A frontal-vagal network theory for Major Depressive Disorder: Implications for optimizing neuromodulation techniques

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ABSTRACT

Major Depressive Disorder (MDD) is a psychiatric disorder characterized by high comorbidity with cardiovascular disease. Furthermore, a combination of high heart rate (HR) and low heart rate variability (HRV) has been frequently reported in depressed patients. The present review proposes a frontal-vagal (brain-heart) network that overlaps with functional nodes of the depression network. Moreover, we summarize neuromodulation studies that have targeted key nodes in this depression network, with subsequent impact on heart rate (HR) or heart-rate-variability (HRV), such as the dorsolateral prefrontal cortex (DLPFC), subgenual anterior cingulate cortex (sgACC), and the vagus nerve (VN). Based on the interplay of this frontal-vagal network, we emphasize the importance of including HR and HRV measurements in human depression studies, in particular those that conduct neuromodulation, in order to obtain a better understanding of the pathways that are affected, and we explore the possibilities of using this frontal-vagal interplay as a method for target engagement in neuromodulation treatments. This frontal-vagal network theory opens-up the possibility for individualizing neuromodulation treatments such as rTMS. A recent development called Neuro-Cardiac-Guided TMS (NCG-TMS), was developed based on this theory, and an individual-participant meta-analysis is presented. Four studies provide consistent and replicable support for NCG-TMS as a target engagement method, with consistent HR deceleration during frontal TMS and HR acceleration during motor strip TMS.

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Introduction

Major Depressive Disorder (MDD) is a chronic, heterogeneous psychiatric disorder with a remitting and relapsing course. Despite the variety of available treatments (e.g. antidepressants and psychotherapy), up to 40–50% of patients fail to respond [1]. Antidepressant medication is considered a first-line treatment for MDD, in particular the use of selective serotonin reuptake inhibitors (SSRI's) and serotonin-norepinephrine reuptake inhibitors (SNRI's) [2]. New neuromodulation treatments such as repetitive Transcranial Magnetic Stimulation (rTMS), transcranial Direct Current Stimulation (tDCS) and Deep Brain Stimulation (DBS) show promising clinical benefit in MDD [3–7]. These new 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 cingulate cortex (sgACC), and the vagus nerve (VN). Stimulation of these regions is associated with symptom improvement in MDD [6,8–10]. Recent insights into how these neuromodulation treatments work suggest network connectivity between the DLPFC and the (sg)ACC, which may be mediating clinical response [11,12]. The VN, part of the parasympathetic branch of the autonomic nervous system, influences bodily functions such as heart rate (HR) and respiration, and stimulation of the VN consistently leads to HR decelerations [13]. Interestingly, several studies have also reported HR decelerations after stimulation of the DLPFC using rTMS and tDCS [14]. It is further known that heart rate in MDD is often dysregulated, expressed in overall higher HR and lower heart rate

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variability (HRV) [15–17], which has been reported to be normalized after neuromodulation treatment, but not after treatment with SSRI's [18,19]. The goal of this narrative review is to outline the brain-heart network or frontal-vagal network and the overlap with the depression network, as identified with neuromodulation treatment. As an extension to this narrative review, a commentary is provided how to use the heart-brain link to identify potential targets for future neuromodulation interventions and to refine target selection in neuromodulation treatments, as well as an individual participant meta-analysis demonstrating the consistency of this effect.

An anatomical framework of the brain-heart connection

In Fig. 1 below a summary can be found outlining the neuro-anatomical framework of the brain-heart connection. A more elaborate review on all these specific components can be found in the supplementary material.

Major Depressive Disorder (MDD) and the autonomic nervous system

Previous research indicates comorbidity between cardiovascular disease and MDD which is a pertinent public health concern due to the fact that both diseases are leading causes of disability [20–22]. Several studies have shown that depression increases risk for cardiovascular illness from two to fivefold. Moreover, autonomic regulation is already disturbed in depressed patients without heart disease, manifested in an overall higher HR, and lower HRV in comparison to healthy controls [15,16,23,24], which is more pronounced in patients with severe MDD [25], indicating overlap between the depression network and the heart-brain axis.

