

Pretreatment pupillary reactivity is associated with differential early response to 10 Hz and intermittent theta-burst repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD)

Cole Citrenbaum^{a,b}, Juliana Corlier^{a,b}, Doan Ngo^{a,b}, Nikita Vince-Cruz^{a,b}, Andrew Wilson^{e,f}, Scott A. Wilke^{a,b}, David Krantz^{a,b}, Reza Tadayonnejad^{a,b,d}, Nathaniel Ginder^{a,b}, Jennifer Levitt^{a,b}, John H. Lee^{a,b}, Michael K. Leuchter^{a,b}, Thomas B. Strouse^{a,b}, Andrew Corse^{a,b}, Pooja Vyas^c, Andrew F. Leuchter^{a,b,*}

^a TMS Clinical and Research Program, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, USA

^b Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90024, USA

^c Department of Psychiatry, University of California San Diego, San Diego, CA, USA

^d Division of the Humanities and Social Sciences, California Institute of Technology, Pasadena, CA, USA

^e Cooperative Institute for Research in Environmental Sciences (CIRES), University of Colorado Boulder, Boulder, CO, USA

^f NOAA National Centers for Environmental Information (NCEI), Boulder, CO, USA

ABSTRACT

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment for Major Depressive Disorder (MDD). Two common rTMS protocols, 10 Hz and intermittent theta burst stimulation (iTBS), have comparable rates of efficacy in groups of patients. Recent evidence suggests that some individuals may be more likely to benefit from one form of stimulation than the other. The pretreatment pupillary light reflex (PLR) is significantly associated with response to a full course of rTMS using heterogeneous stimulation protocols.

Objective: To test whether the relationship between pretreatment PLR and early symptom improvement differed between subjects treated with iTBS or 10 Hz stimulation.

Methods: PLR was measured in 52 subjects who received solely 10 Hz ($n = 35$) or iTBS ($n = 17$) to left dorsolateral prefrontal cortex (DLPFC) for the first ten sessions of their treatment course. Primary outcome measure was the percent change of Inventory of Depressive Symptomatology – Self Report (IDS-SR) from session 1 to session 10.

Results: There was a positive association between normalized maximum constriction velocity (nMCV) and early improvement in subjects receiving 10 Hz stimulation ($R = 0.48$, $p = 0.004$) and a negative association in subjects receiving iTBS ($R = -0.52$, $p = 0.03$). ANOVA revealed a significant interaction between nMCV and the type of initial stimulation ($p = 0.001$). Among subjects with low nMCV, those initially treated with iTBS showed 2.6 times greater improvement after 10 sessions ($p = 0.01$) than subjects initially receiving 10 Hz stimulation.

Conclusion: nMCV may detect physiologic differences between those likely to benefit from 10 Hz or iTBS treatment. Future studies should examine whether PLR could guide prospective treatment selection.

1. Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment for treatment-resistant Major Depressive Disorder (MDD). The most commonly used treatment protocols are either 10 Hz or intermittent theta burst stimulation (iTBS) (50 Hz triplet pulses administered on a 5 Hz carrier wave) [1]. When administered to left dorsolateral prefrontal cortex (DLPFC), these two forms of excitatory stimulation have

comparable rates of treatment efficacy in groups of patients [2].

There is significant variability, however, in both the trajectory and degree of response to rTMS across individuals. Some patients show substantial improvement within the first ten sessions of treatment, which has been shown to predict benefit from an entire course of treatment [3–6]. Recent data also indicate that some patients respond to a course of 10 Hz or iTBS treatment, but not both [7]. Similarly, “theta-burst priming” stimulation (addition of 600 pulses of iTBS prior to

* Corresponding author. TMS Clinical and Research Program, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, USA.

E-mail address: afl@ucla.edu (A.F. Leuchter).

<https://doi.org/10.1016/j.brs.2023.10.006>

Received 10 August 2023; Received in revised form 4 October 2023; Accepted 8 October 2023

Available online 18 October 2023

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3000 pulses of 10 Hz stimulation) has been shown to improve outcomes in 10 Hz treatment non-responders [5].

