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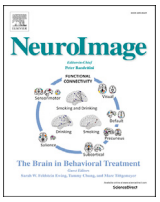

Behavioral and neurophysiological evidence for altered interoceptive bodily processing in chronic pain

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Whereas impaired multisensory processing of bodily stimuli and distorted body representation are well-established in various chronic pain disorders, such research has focused on exteroceptive bodily cues and neglected bodily signals from the inside of the body (or interoceptive signals). Extending existing basic and clinical research, we investigated for the first time interoception and its neurophysiological correlates in patients with complex regional pain syndrome (CRPS). In three different experiments, including a total of 36 patients with CRPS and 42 aged-gender matched healthy controls, we measured interoceptive sensitivity (heart beat counting task, HBC) and neural responses to heartbeats (heartbeat evoked potentials, HEPs). As hypothesized, we observed reduced sensitivity in perceiving interoceptive bodily stimuli, i.e. their heartbeat, in two independent samples of CRPS patients (studies 1 and 2). Moreover, the cortical processing of their heartbeat, i.e. the HEP, was reduced compared to controls (study 3) and reduced interoceptive sensitivity and HEPs were related to CRPS patients' motor impairment and pain duration. By providing consistent evidence for impaired processing of interoceptive bodily cues in CRPS, this study shows that the perceptual changes occurring in chronic pain include signals originating from the visceral organs, suggesting changes in the neural body representation, that includes next to exteroceptive, also interoceptive bodily signals. By showing that impaired interoceptive processing is associated with clinical symptoms, our findings also encourage the use of interoceptive-related information in future rehabilitation for chronic pain.

1. Introduction

Patients who experience pain over a prolonged period and beyond the expected clinical time for healing (i.e. chronic pain) may present abnormalities in processing body-related signals (including proprioception, touch, and distorted own body perceptions) (Catley et al., 2014; Tsay et al., 2015). Such disturbances have been extensively studied in patients suffering from complex regional pain syndrome (CRPS), a chronic pain condition usually affecting a single limb and characterized by chronic pain in combination with sensory, motor, trophic and autonomic abnormalities on the affected limb (Marinus et al., 2011). Moreover, CRPS patients may present tactile dysfunction (Birklein, 2005), experience difficulties in determining the position of their affected limb (Lewis et al., 2010), suffer from illusory own body perceptions such as perceiving the affected limb to be larger than its normal size (i.e. Moseley, 2005), or feel that the affected limb is missing (i.e. Lewis et al., 2010). It has been argued that such tactile-proprioceptive changes in perception and own body illusions are of clinical interest as their investigations may enable a better and more comprehensive understanding and characterization of CRPS as well as other complex pain disorders, potentially enabling the development of new therapeutic strategies (Lotze and Moseley, 2007; Moseley and Flor, 2012; Senkowski and Heinz, 2016).

The brain's body representation is based on continuously updating multisensory signals and crucially depends on successful integration of these multiple inputs (Ehrsson, 2012; De Vignemont, 2011; Knoblich, 2002; Tsakiris et al., 2010). Moreover, it has been argued that this multisensory body representation is a fundamental mechanism for enabling conscious bodily experience and related aspects of self-consciousness (Blanke, 2012; Blanke et al., 2015). Although cognitive neuroscience has traditionally focused on exteroceptive multisensory signals when investigating neural body representations (Blanke et al., 2015; De Vignemont, 2011; Knoblich, 2002; Tsakiris et al., 2010), recent research has highlighted the importance of other sensory bodily signals, namely those coming from the inside of the body (i.e. visceral interoceptive signals) (Blanke et al., 2015; Craig, 2009; Critchley and Harrison, 2013; Damasio and Carvalho, 2013; Park and

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Abbreviations

CRPS	complex regional pain syndrome
HBC	heart beat counting task
HEP	Heartbeat evoked potential
ECG	Electrocardiography
EEG	Electroencephalography

Blanke, 2019a; Park et al., 2014, 2018; Seth, 2013; Seth and Tsakiris, 2018). Yet, despite the cited evidence for altered body representation in chronic pain, the processing of signals from the visceral organs in such population has been poorly investigated. Interestingly, emerging behavioral evidence suggest that interoceptive sensations are altered in patients with chronic pain (Di Lernia et al., 2016), comparable to the described alterations in tactile-proprioceptive processing (Birklein, 2005; Catley et al., 2014; Lewis et al., 2010). Indeed, it has been recently shown that patients suffering from fibromyalgia (Duschek et al., 2017) and multisomatoform chronic pain disorder (Pollatos et al., 2011; Weiss et al., 2014) have a reduction in the heart beat counting (HBC) task, that is reduced performance compared to healthy subjects when asked to mentally count the number of times they perceive their heart beat during specified time periods (Schandry, 1981).

