Clinical Neurophysiology 123 (2012) 1950–1957

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Heartbeat evoked potentials mirror altered body perception in depressed patients

Janneke Terhaar [a], Filipa Campos Viola [b,c], Karl-Jürgen Bär [a,*], Stefan Debener [b,c]

[a] Pain and Autonomics – Integrative Research (PAIR), Department of Psychiatry and Psychotherapy, Philosophenweg 3, University Hospital, Jena, Germany
[b] Biomagnetic Center, Department of Neurology, University Hospital Jena, Germany
[c] Neuropsychology Lab, Department of Psychology, University of Oldenburg, Germany

See Editorial, pages 1899–1900

ARTICLE INFO

Article history:
Available online 25 April 2012

Keywords:
Depression
Heartbeat perception
Heartbeat-evoked potentials
Interoception

HIGHLIGHTS

- Heartbeat evoked potentials are objective markers of altered bodily awareness.
- Reduced interoception in major depression has been shown in comparison to controls.
- Interoception in depression may be linked to decreased capacity for decision-making.

ABSTRACT

Objective: Awareness of stimuli originating inside of the body (interoceptive awareness) is thought to have an impact on psychopathology. The aim of the present study was to analyze whether heartbeat perception accuracy is reduced in depressed patients. Furthermore, we investigated whether putative differences are reflected in heartbeat-evoked potentials.
Method: We assessed the heartbeat perception score in 16 depressed patients and in matched healthy controls. A 63-channel EEG was recorded while participants counted pseudo-randomly presented target tones or heartbeats during a fixed number of cardiac cycles. ECG R-waves served as the trigger for EEG averaging. The cardiac-field artifact was minimized using independent component analysis and current–source density.
Results: Behaviorally, the depressed sample showed less accurate heartbeat perception in comparison to the control group ($p = .011$). The two groups also demonstrated psychophysiological differences, showing that heartbeat-evoked potentials were significantly reduced in depressed patients.
Conclusions: Our results suggest that heartbeat evoked potentials are objective markers of altered bodily awareness. Reduced interoception during depression may be linked to alexithymia, as well as to both decreased capacity for decision-making and for cognitive processing.
Significance: It may be helpful to practice interoceptive awareness to improve depressive symptoms, for example by practicing meditation.

1. Introduction

Major depression has been projected to become the second leading cause of disability worldwide by 2020 after ischemic heart disease (Bromet et al., 2011). During depressive episodes, many patients suffer from cognitive impairment, loss of awareness of their feelings, physical comorbidity and a lack of decisiveness. It has been found that people with decreased interoceptive awareness likewise show less developed information processing, less self-regulation of physical load, a reduced capacity for decision making and less intense experiencing of emotions (Bechara et al., 1996; Herbert et al., 2007b; Pollatos et al., 2007a,b).

The theoretical underpinnings of these findings were first provided by William James who claimed that emotions were caused by the perception of bodily changes. He wrote, "we feel sorry because we cry [...] [and] afraid because we tremble" (James, 1884). Based on this and related observations, Damasio (1994) developed the somatic marker hypothesis, which defines emotions as collections of bodily changes evoked by thoughts (Damasio, 1994; Bennett and Hacker, 2005). Furthermore, it has been argued that a person's degree of bodily awareness helps him or her to regulate decision making and that emotional biasing signals originating in the body are integrated and stored in higher brain structures

* Corresponding author. Tel.: +49 3641 9 390451; fax: +49 3641 9 390452.
E-mail address: karl-juergen.baer@med.uni-jena.de (K.-J. Bär).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2012.02.086

and are involved in complex decision-making processes (Damasio, 1994; Dunn et al., 2006).

Given these theories and findings, one would assume a reduction in interoceptive awareness during depression, since cognitive function and decision-making are known to be impaired. However, studies linking depression and bodily awareness are rare and contradict one another. While some authors (Mussgay et al., 1999; Van der Does et al., 1997) have reported a tendency towards decreased heartbeat perception in depressed patients, Dunn et al. (2007) found decreases in heartbeat perception only in mildly depressed participants, while more severely depressed individuals showed normal levels of heartbeat perception. Hence, more research is necessary to further understand the link between depression and interoceptive accuracy.

Assessment of heartbeat perception is one of the most common methods to quantitate interoceptive awareness and has been shown to be sufficiently reliable (Mussgay et al., 1999; Schandry, 1981; Van der Does et al., 1997). Furthermore, heartbeat perception has been related to neural systems such as the insular, cingulated and somatomotor cortices (Critchley et al., 2004). Moreover, heartbeat evoked potentials (HEPs) resulting from afferent transmission have been studied in several EEG-studies (Dirlich et al., 1998, 1997; Schandry et al., 1986). The HEPs are thought to provide an objective correlate of interoceptive processing, even though the exact brain source configuration contributing to HEP remains poorly understood.

HEPs have been shown to appear mainly close to the somatosensory cortex and the prefrontal and frontal cortices (Pollatos and Schandry, 2004). However, others have reported HEPs over various other regions, including the parietal and temporal regions (Dirlich et al., 1998; Gray et al., 2007). Despite the apparent lack of topographical consistency across studies, HEPs have been proven to be sensitive markers of the accuracy of heartbeat perception. Accordingly, significant group differences between accurate and poor heartbeat perceivers as shown through measurements of HEP amplitudes were repeatedly found, in particular at frontal and central electrode sites (Katkin et al., 1991; Pollatos and Schandry, 2004; Schandry and Weitkunat, 1990; Yuan et al., 2007). Furthermore, the HEP has been proven to be sensitive to changes in directed attention. Attention effects are stronger in good heartbeat perceivers (Yuan et al., 2007) and, surprisingly, amplitudes at some individual electrodes have been shown to be smaller during the attention state than in the distraction state (Montoya et al., 1993).

