Cardiovascular differences between sham and active iTBS related to treatment response in MDD

Tabitha A. Iseger a, b, Martijn Arns a, b, c, Jonathan Downard d, e, Daniel M. Blumberger e, f, Zafiris J. Daskalakis e, f, Fidel Vila-Rodriguez g, *

* Research Institute Brainclinics, Nijmegen, the Netherlands
b Dept. of Experimental Psychology, Utrecht University, Utrecht, the Netherlands
c NeuroCare Group, Munich, Germany
d MRI-Guided RTMS Clinic and Krembil Research Institute, University Health Network, Toronto, Canada
e Department of Psychiatry, Faculty of Medicine, University of Toronto, Canada
f Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Canada
g Non-Invasive Neurostimulation Therapies (NINET) Laboratory, University of British Columbia, Vancouver, BC, Canada

Article history:
Received 2 May 2019
Received in revised form 21 September 2019
Accepted 28 September 2019
Available online xxx

Abstract
Background: Heart rate in MDD is often dysregulated, expressed in overall higher heart rates (HR) and lower heart rate variability (HRV). Interestingly, HR decelerations have been reported after stimulation of the DLPFC using rTMS, suggesting connectivity between the DLPFC and the heart. Recently, a new form of rTMS called theta burst stimulation (TBS) has been developed. One form of TBS, intermittent TBS (iTBS), delivers 600 pulses in just 3 min.

Objective: To determine whether iTBS aimed at the DLPFC also affects HR, blood pressure and HRV, and whether these cardiac responses at baseline are associated with treatment response.

Methods: ECG and blood pressure were recorded during both sham and active iTBS in 15 MDD patients, over 30 sessions.

Results: We found a significantly larger HR deceleration for active iTBS, compared to sham, within the first minute of stimulation. Also, a trend towards an association between HR deceleration and treatment response was found, explaining 26% of the variance. Furthermore, several measures of heart rate variability were significantly higher during iTBS stimulation over sessions, compared to sham. Both systolic and diastolic blood pressure, were lower during active iTBS.

Conclusion: Active iTBS applied to the DLPFC is able to transsynaptically modulate the autonomic nervous system, in particular the parasympathetic branch, similar to what has been found for conventional rTMS methods. Furthermore, data suggest that the larger the autonomic changes induced at baseline, the better the clinical response after 30 sessions of iTBS.

© 2019 Elsevier Inc. All rights reserved.

Introduction

Neuromodulation treatments such as repetitive Transcranial Magnetic Stimulation (rTMS), transcranial Direct Current Stimulation (tDCS) and Deep Brain Stimulation (DBS) show promising clinical benefit in Major Depressive Disorder (MDD) [1–5]. These neuromodulation treatments target key structures that are affected in depression such as the dorsolateral prefrontal cortex (DLPFC), the dorsomedial prefrontal cortex (DMPFC) and the subgenual anterior cingulate cortex (sgACC). Stimulation of these regions is associated with symptom improvement in MDD [4,6,7]. Recent insights into how these neuromodulation treatments work suggest network connectivity between the DLPFC and (sg)ACC may mediate clinical response to these treatments [8,9]; of note, the sgACC is a brain area involved in cortical modulation of the autonomic nervous system known as the central autonomic network (CAN) [10]. Interestingly, several studies have also reported HR deceleration after stimulation of the DLPFC using rTMS and tDCS [11], suggesting that there is indeed a connection between the DLPFC and autonomic network.
is further known that heart rate in MDD is often dysregulated, expressed in overall higher HR and lower heart rate variability (HRV) \([12–14]\), which has been reported to be normalized after neuromodulation treatment \([15]\). In addition, recent studies have shown that heart rate decelerations may be used as a functional outcome measure for verifying correct targeting of the depression network, called Neuro-Cardiac-Guided TMS (NCG TMS) \([16]\), meaning that stimulation of the DLPFC results in acute heart rate decelerations as well.

