The dynamic role of the left dlPFC in Neurovisceral Integration: Differential effects of Theta Burst Stimulation on vagally-mediated Heart Rate Variability and cognitive-affective processing

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Abstract

Adapting to the ever-changing demands of the environment requires a complex interplay between cognitive-affective, neuronal, and autonomic processes. Vagally-mediated heart rate variability (vmHRV) is positively associated with both cognitive-affective functioning and prefrontal cortex (PFC) activity. Accordingly, the Neurovisceral Integration Model has posited a shared role of the PFC in the regulation of cognitive-affective processes and autonomic nervous system (ANS) activity. While there are numerous correlational findings in this regard, no study so far has investigated whether the manipulation of PFC activity induces changes in vmHRV and cognitive-affective processing in an inter-dependent manner. In this study, we examined the effects of continuous (cTBS) and intermittent theta-burst stimulation (iTBS) over the left dorsolateral PFC (dlPFC) on vmHRV and cognitive-affective processing within an emotional stop-signal task (ESST) in 66 participants. Our results revealed that both resting vmHRV and reactivity, at least partly, predicted cognitive-affective processing. Furthermore, we found a dampening effect of cTBS on resting vmHRV, as well as an enhancing effect of iTBS on ESST performance. Our results show no direct association between vmHRV changes and ESST performance alterations following stimulation. We interpret our results in the light of a hierarchical model of neurovisceral integration, suggesting a dynamical situation-dependent recruitment of higher-order cortical areas like the dlPFC in the regulation of the ANS. In conclusion, our results highlight the complex interplay between PFC activity, autonomic regulation, and cognitive-affective processing, emphasizing the need for further research to understand the causal dynamics of the underlying neural mechanisms.

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Abstract

Adapting to the ever-changing demands of the environment requires a complex interplay between cognitive-affective, neuronal, and autonomic processes. Vagally-mediated heart rate variability (vmHRV) is positively associated with both cognitive-affective functioning and prefrontal cortex (PFC) activity. Accordingly, the *Neurovisceral Integration Model* has posited a shared role of the PFC in the regulation of cognitive-affective processes and autonomic nervous system (ANS) activity. While there are numerous correlational findings in this regard, no study so far has investigated whether the manipulation of PFC activity induces changes in vmHRV and cognitive-affective processing in an inter-dependent manner. In this study, we examined the effects of continuous (cTBS) and intermittent theta-burst stimulation (iTBS) over the left dorsolateral PFC (dlPFC) on vmHRV and cognitive-affective processing within an emotional stop-signal task (ESST) in 66 participants. Our results revealed that both resting vmHRV and reactivity, at least partly, predicted cognitive-affective processing. Furthermore, we found a dampening effect of cTBS on resting vmHRV, as well as an enhancing effect of iTBS on ESST performance. Our results show no direct association between vmHRV changes and ESST performance alterations following stimulation. We interpret our results in the light of a hierarchical model of neurovisceral integration, suggesting a dynamical situation-dependent recruitment of higher-order cortical areas like the dlPFC in the regulation of the ANS. In conclusion, our results highlight the complex interplay between PFC activity, autonomic regulation, and cognitive-affective processing, emphasizing the need for further research to understand the causal dynamics of the underlying neural mechanisms.

Introduction

To successfully adapt to the ever-changing demands of the environment, individuals need to process environmental stimuli, both cognitively and affectively. It has been suggested that the same neuronal circuits and mechanisms involved in cognitive-affective processing contribute to the regulation of the autonomic nervous system (ANS), thus allowing an efficient and coordinated adaption on different levels (Smith et al., 2017; Thayer et al., 2009). Consistent with these assumptions, vagally-mediated heart rate variability (vmHRV), a measure of vagal regulation of the heart or so called cardiac vagal activity, has been found to correlate with cognitive and affective functioning (Appelhans & Luecken, 2006; Balzarotti et al., 2017; Magnon et al., 2022). Furthermore, higher vmHRV has been associated with higher activity of the prefrontal cortex (PFC) which displays a key node involved in cognitive, attentional, and affective processes (Thayer et al., 2012). Although these results suggest a shared prefrontal regulation of cognitive, affective, and autonomic functions, they do not allow causal inferences about potential common underlying mechanisms given their correlative nature. In this study, we used repetitive transcranial magnetic stimulation (rTMS) to clarify whether common neuronal processes within the PFC directly contribute to cognitive-affective and autonomic processing alike.

The PFC is well known for its contribution to cognitive and affective control (see e.g., Etkin et al., 2011; Miller & Cohen, 2001; Ochsner & Gross, 2005). Besides that, it has been suspected to be integrated into a neuronal network consisting of various cortical and subcortical structures regulating the ANS, termed the central autonomic network (CAN, Benarroch, 1993). The *Neurovisceral Integration Model*suggests that activity in different areas of the PFC regulates the heartbeat via GABAergic inhibitory projections to subcortical cardioacceleratory circuits of the CAN which are eventually transmitted to the heart via the vagus nerve (Thayer & Lane, 2000). Accordingly, these inhibitory projections are also involved in processes such as cognitive control and emotion regulation, leading to cognitive-affective and autonomic regulation being closely linked in adaptation to environmental demands. Supporting this suggested link, higher levels of vmHRV have been widely demonstrated to be associated with better cognitive functioning, emotion regulation and mental health (Appelhans & Luecken, 2006; Holzman & Bridgett, 2017; Magnon et al., 2022. Further support is provided by results from brain imaging studies in which higher vmHRV levels have been related to greater activity in various prefrontal areas such as the dorsolateral PFC (dlPFC) and ventromedial PFC (vmPFC) (McIntosh et al., 2020; Thayer et al., 2012). While activity in the vmPFC has been found to be positively correlated with vmHRV across situations, activity in the dlPFC appears to be correlated with vmHRV only in certain circumstances, such as when high cognitive or affective control is required (Lane

et al., 2009). While these results suggest a close relationship between vmHRV and prefrontal activity, as well as associated cognitive and affective processes, they do not allow any inferences regarding causality or direction of effects given their correlational nature. Thus, it remains to be clarified whether the link between prefrontal activity and vmHRV reflects top-down regulation of both cardiac and cognitive-affective outcomes or bottom-up processing of cardiac signals which in turn facilitates cognitive-affective processes, or even both.

Repetitive TMS has proven to be a powerful non-invasive tool for establishing causal relationships between activity in specific brain regions and behavioral and physiological outcomes by inducing long lasting changes in the stimulated cortical area and areas with functional connectivity. Theta burst stimulation (TBS) is a relatively new rTMS protocol that produces long-lasting aftereffects while having a short duration of implementation. Whereas continuous TBS (cTBS) over the primary motor cortex has been shown to suppress motor evoked potentials, intermittent TBS (iTBS) enhances motor evoked potentials (Huang et al., 2005). Thus, cTBS is assumed to inhibit the targeted cortical area by producing long-term depression-like effects, whereas iTBS is thought to produce long-term potentiation-like effects (Kirkovski et al., 2023). Previous findings suggest that the application of TBS over prefrontal areas, particularly over the left dlPFC, affects both cognitive and affective processing, with iTBS having enhancing effects (Pabst et al., 2022, Dumitru et al., 2020, Moulier et al., 2021) and cTBS having disrupting effects (see Ngetich et al., 2020, e.g., Keuper, Dellert, Junghoefer et al., 2019, Lowe, Staines, Mannochio et al., 2018, Maier, Rosenbaum, Haeussinger et al., 2018, Perach-Barzilay, Tauber et al., 2013, Rosemann, Dellert, Junghoefer et al., 2019). In addition, there is recent meta-analytic evidence that rTMS targeting the left dlPFC exerts modulatory effects on CVC (Makovac et al., 2017; Schmaußer et al., 2022). In specific, inhibition of the left dlPFC by cTBS has been found to decrease vmHRV (Era et al., 2021) whereas iTBS increases levels of vmHRV (Iseger et al., 2020). While these results demonstrate that stimulation of the left dlPFC influences cognitive and affective processing as well as vmHRV, it remains unclear whether the induced changes are directly related to each other, as posited by the*Neurovisceral Integration Model* .

