Investigating Factors Correlated with Patient Response to Transcranial Magnetic Stimulation for Treatment-Resistant Depression

Evrim Sude Dzhon

Under the direction of

Dr. Daniel Press
Associate Professor of Neurology
Dr. Subha Subramanian
Neuropsychiatry Fellow
Berenson-Allen Center at Beth Israel Deaconess Medical Center

Research Science Institute
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Abstract

Depression is a leading worldwide public health concern. New treatment techniques have become paramount, especially with the exponential increase of depression in society post-pandemic. Transcranial Magnetic Stimulation (TMS) is a treatment for patients diagnosed with treatment-resistant depression (TRD) after they fail two or more antidepressant alternatives. TMS offers each patient a personalized treatment according to their motor threshold (MT) value and their progress is recorded using the Beck Depression Inventory (BDI). This study investigates whether there is a correlation between initial MT values and the response rate of adults who completed 30 sessions of TMS treatment at the Berenson-Allen Center for Noninvasive Brain Stimulation. We analyzed a total of 195 patients who started coming to the clinic after 2018 and who received treatments either with the DASH or intermittent theta burst stimulation (iTBS) protocols. Further analysis was performed to determine if age was a confounding factor. Regression, Spearman's Rank Correlation Hypothesis Testing, f-testing, and ANOVA testing were performed. We determined that the response rate was not correlated with initial MT, age, or the protocol used on the patient. Thus, we conclude that the current delivery of TMS is an effective treatment strategy.

Summary

Transcranial Magnetic Stimulation (TMS) induces a current to pass through the neurons, activating certain parts of the brain. This technique has been shown to treat people with treatment-resistant depression (TRD). TMS is applied by different machine outputs according to the patients' needs. This value is called the motor threshold (MT). MT is the minimum amount of stimulation needed for a subject to move their right thumb. The MT value is obtained from a particular brain region called the motor cortex, controlling movement response, then used on another area called the dorsolateral prefrontal cortex (DLPFC) to treat depression. However, there is no evidence that these two parts of the brain are related and whether MT is the optimal value for TMS treatment. Our study tries to answer the question of whether different intensities of stimulation affects response to the treatment. We further investigate age, machine output range, and protocol used on the patient. Statistically, no correlation was observed in the whole data group between MT and response rate. In addition, the smaller data sets showed similar behavior for independence of recovery rate for different ages and MT. These results conclude that TMS has the same chance of success for any patient of any age, MT, and protocol meaning it is an effective treatment strategy for everyone.

1 Introduction

Depression is a leading worldwide illness and poses important public health issues that can be episodic or chronic [1]. It is the prevailing cause of suicides, disabilities, and all cause-mortality. The rates of depression have been shown to increase since the COVID-19 pandemic began [2]. A person is diagnosed with depression if they meet at least five of the nine DSM-5 criteria: depressed mood, loss of interest or pleasure in most or all activities, fatigue or loss of energy, insomnia or hypersomnia (sleeping too little or too much), recurrent thoughts of death or suicide, change in appetite or weight, feelings of worthlessness or excessive guilt, psycho-motor agitation or retardation (restlessness or sluggishness), and loss of concentration [3]. The first pharmacotherapy approach are antidepressants. Many first-line antidepressants modulate levels of neurotransmitters such as serotonin and dopamine which were shown to decrease the receptor activity of N-methyl-d-aspartate (NMDA) that is correlated with depression [4]. Thus, many patients with mild depressive symptoms rely on selective serotonin re-uptake inhibitors (SSRIs) since they are the safest drug that has the least side effects [3]. However, if they are not responding to this medication, their psychiatrist may prescribe serotonin and nor-epinephrine re-uptake inhibitors, atypical antidepressants (SNRIs) [5]. If none of these drugs show significant difference in depressive mood and symptoms, then a patient would be diagnosed with treatment-resistant depression (TRD) [6][7].

Despite the various antidepressant treatments available, one third of patients do not respond to pharmacotherapy [8]. Thus, alternative treatments are pursued for patients with TRD such as bupropion, aripiprazole as augmentation, ketamine, or electroconvulsive therapy (ECT) depicted in Figure 1[9][10][11][12]. In addition, transcranial magnetic stimulation (TMS) has emerged as an option which is a safe, well-tolerated, and effective for TRD [9].

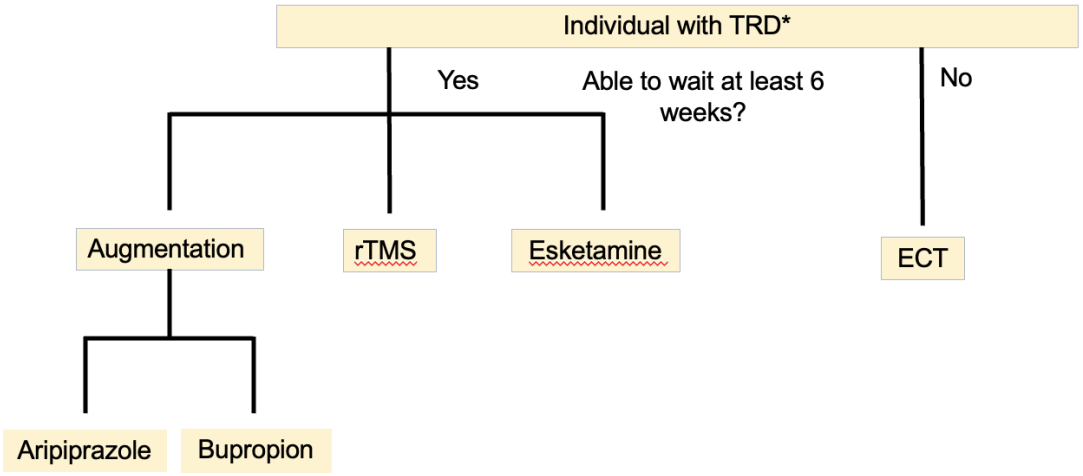

Figure 1: Proposed Clinical Algorithm for Treatment-Resistant Depression (TRD) [13]

Transcranial Magnetic Stimulation (TMS) is a non-invasive brain procedure to treat patients with TRD by positioning a magnetic coil over the brain area associated with depression called the dorsolateral prefrontal cortex (DLPFC) and applying magnetic stimulation to induce current [14][15]. It has been increasingly used at clinics since the 2010s following new cooling technologies allowing frequent impulse and continuous use [16]. TMS has been shown to cure only 1 out of every 2 TRD patients. TMS is administered daily for six weeks. While the 50% rate is significant in the TRD population, the time and costs required to receive treatment regularly, such as driving to the clinic every day, create a burden. Therefore, the goal in TMS-based research is to improve the TMS protocol to increase response rate (i.e., the number of individuals who respond to treatment). The TMS machine has different output levels which are uniquely determined for every patient. This quantifying stimulus is called the motor threshold (MT) and each patient's MT value is determined during the first TMS treatment session [17]. This value is then recorded and used to stimulate the DLPFC although there is no definite correlation between the cortices' relative excitability states [18]. Although there is no evidence for correspondence between motor cortex and DLPFC thresholds, this procedure is accepted by the scientific community [19]. Since there is no way to measure or observe the DLPFC threshold similar to MT measurement using motor-evoked

potentials (MEP), MT has shown to be useful. The patient's progression is recorded using the Beck Depression Inventory (BDI) which is a self-reporting scale of depressive symptoms out of 63 [20]. If a patient's BDI score decreased by at least 50%, the patient is considered to have a response to TMS.