HRV is extensively studied in depressed patients and healthy individuals (for meta-analysis, see Ref. [19]), for a general background on HRV measures see part 2.3 of the supplementary material). Low HRV is related to maladaptive and hyper-vigilant processing of emotional stimuli [26], which is believed to be a right-hemispheric function. In addition, low HRV is linked to a hypoactive prefrontal regulation and is associated with disturbed processing of environmental changes. In contrast, higher HRV is associated with an effective functioning of inhibitory circuits between the prefrontal cortices and the subcortical areas, and enables flexible responses to environmental influences [27,28]. Higher HRV is also related to an adaptive and increased top-down and bottom up modulation of cognitive emotional processing and to effective processing of negative stimuli [29].

Interestingly, HRV is related to several factors which are linked to depression as well, such as circadian rhythm, seasonality, gender, exercise and smoking [30,31]. Furthermore, dysregulated HR patterns are also seen when sleep patterns are disturbed due to misalignment of the circadian rhythm [32], and for other somatic processes such as an increased appetite [33].

The vagus nerve projects to visceral organs and was shown to affect appetite [34,35]. It was also shown that transcutaneous vagus nerve stimulation improved insomnia even before improving symptoms of depression [35], thus indicating that both appetite and insomnia, common symptoms of MDD, are also vagally mediated, though perhaps afferent instead of efferent.

Depression is found to be more common in women compared to men, in general, and HRV is lower in females as well [36]. However, there are some mixed findings for this assertion as gender differences in HRV seem to be age and measure dependent, and age is an important modulator of HRV [37]. Gender differences decrease with age, starting from 30 years old, and disappear around the age of 50, dependent on what measure for HRV is used [38]. This may be

attributed to the level of estrogen [39]. It appears that depressed men have lower HRV levels compared to nondepressed men. Yet, depressed women show higher HRV levels compared to nondepressed women, although this finding from one study had a small sample size [40]. Still, in another small sized study, the same trend was found in healthy subjects when investigating HRV and daily sadness [41], so this assertion is not settled yet. However, depressed women seem to have higher HRV levels than depressed men [42] and this might explain the higher mortality rates for men [43]. Other studies have found reduced vagal activity (higher LF/HF ratios) and higher HR in depressed patients compared to healthy controls, when controlling for gender in a small sample [44]. HRV seems to fluctuate during winter/summer [31] and a peak of patients with heart failure also occurs in winter [45]. Contrary, increased vagal tone has been found in patients with seasonal affective disorder (SAD) during winter, however, the symptomology of this disorder (weight gain, increased appetite, hypersomnia) is different to that from depression (weight loss, decreased appetite, insomnia) [46]. Interestingly, season of birth seems to influence HRV later in life [47] and being born in winter seems to be cardioprotective [48]. In line with this, there is a higher risk for depression when being born in spring, and this is lower in winter [49,50]. Exercise tends to increase HRV [36], and lower HR. Several studies suggest that exercise has a preventive action on depression and may serve as treatment option [51]. Thus, HR and HRV is associated with many factors that are dysregulated in depression as well, further suggestive of a link between the depression network and the heart-brain axis.

A biofeedback technique called Heart Rate Variability Biofeedback (HRV-BF) has been shown to have anti-depressive effects, either by itself or when combined with evidence based behavioral treatments. During HRV-BF, patients are assessed to find a breathing frequency that produces the maximum effect on the vagal pacing of the heart (called respiratory sinus arrhythmia). A recent review on the effects of HRV-BF and emotion regulation, concludes that HR oscillations can enhance emotion by entraining brain rhythms in ways that enhance regulatory brain networks [52]. An open-label study where 11 depressed patients practiced HRV-BF as the sole treatment, indicated that by session 4, patients with mild depression showed improvements in sleep, hygiene, fatigue, and concentration. In addition, after receiving HRV-BF, there was a decrease in depression severity and an increase in HRV, after 10 sessions [53]. The effects of HRV-BF in MDD patients were also compared to a control group, and to healthy subjects: After two weeks of treatment HRV increased for the HRV-BF group, but not in the active control group (relaxed rest) or in healthy subjects receiving biofeedback. Furthermore, at follow-up, mood was improved in depressed patients [54]. Other studies have shown reductions in depressive symptoms in various patient groups [55,56].

