UBC Department of Psychiatry

Does Low-Frequency Repetitive Transcranial Magnetic Stimulation Modulate Heart Rate Variability in Depression?

Jaeyoon Kim[1], Bazyl Carroll[1], William Sun[1], Elizabeth Gregory[1], & Fidel Vila-Rodriguez[1]

1 Non-Invasive Neurostimulation Therapies Laboratory, Department of Psychiatry, University of British Columbia

Background

- Major Depressive Disorder (MDD) is associated with significant dysregulation of the autonomic nervous system (ANS), reflecting the profound interconnection between mental health and physiological function.[1]

- Heart Rate Variability (HRV), the variation in time between successive heartbeats, can be used as an index to provide valuable insight into this relationship, underscoring how dysregulation of the ANS may contribute to the pathological mechanisms of MDD[2].
- The central autonomic network (CAN) is a collection of brain areas involved in regulating ANS activity[3].
- Repetitive transcranial magnetic stimulation (rTMS), is a safe and effective non-invasive neuromodulation technique for MDD.
- rTMS targets brain regions within the CAN, and demonstrates an increase in HRV in select high-frequency protocol studies[4, 5].

Objective & Hypothesis

This study investigates HRV during low-frequency rTMS (LF-rTMS) and hypothesizes that LF-rTMS increases HRV through enhanced parasympathetic tone.

Methods

- Participants with MDD (N=22, mean=45.6 years old) underwent four weeks of daily 1Hz rTMS to the right dorsolateral prefrontal cortex (rDLPFC) at 120% motor threshold for 30 minutes.
- Electrocardiogram was recorded immediately prior to and during the first rTMS treatment.
- A Wilcoxon signed-rank test compared HRV metrics five minutes immediately before stimulation to the first five minutes of stimulation during the first treatment.

Table 1. *HRV Metrics analyzed in this study and brief description of ANS representation of each variable*[6, 7]

Variable	Description
Standard Deviation of Interbeat Intervals (SDNN)	influenced by both sympathetic and parasympathetic activity; in short-term resting recordings, primarily reflects parasympathetic activity
Root Mean Square of Successive Differences in Interbeat Intervals (RMSSD)	reflects parasympathetic influence
Low Frequency (LF) band (0.04-0.15Hz)	total power of low frequency, reflects mainly parasympathetic and baroreflex activity as well as sympathetic activity during short-term resting conditions
High Frequency (HF) band (0.15-0.40Hz)	total power of high frequency, reflects parasympathetic influence
LF-HF ratio (LF/HF)	previously used in studies as an index of balance between sympathetic and parasympathetic tone

Results

- LF/HF ratio and SDNN values decreased significantly ($p < 0.05$) during stimulation
- RMSSD, LF power and HF power were not significantly different between baseline and stimulation.

Table 2. *HRV metrics during the last five minutes of baseline and the first five minutes of stimulation, including means, standard error, and the Wilcoxon signed-rank test results*

HRV Metric	Baseline Mean (SD)	Stimulated Mean (SD)	p-value	Effect Size
SDNN	42.8 (23.3)	34.0 (17.5)	0.010	0.613
RMSSD	25.2 (12.7)	26.6 (15.1)	0.874	-0.0435
LF	516 (408)	451 (486)	0.113	0.391
HF	339 (297)	460 (683)	0.147	-0.360
LF/HF	2.09 (1.59)	1.66 (1.64)	0.035	0.518

