Altered Patterns of Heartbeat-Evoked Potentials in Depersonalization/Derealization Disorder: Neurophysiological Evidence for Impaired Cortical Representation of Bodily Signals

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ABSTRACT

Objective: Core features of depersonalization/derealization disorder (DPD) are emotional numbing and feelings of disembodiment. Although there are several neurophysiological findings supporting subjective emotional numbing, the psychobiology of disembodiment remains unclear.

Methods: Heartbeat-evoked potentials (HEPs), which are considered psychophysiological indicators for the cortical representation of afferent signals originating from the cardiovascular system, were assessed in 23 patients with DPD and 24 healthy control individuals during rest and while performing a heartbeat perception task.

Results: Absolute HEP amplitudes did not differ between groups. Nevertheless, healthy individuals showed higher HEPs during the heartbeat perception task than during rest, whereas no such effect was found in patients with DPD ($p = .031$). Patients with DPD had higher total levels of salivary α-amylase than did healthy individuals (9626.6 [8200.0] versus 5344.3 [3745.8] kU min/l; $p = .029$), but there were no group differences in cardiovascular measures (heart rate = 76.2 [10.1] versus 74.3 [7.5] beats/min, $p = .60$; normalized low-frequency heart rate variability = 0.63 [0.15] versus 0.56 [0.15] normalized units, $p = .099$; low frequency/high frequency ratio = 249.3 [242.7] versus 164.8 [108.8], $p = .10$), salivary cortisol (57.5 [46.7] versus 55.1 [43.6] nmol min/l, $p = .86$), or cortisone levels (593.2 [260.3] versus 543.8 [257.1] nmol min/l, $p = .52$).

Conclusions: These results suggest altered cortical representation of afferent signals originating from the cardiovascular system in patients with DPD, which may be associated with higher sympathetic tone. These findings may reflect difficulties of patients with DPD to attend to their actual bodily experiences.

Key words: depersonalization, heartbeat-evoked potentials, hypothalamic-pituitary-adrenocortical axis, interoception, sympathetic nervous system, visceral perception.

INTRODUCTION

A core feature of depersonalization/derealization disorder (DPD) is a specific impairment of self-awareness (1), such as feelings of disembodiment and emotional numbing. Patients with DPD feel detached from their sensations, actions, feelings, and their body. The prevalence of DPD is approximately 1% in the general population (2,3), it has high comorbidity with depression and anxiety

AA = α-amylase, **ACC** = anterior cingulate cortex, **AUC_G** = area under the curve with respect to ground, **BMI** = body mass index, **CDS** = Cambridge Depersonalization Scale, **CTQ** = Childhood Trauma Questionnaire, **CV** = coefficient of variation, **DPD** = depersonalization/derealization disorder, **ECG** = electrocardiogram, **EEG** = electroencephalogram, **HC** = healthy control group, **HEPs** = heartbeat-evoked potentials, **HPA axis** = hypothalamic-pituitary-adrenocortical axis, **HR** = heart rate, **(n)LF** = (normalized) low frequency, **SAM axis** = sympathoadrenomedullary axis, **TAS** = Toronto Alexithymia Scale

SDC Supplemental Content

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disorders, and its course is typically chronic (4). Although there are several neurophysiological correlates of the impairment of emotional processing (5–10), psychobiological mechanisms underlying the development and maintenance of the core symptom "disembodiment" in DPD remain unclear.

Seth and colleagues (11) have hypothesized that interoceptive signal processing may be deficient in DPD. In partial support of this hypothesis, during emotional picture viewing, patients with DPD show reduced activity in brain regions that are involved in interoceptive signal processing (5,6,8), for example, the anterior insula and the anterior cingulate cortex (ACC) (12). Difficulties in identifying emotions are a common alexithymic feature in patients with DPD (5,13). As awareness for emotions and bodily signals are closely related (14,15), we assume that impairments of interoceptive signal processing may contribute to alexithymic traits in DPD. However, there remains uncertainty about any differences in interoceptive accuracy and associated psychophysiological processes between patients with DPD and healthy individuals. In contrast to their feelings of disembodiment, patients with DPD perform similarly well in heartbeat perception tasks compared with healthy individuals (16). Nevertheless, there is evidence that patients with DPD may have difficulties with sustained attention to interoceptive signals, as patterns of performance in heartbeat perception accuracy over time differ between patients with DPD and healthy controls, with a decrease in performance observed in DPD and an increase in healthy controls. Differences in interoception should, therefore, be investigated using approaches with greater independence from conscious perception, for example, heartbeat-evoked potentials (HEPs).

