The Relationship Between Clinical Outcome and Heart Rate Variability During Repetitive Transcranial Magnetic Stimulation

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Introduction

- rTMS can target and modulate focal brain areas for therapeutic benefit, namely the stimulation of the left dorsolateral prefrontal cortex (DLPFC) for treatment of Major Depressive Disorder (MDD).
- Recent evidence suggests site-specific brain stimulation engages a prefrontal cortex-vagus nerve output pathway to induce downstream decelerations in heart rate.[1,2]
- This rTMS-induced heart rate change could serve as a biomarker of target engagement.
- In this study, heart rate variability was recorded during the first and final treatment visits for patients in the University of Iowa TMS Clinic receiving rTMS of the left DLPFC for depression therapy.
- The researchers sought to determine whether changes in heart rate occurring in the first minute of rTMS treatment could predict treatment response in a clinical setting.

Materials and Methods

- Within-TMS treatment session ECG was collected with BIOPAC MP150 on 16 patients (6 females; mean age=46; SD=17) from the TMS Clinic at the University of Iowa Hospitals & Clinics (UIHC) who were diagnosed with treatment-resistant MDD and deemed eligible for TMS treatment by clinical staff at UIHC.
- To determine clinical outcome of the treatment course, percent change in scores for the PHQ-9 and the MADRS were calculated.
- The researchers generated Z-scores depicting stimulation-induced heart rate accelerations or decelerations following the methods described in Iseger et al. (2017).[1] See Figure 1.

Table 1. Patient Demographics

N	16
Age (range)	48±17 (26-70)
Sex	10 Male (62.5%) 6 Female (37.5%)
Treatment Stimulation	11 iTBS (68.75%) 5 10Hz (31.25%)
Comorbid Medical Conditions	Anxiety Disorder (50%) Cardiovascular Disease (40%) PTSD (19%) ADHD (18.8%) BPD (10%)
Current Medications at Treatment	Antidepressants (93.75%) Mood Stabilizers (56.25%) Antipsychotics (37.5%) Stimulants (31.25%) Anxiolytics (25%) Cardiovascular (25%) Hypnotics (12.5%) Opioids (6.25%)

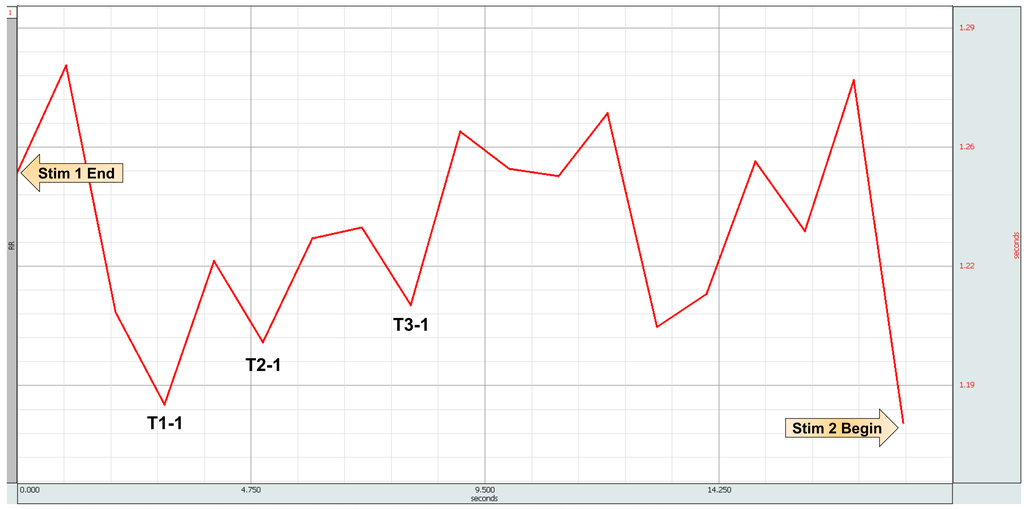
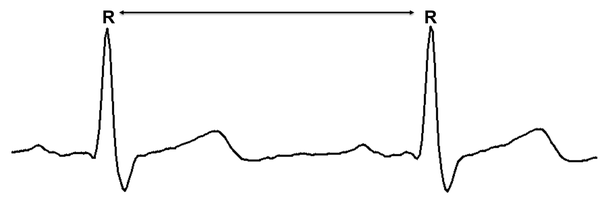


Figure 1. Raw Tachogram of Interstimulus Interval for Generation of HR-Change Z Scores.



R-R interval data was drawn from the tachogram for the time period between TMS pulses. Heart rate decelerations were characterized as an increase in the R-R interval immediately post-TMS stimulus, as measured by the R-R interval troughs to account for respiratory-sinus arrhythmia changes. Pre-stimulation troughs were labelled as T0. The first 3 troughs after stimulation were labelled as T1, T2, T3. Three troughs for the first three stimulations were averaged and transformed into Z-scores, using the pre-stimulation R-R (T0) for normalization.

