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CLINICAL ELECTROPHYSIOLOGY - NEURAL CONTROL

Attenuation of the Heartbeat-Evoked Potential in Patients With Atrial Fibrillation

Deniz Kumral, PhD,[a,b,c] Esra Al, PhD,[a,d,e] Elena Cesnaite, MSc,[a] Jelena Kornej, MD,[f,g] Christian Sander, PhD,[g,h] Tilman Hensch, PhD,[g,h,i] Samira Zeynalova, PhD,[g] Sandra Tautenhahn, MD,[j] Andreas Hagendorf, MD,[j] Ulrich Laufs, MD,[j] Rolf Wachter, MD,[j] Vadim Nikulin, PhD,[a,k] Arno Villringer, MD[a,d,e,g]

ABSTRACT

BACKGROUND The heartbeat-evoked potential (HEP) is a brain response to each heartbeat, which is thought to reflect cardiac signaling to central autonomic areas and suggested to be a marker of internal body awareness (eg, interoception).

OBJECTIVES Because cardiac communication with central autonomic circuits has been shown to be impaired in patients with atrial fibrillation (AF), we hypothesized that HEPs are attenuated in these patients.

METHODS By simultaneous electroencephalography and electrocardiography recordings, HEP was investigated in 56 individuals with persistent AF and 56 control subjects matched for age, sex, and body mass index.

RESULTS HEP in control subjects was characterized by right frontotemporal negativity peaking around 300 to 550 ms after the R-peak, consistent with previous studies. In comparison with control subjects, HEP amplitudes were attenuated, and HEP amplitude differences remained significant when matching the samples for heart frequency, stroke volume (assessed by echocardiography), systolic blood pressure, and the amplitude of the T-wave. Effect sizes for the group differences were medium to large (Cohen's *d* between 0.6 and 0.9). EEG source analysis on HEP amplitude differences pointed to a neural representation within the right insular cortex, an area known as a hub for central autonomic control.

CONCLUSIONS The heartbeat-evoked potential is reduced in AF, particularly in the right insula. We speculate that the attenuated HEP in AF may be a marker of impaired heart-brain interactions. Attenuated interoception might furthermore underlie the frequent occurrence of silent AF. (J Am Coll Cardiol EP 2022;8:1219-1230)

From the [a]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [b]Institute of Psychology, Neuropsychology, University of Freiburg, Freiburg, Germany; [c]Clinical Psychology and Psychotherapy Unit, Institute of Psychology, University of Freiburg, Freiburg, Germany; [d]MindBrainBody Institute at Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany; [e]Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Berlin, Germany; [f]Sections of Cardiovascular Medicine and Preventive Medicine, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA; [g]LIFE-Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany; [h]Department of Psychiatry and Psychotherapy, University of Leipzig Medical Center, Leipzig, Germany; [i]Department of Psychology, International University of Applied Science, Erfurt, Germany; [j]Clinic and Policlinic for Cardiology, University Hospital Leipzig, Leipzig, Germany; and the [k]Berlin Center for Advanced Neuroimaging, Charité-Universitätsmedizin Berlin, Berlin, Germany.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BP = blood pressure
BMI = body mass index
CAN = central autonomic network
CO = cardiac output
ECG = electrocardiography
ECHO = echocardiography
EEG = electroencephalography
FDR = false discovery rate
HEP = heartbeat-evoked potential
HR = heart rate
IBI = interbeat interval
PS = pattern similarity
SBP = systolic blood pressure
SV = stroke volume

Atrial fibrillation (AF) is extremely frequent with a lifetime incidence in Westernized countries of about 25%, which significantly increases the risk for heart failure, dementia, and stroke.[1] Although some patients experience symptoms such as palpitations, fatigue, dizziness, dyspnea, chest pain, and anxiety,[2] 10% to 40% have asymptomatic ("silent") AF.[3] One reason for silent AF might be a disturbed heart-brain interaction which might also play a pathogenetic role in the development of AF and other cardiac arrhythmias.[4] It is therefore important to identify potential biomarkers.

A candidate biomarker is the heartbeat-evoked potential (HEP), a neural response to each heartbeat.[5] It is obtained by averaging electroencephalography (EEG) recordings time-locked to the electrocardiogram (ECG; to R-peak or T-wave). The HEP peaks 250 to 450 ms after the R-peak, and EEG sources were located in the anterior cingulate, the right insula, the prefrontal cortex, and the left somatosensory cortex.[6]

SEE PAGE 1231

Neural processing of the heartbeat serves several functions. Foremost, peripheral-central feedback loops are adjusting heart rate (HR) and blood pressure (BP) to bodily needs. Another function is to compensate for heartbeat-related pulsations/noise in the body to stabilize perception. Finally, whereas heart-related neural processing remains usually unconscious, we may feel the heartbeat, for example, during heavy exercise, certain forms of meditation, or in pathological conditions such as extrasystoles or panic attacks.

Notably, little is known about neural processing of the heartbeat in cardiac diseases. Only few studies have addressed this issue by assessing HEPs in patients with heart disease. For example, in patients with ventricular dysfunction, stress-induced changes in cardiac output (CO) correlated with late HEP amplitudes at left temporal and lateral frontal electrodes.[7] In patients after cardiac arrest, amplitudes of late HEP at frontal electrodes were reported to be inversely associated with mortality.[8] Although HEP changes were linked to stroke volume (SV) or CO in several studies,[7,9] it is not yet clear whether other crucial aspects of cardiac function, specifically normal electrical pacemaker activity in the atrium, also influence the heart's neural representation.

To test the hypothesis that HEP is altered in AF, using simultaneous EEG/ECG recordings, we assessed HEPs in patients with persistent AF and control subjects matched for age, sex, and body mass index (BMI). To answer the question of whether presumed alterations of HEP are related to the arrhythmic condition per se or associated cardiovascular changes, we additionally compared subsamples matched for heart frequency, systolic BP (SBP), and SV. In EEG source analysis, we investigated which brain areas are involved in HEP modulation.