Currently, naturalistic remission rates to rTMS are around 37% \([17]\), and can be higher when combined with psychotherapy 56% \([18]\). Improvements in TMS protocols that include the spacing of sessions (accelerated TMS), frequency of stimulation or improvement of localization of treatment targets may enhance outcomes. A recent study demonstrated equivalent efficacy for iTBS compared to 10 Hz TMS in reducing depressive symptoms in patients with depression, leading to both FDA approval in the United States and CE marking in Europe \([19]\). Due to its rapidity of administration, iTBS may be particularly well-suited to NCG TMS in clinical settings.

In the current study, ECG and blood pressure were recorded during both sham and active iTBS. It was hypothesized that 1) subjects would show heart rate decelerations during active iTBS, but not during sham treatment, similar to conventional 10 Hz TMS, and in line with the results reported by Iseger et al. \((2017)\) \([16]\); and 2) MDD patients with the largest HR decelerations at the first session of active iTBS, would be more likely to respond to treatment; and 3) Since the hypothesized network should synchronically activate the vagus nerve, general parasympathetic activation is expected, reflected as reduced heart rate, increased heart rate variability (HRV) and decreased blood pressure (BP). These parameters were also assessed repeatedly over the course of treatment, in order to determine whether these would normalize over time and/or are associated with treatment response.

**Methods**

**Study design and participants**

15 MDD patients between 20 and 54 years old who had a MINI International Neuropsychiatric Interview-confirmed diagnosis of major depressive disorder, as a single or recurrent episode, were included. Patients met inclusion criteria if their current episode showed a 17-item Hamilton Rating Scale for Depression (HRSD-17) score of at least 18, showed no clinical response to an adequate dose of an antidepressant (based on an antidepressant treatment history form score of more than 3 in the current episode) or were unable to tolerate at least two separate trials of antidepressants of inadequate dose and duration, and they had received a stable antidepressant regimen for at least 4 weeks before treatment, which continued during treatment. Exclusion criteria included substance abuse or dependence in the past 3 months, active suicidal intent, pregnancy, bipolar disorder, any psychotic disorder or current psychotic symptoms, previous rTMS treatment, a lifetime history of non-response to an adequate course—i.e. a minimum of eight treatments—of electroconvulsive therapy, personality disorder deemed to be the primary pathology, an unstable medical illness, substantial neurological illness, abnormal serology, or the presence of a cardiac pacemaker, intracranial implant, or metal in the cranium. Participants were also excluded if they were taking more than 2 mg lorazepam (or equivalent) or any anticonvulsant or if more than three adequate antidepressant trials had failed (determined by antidepressant treatment history form). Ethics approval was granted by the research ethics board at University of British Columbia and Vancouver Coastal Health Authority. All participants provided written, informed consent. Participants were a subsample taken from a clinical trial (ClinicalTrials.gov NCT02729792).

**Procedures**

Before treatment, participants underwent high resolution anatomical MRIs, and during the first treatment session real-time MRI-guided neuronavigation with a Visor neuronavigation system (ANT Neuro, Enschede, Netherlands) was used for coil positioning. The remainder of treatment sessions used the MRI guided spot without real-time neuronavigation \([20]\). The left dorsolateral prefrontal cortex target was located in each participant by reverse co-registration from the MN152 stereotaxic coordinate \((x\sim 38, y\sim -44, z\sim -26)\), which was previously identified as optimal on the basis of clinical outcomes and whole-brain functional connectivity \([9]\).

rTMS was delivered with a MagPro X1000, equipped with a B70 fluid cooled coil and high performance cooler (MagVenture, Farum, Denmark). Each participant’s resting motor threshold (RMT) was determined by use of visual observation in accordance with standard methods \([21,22]\). iTBS was delivered at 120% RMT identical to the settings described in a recent non-inferiority clinical trial comparing iTBS to 10Hz \([19]\).