As a result, this study was designed to investigate whether cTBS and iTBS applied to the left dlPFC will induce alterations in vmHRV during both resting state and cognitive-affective processing. Furthermore, the study aimed to examine TBS-induced changes in cognitive-affective processing and explore whether these changes are directly related to vmHRV alterations. Cognitive-affective processing was operationalized as the performance in an emotional Stop-Signal Task (ESST). Recently, we found that resting vmHRV , vmHRV reactivity, and the interaction between both measures significantly predicted stop-signal reaction times (SSRTs), a measure of response inhibition, in an ESST (Schmaußer & Laborde, 2023). More specifically, our results indicated higher levels of resting vmHRV to be associated with faster SSRTs, whereas on-task decreases in vmHRV predicted slower SSRTs. Interestingly, these effects of vmHRV reactivity were more pronounced in individuals with low levels of resting vmHRV, suggesting that high levels of vmHRV protect from adverse effects of vagal withdrawal on cognitive-affective processing.

In this study, we aim to replicate these findings and extend them by investigating whether TBS induced changes in vmHRV will be related to changes in cognitive-affective processing. Consequently, we hypothesized that individuals with higher resting vmHRV levels will produce faster SSRTs than individuals with low resting vmHRV levels. In addition, we expected that vagal withdrawal during performance of the ESST would predict slower SSRTs, with this effect being more pronounced in participants with low resting vmHRV levels. As we have outlined above, cTBS and iTBS have been found to exert differential effects on both cognition and vagal activity. Accordingly, we further hypothesized that the excitatory effect of iTBS over the left dlPFC would lead to both improved cognitive-affective processing (i.e., faster SSRTs) and increased levels of vmHRV during rest and during the performance of the ESST. Opposite effects were expected for cTBS given its proposed inhibitory effects. Lastly, based on the assumptions of the*Neurovisceral Integration Model* proposing a shared role of the PFC in the regulation of cognitive-affective as well as autonomic processing, we hypothesized that TMS-induced changes in vmHRV and SSRT would be directly linked to each other. In specific, we expected increases in resting vmHRV to predict fast SSRTs in the ESST and vice versa.

Methods

Participants

A required sample size of 57 was determined using G*Power . To account for the potential loss of ECG data and the possibility of a smaller TBS effect reported in the published research literature, a total of 78 participants was recruited in this study. According to the TMS safety guidelines (Rossi et al., 2021) and HRV study recommendations (Laborde et al., 2017), exclusion criteria included a history or current diagnosis of a psychiatric, neurologic or cardiovascular disorder, family history of epilepsy or hearing loss, use of psychopharmacological or cardioactive medication, pregnancy, inner ear prosthesis, recent neurosurgical procedures, pacemaker or other electronic implants, metal objects or magnetic object in the brain or around the head (only removable earrings and piercing were allowed), and skin disorders at the level of the head. Further, participants were asked to follow a normal sleep routine and to have no intense physical training the day before the experiment, to have no meal or any caffeinated drinks 2 hours before the experiment and to abstain from alcohol 24 hours before the experiment. 12 participants were excluded following the stop signal task quality control (see section 2.5.1). Two more participants were excluded after outlier detection (see section 2.5.1). The exclusion of 12 participants resulted in a final sample of 66 participants.

Experimental design and procedure

Upon arrival, all participants provided written informed consent. The local ethics committee approved the study.

At the beginning of the session, the participants were attached to ECG electrodes and completed socio-demographic questionnaires. Afterwards, participants were asked to sit and rest quietly in the sound-isolated experimental room for 10 minutes to habituate to the situation and to collect their resting baseline HRV. Participants then performed the ESST. Each participant received standardized written instructions. The investigator was available to answer any remaining questions. To become familiar with the ESST, each participant performed a practice run including 5 stop trials. After completion of the first ESST, the respective TMS protocol was applied, including determination of the resting motor threshold (RMT), determination of the left dlPFC by neuronavigation, and the specific stimulation protocol (iTBS vs. cTBS. vs. sham). Participants were assigned to the specific stimulation protocol in a randomized manner. Specifically, participants were assigned to the protocols by using an excel table, where the order of the respective protocols to apply were shuffled by a randomization algorithm. The TMS protocol was followed by a 10-minute resting period and the completion of the second ESST. Finally, the participants were debriefed about the purpose of the study and received 20 euros for their participation. See Figure 1 for an overview of the experimental procedure.

ECG recordings and analyses

VmHRV was indexed using the root mean square of successive differences (RMSSD). VmHRV was measured via electrocardiography (ECG; Faros 180°, Bittium, Kuopio, Finland), at a sampling rate of 500 Hz. Two disposable pregelled ECG electrodes (Ambu L-00-S/25, Ambu GmbH, Bad Nauheim, Germany) were used. The negative electrode was placed on the right infraclavicular fossa (just below the right clavicle). The positive electrode was placed on the left side of the chest, below the pectoral muscle in the left anterior axillary line. To extract RMSSD, we used*EDFbrowser* software (van Beelen, 2019) and the *RHRV* package in R, software version 4.0.2 (R Core Team, 2020). To remove artifacts in the ECG signals, the default settings of the*FilterNIHR()* function of *RHRV* were used. Subsequently, the ECG signals were visually inspected, and remaining abnormal beats were manually removed. The ECG signal cleared of artifacts was interpolated using the *InterpolateNIHR()* function from the *RHRV* package. To determine vmHRV during rest periods, RMSSD of the last 5 min of the 10-min habituation period and the 10-min post-TMS rest period was used. For the vmHRV reactivity scores, RMSSD was taken from the course of the respective ESST, and this value was subtracted from the baseline RMSSD. To determine the average RMSSD throughout the ESST, the RMSSD recording of the entire ESST was divided into five 5-minute periods, for each of which an RMSSD value was calculated. The average of these five RMSSD values was then calculated. A positive reactivity score indicates a decrease in vmHRV, whereas a negative reactivity score indicates an increase in vmHRV.

Theta Burst Stimulation

Both continuous and intermittent theta burst stimulation (TBS) were administered using a D70 Alpha figure-of-8 coil connected to a Magstim2 stimulator (Magstim Company Limited, Minneapolis, USA). For sham stimulation, a D70 Alpha figure-of-8 sham coil was used, which mimics the acoustic and somatosensory effects of active TBS. The Visor 2.0 Neuronavigation system (ANT Neuro, Enschede, The Netherlands) was employed to identify the left dorsolateral prefrontal cortex (dlPFC) and the corresponding scalp site where the coil was positioned during MRI-guided rTMS. Instead of utilizing individual MRI scans, a template MNI-152 scan was transformed to match the participant's head for neuronavigated rTMS. Previous research has demonstrated that this approach accurately determines the location of the left dlPFC with minimal deviation compared to the use of individual scans (Caulfield et al., 2022). The coordinates reported in Rusjan et al. (Rusjan et al., 2010) were employed to determine the position of the left dlPFC.

In the cTBS protocol, a theta burst stimulation pattern consisting of 3 pulses at 50 Hz every 200ms was administered continuously within a 40-second train, resulting in a total of 600 pulses. In the intermittent iTBS protocol, the same stimulation pattern was delivered for 2 seconds every 10 seconds for a total of 600 pulses (Huang et al., 2005). Both cTBS and iTBS were administered at an intensity of 80% of each participant's resting motor threshold (RMT). RMT was determined prior to the respective stimulation protocol and defined as the minimum intensity of TMS output required to elicit a visible motor response in the right abductor brevis muscle in 5 out of 10 consecutive attempts.

Emotional Stop Signal Task

The ESST is a modified version of the traditional stop-signal task, initially developed by Logan and Cowan (1984) to examine response inhibition by estimating so-called stop-signal reaction times (SSRT). In the ESST, participants are asked to categorize via keypress the valence of serially presented stimuli from the International Affective Picture System (IAPS, Lang et al., 2008), randomized by valence within-block, as either 'pleasant/positive' or 'unpleasant/negative' as quickly and accurately as possible (i.e., go response). Given that in our experimental design, the ESST had to be performed before and after stimulation, two equivalent versions of the ESST were designed, each containing 64 images (32 per IAPS category, i.e., negative, positive) from the IAPS. In both versions, negative and positive pictures were matched regarding arousal and intensity. Furthermore, to reach equivalence between both ESST versions, we aimed to use thematic similar images with comparable arousal and intensity levels in both versions (see supplementary files). Both versions consisted of 4 blocks with 110 trials each leading to a total of 440 trials. On a minority of the trials, a stop signal (i.e., auditory beep tone) was presented after a variable delay, instructing the participants to suppress the ongoing go response. As recommended , the task was designed so that approximately 25% of the trials (120 out of 440 trials) were stop trials, i.e., contained an auditory stop-signal. In our version of the ESST, the temporal delay of the stop signal was continuously adjusted in 50ms steps based on individual performance using a single staircase tracking algorithm. This adaptive component is essential to estimate SSRTs using the integration method (see Verbruggen et al., 2019), which requires the accuracy or the total commission errors (false alarms) to remain around 50%. The order in which the two versions of the ESST were presented to the single participants was randomized.