The mechanisms behind HRV-BF may parallel the pathways implicated in VN stimulation (VNS). By using Heart Beat Evoked Potentials (HEP), researchers discovered that perception of visceral phenomena such as HR may be mediated by vagal afferent pathways [57]. MacKinnon et al. showed that the HEP (n250) responded to paced breathing at the optimal or resonance frequency used in HRV-BF [58]. 5 training sessions in HRV-BF vs. EMG relaxation, greatly increased the signal to the brain from the heart, further reinforcing this finding [59].

Thus, MDD, HR and HRV are linked to each other. Interestingly, different neuromodulation techniques, such as VNS, TMS, and potentially DBS, have proven to be successful and effective in treating depression in patients, and also have subsequent effects on cardiac measures such as HR and HRV, possibly (1) increasing

parasympathetic activity, (2) decreasing sympathetic activity, or (3) both.

Cardiac effects of neuromodulation on MDD treatment targets

Vagus nerve

In the treatment of severely treatment-resistant depression, the VN has been considered a target for treatment, using Vagus Nerve stimulation (VNS). The VN is the most direct (parasympathetic) connection to the heart, thus during VNS HR consistently decreases [13,60], with a maximum effect approximately within 5 s from onset of stimulation. VNS is an invasive technique that stimulates the left branch of the VN through electrical current [61,62], although new noninvasive techniques to target the VN are emerging, such as transcutaneous VNS (tVNS) [63], that also increased HRV [64]. VNS in MDD patients has been shown to produce increases in time-domain HRV measured by RMSSD (Root Mean Square of the Successive Differences) [65]. Animal research indicates that VNS can affect widespread brain regions, such as the orbital cortex, lateral frontal cortex, anterior rhinal sulcus and amygdala [66], and influence cardiac responses [67].

