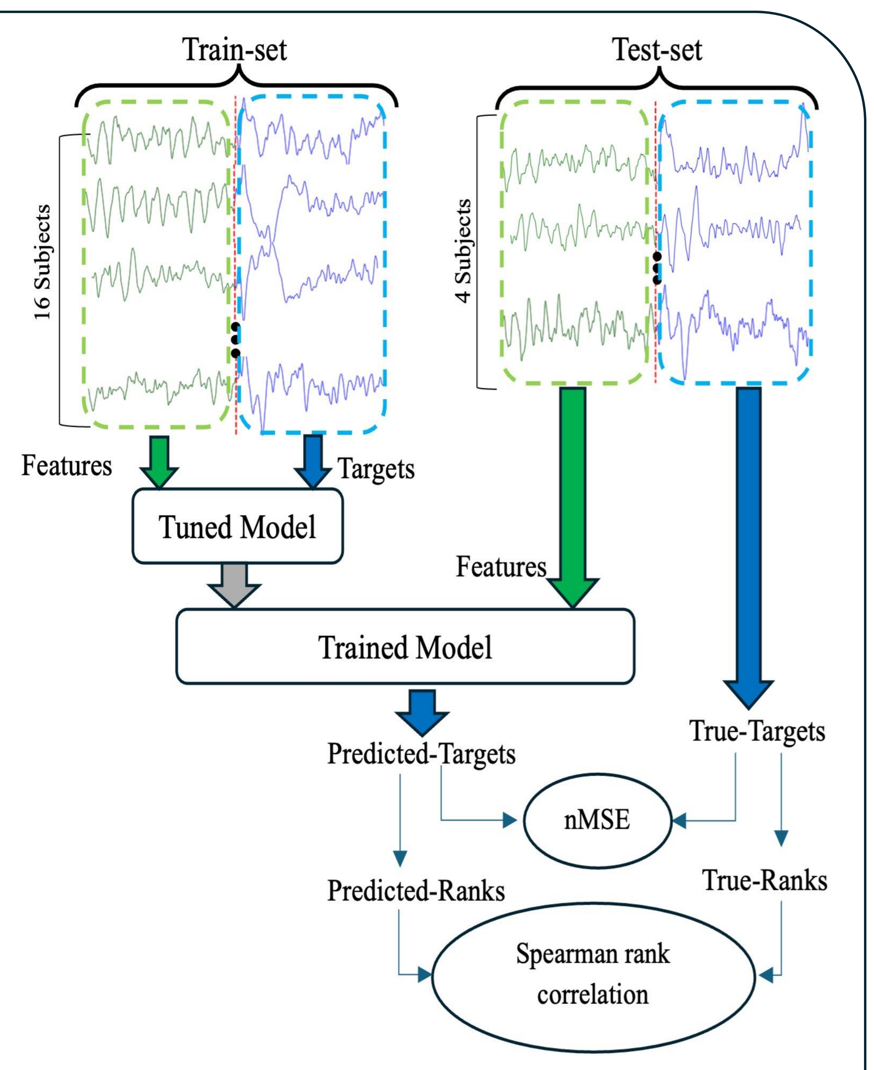

Fig2. Machine learning pipeline illustrating one fold of the subject-stratified 5-fold cross-validation. Features and targets were extracted from pre- and post-stimulus EEG segments, respectively. The model was tuned and trained on data from 16 subjects, and tested on 4 held-out subjects. Performance assessed using nMSE and Spearman's ρ.

Interpretability & Visualization:

SHAP analysis: identified the most influential frequency bands.
Quartile-based visualization: compared predicted vs. true trial groupings across response magnitude.

Results

Performance Metric Table

Target Method	nMSE [95%Confidence Interval]	Spearman's ρ [95%Confidence Interval]
Area (all freq bands)	0.49 [0.44-0.54]	0.76 [0.73 – 0.78]
Peak (all freq bands)	0.8 [0.74 – 0.88]	0.6 [0.57 – 0.63]
Area (alpha band)	1.78 [1.67 – 1.9]	0.11 [0.06 – 0.16]
Peak (alpha band)	1.76 [1.65 – 1.88]	0.11 [0.07 – 0.17]

Predicting **Area** yields better results than predicting **Peak** amplitude:
- Lower nMSE
- Higher Spearman's ρ

Using **all frequency bands** significantly improves performance.

SHAP Summary Plot

SHAP values quantify the influence of each frequency band on model predictions. The plots show feature the importance for predicting the **Area** and **Peak** targets.

Findings:

- **Gamma power** is the strongest predictor for both targets.
- For **Area**: Gamma > Theta > Beta
- For **Peak**: Gamma > Alpha > Beta
- **Alpha** is more relevant to transient peak fluctuations, while **gamma** is linked to sustained excitability.