Data analysis

Data cleaning

As mentioned above, a total of 12 participants were excluded prior to the final data analysis. Nine participants were excluded due to poor or non-compliant performance on the ESST, following current recommendations (Verbruggen et al., 2019). Of these: (a) One participant was excluded due to a false alarm rate deviating strongly from 50% (i.e., 40%); (b) Seven participants with more than 10% go omissions in either the first or the second ESST or in both, which may lead to biased SSRT estimates given the number of trials used in this study; (c) One participant reported after the experimental procedure to have employed a strategy wherein they awaited the occurrence of a stop signal before executing the respective key presses.

Three additional participants were excluded from data analysis due to extreme values in pre-TMS SSRTs (9.39 ms; z = 4.04), pre-TMS on-task RMSSD (282.14 ms; z = 6.33), and in the change of RMSSD reactivity (74.82 ms; z = 4.11), respectively.

Statistical analysis

Vagally-mediated HRV predicting ESST performance

In order to replicate our previous findings, which suggest a significant effect of resting vmHRV, vmHRV reactivity as well as the interaction between both on ESST performance, we performed two linear regressions (for the pre and the post-stimulation ESST, respectively) in R Studio (R Core Team, 2022). To test whether resting vmHRV and vmHRV reactivity predict SSRT, resting RMSSD, the RMSSD reactivity score, as well as the interaction between both values were entered as predictors. Potential confounders, namely mean reaction time on go-trials, age, and sex were included as covariates.

Effects of theta burst stimulation on vmHRV

To analyze the effects of cTBS and iTBS compared to sham stimulation on vmHRV, we performed three linear regression models in R Studio (R Core Team, 2022). In the respective models, changes in resting vmHRV, on-task vmHRV, and vmHRV reactivity scores were included as outcome variables. These changes were operationalized as change scores calculated by subtracting the respective RMSSD values from the pre-stimulation periods from the respective post-stimulation values. As such, positive/negative change scores reflect increases/decreases of vmHRV following stimulation for resting vmHRV and on-task vmHRV. For vmHRV reactivity, positive change scores indicate a shift in vmHRV reactivity (i.e., vmHRV changes from rest to ESST performance) towards greater increase/lesser decrease during the post-stimulation period and vice versa. Participants' age and sex were included as covariates in all models. As it has been demonstrated that individual levels of state anxiety may influence the effects of TBS on vmHRV (Poppa et al., 2020), we included the results of the STAI-S as an additional covariate.

Effects of theta burst stimulation on cognitive-affective processing

To analyze the effects of cTBS and iTBS compared to sham stimulation on cognitive-affective processing (operationalized as SSRT), we performed a linear regression in R Studio (R Core Team, 2022). Changes in SSRT from the pre-TMS trial to the post-TMS trial were included as outcome variables. These changes were operationalized as change scores calculated by subtracting SSRTs from the pre-TMS trial from the corresponding post-TMS SSRTs. As such, positive change scores reflect a slowing in SSRTs following stimulation and vice versa. Participants' age and sex were included as covariates.

Changes in resting vmHRV predicting changes in SSRTs

To test our hypothesis that increases in resting vmHRV will lead to improvements in the ESST performance (i.e., faster SSRTs) and vice versa, a linear regression model was performed in R Studio (R Core Team, 2022). In this model, resting vmHRV change scores were entered as predictor, whereas SSRT change scores were entered as outcome variable. Participants' age and sex were included as covariates.

Results

The final sample comprised $N = 66$ participants (55.0 % females), with a mean age of 22.39 ($SD = 3.08$) (see table 1).

Vagally-mediated HRV predicting ESST performance (pre stimulation)

The linear regression model revealed a significant effect of sex on SSRT with males producing significantly slower SSRTs than females, $\beta = 19.31$, $SE = 9.73$, $t\ (125) = 1.99$, $p < .05$. There were no further significant effects (see Table 2).

Vagally mediated HRV predicting ESST performance (post stimulation)

The linear regression revealed a significant effect of vmHRV reactivity on SSRT with phasic increases in vmHRV during the ESST predicting faster SSRTs and vice versa, β = -4.09, SE = 1.93, t (51) = 2.12, $p < .05$. We further found the interaction between tonic and phasic CVA to exert a significant effect on SSRTs, β = 0.05, SE = 0.03, t (51) = 2.20, $p < .05$ (see Table 3). A post-hoc simple slope analysis revealed that the effect of vmHRV reactivity on ESST performance differed significantly between participants with high and low resting vmHRV (see Table 4). Compared to participants with high resting vmHRV, an increase/decrease of vmHRV during the ESST predicted faster/slower SSRTs in participants with low resting vmHRV (see Figure 2). Additionally, the results of the linear regression show a significant effect of age on ESST performance, in that higher age predicted slower SSRTs, β = 4.49, SE = 1.69,t (51) = 2.65, $p < .05$. No further significant associations were found (see Table 3).

Effects of theta burst stimulation on vmHRV

Resting vmHRV

Our linear regression model revealed a significant effect of stimulation on resting vmHRV from baseline to the post-stimulation resting period,F (2,60) = 4.42, $p < .05$. Specifically, the results show that cTBS over the left dlPFC lead to a significant decrease of vmHRV compared to iTBS, β = -9.96, SE = 4.06,t (60) = 2.45, $p < .05$, and to sham stimulation,β = -10.31, SE = 3.97, t (60) = 2.59, $p< .05$. Compared to sham stimulation, iTBS did not lead to any significant changes in resting vmHRV, β = -.35, SE = 4.22,t (60) = .08, p = .93 (see figure 3). None of the included covariates exerted a significant effect on the change of resting vmHRV.

On-task vmHRV

The results of the linear regression analysis indicate that there was no significant effect of stimulation on-task vmHRV, F (2,60) = 1.05,$p > .05$ (see Figure 4). We further found none of the included covariates to significantly predict changes in on-task vmHRV.

vmHRV reactivity

The results of the linear regression analysis revealed no statistically significant effect of stimulation on vmHRV reactivity between the first and second performance of the ESST, F (2,60) = 1.95, $p> .05$. While our results indicate that participants that received cTBS over the left dlPFC showed less vagal withdrawal/greater vagal activation during the second ESST compared with the first ESST than participants having received iTBS, β = -5.98, SE = 4.19, t (60) = 1.42, p = .16 or sham stimulation, β= -7.64, SE = 4.10, t (60) = 1.86, p = .07, this effect was not significant (see Figure 5). None of the included covariates exerted a significant effect on the change of vmHRV reactivity.

Effects of theta burst stimulation on cognitive-affective processing

Our linear regression model revealed a significant effect of stimulation on ESST performance, F (2,60) = 4.42, $p < .05$. Specifically, the results show that iTBS over the left dlPFC lead to a significant decrease in SSRTs compared to sham stimulation, β = -34.28, SE = 12.73, t (61) = 2.69, $p < .01$. Compared to sham stimulation, cTBS was also associated with shorter SSRTs, with this effect, however, not being significant, β = -23.91, SE = 12.27, t (61) = 1.95, p = .05. Changes in SSRTs did not differ between cTBS and iTBS, β = -10.37,SE = 12.59, t (61) = 0.82, p = .41 (see Figure 6). Our analyses also show a significant effect of age, with higher age predicting a slowing of SSRTs in the second compared with the first ESST, β = 4.31, SE = 1.76, t (61) = 2.45, $p< .05$. Participants' sex did not significantly predict changes in SSRTs from first to second ESST, β = -20.26, SE = 10.88, t (61) = 1.86, p = .06.