VMPFC

The VMPFC includes both the rostral anterior cingulate cortex (rACC) and the sgACC, which are subdivisions of the ACC. The sgACC has been implicated in depression and autonomic nervous system activity. This area is observed to be hyperactive in depressed adults and adolescents compared to healthy individuals, observed with positron emission tomography (PET) scans and with functional magnetic resonance imaging (fMRI) [6,11]. The antidepressant response after deep brain stimulation (DBS) in the sgACC is mediated by the direct down regulation of this area [6]. DBS is an invasive neuromodulatory technique that uses electrodes that need to be placed in different subcortical nuclei through surgery. Compared to healthy subjects, depressed patients show an altered emotional state shifting, due to abnormal sgACC activity, which subsequently leads to altered vagal control [68]. There have not been many studies investigating the direct effect of deep brain stimulation on the VMPFC in relation to HR, although it was demonstrated in monkeys that electrical stimulation in the pre-genual ACC was associated with cardiac slowing [69]. Furthermore, bradycardia was observed after electrical stimulation of the rostral cingular region in monkeys [70]. Stronger stimulation also produced increased slowing of the HR. The inhibitory effect on the heart was accentuated and prolonged in monkeys that have received eserine, indicating vagal activity, since eserine prevents the break-down of acetylcholine [70]. Also in rabbits, electrical stimulation of the medial frontal cortex led to bradycardia [71].
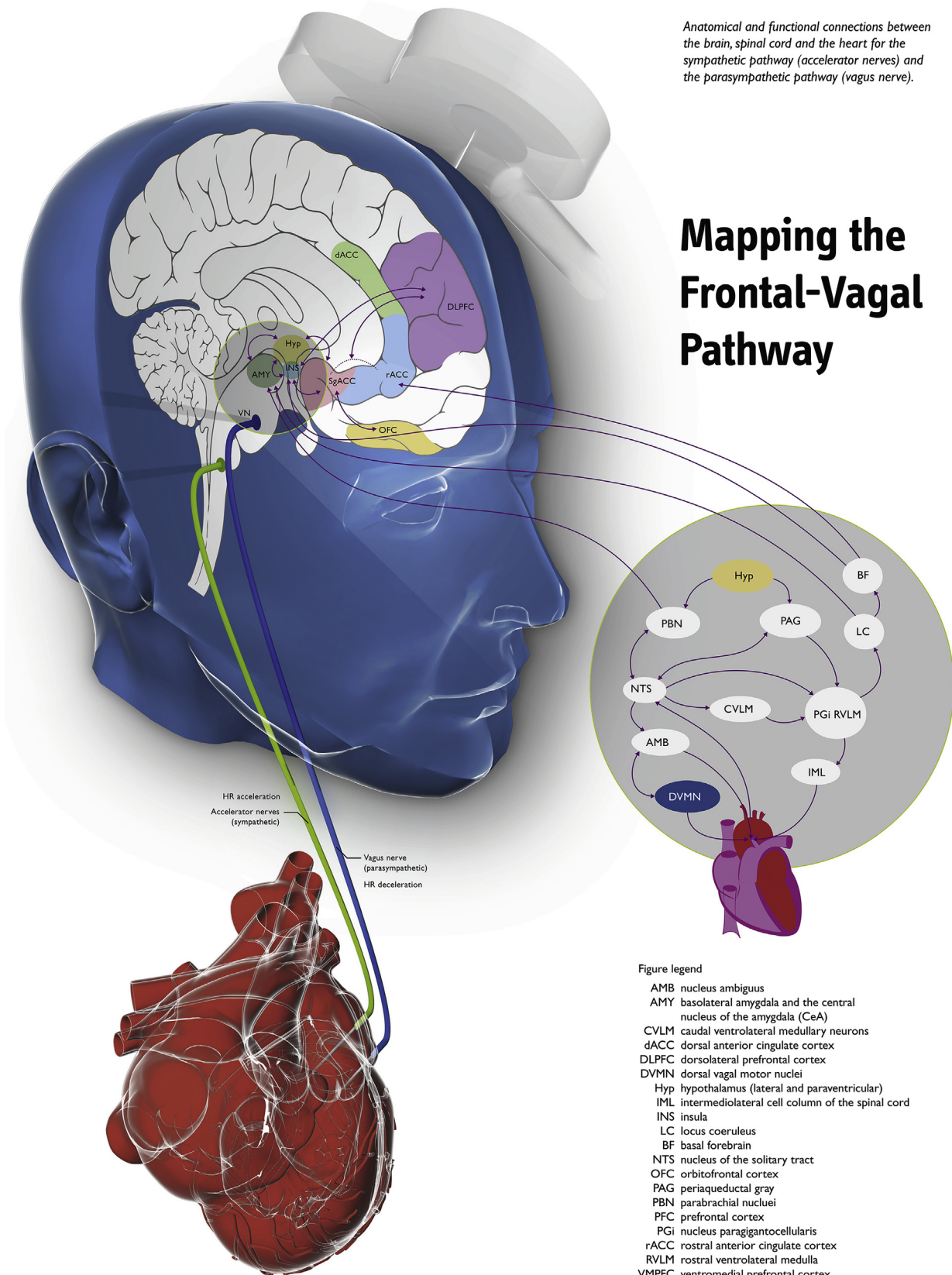
The studies on deep brain stimulation and HR effects in human subjects are limited and use often different targets: the PAG, sub-thalamic nucleus (STN), globus pallidum and hypothalamus, all showing an increase in HR [72]. Only recently, it was shown in 7 MDD patients that deep brain stimulation of the subgenual cingulate (SCC) white matter (which corresponds to the sgACC) was associated with larger HR acceleration than sham stimulation, in cases where an intraoperative behavior response was observed, but only after left hemispheric stimulation. Thus, this study indicates that with DBS, HR accelerates rather than decelerates after SCC stimulation. This may be explained by the finding that across all 7 patients, there was a significant relationship between the estimated structural connectivity of the left SCC VTA to the mid-cingulate cortex and the change in HR: the greater the structural connectivity, the more the HR increased [73]. Furthermore, it was suggested that the SCC has greater connectivity to the dorsal anterior cingulate which is thought to be linked to the sympathetic system [74,75], subsequently causing HR accelerations. Another important consideration is the true focality of DBS in these studies, since the electrical stimulation intensity in MDD DBS studies is often higher relative to Parkinson DBS studies, and more diffuse as demonstrated by electrical field modelling [76]. The latter SCC DBS study applied stimulation at 6 mA [73], while for example in the rabbit study HR decelerations were observed at 40 μA [71], and 0.5−1 mA in monkeys [69]. Therefore, more human studies with adequate stimulation parameters are needed to confirm the sgACC to be the relay station in this frontal-vagal network.

