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Transcranial magnetic stimulation induces heart rate decelerations independent of treatment outcome

Dear Editor,

Repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (dlPFC) is an effective intervention for treatment-resistant depression (TRD). Despite its efficacy, the optimal target within the dlPFC remains unclear, as this brain region is large, functionally heterogeneous, and lacks reliable real-time measures of target engagement. One putative biomarker of target engagement is rTMS-induced heart rate deceleration via the fronto-vagal pathway, involving the dlPFC and vagus nerve [1]. Indeed, Iseger and colleagues reported site-specific heart rate decelerations with rTMS stimulation [2] on the order of 8 beats per minute (bpm) during intermittent theta burst stimulation (iTBS) applied to the left dlPFC in patients receiving rTMS therapy for TRD [3]. This finding has been internally replicated [4], suggesting that rTMS modulates the autonomic nervous system (ANS) and may be a promising biomarker of dlPFC engagement. Although autonomic dysfunction is often reported in people with depression [5], the association between rTMS-induced autonomic engagement and treatment outcome is underexplored. Here, we attempt to independently replicate prior findings to further explore the relationship between rTMS-induced heart rate slowing and TRD treatment outcome.

This analysis includes 31 patients who received a standard treatment course of iTBS and consented to IRB-approved research procedures. Patients were evaluated by board-certified psychiatrists specializing in rTMS therapy, had a diagnosis of TRD, and deemed appropriate for rTMS treatment. Patients remained on medications and adjustments were made as clinically indicated throughout the treatment course.

iTBS treatments were delivered at 120% of an individual's resting motor threshold to the left dlPFC using the MagVenture MagPro stimulator and a Figure-8 coil (Alpharetta, GA, United States). Up to 36 daily treatments were given, and treatment courses could be terminated early if clinically indicated.

We recorded 3-lead electrocardiogram (ECG) data with the BIOPAC MP150 physiological measurement system (BIOPAC Systems, Inc., Goleta, CA, United States). Data were processed with Kubios Premium software (Kubios Oy, Kuopio, Finland). Analytical methodology was previously conducted by Iseger et al. [3] and modified here. In brief, we used ECG epochs of 30, 45, 60, and 189 seconds before ("Baseline") and during ("Stimulation") active iTBS to the left dlPFC. Baseline timepoints were used as a within-subject control instead of sham stimulation. RR interval mean and standard deviation were calculated for each epoch.

Patients were included in RR interval analyses if they had continuous ECG recordings before and during the first iTBS treatment. Depressive symptoms were measured with the Patient Health Questionnaire-9 (PHQ-9). For the treatment outcome analyses, patients needed to have completed at least 20 total treatments, a pre-treatment PHQ-9 within a week of starting treatment, and a post-treatment PHQ-9 within a week of finishing treatment.

Of the 31 subjects, 58% were female (average age = 34, standard deviation [SD] = 10.9). 29 patients had pre- and post-treatment PHQ-9 scores and were included in the treatment outcome analyses. Treatment response rate (reduction in PHQ-9 score $\geq$50%) in this group was 38.7%. There were no significant differences in demographic variables between treatment responders and non-responders (Supplemental Table 1).

We found a significant increase in mean RR intervals from Baseline 30s [mean (M) = 725.5 ms, SD = 116.7 ms] to Stimulation 30s (M = 754.4 ms, SD = 121.2 ms) [$t(30) = -6.272$, $p < 0.000001$] (Fig. 1a), with similar effects for 45s, 60s, and 189s epochs. The RR interval increase translated to approximately a 3 bpm heart rate decrease. Because all epochs showed similar effects (Supplemental Fig. 1), we used the 30 second epoch for subsequent analyses.

Previous work has demonstrated differential effects of coil location on heart rate deceleration [4]. As this dataset was a subset of a larger study assessing comparative efficacy of two common dlPFC targeting methods [Beam F3 (n = 17) and the 5.5 cm rule (n = 14)], we were able to test the effect of coil placement on heart rate deceleration. There were no significant differences in RR deceleration between the groups.

As the association between heart rate variability and depression is well-documented [6], we evaluated the association between PHQ-9 improvement and TMS-induced change in RR intervals. There was no significant correlation between percent change in PHQ-9 and percent change in RR mean from Baseline-to-Stimulation (Fig. 1b). Furthermore, there were no significant differences in Baseline or Stimulation between antidepressant responders and non-responders (Fig. 1c and d, respectively).