Changes in resting vmHRV predicting changes in SSRTs

Our linear regression model revealed that there were no significant associations between changes in resting vmHRV and changes in SSRTs,β = .53, SE = .39, t (62) = 1.34, p = .18 (see Table 5). As already observed in a previous linear regression model, we found a significant effect of age on the changes in SSRTs from the first to the second ESST, β = 4.18, SE = 1.85,t (62) = 2.26, $p < .05$.

Discussion

Based on a vast amount of evidence demonstrating correlations between cognitive functioning as well as emotional well-being and vmHRV, current theories in the fields of autonomic neuroscience and psychophysiology (see Laborde et al., 2018; Smith et al., 2017; Thayer & Lane, 2000) suggest the regulation of cognitive-affective and autonomic processes to be highly linked to each other. Accordingly, this connection is established by a shared neural network consisting of widespread cortical and subcortical regions. Meta-analytical evidence indicates the PFC to be a key hub within this network, showing that higher prefrontal activity is associated with higher levels of vmHRV (Thayer et al., 2012). However, since these results are correlational in nature, they do not allow to draw any causal inferences regarding the mechanism underlying these relationships. In this study, we used rTMS (i.e., cTBS and iTBS) over the left dlPFC to test the proposed links between PFC activity, cognitive-affective processing, and vmHRV. As such, the goal of the present study was threefold. First, we aimed to replicate our previous findings indicating that resting vmHRV, vmHRV reactivity as well as the interaction between both predicts cognitive-affective processing in an ESST (Schmaußer & Laborde, 2023); second, to investigate the effects of cTBS and iTBS on cognitive-affective processing as well as on resting vmHRV, vmHRV during performance of the ESST, and vmHRV reactivity; and third, to examine whether stimulation-induced changes in vmHRV directly predict changes in cognitive-affective processing operationalized as SSRT.

In regards of our assumptions concerning the predictive value of resting vmHRV and vmHRV reactivity in relation to cognitive-affective processing, the results of this study provide partial support for our hypotheses. While there were no significant associations between neither resting vmHRV nor vmHRV reactivity and task performance in the first ESST trial (see Table 2), such links could be found for the execution of the ESST after stimulation (see Table 3). As such, we found that vagal withdrawal during the execution of the ESST after stimulation was associated with slower SSRTs, whereas increase of vagal activity predicted faster SSRTs. Decreases of vmHRV, as a marker of vagal withdrawal, have been widely associated with increased arousal as part of the physiological fight or flight response (Appelhans & Luecken, 2006; Hildebrandt et al., 2016). In line with our results, previous research indicates that increased arousal (e.g., as a consequence of acute stress or anxiety) leads to increased early sensory processing (Shackman et al., 2011) as well as to a more sensitive, though relatively indiscriminate, processing of biologically salient stimuli within the amygdala (van Marle et al., 2009). Employing a predictive coding approach, Cornwell et al. (2017) suggest that heightened arousal increases primary cortical excitability and decreases prefrontal feedback modulation (i.e., decreasing precision of prior goal representations), thereby amplifying prediction errors. Consequently, sensory-perceptual processes may depend exclusively on local stimulus variations, supporting a rapid and direct sequence between detection and response to potentially threatening stimuli. However, according to Cornwell et al., (2017) these mechanisms, though promoting self-preservation under dangerous conditions, may have profound, downstream effects on cognitive processes that rely on more complex perceptual processing and controlled behavioral responding, such as working memory and response inhibition. Increases in vmHRV, on the other hand, may be associated with increases in the precision of goal representations, thereby facilitating cognitive processes critical for goal-directed behavior, such as working memory and response inhibition.

As hypothesized, effects of vmHRV reactivity on ESST performance were more pronounced in participants showing low levels of vmHRV at rest compared to those with high levels of resting vmHRV. Given that, contrary to our expectations, higher resting vmHRV was not found to be linked with faster SSRTs, our results suggest that higher resting vmHRV may contribute to enhanced cognitive processing stability under demanding situations rather than predicting a heightened degree of goal-relevant processing per se. These findings are in line with recent evidence from Spangler and MCGinley (2020) who found that higher resting vmHRV was not associated with mean inhibition performance in a stroop task, but with performance stability across different stroop conditions including different kinds of emotional auditory distractors.

Another aim of this study was to investigate the effects of two rTMS protocols, namely cTBS and iTBS, on both vmHRV and cognitive-affective processing. Based on an extensive theoretical background suggesting

the role of the PFC in regulating autonomic processing (Smith et al., 2017; Thayer et al., 2009), as well as recent meta-analytic evidence (Makovac et al., 2017; Schmaußer et al., 2022), we hypothesized that increasing the excitability of the left dlPFC by iTBS will lead to increased vmHRV at rest and during task performance. Given the supposed inhibitory effects of cTBS, we expected the use of cTBS to produce opposite outcomes. While we found no effects of stimulation on neither on-task vmHRV nor vmHRV reactivity during task performance, a significant effect of stimulation was found on resting vmHRV. In accordance with our assumptions, we observed that cTBS lead to a significant decrease in vmHRV at rest compared to iTBS and sham stimulation. Within the*Neurovisceral Integration Model* , it is proposed that activity within the PFC constantly exerts inhibitory effects on cardioacceleratory circuits within the CAN (Smith et al., 2017; Thayer et al., 2009). In line with these assumptions, we suggest that cTBS over the left dlPFC reduced prefrontal activity, leading to disinhibition of the circuits mentioned above, thereby decreasing vmHRV. However, contrary to our hypotheses, our results yielded no effect of iTBS compared to sham on resting vmHRV. Whereas we had expected iTBS to increase prefrontal activity and thus vmHRV at rest, our results suggest that iTBS elicited rather variable responses instead of a constant increase in resting vmHRV (see Figure 3). By including levels of state anxiety as covariate in our statistical models, we were able to rule out that these variable responses were driven by the effects of state anxiety which have been found previously (Poppa et al., 2020). Another possible explanation for this response pattern lies in the nature of iTBS. Previous evidence has demonstrated high variation in the neural response to standard iTBS (Hamada et al., 2014; López-Alonso et al., 2014). Consequently, there may have been a high inter-individual variability in how iTBS affected neuronal dynamics within the CAN, thereby producing variable responses in vmHRV. As recent attempts have demonstrated the efficacy of individualized iTBS in decreasing variance in induced neuronal responses (Chung et al., 2019), we want to stimulate future research to investigate the effects of individualized rTMS protocols on the robustness of TMS-induced responses in vmHRV.

In addition to the effects of TBS on vmHRV, we also aimed to investigate the effects of TBS on cognitive-affective processing in an ESST (Allen et al., 2021). As hypothesized, we found a significant effect of stimulation on ESST performance with iTBS leading to a more pronounced decrease in SSRTs compared to sham stimulation. This result adds to a substantial body of evidence demonstrating iTBS over the left dlPFC to exert amplifying effects on cognitive and affective processes (Pabst et al., 2022). Given the role of the dlPFC in the maintenance of contextual goal representations (Curtis & D'Esposito, 2003), we assume that the positive effects of iTBS on ESST performance may act by strengthening ESST-related goal representations (i.e., inhibition of motor response), thereby counteracting stimulus-driven action tendencies. Interestingly, the decrease in SSRTs did not differ between iTBS and cTBS. Furthermore, contrary to our assumptions, SSRTs decreased more in participants that received cTBS compared to those that received sham stimulation, though this effect was not significant. While prevailing literature largely denotes inhibitory outcomes of cTBS over the left dorsolateral prefrontal cortex (dlPFC) on cognition, there have been sporadic cases reporting ameliorative effects (Ngetich et al., 2020). These contradictory effects have been suggested to be a result of so-called addition-by-subtraction (Luber & Lisanby, 2014). Followingly, cTBS may inhibit competing or distracting cognitive processes, hence improving task-performance. Therefore, it seems plausible that the noted enhancement in ESST performance subsequent to cTBS may arise from the disruption of cognitive processes that either compete with or distract response inhibition.

