IMPORTANCE  The ability to perceive and regulate one's own emotions has been tightly linked to the processing of afferent bodily signals (interoception). Thus, disturbed interoception might contribute to the core feature of emotional dysregulation in borderline personality disorder (BPD), as increased levels of depersonalization, body image disturbances, and reduced sensitivity to physical pain suggest poor body awareness in BPD.

OBJECTIVE  To determine neural correlates of disturbed body awareness in BPD and its associations with emotional dysregulation and to explore improvements in body awareness with BPD symptom remission.

DESIGN, SETTING, AND PARTICIPANTS  Case-control study performed at Heidelberg University Hospital, Heidelberg, Germany. Heartbeat evoked potentials (HEPs), an indicator of the cortical representation of afferent signals from the cardiovascular system, were investigated in 34 medication-free patients with BPD, 31 healthy volunteers, and 17 medication-free patients with BPD in remission. The HEPs were assessed using 5-minute resting-state electroencephalograms and parallel electrocardiograms. Core BPD symptoms, history of childhood traumatization, and psychiatric disorders were assessed by means of self-reports and structured interviews. To measure neural correlates of disturbed body awareness, high-resolution T1-weighted structural magnetic resonance imaging scans were collected and analyzed using voxel-based morphometry and region-of-interest–based approaches. The study was performed between 2012 and 2014, and data analysis was performed in 2014.

MAIN OUTCOMES AND MEASURES  Mean HEP amplitudes in resting-state electroencephalograms and their correlation with self-reported emotional dysregulation, as well as with gray matter volume.

RESULTS  Patients with BPD had significantly reduced mean HEP amplitudes compared with healthy volunteers ($F_{(1,61)} = 11.32, \ P = .001$), whereas the mean HEP amplitudes of patients with BPD in remission lie somewhere in between these 2 groups of participants ($P > .05$). The HEP amplitudes were negatively correlated with emotional dysregulation ($R = −0.30, \ P = .01$) and positively associated with gray matter volume in the left anterior insula ($R = 0.53, \ P < .05$) and the bilateral dorsal anterior cingulate cortex ($R = 0.47, \ P < .05$), 2 structures that have been identified as core regions for interoception.

CONCLUSIONS AND RELEVANCE  The results indicate state-dependent deficits in the cortical processing of bodily signals in patients with BPD, which appear to be associated with core features of BPD. The analysis of patients with BPD in remission suggests an improvement in cortical representation of bodily signals with symptom remission. Results recommend the integration of techniques to strengthen bodily awareness in psychotherapeutic interventions of BPD.

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Emotional dysregulation is a core feature of borderline personality disorder (BPD). Patients with BPD are highly reactive to other people’s emotions and show increased activation of the amygdala and anterior insula and reduced prefrontal inhibition of these limbic regions for emotional stimuli. According to prominent theories, these alterations in the perception and regulation of emotions may stem from consistent invalidation (i.e., emotional experiences that were ignored, dismissed, or punished during childhood). Growing up in such an invalidating environment may lead individuals with BPD to focus more on external cues to guide their behavior than on internal experiences.

Since the James-Lange theory, the ability to perceive and regulate emotions has been tightly linked to the perception of afferent bodily signals (interoception). This has been confirmed by results indicating a positive relationship between interoceptive awareness and the ability to perceive one’s own emotions and altered processing of interoceptive signals in mental disorders characterized by emotional dysregulation, such as major depression or depersonalization. Alterations in the processing and regulation of emotions in a patient with BPD might hence be related to deficits in the representation of the patient’s own bodily signals. Indications of interoceptive deficits in patients with BPD come from studies showing increased levels of alexithymia. Since the James-Lange theory, the ability to perceive and regulate emotions has been tightly linked to the perception of afferent bodily signals (interoception). This has been confirmed by results indicating a positive relationship between interoceptive awareness and the ability to perceive one’s own emotions and altered processing of interoceptive signals in mental disorders characterized by emotional dysregulation, such as major depression or depersonalization. Alterations in the processing and regulation of emotions in a patient with BPD might hence be related to deficits in the representation of the patient’s own bodily signals. Indications of interoceptive deficits in patients with BPD come from studies showing increased levels of alexithymia. Indications of interoceptive deficits in patients with BPD come from studies showing increased levels of alexithymia.