The FDA approved two protocols for TMS treatment: DASH and intermittent theta burst stimulation (iTBS). The DASH protocol, approved by the FDA in 2016, made the treatment session time decrease from 37.5 minutes to 18.75 minutes with a reduced inter-train interval (ITI) that are rest periods of the machine [21]. Similar to previous protocols, DASH also targets the left side of DLPFC with a pulse frequency of 10Hz [21]. iTBS is a shorter technique by delivering 50Hz in 10 seconds, reducing one session to approximately 3 minutes [22]. In addition to its efficiency in time, research has shown iTBS still has long-lasting impacts on the patient and iTBS has shown no inferior outcomes compared to older protocols [22]. There is also 1Hz on the right DLPFC protocol. However, this technique is not frequently used in the field since left DLPFC is a more prevalent approach although they have similar antidepressant effects [23]. It is only operated when the patient has a history of seizures.

As individuals age, their neural connections get weaker and result in brain atrophy that is defined as the loss of neurons. Brain atrophy is prevalent in patients of dementia and it is more frequently seen as individuals age [24]. One question that remains is whether smaller brain matter is associated with a greater MT. According to laws of magnetism and induction where r is the distance to the magnetic coil in Equation (1), a greater magnetic field would be needed to stimulate the brain area targeted since it is further away due to shrinkage. This phenomenon is significant because age might potentially confound an analysis between response and MT.

$$B = \frac{\mu_0 I}{2\pi r} \tag{1}$$

Overall, due to the differences in DASH and iTBS, as well as the differences in MT between patients, we analyzed the differences in MT between the two techniques as well as

the effect of higher motor thresholds on TMS treatment. Research conducted by Dolberg et al. investigated this relationship, and reported no correlation in 2002. This research is outdated due to updates in protocols in the recent years and it is done on individuals with a narrower interval of motor threshold values (range: 55.9-63.1) [25] Our study examines how a greater range of motor threshold impacts response to TMS in TRD with patients of differing ages.

2 Methods

2.1 Clinical population

This study uses the Berenson-Allen Center's archive consisting of 463 adults. Berenson-Allen Center performs TMS procedures on individuals who meet criteria for treatment-resistant depression (TRD). The data has already been collected by the physicians in the center and patients who have started treatment in 2018 and on-wards will be analyzed in this study to select for the current protocols still in use.

2.1.1 Inclusion criteria

Every patient who received 30 sessions of TMS treatment in the span of 6 weeks was included in the data analysis. Two different protocols delivered by three different machines were used in this study: DASH protocol of 10Hz to the left DLPFC and iTBS; MagPro, Nexstim, and Maxstim.

2.1.2 Exclusion criteria

Patients who did not complete 30 treatments or took breaks between the 6 week span were excluded from the data. Some patients come to the clinic regularly every year to renew their treatment. However, only the first 6 weeks of their treatment was considered in this study to reduce over-representation. Individuals who started receiving treatment before 2018 were

excluded from the data, due to variances in protocols. There are 3 current protocols running in the Berenson-Allen Center: DASH, applying 10Hz stimulation on the left DLPFC, iTBS, applying theta-burst stimulation in a shorter time interval, and 1Hz on the right DLPFC. The center started using DASH after 2018 with new machines of the same caliber. iTBS was approved by the FDA after 2019 and the center started using the new protocol after 2020. Individuals who received 1Hz on the right DLPFC were excluded due to insufficient data to conclude a result. The outlined protocols were delivered per FDA approved standards. Patients who did not have motor threshold, BDI score, or dates reported properly were excluded due to missing data. Patients with no age information were included in gross data. However, they do not appear in age analysis. Individuals who have changed protocols or machines in the middle of one treatment cycle were excluded.

2.2 Clinical assessments

Patients completed the Beck Depression Inventory (BDI) questionnaire weekly in clinic to record their progress during the treatment. This study utilized initial and final BDI scores (baseline, week 6). If a patient's BDI score was not recorded on the first or the last session, the nearest recorded BDI value until 7 days was used. If the BDI score reporting was rare, the patient was excluded from the study due to insufficient data.

2.3 Data analysis

The initial MT values, initial and final BDI scores after 30 sessions, the initial and final dates of treatment, the age and sex of the patient, the protocol and machine used, and additional technician notes were recorded for every patient in the archive used for this study.

The patients were analyzed grossly to investigate the relationship between their initial MT and their rate of recovery. Recovery rate was reported in percent difference in BDI scores since it is more conclusive and frequently used in existing literature. However, absolute differences in BDI scores are reported in the Appendix A. The top and bottom deciles of

initial MT values were graphed in order to compare two ends of the spectrum and the standard deviations were reported. The data set was analyzed in different groups according to protocols to further investigate any possible correlation between the variables. These groups included the DASH and iTBS protocols. 1Hz on the right DLPFC protocol was not analyzed due to the small data set. In order to include the effect of age, two more analyses were made for each data set comparing initial MT and age as well as recovery rate and age. These graphs and reported correlation values determined whether age was a confounding factor. The results were recorded on scatter charts with best fit lines. In order to comment on the correlation, R^2 values of each best fit line were reported using linear regression testing and Spearman's Rank Correlation Hypothesis Testing for data sets of smaller size for more flexibility. The significance level for regression was determined to be 0.03 considering the characteristics of the data set and the convention of the Berenson-Allen Center. If R^2 was greater than 0.03, there was a significant linear relationship between the variables. Furthermore, to statistically comment on the relationship, f-testing was used for each data set. ANOVA testing was utilized to comment on the relationship between same categories of different ranges. $p - values$ were reported to see how significant the results were. 95% confidence level was used to comment on reported $p - values$.

