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Heart Rate Variability Features as Predictors of Intermittent Theta-Burst Stimulation Response in Posttraumatic Stress Disorder:

Intermittent Theta-Burst Stimulation in PTSD

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Abstract

Background: Posttraumatic stress disorder (PTSD) is associated with autonomic dysfunction as indicated by deficits in the sympathetic and parasympathetic nervous systems. These abnormalities are expressed as elevated heart rate and reduced heart rate variability (HRV), respectively. Intermittent theta-burst stimulation (iTBS), a form of transcranial magnetic stimulation, has demonstrated effectiveness in PTSD. Nevertheless, it remains unclear whether HRV may be an iTBS biomarker for PTSD and whether iTBS impacts autonomic activity.

Materials and Methods: —Fifty Veterans with PTSD participated in a randomized controlled trial, receiving 10 daily sessions of sham-controlled iTBS (right dorsolateral prefrontal cortex, 1,800 pulses/day, 80% active motor threshold, 9.5min). With a usable dataset of (n=47), HRV parameters were assessed as predictors of clinical response immediately after stimulation. iTBS effects on autonomic response (mean RR interval, RMSSD, total power, and LF/HF ratio) were evaluated using an ultra-short approach.

Results: Total power and RMSSD were significant predictors of acute clinical response to iTBS. Individuals with higher total power had better response to iTBS with improved symptoms on the Clinician Administered PTSD Scale (r_s=−0.58,p=0.004), and higher functionality on the Social

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Authorship Statement

Noah S. Philip, Emily M. Aiken and Mascha van 't Wout-Frank designed and conducted the study, including patient recruitment, and data collection. Camila Cosmo performed the data analysis and prepared the manuscript draft with important intellectual input from Noah S. Philip and Antonia V. Seligowski. In addition, Camila Cosmo, Antonia V. Seligowski, Emily M. Aiken, Mascha van 't Wout-Frank, and Noah S. Philip performed a critical review of the manuscript. All authors approved the final manuscript.

Conflict of Interest Statement

The authors have no conflict of interests to report.

and Occupational Function Scale (r_s=0.43,p=0.04). Similarly, higher RMSSD was associated with superior outcomes (r_s=−0.44,p=0.04). No other significant changes in HRV metrics were observed (p≥.05).

Conclusions: Our findings indicate that autonomic activity is a potential low-cost and technically simple predictive biomarker of iTBS response in PTSD. Less autonomic dysfunction was associated with superior clinical improvements with iTBS. Future studies might consider HRV acquisition during iTBS, as well as prospective testing of these findings in patients with elevated hyperarousal.

Keywords

Posttraumatic Stress Disorder; Autonomic Nervous System; Theta Burst Stimulation; Heart Rate Variability; Biomarker

Introduction

Post-traumatic Stress Disorder (PTSD) is a chronic psychiatric illness experienced by approximately 8% of individuals exposed to trauma [1]. PTSD is characterized by avoidance of trauma-related stimuli, intrusive symptoms, negative changes in mood and cognition, and hyperarousal, which result in remarkable distress and functional impairment [2–4]. Notably, individuals with PTSD demonstrate exaggerated fear responses (e.g., heightened startle) and impaired fear inhibition (e.g., hypervigilance), reflecting disruption of the sympathetic and parasympathetic nervous systems, respectively. These autonomic nervous system (ANS) abnormalities are generally expressed as elevated heart rate (HR) or blood pressure (sympathetic) and reduced heart rate variability (HRV; parasympathetic). Given that dropout rates remain high for PTSD treatments [5], there is a critical need to establish biomarkers of treatment response, and ANS indices are strong candidates given their established role in the disorder.

HRV is a neurocardiac parameter based on time intervals of successive heartbeats, more specifically R waves, which is indicative of the ANS response to physical and/or psychological stressors[6–9]. There are several indices of HRV, including time domain measures such as the root mean square of successive differences between normal-to-normal R intervals (RMSSD) and the standard deviation of normal-to-normal R intervals (SDNN), and frequency measures such as high-frequency (0.15–0.40 Hz; HF), low-frequency (0.01–0.15 Hz; LF), and the low/high frequency ratio (LF/HF). High frequency or HF-HRV is thought to reflect parasympathetic nervous system activity, or specifically cardiac vagal control over HR. HRV at rest is a common indicator of emotion regulation capacity and overall psychological health, with higher levels of resting HF-HRV being associated with better outcomes[10]. Numerous studies have demonstrated that individuals with PTSD exhibit lower HF-HRV at rest and in response to stressful stimuli compared to healthy and trauma-exposed controls[11–14]. Similar findings were observed in a recent systematic review and meta-analysis that included 19 studies assessing HRV parameters in individuals with PTSD compared to healthy controls[15]; this study found that PTSD was associated with reduced HF-HRV, as well as RMSSD (a time domain measure of overall ANS activity). A study by Hopper and colleagues (2006) indicated that HR was only elevated among individuals with

PTSD and low HF-HRV, suggesting that HF-HRV may be a more specific marker of ANS dysfunction than HR alone[12].