Subjects were randomized to two treatment arms receiving four treatment sessions in blocks of two sessions 1 h apart. Specifically, Arm A: [block 1: Session1-sham, session 2-active], (block 2: session 1 active, sham) or Arm B [block 1: Session1-sham, session2-sham active], (block 2: session1-active, session2-active]. The first two and last two sessions were directly following each other, but between the first block and the second block there was a pause of 54 min. In other words, 50% of the sessions were sham and the other 50% of the sessions were active. Thus, all subjects received both sham and active stimulation. iTBS was delivered at the same site and intensity (120% RMT), differing only in stimulation pattern and total number of pulses (triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; total duration of 3 min 9 s). Treatment comprised 30 treatment days (on weekdays), each with 2 sessions spaced by 1 h as described above. A sham (internally-shielded) coil without electrical stimulation was positioned over the vertex for the sham stimulation, to avoid differences in sensation that are universally perceptible between active versus sham stimulation when both are delivered over DLPFC in the same subject, even when ‘sham’ electrodes are used. Subjects were told that the sensation would be different because of the different areas sites of stimulation; the design ensured that all subjects would receive 2 sessions of sham and 2 of active iTBS on each day. An HRSD-17 score was determined by trained research staff at baseline, after every five treatments, and 1 week, 4 weeks, and 12 weeks after treatment. Participants missing scheduled sessions due to illness or scheduling conflicts received additional sessions at the end of the treatment course to achieve the intended course length. However, participants missing 4 consecutive treatment days were withdrawn.

**Physiological data acquisition**

Physiological data was recorded on treatment days 1, 10, 20 and 30 during all four sessions of that day. All physiological recordings were obtained with a Biopac MP 150 system (Biopac Systems Inc., Goleta, CA, USA) comprising modular hardware and “AcqKnowledge” software. The ECG100C Electrocardiogram Amplifier module records electrical activity generated by the heart on one channel ECG signal using three electrodes placed on the participant’s arms and left ankle. To measure continuous NIBP signal, the non-invasive NIBP100D system (CNP Monitor 500; CNSystems Medizin technik AG, Graz, Austria) was used. The CNAP device is easy to set-up and
use one double-finger sensor that is comfortable to wear for measuring blood pressure.

**Data processing**

ECG data were time locked with the TMS pulses and segmented onto the actual stimulation period (i.e 189 s). R waves (i.e. the main spikes observed in the graphical deflections observed in an ECG) were detected in the ECG and converted to a RR tachograph, which is a graph of the numerical value of the RR-interval (i.e., the interval between two R peaks) and time, using Kubios software. Here, medium artefact correction was applied, correcting possible occurrences of ectopic beats or other outliers. The recording was divided into 4 segments: the whole 189 s, since the heart rate changes might be more pronounced at the start of recording. For each segment, the mean RR intervals and the slope of the RR-interval data were calculated, as measure of RR interval change against time. HRV variables were obtained over the whole 189 s, since HRV variables are more reliable in recordings of longer duration. Within the frequency domain, absolute very low frequency power (VLF: 0.0033–0.04 Hz), low frequency power (LF: 0.04–0.15 Hz) and high frequency power (HF: 0.15–0.4 Hz) were calculated in ms², as well as the ratio of low frequency power to high frequency power (LF/ HF). The standard deviation of the NN (RR) intervals (SDNN) and root mean square of the successive differences (RMSSD) were taken within the time-domain. The natural logarithm (LN) was calculated for the HRV variables, similar to Iseger et al. (2018) in order to obtain a normal distribution. Furthermore, mean blood pressure, systolic blood pressure and diastolic blood pressure were measured over the whole 189 s of which also the LN was calculated to meet statistical assumptions of normal distribution. For all variables the two sham sessions were averaged per individual as well as the two active sessions.

**Statistical analysis**

In the first part, data were analyzed in a blinded fashion, where stimulation type (sham or real) was not known to the processing analysts (TAI and MA). RR-interval waveforms were visually inspected for RR interval lengthening and the primary outcome measure was defined in this blinded stage. After unblinding, sham and active TMS were compared using repeated measures ANOVA with Stimulation Type (sham or active) as within-subject factors. Paired and one-sample t-tests were performed. Discriminant analysis was used to predict whether a session was active or sham based on the obtained outcome measures from the first analysis. Secondly, after the data was unblinded and the primary outcome measure for measuring RR interval changes was set, further analyses were performed. Sham iTBS slopes were extracted from active iTBS slopes, creating slope difference scores which were correlated to HRSD difference scores, in order to investigate whether heart rate decelerations during session one could predict treatment outcome.