Results

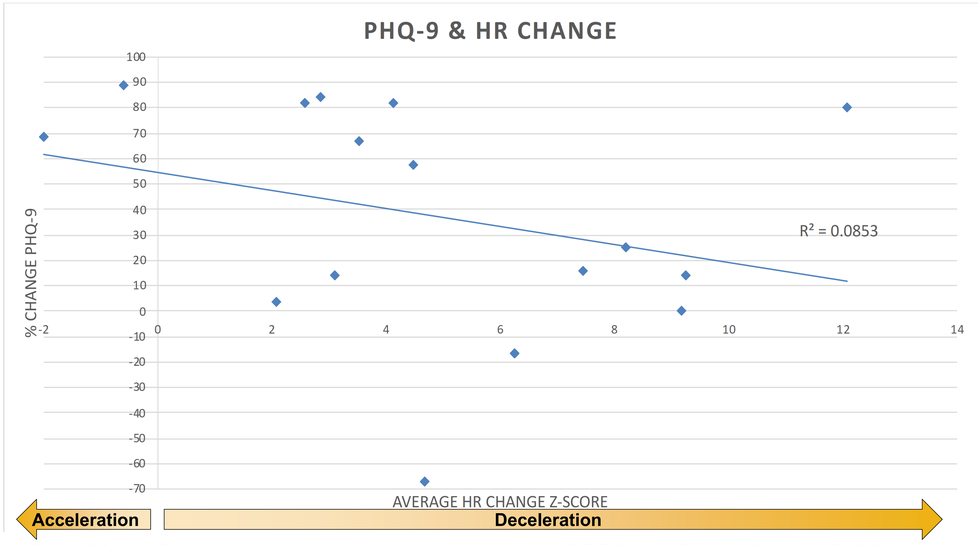


Figure 2. Linear Regression depicting relationship between Average R-R Z-Score & Percent Change in PHQ-9 Scores.

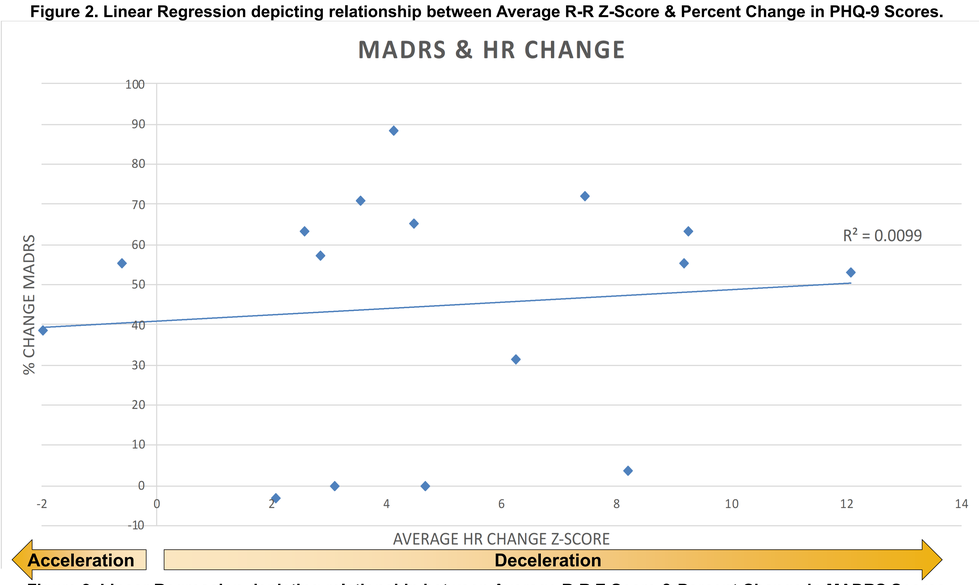


Figure 3. Linear Regression depicting relationship between Average R-R Z-Score & Percent Change in MADRS Scores. Linear regression analysis for each of the clinical scales revealed that percent change in clinical scale scores does not significantly correlate with heart rate Z-score change during TMS treatment. This lack of a significant relationship was noted for MADRS scores ($F(1,14)=0.141$, $p=0.713$, $R^2=0.0099$) and PHQ-9 scores ($F(1,14)=1.305$, $p=0.272$, $R^2=0.085$).

Conclusions & Future Directions

- While rTMS-induced heart rate decelerations were observed consistently in this sample, its relationship with clinical outcome is unclear.
- Counter to our hypothesis, there was no significant association between during-stimulation HR decelerations and depressive symptom change as measured by either of the clinical scales collected (PHQ-9 and MADRS).
- Consequently, the utility of TMS-induced HR decelerations as a marker of autonomic network engagement or, further, as a predictive biomarker of treatment response, is not robust and may require a larger dataset to identify any potential relationship.
- Further research could investigate stimulation site connectivity using functional connectivity MRI or diffusion tractography (DTI) to better understand the network patterns and neuroanatomical relationships underlying rTMS-induced heart rate decelerations in humans.
- Target localization technique (BeamF3 vs. 5.5cm) could be analyzed further for differences in HR decelerations and their association with treatment outcome.

References

1. Iseger, T. A., Padberg, F., Kenemans, J. L., Gevirtz, R., & Arns, M. (2017). Neuro-Cardiac-Guided TMS (NCG-TMS): Probing DLPFC-sgACC-vagus nerve connectivity using heart rate – First results. Brain Stimulation, 10(5), 1006–1008. https://doi.org/10.1016/j.brs.2017.05.002
2. Iseger, T. A., van Bueren, N. E. R., Kenemans, J. L., Gevirtz, R., & Arns, M. (2020). A frontal-vagal network theory for Major Depressive Disorder: Implications for optimizing neuromodulation techniques. Brain Stimulation, 13(1), 1–9. https://doi.org/10.1016/j.brs.2019.10.006