METHODS

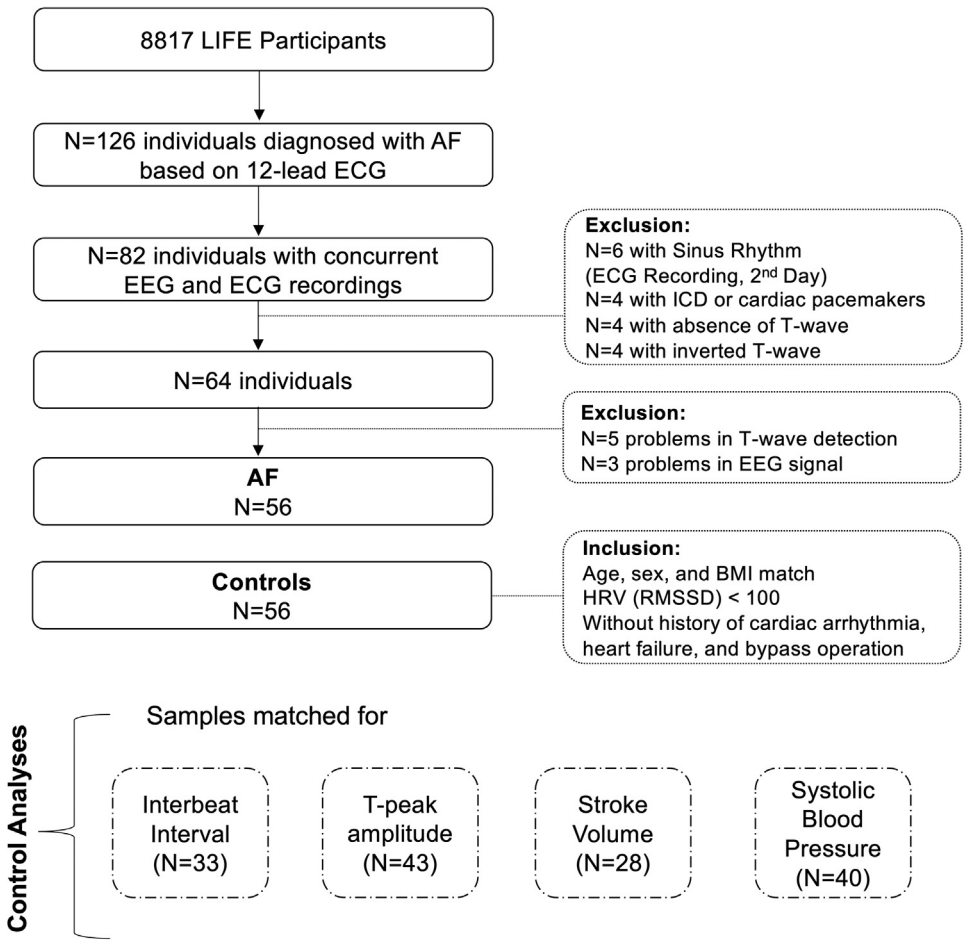
LIFE STUDY. Participants were drawn from the population-based study of the LIFE-Adult (Leipzig Research Centre for Civilization Diseases).[10] All participants provided written informed consent approved by the ethics committee of the medical faculty at the University of Leipzig, Germany. The study was in agreement with the Declaration of Helsinki.

PARTICIPANTS. Of 8,817 subjects who underwent a 12-lead resting ECG recording during the baseline visit of the study, there were 126 participants who met the criteria for AF (diagnosed by cardiologist J.K.). For 82 of those participants, 20-minute resting-state ECG/EEG recordings were available, which were performed between 3 and 89 days after the first 12-lead ECG. These ECG/EEG recordings were manually checked (D.K.) and presence/absence of AF was confirmed by a cardiologist (J.K.). Only subjects with AF on both occasions were included for further analysis. Furthermore, subjects with a cardiac pacemaker, electrocardiogram with poor signal-to-noise ratio so that the T wave could not be seen and automatically detected or inverse T-wave, or insufficient EEG quality were excluded (**Figure 1**). Finally, ECG/EEG data from 56 AF patients (12 females, $M = 72.02$, SD = 4.15 years of age) were analyzed. Of these, there were 46 individuals who met the criteria for persistent AF. For 8 individuals, it was not possible to distinguish whether they had a long episode of paroxysmal AF or a persistent AF because the 2 electrocardiogram recordings were performed within 3 to 7 days.

We matched AF patients (n = 56) to control subjects (n = 56), who did not report any past or present cardiovascular diseases such as heart failure, bypass operation, or cardiac arrhythmia. We employed nearest-neighbor matching based on age and BMI, and exact matching for sex (12 women). We further assessed HR variability in control subjects, computed as the root mean square of successive differences between heart peaks.

12-LEAD ECG (FIRST ECG RECORDING). Ten seconds of a standard medical 12-lead resting ECG were

FIGURE 1 Flow Chart



Flow chart visualizing the selection process of the individuals with atrial fibrillation (AF) and control subjects. BMI = body mass index; ECG = electrocardiography; EEG = electroencephalography; HRV = heart rate variability; ICD = implantable cardioverter-defibrillator; LIFE = Leipzig Research Centre for Civilization Diseases study; RMSSD = root mean square of successive differences.

acquired using a Page-Writer TC50 ECG system (Philips Healthcare) after a supine resting period of at least 10 minutes.[10]

ECHOCARDIOGRAPHY. Cardiac ultrasound examination was performed using the GE Vivid 7 BTO8 Dimension echocardiography (ECHO) station (GE Healthcare). Standardized reading of the ECHO assessments was performed. SV was computed as the differences between end-diastolic and end-systolic volume, CO was computed as the product of HR and SV, and left ventricular outflow tract velocity time integral was computed.

SIMULTANEOUS EEG AND ECG RECORDINGS. Resting-state EEG activity was recorded for 20 minutes in an electrically and acoustically shielded room using 34 passive Ag/AgCl electrodes: 31 scalp electrodes were mounted on an EEG cap with the 10-20 system. Two electrodes recorded vertical and horizontal eye movements while 1 bipolar electrode was placed on the forearm and was used for electrocardiogram recordings. The signal was amplified with a QuickAmp amplifier (Brain Products). The EEG activity was referenced against the common average and sampled at 1,000 Hz with a low-pass filter of 280 Hz. Impedances were kept below 10 kΩ. For each subject, we further computed HR, HR variability, and interbeat interval (IBI).

OTHER VARIABLES. Acquisition information of the other variables (e.g., BMI) can be found in the Supplemental Appendix.

