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The heartbeat-evoked brain potential in patients suffering from diabetic neuropathy and in healthy control persons

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Abstract

Objectives: Neurotransmission from the heart to the brain results in a heartbeat evoked potential (HEP). This potential appears as a positive waveform ranging from 250 to 600 ms after the onset of ventricular contraction. Only limited information exists as to what extent the HEP is sensitive to a dysfunction in cardio-afferent pathways. Thus, the HEP was studied in patients with autonomic diabetic neuropathy.

Methods: Twenty-five patients and a healthy control group of equal size participated. The HEP was obtained as the average over 1200 EEG sweeps (18 channels) sampled contingent upon the onset of ventricular contraction. A heartbeat attention task and a distraction task were employed. Patients answered a questionnaire pertaining to the frequency of subjective symptoms related to diabetic neuropathy.

Results: The HEP amplitude at frontal, central and temporal locations was significantly diminished in patients in the latency range of 280–330 ms. A significant correlation was found between the questionnaire score of subjective autonomic symptoms and the reduction in the HEP.

Conclusions: We conclude that the HEP is sensitive to a comparably moderate abnormality in nerve function. Furthermore, we assume that the processing of subjective symptoms of the disease and the generation of the HEP share some common neuronal pathways. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Diabetic neuropathy; Evoked potential; Autonomic nervous system; Heartbeat perception; Subjective symptoms

1. Introduction

Systematic research has been conducted on the viscero-afferent neurotransmission in humans for about twenty years. It has been proven that a rich innervation of the viscera with afferent pathways exists (e.g. Cervero and Morrison, 1986). The investigation of these fibers with neuroanatomical methods, however, is difficult due to their small diameter. Consequently, only very limited information exists on the higher CNS projections of signals arising from the viscera.

Aside from the use of classical neuroanatomical methodology, the processing of viscero-afferent information may be studied by employing an approach which originates from the behavioral sciences. The subjective perception of signals arising in one's body, i.e. the interoception, has gained considerable interest during the last two decades (cf. Pennebaker, 1982; Vaitl and Schandry, 1995). Conscious perception of visceral activity has been studied in healthy subjects as well as in several patient groups. This has been performed, for instance, for heart rate (e.g. Vaitl and Gruppe, 1990), blood glucose level (e.g. Cox et al., 1985), muscular tonus (e.g. Waters et al., 1989), airway obstruction (e.g. Noseda et al., 1993), gastric and bowel activity (e.g. Whitehead and Drescher, 1980), and heart activity (e.g. Schandry, 1981).

From a clinical point of view, interoception is investigated primarily with respect to the perception of subjective symptoms associated with certain diseases. An especially important point is the perception of warning signals arising prior to critical bodily events. Correlations have been reported, for instance, between silent ischemia (i.e. ischemia not noticed by the patient) and elevated morbidity from cardiac infarction (Faerman et al., 1977; Niakan et al., 1986), as well as for hypoglycemia unawareness and increased morbidity from typical complications resulting from diabetes (The DCCT Research Group BM, 1991).

There is ample evidence that interoception underlies similar processing mechanisms such as the perception of external signals. For instance, a strong dependence exists between stimulus intensity and accuracy of signal perception (cf. Pennebaker, 1982). However, in contrast to the

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perception of external signals, only very limited information exists about the cortical mechanisms involved in interoception.

The brain electrical activity accompanying cardio-afferent input has been studied to elucidate the processing of signals of cardiac origin (Jones et al., 1986; Riordan et al., 1990; Montoya et al., 1993a; Schandry and Montoya, 1996; Dirlich et al., 1997, 1998). Considerable evidence that evoked potentials arising from cortical projections of cardio-afferent signals can be reliably observed at the scalp stems especially from the work of Montoya et al. (1993a) and Dirlich et al. (1998). When the EEG is sampled contingent to a well-defined cardiac event (e.g. the EKG R wave), this so-called heartbeat evoked potential (HEP, cf. Montoya et al., 1993a) appears at about 250–600 ms after the R wave. However, results are not unequivocal pertaining to the scalp region where the HEP primarily occurs. Montoya et al. (1993a) observed this activity as a positive potential shift predominantly at the anterior electrodes (referenced to linked mastoids), whereas Dirlich et al. (1998) reported a more posterior distribution (referenced to Cz) of the HEP. The cause for this discrepancy still has to be clarified. Among the features of the HEP being observed thus far are, for example, a sensitivity to focus of attention (Montoya et al., 1993a) and a reduced amplitude in patients with spinal cord lesions (cf. Montoya et al., 1993b).

