1 Introduction

The emergence of new computational models has provided neuroscientific research with novel methods for extracting significant insights from experimental results. This paper takes a computational approach to challenges arising in the analysis of transcranial stimulation (TMS) data. We argue that conducting TMS experiments under the double-pulse paradigm enables the use of machine learning models. In particular, we formulate pulse-specific measures of relative amplitude between paired and test pulses. These has potential implications in both *a*. the production of evidence and *b*. the diagnosis of clinical disorders.

2 Background

Transcranial magnetic stimulation (TMS) is a common, non-invasive experimental technique used to evoke action potentials in cortical regions of the brain. In particular, researchers often target the motor cortex and measure the motor evoked potential (MEP) aroused by the stimulation. When the purpose of the experiment is to inquire on neuroplasticity, such stimulations are performed under the *paired pulse paradigm*.

The *paired pulse paradigm* (or *double pulse paradigm*) consists in eliciting a series of two temporally proximate pulses (in the order of miliseconds). The evoked potentials of the double-stimulation are compared to those of single test stimulations, and their relative amplitude is taken as a proxy of neuroplasticity in the brain. The time separating each of the paired pulses is termed *interstimulus interval* (ISI). It is the general case that low intervals (4 or 5 miliseconds) produce intracortical inhibition, with the evoked potentials of paired stimulations being generally lower than those of single pulses. Greater intervals, on the other hand, tend to produce facilitation.

In the context of this paper, we shall term any coefficient that serves to represent the proportional relationship between the potentials evoked by paired and test pulses a *measure of relative amplitude*.

The goal of this paper is to provide pulse-specific measures of relative amplitude. This is, coefficients that represent the relative amplitude of each individual paired pulse with respect to the set of test pulses in an experimental session. The purpose of this endeavor is to keep data resolution at its highest, which on its turn allows for the implementation of data-driven artificial intelligence in the analysis of the experimental results. Thus, from a computer science perspective, our objective is constrained to the sphere of feature engineering.

We will show how pulse-specific measures of relative amplitude allow for otherwise unfeasible computational analyses of TMS data, such as the use of machine learning models for the detection of different pulse-response patterns among different groups of clinical subjects. In particular, we will show they allow for a machine learning classifier to correctly determine whether a subject belongs to one of four clinical categories, based only on its evoked potentials and across different inter-stimulus intervals, with an accuracy of up to 90%.

3 Data collection

We used data collected across $N =?$ subjects at the *Laboratory for the Study of Slow-wave sleep activity*, University of Pennsylvania, with $H =?$ healthy controls and $D =?$ diagnosed with major depressive disorder (MDD). Transcranial magnetic stimulation of the motor cortex was elicited to them after a night of baseline sleep and after a night of slow-wave disruption (SWD) sleep. Motor evoked potentials were measured via an electrode (?) placed on the subjects' thumb (?). In the slow-wave disruption session, an auditory stimulus with sufficient strength to interrupt the normal occurrence of slow-wave sleep, yet not strong enough to wake the subjects, was elicited. This experimental setting produces four distinct categories, two depending on the subject group and two on the type of sleep session underwent, as shown in the table below.

	Baseline	Slow-wave disruption
Healthy control	HC BL	HC SWD
Major depressive disorder	MDD BL	MDD SWD

Each observation in the data was a specific experimental sample resulting from an individual transcranial stimulation. The original features of the data were:

1. An ***EMG*** variable with the EMG peak-to-peak of each observation.

2. A *Label* categorical feature, which encoded the group of the subject of each observation, was the target variable.

3. An *ISI* feature that econded the inter-stimulus interval of each pulse. A value of -1 indicated that the given pulse was a test pulse (no inter-stimulus interval).

4 Limitations of the traditional analysis

Measures of relative amplitude in neuroscience are generally computed at the subject level by repeatedly taking averages in the following manner. First, the quotient of the average paired-pulse and the average test pulse is found per every subject. Secondly, those quotients are averaged out across all subjects in a subject group. This is reasonable, since hypotheses generally deal with differences across subject groups.