EEG PREPROCESSING. Resting-state EEG data were preprocessed using EEGLAB toolbox and custom-written scripts in MATLAB (MathWorks). We filtered data between 1 and 45 Hz and applied a notch filter at 50 Hz. We then down-sampled the data to 500 Hz and ran a semiautomatic pipeline for artifact rejection. Next, using independent component analysis, the activity associated with the confounding sources was removed. In this step, we focused particularly on cardiac field artifacts, which were determined by segmenting independent component analyses depending on the R-peak of the electrocardiogram.

HEARTBEAT-EVOKED POTENTIALS. HEPs are cortical electrophysiological responses time-locked to the specific events of the electrocardiogram.[5,11] We visually inspected R-and T peaks and marked premature ventricular contractions. We excluded epochs before and after premature ventricular contractions. Based on the HEP time window reported in a former study,[11] we averaged EEG signals from 100 ms before the T-peak to 400 ms after the T-peak (**Figure 2A**).

HEP statistical analyses. To assess significance of group differences, in HEP amplitude and their topographical distribution over the scalp, cluster-based non-parametric permutation tests were implemented in FieldTrip (MathWorks). In this procedure, neighboring spatiotemporal points that exceed a t-value threshold are clustered. The cluster statistics are calculated by taking the sum of t-values of all points within each cluster. Condition labels were randomly shuffled 5,000 times to estimate the distribution of maximal cluster-level statistics obtained by chance. Clusters with a P value <0.05 (2-tailed) were considered significant with at least 2 neighboring electrodes at each time frame. This procedure was applied in the time window from 50 to 250 ms after the T-wave. To investigate ECG amplitude differences, a similar cluster-based permutation test was applied to the ECG signal in the time window from 50 to 250 ms after the T-wave.

Source space analysis. Source reconstruction was applied to the grand-average HEP data for all participants to increase the signal-to-noise ratio; this was done at peak response intervals indicated by the HEP analysis in the preceding text. We calculated the leadfield matrix based on the standard head model and electrode positions. Approximately 2,000 cortical dipolar sources were modeled for each topography. Source activity of the HEP amplitude was reconstructed with a 3-shell boundary element model using exact low-resolution tomography. Next, the cortical mantle was divided into 68 regions of interest using the Desikan Killiany Atlas.

Previous studies with source localization analysis have reported HEP modulations in several brain regions including the insula,[6,12] anterior/posterior cingulate regions,[6,11] ventromedial prefrontal cortex,[11] and somatosensory cortex.[6,13] Based on these findings, we selected 12 regions of interest: medial orbitofrontal, caudal, and rostral anterior cingulate, posterior cingulate, insula, and postcentral cortices, separately for the right and left hemispheres. HEP amplitude differences were computed using 2-sample t-tests, corrected for false discovery rate (FDR).

Topographical similarity analyses. Based on the group differences, the topographic similarity was calculated. This was done by measuring a cosine of an angle between 2 patterns, which is a normalized dot product between the 2 pattern vectors, called pattern similarity (PS) (1 = similar, 0 = dissimilar). We calculated the PS of grand-averaged HEPs for EEG sensor and source space.

Exploratory correlation analyses with HEP. Exploratory correlation analyses were carried out to investigate the association between the mean amplitude of the late frontal-temporal HEP component and other physiological parameters. More precisely, mean HEP amplitude within the 50 to 152-ms time window after the T-peak was averaged across the significant frontotemporal electrodes, where the timing and location of the HEP was the most prominent and consistent. We then computed Spearman correlations between the average HEP amplitude and cardiac parameters. Results were corrected by FDR.

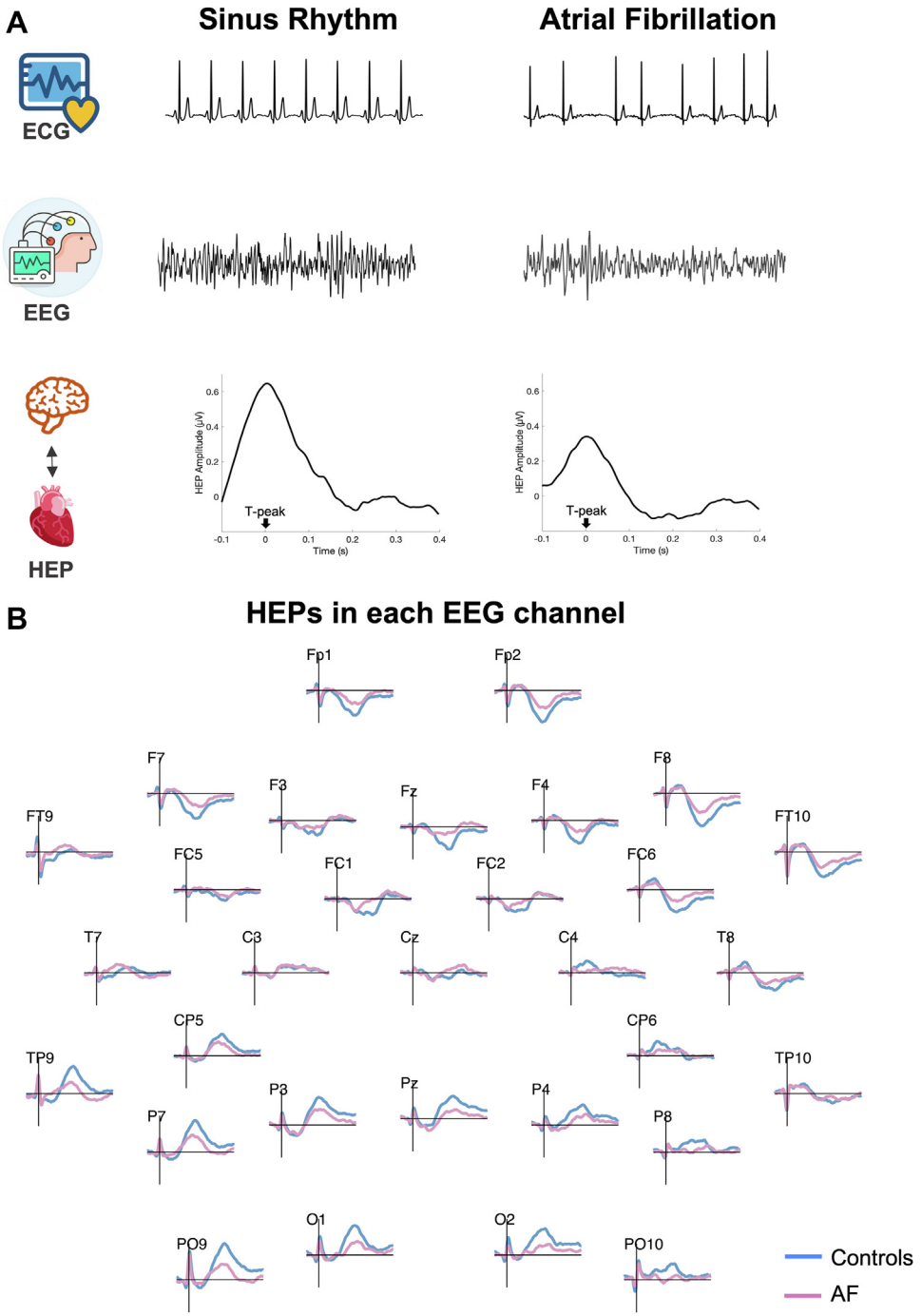
CONTROL ANALYSES. To test whether potential differences of HEP between samples were related to specific differences in cardiac function, several control analyses were performed including matching samples for IBI, T-peak, SV, and SBP.

