Title

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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)

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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 (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 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 2.7 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.

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 (iTBS) stimulation (50 Hz triplet pulses administered on a 5 Hz carrier wave) [5]. When administered to left dorsolateral prefrontal cortex (DLPFC), these two forms of excitatory stimulation have comparable rates of treatment efficacy in groups of patients [6].

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 [1–4]. 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 3000 pulses of 10 Hz stimulation) has been shown to improve outcomes in 10 Hz treatment non-responders [3].

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 humans 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. There is preliminary evidence that iTBS and 10 Hz stimulation may have different acute effects on the ANS: iTBS appears to elicit greater heart rate deceleration than 10 Hz [18], perhaps reflecting greater activation of the parasympathetic nervous system (PNS). 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 [19–23]. 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 [24]. This finding is consistent with previous HRV findings suggesting that greater pretreatment parasympathetic activity is associated with better rTMS treatment outcomes [25,26], although not all studies have detected this association [27].

If 10 Hz and iTBS are beneficial to different populations of patients with MDD, it would be useful to identify pre-treatment biomarkers of outcome for each protocol [3,28–30] and determine which form of stimulation is most likely to be efficacious for different MDD phenotypes. In this study, we extended 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 those with dysregulated PNS at baseline would have greater early improvement with iTBS than 10 Hz stimulation.

Methods

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) [31].

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) [32] and 17.9 on the Patient Health Questionnaire-9 (PHQ) [33]. 47 out of 52 subjects were receiving at least one concomitant psychotropic medication for treatment of MDD during rTMS treatment. All subjects underwent standard safety screening and medical clearance to receive TMS [34]. The UCLA Institutional Review Board (IRB) approved this retrospective analysis of de-identified clinical data.

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 (Beam 2009) 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 or 26 seconds. Subjects receiving iTBS were

administered 1800 pulses in 2s trains of triplet 50 Hz bursts repeated at 5 Hz, with an 8s ITI. 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 [3].

Outcome measurement

The primary outcome was measured as IDS-SR percent improvement from session 1 to 10 [2,3]. Early symptom change has been previously shown to be a significant predictor of benefit from a full course of rTMS treatment [1,4]. 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 [24].

Pupillometry

The pupillary light reflex (PLR) was measured using the Neuroptics PLR-200 prior to the first TMS treatment session using methods described previously [24]. The normalized maximum constriction velocity (nMCV) and the pupillary constriction amplitude (CA) were calculated based on their established utility in detecting parasympathetic activation and dysregulation

[35,36]. 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.

Data analysis

Characteristics of 10 Hz and iTBS protocol groups at baseline with regard to gender and concomitant medications were compared using Fisher exact tests, and unpaired t-tests for 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 scores. Relationships between baseline pupillary reactivity and primary outcomes were first examined separately for each protocol group, using Pearson correlations. 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.

Results

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).

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) (Figure 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 non-significant 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 2.7 times greater improvement (p=0.01) than those who received 10 Hz treatment. In the high nMCV group, subjects assigned to 10 Hz treatment reported 1.9

times greater improvement at treatment 10 (p=NS) than subjects who received iTBS treatment.

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 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 significantly 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 were more likely to show early improvement than those who received 10 Hz stimulation.

These analyses are an important extension of previous work and suggest additional potential utility for PLR measurements in the treatment of MDD. These findings indicate that nMCV and CA may have differential associations with outcomes from the two most common forms of excitatory rTMS treatment. 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. Our findings are in line with previous work revealing distinct underlying plasticity-related mechanisms for the two stimulation protocols. While animal studies show that iTBS and 10 Hz stimulation protocols result in differential activation of cellular assemblies and protein expression, in humans, changes in excitability following 10 Hz vs. iTBS differentially predict future treatment outcomes[17].

Our findings provide a new context for prior evidence regarding the distinct effects of iTBS and 10 Hz stimulation on the ANS. Prior research suggests that iTBS may have a stronger effect on cardiac measures than does 10 Hz stimulation [18]. The current findings suggest that pretreatment PLR measures may be useful for identifying those individuals in whom iTBS or 10 Hz treatment may have a greater effect. If such a physiologic distinction proves to be reliable and underlies the clinical outcome findings reported here and elsewhere [7], PLR may prove helpful in exploring and characterizing the clinical significance of mechanistic differences between treatment protocols. Taken in the broader context of ANS research, these findings may suggest that the baseline level of autonomic dysregulation may be associated not only with overall rTMS treatment benefit, but also trajectory of improvement with specific treatment parameters.

The present findings may shed light on the origins of heterogeneity in previous studies examining heart rate variability (HRV) in rTMS subjects, which have yielded both positive and null findings. Given our results, we speculate that some variability in the rTMS-HRV literature may be due in part to differential relationships between the specific treatment protocol used and the ANS. Inter-study differences in treatment targets, frequency, and subject diagnosis may all contribute to the range of findings in the literature and should be investigated in a meta-analysis.

In addition, future work should consider including pupillometry as a routine measure in rTMS treatment studies. The PLR is easy to collect, requiring only 6s per measurement. Measuring pupillometry imposes minimal burden on patient or clinician compared to neuroimaging or cardiac measures. These characteristics make the PLR a promising and practical biometric to include in work developing precision-psychiatry approaches.