However, the 2 studies that investigated the actual interoceptive accuracy (IA) of patients with BPD in interoceptive tasks yielded mixed results. Although reduced IA in a group of patients with personality disorders, including BPD, compared with patients with somatoform disorders and healthy volunteers was reported in Mussgay et al., in a more recent study, no significant differences in IA were found between patients with BPD and healthy volunteers. In these studies, IA was assessed with heartbeat perception tasks, which are commonly used, and valid methods. Interestingly, IA in these tasks has been associated with volume and activity in the anterior insular, dorsal anterior cingulate, and somatomotor cortices. However, these “conventional” methods have one important shortcoming: they are unable to differentiate between actual afferent bodily signals and the active process of attention focusing and perception.

By contrast, heartbeat evoked potentials (HEPs), cortical potentials measured in the resting electroencephalogram (EEG), are considered as indicators of the cortical representation of afferent signals from the cardiovascular system independent of an attentional focus on the heartbeat. This is of importance for the assessment of interoception in patients with BPD because manipulating the attentional focus alters the patients’ emotional reactivity. With regard to the neural correlates of HEPs, the results of a dipole localization EEG study indicate that the insular and anterior cingulate cortices, key regions for IA, are generators of HEPs. Neuroimaging studies on neural correlates of HEPs are still lacking, and little is known about the clinical relevance of interoception in mental disorders with emotional dysregulation, such as BPD. This is surprising because several successful psychotherapeutic treatments incorporate interventions that focus on the improvement of a patient’s awareness of bodily signals and may decrease insular hyperreactivity to emotional stimuli. First evidence suggests that cardiac awareness training may improve performance in heartbeat perception tasks, increase HEP amplitudes, and decrease symptom distress in patients with somatoform disorders.

Taken together, there are indications of an association of emotional dysregulation with altered interoception in patients with BPD, but barely anything is known about the cortical representation of bodily signals and its neural correlates. Moreover, a group of patients with BPD in remission might allow for the identification of state-independent psychobiological characteristics. The present study aimed to investigate the cortical representation of bodily signals with HEPs, its association with emotional dysregulation, and its neural correlates in patients with BPD compared with healthy volunteers. We additionally explored HEPs in a group of patients with BPD in remission to gather information on the state dependence of alterations in interoceptive processes. We expected to find smaller HEP amplitudes in patients with BPD than in healthy volunteers, and we assumed that HEPs would correlate negatively with emotional dysregulation. We expected that HEP amplitudes as a measure of the cortical representation of bodily signals, and thus interoceptive signals, would be associated with anterior insular and dorsal anterior cingulate gray matter volume.

Methods

Participants

In our study, the participants were 34 medication-free patients who received a DSM-IV diagnosis of BPD (20 were female, and the mean [SD] age was 27.7 [6.8] years) and 31 healthy volunteers (16 were female, and the mean [SD] age was 27.9 [6.7] years) matched for age, sex, and intelligence. In addition, we collected EEG data from 17 medication-free female patients with BPD in remission. General exclusion criteria comprised neurological disorders; current alcohol or drug abuse or dependence in the last 12 months; lifetime diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; severe medical illness, including cardiac dysregulations; and use of psychotropic medication (Table 1 and Appendix in the Supplement). The study was part of the German Research Foundation Clinical Research Group 256 and was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, Germany, and all participants provided written informed consent.
Measures

Qualified diagnosticians assessed borderline, comorbid antisocial, or avoidant personality (using the International Personality Disorder Examination51) and Axis I disorders (using the Structured Clinical Interview for DSM-IV for Axis I disorders52), emotional dysregulation (using the Difficulties in Emotion Regulation Scale53), depersonalization (using the Fewtrell Depersonalisation Scale54), borderline symptom severity (using the Zanarini Rating Scale for Borderline Personality Disorder55 and the Borderline Symptom List56), depressiveness (using the Beck Depression Inventory II57), childhood traumatization (using the Childhood Traumatization Questionnaire58), and intelligence (using Raven’s progressive matrices59). Demographic information was assessed in a standardized questionnaire; height and weight were measured on the day of assessment (Table 1).