Because, in the previous literature, HEPs were mainly computed time-locked to the R-peak,[14] we also performed an R-peak locked analysis. Thus, we were able to describe the overall HEP morphology, to compare it to previous findings and to test the robustness of our main findings. For that, we averaged baseline-corrected (−100 to 0 ms) EEG relative to the detected R-peak in epochs ranging from 100 ms before the R-peak to 600 ms after the R-peak. The cluster-based statistic was then applied at the sensor level in the time window from 300 to 550 ms.

RESULTS

SAMPLE CHARACTERISTICS. Details about other measures and medical status can be found in **Table 1** and Supplemental Table 1, respectively.

FIGURE 2 **HEP**



(A) Method: Brain activity acquired with resting-state EEG is extracted, averaged, and time-locked to the T-peak of the ECG. **(B)** Time-locked (R-peak) heartbeat-evoked potentials (HEP) in each EEG channel. EEG data were averaged relative to the R-peak in epochs ranging from 100 ms before the R-peak to 600 ms after the R-peak and baseline-corrected (−100 to 0 ms). Overall, the influence of the ECG R-wave appears at the beginning of the traces. At around 300 ms after the R-peak and thereafter, the potentials of control subjects and individuals with AF differ clearly at most electrodes. The x-axis ranges from −100 to 600 ms, whereas the y-axis ranges from −0.828 μV to 0.921 μV. Abbreviations as in Figure 1.

TABLE 1 Sample Characteristics

	AF (n = 56)	Control Subjects (n = 56)	*P* Value
Age, y	72.02 ± 4.15	71.73 ± 4.26	0.711
Female/male	12/44	12/44	
IBI, ms	865.29 ± 179.08	939.35 ± 122.47	0.012
HR, beats/min	72.18 ± 14.56	64.975 ± 8.74	0.002
HRV, RMSSD	268.18 ± 121.57	28.24 ± 17.25	<0.001
BMI, kg/m^2	29.50 ± 4.51	29.43 ± 5.07	0.941
Waist to hip ratio	0.99 ± 0.09	0.99 ± 0.08	0.989
Systolic BP, mm Hg	129.96 ± 20.66	134.74 ± 17.27	0.191
Diastolic BP, mm Hg	77.59 ± 12.34	73.79 ± 9.16	0.069
Cardiac output, L/min	5.120 ± 1.160	5.140 ± 1.05	0.927
Stroke volume, mL	63.44 ± 15.83	78.21 ± 15.21	<0.001
Velocity time integral, cm	17.35 ± 3.40	22.82 ± 4.66	<0.001
Smoking			
Current	7	2	0.633
Previous	18	20	
Nonsmokers	28	28	
Renal failure			
No	47	51	0.207
Yes	5	1	
Diabetes mellitus			
No	35	40	0.153
Yes	18	16	
Myocardial infarction			
No	45	56	0.006
Yes	8	–	
Heart failure			
No	42	52	0.006
Yes	8	–	
Stroke			
No	51	56	0.229
Yes	3	–	
Bypass operation			
No	51	56	0.229
Yes	3	–	

Values are mean ± SD or n unless otherwise indicated. Independent sample *t*-tests on continuous variables and chi-square tests on categorical variables were used to detect group differences.

AF = atrial fibrillation; BMI = body mass index; BP = blood pressure; HR = heart rate; HRV = heart rate variability; IBI = interbeat interval; RMSSD = root mean square of successive differences.

HEARTBEAT-EVOKED POTENTIALS. HEP morphology. Grand-averages of all electrode positions for both groups are depicted in Figure 2B. In control individuals, the neural responses time-locked to the heartbeat were most prominent at the right frontal and temporal electrodes, whereas the HEPs were more variable and diminished in AF.

HEP differences. We assessed HEP differences between groups in the 50 to 250 ms time window after the T-peak. We found a significant negative cluster over the right frontal, frontocentral, and temporal channels (Fp1, Fp2, F8, F4, Fz, FC1, C4, CP6, TP10, T8, FC6, FT10) between 50 and 140 ms (Monte Carlo $P = 0.002$; Cohen's $d = 0.697$). This indicates that HEP amplitude was reduced in patients vs control subjects (Figure 3A). Moreover, another significant positive cluster over the left temporal-occipital channels (T7, CP5, Pz, P3, P4, TP9, P7, O1, O2, PO1, PO2) between 50 and 152 ms was observed (Monte Carlo $P = 0.001$; Cohen's $d = 0.601$), indicating that HEP amplitude was reduced in patients vs control subjects. Importantly, there was no significant difference in the amplitude of the T-wave in the electrocardiogram, ruling out the possibility that the observed effect on HEP was due to volume conduction (Figure 3B).

Source space analysis. We grand-averaged the HEP data in the 50 to 152-ms time window after T-peak for all individuals separately and compared HEP differences between AF and control subjects. The main difference in HEP amplitude was localized in the right insula ($M = -0.48$ in control subjects, $M = -0.198$ in AF, $t(98) = -3.11$, 95% CI: −0.46 to −0.10, $P_{FDR} = 0.029$, units in current source density) suggesting that individuals with AF have reduced HEP amplitude compared with control subjects in the right insula (Supplemental Figure 1, Supplemental Table 2).