We have recently shown that the brain has distinct neurophysiologic responses to different frequencies of stimulation that are related to variability in clinical outcome [8]. It therefore may be possible to use physiologic monitoring to identify divergent physiologic characteristics in subpopulations of patients most likely to benefit from iTBS or 10 Hz treatment, consistent with prior preclinical as well as clinical studies suggesting that these two stimulation protocols have different mechanisms of action. iTBS and 10 Hz stimulation have been shown to affect different cell populations: 10 Hz stimulation primarily depolarizes cortical pyramidal cells [9–11] while iTBS primarily depolarizes parvalbumin-positive fast spiking interneurons in animal models [12–14]. The two stimulation protocols also induce the expression of different proteins in rodent brain [15] cf [16]. Hinchman and colleagues showed in human subjects that while corticomotor plasticity after 10 Hz stimulation predicted later clinical outcome in depression, the same metric following iTBS stimulation did not [17], suggesting the two protocols may modulate neuroplasticity through distinct mechanisms.

The autonomic nervous system (ANS) has emerged as a promising domain of investigation of physiologic biomarkers of response to rTMS. The ANS includes the branches of sympathetic and parasympathetic nervous systems (SNS and PNS, respectively) that are regulated by brain regions including the prefrontal cortices, basal forebrain, insula, anterior cingulate cortex (ACC), hypothalamus, and locus coeruleus [18]. These regions are components of brain networks (such as the salience network) whose function is disrupted in mood disorders [19–21]. Autonomic dysregulation is common in MDD and may present with sleep disturbances, cardiovascular changes, or other indicators of physiologic dysfunction [22]. The degree of diminished PNS activity in particular has been linked to severity and duration of MDD [23–27].

Preliminary evidence indicates that iTBS and 10 Hz stimulation may have different acute effects on the PNS, with iTBS possibly eliciting greater heart rate deceleration than 10 Hz [28]. This finding is particularly interesting given that changes in heart rate variability (HRV) correlate with changes in depression symptom severity [29]. Given that specific stimulation protocols may differentially activate the PNS, it may be fruitful to examine other indicators of PNS function in the context of different treatment protocols.

One ANS measure that is relatively unexplored in patients receiving rTMS treatment is the pupillary light reflex (PLR), which measures reactivity to a brief light stimulus and is a sensitive indicator of autonomic dysfunction [30–34]. We previously reported that pupillary Constriction Amplitude (CA) measured at baseline in rTMS subjects was positively associated with outcomes of a 30-session rTMS treatment course [35]. Because CA reflects parasympathetic activity, this finding is consistent with previous HRV findings suggesting that greater pre-treatment parasympathetic activity is associated with better rTMS treatment outcomes [36,37], although not all studies have detected this association [38].

Because 10 Hz and iTBS treatment may be beneficial to different populations of patients with MDD, it would be useful to identify pre-treatment ANS biomarkers to help determine which form of stimulation might be most likely to be efficacious for each individual [5,39–41]. In this study, we extend prior work by examining the relationship between baseline PLR and clinical outcomes of rTMS in subjects receiving an initial 10 sessions of either 10 Hz or iTBS stimulation. We tested whether PLR indices showed distinct associations with outcome in iTBS and 10 Hz subjects, with the goal of identifying putative prospective biomarkers for treatment individualization. We hypothesized that because iTBS may have a greater effect on the PNS than 10 Hz, individuals with dysregulated PNS at baseline would have greater improvement with iTBS than 10 Hz stimulation.

2. Methods

2.1. Subjects

Subjects were 52 individuals 18–75 years of age (mean 43.8) referred to the TMS Clinical and Research Service at UCLA with primary diagnoses of MDD confirmed by the Mini International Neuropsychiatric Interview (MINI) [42]. They were with 53.9% females, and had moderately severe MDD based on an average baseline depressive symptom rating of 44.5 on the Inventory of Depressive Symptomatology Self-Report (IDS-SR) [43] and 17.9 on the Patient Health Questionnaire-9 (PHQ) [44]. 47 out of 52 subjects were receiving at least one concomitant psychotropic medication for treatment of MDD during rTMS treatment. Three subjects had comorbid tinnitus and two subjects had comorbid chronic pain. All subjects were rTMS treatment naïve and underwent standard safety screening and medical clearance to receive TMS [45]. The UCLA Institutional Review Board (IRB) approved this retrospective analysis of de-identified clinical data.