The prefrontal cortex exerts top-down control over brain regions involved in the regulation of the ANS, such as the amygdala [16]. Stimulation of prefrontal cortical areas might therefore result in modulation of ANS, as shown by prior trials [17–19 20]. Theta-burst stimulation (TBS), a newer form of repetitive transcranial magnetic stimulation (rTMS) [21,22], is a promising tool to modulate the ANS [17–19]. In particular, intermittent TBS (iTBS) has been linked to enhanced cortical excitability by facilitating synaptic connections presumably due to long-term potentiation-like (LTP) effects[21]. Among the available neuromodulation modalities, iTBS stands out for its efficacy and safety profile, as well as the advantage of being able to be delivered in a short period of time. In this context, iTBS has been investigated as a potential therapeutic alternative to traditional psychological and pharmacological therapies. In a double-blind, sham-controlled clinical trial, Iseger et al. evaluated the effects of iTBS on ANS parameters, including multiple HRV measures, upon stimulation of the dorsolateral prefrontal cortex (DLPFC) in 15 patients with Major Depressive Disorder (MDD). The authors detected significant improvements in multiple HRV indices during active iTBS application (LF-HRV, HF-HRV, SDNN, and RMSSD), suggesting that it may have enhanced parasympathetic activity by transsynaptic activation. [17] Prefrontal iTBS in a PTSD population has been shown to have therapeutic benefits, with stimulation enhancing social/occupational function and improving depressive and PTSD symptoms [23]. However, it is not yet clear whether these benefits are accompanied by HRV changes, and if so, whether HRV features might work as potential biomarkers to predict response to iTBS in PTSD.

Given that impaired baseline/resting HRV measures have frequently been implicated in PTSD[14, 15], the current study used a sub-sample from Philip et al. to examine HRV in the context of iTBS for PTSD [23]. The goals of this study were to: (a) describe baseline HRV frequency and time-domain parameters in Veterans with PTSD; (b) evaluate HRV parameters as potential predictors of clinical response; and (c) assess the effects of active iTBS, compared to sham, on ANS response (ultra-short-term HRV features) in PTSD.

Materials and Methods

Trial design

The parent modified parallel-group double-blind sham-controlled trial was performed at the Veterans Affairs Medical Center (VAMC) in Providence, Rhode Island, from May 2016 to December 2017. Methods were previously reported by Philip et al., please refer to the original study for a more detailed description of the methods (ClinicalTrials.gov NCT02769312) [23].

Participants

Fifty individuals with PTSD participated in the parent trial based on the following inclusion criteria: (a) diagnosis of chronic PTSD based on DSM-5 criteria; (b) between ages 18 and 70 years; (c) failure of at least one evidence-based treatment for PTSD (defined

as failure to achieve clinically significant reduction in symptoms with adequate trial(s) of pharmacotherapy and/or psychotherapy); (d) remained clinically symptomatic despite ongoing treatment for at least 6 weeks prior to the study procedures; and (e) being capable of understanding and providing informed consent. Participants who had any primary psychotic disorder, bipolar I disorder, ongoing substance use disorder (moderate/severe), or active suicidality were excluded from the study. Other exclusions criteria were non-MRI safe cardiac pacemaker, implanted device or metallic implant at the upper thoracic spine or higher, in addition to TMS-specific exclusions such as pregnancy risk, history of moderate or severe traumatic brain injury, active unstable medical conditions, severe neurological disorders/impairment, CNS tumors, seizures, or cerebrovascular disease.

Setting

Recruitment began in May 2016 utilizing a combined approach including a broad-based strategy, by placing advertisements to Veterans in the community, and a targeted plan by contacting professionals from the Providence VAMC Mental Health/PTSD services, and VA community-based outpatient clinics. Furthermore, the VA Computerized Patient Record System (CPRS) was also reviewed as an additional recruitment tool. One hundred sixteen potential participants were prescreened by phone interview, and 56 eligible subjects were screened during an on-site visit at the laboratory. In the end, a naturalistic sample of 50 Veterans with chronic PTSD was included in the parent trial. For this secondary analysis, individuals who concluded the double-blind iTBS period (10 sessions) and had at least one ECG recording were included.

Randomization and Blinding

Subjects were randomly allocated to undergo active iTBS vs. sham stimulation on a 1:1 basis, stratified by sex and PTSD symptom severity. An external investigator, who had no knowledge of other aspects of the trial, performed the randomization procedure.