Finally, based on the presumed shared role of the PFC in both cognitive-affective and autonomic processing, we expected a direct link between the effects of TBS on vmHRV and on ESST performance. In detail, we hypothesized that increases in resting vmHRV after stimulation will predict improved ESST performance and vice versa. Nevertheless, our analyses detected no such link between changes in vmHRV and ESST performance (see table 5). The absence of significant findings in this context may be explained by prior literature emphasizing the dynamic involvement of the dlPFC in neurovisceral integration. As such, previous research proposes that the influence of dlPFC on cardiac vagal activity may strongly depend on situational demands. Notably, McIntosh et al. (2020) demonstrated stronger connectivity of dlPFC with the middle frontal gyrus to be linked with higher vmHRV during resting state in a large sample of 271 individuals. Additionally, dlPFC was found to exhibit a positive correlation with vmHRV during experimental emotion

induction (Lane et al., 2009) and cognitive emotion regulation (Neacsiu et al., 2022), yet no such associations emerged in an emotional counting Stroop task (Lane et al., 2013; Smith et al., 2014) and dietary self-control challenges (Maier & Hare, 2017). Intriguingly, despite the emotional or motivational aspect across tasks, differences in participant instruction regarding cognitive resource direction were apparent. Whereas dlPFC activity correlated with vmHRV when participants were explicitly directed to engage with emotional stimuli, no such connection was evident when no deeper cognitive processing of the emotional stimuli was emphasized. In this context, Lane et al. demonstrated that during emotion induction, dlPFC activity was linked to vmHRV in both emotional and neutral conditions, while they found no emotion-specific association between dlPFC activity and vmHRV. Since the authors explicitly asked participants to uphold the goal of preserving the intended emotion or neutral state throughout each scan, they posited that dlPFC activity reflects emotional state maintenance in working memory, thereby influencing vmHRV. Consistent with these observations, Smith et al. (2017) have recently posited, within a hierarchical model of neurovisceral integration, that connectivity among distinct regions contributing to ANS activity can be dynamically modulated. Consequently, the impact of higher-level regions such as the dlPFC on vagal output is engaged selectively in situations demanding their influence.

Building upon this line of evidence, we assume the absence of a significant association between stimulation-induced changes in resting vmHRV and ESST performance in our study to be a result of dynamic dlPFC recruitment in the regulation of vmHRV. In this light, our findings indicate that TBS administered to the dlPFC resulted in alterations of dlPFC activity, influencing vmHRV during resting state but not during the execution of the ESST. This explanation further provides insight into why, in contrast to our hypotheses, stimulation effects were absent on task-related vmHRV and vmHRV reactivity, while still resulting in a significant impact on ESST performance. Nonetheless, it has to be noted that the ESST version used in this study did contain emotional stimuli which need to be processed. However, we contend that the particular nature of the ESST employed in this study recruits dlPFC activity primarily for maintaining the goal representation concerning response inhibition within working memory. In contrast, the evaluation of emotional stimuli (positive vs. negative) rather demands sensory-perceptual processing than the retention of emotional evaluation within working memory. As we are aware of the speculative nature in which we interpret our results in this regard, we know that future research is highly warranted in order to test our assumptions. Hence, to validate our assumptions, we suggest investigating whether changes in vmHRV via dlPFC stimulation distinctly predict performance shifts in tasks that exhibit varying levels of dlPFC engagement in regulating emotional and autonomic processes.

Limitations

Despite its strengths, certain limitations of this study should be acknowledged. First, it should be noted that the experimental session, including stimulation, as well as the statistical analysis were conducted by the first author in an unblinded manner. Hence, it remains plausible that potential experimenter expectation effects might have unintentionally influenced the experimenter's conduct throughout both the experimental session and statistical analyses, even though we tried to counteract such effects by a strict experimental protocol. Another limitation concerns the interpretation and categorization of our results. While our results indicate a different contribution of the left dlPFC to autonomic regulation at rest and during ESST execution, they do not allow insights into the neural underpinnings of this phenomenon. We believe that integrating the methods employed in this study with imaging techniques such as fMRI and EEG will enable the assessment of contextual shifts in neuronal dynamics and functional connectivity among brain regions. Consequently, this attempt may hold potential to improve our understanding of the complex interplay between cognitive-affective, autonomic, and neuronal processes.

Conclusion

Overall, our findings build upon existing evidence highlighting the role of the left dlPFC in regulating cognitive-affective and autonomic processing. While we found TBS effects on both ESST performance and vmHRV, our results also demonstrate the substantial intra-individual variability within TBS outcomes reported in current literature. Further, our findings reveal no significant correlation between changes in vmHRV

and ESST performance, alongside distinct effects of TBS on these two measures. These results can be interpreted within the framework of a hierarchical model of neurovisceral integration, suggesting that the recruitment of higher-order cortical areas, such as the left dlPFC, to autonomic regulation proceeds flexibly in accordance with situational demands. While more research in this regard is highly warranted, these findings represent an important step in uncovering the complex interactions between cognitive-affective processes, autonomic control, and cortical dynamics.

Author Contributions

Maximilian Schmaußer: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; software; visualization; writing – original draft.**Markus Raab:** Conceptualization; funding acquisition; project administration; resources; supervision; validation; writing – review & editing. **Sylvain Laborde:** Conceptualization; funding acquisition; project administration; resources; supervision; validation; writing – review & editing.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Data availability statement

The data and code of the present study are available here: OSF Link will be provided after the review process

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References

Appelhans, B. M., & Luecken, L. J. (2006). Heart Rate Variability as an Index of Regulated Emotional Responding. Review of General Psychology, 10(3), 229–240. https://doi.org/10.1037/1089-2680.10.3.229

Balzarotti, S., Biassoni, F., Colombo, B., & Ciceri, M. R. (2017). Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. Biological Psychology, 130, 54–66. https://doi.org/10.1016/j.biopsycho.2017.10.008

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

Caulfield, K. A., Fleischmann, H. H., Cox, C. E., Wolf, J. P., George, M. S., & McTeague, L. M. (2022). Neuronavigation maximizes accuracy and precision in TMS positioning: Evidence from 11,230 distance, angle, and electric field modeling measurements. Brain stimulation, 15(5), 1192–1205. https://doi.org/10.1016/j.brs.2022.08.013

Chung, S. W., Sullivan, C. M., Rogasch, N. C., Hoy, K. E., Bailey, N. W., Cash, R. F. H., & Fitzgerald, P. B. (2019). The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. Human Brain Mapping, 40(2), 608–627. https://doi.org/10.1002/hbm.24398

Cornwell, B. R., Garrido, M. I., Overstreet, C., Pine, D. S., & Grillon, C. (2017). The Unpredictive Brain Under Threat: A Neurocomputational Account of Anxious Hypervigilance. Biological Psychiatry, 82(6), 447–454. https://doi.org/10.1016/j.biopsych.2017.06.031

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. Trends in Cognitive Sciences, 7(9), 415–423. https://doi.org/10.1016/S1364-6613(03)00197-9

Era, V., Carnevali, L., Thayer, J. F., Candidi, M., & Ottaviani, C. (2021). Dissociating cognitive, behavioral and physiological stress-related responses through dorsolateral prefrontal cortex inhibition. Psychoneuroendocrinology, 124, 105070. https://doi.org/10.1016/j.psyneuen.2020.105070

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences, 15(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004

Hamada, M., Galea, J. M., Di Lazzaro, V., Mazzone, P., Ziemann, U., & Rothwell, J. C. (2014). Two distinct interneuron circuits in human motor cortex are linked to different subsets of physiological and behavioral plasticity. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34(38), 12837–12849. https://doi.org/10.1523/JNEUROSCI.1960-14.2014

Hildebrandt, L. K., McCall, C., Engen, H. G., & Singer, T. (2016). Cognitive flexibility, heart rate variability, and resilience predict fine-grained regulation of arousal during prolonged threat. Psychophysiology, 53(6), 880–890. https://doi.org/10.1111/psyp.12632

Holzman, J. B., & Bridgett, D. J. (2017). Heart rate variability indices as bio-markers of top-down self-regulatory mechanisms: A meta-analytic review. Neuroscience & Biobehavioral Reviews, 74, 233–255. https://doi.org/10.1016/j.neubiorev.2016.12.032

Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. Neuron, 45(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Iseger, T. A., Arns, M., Downar, J., Blumberger, D. M., Daskalakis, Z. J., & Vila-Rodriguez, F. (2020). Cardiovascular differences between sham and active iTBS related to treatment response in MDD. Brain Stimulation, 13(1), 167–174. https://doi.org/10.1016/j.brs.2019.09.016