HEPs are related to the processing of cardiac signals (e.g., heartbeats). HEPs are substantially reduced in individuals with a degeneration of afferent autonomic nerves (17) or reduced cardiac functioning (18). HEPs can be found with or without the conscious perception of heartbeats. Because afferent signals from the cardiovascular system continuously reach cortical structures, HEP amplitudes assessed during rest can be interpreted as indicators of central nervous system representation of cardiac interoceptive signals independent of active awareness of cardiac sensations (19,20). When assessed during a heartbeat perception task, HEP amplitudes are correlated with heartbeat perception accuracy (21–23), motivation to perform in those tasks (24), and attentional focus on heartbeats (25–27). There is only one study comparing HEPs between patients with mental disorders (major depression) and healthy individuals, reporting reduced HEP amplitudes in patients (28).

The onset of DPD is often related to stressful life events (1,29), which may be associated with the repeated findings of abnormalities in both physiological stress systems (i.e., the sympathoadrenomedullary [SAM] and the hypothalamic-pituitary-adrenocortical [HPA] axis) in patients with DPD. For example, there is a strong negative correlation ($r = -0.88$) between urinary norepinephrine and depersonalization severity (30). Patients with DPD have lower basal cortisol levels compared with healthy (31) and depressive individuals (32), as well as a reduced suppression of cortisol release after dexamethasone intake (31,33); yet, there are no differences in cortisol reactivity to psychosocial stress (31). Previous findings suggest that exposure to a laboratory stressor (34,35) affect the processing of interoceptive signals. Both physiological stress axes may be involved in this process: first, peripheral sympathetic activation may drive the cardiovascular system and, therefore, increase the afferent neurotransmission from cardiac interoceptors (e.g., baroreceptors), as implied by increased interoceptive accuracy by selective β_1-adrenergic drugs (36). Second, cortisol levels have been demonstrated to affect the cortical representation (19) and perception of bodily sensations (37–39). It could be argued, therefore, that dysregulation of the respective stress axes contributes to altered perception of bodily signals in DPD.

The objectives of the current study were to compare HEP amplitudes in patients with DPD with healthy individuals during rest and while focusing on cardiac signals (i.e., heartbeat perception task). Disembodiment could be reflected in a reduction of the overall amplitude of HEPs, as previously shown for major depression (28). A decrease of interoceptive accuracy over time (16) may imply deficits in focusing attention on bodily sensations. Given that HEPs assessed during a heartbeat perception task reflect attentional focus (25–27), it is plausible to assume that HEP amplitudes may be impaired to reflect attention focused on heartbeats in DPD. We, therefore, expected to find a) an altered pattern of HEP amplitudes in patients with DPD compared with healthy individuals. In addition, we were interested in investigating related dysregulations in physiological stress parameters. We expected b) differences in physiological stress parameters (SAM and HPA axes) between patients with DPD and healthy individuals, and c) associations between HEP amplitudes and physiological stress indicators.

METHODS

Participants

The study was approved by the Ethics Committee of the State Board of Physicians of Rhineland-Palatinate (Germany) and was part of an extended protocol, which is in parts reported elsewhere (16). All participants provided written informed consent. Twenty-seven patients with DPD were recruited from the DPD clinic of the Department of Psychosomatic Medicine and Psychotherapy (Mainz, Germany) and 27 healthy controls (HCs) via advertisement, who participated in the study between July 2012 and December 2013. Four patients with DPD and three HC individuals were later excluded from analysis due to low quality of psychophysiological data (e.g., multiple ectopic heartbeats), resulting in a final sample of 23 patients with DPD and 24 healthy individuals. Sample characteristics are described in Table 1. The diagnosis of DPD was established by M.M. according to the

TABLE 1. Group Differences Between Healthy Control Individuals and DPD Patients With Regard to Demographics, Questionnaire Data, and Biochemical Measures

Measure	Unit	Healthy Control Group (n = 24), M (SD)	DPD Patient Group (n = 23), M (SD)	t/χ^2	df	p
Sex	M/F	11/13	11/12	0.02	1	.90
Age	y	26.4 (2.0)	26.8 (6.5)	−0.32	25.91	.75
BMI	kg/m^2	21.6 (2.4)	24.1 (5.3)	**−2.06**	**28.56**	**.049**
Questionnaire measures						
CDS trait		6.4 (8.4)	132.9 (40.9)	**−14.22**	**22.64**	**<.001**
CDS state		36.7 (60.0)	983.2 (393.8)	**−11.16**	**21.90**	**<.001**
BDI-II		3.6 (3.3)	26.9 (6.5)	**−9.39**	**24.27**	**<.001**
STAI trait		36.8 (7.4)	62.4 (8.8)	**−10.53**	**44**	**<.001**
Biochemical measures						
Cortisone AUC_G	nmol min/l	543.8 (257.1)	593.2 (260.3)	−0.66	45	.52
Cortisol AUC_G	nmol min/l	55.1 (43.6)	57.5 (46.7)	−0.18	45	.86
α-Amylase AUC_G	kU min/l	5344.3 (3745.8)	9626.6 (8200.0)	**−2.29**	**30.51**	**.029**

Values in bold indicate the significant differences between groups, $p < .05$ or below.
DPD = depersonalization/derealization disorder; M = mean; SD = standard deviation; BMI = body mass index; CDS = Cambridge Depersonalisation Scale; BDI = Becks Depression Inventory; STAI = State Trait Anxiety Inventory; AUC_G = area under the curve with respect to ground.