For reliable blinding, neither subjects nor raters had any information as to whether active or sham stimulation had been applied. Given that iTBS requires use of different coils for active and sham interventions, a research assistant was invited exclusively for designating the coils. To assess the blinding effectiveness, at the end of the 10th session, subjects were asked to guess whether they had been assigned to the active or sham group.

Ethics Statement

The Providence VA Institutional Review Board approved the study protocol. In accordance with the ethical principles for medical research involving human beings of the Declaration of Helsinki, all participants were provided with detailed verbal and written information about the study and signed written consent [24].

Interventions

Participants received daily session of sham-controlled iTBS for 2 consecutive weeks (10 business days), delivered to the right dorsolateral prefrontal cortex (DLPFC), 1,800 pulses/day at an intensity of 80% of the active motor threshold (AMT), for 9.5 minutes, using a Magstim Rapid 2+1 system (Magstim, Whitland, U.K.). Right DLPFC was adopted

as the stimulation target given prior evidence of successful clinical outcomes in PTSD studies [25,26], in addition to decreased amygdala activation to trauma-related stimuli [16], Utilizing scalp measures, the coil was placed over the F4 electrode location, based on the 10–20 EEG International System, as it corresponds to the right DLPFC area. The targeted location was rechecked in each session to secure reliable and precise placements. At the end of the double-blind period, all subjects were offered the possibility of undergoing 10 unblinded active iTBS sessions, aiming to assess the cumulative effects of a greater number of iTBS sessions. The parent study flow diagram based on CONSORT may be found at Philip et al. [23], and a schematic diagram outlining the study procedures that are relevant for this secondary analysis is illustrated in Figure 1.

Safety

Safety assessment was performed at the end of each stimulation session by documenting spontaneous reported adverse events, in addition to the active query of possible iTBS side effects such as seizure, headache, and dizziness.

HRV data acquisition and analysis

Preceding the first stimulation session and following the last intervention of the double-blind phase, subjects underwent resting electrocardiogram (ECG) recording, for at least 5 minutes, while sitting in a comfortable chair (the position was standardized for all participants). Two electrodes were applied on the patient's right upper and left lower chest, using Biopac ECG100C amplifier with MP150 data acquisition and AcqKnowledge 4.1 software (Biopac Systems Inc., Goleta, CA, USA). HRV analysis was conducted separately utilizing Kubios software (version 3.4.1, HRV Premium, Kuopio, Finland)[27]. An automatic QRS detection (manually reviewed by two staff members), and automated algorithms for RR interval artifacts correction, addressing missing, extra and/or ectopic beats, were performed.

An ultra-short-term HRV approach was used, carrying out the analysis on ECG excerpts of less than 5 minutes (periods of 30s, 45s, 60s, and 195s). Ultra-short-term HRV features have been previously shown to be reliable surrogates of short HRV features (5 min recordings)[28,29], including in a study addressing HRV parameters on psychological stress [29].

For this secondary analysis, our HRV outcomes were RMSSD, very-low-frequency (VLF - 0.0033–0.04 Hz), low-frequency (LF - 0.04–0.15 Hz), and high-frequency (HF - 0.15–0.4 Hz) bands (all expressed in absolute signal and presented in ms2), as well as the total power (TP), low frequency/high frequency power ratio (LF/HF), and parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) indexes [6,30]. These PNS and SNS indexes were generated by Kubios software through algorithms based on: the mean RR interval, RMSSD, and Poincaré plot index SD1 (in normalized units); and mean RR, Baevsky's stress index, and Poincaré plot index SD2 (in normalized units), respectively. Although the longer recording epoch (195s) better represents autonomic activity, measures of both HRV domains were calculated for all epochs based in prior findings of more significant heart rate changes at the beginning of the ECG recording[17]. The mean RR

interval, mean HR, as well as their respective standard deviations, were determined for each ultra-short-term period.

Statistical analysis

The Shapiro–Wilk test was applied to assess the normality of data. Continuous variables were described as means and standard deviations (SD), while categorical data were summarized as a percentage. A non-parametric two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare HRV outcomes between the active iTBS and sham groups, while the Wilcoxon matched-pairs signed rank test was applied for within-group comparisons. Additionally, Spearman's correlation was performed to assess the relationship between baseline HRV parameters and clinical measures following iTBS. The clinical outcomes included: (a) changes in PTSD symptoms measured by the Clinician Administered PTSD Scale for DSM-5 (CAPS)[31], in addition to (b) the Social and Occupational Function Scale (SOFAS)[32], and (c) the Inventory of Depressive Symptomatology Self-Report (IDSSR)[33], all considering outcomes obtained immediately after the last iTBS. No imputation method was utilized for missing HRV data. Regarding clinical outcomes, missing data was handled by applying multiple imputations (n=20 imputations; for further information, please refer to Philip et al.) [23]. Statistical analysis was performed using Stata statistical software program, version 15.0 (StataCorp LP, College Station, TX, USA). Statistical significance was determined at 5% and all p-values were two-sided.