The present study independently replicated the iTBS-associated heart rate deceleration phenomenon reported previously [3]. Our results support the idea that modulating the dlPFC has downstream effects on the ANS, regardless of dlPFC targeting method. Yet, our study could not find an association between iTBS-induced heart rate deceleration and depression improvement despite the implication of the ANS in depression pathophysiology [5]. While Iseger et al. found 26% of the variance in antidepressant response was explained by the association with heart rate deceleration [3], our model could only explain 1% of the variance. Finally, there was no significant difference in RR intervals between responders and non-responders.

Although its utility as a predictive biomarker of therapeutic response may be drawn into question by these results, further research evaluating the utility of iTBS-induced heart rate change as a biomarker of target engagement is warranted. Possible confounds for our findings are pain or discomfort from the TMS treatment [7], state anxiety [8], or fear [9], which can also modulate ANS activity. Our study cannot rule out the possibility that the effects of iTBS on the ANS are mediated by pain or a

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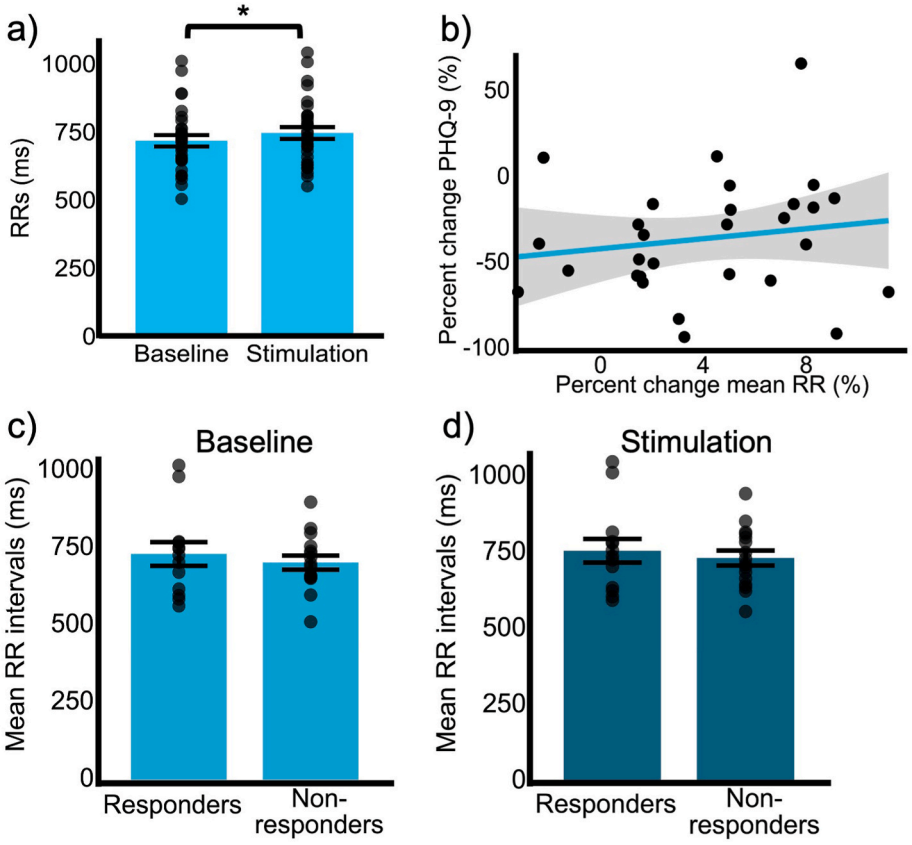

Fig. 1. Differences in mean RR intervals between Baseline and Stimulation and association with antidepressant response. a. There was a significant increase in RR interval values from Baseline to Stimulation at 30s, suggestive of heart rate deceleration. b. There was no significant correlation between percent change in mean RR intervals and percent change in PHQ-9 scores. c. There was not a significant difference between the mean Baseline, nor Stimulation (d) RR intervals at 30 seconds between treatment responders and non-responders. *: $p < 0.000001$.

general orienting or salience response [10]. Additionally, our relatively small sample size limited our ability to control for other factors that may modulate heart rate, such as psychiatric or medical comorbidities, medications, and/or activity levels, albeit the within-subject design controlled for some of these variables. Strengths of the study include use of a naturalistic clinical sample.

In conclusion, the clinical utility of TMS-induced heart rate decelerations remains to be demonstrated. Future work should focus on validating heart rate decelerations as centrally-mediated, rather than pain- or peripherally-mediated, phenomena. Finally, anatomical studies and functional imaging may further elucidate the relationship between the ANS and heart rate-responsive TMS sites.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.06.005.

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