German version of the Structured Clinical Interview for Dissociative Disorders (40). Participants fulfilled the criteria for DPD according to *Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition* (300.6) and the criteria for depersonalization/derealization syndrome according to International *Classification of Diseases, 10th Revision* (F48.1), with all patients with DPD experiencing chronic and persistent depersonalization. The mean (standard deviation) age at onset was 18.7 (8.9) years, with an average duration of 7.8 (7.2) years. Lifetime diagnosis of psychotic disorder, brain damage, or cardiovascular disease and current intake of benzodiazepines or antipsychotics were exclusion criteria. Current mental disorders comorbid with DPD are listed in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A215.

Questionnaires

Depersonalization was assessed with the Cambridge Depersonalization Scale (CDS) (41,42). The CDS consists of 29 items and measures frequency and duration of depersonalization over the last 6 months. Scores range from 0 to 290. Patients with DPD typically score higher than 70 (42). Furthermore, the state version of the CDS was applied after the experiment. The state version of the CDS comprises 22 items and reflects intensity of state depersonalization. Scores range from 0 to 2200. Depression was assessed with the Beck Depression Inventory-II (43) and anxiety with the State-Trait Anxiety Inventory (44). Alexithymia was assessed using the Toronto Alexithymia Scale (TAS) (45). Adverse childhood experiences were measured using the Childhood Trauma Questionnaire (CTQ) (46).

Experimental Procedure

Experimental sessions took place between 1300 and 1700 hours. Before the experimental procedure, participants completed trait questionnaires. Psychophysiological data were first assessed during a resting period (300 seconds), which was divided into two 150-second periods, one with eyes open and one with eyes closed. The order was counterbalanced across participants. Although findings from earlier studies suggest no main effect of open versus closed eyes on HEPs (19,47), this design was intended to retest this hypothesis in an a priori fashion. Participants were unaware during this phase that the later experimental task would involve their attention-focus on heartbeats. Thereafter, participants completed two heartbeat perception paradigms in a counterbalanced order across participants: a) a Whitehead-based task, in which participants were requested to judge whether a sequence of auditory stimuli occurs simultaneously or delayed with their own heartbeats (48); b) a Schandry heartbeat counting task (49) that consisted of seven intervals of 20, 25, 35, 45, 55, 65, and 75 seconds in a randomized order. Before the task started participants were asked to focus their attention on their own heartbeat. They were instructed not to take their own pulse or try any other manipulations facilitating the perception of heartbeats. Later calculation of HEPs was based on the actual length of these intervals (overall: 320 seconds). The length of the experimental session was approximately 40 minutes.

Electroencephalogram Measurement and Preprocessing

Electroencephalogram (EEG) and vertical electro-oculogram were recorded continuously using Ag/AgCl passive electrodes (Biopac MP150, EEG100C). Electrodes (Fz, Cz) were mounted according to the 10- to 20-electrode placement system. Impedances of the EEG electrodes were less than 10 kOhm. EEG signals were recorded with a hardware high-pass filter of 0.1 Hz, digitized at 1 kHz, and stored for offline analysis. The EEG was digitally refiltered (band pass: 0.1–35 Hz; 24 dB/octave) to minimize drifts and noise, and resampled at 250 Hz. All data were visually inspected. Epochs with nonstereotyped artifacts (e.g., electrode cable movements, swallowing, etc) were excluded from further analysis. As described in previous studies on HEPs (19,22,47,50), eye blink correction was carried out using the Gratton-Coles algorithm (51). EEG analysis was performed with Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany).

Cardiovascular Data

Electrocardiogram (ECG) electrodes (Tyco Healthcare H34SG Ag/AgCl electrodes) were placed in a standard lead II configuration. The ECG signal was high-pass filtered (0.05 Hz) at 1-kHz sampling rate. ECG data were analyzed with WinCPRS 1.160 software (Absolute Aliens Oy, Turku, Finland). Interbeat intervals were calculated from the ECG and manually corrected, with a normal cycle RR-interval time series as output signal, of which heart rate (HR) data were derived. Ventricular ectopic beats occasionally occurred in two individuals in the control group with a frequency of 0.04% and 0.09% of the respective number of cardiac cycles, but never in adjacent heartbeats. They were handled by simple interpolation of the two affected interbeat intervals (sum of both intervals, divided by 2).

Spectral analysis of RR interval series was carried out using Fast Fourier Transformation. The RR-interval time series was linearly interpolated and resampled with a sampling rate of 5 Hz, the resampled data were tapered using a Hanning window, and the windowed data zero padded to the next power of 2. The Fast Fourier Transformation spectrum was smoothed using a sliding triangular weighting function to increase degrees of freedom and thus improve the statistical relevance of the spectrum. The high-frequency (HF) band was defined as 0.14 to 0.4 Hz, the low-frequency (LF) band as 0.06 to 0.13 Hz, and oscillations less than 0.06 Hz as very LF. Normalized LF (nLF) power represents the proportion of LF band power relative to the total power, except for the very LF component (52). By using nLF and LF/HF ratio, we aimed to include indicators sensitive to central sympathetic activation (53,54), in addition to an indicator of peripheral sympathetic activation (i.e., α-amylase [AA]; see below).