DLPFC

rTMS is a non-invasive neuromodulation antidepressant treatment which has been shown to be able to influence HR, when aimed at the DLPFC [14]. The efficacy of rTMS in the treatment of MDD has been well established in recent years, especially for non-responders to conventional treatments. Currently, remission rates to rTMS are around 37% [77], and higher when combined with psychotherapy 56% [78]. As rTMS is limited to cortical surfaces, it is hypothesized that DLPFC-rTMS might exert its antidepressant effect via trans-synaptic activation of deeper regions, such as the sgACC. The sgACC could carry the signal further to deeper brain structures and subsequently have an impact on HR via the VN. Fox et al. (2012) demonstrated a negative correlation between BOLD activity in the sgACC and the DLPFC which was hypothesized to be associated to the antidepressant mechanism of rTMS [12], the higher the anticorrelation, the better the treatment response. In addition, DBS of the sgACC which suppresses activity, results in an up regulation of the activity in the DLPFC [6]. It is suggested that DLPFC-rTMS exerts its clinical effect via functional connectivity to the sgACC, the more negative the correlation between the two areas was, the better a patient responded to rTMS [12]. In summary, irrespective of the direction and causality, there is an intricate interplay between the sgACC and DLPFC, and this interplay mediates antidepressant response to rTMS.

The DLPFC has been frequently selected as a target area in non-invasive neuromodulation research such as rTMS and tDCS due to the accessibility of this node in the depression network. For both rTMS and tDCS, several studies have investigated the effects on HR (for a complete overview see Ref. [14]). In short, it was found that both tDCS and TMS reduced HR, but the cardiac effects of TMS were stronger relative to tDCS [14]. Furthermore, prefrontal stimulation was more effective in reducing HR relative to Motor Cortex stimulation. The DLPFC is usually targeted either on the right side with low (1 Hz) or on the left side with high frequency (10−20 Hz) stimulation. A study conducted in healthy subjects found reduced HR after rTMS over both the left and right DLPFC and decreased arterial pressure after left DLPFC-rTMS [79]. A study by Udupa et al. (2007) compared the effects of 2 weeks of rTMS with 4 weeks of SSRIs on HRV in antidepressant naïve MDD patients. This study did not implement a sham rTMS intervention in order to control for placebo effects, but measured HRV before and after each treatment. No difference was found on treatment outcome (all interventions were equally effective) and reduced sympathovagal balance was found in both groups. An interaction effect with treatment type was found for SDNN, RMSSD, LF and LF/HF ratio, which indicated a greater reduction in sympathovagal balance in the rTMS group. However, no significant correlation between clinical improvement and autonomic function parameters was found [80]. Another study, using intermittent theta burst stimulation (iTBS) in 15 MDD patients, showed that within the first minute of stimulation on the DLPFC a HR deceleration was observed that was significantly larger

Fig. 1. Visual overview of sympathetic and parasympathetic brain-heart connections. Anatomical and functional connections between the brain, spinal cord and the heart for the sympathetic pathway (accelerator nerve, indicated in green) and the parasympathetic pathway (vagus nerve, indicated in blue).
AMB: nucleus ambiguus; AMY: basolateral amygdala and the central nucleus of the amygdala (CeA); CVLM: caudal ventrolateral medullary neurons; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; DVMN: dorsal vagal motor nuclei; Hyp: hypothalamus (lateral and paraventricular); IML: intermediolateral cell column of the spinal
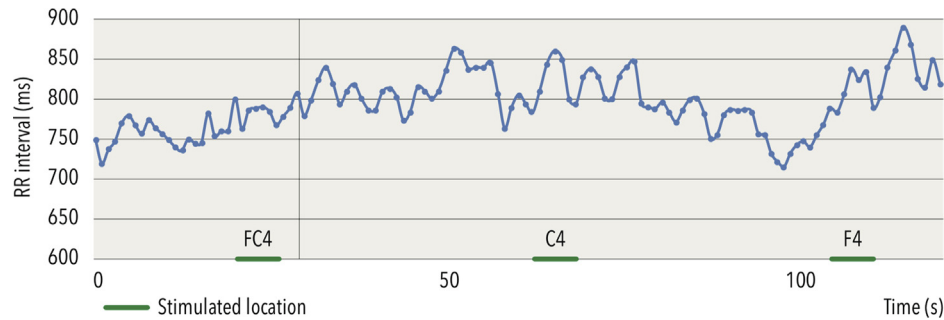
Fig. 2. Example of the NCG-TMS method.
This figure shows an example of the NCG-TMS method, in where heart rate is recorded during stimulation on different cortical locations, with TMS. Here, 3 locations are being stimulated (respectively FC4, C4 and F4; gray blocks on the x-axis), with 10HZ TMS, lasting 5 s per location. Plotted on the y-axis are the intervals between two consecutive r-peaks, as recorded by ECG. During stimulation on F4, lengthening of the RR intervals is observed, showing heart rate deceleration.