In addition, RR interval change, mean RR, HRV and BP were analyzed over Sessions, in order to investigate whether the variables are state- or trait-related, using repeated measures ANOVA with both Session and Stimulation Type as a within-subject factors. When a significant interaction was obtained, analyses proceeded to univariate ANOVA to investigate the effects over Sessions for Stimulation Type separately.

**Results**

HRV and blood pressure data were available for 15 MDD patients (5 males) with a mean age of 32.0. One subject withdrew consent treatment before day 5 due to lack of effect, and no further data was available. At baseline mean HRSD score was 21.72 compared to 11.57 at end of treatment (in 14 patients) (Table 1).

Analysis was initially performed blinded to treatment condition. By visually inspecting the data, subjects showed pronounced differences between recordings, mainly visible in the increased variation in RR interval length, but also the slope of RR interval lengthening over the first minute. Since parasympathetic responses are fast, the largest changes were expected in the first 30–60 s as observed in the blinded data of stimulation (Fig. 1).

Thus, the slope of RR intervals of the first 30, 45 and 60 s were analyzed with a repeated measures ANOVA with Timeframe and Stimulation Type as within subject factors. This resulted in a main effect of Stimulation Type (F(1,12) = 9.514, p = .009), but also a main effect of Timeframe (F(3,10) = 11.9, p = .001). Paired t-test between sham and active stimulation indicated that the RR change was significantly larger for active iTBS with large effect sizes (Cohens’ d), compared to the sham condition: 30s (t(12) = 2.284; p = .041; d = −0.5); 45s (t(12) = −3.499; p = .004, d = −1.2) and 60s (t(12) = −3.637; p = .003; d = −1.3). When analyzing the slopes of the whole recording there was no significance for sham nor active stimulations and also there was no difference between the two, as expected (Fig. 2, Table 2).

Separate investigation per Timeframe indicated that all slopes significantly deviated from zero, for active iTBS: 30s (t(14) = 4.074; p = .001); 45s (t(14) = 5.552; p = .001); 60s (t(14) = 4.717; p < .001), but also for sham stimulation: 30s (t(12) = 3.129; p = .009); 45s (t(12) = 3.334; p = .006) and 60s (t(12) = 2.551; p = .025).

**Discriminant analysis**

A discriminant analysis was performed on the slopes of the RR interval plots to assess their predictive value in distinguishing active from sham iTBS. The slope of the first 60 s and the slope of the first 45 s achieved significant discrimination of the two conditions: 90.9% and 81.8% accuracy, respectively (Table 2), indicating marked effects of real-iTBS on HR changes over a short 30–60 s timeframe.

The RR interval slope difference between sham and active iTBS was used to predict treatment outcome at the end of the course. A non-statistically significant trend was obtained between the difference in slope of the first 30 s and HRSD difference scores (r(11) = 0.507, p = .092), explaining 26% of the variance. None of the other variables correlated with HRSD change (Fig. 3).

**Treatment effects: active vs sham iTBS over time**

**Mean RR**

Repeated measures ANOVA with Stimulation Type (sham vs. active) as a between subjects factor and Session (ie. measurements on day 1, 10, 20 and 30 of the treatment) as a within subjects factor resulted in a significant main effect of Stimulation Type (F(1,18) = 45.870, p = .001, d = 1.062) but no main effect of Session. Thus, RR interval lengthening (lower heart rates) occurred consistently during active iTBS stimulation, and this effect persisted across sessions (Fig. 4G).
Within the first 30 s, a main effect was found for Stimulation Type \((F(1, 8) = 12.61, p = .007, d = 1.325)\), as well as the first 45 s \((F(1, 8) = 12.81, p = .007, d = 1.303)\) and 60 s \((F(1, 8) = 11.36, p = .010, d = 1.364)\), where larger heart rate decelerations were found during active iTBS. For none of the timeframes an interaction with session was found, thus, there were no changes over time.

**Heart rate variability**

A main effect of Stimulation Type was found for low frequency power \((F(1,8) = 12.475, p = .008, d = -1.156)\), high frequency power \((F(1,8) = 9.232, p = .016, d = -0.559)\), SDNN \((F(1,8) = 10.148, p = .013, d = -0.805)\), RMSSD \((F(1,8) = 13.449, p = .006, d = -0.671)\), and marginally for the low to high frequency ratio \((F(1,8) = 4.334, p = .071, d = -0.406)\). None of the HRV variables changed significantly over Sessions and all HRV variables were found to be higher during active stimulation compared to sham stimulation. Hence, there were no changes across sessions, only acute effects of stimulation in every session (Fig. 4A–F).