Within the framework of interoception, autonomic neuropathy is of special interest. This disease is seen in up to 90% of diabetic patients (Husstedt et al., 1997). Here, nerve conduction in efferent and afferent pathways innervating the viscera, as well as the periphery, is deficient. Impairment of fibers supplying the viscera, especially the heart, is an early manifestation of the disease. A broad range of subjective symptoms may appear with autonomic neuropathy. Included here are palpitations, dizziness, and the perception of tachycardia. To which extent the predominance of these subjective symptoms is quantitatively related to the clinical signs of autonomic neuropathy has not been investigated in the past.

It is speculated that the relatively high incidence of unrecognized cardiac complications in diabetic patients (Faerman et al., 1977) may be a consequence of deficits in the afferent conduction of cardiac (pain) signals (Niakan et al., 1986) due to neuropathy. Pauli et al. (1991) reported a reduced perception of heart activity and arrhythmias in patients with diabetic autonomic neuropathy as compared to diabetics without neuropathy and healthy control subjects. Thus, the deficits in the function of viscero-afferent pathways are obviously reflected in an impaired cardiac perception.

In the present study we employed the method of the HEP for the examination of cardio-afferent neurotransmission in patients suffering from diabetic neuropathy.

Our aim was to elucidate the following main questions. (a) Is the HEP sensitive to neurophysiological deficits in cardio-afferent pathways? (b) Is there a relation between the clinical stage on cardiac autonomic neuropathy and the HEP amplitude? (c) Is a relation between subjectively perceived concomitants of autonomic neuropathy and the HEP amplitude observable?

2. Methods

2.1. Subjects

Twenty-five patients with type I diabetes (insulin-dependent diabetes; IDD), suffering from cardiac autonomic neuropathy (18–52 years, mean age 34 years, 11 men, 14 women) and 25 healthy control subjects participated. The individuals of the two groups were matched in pairs for age (maximum difference between pairs: 2 years) and gender.

Diabetes patients had visited a local municipal hospital in order to check their therapy regimen, to treat actual diabetes exacerbations, because of neuropathic complaints or because of other causes unrelated to diabetes. In connection with these concerns patients obtained a routine examination for cardiovascular autonomic neuropathy and for cardiovascular diseases.

Patients finally enrolled in the study had to be free of cardiovascular diseases. Hence patients were not under regular antihypertensive therapy. At the time of data collection there were no group differences for blood pressure levels (Table 1). None of the participants was under psychotropic medication. All patients were free from other severe diseases. Neuropathy of other origin than diabetes was excluded. Mean duration of diabetes was 5.5 years and mean duration of neuropathy was 2.2 years.

The diagnosis of the presence as well as the stage of cardiac autonomic neuropathy was based on 10 different parameters of heart rate (cf. Ziegler et al., 1992). (1) Coefficient of variation; (2) root mean square of successive differences; power spectra of the fast Fourier transformation for the (3) low- (0.01–0.05 Hz), (4) mid- (0.05–0.15 Hz), (5) high (0.15–0.50 Hz) frequency band; (6) mean circulant resultant; (7) maximum R-R interval; (8) minimum R-R interval; (9) difference of both (maximum − minimum); (10) ratio of both (maximum/minimum) for inspiration and expiration. If at least one of these parameters showed a difference of more than two standard deviations from the normal value of the corresponding age group, cardiac autonomic neuropathy (mildest stage) was diagnosed.

Table 1
Comparing systolic and diastolic blood pressures during experimental session between patients and controls

	Controls		Patients		F	P[a]
	Mean	SD	Mean	SD		
Systolic (mmHg)	128	8.58	137	9.52	1.48	NS
Diastolic (mmHg)	77	6.08	79	5.32	0.54	NS

[a] NS, not significant.

Patients were recruited in cooperation with a local municipal hospital, control subjects responded to announcements in local newspapers. Prior to the experiment, written informed consent was obtained. Both patients and control subjects received DM 50 (about 25 US$)for their participation.

2.2. Registration of physiological activity

After fitting of the electrodes, subjects were seated in a dimly lit, sound-attenuated room adjacent to the laboratory. Communication via intercom was possible throughout the whole experiment.

EEG was recorded by use of an elastic cap supplied with tin electrodes (Electro Cap, Neuromedical Supplies). The following 18 electrode positions (10–20 system) were used: C3, C4, Cz, F3, F4, F7, F8, Fp1, Fp2, Fz, Oz, P3, P4, Pz, T3, T4, T5, T6. Linked earlobe electrodes served as a reference. Electrode impedance was kept below 5 kΩ and signals were sampled at a frequency of 200 Hz. EEG was amplified by a Picker-Schwarzer EEG apparatus (ED 24), band limits set at 0.016 and 70 Hz.

The electrooculogram was registered from electrodes positioned at the outer canthus of the left eye and above the left eyebrow in order to register horizontal as well as vertical eye movements.

EEG sweeps were triggered by the upstroke of the R wave of the EKG and lasted from 50 ms pre-R wave to 530 ms post-R wave. Heartbeat evoked potentials were obtained by averaging for each of the two conditions (see below) over the total of 1200 EEG sweeps.