Kirkovski, M., Donaldson, P. H., Do, M., Speranza, B. E., Albein-Urios, N., Oberman, L. M., & Enticott, P. G. (2023). A systematic review of the neurobiological effects of theta-burst stimulation (TBS) as measured using functional magnetic resonance imaging (fMRI). Brain Structure & Function, 228(3–4), 717–749. https://doi.org/10.1007/s00429-023-02634-x

Laborde, S., Mosley, E., & Mertgen, A. (2018). Vagal Tank Theory: The Three Rs of Cardiac Vagal Control Functioning – Resting, Reactivity, and Recovery. Frontiers in Neuroscience, 12. https://www.frontiersin.org/articles/10.3389/fnins.2018.00458

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research—Recommendations for Experiment Planning, Data Analysis, and Data Reporting. Frontiers in Psychology, 8, 213. https://doi.org/10.3389/fpsyg.2017.00213

Lane, R. D., McRae, K., Reiman, E. M., Chen, K., Ahern, G. L., & Thayer, J. F. (2009). Neural correlates of heart rate variability during emotion. NeuroImage, 44(1), 213–222. https://doi.org/10.1016/j.neuroimage.2008.07.056

Lane, R. D., Weidenbacher, H., Smith, R., Fort, C., Thayer, J. F., & Allen, J. J. B. (2013). Subgenual anterior cingulate cortex activity covariation with cardiac vagal control is altered in depression. Journal of Affective Disorders, 150(2), 565–570. https://doi.org/10.1016/j.jad.2013.02.005

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. Psychological Review, 91(3), 295–327. https://doi.org/10.1037/0033-295X.91.3.295

Lopez-Alonso, V., Cheeran, B., Rio-Rodriguez, D., & Fernandez-Del-Olmo, M. (2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimulation, 7(3), 372–380. https://doi.org/10.1016/j.brs.2014.02.004

Luber, B., & Lisanby, S. H. (2014). Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). NeuroImage, 85, 961–970. https://doi.org/10.1016/j.neuroimage.2013.06.007

Magnon, V., Vallet, G. T., Benson, A., Mermillod, M., Chausse, P., Lacroix, A., Bouillon-Minois, J.-B., & Dutheil, F. (2022). Does heart rate variability predict better executive functioning? A systematic review and meta-analysis. Cortex, 155, 218–236. https://doi.org/10.1016/j.cortex.2022.07.008

Maier, S. U., & Hare, T. A. (2017). Higher Heart-Rate Variability Is Associated with Ventromedial Prefrontal Cortex Activity and Increased Resistance to Temptation in Dietary Self-Control Challenges. Journal of Neuroscience, 37(2), 446–455. https://doi.org/10.1523/JNEUROSCI.2815-16.2016

Makovac, E., Thayer, J. F., & Ottaviani, C. (2017). A meta-analysis of non-invasive brain stimulation and autonomic functioning: Implications for brain-heart pathways to cardiovascular disease. NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS, 74(B, SI), 330–341. https://doi.org/10.1016/j.neubiorev.2016.05.001

McIntosh, R. C., Hoshi, R., Nomi, J. S., Di Bello, M., Goodman, Z. T., Kornfeld, S., Uddin, L. Q., & Ottaviani, C. (2020). Neurovisceral integration in the executive control network: A resting state analysis. Biological Psychology, 157, 107986. https://doi.org/10.1016/j.biopsycho.2020.107986

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience, 24, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Neacsiu, A. D., Beynel, L., Graner, J. L., Szabo, S. T., Appelbaum, L. G., Smoski, M. J., & LaBar, K. S. (2022). Enhancing cognitive restructuring with concurrent fMRI-guided neurostimulation for emotional dysregulation–A randomized controlled trial. Journal of Affective Disorders, 301, 378–389. https://doi.org/10.1016/j.jad.2022.01.053

Ngetich, R., Zhou, J., Zhang, J., Jin, Z., & Li, L. (2020). Assessing the Effects of Continuous Theta Burst Stimulation Over the Dorsolateral Prefrontal Cortex on Human Cognition: A Systematic Review. Frontiers in Integrative Neuroscience, 14, 35. https://doi.org/10.3389/fnint.2020.00035

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. Trends in Cognitive Sciences, 9(5), 242–249. https://doi.org/10.1016/j.tics.2005.03.010

Pabst, A., Proksch, S., Mede, B., Comstock, D. C., Ross, J. M., & Balasubramaniam, R. (2022). A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement. Neuroscience and Biobehavioral Reviews, 135, 104587. https://doi.org/10.1016/j.neubiorev.2022.104587

Poppa, T., de Witte, S., Vanderhasselt, M.-A., Bechara, A., & Baeken, C. (2020). Theta-burst stimulation and frontotemporal regulation of cardiovascular autonomic outputs: The role of state anxiety. INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY, 149, 25–34. https://doi.org/10.1016/j.ijpsycho.2019.12.011

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmoller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Lefaucheur, J. P., Leocani, L., ... basis of this article began with a Consensus Statement from the IFCN Workshop on „Present, Future of TMS: Safety, Ethical Guidelines“, Siena, October 17-20, 2018, updating through April 2020. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 132(1), 269–306. https://doi.org/10.1016/j.clinph.2020.10.003

Rusjan, P. M., Barr, M. S., Farzan, F., Arenovich, T., Maller, J. J., Fitzgerald, P. B., & Daskalakis, Z. J. (2010). Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Human Brain Mapping, 31(11), 1643–1652. https://doi.org/10.1002/hbm.20964

Schmausser, M., Hoffmann, S., Raab, M., & Laborde, S. (2022). The effects of noninvasive brain stimulation on heart rate and heart rate variability: A systematic review and meta-analysis. Journal of Neuroscience

Research, 100(9), 1664–1694. https://doi.org/10.1002/jnr.25062

Schmausser, M., & Laborde, S. (2023). Tonic and phasic cardiac vagal activity predict cognitive-affective processing in an emotional stop-signal task. International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 191, 9–18. https://doi.org/10.1016/j.ijpsycho.2023.06.008

Shackman, A. J., Maxwell, J. S., McMenamin, B. W., Greischar, L. L., & Davidson, R. J. (2011). Stress Potentiates Early and Attenuates Late Stages of Visual Processing. The Journal of Neuroscience, 31(3), 1156–1161. https://doi.org/10.1523/JNEUROSCI.3384-10.2011

Smith, R., Allen, J. J. B., Thayer, J. F., Fort, C., & Lane, R. D. (2014). Increased association over time between regional frontal lobe BOLD change magnitude and cardiac vagal control with sertraline treatment for major depression. PSYCHIATRY RESEARCH-NEUROIMAGING, 224(3), 225–233. https://doi.org/10.1016/j.pscychresns.2014.08.015

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. Neuroscience and Biobehavioral Reviews, 75, 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003

Spangler, D. P., & McGinley, J. J. (2020). Vagal Flexibility Mediates the Association Between Resting Vagal Activity and Cognitive Performance Stability Across Varying Socioemotional Demands. Frontiers in Psychology, 11. https://www.frontiersin.org/articles/10.3389/fpsyg.2020.02093

Thayer, J. F., Ahs, 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

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine, 37(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. Journal of Affective Disorders, 61(3), 201–216. https://doi.org/10.1016/S0165-0327(00)00338-4

van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernandez, G. (2009). From specificity to sensitivity: How acute stress affects amygdala processing of biologically salient stimuli. Biological Psychiatry, 66(7), 649–655. https://doi.org/10.1016/j.biopsych.2009.05.014

Verbruggen, F., Aron, A. R., Band, G. P., Beste, C., Bissett, P. G., Brockett, A. T., Brown, J. W., Chamberlain, S. R., Chambers, C. D., Colonius, H., Colzato, L. S., Corneil, B. D., Coxon, J. P., Dupuis, A., Eagle, D. M., Garavan, H., Greenhouse, I., Heathcote, A., Huster, R. J., … Boehler, C. N. (2019). A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. eLife, 8. https://doi.org/10.7554/eLife.46323