**Blood pressure**

Since there was no predefined hypothesis of how fast blood pressure changes would appear, a repeated measures ANOVA with both Timeframe and Stimulation Type as within subject factors was used. This showed a main effect of Stimulation Type over sessions \((F(1,8) = 10.927, p = .011, d = 1.079)\), showing that blood pressure was significantly lowered during active stimulation. This was not more prominent in one of the different timeframes \((F(3,6) = 0.459, p = .721)\). The difference was not attributable to either systolic or diastolic pressure, both lowered significantly during active stimulation (Fig. 4H–J).

**Discussion**

This study examined the effect of iTBS on cardiovascular parameters such as heart rate, heart rate variability and blood pressure. As hypothesized, active iTBS led to significantly larger heart rate decelerations than sham iTBS. This difference was readily detectable even in the first 30–60 s of the first treatment session. More importantly, heart rate decelerations could successfully differentiate between sham and active iTBS with very high accuracy (>91%), demonstrating the profound influence of iTBS on HR.

These findings illustrate the ability to use heart rate as a direct outcome measure to verify target engagement for rTMS during treatment, via the methodology we have previously described as Neuro-Cardiac-Guided TMS (NCG-TMS), as described earlier in Iseger et al. (2017) [16] that were replicated in an independent samples as well (Iseger et al. (2019; under review)). HR decelerates more during active iTBS, compared to sham stimulation. Although the original NCG TMS method was based on 10 Hz TMS, we now demonstrate that iTBS has similar or even more pronounced effects on heart rate. As an illustration, 1 min of iTBS led to an average heart rate deceleration of 8.36 BPM, while 3 rounds of 5s 10 Hz TMS (original NCG-TMS method) applied to the DLPFC location led to an average deceleration of 1.85 BPM (unpublished results from Iseger et al. (2017)). Furthermore, we showed an association between heart rate decelerations and treatment response, which has not

---

**Table 1**

Demographic characteristics of participants.

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 15))</th>
<th>Males ((n = 5))</th>
<th>Females ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>32.00 (8.90)</td>
<td>29.00 (8.16)</td>
<td>33.50 (9.29)</td>
</tr>
<tr>
<td><strong>HRSD baseline</strong></td>
<td>21.72 (4.61)</td>
<td>19.40 (1.14)</td>
<td>22.90 (5.28)</td>
</tr>
<tr>
<td><strong>HRSD post treatment</strong></td>
<td>11.57 (5.77)</td>
<td>14.25 (3.21)</td>
<td>10.50 (6.35)</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>17.80 (8.56)</td>
<td>14.60 (8.792)</td>
<td>19.40 (8.43)</td>
</tr>
<tr>
<td><strong>Length of current episode (months)</strong></td>
<td>47.53 (57.48)</td>
<td>29.20 (18.78)</td>
<td>56.70 (68.58)</td>
</tr>
</tbody>
</table>

RR Interval Change: Active vs. Sham iTBS on first session.
Predicting treatment response. It has been investigated before. The trend towards a significant correlation was found demonstrating that within 30 s, the larger the slope of RR intervals for active iTBS compared to sham, the larger the HRSD change. Thus, larger heart rate decelerations were associated with better treatment response. This effect was seen already during the first session. Although in this small sample not significant, the explained variance was quite high. It has to be noted that both sham and active iTBS led to significant heart rate decelerations, when compared to zero, but that these were significantly larger for active iTBS. This suggests that there might be some non-specific habituation effect during iTBS stimulation, expressed as an initial higher HR, subsequently leading to lower heart rates, however active iTBS provides additional HR deceleration with a large effect size (d > 1.3) difference, compared to sham stimulation.