EKG electrodes were placed at the left lowest rib and at the right collarbone. EKG R waves were detected on-line and were stored on a separate trigger channel to be used for later off-line EEG averaging. Additionally, the raw EKG was stored in an analogous manner as the EEG.

Data acquisition and analysis was performed with Scan 3.1 software (Neurosoft Inc.)

2.3. Experimental design

A modification of the Mental Tracking method (Schandry, 1981) served as the heartbeat detection task. In the original version, participants have to undergo 3 heartbeat detection intervals of 15, 30, and 45 s duration. From earlier investigations in our laboratory, it is known that about 1000 cardiac cycles are necessary to obtain a stable heartbeat evoked potential. Hence, we used heartbeat-counting intervals of 100 cardiac cycles (approx. 90 s) and presented 12 intervals during heartbeat detection. During this task, participants were asked to count their own heartbeats silently. The beginning and end of the counting period were signaled by a start and a stop tone. During heartbeat counting, subjects should not to take their pulse or attempt to use other manipulations facilitating the counting of heartbeats. Even if a precise sensory perception was lacking, they should try to count in sychrony with their heartbeats. After the stop signal subjects were required to verbally report the number of counted heartbeats. Subjects were not informed about the fact that the length of the counting interval was determined by the occurrence of 100 heartbeats.

During the counting task EEG was recorded in order to obtain the HEP.

A Distraction Task served as a control condition for the effect of directing attention to the heartbeat. Analogously to the Heartbeat-Detection Task, subjects were now required to silently count weak (45 dB) tones appearing in random order within a series of standard tones (75 dB). As in the Heartbeat-Detection Task, the length of the series was signaled by tones and the series lasted for 100 heartbeats. Subjects had to report the number of detected weak tones after the stop signal.

After 6 Heartbeat Detection Tasks and 6 Distraction Tasks had been presented alternatingly, a pause (10 min) was introduced. The patients took their actual blood glucose levels during this pause. Control subjects filled in questionnaires. A second series of 6 tasks of each type followed after the pause, resulting in a total of 12 tasks of each type for the entire experiment.

At the end of the physiological recordings and after dismounting the electrodes, patients answered a questionnaire related to symptoms of diabetic neuropathy. This symptom questionnaire asked for the frequency of 12 symptoms of distal symmetric neuropathy and 10 symptoms of autonomic neuropathy during the last 4 weeks. On the basis of this instrument (details reported in Schandry and Leopold, 1998) two overall scores (by averaging the scores of the single items), one for autonomic neuropathy and one for distal symmetric neuropathy could be obtained for each patient.

2.4. Data analysis

The averaged and baseline corrected EEG sweeps were divided into 6 adjacent intervals of 50 ms length: 230–280, 280–330, 330–380, 380–430, 430–480, and 480–530 ms. To exclude EOG artifacts all EEG sweeps being accompanied by an EOG signal exceeding 50 μV were excluded.

Accuracy of heartbeat perception was quantified in the following manner: For each of the 12 heartbeat counting phases, the value of (1 − [number of counted beats − 100]/100) was calculated. The mean value across the 12 phases was then computed. The closer the latter value comes to 1, the better is the heartbeat perception.

For statistical testing of hypotheses two-tailed tests for differences between means were generally applied (significance level 5%). Only differences in heartbeat perception were tested one-sided because of the results of Pauli et al. (1988, 1991). Since patients with neuropathy reveal a poorer heartbeat perception, a directed hypotheses could be formulated.

In order to test for gross effects of scalp area we reduced

the 18 electrode locations to 4 aggregated scalp sectors: frontal (F3, F4, F7, F8, Fp1, Fp2, Fz), central (C3, C4, Cz), parietal (P3, P4, Pz), and temporal (T3, T4, T5, T6).

The effects of the factor Group (patients vs. control subjects), Latency (the 6 latency intervals from 230 to 530 ms) and Condition (heartbeat detection task vs. distraction task) were analyzed by MANOVA. Hotellings T^2-procedure (Babiloni et al., 1994) was employed. For post hoc comparisons of means, Tukey's test was performed. In the case of multiple testing the significance level was adjusted by the Bonferroni procedure.

For the correlations between the HEP amplitude and the neuropathy symptom scores on the one hand and the number of pathological indices in the heart rate variability tests on the other, we also employed a directed hypothesis.

Due to heart cycle-related EEG, averaging the registered scalp potentials may contain signals originating from the cardiac field. However, in an extensive analysis Dirlich et al. (1997) were able to identify an artifact-free interval within the time course of the heartbeat-contingent HEP. They state that "…The CFA (Cardiac Field Artifact) free window during the post T interval allows the undisturbed study of heart cycle-related potentials" (Dirlich et al., 1997, p. 313).