Two major limitations arise from this method. The principle one is the fact that it implies greatly downscaling the data resolution Secondly, potentials evoked by test and paired pulses present a very high variance (Rossini et. al., 20015; Orth, Snijders and Rothwell, 2003; Wassermann, 2002), which —being that it is a quotient of two means— raises questions about the quality of the representation where relatively few pulses are elicited.

When considering the size of the data across multiple experimental subjects, this shrinkage in data resolution is far from being negligible. And in times when scientific inquiry can greatly benefit from forms of artificial intelligence that rely on large amounts of data (e.g. machine learning), it is clearly limiting to only count with low-resolution measures to interpret experimental results.

5 Proposed approach

5.1 Pulse-specific relative amplitude measures

Considering the limitations of the traditional approach, this paper proposes two pulse-specific relative amplitude measures. This allows for otherwise unfeasible computational analyses of TMS data, such as the use of machine learning (ML) models for the detection of different pulse-response patterns among different groups of clinical subjects.

To empirically test the validity of these measures, we evaluated whether they improved the performance of a classification model, and in what degree. (We chose a classification model for practical reasons – namely, because the samples in our data were conveniently labeled by subject group and sleep session).

In order to do this, we defined a random forest model in Python under the following parameters: ...

The model was tasked with classifying every observation with the appropriate subject label. In other words, it was set out to infer, based on the properties of each transcranial stimulation response, the group of the subject upon which the stimulation was elicited, as well as the type of sleep session after which it occurred.

The model was first trained on the raw data, with the features described in **3.1**. Then, it was trained with the inclusion of one or many engineered features of relative amplitude (see section **4**). These features were computed for each observation using the Julia programming language.

Since the neural response to transcranial stimulations follows an exponential distribution (see **Cite section**), we experimented with the inclusion of the features above applied to the logarithmically transformed peak-to-peak EMG.

As stated earlier, action potentials evoked by transcranial magnetic stimulations follow a Gamma distribution that is very close to the exponential. (see **Statistics** section). Experimentation has shown that the inclusion of weighted variants of the features defined above greatly improves the performance of a random forests model (see **Empirical results**).

The use of weighted instead of arithmetic averages may be useful in dealing with the excessive influence of outliers or highly spread out points in the feature. For example, the weight vectors may be computed using the MAD or the inverse-variance of each x.

Thus, our hypothesis is that pulse-specific measures of relative amplitude will significantly improve a random forest's performance.

The following section (**Cite section**) defines the proposed measures of relative amplitude. In section **Results**, we show the impact of these measures on the performance of the random forest model.

5.2 Definitions: Pulse specific relative amplitudes

For simplicity, we will deal with the hypothetical situation in which a single ISI was used for paired

stimulations. All of our results generalize to different inter-stimulus intervals.

Let k be the number of experimental subjects in some subject group $\mathcal{G}$, to each of whom n paired stimulations and m test stimulations were elicited.

Definition 1 *Let $\boldsymbol{P}^{n\times k}$, $\boldsymbol{T}^{n\times k}$ be matrices over the vector space $\mathbb{R}^+$ representing the paired and test potentials evoked across each of the k subjects.*

Definition 2 *Let $x \in \boldsymbol{P}_{\star i}$ be the MEP of a single paired stimulation elicited on the ith experimental subject, and $\boldsymbol{t} = \boldsymbol{T}_{\star i}$ the vector containing the MEPs of all test pulses elicited on that subject. Let $\boldsymbol{w}$ be some appropriate weight vector. Then we define two pulse-specific relative amplitude measures,*

$$\rho(x) := \frac{mx}{\sum_{i=1}^{m} t_j} \tag{1}$$

$$\delta(x) := \frac{x}{m}\sum_{j=1}^{m}\frac{1}{t_j} \tag{2}$$

$$\rho_w(x) := \frac{xm\sum_{j=1}^{m} w_j}{\sum_{j=1}^{m} t_j w_j} \tag{3}$$

$$\delta_w(x) := \frac{\frac{x}{m}\sum_{j=1}^{m}\frac{w_j}{t_j}}{\sum_{j=1}^{m} w_j} \tag{4}$$