Figure 1. Experimental Design

Figure 2. Scatter plots depicting the results of simple slope analysis showing the relationship between vmHRV reactivity and SSRTs in subjects with low (- 1 SD), medium (mean), and high (+ 1 SD) tonic CVA

Figure 3. Violin plot depicting the effects of theta burst stimulation on resting vmHRV

Figure 4. Violin plot depicting the effects of theta burst stimulation on on-task vmHRV

Figure 5. Violin plot depicting the effects of theta burst stimulation on vmHRV reactivity

Figure 6. Violin plot depicting the effects of theta burst stimulation on SSRTs

Table 1. Summary of sample descriptive data

Table 2 . Results of linear regression model regarding the effects of vmHRV on SSRT (pre stimulation)

Table 3 . Results of linear regression model regarding the effects of vmHRV on SSRT (post stimulation)

Table 4 . Simple effects of vmHRV reactivity (post stimulation)

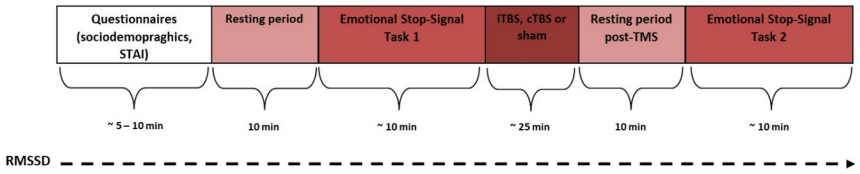

Figure 1. Experimental Design

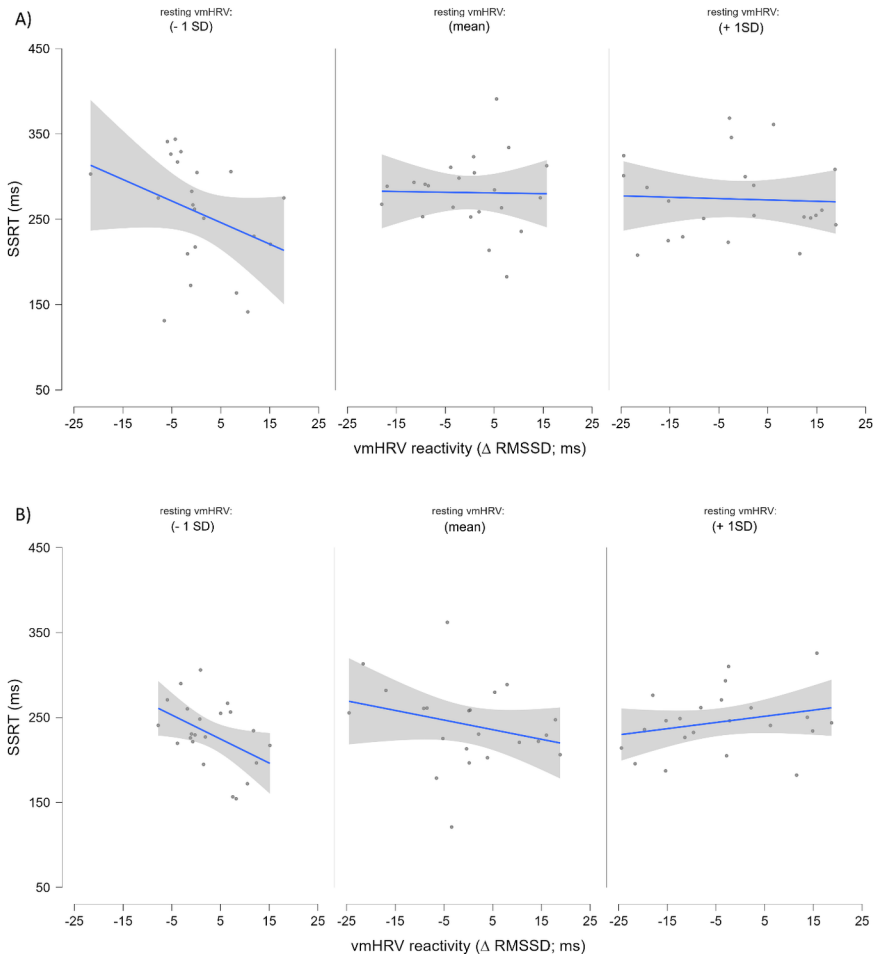

Figure 2. Scatter plots depicting the results of simple slope analysis showing the relationship between vmHRV reactivity and SSRTs in subjects with low (- 1 SD), medium (mean), and high (+ 1 SD) tonic CVA. A) Scatter plot showing the results of the pre-stimulation session. B) Scatter plot showing the results of the post-stimulation session

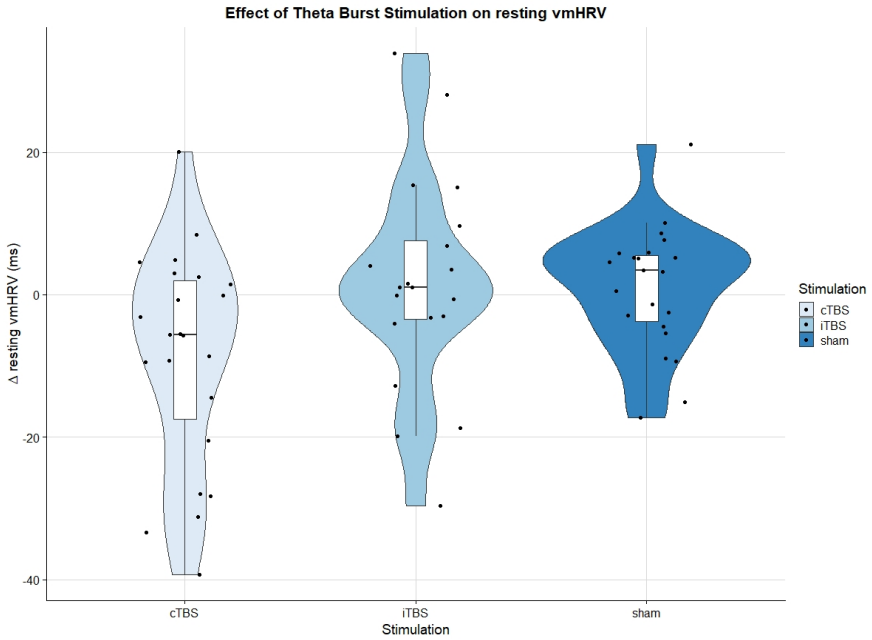

Figure 3. Violin plot depicting the effects of theta burst stimulation on resting vmHRV

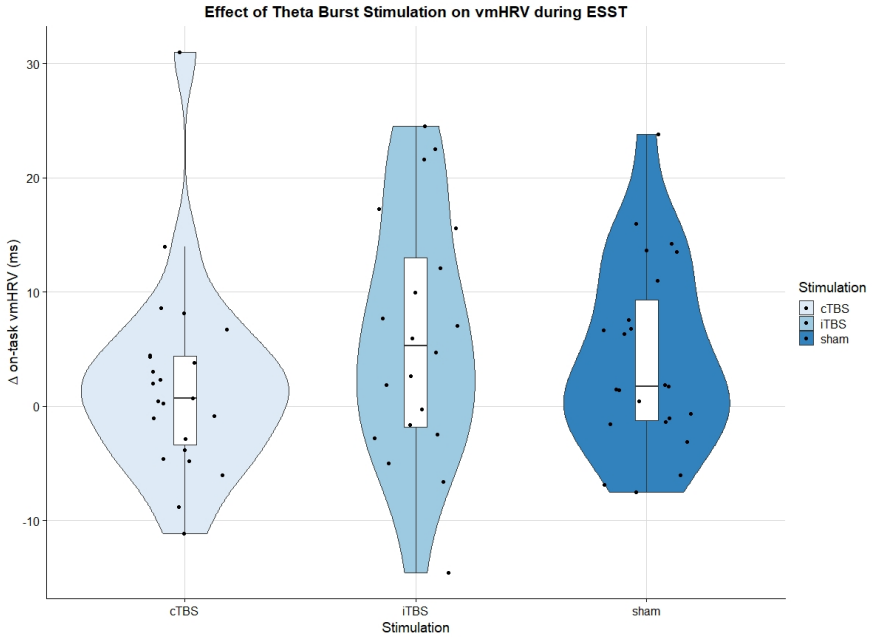

Figure 4. Violin plot depicting the effects of theta burst stimulation on on-task vmHRV