Electroencephalographic and Electrocardiographic Data

Data Acquisition

A 5-minute resting-state EEG (eyes closed) and electrocardiogram (ECG; Einthoven II) were recorded in a sound-attenuated, dimly lit room (60 Ag/AgCl electrodes; EasyCap; an equidistant referencesystemwithanaveragereferenceand all impedances <10 kΩ) amplified with a 72-channel QuickAmp amplifier (Brain Products; with a passband of 0.01-200 Hz and a sampling rate of 1000 Hz).

Data Processing

Data preprocessing (BrainVision Analyzer 2.0; Brain Products) included downsample (250 Hz), digital filtering (bandpass of 0.1-35 Hz and 24-dB/ octave roll-off), correction of eye-movement artifacts,17,38,41,43,60 semiautomatic rejection of trials...
with nonphysiological artifacts, and segmentation (~200 to 1000 milliseconds of ECG R wave). Separate averages were computed for each electrode and participant. Statistical analyses were conducted on the mean voltage from 455 to 595 milliseconds after the ECG R wave because the impact of the electrocardiogram artifact in this time window is less than 1%. For mean HEP amplitudes, we calculated the average across all 60 head electrodes. ARTiiFACT was used to calculate the heart rate.

Statistical Analyses
Data were subjected to analysis of covariance (ANCOVA), controlling for age and sex, to analyze group differences in HEPs. First, mean HEP amplitudes were compared between patients with BPD and healthy volunteers; heart rate, body mass index, and current affective and anxiety disorders were added as control factors. Next, a repeated-measures ANCOVA was performed that included electrode position (Fz, Cz, Pz, and Oz), using the Huynh-Feldt procedure to correct for violations of sphericity and the Dunn multiple comparison test as post hoc tests. Another ANCOVA of the 3 groups of participants (healthy volunteers, patients with BPD, and patients with BPD in remission) was also performed. Partial correlations controlling for group were used to explore associations between mean HEP amplitudes and questionnaire data.

Structural Magnetic Resonance Imaging Data
Data Acquisition
A 3-dimensional sagittal isotropic magnetization-prepared rapid acquisition gradient-echo sequence was obtained using a 3-T scanner (Siemens Tim Trio) with a 32-channel head coil (240 slices, 1 × 1 × 1-mm voxel size, flip angle of 9°, repetition time of 2300 milliseconds, echo time of 2.98 milliseconds, 256-mm field of view, matrix size of 256 × 256 pixels, and 1-mm slice thickness). Experienced neuroradiologists reviewed all scans to exclude clinically important abnormalities.

Data Processing
Processing of structural magnetic resonance imaging (MRI) data was performed with Statistical Parametric Mapping, version 8 (http://www.fil.ion.ucl.ac.uk/spm), and the voxel-based morphometry (VBM) toolbox (VBM8; Department of Psychiatry, University of Jena) following the standard VBM8 workflow (eAppendix in the Supplement).

Statistical Analyses
Using both unbiased VBM (uncorrected \( P < .001 \) and an cluster-extension level of \( k > 79 \) voxels) and region-of-interest (ROI)-based approaches (familywise error-corrected \( P < .05 \)), the relationship between mean HEP amplitudes and gray matter volumes was assessed with random-effects multiple regression analysis, which included mean HEP amplitudes, group, age, and sex as regressors. Hypothesis-driven ROI analyses were performed for the anterior cingulate and insular cortices (anatomical masks were derived from the Wake Forest University PickAtlas; http://imri.wufu.edu/software/pickatlas). To assess the specificity of associations between HEP amplitudes and anterior cingulate and insular gray matter volumes, we performed further ROI analyses for the amygdalae and hippocampi and ROI-based group comparisons of anterior cingulate and insular gray matter volumes.

Source Analysis
Data Processing
To emphasize the functional relevance of the regions extracted from the MRI data for the HEP amplitudes, the averaged EEG data were subjected to an adapted form of spatiotemporal source analysis implemented in Brain Electric Source Analysis, version 5.1, with regional sources in the left anterior insular and right anterior cingulate cortices and bilateral opercula (spatial coordinates set to relevant peak voxels from the MRI analysis), as well as a principal component to control for ECG R-wave activity (eAppendix in the Supplement).