3. Results

3.1. Severity of autonomic neuropathy in the patient group

Sixty-four percent of the patients showed 1–3 pathological indices in heart rate variability, indicating moderate cardiac autonomic neuropathy; 20% presented 4–5 pathological values. Severe cardiac autonomic neuropathy was present in 16% of the subjects (6–10 pathological indices).

3.2. Heartbeat perception

Heartbeat perception was significantly poorer in patients than in healthy control subjects. The mean heartbeat perception score for the patients was 0.60 (SD 0.28) and 0.75 (SD 0.22) for the control subjects. The one-tailed *t*-test resulted in $t(48) = 2.10$ ($P = 0.022$).

3.3. Heartbeat evoked potentials

3.3.1. HEP Morphology

Grand averages of all electrode positions are depicted in Fig. 1. Generally, influence of the EKG R wave appears at the beginning of the traces. In the latency ranges later than about 150 ms, the potentials of controls and patients reveal pronounced differences at most electrodes.

In Fig. 2, brain maps are displayed for the condition 'Heartbeat Counting.' Obviously the positive activity was most prominent at frontal and frontocentral electrodes. In healthy subjects, the maximum of the frontal positivity is higher and extends farther posteriorly than in patients.

The means (over the respective latency ranges) of the amplitudes computed for the 4 aggregated scalp areas (Fig. 3) show a reduced positivity of the HEP in the patient group over the whole latency range from 230 to 530 ms.

A MANOVA performed for the 4 aggregated scalp areas yielded highly significant effects for the factors Group ($F(4/46) = 48.46$, $P < 0.001$) and Latency ($F(20/230) = 9.53$, $P < 0.001$). For the factor Condition and the interactions between factors, no significant effects were obtained. The latter indicates that the direction of attention (towards the heartbeat vs. external stimulation) has no substantial effect on the HEP.

A post hoc analysis for differences in voltages yielded significant differences for the aggregated frontal, central and temporal areas in the latency range 280–330 ms (see Table 2).

In the following statistical analyses, we primarily concentrated on this latency range (280–330 ms) because of the above mentioned result.

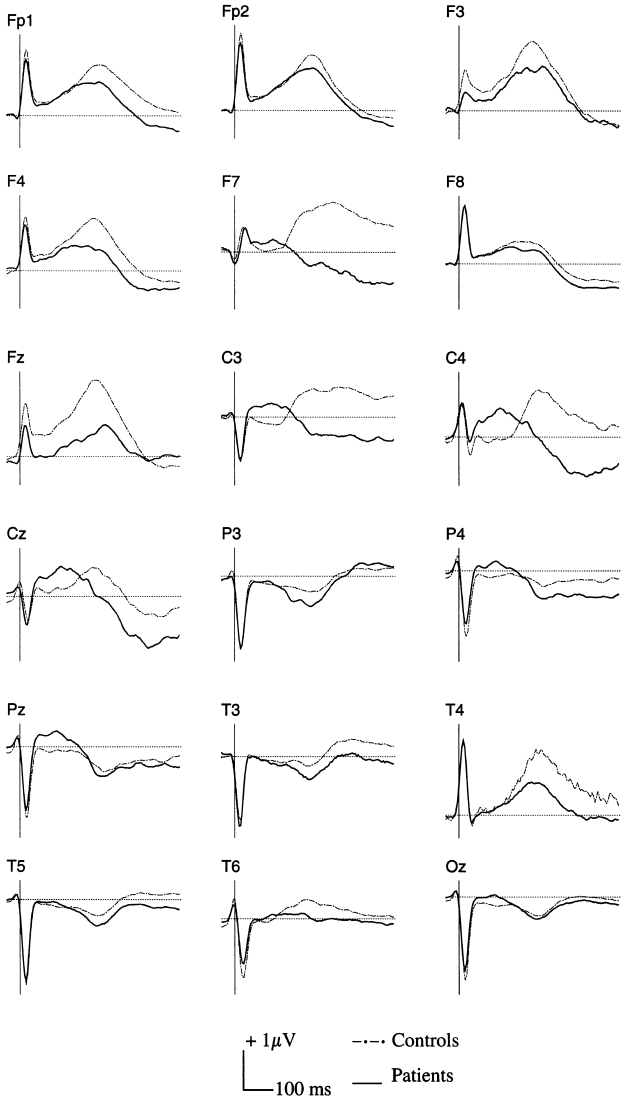

Fig. 1. Grand averages of the HEP for the heartbeat counting condition.