3 Results

3.1 Overview

Berenson-Allen Center archive of 195 patients receiving TMS since 2018 was analyzed in order to determine the relationship between different MT values and recovery rates. Age was also identified as a possible factor in recovery magnitude, thus age was taken into account during the statistical analyses. There was no correlation found between initial MT and recovery rate for patients across ages 19-93 (refer to Table 1). Top and bottom deciles' average recovery rates, MT, and BDI score difference correlations were compared. The

bottom decile had a higher average percent difference in BDI scores. However, there was no clinically significant difference in response rate of the deciles when ANOVA test was conducted. The clinic performs three protocols which are DASH, iTBS and 1Hz on the right DLPFC. This study looked at the two more prevalent protocols which are DASH and iTBS since there was not enough data to conclude a relationship for the 1Hz on the right DLPFC treatment. There was no correlation observed in the DASH data set while the iTBS data showed an almost correlation between the initial MT values and response rate.

3.2 No correlation found between initial MT and response rate of TRD patients to TMS treatment at Berenson-Allen Center

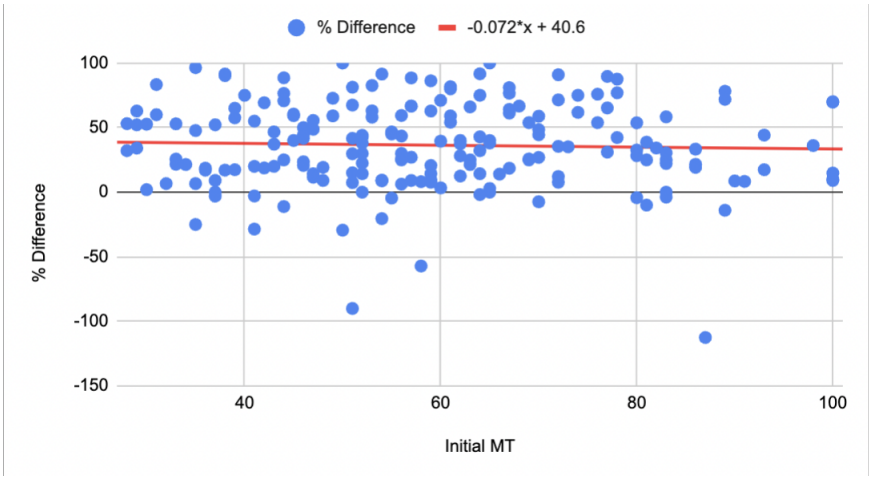

Figure 2: Percent differences of BDI scores against initial MT in the gross data did not show any correlation with $R^2 = 0.001$ between the variables using the f-testing for regression. The $p - value = 0.557$ was insignificant, meaning the null hypothesis can not be rejected.

On the patient data set ($n = 195$), there was no correlation found between higher MT and higher recovery rates. This is depicted in Figure 2. The R^2 value is reported as 0.001 showing no linear relationship. The $p - value = 0.557$ associated was greater than 0.05, meaning the data set had no correlation and we failed to reject the null hypothesis.

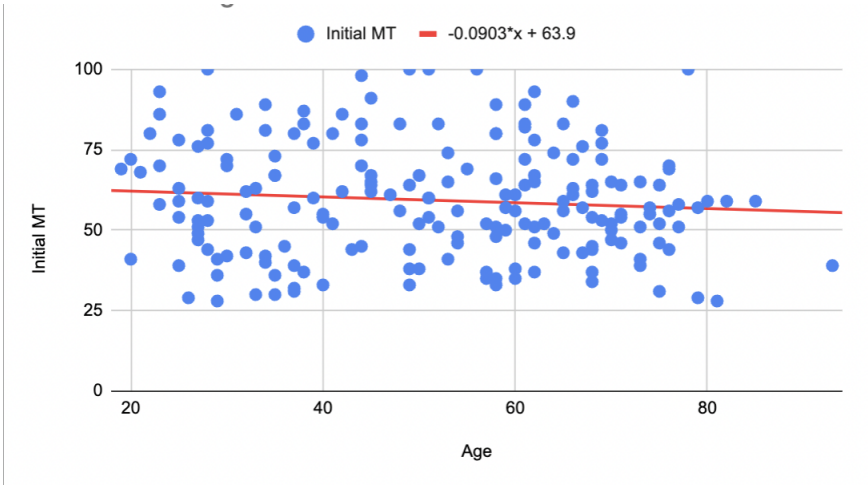

Figure 3: Initial MT against age (range: 19-93) in the gross data showed an opposite correlation than what was expected with $R^2 = 0.008$ between the variables. However, the $p - value = 0.140$ suggested no significance, meaning the null hypothesis failed to be rejected.

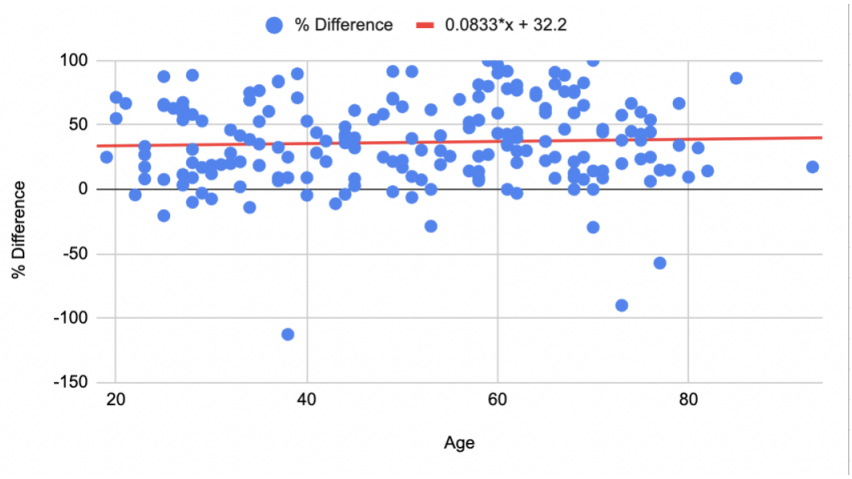

Figure 4: Percent differences of BDI scores vs. age for the gross data showed no correlation with $R^2 = 0.002$ and we failed to reject the null hypothesis because $p - value = 0.743$, meaning age does not effect TMS response

The patient age range was 19 to 93 years. Due to brain atrophy, it was suspected that age might affect initial MT values. To test this hypothesis, initial motor threshold was graphed against age in Figure 3 and there was an unexpected negative correlation found between the variables according to $R^2 = 0.008$. However, this value was not significant since R^2 was less than 0.03. The reported $p - value = 0.140$ was greater than the significance level, meaning there was no correlation between the variables in accordance with the regression test. To determine whether age was a factor in recovery, recovery rate was graphed against

age in Figure 4. Percent change in BDI scores and age of the patient had no correlation between them according to their $R^2 = 0.002$ which is less than 0.03. $p - value = 0.743$ for the relationship was greater than 0.05, meaning we fails to reject the null hypothesis (See Appendix A for figures).