The aim of the present study was to investigate whether heartbeat perception accuracy is reduced in depressed patients. Therefore, heartbeat perception scores were assessed in patients and controls. In order to explore the significance of a more objective means of interoceptive awareness, HEP amplitudes were analyzed. Given the topographical inconsistencies of previous HEP reports, this one was done by means of a global field power (GFP) analysis, which is a measure of evoked potential strength across the scalp (Lehmann and Skrandies, 1984). The value of HEPs is that they yield information independently from the participants' motivation to perform the task. As the majority of studies found reduced accuracy of heartbeat perception in depressed patients, we hypothesized that heartbeat perception is decreased in depressed patients and, accordingly, we expected the amplitudes of HEPs to be reduced.

2. Methods and materials

2.1. Participants

Sixteen depressed patients (13 females, mean age 41.75 ± 12.4 years) and an age- and gender-matched control group consisting of 16 healthy volunteers (12 females, mean age 39.81 ± 17.6 years) were included in the study after applying exclusion criteria. Two participants (one patient and one control subject) were excluded because of invalid HEPs; in these participants, the GFP HEPs were larger than mean ± 2 SD and thus were considered as outliers (Montoya et al., 1993). Groups did not differ significantly with regard to their age, as revealed by means of a two-sided *t*-test ($p = .721$). All patients were diagnosed by a staff psychiatrist or psychologist, and fulfilled DSM-IV criteria for a major depressive disorder (MDD). Six patients suffered from single episodes (2 = mild, 4 = moderate) while 10 subjects were included with recurrent depressive episodes (1 = mild, 5 = moderate, 4 = severe). Eleven patients were taking antidepressants at the time of investigation. Note that participants were not excluded based on medication. Although this might normally be considered a confounding factor, Mussgay et al., 1999 reported that antidepressant medication does not influence heartbeat perception in patients with depression. In addition, two patients and three controls received thyroid hormone replacement therapy without any clinical significance, and three patients and one control subject were treated with beta-blockers for borderline hypertension. Panic disorder served as an exclusion criterion, as panic disorders have been shown to influence heartbeat perception substantially (Dunn et al., 2007). The Hamilton Depression Rating Scale (HAMD) and the Beck Depression Inventory (BDI) were used to estimate the severity of the disease. Healthy controls were recruited from the general community via newspaper and flyer advertisement. They were examined by a staff psychologist before the experiment and were only included if they showed absence of any psychiatric illness. Accordingly, HAMD and BDI scores were within the normal range in the control group. The clinical profile of the participants is presented in Table 1. After having been thoroughly informed about the nature of the procedure, all participants gave their informed consent to a protocol approved by the Ethics Committee of the University Hospital, Jena. The study was carried out in accordance with the Declaration of Helsinki.

2.2. Procedure

Participants were seated comfortably in a recliner in an electrically shielded and sound-attenuated chamber. First, to determine

Table 1
Medication, psychometric and physiological parameters of controls and patients.

Parameter	Controls	Patients
Depressive symptoms		
HAMD (mean ± SEM)	1.81 ± 0.54* [$t(30) = -12.87$; $d = 4.9$]	23.9 ± 1.63
BDI (mean ± SEM)	2.31 ± 0.72* [$t(30) = -7.68$; $d = 2.8$]	22.63 ± 2.54
Cardiac parameters		
Heart rate (mean ± SEM)	67.26 ± 2.66	71.31 ± 3.47
Systolic blood pressure (mean ± SEM)	127.43 ± 3.09	126.25 ± 4.33
Diastolic blood pressure (mean ± SEM)	83.00 ± 1.52	81.94 ± 2.27
Thyroid medication	$n = 3$	$n = 2$
Beta-blocker	$n = 1$	$n = 3$
Antidepressive medication		
SSRI	$n = 0$	$n = 2$
SNRI	$n = 0$	$n = 8$
Elontril	$n = 0$	$n = 1$
Valdoxan	$n = 0$	$n = 2$
Antipsychotic medication		
Aripiprazol (5 mg)	$n = 0$	$n = 1$
Olanzapine (2.5 mg)	$n = 0$	$n = 1$

HAMD – Hamilton rating scale for depression. BDI – Beck depression inventory. SSRI – selective serotonine reuptake inhibitor. SNRI – Serotonine-norepinephrine reuptake.

* $p < .001$ (*p*-values obtained by applying a two-tailed *t*-test for independent samples).

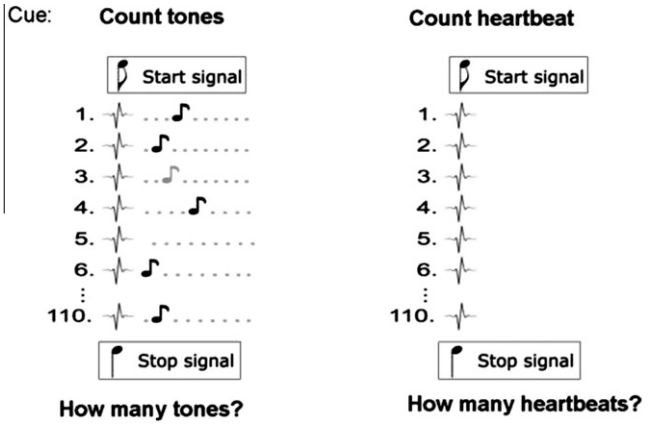

Fig. 1. Experimental set-up during EEG-recording. The right column represents the attention condition and the left column shows the distraction condition. Grey colored note symbols represent target tones. Tones are presented independently of heartbeats (indicated by the dots before and after the notes). Conditions were alternated pseudo-randomly.

the original heartbeat perception score, participants were asked to silently count their heartbeats for 35, 25 and 45 s. This procedure followed the Mental Tracking Task (Schandry, 1981) frequently used to access the accuracy of heartbeat perception. Participants were not told about the length of the run and were asked not to take their pulse. After each trial, individuals were prompted to verbally report the number of heartbeats they counted.