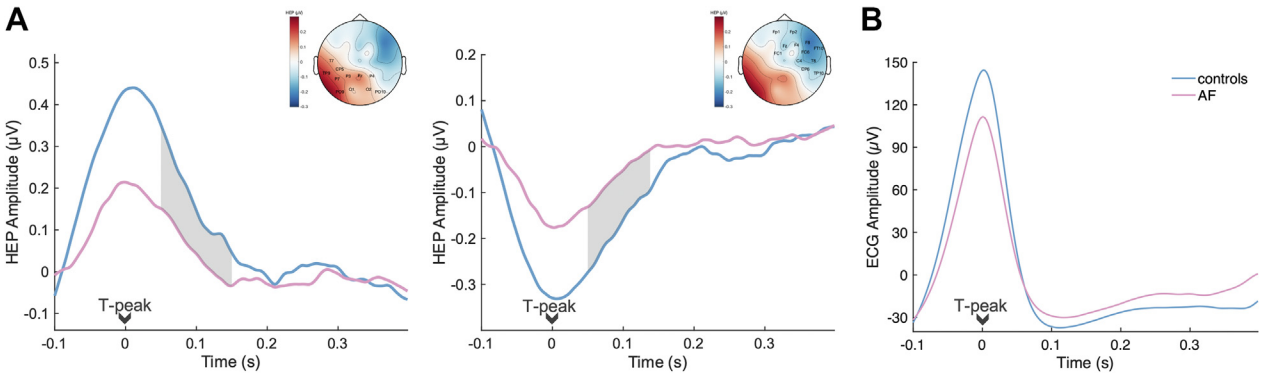
Topographical similarity analyses. We compared the similarity of HEP topographical maps between samples. For the HEP topographies in the 50 to 152-ms time window post-T-peak period, the PS was 0.812 in sensor space, and 0.777 in source space. This suggests that HEP topographies between samples were similar, but not identical (Figure 4).

Exploratory correlation analyses with HEP. We tested whether the HEP amplitude difference reflected alterations of other physiological parameters. Spearman correlation analyses did not indicate any significant association between the mean amplitude of the late frontal-temporal HEP and parameters of cardiac function or BMI, neither in AF nor in control subjects (all $P_{FDR} > 0.05$) (Supplemental Figure 2). Similarly, on the source level, we confirmed these findings (all $P_{FDR} > 0.05$).

CONTROL ANALYSES. IBI-matched subsample. Because both HR and IBI have been reported to influence HEP amplitude,[15] we matched samples based on their averaged IBI using a 50-ms interval bin. This process resulted in 33 subjects per group ($M = 906.97$ ms in control subjects, $M = 905.86$ ms in AF, $t(64) = 0.03$; 95% CI: −65.89 to 63.66; $P = 0.972$) (Supplemental Figure 3A). Accordingly, we found 1 significant negative cluster over the right frontal, central, and temporal channels between 58 and 130 ms (Monte Carlo $P = 0.01$; Cohen's $d = 0.789$) (Figure 5A, Supplemental Figure 4).

T-peak–matched subsample. To make sure that a projection of the electrocardiogram signal was not the reason for differences in HEPs, we compared AF

FIGURE 3 HEP Amplitude Differences



(A) We observed 1 positive cluster in the 50 to 152-ms time window over left temporal-occipital channels and 1 negative cluster in the 50 to 140-ms time window after T-peak over right frontal-temporal channels (Monte Carlo $P = 0.002$ and 0.001, respectively). **The gray-shaded area** highlights the time window in which a significant difference is observed. **(B)** No significant differences were found in the ECG signals between groups (all $P > 0.10$). Abbreviations as in **Figures 1 and 2**.

and control subjects by matching the samples based on the T-peak amplitude. Fifty-microvolt interval binning was used ($M = 125.13$ in control subjects, $M = 126.42$ in AF, t(84) = −0.098; 95% CI: −24.82 to 27.401; $P = 0.922$) (Supplemental Figure 3B), resulting in 43 individuals per each group. We observed 1 negative cluster in the 44 to 138-ms time window post-T-wave period over right frontal-central and temporal channels (Monte Carlo $P = 0.01$; Cohen's $d = 0.671$) (**Figure 5B,** Supplemental Figure 5).

SV-matched subsample. We matched samples based on their averaged SV using 10-mL interval binning ($M = 71.03$ mL in control subjects, $M = 70.58$ mL in AF, t(54) = 0.104; 95% CI: −8.16 to 9.06; $P = 0.916$) (Supplemental Figure 3C), resulting in 28 individuals per each group. The results revealed 1 negative cluster in the 68 to 128-ms time window after T-peak over the right frontal-central and temporal channels (Monte Carlo $P = 0.013$; Cohen's $d = 0.909$) (**Figure 5C,** Supplemental Figure 6).

SBP-matched subsample. We matched samples based on their averaged SBP using 15 mm Hg interval binning ($M = 134.25$ mm Hg in control subjects, $M = 132.20$ mm Hg in AF, t(78) = 0.50; 95% CI: −5.95 to 10.05; $P = 0.611$) (Supplemental Figure 4D), resulting in 40 individuals per each group. We observed 1 negative cluster in the 50 to 124-ms time window after T-peak over the right frontal temporal channels (Monte Carlo $P = 0.002$; Cohen's $d = 0.910$) (**Figure 5D,** Supplemental Figure 7).

HEP R-locked. Using R-locked HEP in the overall sample, we found a significant negative cluster over the right frontal, central, and temporal channels between 300 and 550 ms (Monte Carlo $P = 0.001$; Cohen's $d = 0.838$). Another significant positive cluster was observed over the left temporal-occipital channels between 300 and 550 ms after R-peak (Monte Carlo $P = 0.001$; Cohen's $d = 0.840$) (Supplemental Figure 8).

EXPLORATORY ANALYSIS TO CONTROL FOR DEPRESSIVE SYMPTOMATOLOGY. We assessed the level of depression using the Inventory of Depressive Symptomatology.[16] For our analyses, we computed the total depression score and compared the group differences using an independent-sample t-test. Spearman correlation was computed to investigate the association between the mean amplitude of the late frontal-temporal HEP and total depression score. The detailed results are given in Supplemental Figure 9.