Statistical Analysis
Mean dipole amplitudes in the time window from 455 to 595 milliseconds were subjected to ANCOVA with the factors of group and dipole and with the control factors of age, sex, and residual ECG R-wave activity.

Results
HEPs and BPD Symptomatology
The mean HEP amplitudes of patients with BPD were significantly reduced compared with healthy volunteers \( (F_{1,65} = 11.32, P = .001) \) (Figure 1), and the effect remained significant after including control variables \( (P < .05) \). The group-by-electrode ANCOVA revealed the most pronounced reductions in amplitude in patients with BPD at parietal and occipital electrodes (group by electrode: \( F_{3,165} = 4.24, P = .01 \); at electrodes Pz and Oz, \( P < .01 \)), whereas the mean HEP amplitudes were larger in patients with BPD than in healthy volunteers at the frontal electrodes (ie, at Fz, \( P < .05 \); eTable in the Supplement). Groups did not differ with regard to heart rate, body mass index, or age \( (P > .05; \text{Table I}) \).

The exploratory analysis of the mean HEP amplitudes of patients with BPD in remission compared with those of patients with BPD and healthy volunteers confirmed the significant main effect of group \( (F_{2,77} = 6.24, P = .003) \) (Figure 1), with post hoc tests revealing significantly reduced mean HEP amplitudes in patients with BPD compared with healthy volunteers \( (P < .01) \), whereas the mean HEP amplitudes of patients with BPD in remission lie somewhere in between the patients with BPD and the healthy volunteers and did not significantly differ from the mean HEP amplitudes of these 2 groups \( (P > .05; \text{Figure I}) \). The mean HEP amplitudes were negatively associated with emotional dysregulation (using the Difficulties in Emotion Regulation Scale: \( R = −0.30, P = .01 \)), BPD symptom severity (using the Zanarini Rating Scale for Borderline Personality Disorder: \( R = −0.21, P = .06 \); using the Borderline Symptom List: \( R = −0.28, P = .01 \)), depressiveness (using the Beck Depression Inventory II: \( R = −0.25, P = .03 \)), and emotional abuse
(using the Childhood Traumatization Questionnaire: \( R = -0.21, P = .06 \)).

**Structural MRI Analysis**

The mean HEP amplitudes were significantly related to gray matter volumes in the dorsal anterior cingulate cortices \( (R = 0.47; \text{Figure 2}) \) and the left anterior insula \( (R = 0.53, \text{Figure 2}) \). The VBM analysis also revealed an association between HEP amplitudes and bilateral frontal opercula (Table 2). No significant associations were found between HEP amplitudes and amygdala or hippocampal gray matter volumes, and group comparisons revealed no significant differences in insular or anterior cingulate cortex gray matter volumes between patients with BPD and healthy volunteers.

**Source Analysis**

Our model with 4 regional sources (the left anterior insula, the right anterior cingulum, the left frontal operculum, and the right frontal operculum) and a principal component for ECG R-wave activity explained 74.4\% of the mean dipole amplitude between 455 and 595 milliseconds. The mean dipole amplitudes of patients with BPD were significantly smaller (455-595 milliseconds) than those of healthy volunteers (main effect of group: \( F_{1,60} = 8.55, P = .01 \); no significant effects of dipole, dipole by group, or covariates: \( F_{1,60} \leq 1.74, P \geq .19 \)) (Figure 3).

**Discussion**

The present study revealed reduced HEP amplitudes, an indicator of cortical processing of bodily signals, in patients with BPD compared with healthy volunteers. In addition, HEP amplitudes correlated negatively with emotional dysregulation and with self-reported emotional childhood abuse. Morphometric analyses revealed specific, positive associations between HEP amplitudes and gray matter volumes of the left anterior insular cortex and the right anterior cingulate cortex. The analysis of patients with BPD in remission indicated improved cortical representation of bodily signals with symptom remission.

