# Heartbeat evoked potential in major depressive disorder

Zwienenberg, Lauren; van Dijk, Hanneke; Enriquez Geppert, Stefanie; van der Vinne, Nikita; Gevirtz, Richard; Gordon, Evian ; Sack, Alexander T. ; Arns, Martijn

*Published in:*
Neuropsychobiology

*DOI:*
10.1159/000529308

Neuropsychobiology

Research Article

Neuropsychobiology 2023;82:158–167
DOI: 10.1159/000529308

Received: August 24, 2022
Accepted: January 13, 2023
Published online: March 16, 2023

# Heartbeat-Evoked Potential in Major Depressive Disorder: A Biomarker for Differential Treatment Prediction between Venlafaxine and rTMS?

Lauren Zwienenberg[a, b, c] Hanneke van Dijk[a, c] Stefanie Enriquez-Geppert[d] Nikita van der Vinne[a, b] Richard Gevirtz[e] Evian Gordon[f, g] Alexander T. Sack[c] Martijn Arns[a, c]

[a]Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, The Netherlands; [b]Synaeda Psycho Medisch Centrum, Leeuwarden, The Netherlands; [c]Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; [d]Department Clinical and Developmental Neuropsychology, Faculty of Behaviour and Social Sciences, University of Groningen, Groningen, The Netherlands; [e]CSSP@Alliant International University, San Diego, CA, USA; [f]Brain Resource Ltd, Sydney, NSW, Australia; [g]Brain Resource Ltd, San Francisco, CA, USA

**Keywords**
Heartbeat-evoked potential · EEG · Electrocardiogram · Venlafaxine · rTMS

**Abstract**
***Introduction:*** Currently, major depressive disorder (MDD) treatment plans are based on trial-and-error, and remission rates remain low. A strategy to replace trial-and-error and increase remission rates could be treatment stratification. We explored the heartbeat-evoked potential (HEP) as a biomarker for treatment stratification to either antidepressant medication or rTMS treatment. ***Methods:*** Two datasets were analyzed: (1) the International Study to Predict Optimized Treatment in Depression (iSPOT-D; $n$ = 1,008 MDD patients, randomized to escitalopram, sertraline, or venlafaxine, and $n$ = 336 healthy controls) and (2) a multi-site, open-label rTMS study ($n$ = 196). The primary outcome measure was remission. Cardiac field artifacts were removed from the baseline EEG using independent component analysis (ICA). The HEP-peak was detected in a bandwidth of 20 ms around 8 ms and 270 ms (N8, N270) after the R-peak of the electrocardiogram signal. Differences between remitters and non-remitters were statistically assessed by repeated-measures ANOVAs for electrodes Fp1, Cz, and Oz. ***Results:*** In the venlafaxine subgroup, remitters showed a lower HEP around the N8 peak than non-remitters on electrode site Cz ($p$ = 0.004; $d$ = 0.497). The rTMS group showed a non-significant difference in the opposite direction ($d$ = −0.051). Retrospective stratification to one of the treatments based on the HEP resulted in enhanced treatment outcome prediction for venlafaxine (+22.98%) and rTMS (+10.66%). ***Conclusion:*** These data suggest that the HEP could be used as a stratification biomarker between venlafaxine and rTMS; however, future out-of-sample replication is warranted.



Alexander T. Sack and Martijn Arns share senior authorship.

Karger@karger.com
www.karger.com/nps



Correspondence to:
Lauren Zwienenberg, l.zwienenberg@synaeda.nl

## Introduction

Although there are various antidepressant treatments for major depressive disorder (MDD), remission rates remain low [1]. One reason could be the current way of treatment selection which is based on trial-and-error with first-choice treatments consisting of psychotherapy and antidepressant medication (AD). A possible strategy to increase remission rates could therefore be treatment stratification between equally effective treatments based on biomarkers [2]. In this regard, specifically, heart rate (HR) and heart rate variability (HRV) have been suggested as useful candidates [3].

Against this background, an overall higher HR and lower HRV have been reported in patients with MDD, indicating dysregulation of their autonomic nervous system [4]. It is therefore not surprising that MDD has been found to be an independent risk factor for developing cardiovascular diseases [5]. Interestingly, it was shown that both HR and HRV can be normalized during neuromodulation treatment. However, this effect does not seem to be long lasting and was not found in treatment with antidepressant medication [4, 6]. In addition, treatment with venlafaxine can lead to a higher HR and lower HRV [7].

Afferent influence from the heart on the brain might play an important role in cognitive processing and emotions, as it was found in earlier reports of gut and stomach influences over brain networks such as the default mode network; however, knowledge is still limited [8, 9]. The heart and brain have an interactive connection [10]. Stimulation with rTMS to the dorsolateral prefrontal cortex activates the downstream frontal-vagal pathway [11], which results in lower HR and higher HRV [6, 12, 13]. Besides the frontal-vagal pathway, there are also bottom-up influences from the heart to the brain. The heart and brain are connected in four ways [14]: (1) physically by the pulsating (cerebral) blood flow, (2) biochemically through hormones and neurotransmitters, (3) electrically by an electric field of the heart that continually affects the whole body, and (4) the nervous system that controls HR and HRV. Although the knowledge about the afferent influence of the heart on the brain is still limited, this might play an important role in cognitive processing and emotions.