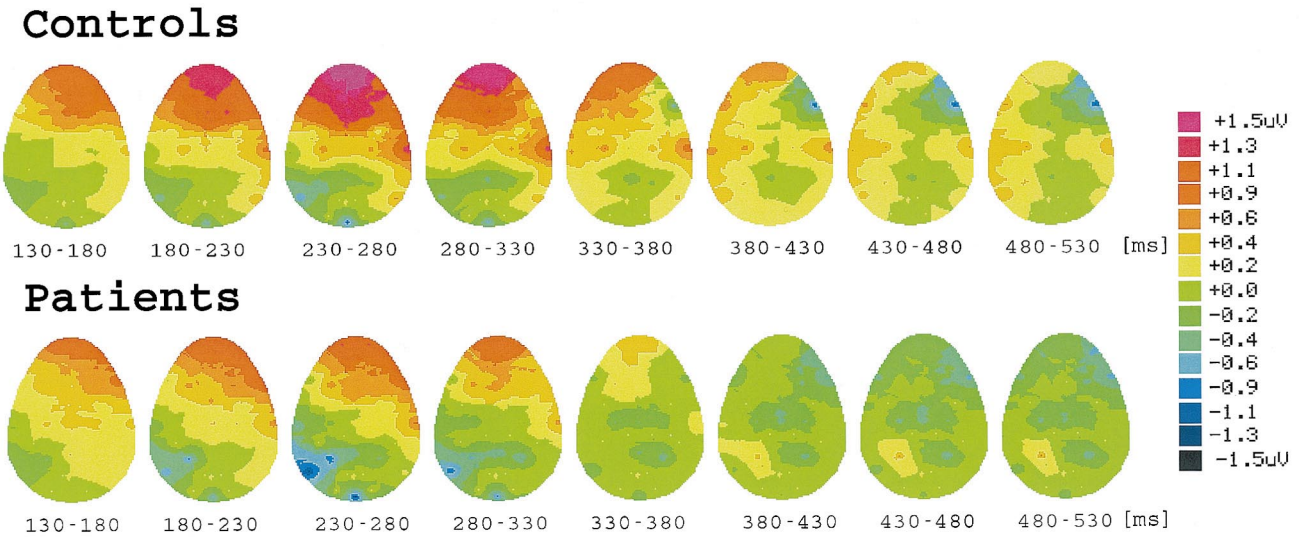

Fig. 2. Brain maps of grand averages for heartbeat detection task. Fifty ms intervals from 130 to 530 ms for patients and controls. Data from 18 electrodes, interpolating the next 4 neighboring electrodes. Frontal position up.