2.2. rTMS treatment procedures

All rTMS treatments were performed with either a MagPro X100 (Magventure, Farnum, Denmark) or Magstim Horizon (Magstim, Whitland, UK) system. Resting motor threshold (MT) was determined before the first treatment as the minimum stimulator intensity required to elicit a visually detectable hand movement in 5 of 10 single pulse trials. Selection of either 10 Hz TMS or iTBS was determined naturalistically based upon clinician and patient preference. Regardless of protocol, treatment was delivered initially at 100% MT to left DLPFC based on the Beam F3 targeting method [46] with intensity increased to 120% MT over the first several treatments as tolerated. Subjects receiving the 10 Hz protocol were administered 3000 pulses, with a 40-pulse train and inter-train interval (ITI) of 11, 16, or 26 s ($n = 22$, $n = 4$, and $n = 9$, respectively). Subjects receiving iTBS were administered 1800 pulses in 2 s trains of triplet 50 Hz bursts repeated at 5 Hz with an 8 s ITI (one subject received 600 and another 1200 pulses instead). All subjects received daily weekday treatment. After treatment session ten, subjects continued in treatment according to a measurement-based care paradigm, receiving additional forms of stimulation to augment early non-response as presented previously [5].

2.3. Outcome measurement

The primary outcome was measured as IDS-SR percent improvement from session 1 to 10 [4,5]. Early symptom change has been previously shown to be a significant predictor of benefit from a full course of rTMS treatment [3,6]. We report here only on the initial 10 sessions of treatment, both because of the specific hypothesis examining the relationship between PLR and early response to iTBS vs 10 Hz treatment, and because heterogeneity in stimulation protocols after session 10 could confound these analyses; data for the more heterogeneous later phase of treatment were reported previously [35].

2.4. Pupillometry

The pupillary light reflex (PLR) was measured using the Neuroptics PLR-200 prior to the first TMS treatment session using methods described previously [35]. Initial pupil diameter (D0), maximally constricted pupil diameter (D1), latency of constriction (LAT), constriction velocity (CV), maximum constriction velocity (MCV), and time to 75% pupil re-dilation (T75) were also calculated automatically. The normalized maximum constriction velocity (nMCV) and the pupillary constriction amplitude (CA) were examined because of their association with parasympathetic activation and dysregulation [47,48]. nMCV was calculated by dividing MCV by D0, and CA was calculated as the difference between initial and maximally constricted pupil diameters

(D0-D1) divided by the initial diameter (D0).

2.5. Data analysis

Gender composition and concomitant medication use in the 10 Hz and iTBS protocol groups were compared using Fisher's exact tests. Unpaired *t*-tests between protocol groups compared age, baseline depression severity, clinical improvement, and baseline PLR variables. Symptom improvement from baseline to treatment 10 was examined using paired *t*-test comparing IDS-SR scores. Relationships between baseline pupillary reactivity and primary outcomes were first examined separately for each protocol group, using Pearson correlations.

To examine a differential role of nMCV on outcome according to treatment protocol, interactions between baseline pupillary reactivity and the different rTMS protocols were assessed with a two-way ANOVA with the factors 1) rTMS protocol (10 Hz or iTBS) and 2) nMCV or CA, with percent improvement as dependent variable. ANOVA was performed with type III sum-of-squares to test significant interactions between treatment protocol and pupillary reactivity. Post-hoc unpaired *t*-tests were conducted to test whether subjects with high or low nMCV (based on a median split) reported more clinical benefit with iTBS or 10 Hz, and a post-hoc type-III ANOVA was performed to test for an interaction between ITI (11, 16 or 26s) and nMCV or CA in the 10 Hz group.

3. Results

3.1. Overview

52 participants were included (10 Hz [*n* = 35], iTBS [*n* = 17]). Subjects showed significant improvement on the IDS-SR at treatment 10 (*p* = 3.53e-11), with no significant difference in clinical improvement between the 10 Hz and iTBS groups. There were no significant differences in demographics, clinical characteristics, medication use, or pupillary reactivity at baseline between groups (Table 1).

3.2. Baseline PLR and clinical outcomes

In the 10 Hz group, pre-treatment nMCV and CA were positively correlated with symptom improvement (*R* = 0.48, *p* = 0.004 and *R* = 0.44, *p* = 0.008, respectively). In the iTBS group, baseline nMCV was negatively associated with improvement (*R* = -0.52, *p* = 0.03) (Fig. 1). Supplementary Table 1 shows correlations between other baseline PLR variables and symptom improvement for each group.