One way to operationalize the heart's effect on the brain is to look at the neural electrophysiological response in the brain that is phase locked to the R-peak in the electrocardiogram (ECG), or the so-called heartbeat-evoked potential (HEP) [15]. The HEP, known as an objective marker of interoceptive awareness, has a decreased amplitude in MDD patients relative to healthy controls [16] and can be increased by cardiac awareness training [17]. Studies on the localization and intracranial recordings of the HEP generators show the contribution of the insular cortex, cingulate cortex, amygdala, and somatosensory cortex [18–20]. Current knowledge proposed furthermore that the HEP provides a sensitive cortical index of cardiac processing, reflecting changes in emotional and arousal states [21].

Given the low remission rates in MDD treatment, functional subgroups within MDD patients are suggested to respond differently to treatments. Based on the knowledge that (1) interoceptive awareness could be used as a somatic marker for depression, (2) the HEP is correlated to interoceptive awareness, and (3) treatment with venlafaxine and rTMS have opposite outcomes on HR and HRV, we tested whether the HEP could function as a biomarker for treatment stratification [2] in MDD and thereby help parsing inherent heterogeneity into more homogenous subgroups. Therefore, we aimed to investigate whether there are differences in resting state baseline HEP amplitude between remitters and non-remitters to antidepressant medication and rTMS treatment.

## Materials and Methods

*Design*

Sample 1: iSPOT-D

This study is based on data acquired from the International Study to Predict Optimized Treatment in Depression (iSPOT-D), an international, randomized, prospective, practical, clinical open-label trial aimed at finding biomarkers for antidepressant treatment response, in which MDD participants were randomized to escitalopram, sertraline, or venlafaxine-XR in a 1:1:1 ratio. A complete description of the study methods is published elsewhere [22, 23].

Sample 2: rTMS

rTMS data were acquired from a multi-site, open-label study. rTMS treatment consisted of either low-frequency (1Hz) stimulation on the right DLPFC, high-frequency (10 Hz) stimulation on the left DLPFC, or stimulation at both sites. rTMS was complemented with cognitive behavioral therapy. A complete description of the study methods is published elsewhere [24].

*Participants and Treatment*

Sample 1: iSPOT-D

1,008 nonpsychotic adult MDD patients and 336 matched healthy controls participated in the study (for the consort diagram and demographic features of the whole sample, see [23]). MDD patients were treatment-naïve, or medication was washed out (5 half-lives). The Mini-International Neuropsychiatric Interview (MINI-plus) [25] according to the DSM-IV criteria and the Hamilton Rating Scale for Depression (HRSD17), a score ≥16, were

**Table 1.** Overview of participant demographics of samples 1 and 2

| | Sample 1: iSPOT-D | | | | | Sample 2 |
|---|---|---|---|---|---|---|
| | MDD | HC | Escitalopram | Sertraline | Venlafaxine-XR | rTMS |
| N | 552 | 247 | 180 | 193 | 179 | 163 |
| Females | 301 | 141 | 92 | 106 | 103 | 87 |
| 163 | 38.9 (12.9) | 36.5 (12.8) | 39.0 (13.0) | 38.6 (12.5) | 39.1 (13.3) | 43.1 (13.1) |
| Pre-HRSD17 (SD) | 21.63 (3.92) | 1.21 (1.57) | 21.67 (3.92) | 21.72 (4.05) | 21.49 (3.80) | 31.52 (10.26) |
| Pre-BDI (SD) | – | – | – | – | – | 31.26 (10.0) |
| HRSD17 week 8 (SD) | 9.66 (6.33) | 1.13 (1.44) | 9.26 (6.68) | 9.77 (5.92) | 9.96 (6.42) | – |
| BDI week 8 (SD) | – | – | – | – | | 14.39 (12.47) |
| % remission | 44.7 | – | 48.9 | 42.5 | 43.0 | 53.4 |

used to confirm the primary diagnosis of nonpsychotic MDD at baseline visit. All participants took part in the EEG assessment. After 8 weeks of treatment, the participants came in for clinical assessment. An overview of patient demographics can be found in Table 1.

The total amount of usable baseline EEG measurements was 1,296, with a final total of 769 MDD (552 protocol completers) and 247 HC: 124 were excluded due to no/bad peak detection, 144 due to reversed polarization of the R peaks, and 12 did not meet requirements on the minimal number of segments. In 94% of the cases, there was one cardiac-field artifact (CFA) independent component (IC) excluded, in 4% there were no ICs excluded due to unclear CFA, and in 2% of the cases, 2 ICs were excluded.

Sample 2: rTMS

The total sample consisted of 196 patients, 98 female and 98 male, aged 18–78 (43.2 ± 12.9). Patients underwent at least 10 rTMS sessions, with an average of 20.9 sessions (SD = 7.5). The Beck Depression Inventory, second edition Dutch version (BDI-II-NL; BDI) [26], was assessed at baseline, every fifth session, and at the last session. A baseline BDI ≥14 confirmed the diagnosis of MDD. An overview of patient demographics can be found in Table 1.

Of the initial dataset, 163 remained with complete data (one excluded due to missing data; 17 excluded due to missing the ECG channel; seven excluded due to inverse peak polarization; seven excluded because of bad peak detection; and one excluded due to insufficient segments). In 99% of the cases, there was one CFA component excluded; in 1%, there was no component excluded because it was unclear which component represented the CFA.