Then, during EEG recording (see Fig. 1), participants were asked to either count target tones (distraction condition) or heartbeats (attention condition) during a fixed number of cardiac cycles (150, 120, 130, 100, 150, 110, 110, 140, 100, 110). Fixed-cardiac cycles were used in order to ensure that all participants were exposed to the same number of stimuli. In the heartbeat-attention condition, participants were asked to count their heartbeats as explained above. In the heartbeat-distraction condition, participants were exposed to target (40 dB) and non-target (60 dB) tones at a rate of one non-target tone every 1 or 2 s, while target tones were presented randomly between two non target tones. All tones lasted 200 ms and had a frequency of 440 Hz. Ten distraction runs and 10 attention runs were alternated pseudo-randomly. The end and beginning of every phase were signalled by a start and stop tone (Montoya et al., 1993). Start and stop tones were as loud as the non-target tones. The frequency of both tones was 210 Hz. The duration of the start signal was 200 ms and the duration of the stop signal was 447 ms. Participants were asked to keep their eyes open during the whole experiment. After 10 runs, participants relaxed for 1 min. All stimuli were presented using Presentation 14.1 software (Neurobehavioral Systems Inc., www.neurobs.com).

2.3. Calculation of heartbeat and tone perception score

The perception scores were calculated using Schandry's equation (Schandry, 1981):

$$\frac{1}{n}\sum_{i=1}^{n}\left(1-\left(\frac{\text{recorded items}-\text{counted items}}{\text{recorded items}}\right)\right).$$

2.4. Data collection and pre-processing

EEG data were recorded from 63 electrodes placed using a customized cap (Easycap, Herrsching, Germany). The cap was fitted with 62 Ag/AgCL electrodes using an equidistant montage. Furthermore, in order to assess eye movements and to perform an electrocardiogram (ECG), two additional electrodes were placed below the left eye and two on the lower back. This ECG recording scheme is well established in inside scanner EEG recordings (Debener et al., 2007; Strobel et al., 2008) and provides a pronounced R-peak, facilitating automatic peak detection. Data from all electrodes were recorded against a Cz reference with a BrainAmp amplifier system (Brainproducts, Munich, Germany). The data were recorded with a sampling rate of 500 Hz, a 0.1 Hz high-pass and an anti-aliasing analog low pass filter. Electrode impedances were maintained below 20 kΩ prior to data acquisition. The R-wave of the ECG was detected online with the Brain Amp Recorder software in order to monitor the number of cardiac cycles during EEG recording. R-peak detection for the analysis of HEPs was performed off-line, as described below.

2.5. Analysis of EEG data

EEG data were processed using custom scripts and EEGLAB (Delorme and Makeig, 2004) running in the MATLAB (Mathworks, Natick, MA) environment. Data were offline-filtered from 1 to 40 Hz using windowed sinc FIR filters with a Hann window (taken from the FIRfilt plugin for EEGLAB developed by A. Widmann: www.unileipzig.de/~biocog/content/widmann/eeglab-plugins/). Data were then re-referenced to common average and down-sampled to 250 Hz in order to reduce computational time. Extended infomax independent component analysis (ICA), as implemented in EEGLAB, was applied to continuous data, in order to achieve high linear decomposition quality (Debener et al., 2010). To this end, continuous data were first pruned from unique, non-stereotyped artifacts using a built-in EEGLAB joint probability measure (Delorme et al., 2007) and the remaining data was submitted to ICA. For all datasets, independent components (ICs) representing eyeblinks and cardiac-field artifact (CFA) were semi-automatically identified using an EEGLAB plugin called CORRMAP (Viola et al., 2009) and subsequently removed.

Analyzing the HEP presents a challenge because the CFA and the cortical signal of interest (HEP) are time-locked to the same event and thus spatio-temporally overlap. Furthermore, the cardiac artifact evoked by the T-wave is very prominent in the HEP time-window of interest. Different approaches, such as principal component analysis, current–source–density (CSD) or the consideration of largely CFA-free HEP intervals, have been used to attenuate the CFA and obtain reliable HEPs (Dirlich et al., 1998; Gray et al., 2007; Pollatos and Schandry, 2004; Yuan et al., 2007). In similar cases of spatio-temporal overlap, ICA has been shown to efficiently remove artifact signals (Debener et al., 2008; Ohla et al., 2009; Viola et al., 2011). Fig. 2 demonstrates a single case showing that by means of ICA overlapping, cardiac field activity can be attenuated and the relatively small, underlying HEPs recovered.