Results

Baseline demographic and clinical data are shown in Table 1; no statistically significant differences were found between the active iTBS and sham groups. From the 50 individuals included in the original trial, three were not able to be included in this secondary analysis as the ECG recordings had significant artifact that precluded HRV analysis, leaving 47 participants. All patients had ongoing treatment (pharmacotherapy and/or psychotherapy); and were allowed to continue without changes.

Baseline HRV parameters of the Veterans with PTSD included in this analysis are shown in Table 2. These values correspond to parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) indexes, in addition to frequency and time-domain features, all obtained for the longest epoch available (195s), as longer ECG segments generate more reliable parameters of autonomic response [6,17].

The PNS index (mean ± SD= −0.96 ± 1.16; generated in Kubios) was negative, suggesting parasympathetic activity below the normative average value for a healthy population, while the SNS index (mean ± SD= 2.47 ± 2.41) indicated a sympathetic response above the standard values for a healthy population. When assessed by group (active vs. sham), no differences were observed for the HRV variables at baseline.

In the active iTBS group, there was a statistically significant negative correlation between CAPS score and baseline total power (r_s=−0.58,p=0.004) and RMSSD (r_s=−0.44,p=0.04), respectively, in addition to a positive correlation between baseline total power and SOFAS score (r_s=0.43,p=0.04) (Figures 2 and 3). No statistical significance was found for the

correlation analyses in the sham group (all $p \geq 0.05$). Similarly, no statistical significance was found between HRV features and IDSSR scores.

With regard to iTBS direct effects on HRV measures, no significant changes were observed in all excerpts (periods of 30s, 45s, 60s, and 195s) within or between-groups (all $p \geq 0.05$), except for the VLF when comparing pre and post values in the active group ($p = .04$) (Table 2, and tables S1, S2, and S3 in the Supplementary Material).

Discussion

To the best of our knowledge, this is the first study to assess HRV measures as predictors of response to iTBS for PTSD, and to evaluate iTBS effects on ANS activity in PTSD. This secondary analysis examined the relationship between HRV parameters and clinical changes immediately after the last iTBS session. HRV features, total power and RMSSD obtained by applying an ultra-short-term approach, seem to be potential predictors of acute clinical response to iTBS for PTSD. These findings suggest that autonomic activity might serve as a low-cost predictive biomarker to identify PTSD patients most likely to respond to iTBS.

Our results indicate that PTSD patients that have higher baseline RMSSD [6,34], demonstrated better clinical outcomes immediately after the last iTBS session. Similarly, those with higher baseline total power, a sympathetic-driven parameter of autonomic response, had better acute responses to iTBS with improved symptoms on the CAPS, in addition to higher functionality on the SOFAS. Among the HRV features, RMSSD stands out for being an accurate and reliable indirect measure of vagal activity[7], which has also shown high sensitivity and specificity to identify autonomic abnormalities in prior trials[35,36]. This is possibly a reason why RMSSD has been identified as a potential predictor of iTBS response in our study. Our findings are also consistent with prior studies demonstrating that PTSD is associated with abnormalities in ANS activity, such as lower RMSSD and total power values, reflecting reduced parasympathetic and increased sympathetic responding, respectively. Among our sample, despite overall reduced RMSSD and total power, individuals with higher baseline values were found to be more likely to respond to active stimulation. In other words, PTSD patients with less ANS dysfunction were more likely to respond to iTBS.

While iTBS and other TMS modalities have been widely applied in numerous neuropsychiatric disorders with promising results, there is a paucity of successful trials investigating potential biomarkers of treatment response. To date, the most optimistic outcomes have been shown by researchers utilizing sophisticated functional mapping techniques as biological markers, however, these methods are associated with high costs and increased time commitment [37]. In this context, HRV appears as a potential biological marker with broad applicability, given its safe, feasible, low-cost, and technically simple profile.

No significant differences were observed for the HRV features at baseline or post intervention, when assessed between-groups. Overall, we did not observe direct effects of iTBS on HRV itself, except for the VLF when comparing within the active group, which it

is not associated with any specific physiological or clinical meaning. This lack of response might be attributed to the study population profile, including individuals who have failed at least one evidence-based treatment for PTSD (pharmacotherapy and/or psychotherapy). These patients might have a more severe presentation likely marked by pronounced autonomic regulation impairment. Interestingly, our findings are inconsistent with the recent work from Iseger et al. [17]. There are several potential explanations behind this discrepancy; these include pathophysiological differences between the populations under study (i.e., PTSD vs. MDD), some distinct protocol parameters and anatomical target. For instance, in the MDD study, subjects underwent thirty stimulation sessions with an intensity of 120% of the resting motor threshold, and the ECG data was acquired during the stimulation, which allowed them to obtain the effects of iTBS over HRV measures immediately, instead of after a short interval. Iseger et al. found a significantly larger HR deceleration during active iTBS that was limited to the first minute of stimulation. No significance was observed when analyzing the whole recording, which the authors attributed to the probability of HRV changes being more prominent at the beginning of the recording, possibly related to the fast nature of the parasympathetic responses modulated by iTBS. Therefore, based on their hypothesis, our lack of significant findings could be explained by the acquisition of ECG just before and just after the stimulation, when potential effects on HRV parameters might have faded.