*Pre-Treatment Assessments: Eyes Closed Resting State*

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Sydney,NSW, Australia). Details of this procedure [22, 23] and details on the reliability and across-site consistency of the EEG assessment [27, 28] have been published earlier. In short, participants were seated in a sound- and light-attenuated room that was controlled at an ambient temperature of 22°C. 26 channels were used for the EEG acquisition: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, Cp4, T5, P3, Pz, P4, T6, O1, Oz, and O2 (Quikcap; NuAmps; extended 10–20 electrode international system). For the ECG measurements, one electrode was placed on the inner left wrist. Both EEG and ECG data were simultaneously collected for 2 min with eyes closed (EC). Participants were asked to remain relaxed during the assessment. Data were offline referenced to average mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left lower eyelid. Electrode impedance was maintained at <10 kOhms for all electrodes. Sampling rate of all channels was 500 Hz. A low-pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

*Preprocessing EEG and ECG Data*

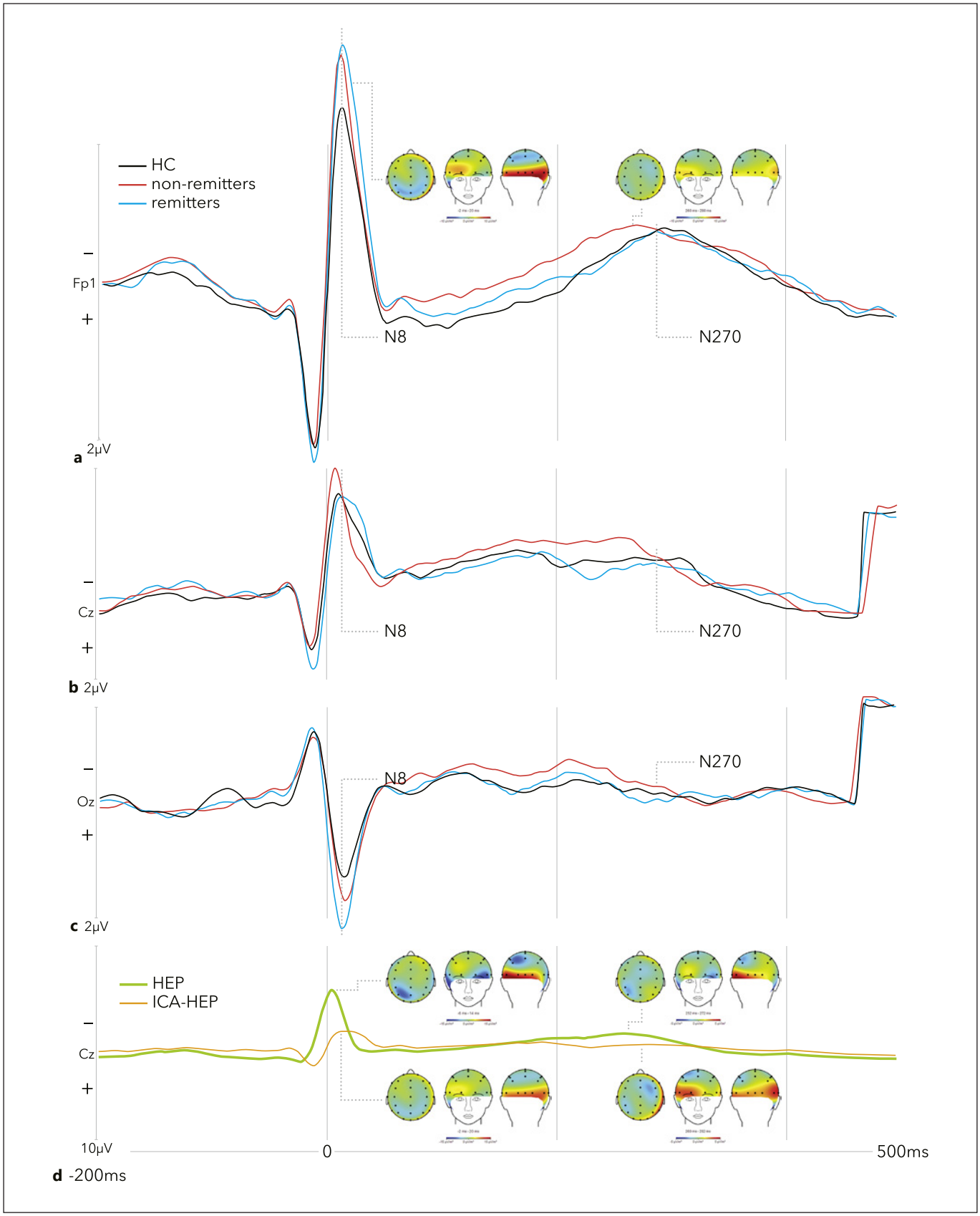
Data were preprocessed using Brain Vision Analyzer 2.2.0.7383 (Brain Products GmbH). The EEG channels were filtered with an infinite impulse response filter with a high pass of 0.05 Hz and a low pass of 40 Hz. The ECG channel was filtered with a high pass of 0.05 Hz and low pass of 25 Hz.

ECG marker R- and T-peaks were detected using automatic peak detection but were manually verified for correctness. ECG data with negative R-peaks were excluded from the analyses. In case of incorrect peak detection, the settings were changed from automatic to positive peak detection. In case peak detection was still incorrect after changing the settings, the data were excluded from analyses.

Segmentation was based on the latency of the R-peak with a total length of 700 ms: 200 ms before and 500 ms after the R-peak. Overlapping segments were allowed. After segmentation, a DC Detrend for segments correction was applied to the data with interval lengths based on time; 200 ms before the start of the segment to 200 ms after the end of the segment.

**Fig. 1.** Average HEP of iSPOT-D study for Fp1 (**a**), Cz (**b**), and Oz (**c**). Visualized are the differences for HC (black), all non-remitters (red), and all remitters (blue) after ICA correction (ICA-HEP). Topographical plots show the top, front, and back views of the EEG amplitudes for all electrode sites for both peaks. **d** The original EEG signal at Cz before (green) and after (orange) ICA-correction. The topographical plots show the EEG amplitudes for both the non-corrected HEP (top) and the ICA-HEP (bottom). Please note that negative amplitudes are plotted upward and positive amplitudes downward.