than during sham stimulation, thereby highlighting the acute effects on HR. More importantly, this study showed a relationship between HR deceleration in the first 30 s (difference between sham and active) with HRSD reduction, indicating that the larger the HR deceleration, the better treatment outcome [96].

These studies suggest that prefrontal TMS is capable of transynaptically decreasing HR, influencing HRV and possibly normalizing parasympathetic functioning in MDD. However, despite the promising clinical results of targeting the DLPFC, one outstanding problem involves identification of an individualized stimulation location [81,82].

Target engagement

In all, because of the overlap of the hubs in the depression network (DLPFC, sgACC, VN) with the heart-brain axis, stimulation of these hubs consequently leads to HR decelerations. This interaction might offer possibilities for improving localization of the stimulation target. As reviewed in the supplementary material, the effect of the VN on the heart is rapid; stimulation of the VN usually results in an immediate response of the heart, typically occurring within the cardiac cycle in which the stimulation occurred, with a peak in HR deceleration within 5 s (in pigs) [13]. The return to a normal HR is very quick after the activity of the VN is reduced [83,84], indicating that it could be verified within a few seconds whether coil or electrode positioning is optimal, taking the time for the signal to travel from the target location to the VN into account. This may be used for choosing an individual optimal target for, for example, TMS. In a proof-of-concept study, TMS was aimed to locate the DLPFC according to HR deceleration [85]. HR data of 10 subjects was collected, while stimulating with 5 s trains of 10 Hz TMS on various prefrontal locations (F4, FC4 and C4, F3, FC3 and C3) according to the 10–20 system. In this study, respiration was "filtered out" by converting the ECG to RR intervals and taking only the troughs of this signal (see Fig. 2). The rationale for this was that the troughs represent the highest HR and could thus show a deceleration more clearly. In line with the hypothesis, it was found that on the group level, the locations that led best to the largest HR decelerations were F3 and F4, and these are conventionally used as rTMS targets (also referred to as the Beam-F3 method). However, individually, some subjects expressed larger HR decelerations at FC3 or FC4, indicating individual variation. On the other hand, no subject expressed the largest HR decelerations at C3 or C4 [85].

This method of Neuro-Cardiac-Guided TMS (NCG-TMS) has now been replicated in both a healthy control sample (n = 30) and an MDD patient sample (n = 33), where stimulation led only to HR decelerations at the F3/F4 and FC3/FC4 sites in both cohorts (healthy controls: F3-C3: ES=.463, FC3-C3: ES=0.487). Up to 6 additional locations were tested, expressing only opposite patterns on the group level [94; unpublished data]. Another independent replication was conducted in a sample of 20 healthy subjects [95; unpublished data].

Individual participant data meta-analysis

In order to objectively test and extend this NCG-TMS approach, an individual participant data meta-analysis was conducted. Here we aimed to 1) increase the power and, 2) to asses laterality differences. Four cohorts were included: the individual data from the original pilot study [85] and the 3 replication cohorts [94,95; unpublished data]. This resulted in a total of 99 NCG measurements from 89 subjects (since subjects from the pilot study were tested with both the left-sided and right-sided NCG-TMS), resulting in 41 NCG measurements obtained at the left hemisphere and 58 from the right hemisphere. However, the C3 or C4 location was not included in every cohort (not in the MDD cohort), leaving a total of 66 measurements in only healthy controls (41 on the left and 25 on the right hemisphere) for F3/4-C3/4 and FC3/4-C3-4 comparisons. Earlier calculations for sample size (GPower 3.1.9.2) indicated that at least 22 subjects per hemisphere group were required to replicate the results from the pilot study for both hemispheres [94; unpublished data], indicating adequate power. It was hypothesized that heart rate deceleration following stimulation at F3/4 would be statistically different from C3/4, as indicated by the single studies, and that there would be no effect of hemisphere. Since all studies were conducted in the same manner, we pooled the data as if one mega-trial, as a one-stage analysis [86]. Repeated measures ANOVA was conducted with location as within-subjects factor and hemisphere as between-subjects factor. To control for differences in dataset, post-hoc analyses with dataset added as between-subjects factor was conducted.