Calculation of Heartbeat-Evoked Potentials

R-waves were automatically detected and manually confirmed in offline ECG signals. In a preliminary analysis segments of R-wave–triggered EEG (R− 200 milliseconds to R+ 1000 milliseconds) were averaged for the open or closed eyes conditions during the resting period separately. Results indicated no effects of eyes open versus closed conditions for HEPs, so both baseline segments will be collapsed for further analyses into one, resulting in two experimental periods all together (resting period, Schandry task). HEPs were not derived from the Whitehead task period because auditory stimuli during that task elicit auditory-evoked potentials, which may interfere with HEPs. Frequencies and distribution of heartbeats across groups and conditions are reported in Supplemental Digital Content 2, http://links.lww.com/PSYMED/A216. Up to 450 milliseconds after the R-wave, the HEP amplitude and the electrocardiac field partially overlap (26,55). We, therefore, calculated mean voltage in the time interval of 455 to 595 milliseconds after the R-wave, during which the electrocardiac field is considered minimal (18,19).

Hormonal and Enzymatic Data

Cortisol and AA were collected using saliva samples (Salivette cortisol swab; Sarstedt, Nümbrecht, Germany). We also assessed cortisone levels because salivary cortisol levels only reflect 50% to 60% of plasma cortisol levels due to the conversion of biologically active cortisol into inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 2 in the parotid and submandibular glands (56). Participants provided samples at the beginning and the end of the experiment. They were instructed to put the swab into their mouth and chew on it for 1 minute. Samples were stored at −20°C before analysis. Concentration of cortisol and cortisone was determined by liquid chromatography tandem mass spectrometry. Sample preparation, apparatus, and system parameters were identical to earlier studies (57,58). The enzymatic colorimetric method using the substrate 4,6-ethylidene-*p*-nitrophenyl-α,D-maltoheptaoside from Roche Diagnostics (Mannheim, Germany) was used for the measurement of AA concentrations in saliva. The diluted saliva samples (1+ 99) were analyzed with a Roche integra system 800. Area under the curve with respect to ground (AUC_G) was determined for cortisol, cortisone, and AA as indicators of total hormonal or enzymatic output during the experimental procedure (59). For liquid chromatography tandem mass spectrometry–based analysis of cortisol and cortisone, the intra-assay coefficients of variation (CVs) were 1.9% to 5.0% (based on $n = 10$), and the interassay CVs were 3.8% to 7.7% ($n = 8$). Interassay and intra-assay CVs for analysis of AA were less than 1.4% ($n = 21$).

Statistical Analysis

A priori group differences (age, sex, body mass index [BMI], AA, cortisol/cortisone) were calculated using a χ^2 test for categorical variables and *t* tests for independent samples for metric variables. In case of inhomogeneity of variances (Levene test), degrees of freedom were corrected accordingly. Preliminary analysis of HEP data from the resting period was performed using a 2 × 2 × 2 mixed-design analysis of variance (ANOVA) with the between-participant factor "group" (HC group, DPD group) and the within-participants factors "electrode" (Fz, Cz) and "eye condition" (open, closed). In the main analysis, HEP amplitudes were subjected to a 2 × 2 × 2 mixed-design ANOVA with the between-participant factor "group" and the within-participant factors "experimental task" (resting period, Schandry task) and "electrode." In two separate analyses, the factor "group" of the main ANOVA was modified to contrast 12 DPD patients with versus 11 patients without anxiety disorder, and 15 DPD patients with versus 8 patients without major depression, respectively. Cardiovascular data were analyzed using a 2 × 2 mixed-design ANOVA with the between-participant factor "group" and the within-participant factors "experimental task." Post hoc analyses were performed using Bonferroni-corrected *t* tests for dependent samples. Pearson correlations between HEPs (grand averages over both experimental conditions and electrodes), heartbeat perception accuracy (Schandry and Whitehead-based paradigm), and indicators of physiological stress axes (cardiovascular indices: averages over both experimental conditions) were calculated across participants. Furthermore, TAS and CTQ scores were correlated with the HEP grand average, the HEP difference between both experimental tasks (Schandry − rest), and accuracy scores in heartbeat perception tasks. Critical α level was set to .05 for all analyses. All statistics were conducted with SPSS 19.0 (IBM, Inc).