Another potential reason for the divergent results may be due to the differing anatomical targets (right vs. left DLPFC). A meta-analysis assessing the efficacy of non-invasive brain stimulation techniques in the modulation of HRV parameters showed that the stimulation target was a significant moderator of response [20]. In particular, trials stimulating the prefrontal cortex (PFC) revealed significant increases in HRV, with the majority having targeted the left PFC. As explained in the original trial by Philip et al., the decision to apply iTBS over the right DLPFC was based on prior findings suggesting PTSD symptom reduction (one of the primary outcomes for that analysis) following high-frequency modulation of this area, likely due to top-down inhibition of the amygdala resulting in decreased response to trauma-related stimuli[16]. Designed to assess the effects of iTBS in the modulation of cardiovascular parameters in MDD, Iseger et al. defined the left DLPFC as their target based on previous trials showing MDD symptom improvement as well as the interconnections between this area and the anterior cingulate cortex (ACC) [17]. The ACC is a critical regulatory area of the anterior limbic circuit that composes the central autonomic network (CAN) [38,39] and has been associated with the modulation of the ANS and, therefore, its indirect stimulation might explain their significant HRV findings.

Our results describing the patient population are generally consistent with the existing literature. Increased sympathetic and attenuated parasympathetic activity are expected adaptive mechanisms in the context of threatening stimuli, preparing the individual for the environmental demand [40]. Our descriptive analysis results are consistent with prior evidence that PTSD is associated with maladaptive ANS activity, as supported by parasympathetic activity below average values observed in healthy populations, as well as an increased sympathetic activity [40,41]. Based on our HRV analysis indexes, enhancement of sympathetic activity was more pronounced than the reduction in parasympathetic activity. Similar findings were observed in prior studies, suggesting that ANS impairment in PTSD is the

result of an overactive sympathetic branch and hypoactive parasympathetic response, with the former being predominant [11–14]. The imbalance results in a sustained fight or flight response, which in turn is associated with poor quality of life and function in PTSD patients. This work underscores the need to develop novel therapeutic methods that might be able to restore ANS activity to a more normative state.

The current study had several limitations: (a) issues inherent to the secondary analysis of clinical trials, namely that recruitment did not focus on autonomic or related activity; (b) the sensitive nature of HRV features and how they fluctuate based on stress-induced physiological changes, resting status, and baseline comorbidities, including cardiovascular diseases, what might represent a challenge to its application as a biomarker in the clinical setting [42,43]; (c) the naturalistic veterans patient population, predominantly composed by males, which may have introduced confounding factors related to ongoing treatment, in addition to cardiovascular and related clinical factors; (d) small sample size, precluding more complex analyses or conclusions; (e) the lack of correction for multiple comparisons, therefore requiring careful interpretation of our findings in the context of its exploratory nature; (f) the lack of recording during stimulation, which may have prevented us from detecting potential modulation of the autonomic response by iTBS given the fast nature of the parasympathetic response; and (g) absence of direct measures of frontolimbic activity (i.e., neuroimaging), making us unable to conclude whether iTBS modulated these networks. Furthermore, unlike RMSS [6,7,28,34,44], total power is a HRV parameter that has not been extensively studied [6], so its physiological meaning is not fully understood and, in addition, its reliability in ultra-short ECG recordings remains unclear.