All data were investigated for normality. See Fig. 3 for results. No differences between left and right-sided stimulation were found on the amount of HR deceleration ($F_{(1)}$=0.837, p = 0.364), nor an interaction of hemisphere with stimulation location ($F_{(1.715)}$= 0.640, p = .506). A main effect of location was found
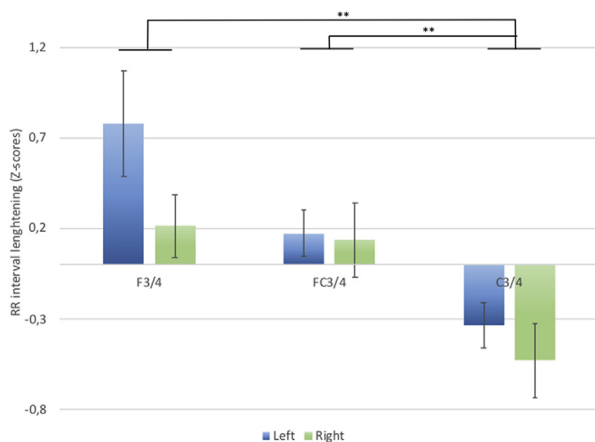
Fig. 3. Results from the individual participant meta-analysis, pooling the results from 4 studies.
RR interval lengthening (z-scores) during stimulation at different 10–20 system scalp locations (F3/4, FC3/4, C3/4), either at the left hemisphere (in blue) or the right hemisphere (in green). Increasing RR intervals represent lengthening of the interval, thus, a decrease in HR. Note that no effect of laterality was found, only an effect of location. Error bars represent standard errors of the mean (SEM). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

($F_{(1.715)} = 7.374$, p = 0.002), as hypothesized. This main effect was due to a significant difference between F3/4 and C3/4 ($t_{(65)} = 3.515$, p = 0.001, Cohens D=0.56) and FC3/4 and C3/4 ($t_{(65)} = 2.916$, p = .005, Cohens D=.47). No differences were found between F3/4 and FC3/4 ($t_{(65)} = 1.774$, p = 0.081). Post-hoc analysis with dataset as between-subjects factor indicated no differences between datasets ($F_{(2)} = 0.932$, p = 0.399).

General discussion

We outlined a frontal-vagal brain-heart network that involves direct autonomic connections to the heart for both the SNS and the PNS from the first relay station of the CNS, showing overlap with several key nodes in depression, highlighted by various neuro-modulation treatments aimed at these nodes. It has been shown that neuromodulation aimed at the DLPFC and the VN, directly influences this network by decreasing HR or increasing HRV, but it remains unclear what the effect of stimulation at the sgACC is.

Interestingly, this framework for MDD is applicable to alternative treatments for depression as well, such as meditation, improving sleep quality, exercise, etc. These therapies have direct influences on autonomic functions such as HR and breathing, thus showing that the different therapies each exert their effect on different levels of the same network. This could imply that combining different treatments might be beneficial for treatment response, as was found for the combination of rTMS with psychotherapy [78] where psychotherapy specifically activates the sgACC [87] and thus works synergistically with the DLPFC rTMS stimulation. With regard to antidepressant treatment, the exact working mechanism is unclear, but a review and meta-analysis by Kemp et al. [19] investigating the effects of antidepressants on cardiac autonomic activity indicated that tricyclic antidepressants decrease HRV, and that SSRIs have no effect on HRV. A study by Olbrich et al. showed that the antidepressant effects of SNRIs was accompanied by higher ANS arousal (e.g. HR) [88]. These findings show that antidepressant medication shares overlap with the heart-brain network as well, but the mechanism and direction of these treatments remain unsettled. This emphasizes also a possible limitation of the NCG-TMS method, since to date, no control for medication

use was included in the MDD patient cohort. Future research should focus on the specific influences of antidepressant medication on NCG-TMS outcomes, as well as a focus on other drugs with a specific cardiac effect, for example, beta-blockers and antipsychotics, which are frequently used among MDD patients. Furthermore, substances such as nicotine or coffee may also confound NCG-TMS results.