For offline R-wave detection an EEGLAB plugin called FMRIB (Niazy et al., 2005) was used and provided reliable peak detection. As HEPs were to be analyzed, datasets were segmented into periods from −200 to 800 ms relative to the R-peak. A baseline correction was performed using the pre-stimulus interval (−200 to 0 ms). HEPs were calculated by averaging time-domains across trials. To further attenuate the residual CFA, the HEPs were CSD transformed, as done elsewhere in this context (Pollatos et al., 2005; Pollatos and Schandry, 2004). We used a freely available toolbox [http://www.psychophysiology.cpmc.columbia.edu/Software/CSDtoolbox] set to its default parameters (Kayser and Tenke, 2006). All HEP analyses reported are based on the global field power (GFP) of the CSD waveforms. For calculation of the GFP, the 44 electrodes corresponding to the scalp area covered by the international 10–20 electrodes layout were used. A systematic evaluation of HEP publications revealed only moderate consistency with regard to the HEP latency ranges of interest. Therefore, the selection of time-windows (tw) was data-driven by running point-wise *t*-tests

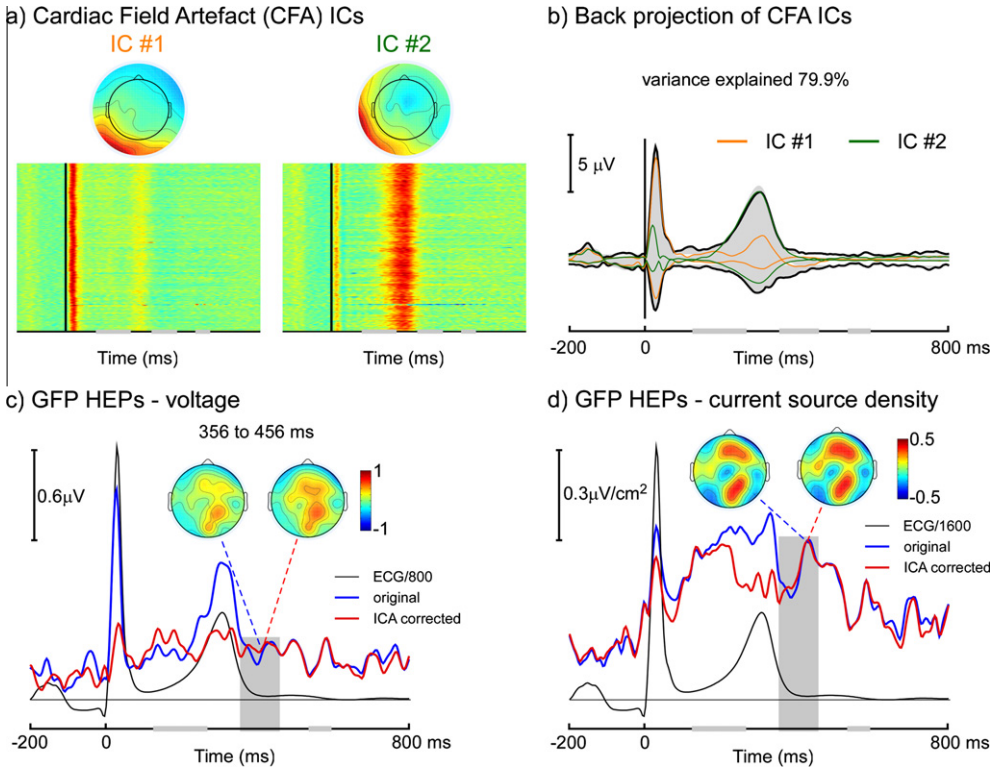

Fig. 2. Example of the effect of CFA correction for a single participant (62 electrodes). (A) Two ICs representing this artifact were semi-automatically identified. Note that the ICs show activity not only in the time-window that corresponds to the R-peak, but also in the time-window corresponding to the T-wave, which interferes with the time-windows of interest. (B) The back projection of ICs into the original dataset. Note that independently, these ICs explain 80% of the variance of the HEP waveform. (C) The global field power for original (blue) and corrected HEP (red), background waveform represents ECG activity (black) downscaled by a factor of 800. The topographies represent mean activity in the time-window between 356 and 456 ms for original and corrected data. (D) The CSD global field power waveform for original (blue) and corrected HEPs (red), background waveform (black), which represents ECG activity, downscaled by a factor of 1600. The topographies represent mean CSD activity in the time-window between 356 and 456 ms for original and corrected data.

for the grand average waveforms of the two groups (Debener et al., 2005). Intervals where significance ($p < .05$) was found for a minimum of 11 consecutive data points (44 ms) were selected for further evaluation. By using this approach, three time-windows were identified that corresponded well to several previous HEP studies (Montoya et al., 1993; Pollatos et al., 2005; Schandry and Weitkunat, 1990; Yuan et al., 2007).

2.6. Statistical analysis

Group differences between depressed patients and controls were evaluated in terms of their heartbeat perception score using a one-tailed *t*-test. Differences of heartbeat and tone perception between groups during EEG recording were evaluated using an ANOVA applying the between-subject factor GROUP (controls, patients) and within-subject factor TIME (successive trials) and CONDITION (attention, distraction). Levels of the factor TIME were reduced to 5 time-points by pooling the two neighboring time-windows.

To investigate differences in HEP-amplitudes, first a mixed 3-way ANOVA with the between-subjects factor GROUP (controls, patients) and the within-subject factors TIME (128–264 ms, 356–456 ms, 536–592 ms) and CONDITION (attention, distraction) was performed. Two-tailed pair-wise comparisons were conducted as post hoc tests. For all analyzes, differences between groups and interaction effects with groups were of special interest. In order to account for the possibility that group differences in HEP arise merely from cardiac field artifacts, we tested for differences in mean ECG voltage using a mixed ANOVA with between-subjects factor GROUP (controls, patients) and within-subjects factor TIME (128–264 ms, 356–456 ms, 536–592 ms). Furthermore, we explored potential differences between medicated and unmedicated patients using a two-tailed *t*-test. A Greenhouse-Geisser correction was used where appropriate. Correlations between heartbeat perception score and amplitudes of the HEPs were performed using Pearson correlation analyzes. Results are reported as mean ± SEM. All statistical analyzes were done using SPSS for windows (version 14.0).