Color gradient (blue → red): indicates the range of feature values and their corresponding SHAP values

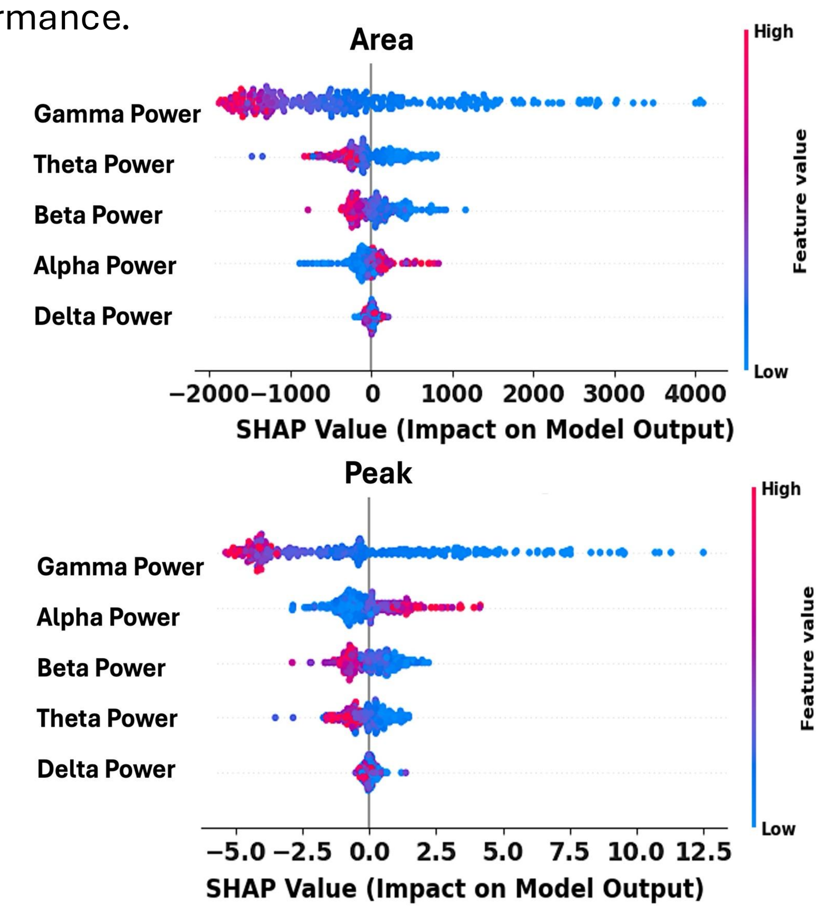

Fig3. The SHAP summary plot for the signal area vs peak target methods, highlighting the most influential features.

Quartile Plot

The trials were ranked based on the **true** and **predicted** values of the **Area** target.
The trials were divided into four quartiles in order to analyze prediction accuracy across response magnitudes.

What It Shows:

- Each subplot displays the average post-stimulus EEG signal (C3) for each quartile.
- The solid blue line = predicted signal
- The dashed red line = true signal

Strong overlap across quartiles confirms:

- The model generalizes well across subjects;
- Pre-stimulus features retain meaningful information about trial-level variability.

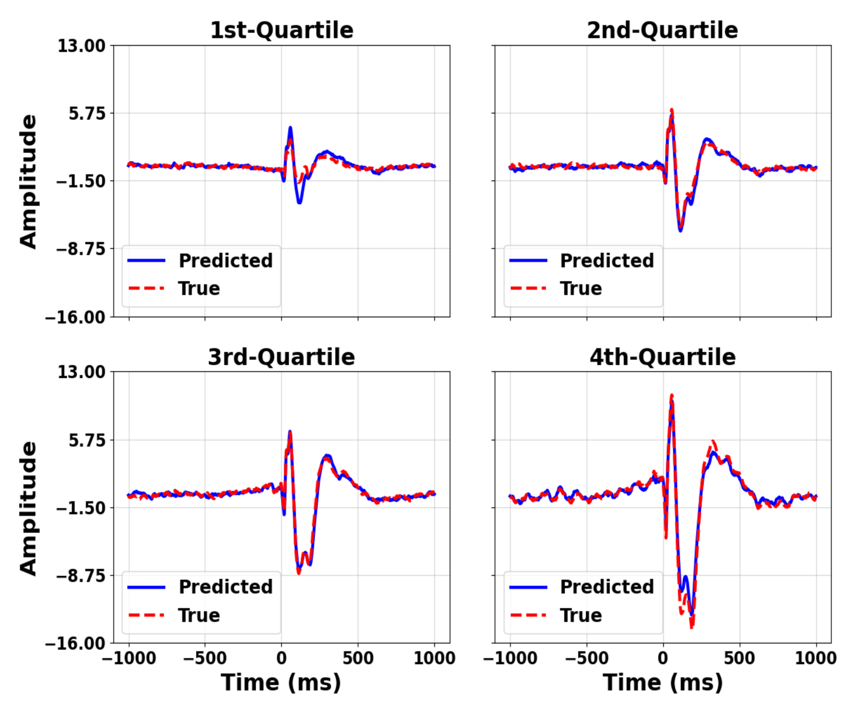

Fig4. Averaged post-stimulus EEG trials for each quartile based on true (dashed red line) and predicted (solid blue line) target values. Results are aggregated across all folds in the subject-aware cross-validation.

Conclusion

- **Machine learning** successfully predicted TMS-evoked responses using **pre-stimulus spectral features**.
- **Gamma power** was the most influential feature for both signal **Area** and **Peak**.
- **Alpha power** was more relevant to transient **Peak** responses, while **theta** and **beta** contributed to **Area**.
- **Delta power** showed minimal impact.

These results confirm that:

- The **full spectrum of frequency bands** is essential for accurate prediction.
- **Gamma activity** may reflect a more excitable or desynchronized cortical state that facilitates stronger TMS responses.
- **Alpha rhythms** may exert inhibitory control, especially over sensorimotor areas.

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