Remark 1 $\forall x : x \in \mathbb{R}^+ : \delta(x) \geq \rho(x)$. *(For a proof of this property, consult the appendix.)*

Notice that $\rho(x)$ is the proportion between the potential x, evoked by a paired stimulation, with respect to the average potential of single test stimulations. On the other hand, $\delta(x)$ is the average proportion of x with respect to each single test pulse.

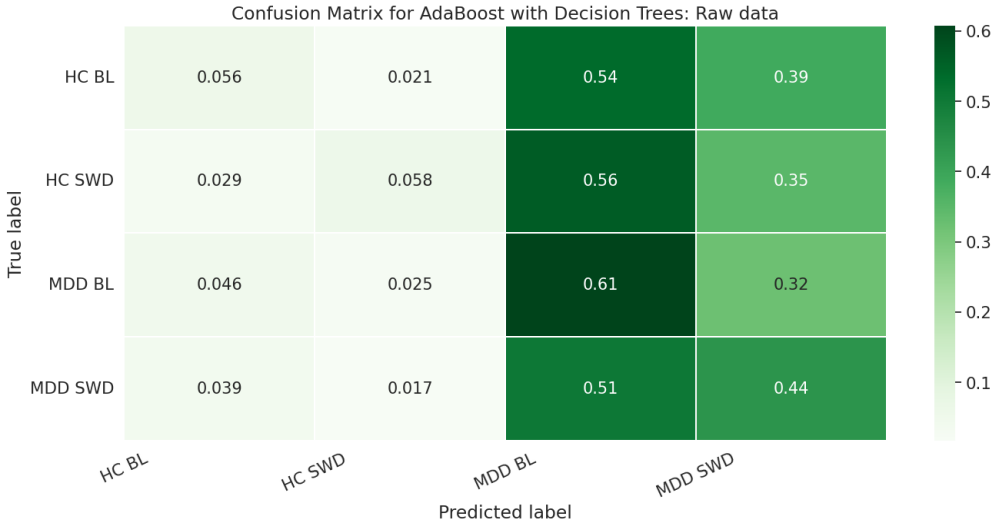
Notice as well that ρ and δ are defined over the test pulses in a specific experimental session i. In other words, whenever we speak of the δ and ρ *features* (*id est*, of the data resulting from broadcasting ρ and δ over a series of observations), such feature is understood to be subject- and session-specific.

In particular, ρ is a representation of the relative importance of each double pulse in relation to the overall distribution of the test pulses in the subject. It measures the deviation of the double pulse x with respect to the average test pulse. On the other hand, δ is a measure of the proportionality of a double pulse with respect to different values in the distribution of the test pulses of the subject.

6 Results

6.1 ML model without relative amplitude measures

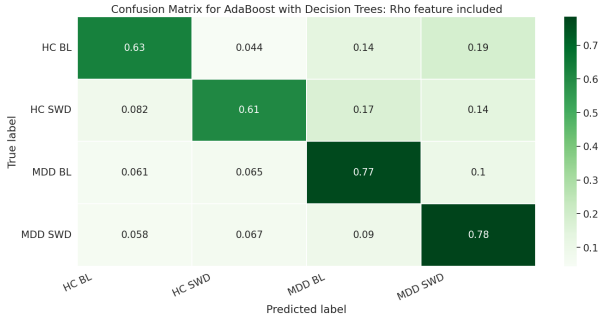
When trained on the raw data, without the inclusion of pulse-specific relative amplitude measures, the model's accuracy was of $\approx 34.2\%$. However, the confusion matrix of the model shows the errors are concentrated on the healthy control categories, while categorization of diagnosed subjects was substantially better. This implies major depressive subjects show statistically significant and distinct patterns in their TMS responses in comparison to healthy controls, and may be considered evidence for depression-induced differences in neuroplasticity.