3. Results

3.1. Behavioral data

As expected, the one-tailed *t*-test for independent samples revealed that patients showed significantly reduced levels of heartbeat perception [controls = 0.81 ± 0.04; patients = 0.67 ± 0.05, $t(30) = 2.44$, $p = .011$, $d = 0.85$]. An illustration of the group comparison is provided in Fig. 3a. With respect to heartbeat and tone counting performance during EEG, the 5 × 2 × 2 ANOVA revealed a significant effect of TIME [$F(2.8, 82.8) = 4.85$, $p = .005$, $\eta^2 = 0.14$], as controls and patients improved significantly over time. Additionally, a significant effect of CONDITION [$F(1,30) = 49.1$, $p < .001$, $\eta^2 = 0.62$] was observed, as tone-counting scores were higher than heartbeat-counting-scores. Moreover a significant interaction effect of CONDITION × TIME [$F(2.8, 85.1) = 2.93$, $p = .041$, $\eta^2 = .09$] was observed as patients improved especially in the attention condition. Furthermore patients scored lower than controls, but GROUP differences were not significant [$F(1,30) = 2.77$, $p = .11$, $\eta^2 = 0.09$]. Additionally, exploratory post hoc comparisons revealed that group differences were more pronounced in the attention state than in the distraction state (Fig. 3b and c). However, no significant interaction effect of CONDITION × GROUP [$F(1,30) = 1.88$, $p = .18$, $\eta^2 = 0.06$] was observed.

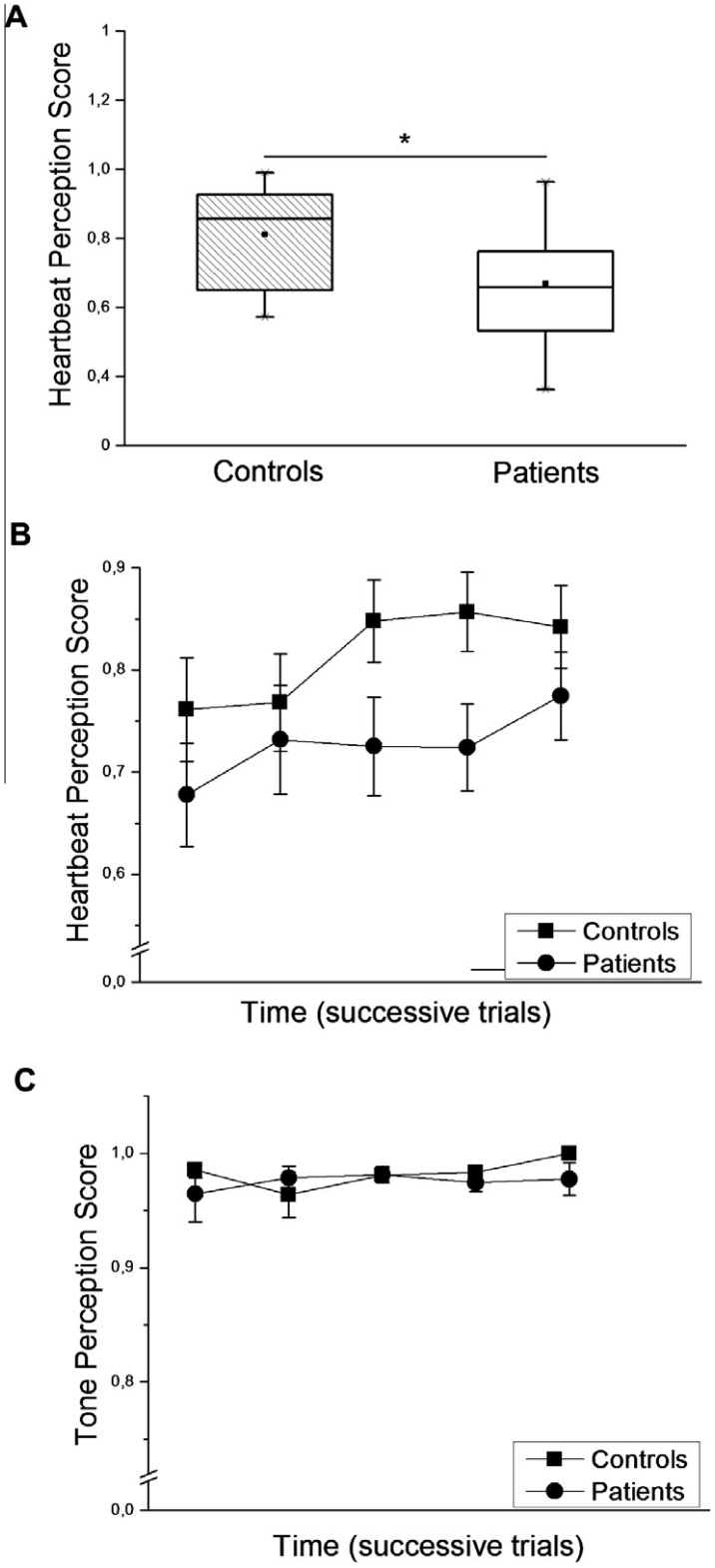

Fig. 3. Comparison of behavioral data between controls and patients. (A) Comparison of heartbeat perception score between depressed patients and controls. Data are presented as box plots. Boxes indicate 25th and 75th percentile with the horizontal line indicating the median, ■ mean, whiskers are drawn from the end of the interquartile range to the furthest observation. (B) Time course of the heartbeat perception score during EEG recording. Data are presented as mean ± SEM. (C) Time course of the tone perception score during EEG recording. Data are presented as mean ± SEM.