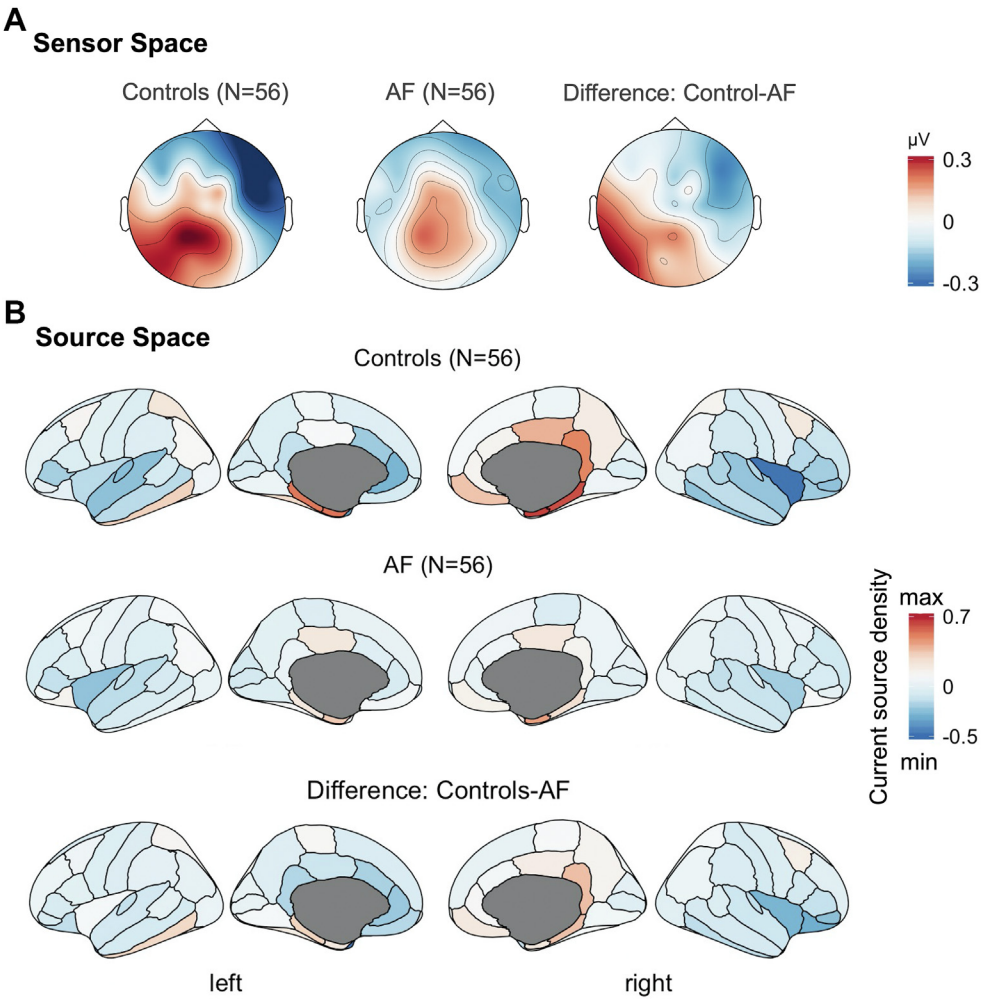
EXPLORATORY CONTROL ANALYSES. In order to exclude that HEP differences were related to concomitant heart disease, in a further analysis subjects with heart failure, myocardial infarction, and bypass surgery were excluded. Accordingly, HEP was reduced in AF patients (n = 43) compared with matched control subjects (Supplemental Figure 10).

We further assessed the laterality using the Edinburgh Handedness Questionnaire and observed that all individuals except 2 persons in the AF group were right-handed. After excluding these subjects (and their respective matches), the main finding of the right insula remains unchanged (t(90) = −3.033; $P_{FDR} = 0.037$).

DISCUSSION

The present study demonstrated an attenuation of HEPs in individuals with AF in comparison to age-, sex-, and BMI-matched control subjects. The HEP

FIGURE 4 HEP in the Source and Sensor Space



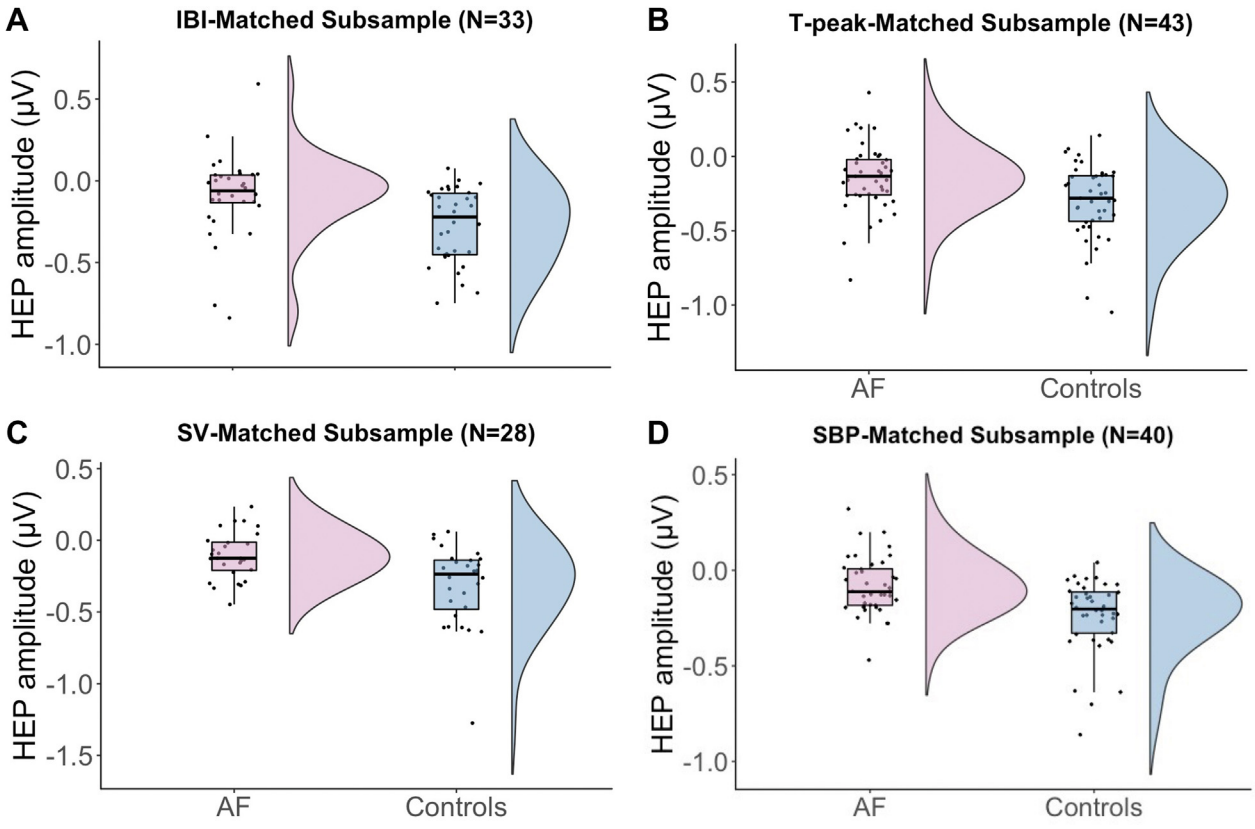
(A) Topographical maps of HEP separately for control subjects, individuals with AF, and differences between samples in the 50 to 152-ms post-T-peak window in the sensor space. **(B)** Topographical maps of HEP separately for control subjects, individuals with AF, and differences between samples in the 50 to 52-ms post-T-peak in the source space. Abbreviations as in **Figures 1 and 2**.