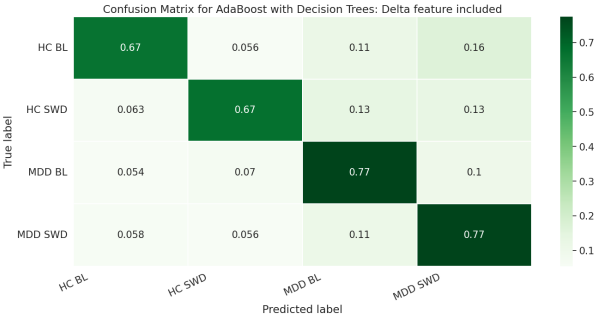


However, it is important to note that the proxy for neuroplasticity in the double pulse paradigm is precisely the relative amplitude of double pulses with respect to test pulses. The raw data lacks any measure of relative amplitude. Besides, regardless of the fact that the model above suggests a critical difference in the response patterns between subject groups, its accuracy is still poor.

6.2 Engineered data

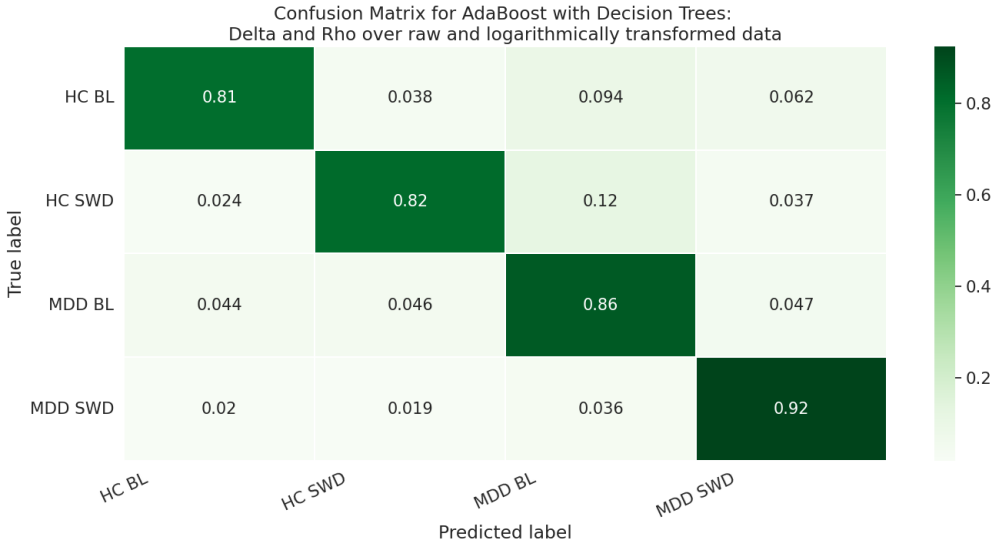
With the inclusion of the ρ feature, accuracy increases by a factor of ≈ 2.1 to 72.6%. The inclusion of the δ feature alone increased it, in comparison to the raw data, had a more or less equivalent impact, increasing accuracy to 73.4%.