RESULTS

A Priori Group Differences

There were no group differences in age, sex distribution, cortisone, or cortisol AUC_G. Mean BMI and AA AUC_G were significantly higher in patients with DPD than in HC, as were depression (Beck Depression Inventory-II), trait anxiety (State/Trait Anxiety Inventory), depersonalization trait, and state scores (see Table 1). Patients with DPD reported significantly more childhood trauma experiences (all *p* values < .05), as indicated by the CTQ total score and all subscales, except for "sexual abuse" ($p = .25$), as well as higher alexithymia as indexed by the TAS total score and its subscales "difficulty identifying feelings" and "difficulty describing feelings" (all *p* values < .001; see Table S1, Supplemental Digital Content 3, http://links.lww.com/PSYMED/A217). Accuracy scores of heartbeat perception tasks are reported elsewhere (16).

Heartbeat-Evoked Potentials

We observed higher HEP amplitudes at electrode Cz (mean [standard error of the mean] = 0.33 [0.17] μV) than at Fz (0.01 [0.20] μV; $F(1,45) = 4.74$; $p = .035$; $\eta^2 = 0.10$; see Table 2). Furthermore, the interaction group by experimental task was significant ($F(1,45) = 4.97$; $p = .031$; $\eta^2 = 0.10$). Post hoc analyses showed that HEP amplitudes in HC individuals were higher during the Schandry task (0.22 [0.27] μV) than during rest (−0.12 [0.23] μV, $p = .010$), whereas there were no trial-related differences in the DPD patient group (Schandry: 0.26 [0.27] μV; rest: 0.32 [0.23] μV). The group by experimental task by electrode effect ($F(1,45) = 4.31$; $p = .044$; $\eta^2 = 0.09$) indicated that this difference was stronger at electrode Cz ($p = .008$; see Table 2), whereas the difference between both trials at

TABLE 2. Heartbeat-Evoked Potentials and Cardiovascular Measures for Each Experimental Task and Both Groups (DPD Patients; Healthy Controls)

		Healthy Control Group (n = 24)		DPD Patient Group (n = 23)	
Measure	Unit	Rest, M (SD)	Schandry Task, M (SD)	Rest, M (SD)	Schandry Task, M (SD)
Heartbeat-evoked potentials[a]					
Fz	μV	−0.35 (1.20)	0.11 (0.99)	0.19 (1.32)	0.45 (1.27)
Cz	μV	−0.07 (1.28)	0.51 (1.28)	0.27 (1.74)	0.26 (1.37)
Cardiovascular measures					
Heart rate	beats/min	73.9 (7.4)	74.6 (7.6)	75.8 (7.6)	76.6 (12.5)
nLF HRV[b]	n.u.	0.53 (0.15)	0.59 (0.15)	0.59 (0.16)	0.66 (0.14)
LF/HF ratio HRV[c]	ratio	142.3 (93.8)	187.2 (122.1)	207.8 (182.3)	290.7 (293.1)

DPD = depersonalization/derealization disorder; M = mean; SD = standard deviation; nLF = normalized low frequency; HRV = heart rate variability; n.u. = normalized units; LF = low frequency (0.06–0.13 Hz); HF = high frequency (0.14–0.4 Hz).

[a] Main effect electrode ($F(1,45) = 4.74$; $p = .035$; $\eta^2 = 0.10$), two-way interaction group by experimental task ($F(1,45) = 4.97$; $p = .031$; $\eta^2 = 0.10$), three-way interaction group by experimental task by electrode ($F(1,45) = 4.31$; $p = .044$; $\eta^2 = 0.09$).

[b] Main effect experimental task ($F(1,45) = 9.10$; $p = .004$; $\eta^2 = 0.17$).

[c] Main effect experimental task ($F(1,45) = 8.95$; $p = .004$; $\eta^2 = 0.17$).

electrode Fz was only marginally significant ($p = .053$). Waveforms of HEPs are illustrated in Figure 1. In post hoc analyses contrasting DPD patients with versus without major depression and anxiety disorders, respectively, there were no significant differences in HEP patterns between DPD subgroups (both F values < 1).