Conclusion

In conclusion, our findings indicate that ultra-short-term HRV features might work as a low-cost and technically simple predictive biomarker of iTBS clinical response in PTSD. Individuals with less autonomic impairment were more prone to acutely respond to iTBS, with improvements in both PTSD symptoms and social & occupational function. In regard to the effects of iTBS in the modulation of HRV parameters, future trials might consider targeting the left DLPFC, simultaneous iTBS delivery and ECG acquisition, combining iTBS to evidence-based treatment for PTSD (e.g. pharmacotherapy and/or psychotherapy), as well as prospective testing of these findings in patients with elevated hyperarousal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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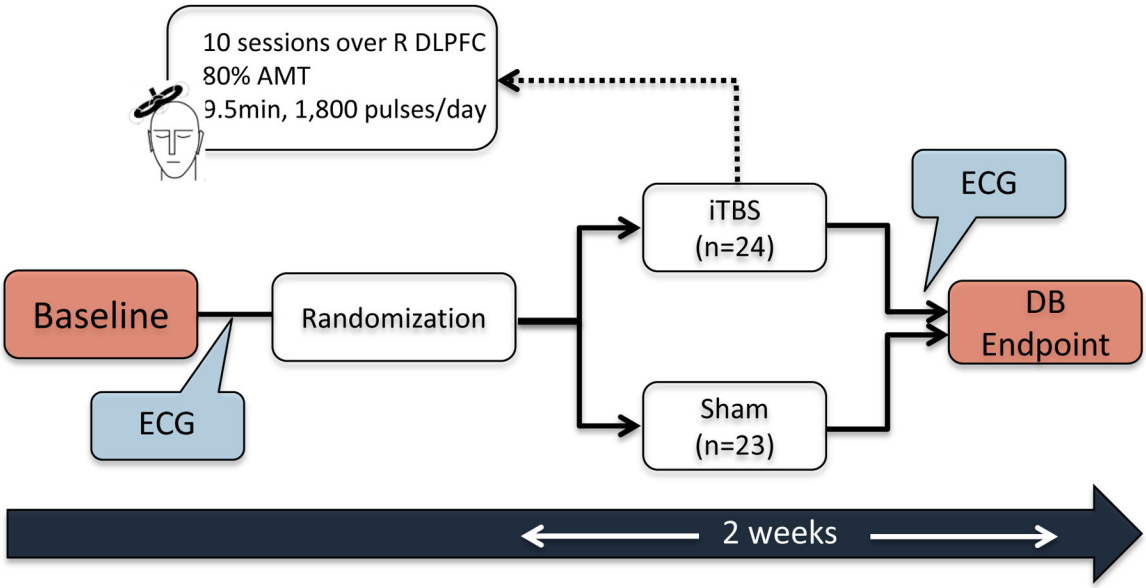
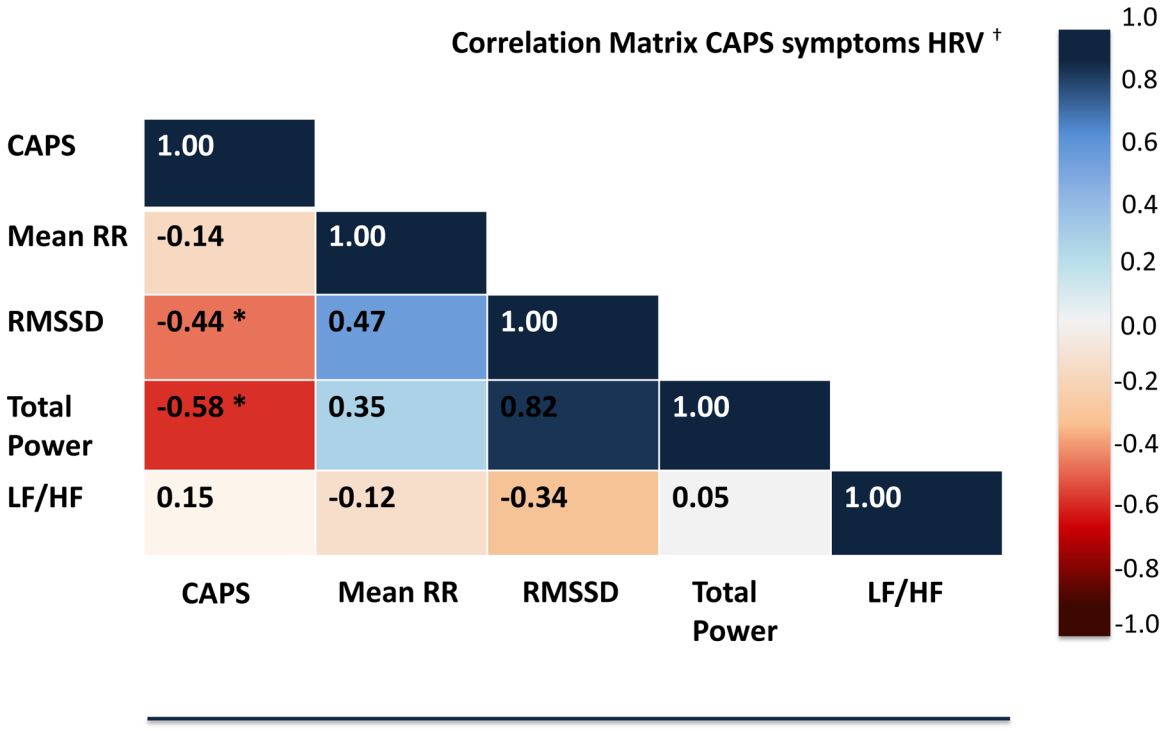