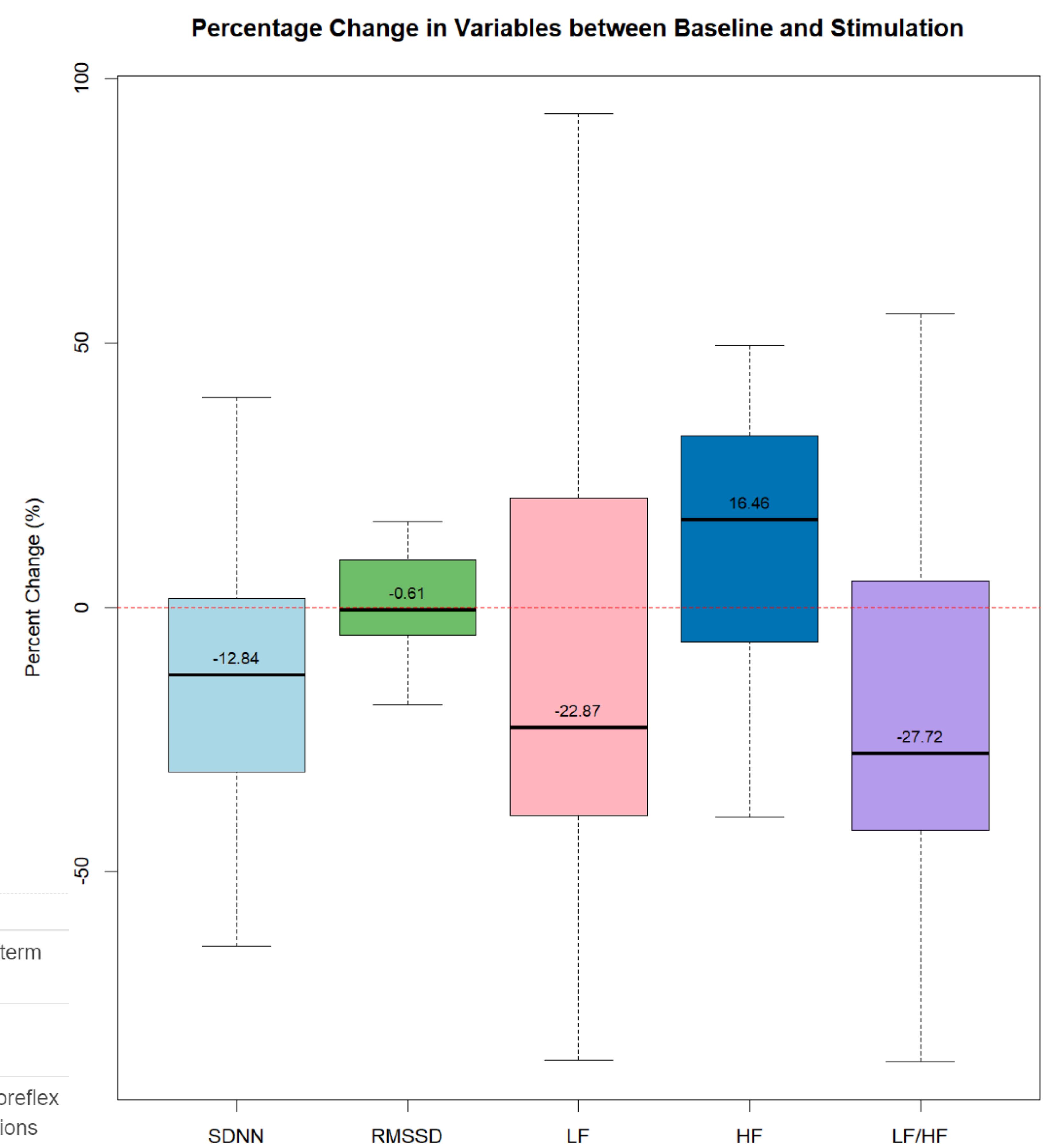

Figure 1. *Boxplot of percent changes for HRV variables in Table 1.*
**variables that changed significantly*

Discussion

Modulation of the rDLPFC with LF-TMS was associated with:

- lowered LF/HF ratio, suggesting a shift in PNS/SNS balance
- a decrease in SDNN, suggesting increased sympathetic tone

Limitations include small sample size and restricted stimulation window for appropriate comparisons.