3.2. Heartbeat evoked potentials

The mixed ANOVA revealed a significant main effect of GROUP [$F(1,30) = 6.43$, $p = .017$, $\eta^2 = 0.18$]. As shown in Fig. 4, the GFP HEP amplitudes in general were smaller in depressed patients. Groups differed significantly in all time-windows. HEP varied strongly across time; thus ANOVA revealed a significant effect of TIME [$F(1.3,38.9) = 32.9$, $p < .001$, $\eta^2 = 0.52$]. Pair-wise comparisons

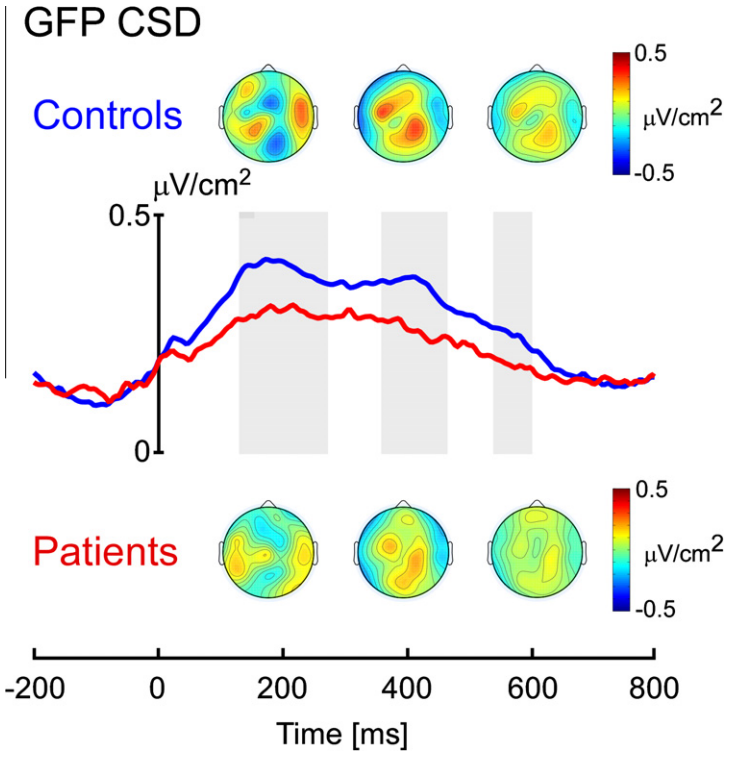

Fig. 4. Global field power comparison of the CSD waveforms (44 electrodes) from controls (blue) and patients (red). The two conditions (distraction and attention) are pooled. Mean CSD topographies are shown for both groups in the time-windows of interest (128–264 ms; 356–456 ms and 536–592 ms).

revealed that amplitudes were highest in the first time-window and smallest in the third time-window ($p < .001$ for all comparisons). No interaction effects ($F < 1$) and no significant effects of CONDITION [$F(1,30) = 2.5$, $p = .13$, $\eta^2 = 0.08$] were observed.

Heartbeat perception scores did not correlate with the amplitude of the heartbeat evoked potential neither in the attention condition (tw 1: $r = .22$, $p = .23$; tw 2: $r = .17$, $p = .35$; tw 3: $r = .15$, $p = .41$) nor in the distraction condition (tw 1: $r = .23$, $p = .22$; tw 2: $r = .17$, $p = .35$; tw 3: $r = .16$, $p = .37$).

In order to control for medication effects, patients taking antidepressants and/or antipsychotics ($n = 11$) and unmedicated patients ($n = 5$) were compared using two-tailed t-tests. Neither condition showed significant differences, either in terms of behavioral parameters (heartbeat and tone counting) or concerning the HEP amplitudes ($p > .362$).

To further control for the influence of the residual volume-conducted ECG, the ECG mean voltage in the three time-windows was analyzed between groups. The ANOVA revealed a significant effect of TIME [$F(1.44,43.28) = 63.823$, $p < .001$, $\eta^2 = 0.68$] but no significant differences between GROUPS [$F(1,30) = 1.71$, $p = .2$, $\eta^2 = 0.054$]. The interaction effect of GROUP $\times$ TIME was not significant [$F(1.44,43.28) = 3.06$, $p = .073$, $\eta^2 = 0.093$].

4. Discussion

Interoceptive awareness has been shown to have an impact on cognition, self-control of physical load, self-perception and decision making (Damasio, 1994; Herbert et al., 2007b; Pollatos et al., 2007b, 2007c). In the present study, we aimed to further elucidate characteristics of interoception during depressive episodes. In terms of behavioral data, a significantly decreased heartbeat perception score was observed in depressed patients. The analyzes revealed reduced GFP HEP amplitudes in depressed patients. Thus, our data are in agreement with the interpretation of reduced interoceptive awareness during depression.