In line with prominent theories such as Damasio’s somatic marker hypothesis\(^{72}\) or the James-Lange theory\(^{9,10}\), our results indicate the fundamental role played by afferent bodily signals in the perception and regulation of emotions. Similar to this, a number of studies have revealed positive correlations between interoceptive indicators and the ability to recognize and regulate emotions\(^{19,20}\) and altered interoceptive signal processing in patients with major depression\(^{15,16}\) or depersonalization disorder.\(^{17,18}\) The HEP amplitudes of the patients with BPD were not only significantly reduced compared with healthy volunteers but nega-
tively related to emotional dysregulation. The HEP amplitudes were also positively related to the gray matter volumes of the left anterior insular cortex and the bilateral dorsal anterior cingulate cortex, 2 structures that have been identified as core regions for interoception. Together with a dipole analysis, this suggests a common neural source of HEP amplitudes and IA measured in conventional heartbeat perception tasks.

Although previous studies highlighted the role played by the right anterior insula in interoceptive awareness and conscious evaluation of bodily signals, we found a strong correlation between HEP amplitudes and the gray matter volume of the left anterior insula. This is in line with the hypothesis that the left anterior insula is associated with the registration of interoceptive experiences and other low-level cortical processing of interoceptive states, whereas the right anterior insula seems to be of particular relevance for the further evaluation and subjective feeling of bodily signals. The finding of reduced cortical representation of bodily signals in patients with BPD may increase our understanding of some of the most characteristic symptoms of this disorder. Parental invalidation, insecurity, and abuse in childhood may result in an individual with BPD focusing on external cues instead of perceiving, integrating, and interpreting his or her own bodily signals and emotions. Consistent with this, we found a negative relationship between self-reported emo-

Table 2. Correlations Between Mean HEP Amplitudes and GM Volume in the Voxel-Based Morphometry and ROI Analyses

<table>
<thead>
<tr>
<th>Anatomical Locationa</th>
<th>Peak MNI Coordinates</th>
<th>Cluster Size, k</th>
<th>t Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-brain analysisb</td>
<td>L ant cingulate cortex/R supp motor area</td>
<td>−15 6 43</td>
<td>941</td>
</tr>
<tr>
<td></td>
<td>R roland operculum/R inf front operculum</td>
<td>52 3 16</td>
<td>223</td>
</tr>
<tr>
<td></td>
<td>R lingual</td>
<td>10 −87 −12</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>R ant cingulate cortex</td>
<td>20 38 19</td>
<td>1156</td>
</tr>
<tr>
<td></td>
<td>L ant insula/L inf orbitofrontal/L sup temp pole</td>
<td>−34 5 32</td>
<td>901</td>
</tr>
<tr>
<td></td>
<td>L inf front operculum</td>
<td>−48 12 19</td>
<td>305</td>
</tr>
<tr>
<td></td>
<td>Cerebellum/brainstem</td>
<td>14 −30 21</td>
<td>87</td>
</tr>
<tr>
<td>ROI analysisc</td>
<td>R ant cingulate cortex</td>
<td>14 32 16</td>
<td>398</td>
</tr>
<tr>
<td></td>
<td>L ant insula</td>
<td>−26 17 −20</td>
<td>101</td>
</tr>
</tbody>
</table>

Abbreviations: GM, gray matter; HEP, heartbeat evoked potential; L, left; MNI, Montreal Neurological Institute; R, right; ROI, region-of-interest.

a Labels are based on the Automated Anatomic Labeling atlas.
b Uncorrected P < .001 (unbiased voxel-based morphometry approach) and an cluster-extension level of k > 79 voxels.
c Familywise error-corrected P < .05.
tional abuse and HEP amplitudes, indicating early trauma-related deficits in the cortical representation of bodily signals that may underlie core BPD symptoms, such as emotional dysregulation or reduced pain sensitivity.\textsuperscript{25,26} Despite this, results of 2 previous heartbeat tracking studies\textsuperscript{27,28} that have investigated IA in samples that included individuals with BPD are contradictory. To overcome shortcomings of conventional methods, we measured HEP amplitudes in a large sample of patients with BPD, patients with BPD in remission, and healthy volunteers.

Schandry and Montoya\textsuperscript{77} have hypothesized that HEP amplitudes at frontal electrodes may reflect a visceral-afferent signal transmission, whereas HEP activity at posterior electrodes may be related to somatosensory signal processing. In a dipole localization study,\textsuperscript{45} HEP activity at frontal sites was associated with dipoles in the anterior cingulate cortex, whereas a dipole originating from the insula headed toward central sites. We observed reduced HEP amplitudes in patients with BPD at parietal and occipital electrodes, whereas the HEP amplitudes did not differ at central sites and were even larger at frontal electrodes compared with healthy volunteers.