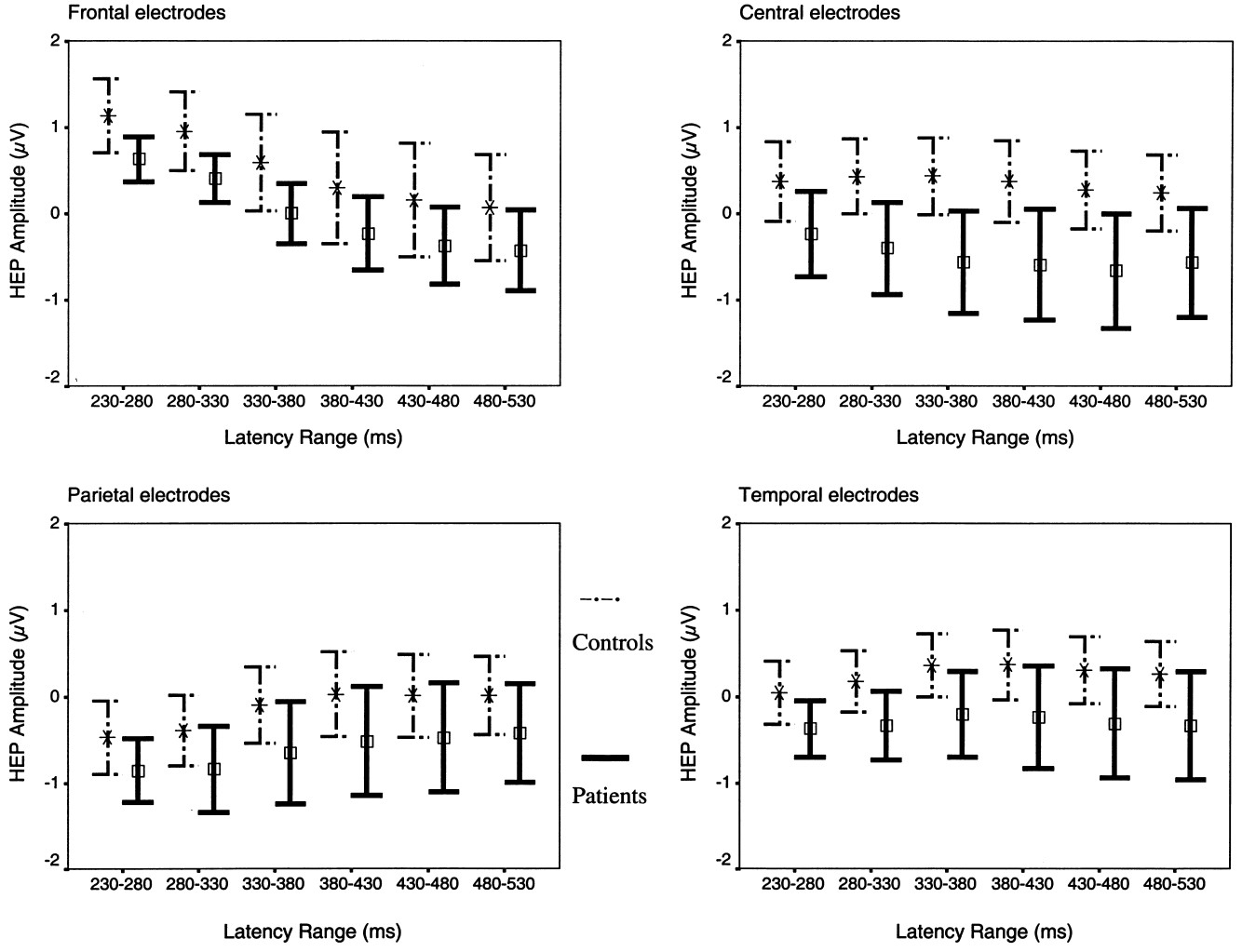

Fig. 3. Means and 95% confidence intervals of aggregated grand average HEP amplitudes (heartbeat detection task) for the 6 latency intervals and 4 scalp areas.

Table 2
Group differences for electrode positions[a]

Electrode area	Mean difference (SE) (controls − patients) (μV)	*P*
Central	0.746 (0.223)	0.001
Frontal	0.568 (0.186)	0.003
Parietal	0.329 (0.215)	0.128
Temporal	0.507 (0.176)	0.005

[a] Post hoc comparisons for the electrode areas between patients and controls. Depicted numbers refer to the post R-wave interval of 280–330 ms. Tukey test with Bonferroni correction for multiple testing.

3.3.2. Lateralization of the HEP

The HEP activity is lateralized to a certain extent, in that the activity is more pronounced at the more central and centro-parietal right electrodes than at the left hemisphere (see Fig. 2). The latter was tested statistically by comparing the mean electrical activity over all left hemisphere electrodes (C3, F3, F7, Fp1, P3, T3, T5) in all participants with those over all right hemisphere electrodes (C4, F4, F8, Fp2, P4, T4, T6). For the mean potentials in the latency range 280 ms to 330 ms, we obtained a significant difference ($t(49) = 2.54$, $P < 0.01$) between the right hemisphere (0.40 μV, SD 0.99 μV) and the left hemisphere (0.11 μV, SD 0.97 μV).

3.3.3. EKG

In order to check for possible influences of the cardiac field on the scalp electrodes, we additionally analyzed the EKG for group differences. We divided the EKG into the identical 6 latency windows as the EEG and performed a similar averaging procedure as for the HEP. *t*-Tests for group differences in mean EKG voltage did not show significant differences for the time windows 230–280, 280–330, or 330–380 ms. At later latencies after 380 ms, mean EKG voltage was significantly more negative in the control group. Obviously, no such differences occurred in the EKG during the latency range where the most pronounced differences in the HEP were observed (280–330 ms).

3.3.4. Index of cardiac autonomic neuropathy and the HEP

The impact of autonomic neuropathy on efferent fibers is assumed to be reflected in the reduction of heart rate variability. We calculated the correlation between HEP amplitude (latency range 280–330 ms) with the number of pathological indices in the heart rate variability tests for all electrode positions.

No significant correlation was obtained for any of the electrode positions (Table 3).

3.3.5. Subjective symptoms and the HEP

Correlations between the overall questionnaire score of autonomic neuropathy as well as the overall score of distal symmetric neuropathy and the HEP amplitude at each of the 18 electrode positions were calculated. To reduce multiple testing we again chose only the latency window of 280–330 ms.

We obtained significant negative correlations ($P < 0.05$, Pearson's *r* ranging from −0.34 to −0.45) in the case of the overall score of autonomic neuropathy at 10 electrode positions (see Table 3). The negative correlations reflect the following: The progression of the disease, as measured by subjective symptomatology, is accompanied in a quantita-

Table 3
Correlations of HEP amplitudes (280–330 ms interval) with results of heart rate variability test and symptom scores of distal and autonomic neuropathy[a]

HEP amplitude	Number of pathological indices	Overall score of distal neuropathy	Overall score of autonomic neuropathy
C3	0.04	−0.12	−0.38*
C4	−0.03	−0.12	−0.35*
Cz	−0.06	−0.09	−0.35*
F3	0.01	−0.03	−0.24
F4	−0.04	0.03	−0.19
F7	−0.09	−0.18	−0.17
F8	0.03	−0.11	−0.19
Fp1	0.09	−0.06	−0.21
Fp2	−0.14	−0.18	−0.15
Fz	0.03	−0.15	−0.39*
Oz	−0.12	−0.06	−0.29
P3	−0.05	−0.05	−0.34*
P4	−0.23	−0.14	−0.30
Pz	−0.12	−0.17	−0.40*
T3	−0.06	−0.27	−0.45**
T4	0.04	−0.09	− 0.34*
T5	0.03	−0.13	−0.37*
T6	−0.07	−0.14	−0.35*

[a] Pearson correlations, one-sided. *$P < 0.05$, **$P < 0.01$.

tive manner by the impairment of the regular cortical processing of heart activity. For the relation between the score of distal symmetric symptoms no significant correlation coefficients were observed at all (Table 3).