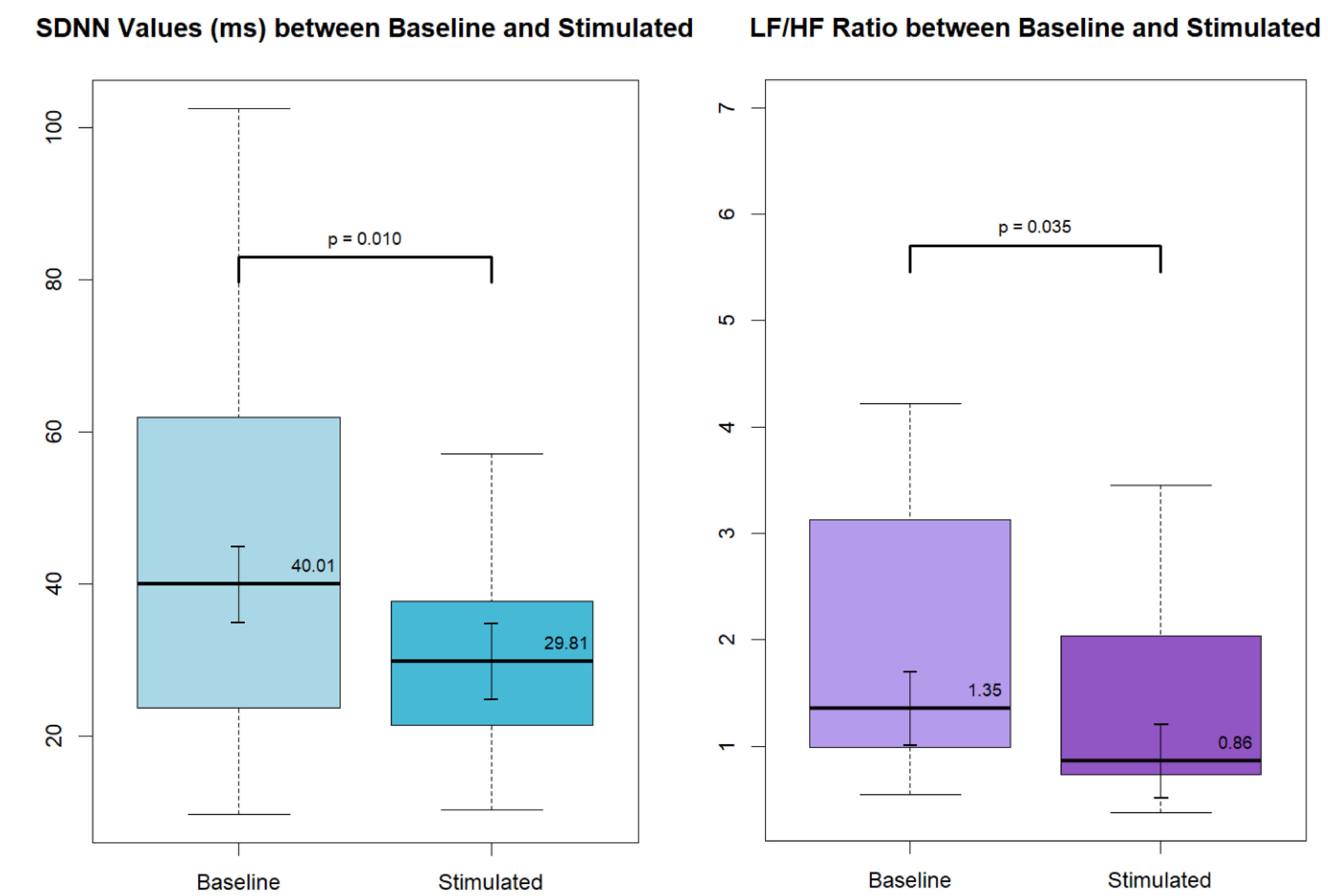

Figure 2. *Boxplots of SDNN and LF/HF values during baseline and stimulation recordings, with their standard errors marked at the center, and the median labeled.*

Conclusions & Future Directions

- Results point to the complex and non-zero sum relationship between the sympathetic and parasympathetic nervous systems.
- Our data suggests that rTMS applied to the rDLPFC can trans-synaptically modulate CAN control.
- Possible future research includes:
  - elucidate whether the modulation of the CAN by rTMS is associated with treatment outcomes.
  - more granular examination of changes in HRV metrics and ANS activity during rTMS

Reference / Bibliography

1. Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of Depression and Antidepressant Treatment on Heart Rate Variability: A Review and Meta-Analysis. Biological Psychiatry, 67(11), 1067–1074. https://doi.org/10.1016/j.biopsych.2009.12.012
2. Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. Neuroscience & Biobehavioral Reviews, 36(2), 747–756. https://doi.org/10.1016/j.neubiorev.2011.11.009
3. Benarroch, E. E. (1993). The Central Autonomic Network: Functional Organization, Dysfunction, and Perspective. Mayo Clinic Proceedings, 68(10), 988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1
4. Berlim, M. T., Van den Eynde, F., & Jeff Daskalakis, Z. (2013). Clinically Meaningful Efficacy and Acceptability of Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Primary Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials. Neuropsychopharmacology, 38(4), 543–551. https://doi.org/10.1038/npp.2012.237
5. Kaur, M., Michael, J. A., Hoy, K. E., Fitzgibbon, B. M., Ross, M. S., Iseger, T. A., Arns, M., Hudaib, A.-R., & Fitzgerald, P. B. (2020). Investigating high- and low-frequency neuro-cardiac-guided TMS for probing the frontal vagal pathway. Brain Stimulation, 13(3), 931–938. https://doi.org/10.1016/j.brs.2020.03.002
6. Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 5, 258. https://doi.org/10.3389/fpubh.2017.00258
7. Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. Frontiers in Public Health, 5, 258. https://doi.org/10.3389/fpubh.2017.00258