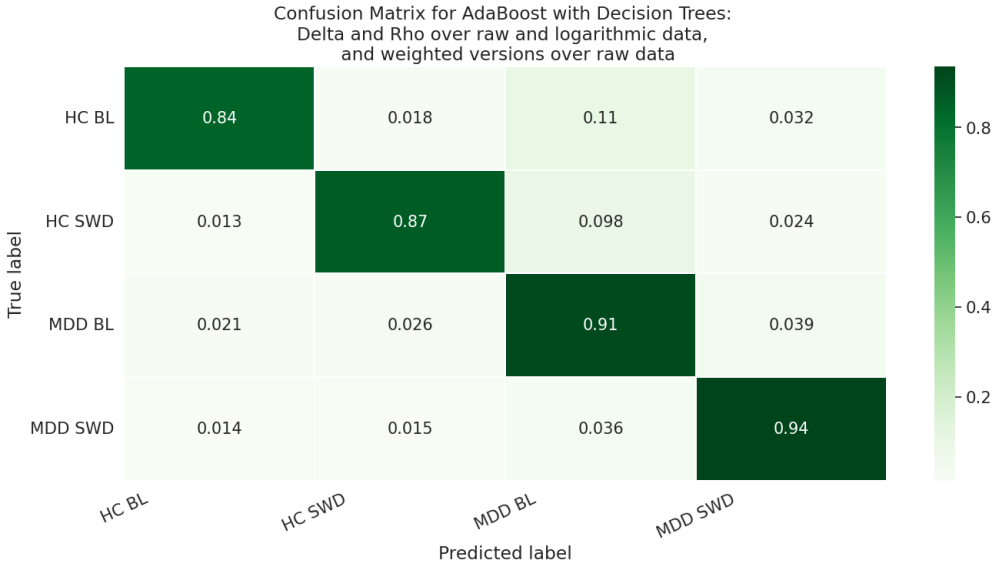


The model still shows a higher accuracy when classifying diagnosed subjects, but the overall accuracy across all categories was significantly improved.

As stated earlier, the inclusion of the δ and ρ features computed over the logarithmically transformed EMG peak-to-peak improved the model's accuracy. Concretely, accuracy was increased to 86%, with the following confusion matrix.



At last, if to the previous model we add also the weighted versions of δ and ρ, using inverse-variance weights, we obtained an accuracy of 89.8%, with the following confusion matrix.



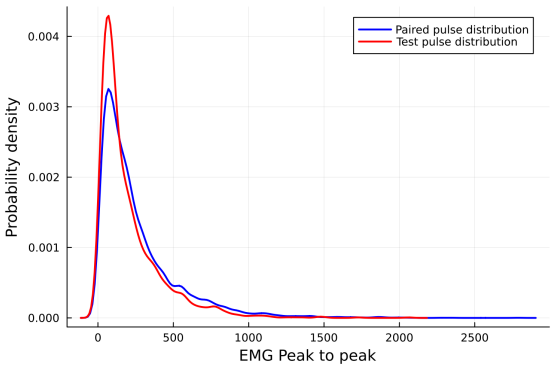
7 Statistics

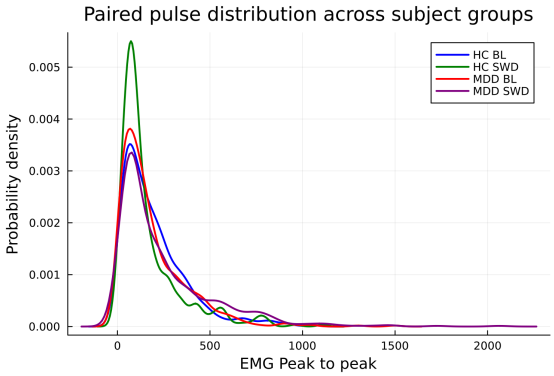
Writing note 1 *The description of the experimental process in this section is poor. Also I do not know the total number of subjects, experiments are still being conducted. Need input from the lab on these matters.*

Although distributions were always exponential, the β parameter of said distributions varied across subject groups and session types.

	Mean	Median
HC BL	196.77	149.36
HC SWD	165.98	99.76
MDD BL	187.56	127.69
MDD SWD	247.57	151.07

Each of the means in the above table correspond to the estimated β parameter of the distribution of the paired pulses on each subject group.