*(For figure see next page.)*




1

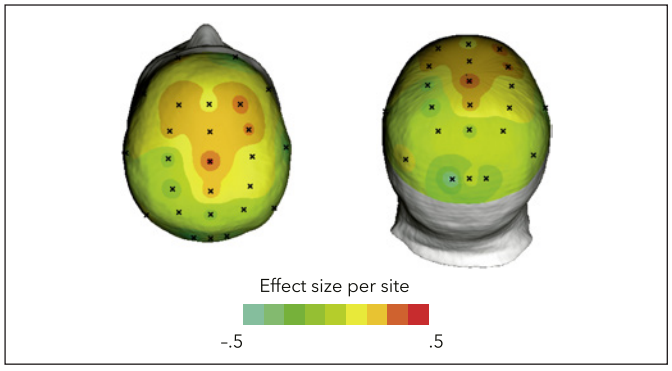



**Fig. 2.** Topography plot showing effect sizes (Cohen's d) of the differences between remitters and non-remitters of the N8 HEP for the venlafaxine group. A significant effect was found at Cz.

Artifact rejection (AR) was carried out using automatic segment selection on all EEG channels (maximum amplitude was 150 μV) [29]. Cases that consisted of <90 segments before AR were excluded from the analysis since this suggests the peak detection was incorrect and/or the patient had an abnormal heartbeat. After AR, cases with <45 segments were excluded to maintain an adequate signal-to-noise ratio.

For the removal of volume conducted CFA from the heart-related brain potential, independent component analyses (ICA) have been shown to be effective in removing artifactual components from the HEP [16]. Thus, a restricted infomax ICA with normal PCA sphering was automatically carried out on the whole data of all EEG channels and the ECG channel. ICs were then compared to the ECG. ICs suggesting reflecting a CFA were semi-automatically identified and satisfied two criteria: (1) the plotted average had to account for the R- and T-peak time course, (2) the topographical maps of the ICA inverse weighs must show a dipole with the maximum around Oz and the minimum around Fp1/Fp2. On average, 1–2 CFA-ICs per subject were identified by one rater. These were then excluded from back-projection to the EEG-channels.

Subsequently, the average of all segments was calculated per subject. Next, group averages for both remitters and non-remitters of both samples were calculated. A new channel was created, containing the group average signal of all EEG channels of the iSPOT-D sample. Based on this new channel, the timing and amplitude of the R-peak (N8) and T-peak (N270) of the ECG signal were determined for usage in the following analyses.

Mean values of 20 ms, 10 ms before and after the peak, were computed and used to extract the area under the curve (AUC; $\mu V^2$) in Brain Vision Analyzer and exported to SPSS (Version 27.0; IBM SPSS Statistics for iOS, Armonk, NY, USA) per individual and channel. Within these bandwidths, the amplitude of the peak was checked for all channels. The electrodes with the highest AUC, the lowest AUC, and a third topographically located in the middle were selected from the iSPOT-D dataset for the analyses in both samples, allowing for stratification. This resulted in the use of electrodes Fp1, Cz, and Oz in the analyses. See online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529308) average peaks, and in the online supplementary Table 2 for the timing and respective AUC values of these electrode sites.

*Statistical Design*

The primary outcome measure was remission and resting state. EC EEG was used since EC is considered a more "interoceptive brain state" [30]. Remission was defined as a score of ≤7 on the HRSD17 (sample 1) or a BDI <12 (sample 2) after 8 weeks or at the last session. HEP AUC values were inspected and were log transformed to assure a normal distribution. Differences in age, sex, education, and baseline severity of sample 1 were already reported by [23]. For sample 2, differences between remitters and non-remitters were tested using *t* tests. Significant variables were considered covariates in the analyses.

All statistical analyses in SPSS for treatment prediction were conducted on protocol completers. Differences between remitters and non-remitters (Fig. 1a–c) were tested with repeated-measures ANOVAs (RM ANOVAs), with the factor being remission type (remitters, non-remitters), the within-subjects variable was electrode site (Fp1, Cz, and Oz), the between-subjects variable was sex (male, female). Baseline severity and age were added as covariates. The iSPOT-D analyses had an extra between-subjects variable: treatment arm (escitalopram, sertraline, or venlafaxine-XR).

Significant (interaction) effects regarding remission were further investigated using RM ANOVAs with the data split by the significant variables. A conventional alpha of $p \leq 0.05$ is used. The effects of site were investigated by creating topography plots of the effect sizes (ESs) over all EEG sites. ES are reported in Cohen's d. Post hoc partial correlations were calculated. To assess the clinical relevance of the HEP, the normalized positive predictive value (N-PPV) of the HEP is examined, based on the Youden's J cut-off.

## Results

*Sample 1: iSPOT-D*

The demographics of the participants with usable EEG data and who completed the protocol can be found in Table 1.

*Remitters versus Non-remitters*

The RM ANOVA on the N8 peak yielded a significant-between subjects remission X treatment effect ($F(2, 1{,}036) = 3.129$, $p = 0.045$). With the data split by treatment, the RM ANOVA showed a between-subjects effect of remission ($F(1, 171) = 3.940$, $p = 0.049$) for the venlafaxine group. In this group, a univariate general linear model (GLM) ANOVA with the three sites showed a significant effect of Cz ($F(1,173) = 8.369$, $p = 0.004$, $d = 0.497$; Figure 2), with venlafaxine remitters having a lower HEP than non-remitters (Fig. 3a). A significant partial correlation between the percentage improvement on the HRSD17 and the AUC of Cz for the venlafaxine group, covaried for age and baseline severity, was found ($r^2 = 2.2\%$, $p = 0.05$). The analyses on the N270 peak yielded no significant effects.