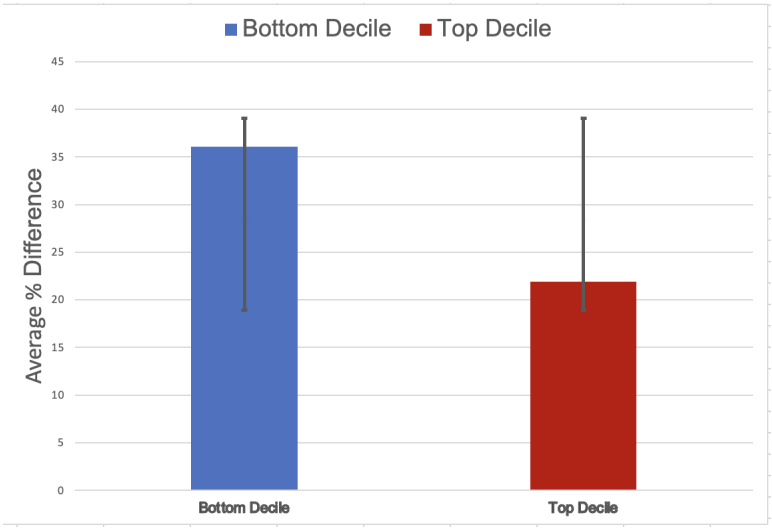

Figure 5: Bar graphs for top and bottom deciles compared the average percent differences 21.881($SD = 40.996$) in the top decile and 36.103($SD = 29.246$) in the bttom decile respectively. The bottom decile showed a better response rate for TMS compared to the top decile. However, the $p - value = 0.214$ demonstrated no clinically significant difference between the deciles when all the data for percent difference in BDI scores were utilized in the ANOVA test.

Top and bottom deciles were analyzed to determine whether they behave similarly to the gross data. The top decile had $R^2 = 0.059$ showing a positive correlation between the initial MT and response rate. In contrast, the bottom decile showed a negative correlation with $R^2 = 0.087$. The greater value of R^2 was not in accordance with the gross data. This showed that different ranges of motor threshold might have differing effects on the patient's recovery. However, this might also be because of the smaller number of data points in each decile. Both deciles had $p - values$ (top: 0.302 & bottom: 0.208) greater than 0.05, thus there was no significance between the variables graphed (See Appendix A for figures).

Each of the deciles' average rate of recovery was compared and it was seen that the bottom decile had a better recovery rate then the top decile despite the negative correlation between the initial MT and recovery rate as seen in Figure 5. We report an average percent difference

in BDI scores of $21.881(SD = 40.996)$ in the top decile and $36.103(SD = 29.246)$ in the bottom decile. On the other hand, when the ANOVA test was conducted, the $p - value = 0.214$ returned did not imply any clinical significance between the recovery rates of the patients.

3.3 DASH protocol demonstrated no correlation between recovery rate and initial MT & showed no confounding effect of age

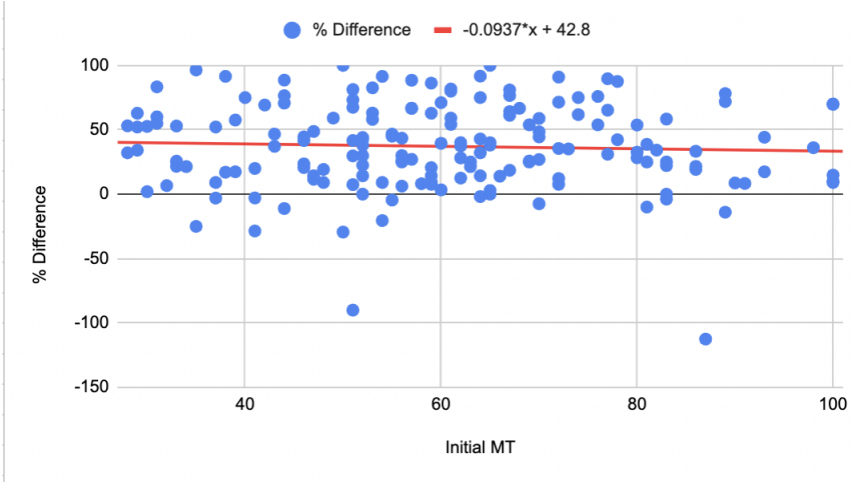

Figure 6: Percent differences of BDI scores graphed against initial MT for DASH protocol did not yield any correlation between the variables with insignificant $R^2 = 0.003$ and $p-value = 0.515$.

The protocols were analyzed separately. Initial MT was graphed against recovery rate for the DASH protocol which applies 10Hz of stimulation to the left DLPFC. Similarly no correlation was found between the patients' unique MT values and their respective BDI score improvements according to $R^2 = 0.003$. The $p - value = 0.515$ was greater than 0.05, meaning the null hypothesis can not be rejected.

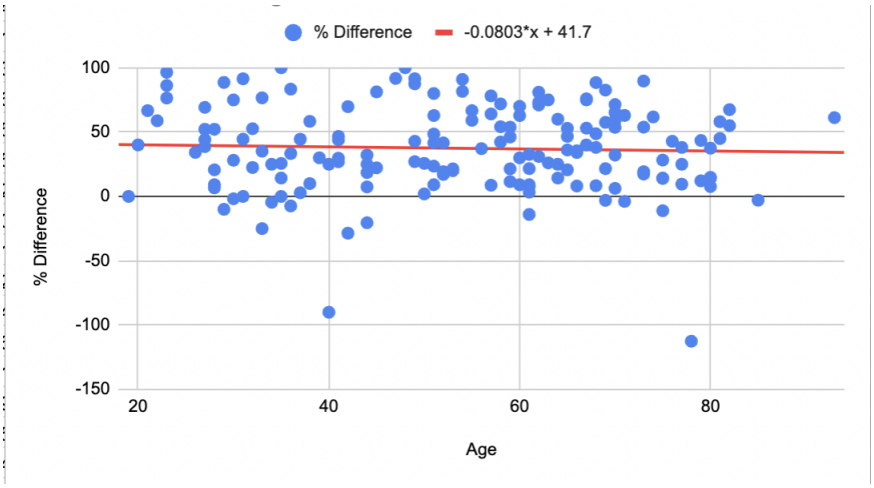

Figure 7: Percent differences of BDI scores vs. age for DASH protocol showed no correlation between variables with insignificant $R^2 = 0.002$ and $p - value = 0.718$ as expected and behaved similar to gross data.