4. Discussion

In patients suffering from cardiac autonomic neuropathy, efferent and afferent pathways innervating the heart are impaired. It was hypothesized that this dysfunction in the viscero-afferent system should result in a reduced perception of heart activity as well as in an attenuation of the heartbeat evoked potential (HEP). Both effects were demonstrated in the present study. Additionally, the subjectively experienced severity of autonomic neuropathy, based on the frequency of typical subjective symptoms, correlated with the degree of attenuation of the HEP.

In our opinion, the most important aspect of the present study is the fact that an impairment of the afferent visceral pathways is reflected in certain characteristics of regularly occurring brain processes. As has been shown previously by research from our group as well as from Dirlich et al. (1998) regular, periodic heart activity is mirrored in a HEP. Obviously, this cortical activity is diminished by a dysfunction in the cardio-afferent system. Interestingly, even in patients displaying at the average only a moderate level of neuropathy, as assessed by cardiac function testing in our sample, this brain electrical symptom of the disease is apparent.

To our knowledge, this is the first time that a specific modification of regularly and permanently occurring brain activity could be demonstrated arising as a consequence of a disease that is manifested in the peripheral nervous system. It has to be kept in mind that, unlike in the typical evoked potential applications in neurology, no external stimulation was applied. Hence, brain activity reflecting the processing of a biological stimulus, i.e. heart activity, is affected permanently.

4.1. Reduced cardiac perception in patients with cardiac autonomic neuropathy

In the patient group, the cardiac perception score was significantly lower than in the healthy control group. This result is in accordance with the data from Pauli et al. (1991). In their Fig. 2, they present mean values of heartbeat perception scores (obtained with the identical method) for controls and neuropathy patients, showing a difference of about 0.15 between the two groups. This comes very close to the value observed in the present study. Thus, reduced perception of regular cardiac activity in patients with autonomic neuropathy seems to be a common and reliable phenomenon. Obviously, the partial denervation of the heart in the patient group leads to an impairment of the conscious processing of information about heart activity.

In the light of these results, it does not seem unlikely, for instance, that signals of physical exertion arising from the heart as well as the typical symptoms of ischemia are attenuated in these patients. This reduced symptom awareness may establish an additional health risk for diabetic patients suffering from autonomic neuropathy: In the case of irregular or pathological cardiac function (being typical sequelae of diabetes), appropriate countermeasures (physical rest, medication, emergency call) may be taken only at an increased and more serious level of symptom intensity.

4.2. HEP morphology and diminished frontocentral activity in patients

HEP amplitudes of control subjects as well as of patients were highest at frontocentral positions. Dirlich et al. (1998), however, present data speaking for both a frontal and a stronger, more posteriorly distributed, potential (depending on latency range).

We are well aware of the fact that the EEG allows conclusions about the sources of brain potentials only to a very limited extent. However, we wish to point out the assumption of a frontocentrally sited projection area for cardiac signals (as is suggested by the HEP distribution observed here) would be in accordance with certain other lines of evidence. The involvement of the frontocentral cortex in cardiac control, particularly the insular region, is a well-established fact. Bennarroch (1993, p. 992)), for instance, states that, "The insular and medial prefrontal cortex and the extended amygdala are involved in high-order processing of viscerosensory information and initiation of integrated autonomic responses…The insular cortex is a primarily viscerosensory area that receives viscerotopically organized inputs from gustatory pathways, gastric mechanoreceptors, arterial chemoreceptors, and baroreceptors and, together with the medial prefrontal cortex, may initiate and regulate various autonomic responses."

The work from Skinner (see e.g. Skinner, 1991 for a summary) shows that severe cardiac arrhythmias may be triggered by irregularities in frontocortical activity. Oppenheimer et al. (1992) review clinical evidence that the insular cortex (in humans) is involved in cardiac control. Rosen et al. (1994) present a PET study underlining the importance of prefrontal structures as projection areas for cardiac pain signals.

Thus, not only the deficit in conscious processing of cardiac signals may establish a risk factor for patients suffering from cardiac autonomic neuropathy. Moreover, the impairment of cardio-afferent connections to the frontal cortex may disturb regulatory mechanisms arising from frontocortical structures (aside from those stemming from subcortical structures).