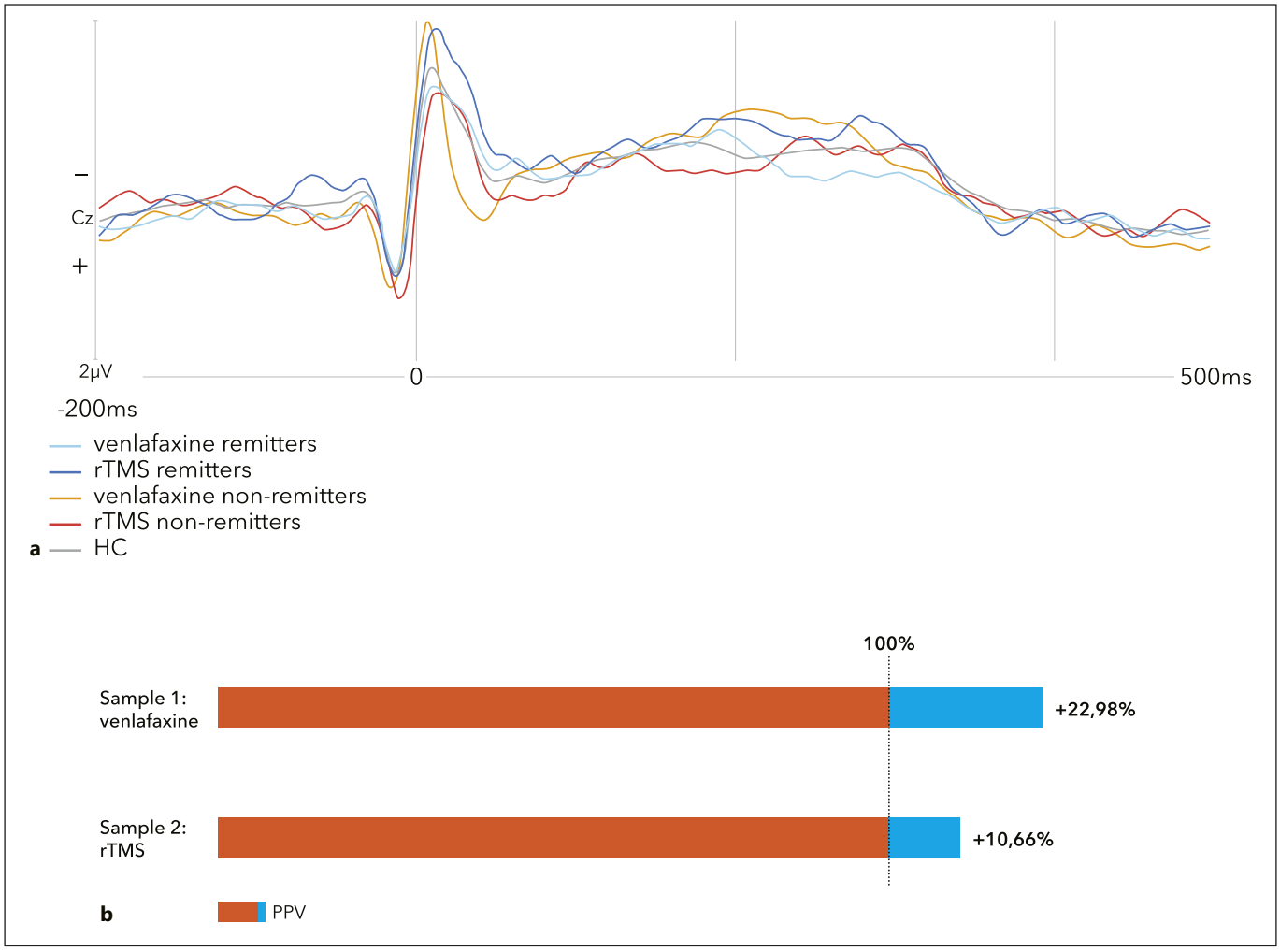



**Fig. 3. a** Average HEP signals on Cz of HC and the (non-) remitters from the venlafaxine and rTMS sample. Please note that negative amplitudes are plotted upward and positive downward. **b** N-PPV when stratifying based on the HEP.

*Sample 2: rTMS*

No differences between remitters and non-remitters were found for age ($t(161) = -0.169$, n.s.) and sex ($t(161) = -0.449$, n.s.). Baseline severity was different between remitters and non-remitters ($t(161) = 5.72$, $p < 0.001$), with non-remitters having higher baseline severity.

The RM ANOVAs for both N8 and N270, as well as the partial correlation between the AUC values of both peaks and the BDI change, correlating for baseline severity, showed no significant effects. Interestingly, the ES of Cz appeared small between remitters and non-remitters but was found in the opposite direction as for venlafaxine ($d = -0.051$), meaning rTMS remitters had a higher HEP than non-remitters (Fig. 3a).

*Sensitivity Analysis*

The ECG AUC value was analyzed per group to verify whether differences in ECG between remitters and non-remitters caused the significant effects in HEP. A one-way ANOVA of the ECG signals was run for the venlafaxine group. This ANOVA showed no significant effects ($p = 0.107$, $d = 0.243$), which suggests that the HEP differences related to remission originate from brain activity and are not directly caused by the electrical field of the heart. In addition, adding the ECG AUC as a covariate to the above analyses did not change the results, suggesting the significant differences were not driven by the ECG channel.