ANOVA revealed a significant interaction of rTMS protocol with baseline nMCV (*F* = 12.0, *p* = 0.001), indicating a differential association between clinical outcome and pupillary reactivity for the two protocols. There was a trend towards an interaction between rTMS protocol and baseline CA (*F* = 3.04, *p* = 0.09).

Post-hoc unpaired *t*-tests showed that based on a median split of nMCV, subjects with low nMCV assigned to iTBS treatment showed a 2.6 times greater mean improvement (*p* = 0.01) than those who received 10 Hz treatment. In the high nMCV group, subjects assigned to 10 Hz treatment reported 1.8 times greater mean improvement at treatment 10 (*p* = 0.13) than subjects who received iTBS treatment.

Within the 10 Hz group, ANOVA showed a significant main effect of nMCV on clinical outcome (*p* = 0.0014) with no significant interaction between ITI and nMCV (*p* = 0.14). Similarly, the interaction between CA and ITI was not significant for 10 Hz-treated subjects (*p* = 0.63), while the main effect of CA on outcome was significant (*p* = 0.014).

4. Discussion

This is the first study to examine the relationship between pre-treatment pupillary reactivity and early symptom improvement with two different forms of rTMS (10 Hz and iTBS) treatment for MDD. While the average degree of improvement from 10 sessions of 10 Hz and iTBS

Table 1

Sample characteristics and treatment outcomes. Table presents demographic characteristics and *p*-values comparing 10 Hz and iTBS groups. For medications, we report the number of subjects taking at least one of the listed medication type.

| | iTBS <i>n</i> = 17 | | 10 Hz <i>n</i> = 35 | | <i>p</i> -values (Unpaired <i>t</i> -test or Fisher's Exact) |
|--------------------------------|--------------------|-------|---------------------|-------|--|
| | Mean | Std. | Mean | Std. | |
| Age (years) | 45.9 | 13.0 | 43.6 | 14.8 | Ns |
| Gender | 11 M, 6 F | | 13 M, 22 F | | Ns |
| Baseline IDS-SR | 44.1 | 10.5 | 44.6 | 9.1 | Ns |
| Baseline PHQ-9 | 17.2 | 4.1 | 18.3 | 5.8 | Ns |
| Tx10 IDS-SR | 34.3 | 12.2 | 35.5 | 11.5 | Ns |
| % Improvement IDS-SR Tx 10 | 23.8% | 16.6% | 21.0% | 20.6% | Ns |
| D0 (mm) | 4.45 | 0.66 | 4.54 | 1.06 | Ns |
| D1 (mm) | 3.00 | 0.37 | 3.10 | 0.74 | Ns |
| LAT (s) | 0.25 | 0.02 | 0.25 | 0.03 | Ns |
| CV (mm/s) | 2.85 | 0.71 | 2.80 | 0.71 | Ns |
| MCV (mm/s) | 4.08 | 0.96 | 4.00 | 1.04 | Ns |
| nMCV (1/s) | 0.92 | 0.16 | 0.90 | 0.18 | Ns |
| DV (mm/s) | 1.18 | 0.27 | 1.24 | 0.27 | Ns |
| DV/D0 (1/s) | 0.27 | 0.06 | 0.28 | 0.07 | Ns |
| T75 (s) | 1.28 | 0.49 | 1.34 | 0.55 | Ns |
| CA (Constriction Amplitude) | 0.32 | 0.06 | 0.32 | 0.06 | Ns |
| SSRI | 4 | | 12 | | Ns |
| SNRI | 2 | | 8 | | Ns |
| TCA | 1 | | 0 | | Ns |
| MAOI | 0 | | 1 | | Ns |
| Atypical Antidepressant | 9 | | 9 | | Ns |
| Atypical Antipsychotic | 2 | | 6 | | Ns |
| Anticonvulsant | 5 | | 15 | | Ns |
| Benzodiazepine | 6 | | 12 | | Ns |
| Psychostimulant | 8 | | 10 | | Ns |
| Lithium | 0 | | 1 | | Ns |
| Total num of meds | 2.47 | 1.3 | 2.29 | 1.5 | Ns |

treatment was not significantly different, we found a significant interaction between nMCV and treatment protocol using early outcome as dependent variable. For 10 Hz subjects, nMCV was positively correlated with clinical outcome; for iTBS-treated subjects, nMCV was negatively correlated with outcome. 10 Hz-treated subjects additionally showed a positive association between CA and early benefit, while those treated with iTBS did not. Subjects with low nMCV at baseline who were treated with iTBS showed greater improvement than those who received 10 Hz stimulation.