Furthermore, blood pressure and most HRV variables were significantly different between sham and active iTBS sessions, but no changes were found over time. Both systolic and diastolic blood pressure were lower during active stimulation. The effects of non-invasive brain stimulation on blood pressure were reviewed by Sampaio et al. (2012) [23]. In short, one study found in 6 healthy subjects a trend for active iTMS decreasing blood pressure [24], as well as for dCS [25]. Another study found only a decreasing effect for the left hemisphere, but not the right hemisphere [26], just in one session. A recent meta-analysis reported a small effect of iTMS on blood pressure [11], although this study did not differentiate between motor strip and DLPFC stimulation, left or right sided stimulation, and frequency. Blood pressure during iTBS has previously not been investigated, but it must be considered possible that iTBS has a stronger effect on the cardiovascular system than other NIBS methods, similar to the more pronounced effects observed for iTBS vs. 10 Hz TMS on HR [16]. Furthermore, the effects over time have not been investigated before. The current study shows that, although BP is different between sham and active iTBS, there are no changes over time.

Regarding HRV variables, the increases in RMSSD and SDNN indicate higher heart rate variability during active stimulation. LF power is often associated with sympathetic tone, while HF is associated with parasympathetic tone [27]. In this study, both LF and HF power increased during active stimulation, suggesting that both the sympathetic and parasympathetic pathways increase signaling. However, this is often criticized as LF may not truly reflect sympathetic tone [28,29]. HF has been related to respiratory sinus arrhythmia (RSA) and is a measure of the natural variation occurring in the HR during a breathing cycle [30]. However, during slow respiration, vagal activity can easily generate oscillations that cross over into the LF band, for example during slow paced breathing, thereby suggesting LF/HF does not adequately reflect the balance between sympathetic and parasympathetic activity, because LF power represents both sympathetic and parasympathetic activity. Thereby, it may be possible that in fact only parasympathetic signaling increased as a result of active iTBS stimulation. This is strengthened by the fact that there is no significant difference in VLF power, which is also thought to represent sympathetic activity, although this too remains unclear [31]. However, the validity of the VLF power can be questioned since our recordings where only 189 s long, while at least 303 s are required in order to have the lower frequencies adequately assessed. In the current data, frequencies between 0.0033 and 0.0053 Hz could not be scored accurately, which, although is a small bandwidth, may have led to discrepancies in the results. Nevertheless, one study showed shorter VLF recordings still highly correlate with 5 min recordings, thus the shorter VLF recordings may give a good indication [32].

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Sham (Mean ± st.dev)</th>
<th>Active (Mean ± st.dev)</th>
<th>Statistics</th>
<th>Discriminant analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR slope 30s</td>
<td>1.091 (1.257)</td>
<td>2.899 (2.443)</td>
<td>t = -2.284, p = .041, d = -.931</td>
<td>81.8%, Wilks' lambda: 0.578, p = .112, chi-square: 4.380</td>
</tr>
<tr>
<td>RR slope 45s</td>
<td>0.782 (0.846)</td>
<td>2.154 (1.366)</td>
<td>t = -3.499, p = .004, d = -1.207</td>
<td>81.8%, Wilks' lambda: 0.384, p = .022, chi-square: 7.657</td>
</tr>
<tr>
<td>RR slope 60s</td>
<td>0.463 (0.654)</td>
<td>1.716 (0.282)</td>
<td>t = -3.637, p = .003, d = -1.275</td>
<td>90.9%, Wilks' lambda: 0.287, p = .007, chi-square: 9.987</td>
</tr>
<tr>
<td>RR slope 189s</td>
<td>0.010 (0.129)</td>
<td>0.174 (0.322)</td>
<td>t = -1.857, p = .088, d = -.670</td>
<td></td>
</tr>
</tbody>
</table>

Predicting treatment response.

Please cite this article as: Iseger TA et al., Cardiovascular differences between sham and active iTBS related to treatment response in MDD, Brain Stimulation, https://doi.org/10.1016/j.brs.2019.09.016
None of the variables changed over time for the group as a whole, in contrast to the findings of Udupa et al. (2007) whom reported normalization of HRV variables after rTMS treatment [33]. It has to be noted that due to the small sample size, the power to detect such effects may be limited. As a post-hoc analyses, we related the variables to response, showing only a positive correlation for VLF power with HRSD difference scores. VLF power is associated with sympathetic activity and it has recently been shown that a reduction in relative VLF power during REM sleep was associated with improvement in HRSD [34], and at baseline predictive of treatment outcome [35], and associated with antidepressant treatment outcome [35]. However, as mentioned earlier, the validity of our VLF recordings may be questionable, indicating that these results should first be replicated with longer HRV recordings.