*Stratification*

As can be seen in Figure 3a, although non-significant, the rTMS sample yields differences in HEP between remitters and non-remitters that are in opposite direction of the venlafaxine results, which opens the possibility to stratify between the two treatments. Although escitalopram ($d$ = 0.067) and sertraline ($d$ = −0.011) also showed opposite effects, the ESs were non-significant and both smaller than the venlafaxine and rTMS sample and were thus disregarded in the stratification analysis.

To test the predictive value of HEP as a biomarker for stratification between treatments, we calculated the N-PPV. The N-PPV shows the added value of using the HEP as a stratification biomarker over the PPV without using the HEP for treatment prediction.

The Youden's J of Cz for the subgroup venlafaxine was highest at an AUC value of 1.17 ($J$ = 0.236); this was set as the cut-off for the predictions. When an individual's HEP on Cz was higher than the cut-off and the person was in the rTMS sample, remission was predicted, whereas a person from the venlafaxine sample was assigned remitter status with a HEP value below that cut-off. These outcomes were retrospectively compared to the real remission rates, which resulted in the calculation of the N-PPV, of which the results can be found in Figure 3b, showing increased remission rates for venlafaxine of 22.98% and 10.66% for the rTMS group.

## Discussion

We explored the differences in baseline HEP between remitters and non-remitters of MDD patients to either AD or rTMS treatment and looked whether the HEP could be used as a biomarker to predict remission outcomes in depression and for stratifying between treatment with venlafaxine and rTMS. Significant differences between remitters and non-remitters were found for the N8 peak at Cz in the venlafaxine group, where remitters showed a smaller HEP amplitude, whereas no differences were found for the selective serotonin reuptake inhibitors (SSRIs) sertraline and escitalopram. For rTMS, numerically the opposite was found, although non-significant, with a larger N8 peak at Cz for remitters, with a small ES. Stratifying without significant effects can still be clinically relevant since we are stratifying between evidence-based treatments. The theory behind this can be clarified using the Monty Hall problem (described in [2]). Based on the significant difference in the venlafaxine group, we know that someone with a high HEP is unlikely to remit to venlafaxine treatment. In the rTMS group, an opposite effect is seen, which makes a person with a high HEP more likely to remit to rTMS treatment and vice versa, which opens the door to treatment stratification based on the HEP.

By calculating the N-PPV, the data showed added value for both treatments when stratifying based on the HEP between treatment with rTMS and venlafaxine. Although using the HEP as a stratification biomarker already results in an added value of 23% for the venlafaxine group and 10% for the rTMS group, when you compare this added value to the decreased value if these participants were stratified to the opposite treatment (−7.33% for the venlafaxine and −31.79% for the rTMS group), the added value of using the HEP as a stratification biomarker appears even larger.

The differences reported for venlafaxine were found at Cz, which directly overlies the somatosensory cortex. The somatosensory cortex is directly connected to the insula, the processor of interoceptive signals [19]. Adding to that, the somatosensory cortex is mainly innervated by the noradrenergic system [31], which agrees with the specificity of this effect being confined to the selective serotonin and noradrenalin reuptake inhibitor venlafaxine.

In this study, we compared the value of HEPs in the assessment of treatment responsiveness to rTMS and various forms of pharmacotherapy including venlafaxine, escitalopram, and sertraline, in patients with major depression. As described earlier, rTMS treatment targeting the dorsolateral prefrontal cortex shows an immediate effect on the heart rate, leading to a heart rate deceleration and lower blood pressure [11, 13]. In contrast, venlafaxine treatment, a selective serotonin and noradrenalin reuptake inhibitor, often results in heart rate acceleration and increasing blood pressure [7]. The SSRIs escitalopram and sertraline may also influence the heart, but this is much less likely and if so, only very mildly [32]. These pharmacodynamic factors could account for the differences found for venlafaxine and, non-significantly, the rTMS group, as well as the absence of differences found for the two SSRIs. Importantly, if the treatment had no effect on heart rate and blood pressure, one would not expect a predictive value in a heart rate-related biomarker like the HEP and subsequently also no differences between remitters and non-remitters.

Terhaar et al. [16] reported MDD patients having a lower HEP than HC. Although they focused on a different HEP latency window, we found HC having a lower HEP than MDD patients over the whole seg-

ment, including their latency window. This could be explained by the different methods used in both studies. In their study, participants had to count their heartbeat during the HEP measurement, an interoceptive task. The HEP has been proven to be sensitive to changes in directed attention [33] which has been confirmed by studies [34] showing that the HEP decreases during somatosensory tasks compared to the resting state. In addition [16], we used the data of 32 participants some of whom already used an AD. Mussgay et al. [35] stated that medication use has no effect on heartbeat perception, but this could have had an influence on the HEP.

Concluding, the lower HEP is the outcome of a lower interoceptive awareness in MDD, likely driven by a reduced noradrenergic tone. This implies that HEP is purely a perception concept in MDD and that the reason for a lower interoceptive awareness should be searched for somewhere other than in physical influences.

Limitations of our study included our choice of HEP timing being data driven, not theory driven, based on the observed group differences. Prior studies examined different HEP latencies from 20 to 592 ms after the R peak [16, 36, 37]. Post hoc sensitivity analyses within the window of 170–270 ms after R peak yielded no different results. Possibly, using a group-ICA as a method of determining the latency of the HEP component can add to the knowledge about the topography of interest of the HEP in MDD.