4.3. Lateralization

We observed higher potential amplitudes of the HEP over the right hemisphere. This observation is in accordance with the report of Riordan et al. (1990), where a so-called

'cardio-cortical potential,' being largest over the right anterior portion of the scalp, has been described. These results are also in line with data from Yoon et al. (1997), where a reduction in heart rate variability and an increase in heart rate was observed through pharmacological disactivation of the right hemisphere. Moreover, from the work of Hari et al. (1993), for example, it is known that the insular cortex as well as the secondary somatosensory area reveal a higher activity on the side contralateral to the stimulation.

The heart is not symmetrically oriented relative to the vertical body axes, but points with the apex of the left ventricle to the lower left side. As a consequence of this, for instance, the region of apical impulse is maximal at the left side of the thorax. Thus, the transfer of mechanical energy from the heart to the mechanosensitive tissue of the thorax is more pronounced on the left side and triggers stronger somatosensory signals from here than from the right side. Due to a predominantly contralateral projection of the afferent fibers, the cortical representation of cardiodynamic activity should be more pronounced in the right hemisphere. Thus, the higher HEP amplitude over this hemisphere is in accordance with the (neuro)anatomy.

4.4. Relation between subjective symptoms of autonomic neuropathy and the HEP

As assessed by a symptom questionnaire, the severity of autonomic neuropathy correlated negatively with the HEP amplitude at several electrode locations. Thus, the HEP seems to be sensitive to the degree of the clinical manifestation of the disease. The specificity of this relation is further stressed by the fact that only the symptom score for complaints with respect to autonomic neuropathy significantly correlated with HEP amplitude, and not the symptom score for distal symmetric neuropathy.

The negative correlation means that the subjectively experienced degree of the disease is accompanied by a greater impairment of cortical processing of heartbeat signals. Besides, this result speaks for the validity of the HEP as a reflection of the cortical processing of visceral-afferent signals.

4.5. Afferent-efferent neuropathy

In contrast to the aforementioned significant correlation, we found no relation between the index of cardiac autonomic neuropathy and the HEP. The reason for this lack of agreement may be explained by the following.

Routine tests for cardiac autonomic neuropathy are based on the observation of heart rate characteristics as a consequence of efferent signals from the brain to the heart. However, it is very unlikely that transmission of afferent signals running from the heart to the cortex is reflected in these measures. From this it follows that the performance in standard tests relying on heart rate variability may be almost unrelated to parameters based on cardio-afferent transmission as the mental tracking score or the HEP amplitude.

There is a great body of evidence for primary efferent vagus lesions in diabetic autonomic neuropathy (Jermendy et al., 1991; Van Buren et al., 1998;). On the other hand research identified the afferent cardiac pathways primarily as liable for the perception or non-perception of cardiac symptoms in animals and man (Pal et al., 1989; Umachandran et al., 1991; Meller and Gebhart, 1992; Jänig, 1995) as belonging to the sympathetic system. Summarizing this knowledge and our results, this would allude to an efferent vagal system being affected by the diabetic neuropathy, and to an afferent sympathetic system being differently affected. Different time courses and/or different pathophysiological mechanisms might be possible reasons (Beylot et al., 1983; Tomlinson and Yusof 1983; Genovely and Pfeifer 1988), and thus leading to little or none significant correlations between system parameters. These hypotheses would stress the need for a differential diagnosis of afferent and efferent autonomic neuropathy deficits.

The consequences of the reduced brain response to cardiac signals in autonomic neuropathy fit well in the clinical picture of this disease. The reduced perception of regular heart activity as shown by the present results, and the reduced perception of arrhythmias (Pauli et al., 1991) and cardiac ischemic pain (e.g. Ambepityia et al., 1990), for instance, are in accordance with the reduced cortical responses to cardio-afferent stimulation. The diminished variability in heart rate during regular cardiovascular activity (e.g. respiratory sinus arrhythmia), as well as during orthostatic testing in the course of the Valsalva maneuver and at physical load, may also be a result in part of the deficits in the cortical monitoring of cardiac activity in neuropathy patients. It does not seem unlikely that the disturbed input to cardioregulatory cortical centers in these patients may also be responsible for deficits in the counterregulatory and adaptive control of heart activity.

We conclude that the methodology of the HEP seems to be suitable for studying brain processes related to viscero-afferent input in healthy persons, as well as in patients with neurological diseases. Further applications of the HEP as a research tool, on the one hand, may aim at patients where deficits in interoception have to be suspected, for instance panic patients, or patients with eating disorders, as well as in patients suffering from silent cardiac ischemia. On the other hand, the HEP may prove to be useful in the study of neurological and cardiological disorders, e.g. cardiac denervation (in heart transplants) or neurodegenerative diseases.

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