The behavioral findings are in agreement with former studies which have reported a trend in decreased heartbeat perception in depressed patients (Mussgay et al., 1999; Van der Does et al., 1997). However, our results are in contrast to the study already mentioned above, which reported reduced heartbeat perception only in mildly depressed persons and not in clinically depressed ones (Dunn et al., 2007). It is suggested that this might be a reflection of the fact that "neurotic" depressed patients perform better on the heartbeat perception tasks than "reactive" depressed patients (Mussgay et al., 1999). To the best of our knowledge, this study provides the first assessment of HEPs in depressed patients. Our findings confirm those of former studies reporting higher amplitudes in persons with better heartbeat perception (Katkin et al., 1991; Montoya et al., 1993; Pollatos and Schandry, 2004; Schandry and Weitkunat, 1990; Yuan et al., 2007). However, the reported electrode locations showing relevant differences vary considerably across studies (Montoya et al., 1993; Pollatos and Schandry, 2004; Schandry and Weitkunat, 1990; Yuan et al., 2007), which may be due to a complex source configuration contributing to the HEP, a relatively small effect size, or poor HEP signal-to-noise ratios due to overlapping volume-conducted electrical heart activity, among other reasons. We believe that we have improved the HEP analysis substantially by combining two powerful tools (ICA and CSD) to reduce far-field activity from scalp EEG recordings. Additionally, we avoided multiple testing and the subjective selection of single electrodes by using a GFP-based methodology.

The observed lack of interoceptive awareness in depressed patients might contribute to a better understanding of various clinical symptoms during depressive episodes. First of all, it is tempting to speculate that lack of awareness of one's body signals leads to mental exhaustion and reactive depression (Herbert et al., 2007b; Mussgay et al., 1999). Secondly, according to the somatic marker hypothesis, difficulties in decision-making are related to reduced interoceptive awareness during depression (Damasio, 1994).

Thirdly, depressed patients often suffer from alexithymia, which might be linked to overall reduced bodily awareness (Herbert et al., 2010, 2007a). Some researchers have suggested that the reduced capacity to experience emotions can disturb social functioning (Lee et al., 2005; Pollatos et al., 2008). However, it has been shown that only emotional arousal is affected by cardiac awareness, whereas valence of emotions is not affected by cardiac awareness (Herbert et al., 2010).

Interestingly, bodily awareness can be trained. Evidence has been presented that cardiac awareness training improves performance of heartbeat perception and increases HEP amplitudes at frontal electrodes (Schandry and Weitkunat, 1990). Concepts emphasizing the importance of awareness of bodily signals for antidepressive treatment (Kabat-Zinn, 1991) receive some indirect support due to the findings presented here.

Finally, some limitations need to be addressed. First, two thirds of the patients were medicated, which could have biased the results. However, Mussgay et al. (1999) did not find any differences in heartbeat perception between medicated and unmedicated depressed patients. And, as reported in the Section 3, no differences were observed comparing medicated and unmedicated depressed patients in this study. Second, one could speculate that the present results might be biased by differences in time estimation accuracy between groups. However, there is no evidence for a related group effect between depressed and healthy persons (Dunn et al., 2007). Third, the Schandry mental tracking task applied here might rather be influenced by assumptions concerning the heart rate and not by actual heartbeat perception accuracy (Brener et al., 1995; Dunn et al., 2007). Therefore, it would be important to replicate the obtained behavioral results with other paradigms.

There are also potential limitations concerning the evaluation of the HEP. First, medication might have an influence on the HEP amplitude, although this was not observed when comparing medicated and unmedicated patients. Second, the sample size studied was relatively small. In combination with the small effects of heartbeat perception accuracy on the HEP amplitude, one might assume that the study lacked sufficient statistical power to detect all relevant differences. Accordingly our not having found differences in the ECG, might also be due to this lack of power. Another limitation of the study was that participants' abstinence from other legal or illegal drugs at the time of the study was only self-reported, and was not biochemically verified. Thus, similar studies should be conducted including more and, if possible, unmedicated depressed patients. Additional research is needed to establish the possible link between depressive symptoms, interoceptive awareness and HEPs. The present study, however, provides evidence that this link exists.

In conclusion, this study shows that bodily awareness is impaired during depression. To the best of our knowledge, this is the first study investigating electrophysiological correlates of heartbeat perception in depressed patients. Decreased heartbeat perception in depressed patients was reflected in reduced HEP amplitudes. This could represent an objective marker of the reduced interoceptive awareness associated with several depressive symptoms. Future studies should explore whether systematic training of interoceptive awareness contributes to an improvement of psychopathology.

Acknowledgment

We thank Anna-Karoline Israel and Jeremy Thorne for technical support. None of the authors has any conflict of interests or any financial conflict to declare.