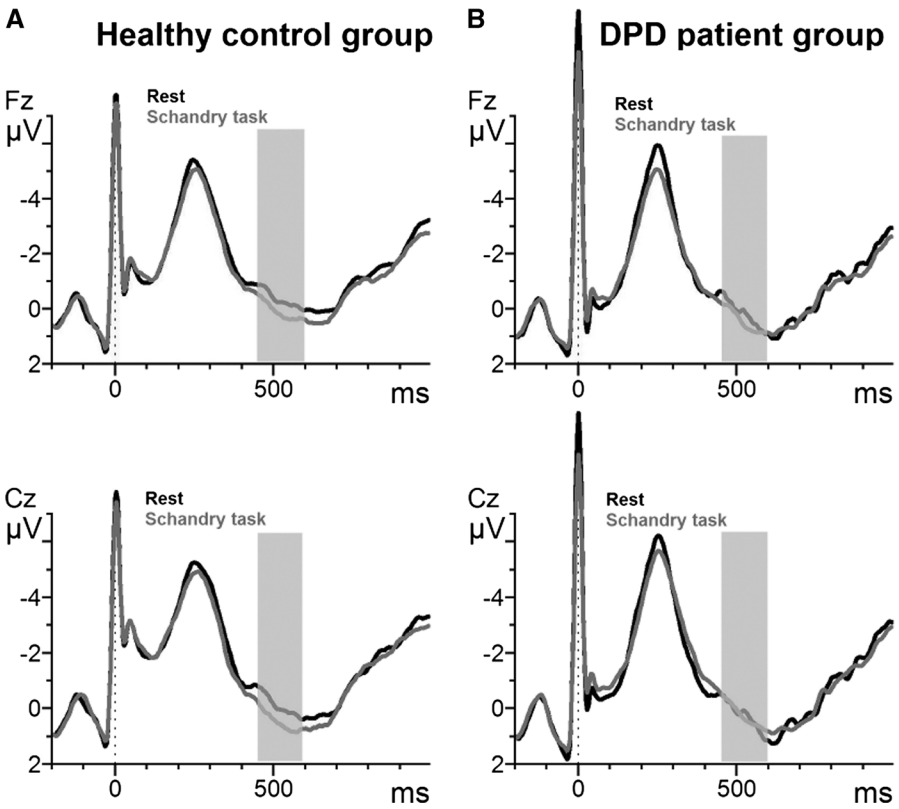

FIGURE 1. HEP waveforms in healthy control individuals (A) and patients with DPD (B). Mean HEP amplitude was extracted between 455 and 595 milliseconds after an R-wave (gray bar). HEP amplitudes were higher when performing the Schandry heartbeat perception task than during a resting period in healthy individuals (A) but not in patients with DPD (B). HEP = heartbeat-evoked potential; DPD = depersonalization/derealization disorder.

Cardiovascular Data

There were no main or interaction effects for HR (all F values < 1; see Table 2). The factor experimental task affected HR variability, with higher nLF power ($F(1,45) = 9.10$; $p = .004$; $\eta^2 = 0.17$) and higher LF/HF ratio ($F(1,45) = 8.95$; $p = .004$; $\eta^2 = 0.17$) during the Schandry task than during rest. Group differences in nLF band power and LF/HF ratio were only marginally significant (nLF: $F(1,45) = 2.84$; $p = .099$; $\eta^2 = 0.05$; LF/HF: $F(1,45) = 2.81$; $p = .100$; $\eta^2 = 0.05$).

Correlations

Age and BMI were positively correlated across participants. They were also associated with indicators of sympathetic activation (nLF, LF/HF ratio, AA AUC_G), which were positively interrelated (nLF-LF/HF ratio, nLF-AA AUC_G; marginally significant: LF/HF-AA AUC_G: $r = 0.280$, $p = .056$), as were cortisone and cortisol total outputs (AUC_G). HEP grand averages were not related to age, BMI, or any cardiovascular measure of sympathetic nervous system activity, but there were moderate negative correlations between HEPs and total output of cortisol ($r = -0.294$, $p = .050$) and cortisone AUC_G ($r = -0.335$, $p = .021$). Heartbeat perception scores derived from the Schandry and Whitehead-based task were neither intercorrelated nor associated with HEP grand averages. However, Whitehead accuracy scores were negatively correlated with nLF ($r = -0.365$, $p = .019$) and LF/HF ratio ($r = -0.335$, $p = .032$) and were marginally associated with AA AUC_G ($r = -0.280$, $p = .076$). Correlation coefficients of demographic data, HEPs, heartbeat perception indices, and indicators of physiological stress axes are presented in Table 3. A description of correlations between TAS, CTQ, and interoceptive indicators is provided in Supplemental Digital Content 4, http://links.lww.com/PSYMED/A218.

DISCUSSION

This is the first study to provide electrophysiological evidence for altered cortical representation of bodily signals in DPD. We investigated HEPs during rest and during a heartbeat perception task in patients with DPD and healthy individuals. In line with previous findings (25–27), we found higher HEP amplitudes during the heartbeat perception task compared with rest in HC individuals. In support of hypothesis (i), this difference in HEPs between rest and heartbeat perception was not apparent in patients with DPD. In partial support of hypothesis (ii), patients with DPD showed higher total levels of AA (AUC_G) compared with HCs, although no group differences in cardiovascular indices of sympathetic nervous system activity (HR, nLF HR variability, LF/HF ratio), cortisol, or cortisone levels were observed. Finally, in support of hypothesis (iii), we found significant negative correlations between absolute HEP amplitudes and total cortisol ($r = -0.29$) and cortisone levels ($r = -0.34$; AUC_G) across all participants.