These results suggest additional potential utility for PLR measurements in guiding the treatment of MDD. We offer preliminary evidence that low baseline values of nMCV may augur early benefit from iTBS treatment, and potentially differentiate between those likely to benefit from 10 Hz or iTBS treatment. These findings build upon past work suggesting that iTBS and 10 Hz may operate through distinct underlying mechanisms: animal studies show that iTBS and 10 Hz stimulation protocols result in differential activation of cellular assemblies and protein expression and, in humans, that changes in excitability following 10 Hz vs. iTBS differentially predict future treatment outcomes [17].

The present findings expand our knowledge regarding the role of ANS biomarkers in guiding treatment of MDD. PLR is a robust indicator of ANS function that has strong correlation with HRV measures [30–34], with the two PLR indices reported on here (CA and nMCV) being most strongly related to PNS activity [47,48]. On a neurochemical level, pupillary response is regulated by cholinergic activity in the cortex and noradrenergic activity of the locus coeruleus, so is a sensitive indicator

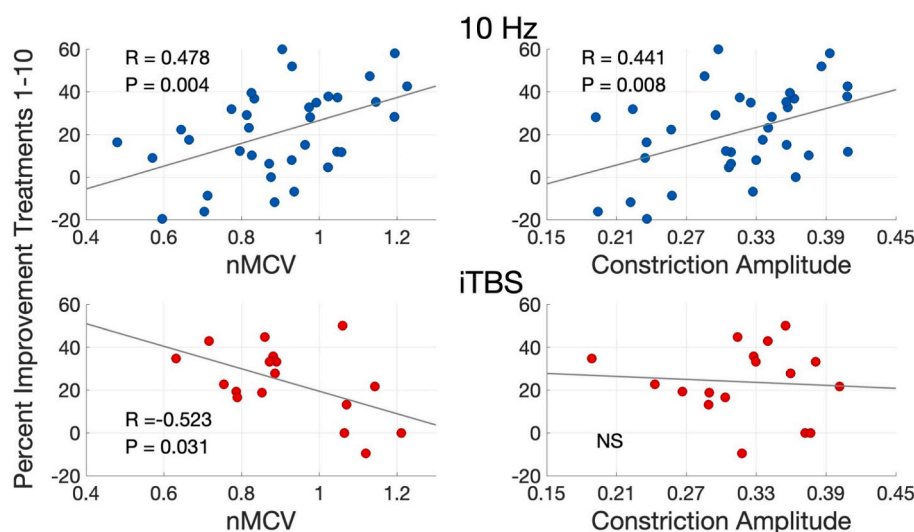


Fig. 1. Correlation of two pre-treatment PLR variables with symptom improvement at treatment 10 for 10 Hz (top) and iTBS protocols (bottom).

of not only autonomic function, but also level of alertness, fear processing and emotional arousal [49–53]. At the level of brain circuitry, regions involved in top-down control of PLR include the DLPFC (the treatment target used here) and two closely related structures, the frontal eye fields (FEF) and lateral habenula [54–56]. These areas' reciprocal connections and the projections to the limbic system and the autonomic nuclei in the brainstem make them relevant to mood regulation. The proximity of these neuroanatomic regions to the site of rTMS stimulation, and the interconnection of these regions to deeper brain structures involved in autonomic regulation, may help explain why PLR may be specifically related to rTMS treatment outcome in these subjects.

We hypothesize that in the future, PLR may prove helpful not only for exploring and characterizing the pre-treatment levels of PNS disturbance, but also for prospective decisions regarding treatment protocol selection. The greater levels of improvement in iTBS-treated subjects with dysregulated ANS at baseline (low nMCV) may be due to a more acute activation of the PNS in iTBS compared to 10 Hz stimulation. This hypothesis is consistent with prior evidence regarding the distinct effects of iTBS and 10 Hz stimulation on the ANS [28], and that the extent of rTMS activation of the PNS may be related to treatment outcomes [57]. It is possible that inconsistencies in prior literature, which include both positive and null results on the relationship between parasympathetic activity and rTMS treatment outcome [36,37,58], may be due in part to the heterogeneous treatment protocols used in previous studies. Inter-study differences in treatment parameters should be examined in relationship to ANS function and treatment outcome in future rTMS studies.