Age analysis was done for DASH receivers and there was no correlation found between the age and initial MT values or recovery rate as reported with $R^2 = 0.01$ and $R^2 = 0.002$ respectively in Figure 15 and Figure 7. The patients who received DASH were between 19-93 years of age. This showed that the type of treatment received does not confound the relationship between MT and response (See Appendix A for figures).

3.4 iTBS protocol showed a weak correlation between MT and response rate of TRD patients to TMS due to high leverage point

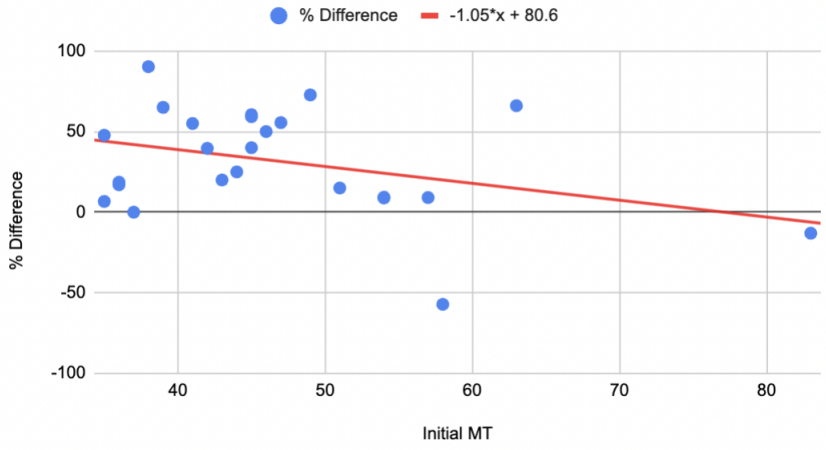

Figure 8: Percent differences of BDI scores against initial MT for iTBS protocol showed a slight correlation $r_s^2 = 0.0210$ using the Spearman's Rank Correlation Hypothesis Testing. However, the $p - value = 0.500$ is not clinically significant.

iTBS protocol was analyzed in terms of initial MT values and BDI score improvement. Since iTBS is a recently approved protocol by the FDA, its data set is smaller than DASH. Thus, high leverage points in the data affect the best fit line more compared to gross data. The iTBS machine has a heavier coil, meaning patients' MT value will be multiplied by 0.78 before being used in the treatment during the protocol. Because of this, although an initial MT value of 83 is possible with an original MT value of 106, it is not typical. This might be possible if the patient is on medications for other neurological diseases such as Parkinson's Disease or for seizures which has shown to increase MT. This results in a slight negative correlation with $r_s^2 = 0.0210$ value. However, the $p - value$ using the Spearman's Rank Correlation Hypothesis Testing did not show a clinically significant relationship. We fail to reject the the null hypothesis with a $p - value = 0.500$ that is greater than 0.05.

When the patient with MT of 83 was excluded from the data to show a more accurate representation of the correlation, the r_s^2 decreased to 0.001 and the $p - value = 0.893$ still showed no correlation between the variables.

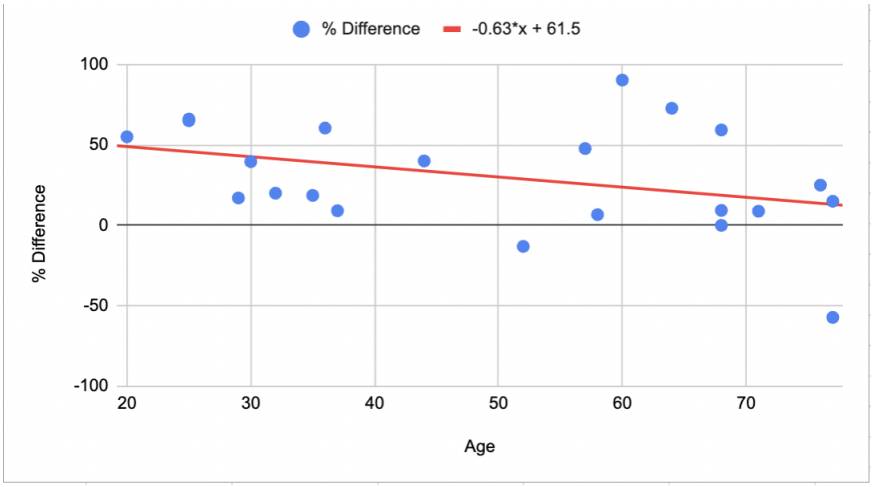

Figure 9: Percent differences of BDI scores graphed against age for iTBS Protocol showed a negative correlation using the Spearman's Rank Correlation Hypothesis Testing: $r_s^2 = 0.162$. However, the associated $p - value = 0.0629$ was still greater than the significance level, thus we fail to reject the null hypothesis.

Age analysis was also done for the iTBS protocol. Age and MT values showed a positive correlation with an $r_s^2 = 0.0713$ as reported in Figure 19. The reported $p - value = 0.230$ concluded variables are not significantly correlated since $p - value$ was greater than 0.05

(See Appendix A for figures).

Age and recovery rate showed a negative correlation for the iTBS protocol. $r_s^2 = 0.162$. The $p-value = 0.0629$ which was greater than 0.05, showed no clinically significant correlation. The data group was relatively small compared to DASH and the age range in between 20-77 was not uniformly distributed as seen in Figure 9. Thus, this smaller data set did not represent the clinical trend seen in other data sets.

4 Discussion

Our aim was to determine if high MT is associated with higher likelihood of TMS response. We found that there was no clinically significant correlation between the initial motor threshold values and recovery rates of the patients receiving treatment from the Berenson-Allen Center in Section 3.2. As a sub-analysis, we examined the effect of age on initial MT and concluded that age did not impact initial motor threshold or the response rate. Different protocols showed similar trends. The DASH protocol performed similarly to the gross data, showing no correlation between the variables discussed in Section 3.3. In addition, the iTBS protocol demonstrated no significant correlation between the initial motor threshold and recovery rate according to the $p - value$ obtained from the Spearman's Rank Correlation Hypothesis Testing shown in Section 3.4. Therefore, our foundings are corroborated in the 2002 study by Dolberg et al. [25]. We hypothesize three possible explanations for these results.