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. We consider that psychotropic medications may have had an effect on the findings reported here, although no significant inter-protocol

differences in concomitant medication use were observed. 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.

Nevertheless, the present findings suggest that the PLR could play an important role as an rTMS treatment biomarker, possibly distinguishing between those subjects most likely to show early benefit from 10 Hz or iTBS stimulation. Future controlled studies should examine the relationships among PLR, rTMS treatment protocol, and outcome over a full treatment course, as well as assess whether using PLR to guide treatment assignment may improve response rates. Ultimately, the PLR may be combined with other differential biomarkers of iTBS and 10 Hz outcome to form a precision-psychiatry approach to treatment selection.

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

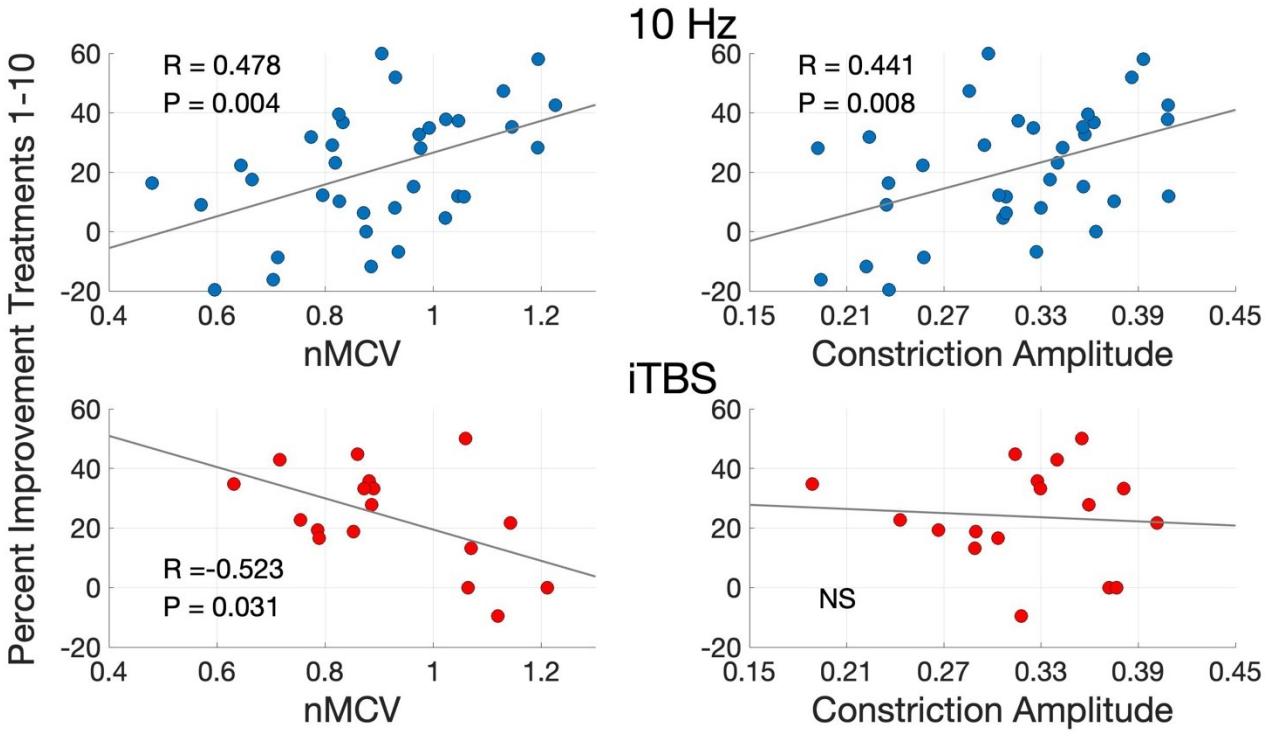

Table 1 – Sample characteristics and treatment outcomes. Table presents demographic characteristics and p-values comparing 10 Hz and iTBS groups. For medications, we report the number of subjects taking at least one of the listed medication type.

	iTBS n=17		10 Hz n=35		P values (Unpaired t test or Fisher Exact)
	Mean	Std.	Mean	Std.	
Age (years)	45.9	13.0	43.6	14.8	Ns
Gender	11M, 6F		13M, 22F		Ns
Baseline IDSSR-30	44.1	10.5	44.6	9.1	Ns
Baseline PHQ-9	17.2	4.1	18.3	5.8	Ns
Tx10 IDSSR-30	34.3	12.2	35.5	11.5	Ns
% Improvement IDSSR-30 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

Supplementary Tables

Supplementary Table 1 – Correlation of each PLR variable at baseline with clinical improvement at treatment 10.

	10 Hz (n=35)			iTBS (n=17)	
	p	R		p	R
D0	NS	0.001		Ns	0.084
D1	NS	-0.163		Ns	0.212
LAT	NS	-0.135		Ns	0.341
CV	**0.018**	**0.396**		Ns	-0.386
MCV	**0.024**	**0.381**		Ns	-0.373
DV	Ns	0.172		Ns	-0.174
T75	NS	0.072		Ns	-0.088
nMCV	**0.0037**	**0.478**		**0.031**	**-0.523**
CA (Constriction Amplitude)	**0.0081**	**0.441**		Ns	-0.057

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