In line with previous observations of patients with major depression,\textsuperscript{35} not only the amplitude but also the spatial distribution of HEPs differed in patients with BPD, who also had smaller mean dipole amplitudes compared with healthy volunteers. One possible explanation for this could be that patients with BPD do not differ from healthy volunteers in the raw visceral-afferent neurotraffict and lower-brain relaying of this information, but show deficits in the integration of afferent bodily signals from different (eg, visceral and somatosensory) sources into neural self-representation. Alternatively, the different spatial distribution of HEP amplitudes in patients with BPD may reflect a disrupted cortical representation of visceral-afferent signals, which is compensated by afferent bodily signals from other sources, such as somatosensory or auditory sensations.\textsuperscript{78,79} Because no differences in heart rate were found among the 3 groups of participants, the differences in HEP amplitudes may be attributed to alterations in central representation, not to peripheral differences.

The question remains as to why we have observed reduced mean HEP and dipole amplitudes in patients with BPD and positive correlations between HEP amplitudes and gray matter volumes in the insular and anterior cingulate cortices and frontal opercula, but no group differences in the gray matter volume of these regions. A possible explanation could be that HEP amplitudes not only reflect volume but also activity (as suggested by the dipole analysis) and the orchestral interplay or functional connectivity of these regions.

An additional analysis revealed that the HEP amplitudes of a smaller group of patient with BPD in remission lie somewhere in between those of patients with BPD and healthy volunteers, indicating an amelioration of the cortical representation of bodily signals with symptom remission. Although we do not have specific information on individual treatment history, it is well known that the most successful and widespread psychotherapies for BPD include elements of emotion recognition and regulation, the perception and integration of bodily signals, and mindfulness.\textsuperscript{8,80,81} Owing to the cross-sectional nature of our study, the current finding can only be regarded as a first indicator of a possible improvement of interoceptive signal processing with symptom remission. The mechanisms of this relationship remain to be elucidated in longitudinal studies. Together with previous studies, the current results indicate that treatments focusing on body awareness not only may be a promising instrument to improve emotional dysregulation but might also decrease the enhanced risk for cardiovascular disease among patients with BPD.\textsuperscript{82} Because HEP amplitudes might represent a state-dependent illness rather than a trait-dependent disorder marker, they could be
used as an indicator of treatment response and symptom reduction in intervention studies.

To our knowledge, this is the first study to examine the cortical representation of bodily signals by use of HEP amplitudes and its neural correlates in BPD. However, several limitations of the present study should be noted. First, diagnostic interviews revealed a number of comorbidities. Although this reflects a typical pattern of comorbid psychiatric disorders in BPD and effects remained significant after controlling for affective and anxiety disorders, we cannot rule out that the neurophysiological characteristics of these disorders may have affected our results. Future studies should include clinical control groups and should assess psychotherapeutic treatment experiences. Second, only exploratory comparisons were possible with the smaller group of female patients with BPD in remission, and the exploratory correlation analyses were not corrected for multiple testing. Third, we decided not to include conventional heartbeat perception analyses, which have a limited face validity for the clinical phenomenology of BPD to separate the genuine cortical representation of visceral-afferent signals from possible attentional or evaluative processes. It remains an interesting question whether patients with BPD have specific deficits in the automatic, nonconscious cortical representation of bodily signals, which they are able to compensate for by motivation or focused attention in conscious tasks. Further studies, which should include different measures for the assessment of interoception and of emotion processing and regulation in patients with BPD, are needed.

Conclusions

Taken together, the present study revealed reduced HEP amplitudes, an indicator of the cortical representation of bodily signals, in patients with BPD, a severe mental disorder that is characterized by emotional dysregulation, compared with healthy volunteers. In line with previous studies, morphometric analysis suggests that the anterior insular and the dorsal anterior cingulate cortices are neural correlates of interoceptive signal processing. Together with the additional, exploratory analysis of patients with BPD in remission, these results indicate deficits in interoceptive processes in patients with BPD, which may be a promising target for psychotherapeutic interventions.

REFERENCES

18. Michal M, Reuchlein B, Adler J, et al. Striking discrepancy of anomalous body experiences with