First, that the initial motor threshold matters for recovery rate in a specific range, meaning that the correlation would be visible in a smaller range of MT. To test this hypothesis, the study analyzes the top and bottom deciles of the gross data to observe if they behave similarly. They behave oppositely in terms of regression. However, when the ANOVA test is done on the response rate of both the deciles, they show no significant differences with their $p - value$. Since coil position on the motor cortex effects the motor response, MT might vary. Thus, the lack of correlation might be because confounding factors like coil position

[26]. If this were the case, the correlation might be more visible in subsets of data where the range is smaller to reduce variance. However, this impact might be because of the smaller sample size not being uniform enough in other factors such as age, sex, or protocol type. Previous research has shown similar trends to our results for stimulus rate. While in bigger groups inter-stimulus interval (ISI) showed no effect on response, ISI had an impact at the individual level [27].

Second, the lack of association between MT and response rate could be that initial motor threshold matters. However, DLPFC and motor cortex thresholds are correlated to one another. In other words, machine output on an individual might have an effect on their recovery but the motor threshold is the ideal machine output which results in the maximum amount of recovery. Thus, comparing different patients would not demonstrate the correlation between initial MT and recovery rate. To test this hypothesis, a population with similar MT would be matched to the same sex, age, and medical history and this population would be given a range of percent stimuli (e.g. 80-150%). It has been shown by previous studies that different motor-evoked potentials (MEP) yield different response to TMS for the motor cortex [28]. Further investigation of relationship between DLPFC and motor cortex could be performed in a larger population.

Our last potential explanation is that TMS treatment is effective because of its placebo effect. This is not a new concept in the treatment of psychiatric disorders, as the effect of placebo for depression has been cited up to 50% [29]. Possible explanations of the placebo effect as it relates to TMS include the behavioral activation and structure involved with the procedure. For example, patients need to drive to the clinic everyday, talk to physicians, socialize with other staff in the hospital, and be active to receive treatment which might be benefiting them by reducing their depressive symptoms.

This investigation yielded several limitations. First, there were high leverage points that changed the correlation in small data sets. Second, the BDI is not an objective method to screen depressive symptoms. It is a self-filled questionnaire, meaning it is open to subjectiv-

ity: patients may under-represent or over-represent their results [30]. Third, the machines used in the center have been in circulation, meaning some patients may have switched to another machine midway independent of their protocol. These machines have different properties, calibers, and strengths which would make the initial motor threshold values independent to one another. Finally, this data set is representative of the population that seeks care from the Berenson-Allen Center. Therefore,the results form this study may not be applicable to a different populations outside the Boston area.

5 Conclusion

This study establishes that there is no clinically significant effect of initial motor threshold on the response rate of TMS treatment. Furthermore, age was shown to have no effect on the initial motor threshold and response to TMS. Thus, it was concluded to not be a confounding factor. Different protocols, DASH and iTBS, exhibited the same trend and showed no correlation and statistical significance. These findings demonstrate that TMS treatment can be effective for anyone of any age, with any MT, and any protocol used. Therefore, TMS is proved to have the same chance of recovery rate for every patient at the Berenson-Allen Center.

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Appendix

A Tables and Figures

Table 1: Demographics of the patients constituting the Berenson-Allen Center archive

Age, years*	51.3 (19-93)
Female Gender (%)	49.3
Gross Dataset (n)	195
iTBS (n)	24
DASH (n)	170
Initial MT*	58.9 (28-100)

* format written as: mean (range)

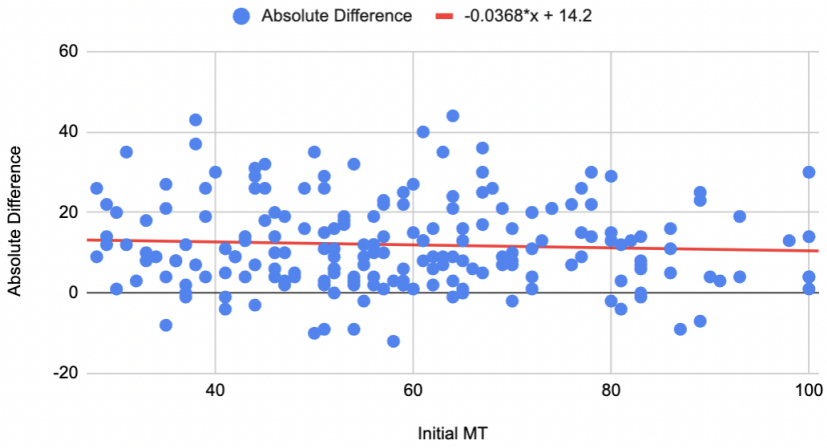

Figure 10: Absolute differences of BDI scores vs. initial MT for gross data $R^2 = 0.004$ and $p - value = 0.345$

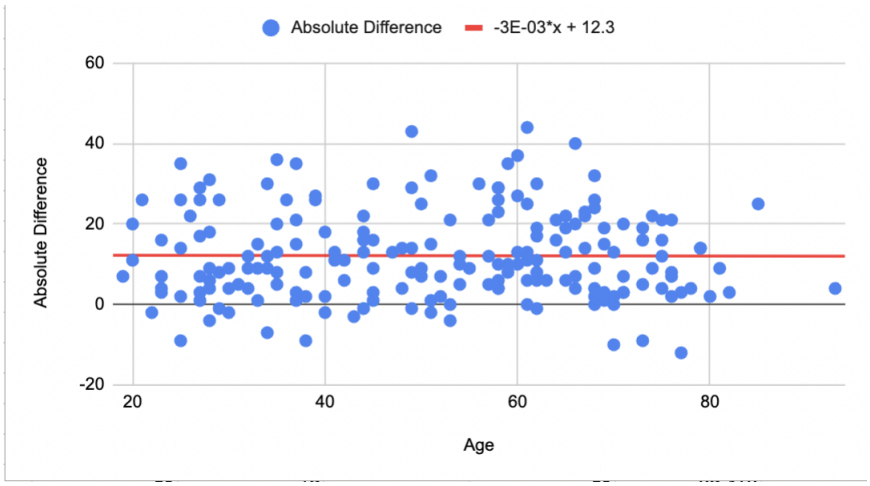

Figure 11: Absolute differences of BDI scores vs. age for gross data $R^2 = 0$ and $p - value = 0.948$