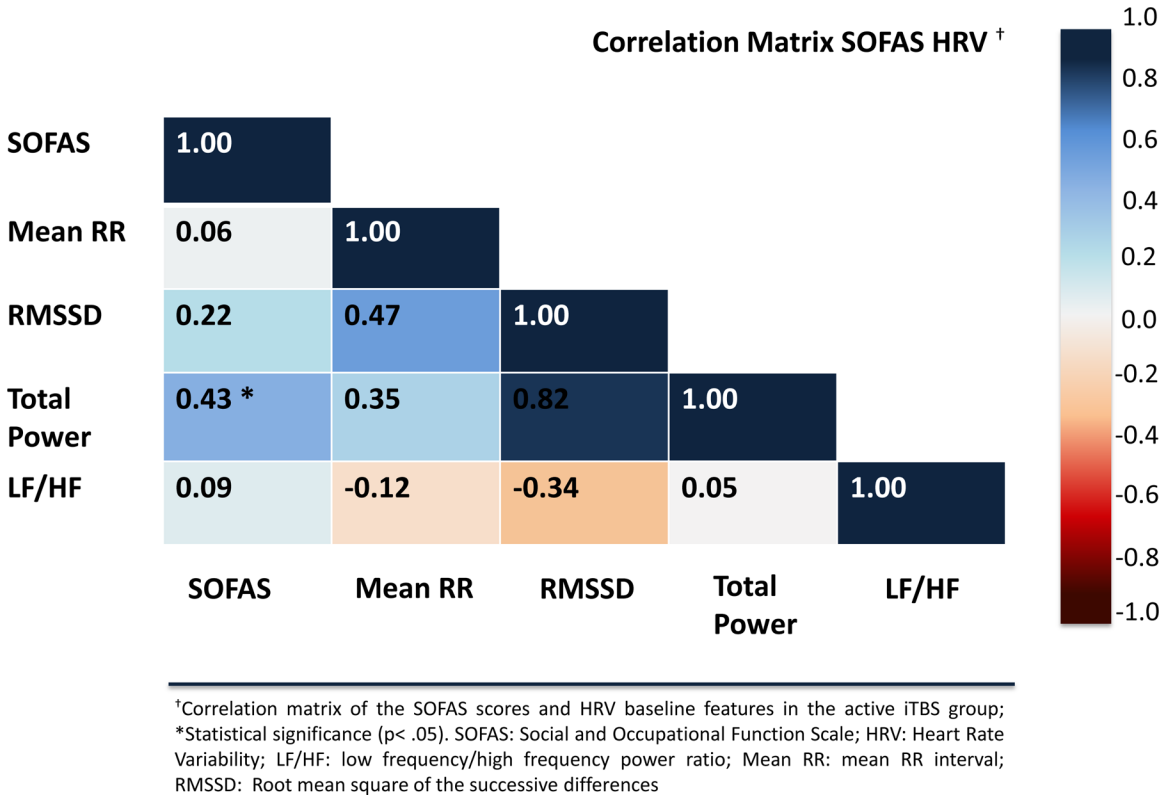
Figure 1.
Study procedures diagram



†Correlation matrix of the CAPS symptoms scores and HRV baseline features in the active iTBS group; *Statistical significance (p< .05). CAPS: Clinician Administered PTSD Scale for DSM-5; HRV: Heart Rate Variability; LF/HF: low frequency/high frequency power ratio; Mean RR: mean RR interval; RMSSD: Root mean square of the successive differences

Figure 2.

Correlation matrix of the CAPS symptoms scores and HRV features in the active iTBS group



†Correlation matrix of the SOFAS scores and HRV baseline features in the active iTBS group; *Statistical significance (p< .05). SOFAS: Social and Occupational Function Scale; HRV: Heart Rate Variability; LF/HF: low frequency/high frequency power ratio; Mean RR: mean RR interval; RMSSD: Root mean square of the successive differences

Figure 3.
Correlation matrix of the SOFAS scores and HRV features in the active iTBS group

Table 1.

Demographic and clinical features at baseline

	iTBS (n=24)		Sham (n=23)	
Age (years) †	49.04 (12.84)		52.13 (11.53)	
	n	%	n	%
Female sex (%)	5	20.83	3	13.04
Race (%) ‡				
African American	0	0	1	4.35
American Indian/Alaska Native	1	4.17	0	0
Multiracial	2	8.33	1	4.35
White	21	87.50	19	82.61
Ethnicity ‡				
Not of Hispanic origin	22	91.67	21	91.3
Hispanic origin	0	0	2	8.70
Education ‡				
Less than high school	1	4.17	1	4.35
High school or equivalent	2	8.33	4	17.39
Some college	10	41.67	7	30.43
Trade or vocational degree	3	12.50	0	0
Bachelor's degree	2	8.33	7	30.43
Advanced degree and/or education beyond college	2	8.33	3	13.05
Employment Status ‡				
Full time	6	25.00	4	17.39
Part time	0	0	2	8.70
Unemployed	10	41.67	9	39.13
Retired	6	25.00	7	30.43
Service connected disability (mental health)	14	58.34	15	65.21
Military History				
Branch ‡				