We stated that autonomic functioning is disturbed in MDD (higher HR, lower HRV) by means of a shift between sympathetic and parasympathetic activity. This could be a result of either increased sympathetic activity, a decrease in parasympathetic activity or both, but the exact mechanism is still unclear. Also, it has yet to be determined whether high HR and low HRV are state or trait related, and thus, will normalize with response to treatment. Previous research suggests that an increase in HRV was related to successful pharmacological treatment [89,90], and also with acupuncture treatment [91] for depression. However, Udupa et al. [80], did not find significant correlations between clinical improvement and autonomic function parameters, for SSRI and rTMS treatment and Brunoni et al., states that HRV is a trait marker of MDD [92], not a state marker. Recently, a study using iTBS also showed no differences over time for HR and several HRV indices as a function of iTBS treatment [96]. Differences between responders and non-responders in terms of HR and HRV have not been investigated to a great extent, although it was recently shown in a small sample that HR and HRV were not related to HRSD improvement [96].

As mentioned, multiple animal studies are available demonstrating HR decelerations after stimulation of the ventral regions of the ACC. However, there is no substantial evidence on the effect of DBS on HR in human subjects, since only a few studies investigated HR changes while stimulating the SCC/sgACC, albeit with relatively low stimulation intensities, relative to non-human studies [69,71,76]. It also remains unclear how the findings from Fox et al. [12], that showed an association between high DLPFC-sgACC anticorrelation and better treatment outcome, relate to the DBS findings, given that the DLPFC is associated with HR decreases. One difference is that the Fox 'method' makes use of a group sgACC seed region, while with DBS electrode placement is performed individually according to structural MRI's, and subjective impressions of the participant and there might be some discrepancy between both locations. This may explain why HR decelerations were found with TMS but not DBS, although both methods are similarly associated with MDD symptom improvement.

This review emphasized the opportunities of using HR and HRV metrics as a reliable marker of targeting the frontal-vagal depression network such as Neuro-Cardiac-Guided TMS, where the target is localized using HR. This method has been successfully replicated in 4 different samples, thereby the proof-of-concept has been validated. However, thus far only preliminary evidence for an association between the amount of HR-deceleration after a first session of iTBS and a better clinical response has been reported [96], therefore the relation to treatment outcome still needs to be assessed more thoroughly. Furthermore, the individual participant data meta-analysis indicated no differences between stimulation of the left or right hemisphere, although earlier studies suggest greater right prefrontal influence over vagal mediated cardiac output. Still, it was also found that both prefrontal cortices are linked to parasympathetic (vagal) activity [93], which is also supported by the individual participant data meta-analysis. It has to be noted that gender differences have not yet been investigated for NCG-TMS application. As mentioned earlier, gender differences have been found for MDD, and HRV [36,42], indicating it is not unlikely that men and women respond differently to NCG-TMS, which would be a topic of interest for future research.

Since the VN is involved in all parasympathetic functions, stimulation of the DLPFC, sgACC or VN might also impact pupil dilation and gastrointestinal function. Thus, these might also be dysregulated in depression, and may also serve as markers of targeting the depression network, but, the adequacy and utility of these have yet to be established. Furthermore, the focus of this review was on MDD, but could be translated to other psychiatric disorders that impact the autonomic nervous system as well.

Conclusion

To summarize, autonomic functioning, such as HR and HRV, could serve as potential target engagement mechanism for optimizing and individualizing neuromodulation treatments in depression. Based on this, we emphasize the importance of including HR and HRV measurements during human depression studies, in particular those that conduct neuromodulation, to investigate to a better extent the acute effects of neuromodulation on autonomic functioning, and to establish the efficacy of ECG metrics in target engagement of the frontal-vagal network.

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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) but does not receive any royalties related to these patents; Research Institute Brainclinics received funding from Brain Resource (Sydney, Australia), neuroCare Group (Munich, Germany) and Urgotech, 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 proceeds or royalties. NERvB, JLK and RV have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.10.006.

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