HEP amplitudes have been shown to be associated with attention focus on heartbeats (25–27), heartbeat perception accuracy (21–23), and the motivation (24) in performing heartbeat perception tasks. Thus, the current difference in

TABLE 3. Pearson Correlation Coefficients of Age, BMI, Indicators of Interoceptive Signal, and Physiological Stress Axes Across all Participants ($n = 47$)

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Age	1								
2. BMI	0.369*	1							
HEPs									
3. HEP grand average	−0.080	0.163	1						
Accuracy in heartbeat perception tasks									
4. Schandry heartbeat counting task	−0.110	0.040	0.151	1					
5. Whitehead heartbeat discrimination task	−0.229	−0.187	0.005	0.214	1				
Autonomic nervous system									
6. Normalized LF HRV (average)	0.529**	0.591**	−0.080	0.049	−0.365*	1			
7. LF/HF ratio (average)	0.313*	0.331*	−0.060	0.125	−0.335*	0.797**	1		
8. AUC_G α-amylase	0.558**	0.349*	−0.080	−0.018	−0.280	0.536**	0.280	1	
HPA axis									
9. AUC_G cortisone	−0.115	0.036	−0.335*	0.022	−0.028	0.100	0.051	0.300*	1
10. AUC_G cortisol	−0.171	−0.064	−0.294*	−0.003	0.059	−0.012	−0.023	0.196	0.917**

BMI = body mass index; HEP = heartbeat-evoked potential; LF = low frequency (0.06–0.13 Hz); HRV = heart rate variability; HF = high frequency (0.14–0.4 Hz); AUC_G = area under the curve with respect to ground; HPA axis = hypothalamic-pituitary-adrenocortical axis.

* $p < .05$, ** $p < .01$.

HEP patterns may reflect difficulties of patients with DPD to focus their attention effectively on interoceptive signals. In line with that, we have previously found that patients with DPD differ from HCs in heartbeat perception accuracy curves: although healthy individuals have lower initial values and show an increase over time, patients with DPD begin with higher initial values and show a decrease over time, resulting in an overall zero effect in heartbeat perception (16). This might indicate that patients with DPD have difficulties with focusing on their actual bodily perceptions (16). Because patients with DPD also show impairments in attention to external stimuli (60–62), future studies should clarify whether DPD is associated with a specific disconnection from interoceptive sensations or whether this disconnection concerns all sensory modalities due to specific impairments of attentional processes.

The onset of DPD is often related to stressful life events (1,29), and the acute experience of stress may amplify DPD symptoms (63). As a consequence, patients with DPD show dysregulation in the SAM axis including the autonomic nervous system (7,64–67) and the HPA axis (30–33). The present results suggest higher AA in DPD, but no group differences in cardiovascular sympathetic indices. This is in concordance with earlier studies finding no differences in normalized HF power or LF/HF ratio between patients with DPD and HCs (7). AA is a protein that is associated with the release of norepinephrine due to sympathetic activation (68), and its secretion is predominantly mediated by peripheral β_1-adrenoceptors (69,70). In contrast, nLF HR variability is considered a cardiac indicator of central sympathetic control (71–73). The current findings suggest that the dysregulation of the SAM axis in patients with DPD may be limited to the peripheral branch, that is, the release of catecholamines. In an earlier study of nine patients with DPD and nine HCs, no group differences in basal plasma norepinephrine level were reported (30). Nevertheless, that study may have been underpowered to reveal an effect in the order of the effect size observed in the current study ($\eta^2 = 0.11$).

The differential response patterns in peripheral and more central indicators of sympathetic activation are corroborated by the high correlation between nLF and LF/HF ratio ($r = 0.80$) as indicators of central sympathetic activity, whereas nLF as an indicator of peripheral sympathetic activity was only moderately correlated ($r = 0.54$) with AA AUC_G. Although there was no correlation between absolute HEP amplitudes and sympathetic indices, our findings imply a coincidence of reduced HEP difference (Schandry − rest) and increased peripheral sympathetic tone in DPD. Increased peripheral sympathetic tone may contribute to altered patterns of HEPs because increased stimulation of cardiac interoceptors (e.g., arterial baroreceptors) may intensify cardiac sensations (34,74,75). This increased stimulation of interoceptors may induce insensitivity to changes in HEPs associated with performing heartbeat perception tasks. Furthermore, we observed negative correlations between heartbeat perception accuracy in the Whitehead task on the one hand, and nLF and LF/HF ratio on the other hand, which is partially in line with earlier findings (76). This suggests that increased central sympathetic activity may interfere with the accurate conscious processing of afferent signals from the cardiovascular system.

Dysregulation of HPA axis activity in DPD is indicated by lower basal cortisol levels compared with healthy (31) and depressive individuals (32), as well as reduced suppression of cortisol release after dexamethasone intake (31,33). In line with a previous report (32), there were no group differences in cortisol or cortisone total output (AUC_G) in the current study. Inconsistencies between study findings may be explained by possible differences between patients with DPD and healthy individuals in cortisol release, which may be limited to secretion during the morning and mid-day hours (31), which were not investigated in the current study.