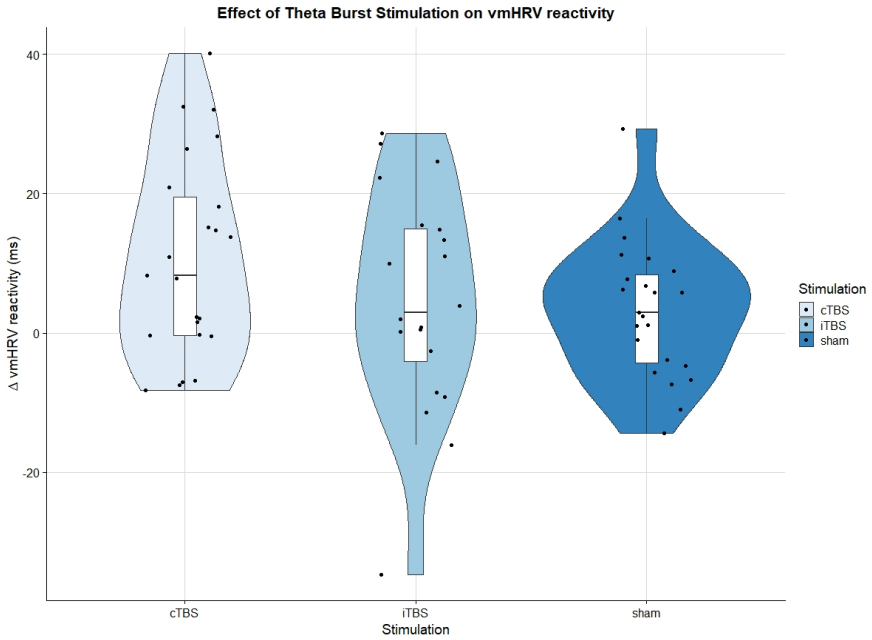

Figure 5. Violin plot depicting the effects of theta burst stimulation on vmHRV reactivity

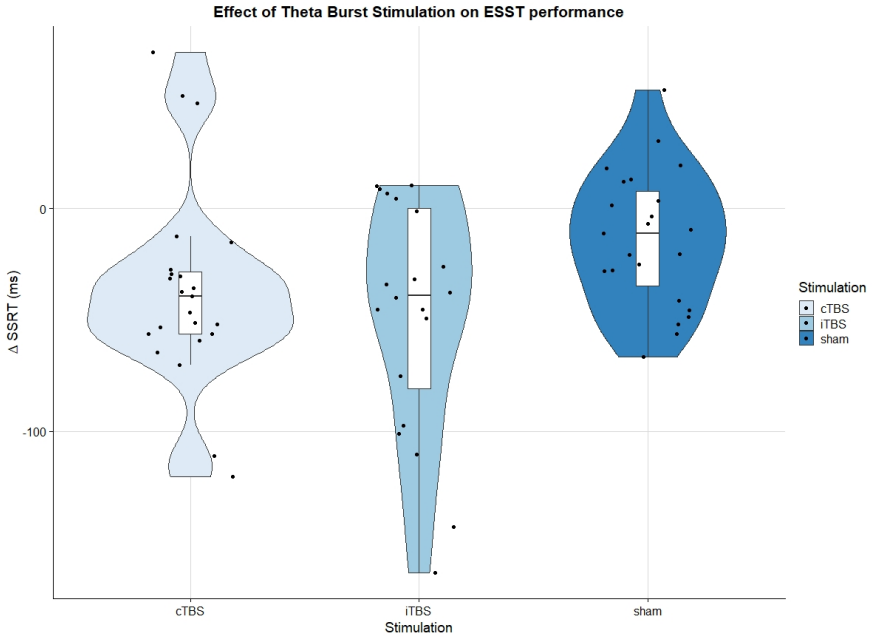

Figure 6. Violin plot depicting the effects of theta burst stimulation on SSRTs

Table 1. Summary of sample descriptive data

Characteristic	**Overall**, N =

Age	23.39 (3.08)
BMI	22.72 (2.44)
Sex	36 / 66 (54.5
Baseline HR (bpm)	68.05 (10.56)
Baseline RMSSD (ms)	55.97 (29.32)
On task RMSSD pre TMS (ms)	49.34 (23.01)
RMSSD reactivity pre TMS (ms)	-6.64 (14.02)
SSRT pre TMS (ms)	270.91 (52.45
Resting RMSSD (ms)	53.73 (27.74)
On task RMSSD post TMS (ms)	53.33 (25.10)
RMSSD reactivity post TMS (ms)	-0.40 (11.01)
SSRT post TMS (ms)	238.97 (42.06
Resting RMSSD (ms)	-2.24 (13.84)
On task RMSSD (ms)	3.99 (9.09)
RMSSD reactivity (ms)	6.24 (13.67)
SSRT (ms)	-31.93 (44.57
Note. [1]Mean (SD); n / N (% females), [2]One-way ANOVA; Pearson's Chi-squared test;	Note. [1]Mean
ms = milliseconds, RMSSD = root mean square of successive differences, SSRT = stop signal reaction time.	ms = millisec

Table 2 Results of linear regression model regarding the effects of vmHRV on SSRT (pre stimulation)

Moderator	Moderator	Moderator
		Intercep
resting vmHRV	*resting vmHRV*	*resting vmHRV*
vmHRV reactivity	*vmHRV reactivity*	*vmHRV reactivity*
*resting vmHRV * vmHRV reactivity*	*resting vmHRV * vmHRV reactivity*	*resting vmHRV * vmHRV reactivity*
Go RT mean	*Go RT mean*	*Go RT mean*
Sex	*Sex*	*Sex*
Female	Female	Female
Age	*Age*	*Age*

Table 3 Results of linear regression model regarding the effects of vmHRV on SSRT (post stimulation)

Moderator	Moderator	Moderator	Estimate	Estimate	Estimate	t	SE	SE	95 % Confidence Intervall SE	95 % Confidence Intervall Lower	95 % Confidence Intervall Upper	Upper	Up
		Intercept	187.87	187.87	187.87	2.57	73.17	73.17	73.17	40.98	334.76	334.76	33
resting vmHRV	*resting vmHRV*	*resting vmHRV*	0.48	0.48	0.48	1.21	0.39	0.39	0.39	-0.31	1.28	1.28	1.2

vmHRV reactivity resting	*vmHRV reactivity resting*	*vmHRV reactivity resting*	- 4.09	- 4.09	- 4.09	2.12	1.93	1.93	1.93	- 7.97	- 0.21	- 0.21	- 0.2
*vmHRV * Stimulation resting*	*vmHRV * Stimulation resting*	*vmHRV * Stimulation resting*	0.05	0.05	0.05	2.20	0.02	0.02	0.02	0.01	0.11	0.11	0.1
*vmHRV reactivity * Stimulation*	*vmHRV reactivity * Stimulation*	*vmHRV reactivity * Stimulation*											
*vmHRV reactivity * Stimulation resting*	*vmHRV reactivity * Stimulation resting*	*vmHRV reactivity * Stimulation resting*											
*vmHRV reactivity * Stimulation*	*vmHRV reactivity * Stimulation*	*vmHRV reactivity * Stimulation*											
Go RT mean Sex	*Go RT mean Sex*	*Go RT mean Sex*	- 0.09	- 0.09	- 0.09	1.46	0.06	0.06	0.06	- 0.23	0.03	0.03	0.0
Female	Female	Female	2.09	2.09	2.09	0.20	10.47	10.47	10.47	- 18.94	23.12	23.12	23
Age	*Age*	*Age*	4.49	4.49	4.49	2.65	1.69	1.69	1.69	1.08	7.89	7.89	7.8

Table 4 Simple effects of vmHRV reactivity (post stimulation)

Moderator levels				95 % Confidence Intervall	95 % Confidence Intervall	
resting vmHRV	Estimate	t	SE	Lower	Upper	p
Mean – 1 SD	-2.61	1.93	1.35	-5.25	0.04	0.06
Mean	-1.02	1.13	0.90	-2.78	0.74	0.26

Mean + 1 SD	0.56	0.62	0.91	-1.22	2.34	0.54