These findings should be interpreted with appropriate caution, given the naturalistic design of this study. This study included a limited number of subjects who were not randomized to protocol groups, and the sizes of the iTBS and 10 Hz samples were imbalanced. In addition, 47 of 52 patients in the study received psychotropic medication concurrently with rTMS treatment. Concomitant psychotropic medications may have affected the findings reported here, although no significant inter-protocol differences in concomitant medication use were observed. 10 Hz subjects also received treatment with different ITIs. ITI has not been shown to significantly affect anti-depressant efficacy [59] and we did not observe a significant interaction between ITI and baseline pupillometry in these subjects, although an effect on outcome cannot be ruled out. Additionally, the subjects in this study generally received prolonged iTBS (1800 pulses of treatment) in contrast to the 600 pulses used in other studies [2,60], and it is not known whether the differences between 10 Hz and iTBS stimulation would be seen with fewer iTBS pulses. Finally, we measured outcome after treatment 10 rather than a

full course of treatment due to the homogeneity of treatment protocol received over the first 10 sessions. It is possible that this differential relationship between outcome and protocol could be distinct after 10 versus 30 rTMS sessions.

The present findings suggest that the PLR, an indicator of ANS function, could play an important role as an rTMS treatment biomarker. The PLR is easy to collect, requiring only 6 s per measurement, and imposes minimal burden on patient or clinician compared to neuroimaging or cardiac measures. PLR may distinguish between those subjects most likely to show early benefit from 10 Hz or iTBS stimulation, and future controlled studies should examine the relationships among PLR, rTMS treatment protocol, and outcome over a full treatment course in order to assess whether PLR could guide treatment assignment to improve response rates. In addition, PLR measured before and after rTMS stimulation, as well as longitudinally throughout a full treatment course, should be examined to determine whether iTBS more acutely activates the PNS compared to 10 Hz stimulation. Ultimately, the PLR may be used to study rTMS mechanisms and, combined with other biomarkers, to develop a precision-psychiatry approach to treatment selection.

Credit authorship contribution statement

Cole Citrenbaum: designed the study, analyzed data, interpreted the findings, and wrote the manuscript. **Juliana Corlier:** designed the study, analyzed data, interpreted the findings, and wrote the manuscript. **Doan Ngo:** acquired data. **Nikita Vince-Cruz:** acquired data. **Andrew Wilson:** designed the study, analyzed data, interpreted the findings, and wrote the manuscript. **Scott A. Wilke:** acquired data. **David Krantz:** acquired data. **Reza Tadayonnejad:** acquired data. **Nathaniel Ginder:** acquired data. **Jennifer Levitt:** acquired data. **John H. Lee:** acquired data. **Michael K. Leuchter:** designed the study, analyzed data, interpreted the findings, and wrote the manuscript, acquired data. **Thomas B. Strouse:** acquired data. **Andrew Corse:** acquired data. **Pooja Vyas:** acquired data. All authors revised and approved the manuscript. **Andrew F. Leuchter:** designed the study, analyzed data, interpreted the findings, acquired data, and wrote the manuscript.

Declaration of competing interest

Mr. Citrenbaum, Ms. Doan Ngo, Ms. Vince-Cruz, Mr. Wilson and Drs. Corlier, Wilke, Krantz, Tadayonnejad, Ginder, Levitt, Lee, Strouse, Corse, Vyas do not have anything to disclose. Dr. Leuchter discloses that

within the past 36 months he has received research support from the National Institute of Health, Department of Defense, and eFovea, Inc. He has served as a consultant to iFovea and ElMindA. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA), and has equity interest in BBA.

Acknowledgements

We thank Ghada Elmachtoub for her expert help in manuscript preparation. Dr. Corlier's work was supported by the K01 award from the NIMH (1K01MH123887-01A1). We also gratefully acknowledge the donation of a pupillometer to UCLA by NeuroOptics, Inc., which made this work possible. This work was supported by the Ryan Family Fund for TMS Research. We are grateful to the Ryan family for their visionary support of innovative research to enhance the effectiveness of TMS treatment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2023.10.006>.

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