HEPs have repeatedly been demonstrated to be associated with activation of frontocentral areas (17,23,25–27,77). Measurements in the current study, therefore, focused on frontal and central electrodes, with the largest effects of HEPs observed in Cz. An alternative explanation for the insensitivity of HEPs when performing a heartbeat perception task is altered activity in brain regions, which are responsible for the processing of interoceptive signals. The cortical generation of HEPs is located in the right insula, the ACC and the left prefrontal cortex (50), which have also been associated with interoceptive signal processing (12,78). These brain regions also show reduced activity in patients with DPD during the processing of emotional stimuli (5,6,8). On the basis of these earlier findings, we would argue that altered activity or connectivity in the ACC and the right insula may have contributed to the observed alteration of HEP patterns.

Previous studies have demonstrated a positive association between heartbeat perception accuracy in the Schandry task and HEPs when assessed during this task, but not when assessed during rest (22,79). In the current study, the correlation between HEPs and accuracy in the Schandry task was low and not significant ($r = 0.151$, $p = .33$), which may be due to the fact that HEPs in the current analysis were aggregated over the Schandry task and the resting period.

DPD is frequently comorbid with depression and anxiety disorders (80,81), which is in line with comorbidity rates in the present study (affective disorders, 78%; anxiety disorders, 52%). Because both may also affect interoception (82–84), one could speculate that the current findings are simply a result of mental comorbidity. Nevertheless, altered body perception in depression is reflected in a general decrease of HEP amplitudes (28), which was not apparent in the DPD patient group. Furthermore, depressive

individuals tend to show reduced accuracy in heartbeat perception (28,83). In contrast, we found no overall differences between patients with DPD and healthy individuals in accuracy of heartbeat perception as assessed by the Schandry- (DPD, 0.69; control, 0.71) or the Whitehead-based task (DPD, 0.35; control, 0.61) (16). Supporting this assumption, post hoc analyses showed no differences between DPD patients with and without major depression or anxiety disorder in their respective HEP pattern. The current findings, therefore, suggest the modulation pattern of HEPs to be specific for DPD. Future studies should explore the possibility of using HEPs as a biologically based diagnostic tool for DPD. In line with previous reports, patients with DPD were more alexithymic than HCs (13). However, alexithymia was related to neither interoceptive accuracy nor HEPs. This argues against a previous assumption that emotional dysregulation in DPD might be caused by restricted interoception. Complementary to self-report data, future studies should clarify whether the identification of actual affective states evoked in laboratory settings (e.g., by using affective pictures or videos) may be related to interoception in DPD. Regarding adverse childhood experiences, patients with DPD were more affected than HCs, although mean scores of the CTQ subscales were all below critical cut-points (85).

In line with previous findings on the modulation of HEPs by exogenous cortisol (19) without affecting cardiovascular activity, no associations between cortisol secretion and indices of cardiovascular activity were observed in the current study. On the basis of previous reports on the effects of exogenous cortisol on blood perfusion in the thalamus (86), it was hypothesized that cortisol may act as a filter in the integration of exteroceptive and interoceptive sensory information (19). Biologically active cortisol is converted into inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (56). Consequently, cortisol and cortisone $AUCs_G$ were highly interrelated in this study ($r = 0.92$). The finding of a negative association between HEP amplitudes and cortisol/cortisone output across all participants suggests that the absolute amplitude of central nervous system representation of interoceptive signals increases with reduced basal cortisol level, independent from sympathetic activation or DPD symptoms.

In terms of clinical implications, the demonstrated deficit of patients with DPD to focus their attention effectively on interoceptive signals despite their normal performance in heartbeat perception suggests that interventions designed to enhance the experience of actual bodily feelings more fully (e.g., mindfulness-based interventions, focus on bodily perception, biofeedback) may prove to be beneficial. Future studies should test, whether these approaches affect HEPs and DPD symptoms, and monitor treatment changes. Furthermore, beyond DPD, our study may stimulate research comparing the effects of depersonalization/derealization on the cortical representation of bodily signals in a transdiagnostic fashion, for example, in posttraumatic stress disorder.

Limitations

The current findings are based on a minimal EEG measurement of two electrodes (Fz, Cz). Notwithstanding previous studies demonstrating that interindividual and intraindividual factors affecting HEPs can be assessed with such a minimal EEG setup (26,27), an extended setup would provide additional information on the topography of the observed effects. However, a minimal EEG setup as applied in the current study may have the advantage of increased feasibility in clinical and diagnostic application.

Although nLF and LF/HF ratio have been repeatedly shown to be sensitive to central sympathetic activation (53,54,72), there is continued debate as to whether they may be also affected by other mechanisms, such as parasympathetic control over HR (52,87,88), or whether values are distorted by mathematical operations (88). The current study may contribute to this debate in demonstrating positive correlations between nLF ($r = 0.54$) and LF/HF ratio ($r = 0.28$) with AA AUC_G as an indicator of peripheral sympathetic activation.

CONCLUSIONS

Patients with DPD show altered cortical representation of afferent neural signals originating from the cardiovascular system, which could represent a neurophysiological indicator for altered body perception. This effect could be related to increased peripheral sympathetic activity in DPD and reduced activity in brain regions that are associated with interoception. Basal cortisol level may be inversely related to the amplitude of the central representation of bodily signals, independent from DPD symptoms.

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