Using ICA as a means of CFA correction is a generally powerful method, but no study has demonstrated a complete removal of the CFA by means of ICA. Terhaar et al. [16] excluded two CFA components, one concerning the R-peak of the ECG and the second concerning the T-peak of the ECG. In our preprocessing, we looked for two CFA components, but in most cases only one CFA component could be found. This could mean not all CFA is removed. Besides not removing all CFA, the ICA can cause removal of actual EEG signals. We focused on removing most CFA, but we intended not to remove the EEG signal (Fig. 1d). Petzschner et al. [36] assumed that with equal cardiac activity in both groups, it is safe to assume that the CFA is constant in those groups and will therefore not affect the differences between remitters and non-remitters. To assure this equal cardiac activity, we both visually and statistically compared the ECG signal amplitude across conditions, and no significant differences were found. Also, when covarying for ECG, the results did not differ.

Another limitation of this study is the lack of uniformity in stimulus frequency and stimulus site in the rTMS group. All rTMS data were combined, but there might be differences in HEP for remitters and non-remitters between the 1 Hz and 10 Hz protocols. To account for this limitation, we compared the baseline HEP values between the rTMS protocols post hoc and found no significant differences. This suggests that you can combine the different rTMS protocols as one treatment, and this has no influence on the study outcome.

## Conclusion

We found that the HEP is a potential differential biomarker in MDD treatment prediction between treating with venlafaxine and rTMS. However, this was the first study to investigate predictive applications, so validation and replication need to be done thoroughly, looking at the timing and localization of the HEP and at different outcome measures as a means of determining remission rates as to looking at removing the CFA.

## Acknowledgments

We thank Mark Koppenberg for creating the table and figures.

## Statement of Ethics

The iSPOT-D study is conducted according to the principles of the Declaration of Helsinki 2008 (http://www.wma.net/en/30publications/10policies/b3/index.html), the International Conference on Harmonization (ICH; http://www.ich.org/home.html) guidelines, and/or in compliance with the laws and regulations of the country in which the research is conducted, including the "Good Clinical Practice" principles in the US FDA Code of Federal Regulations (http://www.fda.gov/ScienceResearch/SpecialTopics/). The rTMS data are from a naturalistic open-label study in which patients enrolled at three outpatient mental health care clinics. They all gave written informed consent to use the data for scientific purposes.

## Conflict of Interest Statement

M.A. is unpaid chairman of the non-profit Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation, and psychophysiology but receives no royalties related to these patents. Research Institute Brainclinics received research funding from neuroCare Group (Munich, Germany), Brain Resource (Sydney, Australia), Urgotech (France), Neuroscience

Software (US), and equipment support from Deymed, neuroConn, and Magventure. AS is Chief Scientific Advisor of PlatoScience, Chief Scientific Advisor of Alphasys, CEO of Neurowear Medical B.V., and Director of the International Clinical TMS Certification Course (www.tmscourse.eu) and got equipment support from MagVenture and MagStim Company. All other authors declare no interests.

## Author Contributions

Conception or design of the work M.A., L.Z., and H.D. Data collection: E.G. and M.A. Data analysis and interpretation: L.Z., M.A., S.E.-G., H.D., and N.V. Drafting the article: L.Z. Critical revision of the article M.A., N.V., H.D., S.E.-G, R.G., E.G., and A.T.S. All authors read and approved the final version of the article.


## Funding Sources

No funding was received.


## Data Availability Statement

iSPOT data are available upon reasonable request at the iSPOT Publication Committee, and data generated for this study are available from the corresponding author. The rTMS data are available in the TDBRAIN dataset [38] which can be downloaded on https://brainclinics.com/resources/.