Fig. 4. Bar graphs showing mean values for sham (grey bars) versus active (blue bars) iTBS, for LF (A), HF (B), LF/HF ratio (C), VLF (D), RMSSD (E), SDNN (F), mean RR interval (G), blood pressure (H), systolic blood pressure (I) and diastolic blood pressure (J). All variables except VLF were significantly different between sham and active iTBS over time. Error bars represent standard error of the mean. Note that no differential effects were found across time, so these represent all acute effects to iTBS stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
A limitation of this preliminary study is the relatively small sample size. Therefore, the association with treatment response, although predicted, requires replication in a larger sample. In addition, for this study, the sham stimulation procedure targeted the vertex rather than the F3 site, leaving open the possibility that different scalp sensations could contribute to the observed differences between active versus sham stimulation. However, this possibility is less likely given that we have previously shown that even for active stimulation across a variety of different frontal sites, the HR decelerations are seen specifically with stimulation over dorsolateral regions (e.g. F3/F4), and less so over more anterior regions where the sensations of stimulation are more intense (FC3/FC4) and not at all for regions overlaying the motor cortex (C3/C4) [16]. In addition, we recently replicated this site-specificity for 10 Hz stimulation in 30 healthy controls and 33 MDD patients (Iseger et al., under review). Following CONSORT statement guidelines [36], we did not test blindness and we appreciate this choice leaves the question of blinding integrity open. Finally, the predictive value of the HR decelerations on treatment outcome trended towards, but did not reach, statistical significance; replication in a larger sample will allow a more precise estimate of the value of HR changes in predicting treatment outcome in the clinical setting.

Conclusion

iTBS appears to have the same effect on cardiac activity as conventional 10 Hz rTMS. There was a pronounced difference between sham and active iTBS for all cardiovascular measures that were used. This suggests that it may be useful to use heart rate as a direct method of verifying correct targeting of the depression network as suggested earlier [16]. Even more, iTBS might provide an improved method for NCG-TMS, since heart rate decelerations are much more pronounced, relative to 10 Hz rTMS. Other HRV measurements and blood pressure might be useful too but require longer recordings. The direction of all found effects suggest that parasympathetic signaling increases as a result of active stimulation on the DLPFC. Unfortunately, no normalization of HRV variables were found, but this may be attributed to the small sample size and the few responders and might require longer follow-up assessments.

Declaration of competing interest

MA is (unpaid) director and owner of Research Institute Brainclinics, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuro-modulation and psychophysiology, but does not receive any royalties related to these patents; Research Institute Brainclinics received funding from Brain Resource (Sydney, Australia) and neuroCare Group (Munich, Germany), and equipment support from Brainsway, Deymed, neuroConn and Magventure, however data analyses and writing of this manuscript were unconstrained. TI and MA are coinventors on a patent covering the Neuro-Cardiac-Guided TMS method (owned by neuroCare Group), but receive no royalties.

DMB has received research support from the CIHR, NIH, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd., and he is the principal site investigator for three sponsor-initiated studies for Brainsway Ltd. He received in-kind equipment support from Magventure for investigator-initiated research. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in an advisory board for Janssen.

In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the National Institutes of Mental Health (NIMH) and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

Dr. Vila-Rodriguez receives research support from CIHR, Brain Canada, Michael Smith Foundation for Health Research, Vancouver Coastal Health Research Institute, and in-kind equipment support for this investigator-initiated trial from MagVenture. He has received honoraria for participation in advisory board for Janssen.

Acknowledgements

We are grateful to research participants and research personnel at all the participating sites for their time and commitment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.09.016.

Funding source

Brain Canada Brain Canada with the support of Health Canada, Multi-investigator research initiative.

References


34. Pawlowski M. Suppression of REM sleep related heart rate variability by antidepressants at week one predicts treatment response at week four. Abstract Book IPEG Meeting Zurich; 2018. 2018.