amplitude reduction remained significant after matching the samples for IBI, SV, SBP, and T-wave amplitude. The most profound HEP attenuation was observed in right frontotemporal electrodes and—in EEG source localization—was primarily located in the right insula, an area known as a hub for autonomic control (**Central Illustration**).[17,18]

The general spatial and temporal characteristics of the HEP as we report it here are highly consistent with previous reports,[7,8] that is, frontotemporal negativity in the EEG peaking 300 to 550 ms after the R-peak in the ECG. Regarding its functional role, most previous HEP studies have focused on its relationship to internal body awareness in healthy subjects and patients with presumed disturbances of interoception.[5,14,15] For example, a recent meta-analysis across 16 studies demonstrated a relationship between interoception performance and the HEP amplitude at frontocentral locations.[14]

In principle, a reduced neural representation of the heart in cardiac disease might be mediated by consequences of altered cardiac function such as changes in SV, BP, or IBI. It is controversial whether and how much these parameters influence HEP.[9,19] Given that the reduced HEP in AF was still present when patients were matched for these parameters, a major determinant for our findings must be something else. One possible confounder/explanation might be AF-associated physiological noise that propagates into the EEG electrodes but does not relate to disease

FIGURE 5 **HEP Control Analyses**

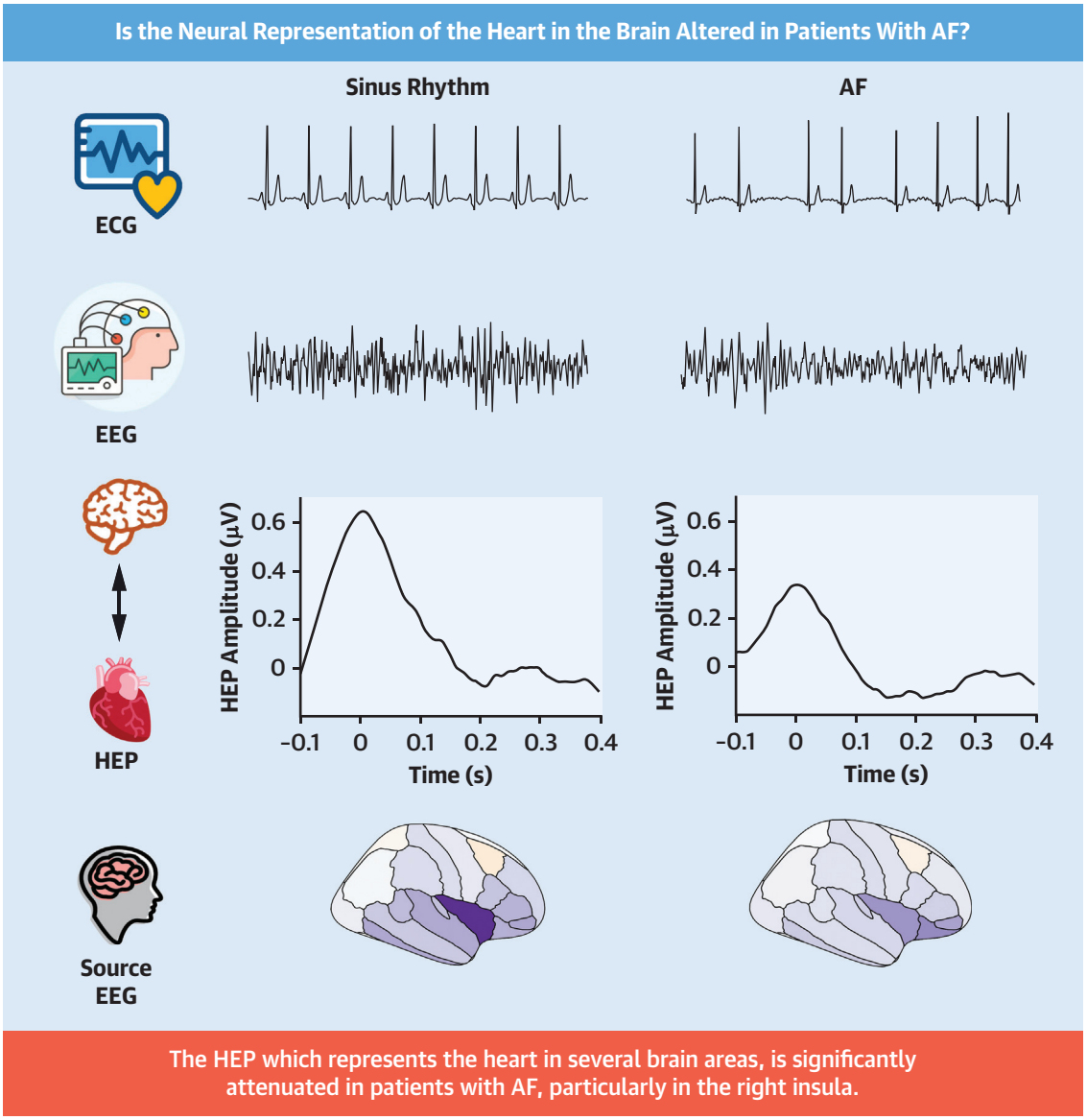


Box and violin plots separately illustrate the HEP differences between AF and control subjects in matched subsamples for **(A)** interbeat interval (IBI), **(B)** the T-wave amplitude, **(C)** stroke volume (SV), and **(D)** systolic blood pressure (SBP).