References

Bechara A, Tranel D, Damasio H, Damasio AR. Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. Cereb Cortex 1996;6:215–25.
Bennett MR, Hacker PM. Emotion and cortical–subcortical function: conceptual developments. Prog Neurobiol 2005;75:29–52.
Brener J, Knapp K, Ring C. The effects of manipulating beliefs about heart rate on the accuracy of heartbeat counting in the Schandry task. Psychophysiol 1995;32:S3–4.
Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2011;9:90.
Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci 2004;7:189–95.
Damasio AR. Descartes' error and the future of human life. Sci Am 1994;271:144.
Debener S, Hine J, Bleeck S, Eyles J. Source localization of auditory evoked potentials after cochlear implantation. Psychophysiol 2008;45:20–4.
Debener S, Makeig S, Delorme A, Engel AK. What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. Brain Res Cogn Brain Res 2005;22:309–21.
Debener S, Strobel A, Sorger B, Peters J, Kranczioch C, Engel AK, et al. Improved quality of auditory event-related potentials recorded simultaneously with 3-T fMRI: removal of the ballistocardiogram artefact. Neuroimage 2007;34:587–97.
Debener S, Thorne J, Schneider TR, Viola FC. Using ICA for the analysis of multi-channel EEG data. In: Ullsperger M, Debener S, editors. Simultaneous EEG and fMRI. New York: Oxford University Press; 2010. p. 121–35.
Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21.
Delorme A, Sejnowski T, Makeig S. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. Neuroimage 2007;34:1443–9.
Dirlich G, Dietl T, Vogl L, Strian F. Topography and morphology of heart action-related EEG potentials. Electroencephalogr Clin Neurophysiol 1998;108:299–305.
Dirlich G, Vogl L, Plaschke M, Strian F. Cardiac field effects on the EEG. Electroencephalogr Clin Neurophysiol 1997;102:307–15.
Dunn BD, Dalgleish T, Lawrence AD. The somatic marker hypothesis: a critical evaluation. Neurosci Biobehav Rev 2006;30:239–71.
Dunn BD, Dalgleish T, Ogilvie AD, Lawrence AD. Heartbeat perception in depression. Behav Res Ther 2007;45:1921–30.
Gray MA, Taggart P, Sutton PM, Groves D, Holdright DR, Bradbury D, et al. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A 2007;104:6818–23.
Herbert BM, Pollatos O, Flor H, Enck P, Schandry R. Cardiac awareness and autonomic cardiac reactivity during emotional picture viewing and mental stress. Psychophysiol 2010;47:342–54.
Herbert BM, Pollatos O, Schandry R. Interoceptive sensitivity and emotion processing: an EEG study. Int J Psychophysiol 2007a;65:214–27.
Herbert BM, Ulbrich P, Schandry R. Interoceptive sensitivity and physical effort: implications for the self-control of physical load in everyday life. Psychophysiol 2007b;44:194–202.
James W. What is emotion? Mind 1884;19:188–205.
Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness. New York: Dell Publishing; 1991.
Katkin ES, Cestaro VL, Weitkunat R. Individual differences in cortical evoked potentials as a function of heartbeat detection ability. Int J Neurosci 1991;61:269–76.
Kayser J, Tenke CE. Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. Clin Neurophysiol 2006;117:369–80.
Lee L, Harkness KL, Sabbagh MA, Jacobson JA. Mental state decoding abilities in clinical depression. J Affect Disord 2005;86:247–58.
Lehmann D, Skrandies W. Spatial analysis of evoked potentials in man – a review. Prog Neurobiol 1984;23:227–50.
Montoya P, Schandry R, Muller A. Heartbeat evoked potentials (HEP): topography and influence of cardiac awareness and focus of attention. Electroencephalogr Clin Neurophysiol 1993;88:163–72.
Mussgay L, Klinkenberg N, Rüddel H. Heart beat perception in patients with depressive, somatoform and personality disorders. J Psychophysiol 1999;13:27–36.
Niazy RK, Beckmann CF, Iannetti GD, Brady JM, Smith SM. Removal of FMRI environment artifacts from EEG data using optimal basis sets. Neuroimage 2005;28:720–37.
Ohla K, Hudry J, le Coutre J. The cortical chronometry of electrogustatory event-related potentials. Brain Topogr 2009;22:73–82.
Pollatos O, Herbert BM, Matthias E, Schandry R. Heart rate response after emotional picture presentation is modulated by interoceptive awareness. Int J Psychophysiol 2007a;63:117–24.
Pollatos O, Kirsch W, Schandry R. Brain structures involved in interoceptive awareness and cardioafferent signal processing: a dipole source localization study. Hum Brain Mapp 2005;26:54–64.

Pollatos O, Kurz AL, Albrecht J, Schreder T, Kleemann AM, Schopf V, et al. Reduced perception of bodily signals in anorexia nervosa. Eat Behav 2008;9:381–8.
Pollatos O, Matthias E, Schandry R. Heartbeat perception and P300 amplitude in a visual oddball paradigm. Clin Neurophysiol 2007b;118:2248–53.
Pollatos O, Schandry R. Accuracy of heartbeat perception is reflected in the amplitude of the heartbeat-evoked brain potential. Psychophysiol 2004;41:476–82.
Pollatos O, Traut-Mattausch E, Schroeder H, Schandry R. Interoceptive awareness mediates the relationship between anxiety and the intensity of unpleasant feelings. J Anxiety Disord 2007c;21:931–43.
Schandry R. Heart beat perception and emotional experience. Psychophysiol 1981;18:483–8.
Schandry R, Sparrer B, Weitkunat R. From the heart to the brain: a study of heartbeat contingent scalp potentials. Int J Neurosci 1986;30:261–75.
Schandry R, Weitkunat R. Enhancement of heartbeat-related brain potentials through cardiac awareness training. Int J Neurosci 1990;53:243–53.
Strobel A, Debener S, Sorger B, Peters JC, Kranczioch C, Hoechstetter K, et al. Novelty and target processing during an auditory novelty oddball: a simultaneous event-related potential and functional magnetic resonance imaging study. Neuroimage 2008;40:869–83.
Van der Does AJ, Van Dyck R, Spinhoven P. Accurate heartbeat perception in panic disorder: fact and artefact. J Affect Disord 1997;43:121–30.
Viola F, Thorne J, Bleeck S, Eyles J, Debener S. Uncovering auditory evoked potentials from cochlear implant users with independent component analysis. Psychophysiol 2011;48:1470–80.
Viola FC, Thorne J, Edmonds B, Schneider T, Eichele T, Debener S. Semi-automatic identification of independent components representing EEG artifact. Clin Neurophysiol 2009;120:868–77.
Yuan H, Yan HM, Xu XG, Han F, Yan Q. Effect of heartbeat perception on heartbeat evoked potential waves. Neurosci Bull 2007;23:357–62.