8 Discussion

The previous results show that the inclusion of pulse-specific relative amplitude measures greatly improve the accuracy of a random forests model trained over TMS data for subject classification. More importantly, it becomes clear that, via the engineered features δ and ρ, researchers can attain evidence in favour or against hypotheses pertaining to differences among subject groups. Particularly, in showing that pulse-specific measures of relative amplitude are significant information to determine the sleep session and group of a subject, and being relative amplitude measures a proxy for neuroplasticity, the previous model provides evidence in favour of sleep-modulated, depression-induced differences in neuroplasticity.

The use of machine learning models over neuroscientific observations is not only a promising tool in the production of evidence. There is a diagnostic potential that is still to be evaluated. Indeed, if machine learning models can detect the neural patterns that distinguish, under specific experimental conditions, healthy control from diagnosed subjects, such models can potentially be implemented in the diagnosis process as powerful clinical tool.

Although long and serious scientific effort is still required to appraise the diagnostic potential of machine learning models, we believe our results allow for a certain amount of conservative optimism on the matter.

In short, pulse-specific relative amplitude features are successful in making machine learning models applicable to TMS experimental data. Thus, they can play an important part in future research by allowing for new ways of analyzing and extracting meaningful information of TMS results.

9 Appendix 1

10 Appendix 2

Proof 1. In **Remark 1**, we observed the following property:

$$\forall x : x \in \mathbb{R}^+ : \delta(x) \geq \rho(x).$$

Such property can be proven via induction. Firstly, recall that

$$\delta(x) = \frac{x}{m} \sum^{m} \frac{1}{t_j}$$
$$\rho(x) = \frac{xm}{\sum^{m} t_j}$$

Let $S_1^m = \sum^m \frac{1}{t_j}, S_2^m = \sum^m t_j$. We operate under the assumption that $t_i \in \mathbb{R}^+$. It is the case that

$$\frac{x}{m} \sum^{m} \frac{1}{t_j} \geq \frac{xm}{\sum^{m} t_j}$$
$$S_2^m S_1^m \geq m^2$$

This holds for $m = 1$, since $\frac{1}{t_1} + t_1 \geq 1 \iff 1 + t_1^2 \geq t_1$. So we may assume $S_1^k S_2^k \geq k^2$. We now set out to show that

$$S_1^{k+1} S_2^{k+1} \geq (k+1)^2$$

This can be proven as follows.

$$S_1^{k+1}S_2^{k+1} \geq (k+1)^2$$
$$(S_1^k + \frac{1}{t_{t+1}})(S_2^k + t_{k+1}) \geq k^2 + 2k + 1$$
$$S_1^k S_2^k + t_{k+1}S_1^k + \frac{1}{t_{k+1}}S_2^k + 1 \geq k^2 + 2k + 1$$
$$S_1^k S_2^k + t_{k+1}S_1^k + \frac{1}{t_{k+1}}S_2^k \geq k^2 + 2k$$

We know $S_1^k S_2^k \geq k^2$ and then it suffices to show $t_{k+1}S_1^k + \frac{S_2^k}{t_{k+1}} \geq 2k$. To prove this, simply observe that

$$\frac{1}{t_{k+1}}\sum_{j=1}^{m} t_j + t_{k+1}\sum_{j=1}^{m}\frac{1}{t_j} \geq 2k$$
$$\left(\frac{t_1}{t_{k+1}} + ... + \frac{t_k}{t_{k+1}}\right) + \left(\frac{t_{k+1}}{t_1} + ... + \frac{t_{k+1}}{t_k}\right) \geq 2k$$
$$\iff \overbrace{a + \frac{1}{a} + b + \frac{1}{b} + ... + n + \frac{1}{n}}^{2k \text{ terms}} \geq 2k$$

We have $\min f = 2$ for $f(x) = x + \frac{1}{x}$ for $x \in \mathbb{R}^+$. Then $\min(a + \frac{1}{a} + ... + n + \frac{1}{n}) = 2k$ for $a, ..., n \in \mathbb{R}^+$, which concludes the demonstration.