## References


1 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905–17.
2 Arns M, van Dijk H, Luykx JJ, van Wingen G, Olbrich S. Stratified psychiatry: tomorrow's precision psychiatry? Eur Neuropsychopharmacol. 2022;55:14–9.
3 Kircanski K, Williams LM, Gotlib IH. Heart rate variability as a biomarker of anxious depression response to antidepressant medication. Depress Anxiety. 2019;36(1):63–71.
4 Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol Psychiatry. 2010;67(11):1067–74.
5 Ehrenthal JC, Herrmann-Lingen C, Fey M, Schauenburg H. Altered cardiovascular adaptability in depressed patients without heart disease. World J Biol Psychiatry. 2010;11(3):586–93.
6 Iseger TA, Padberg F, Kenemans JL, van Dijk H, Arns M. Neuro-Cardiac-Guided TMS (NCG TMS): a replication and extension study. Biol Psychol. 2021;162:108097.
7 Terhardt J, Lederbogen F, Feuerhack A, Hamann-Weber B, Gilles M, Schilling C, et al. Heart rate variability during antidepressant treatment with venlafaxine and mirtazapine. Clin Neuropharmacol. 2013;36(6):198–202.
8 Porciello G, Monti A, Aglioti SM. How the stomach and the brain work together at rest. Elife. 2018;7:e37009.
9 Cao J, Wang X, Lu KH, Tan Z, Phillips R, Jaffey D, et al. SPARC: brain-stomach synchrony observed with functional magnetic resonance imaging and electrogastrogram in rats. FASEB J. 2020;34(S1):1.
10 Lacey BC, Lacey JI. Two-way communication between the heart and the brain: significance of time within the cardiac cycle. Am Psychol. 1978;33(2):99–113.
11 Iseger TA, van Bueren NER, Kenemans JL, Gevirtz R, Arns M. A frontal-vagal network theory for major depressive disorder: implications for optimizing neuromodulation techniques. Brain Stimul. 2020;13(1):1–9.
12 Iseger TA, Padberg F, Kenemans JL, Gevirtz R, Arns M. Neuro-Cardiac-Guided TMS (NCG-TMS): probing DLPFC-sgACC-vagus nerve connectivity using heart rate - first results. Brain Stimul. 2017;10(5):1006–8.
13 Zwienenberg L, Iseger TA, Dijkstra E, Rouwhorst R, van Dijk H, Sack AT, et al. Neurocardiac guided rTMS as a stratifying method between the '5 cm' and 'BeamF3' stimulation clusters. Brain Stimul. 2021;14(5):1070–2.
14 McCraty R. Science of the heart: exploring the role of the heart in human performance. In: A very good review that explore interesting aspects of the science of the heart in the fields of psychophysiology and neurocardiology including pain perception. Boulder Creek: HeartMath Institute; 2015.
15 Schandry R, Montoya P. Event-related brain potentials and the processing of cardiac activity. Biol Psychol. 1996;42(1–2):75–85.
16 Terhaar J, Viola FC, Bär KJ, Debener S. Heartbeat evoked potentials mirror altered body perception in depressed patients. Clin Neurophysiol. 2012;123(10):1950–7.
17 Schandry R, Weitkunat R. Enhancement of heartbeat-related brain potentials through cardiac awareness training. Int J Neurosci. 1990;53(2–4):243–53.
18 Kern M, Aertsen A, Schulze-Bonhage A, Ball T. Heart cycle-related effects on event-related potentials, spectral power changes, and connectivity patterns in the human ECoG. Neuroimage. 20131961;8116:178–90.
19 Salomon R, Ronchi R, Dönz J, Bello-Ruiz J, Herbelin B, Faivre N, et al. Insula mediates heartbeat related effects on visual consciousness. Cortex. 2018;101:87–95.
20 Park HD, Bernasconi F, Salomon R, Tallon-Baudry C, Spinelli L, Seeck M, et al. Neural sources and underlying mechanisms of neural responses to heartbeats, and their role in bodily self-consciousness: an intracranial EEG study. Cereb Cortex. 2018;28(7):2351–64.
21 Park HD, Blanke O. Heartbeat-evoked cortical responses: underlying mechanisms, functional roles, and methodological considerations. Neuroimage. 2019;197:502–11.
22 Williams LM, Rush AJ, Koslow SH, Wisniewski SR, Cooper NJ, Nemeroff CB, et al. International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials. 2011;12:4–17.
23 Arns M, Bruder G, Hegerl U, Spooner C, Palmer DM, Etkin A, et al. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. Clin Neurophysiol. 2016;127(1):509–19.
24 Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: clinical outcomes and predictors from a large naturalistic study. Brain Stimul. 2018;11(2):337–45.
25 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl 20):22–33. quiz 34-57.
26 Does W. Manual of the Dutch version of the Beck depression inventory (BDI-II-NL). Amsterdam, NL: Harcourt; 2002.
27 Williams LM, Simms E, Clark CR, Paul RH, Rowe D, Gordon E. The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "neuromarker". Int J Neurosci. 2005;115(12):1605–30.

28 Paul RH, Gunstad J, Cooper N, Williams LM, Clark CR, Cohen RA, et al. Cross-cultural assessment of neuropsychological performance and electrical brain function measures: additional validation of an international brain database. Int J Neurosci. 2007;117(4):549–68.
29 van Dinteren R, Huster RJ, Jongsma MLA, Kessels RPC, Arns M. Differences in cortical sources of the event-related P3 potential between young and old participants indicate frontal compensation. Brain Topogr. 2017;31(1):35–46.
30 Marx E, Stephan T, Nolte A, Deutschländer A, Seelos KC, Dieterich M, et al. Eye closure in darkness animates sensory systems. Neuroimage. 2003;19(3):924–34.
31 Rodenkirch C, Liu Y, Schriver BJ, Wang Q. Locus coeruleus activation enhances thalamic feature selectivity via norepinephrine regulation of intrathalamic circuit dynamics. Nat Neurosci. 2019;22(1):120–33.
32 Yekehtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular considerations in antidepressant therapy: an evidence-based review. J Tehran Heart Cent. 2013 Oct 28;8(4):169–76.
33 Montoya P, Schandry R, Müller A. Heartbeat Evoked Potentials (HEP): topography and influence of cardiac awareness and focus of attention. Electroencephalogr Clin Neurophysiol. 1993;88(3):163–72.
34 Al E, Iliopoulos F, Nikulin VV, Villringer A. Heartbeat and somatosensory perception. Neuroimage. 2021;238:118247.
35 Mussgay L, Klinkenberg N, Rüddel H. Heart beat perception in patients with depressive, somatoform, and personality disorders. J Psychophysiol. 1999;13(1):27–36.
36 Wei Y, Ramautar JR, Colombo MA, Stoffers D, Gómez-Herrero G, van der Meijden WP, et al. I keep a close watch on this heart of mine: increased interoception in insomnia. Sleep. 2016;39(12):2113–24.
37 Petzschner FH, Weber LA, Wellstein KV, Paolini G, Do CT, Stephan KE. Focus of attention modulates the heartbeat evoked potential. Neuroimage. 2019;186:595–606.
38 van Dijk H, van Wingen G, Denys D, Olbrich S, van Ruth R, Arns M. The two decades brainclinics research archive for insights in neurophysiology (TDBRAIN) database. Sci Data. 2022;9(1):333.