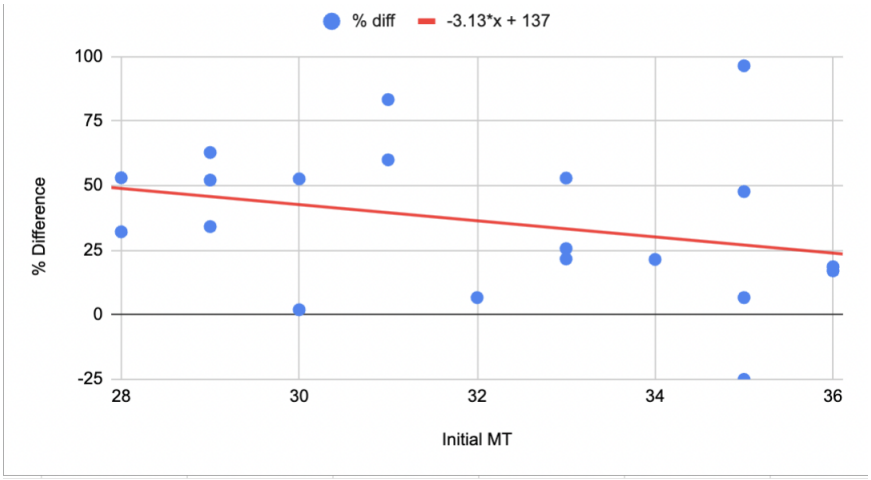

Figure 12: Percent differences of BDI scores vs. initial MT for bottom decile $R^2 = 0.087$ and $p - value = 0.208$

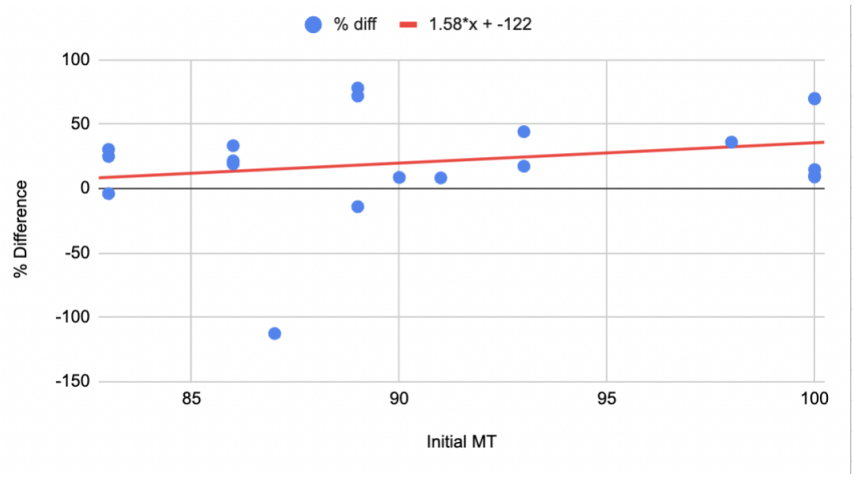

Figure 13: Percent differences of BDI scores vs. initial MT for top decile $R^2 = 0.059$ and $p - value = 0.302$

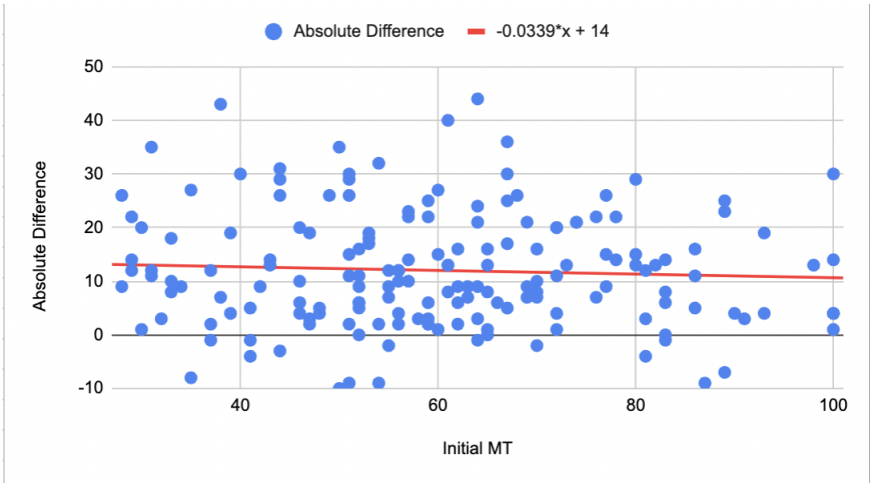

Figure 14: Absolute differences of BDI scores vs. initial MT for DASH protocol $R^2 = 0.003$ and $p - value = 0.468$

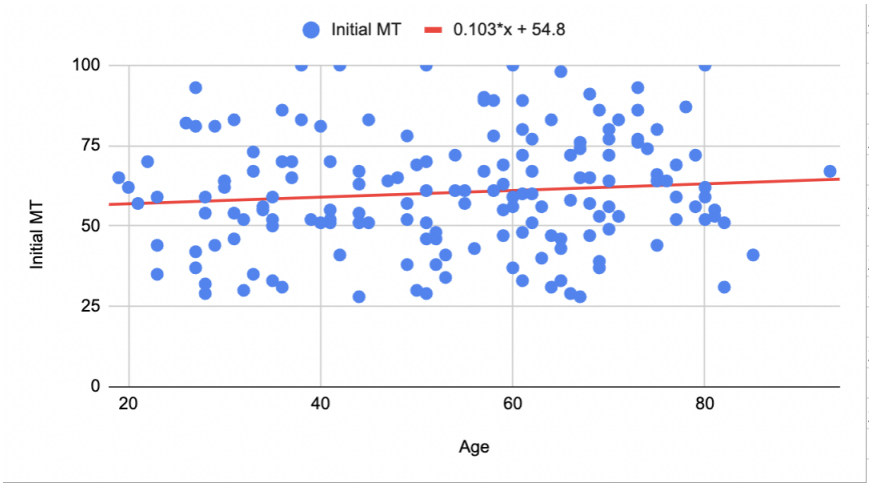

Figure 15: Initial MT vs. age for DASH protocol $R^2 = 0.01$ and $p - value = 0.200$