pathophysiology. A second potential explanation may be altered neural function due to brain damage associated with cardiac disease. Although we cannot completely exclude these 2 explanations, the localization of the altered HEP to the right insula is an argument against physiological noise or brain damage, which both are unlikely to be very localized. However, future studies are needed to address these potential explanations. A third explanation seems plausible to us, that is, that the reason for the HEP attenuation is not to be found exclusively at 1 of the 2 sites (heart or brain), but rather reflects an altered heart-brain interaction. Interestingly, another well-known parameter of heart-brain interaction, the baroreflex, has been shown to be attenuated in patients with AF and more so in persistent vs intermittent AF.[20] Because baroreceptors are most likely also involved in signaling cardiac function for HEP generation, it seems likely that these 2 parameters of heart-brain interaction are similarly affected by cardiac disorders.

The location at which we observed the most significant attenuation of the HEP was the right insula. The insula, a brain area located deep between temporal and frontal lobes, is known as the viscerosensory cortex, the terminus of interoceptive pathways from the viscera.[4,18,21] The insula has posterior, central, and anterior subdivisions. The posterior insula receives interoceptive as well as exteroceptive, sensorimotor, and proprioceptive information; multimodal integration of sensory information probably occurs in the posterior and central insula, and then is relayed to the anterior insula, which makes it potentially accessible to awareness.[22] For a more detailed description of the cellular architecture of the insula, please see Livneh and Andermann[23]. Generally, the insula is a key hub in the brain for representing sensations from within the body, relating them to cognitive/emotional function,[21] and as a part of the central autonomic network (CAN), it is crucially involved in the regulation of cardiac function via the sympathetic and

CENTRAL ILLUSTRATION **HEP in Healthy Controls and Patients With AF**



Kumral D, et al. J Am Coll Cardiol EP. 2022;8(10):1219–1230.

AF = atrial fibrillation; ECG = electrocardiography; EEG = electroencephalography; HEP = heartbeat-evoked potential.

parasympathetic nervous system.[17,24] Importantly, lesions in the right insula have been linked to electrocardiogram abnormalities, including the occurrence of AF, atrioventricular block, premature contractions, and T-wave inversion,[25] but also myocardial injury,[26] increased brain natriuretic peptide level, and Takotsubo syndrome.[27] Most likely, the cardiac effects of lesions in the right insula are mediated by autonomic dysregulation, particularly an up-regulation of sympathetic function.[26]

What are the neurophysiological implications of an attenuated HEP? Clearly, the HEP mainly reflects sensory input providing information about cardiac function to the insula and more generally the CAN. An attenuation of this input might generally reduce/disturb the influence of cardiac information on the regulation of autonomic function in the CAN and contribute to suboptimal functioning. Furthermore, given that the right anterior insula is involved in interoceptive awareness,[22] it might also impair

perception of the heartbeat (interoception), thus underlying the frequent occurrence of silent AF. Both of these potential consequences, however, are speculative and should be systematically evaluated in future studies. Thus, in longitudinal studies, the impact of different HEP amplitudes on (regulation of) cardiac function should be tested. Also, we suggest comparing HEP between silent and symptomatic AF patients combined with the assessment of interoception using heartbeat tracking or discrimination tasks, as well as AF symptoms using the AFSS (Atrial Fibrillation Severity Scale) or EHRA (European Heart Rhythm Association) scale.

STUDY LIMITATIONS. Among the limitations of our study is its cross-sectional design. Thus, we cannot address causality and do not know whether the observed HEP changes in AF precede the onset of AF or occur thereafter. Prospective longitudinal studies will be particularly interesting in the light of the hypothesis that disturbed heart-brain interaction and/or insular function may be involved in the generation of AF. Furthermore, while previous research has related HEP to interceptive awareness,[14] we have not directly measured interoception in our study and due to this limitation, the link between our findings and interoception in AF must remain speculative. Another limitation of our study is that ECHO was not performed simultaneously with the EEG; future studies should attempt to perform ECHO and EEG concurrently. Finally, to better understand the precise role of cardiac arrhythmia on HEP, studies examining the effect of rhythm control intervention on HEP are warranted.

CONCLUSIONS

The HEP is reduced in AF, particularly in the right insula. We speculate that the attenuated HEP in AF may be a marker of impaired heart-brain interactions. Attenuated interoception might furthermore underlie the frequent occurrence of silent AF (**Central Illustration**). Longitudinal studies on the pathophysiological relevance of the disturbed heart-brain interaction for the development of AF are warranted.

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ADDRESS FOR CORRESPONDENCE: Dr Deniz Kumral, Institute of Psychology, Neuropsychology, University of Freiburg, Engelberger Strasse 41, 79085 Freiburg im Breisgau, Germany. E-mail: Deniz.Kumral@psychologie.uni-freiburg.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The HEP, which reflects neural activity associated with the heartbeat, is weaker in patients with AF. The HEP may be a new simple and non-invasive biomarker of disturbed heart-brain interaction (HBI). The attenuated HEP in AF might also explain the frequent occurrence of silent AF.

TRANSLATIONAL OUTLOOK: The HEP, as a potential biomarker for disturbed HBI, should be tested prospectively and longitudinally in patients with cardiovascular risk factors. The clinical vision is that, using HEP, a disturbance of HBI be detected and ideally treated before it contributes to the development of AF and other cardiac disorders.

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KEY WORDS atrial fibrillation, echocardiography, electrocardiogram, electrocardiography, electroencephalography, heartbeat-evoked potential, heart-brain connection

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.