	iTBS (n=24)		Sham (n=23)	
Army	7	29.17	7	30.43
Navy	8	33.33	5	21.74
Marines	2	8.33	1	4.35
Air Force	0	0	3	13.04
Clinical Variables [§]				
PTSD Symptom Severity				
CAPS-5 Score	48.34 (9.97)		46.96 (10.89)	
PCL-5 Score	49.46 (9.55)		49.22 (11.28)	
Social/Occupational Function & Quality of Life				
SOFAS Score	44.50 (13.39)		44.74 (15.57)	
Depressive Symptom Severity				
IDSSR Score	42.58 (12.10)		38.83 (11.95)	

[†]Age presented as mean ± standard deviation (SD);

[‡]Totals do not sum up to 100% due to participants non-response;

[§]Clinical variables described as mean ± SD; CAPS-5, Clinician Administered PTSD Scale for DSM5; IDSSR, Inventory of Depressive Symptomatology, Self-Report; iTBS, Intermittent Theta-burst Stimulation; PCL-5, PTSD Checklist for DSM-5; PTSD, Posttraumatic Stress Disorder; SD, Standard deviation; SOFAS, Social and Occupational Function Scale.

Table 2.

HRV outcomes at baseline and at the end of double-blind period, comparing within and between active iTBS vs. sham in PTSD (195 seconds epoch)

HRV Variables	Baseline† (mean/SD)	Pre (mean/SD)		Post (mean/SD)		Within-groups (p) ‡		Between-groups § (p)
		iTBS	Sham	iTBS	Sham	iTBS	Sham	
PNS index	−.96 (1.16)	−.94 (1.36)	−.99 (.90)	−.98 (1.00)	−.92 (.89)	0.43	0.26	0.60
SNS index	2.47 (2.41)	2.70 (1.92)	2.20 (2.93)	2.12 (1.95)	2.18 (2.86)	0.08	0.88	0.82
Time-domain								
Mean RR (ms)	827.37 (122.99)	812.13 (109.93)	845.83 (137.94)	830.09(132.13)	868.28 (136.56)	0.25	0.15	0.30
Mean HR (bpm)	74.18 (11.71)	75.16 (10.02)	72.99 (13.67)	74.01 (11.52)	71.00 (13.14)	0.17	0.22	0.30
RMSSD (ms)	22.52 (28.41)	25.04 (37.28)	19.46 (11.05)	21.30 (16.80)	17.70 (11.45)	0.50	0.57	0.64
Stress Index	21.62 (11.48)	22.90 (10.27)	20.07 (12.91)	19.58 (9.26)	20.88 (12.71)	0.07	0.57	0.52
Frequency-domain								
VLF (ms^2)	38.90 (48.49)	21.12 (18.16)	60.42 (63.72)	35.27 (33.69)	35.09 (27.98)	0.04 *	0.16	0.99
LF (ms^2)	378.17 (997.19)	478.20 (1342.56)	257.08 (183.58)	403.33 (879.97)	319.99 (478.06)	0.85	0.54	0.82
HF (ms^2)	312.38 (933.09)	422.66 (1252.52)	178.88 (177.10)	186.34 (194.10)	134.90 (155.21)	0.82	0.64	0.66
Total Power (ms^2)	731.91 (1469.38)	926.39 (1962.93)	496.48 (318.92)	625.08 (1015.02)	490.01 (588.17)	0.77	0.47	0.69
LF/HF	2.82 (3.13)	2.43 (2.83)	3.28 (3.48)	3.30 (4.33)	3.76 (5.58)	0.43	0.09	0.92
EDR (Hz)	.25 (.05)	.26 (.05)	.24 (.06)	.26 (.06)	.23 (.05)	0.60	0.88	0.24

† Baseline HRV parameters of all veterans included in the analysis.

‡ P-values correspond to Wilcoxon matched-pairs signed rank test.

§ P-values correspond to Mann-Whitney U test.

* Statistical significance (p< .05). HF, High frequency; HR, Heart rate; HRV, Heart rate variability; LF, Low frequency; LF/HF, Low frequency/high frequency ratio; PNS, Parasympathetic nervous system; PTSD, posttraumatic stress disorder; RMSSD, Root mean square of the successive differences; RR, RR interval; SD, Standard deviation; SNS, Sympathetic nervous system; TP, total power; VLF, Very low frequency.