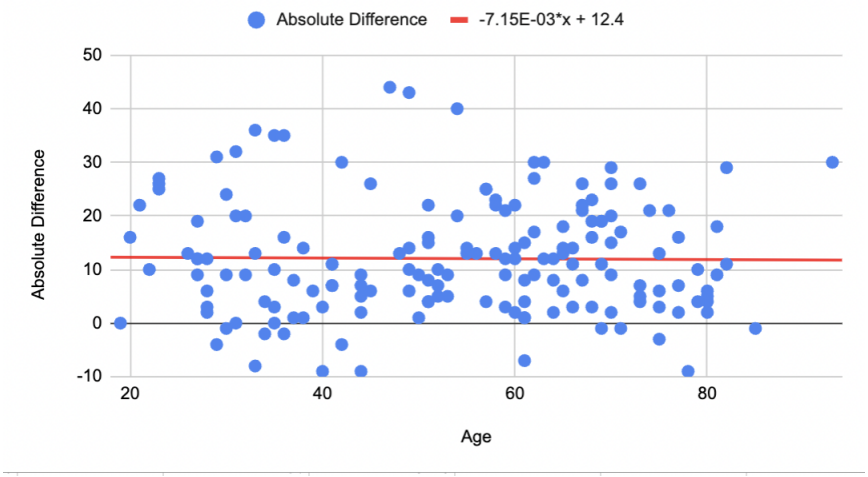

Figure 16: Absolute differences of BDI scores vs. age for DASH protocol $R^2 = 0$ and $p - value = 0.881$

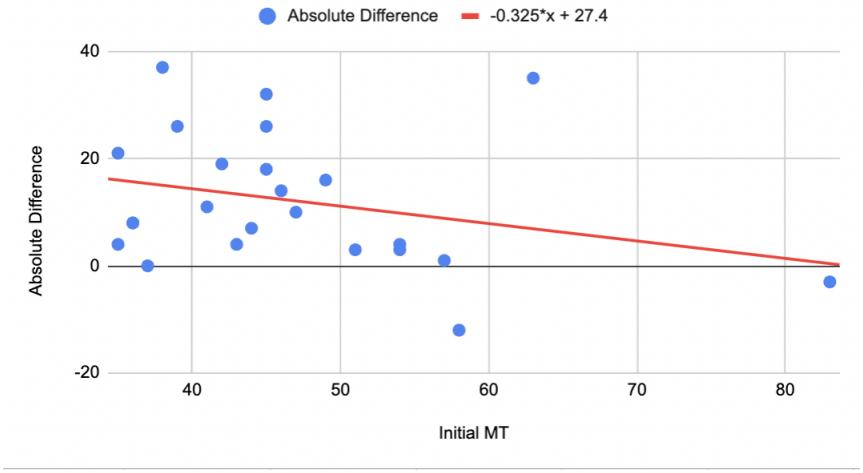

Figure 17: Absolute differences of BDI scores vs. Iiitial MT for iTBS protocol $r_s^2 = 0.0873$ and $p - value = 0.893$

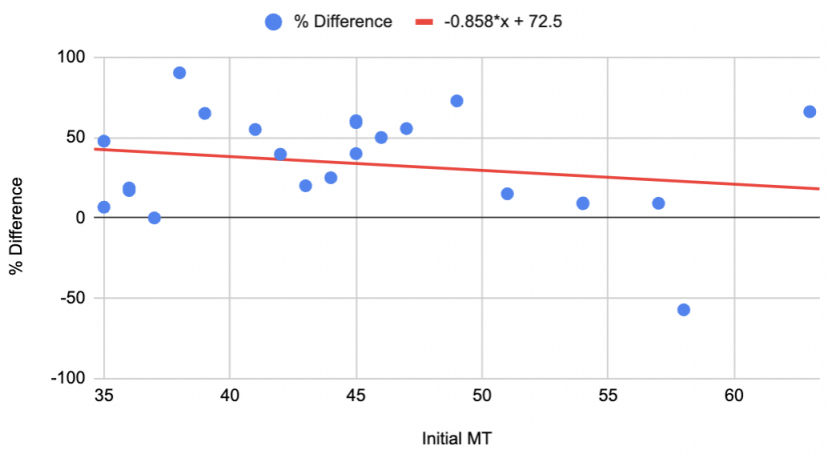

Figure 18: Percent differences of BDI scores vs. initial MT for iTBS protocol $r_s^2 = 0.001$ and $p - value = 0.893$ without the Outlier

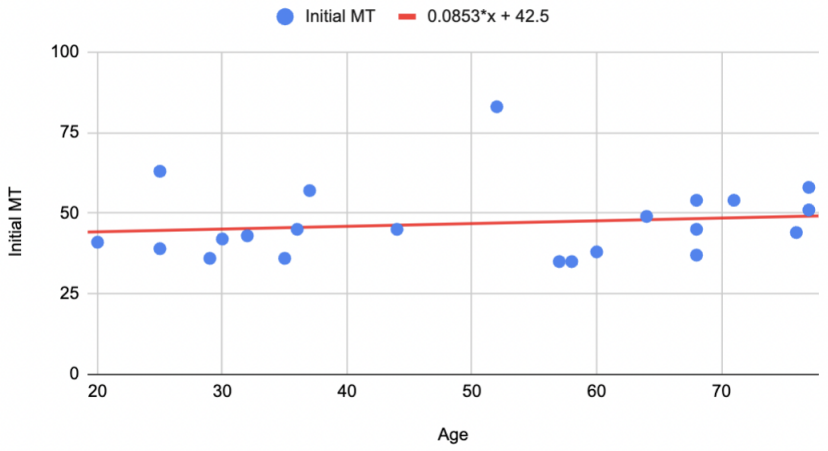

Figure 19: Initial MT vs. age for iTBS protocol $r_s^2 = 0.0713$ and $p - value = 0.230$

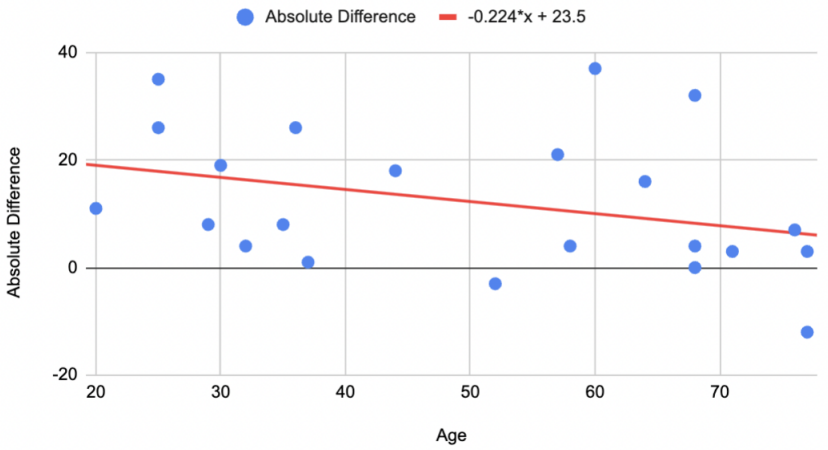

Figure 20: Absolute differences of BDI scores vs. age for iTBS protocol $r_s^2 = 0.195$ and $p - value = 0.0394$