Furthermore, there has, recently, been an upsurge of interest in the neural mechanisms of cardiac processing, which can be investigated by time-locking electrophysiological signals with the QRS complex (as detected with electrocardiography (ECG); i.e. heartbeat-evoked potentials, HEPs). This neural response to heartbeats has been associated with interoceptive behavioral performance (e.g. Pollatos and Schandry, 2004; Pollatos et al., 2005) as assessed with the HBC task (Schandry, 1981). Based on these behavioral and HEP findings and on recent reports showing that the HEP amplitude is associated with experimentally induced changes in bodily self-consciousness (Park et al., 2016), the HEP has been proposed as an objective neural marker of interoception and conscious bodily experience (Park and Blanke, 2019a, 2019b. Finally, pain has been associated with decreases in heartbeat-related brain activity (Shao et al., 2011) and subjective pain experiences change across the cardiac cycle (Edwards et al., 2001, 2002, 2008). This interaction is further supported by the different common subcortical and cortical regions processing both cardiac and pain information, such as the parabrachial nucleus, the nucleus of the solitary tract, the ventromedial and dorsomedial nuclei of the thalamus, the insular cortex, and the anterior cingulate cortex (Bruehl and Ok Yung, 2004; Craig, 2002; Benarroch, 2006

In the present study we investigated interoceptive processing in patients with CRPS and hypothesized that abnormalities previously described for tactile or proprioceptive perceptions also extend to signals originating from their internal organs. First, we measured HBC performance in patients suffering from CRPS and expected, as reported so far for other chronic pain states (Duschek et al., 2017; Pollatos et al., 2005; Weiss et al., 2014), lower HBC performance compared to age-matched controls (Experiment 1 and 2). We, second, investigated the cortical processing of interoceptive cues in CRPS patients, hypothesizing, as described for acute pain (Shao et al., 2011), a decrease in HEPs in chronic pain patients (Experiment 3).

2. Materials and methods

2.1. Data and code availability statement

Non-clinical anonymized data and code used in the study are available upon direct request. Due to ethical considerations, patient's information would remain confidential and would not be shared.

2.2. Participants

24 right-handed CRPS patients (Experiment 1) (14 women, 12 with the right hand affected, mean age: 51.04 years; SD: ±15, range: 25–82 years, mean illness duration: 5.1 months SD: ±5.6) and an another independent group of 12 right-handed CRPS patients (Experiment 2 & Experiment 3) (7 women, 7 with the right hand affected, mean age: 53.3 years; SD: ±12, range: 37–75 years, mean illness duration: 6 months SD: ±3.9) were recruited from the Departments of Orthopedic Surgery of the Geneva University Hospital and the Hand Rehabilitation Unit of the Clinique Romande de Réadaptation in Sion. All patients fulfilled the Harden CRPS research criteria (Harden et al., 2010).

24 healthy age- and gender-matched participants (Experiment 1) (14 women; mean age: 50.3 years; SD: ±13.5, range: 27–80 years) and another independent 18 healthy individuals (Experiment 2 & Experiment 3) (7 women, mean age: 50.6 years; SD: ±11, range: 24–71 years) served as controls. None of the subjects had a history of psychiatric disease or took any kind of psychotropic drug. Initial clinical assessment included a clinical interview investigating the time since the beginning of the disease and pain severity with the brief pain inventory (Tan et al., 2004). Additionally, we measured motor function using the Jamar test following the standardized procedures recommended by the American society of hand therapists (Fess, 1992). Motor impairment was calculated subtracting for each subject the average (in kilograms) of three trials performed on the affected side to the average of three trials performed on the unaffected hand.

The procedures were approved by the ethics committees of the Canton of Geneva and Valais. All participants were naïve about the experiment and gave written informed consent.

2.3. Interoceptive perception (heart beat counting task; experiments 1 & 2)

In experiments 1 and 2, participants underwent a heartbeat counting task (Schandry, 1981) during which they were asked to mentally count their heartbeats during four different time periods. Participants were explicitly instructed not to count seconds or to guess. If they could not feel their heartbeats at all, they were asked to give a response of zero. We compared the true number of recorded heartbeats with the number of heartbeats indicated by the participants during four different fixed time intervals (25s, 35s, 45s, and 100s, given in randomized order). HBC score was calculated using the formula:

$$\frac{1}{4}\sum -\frac{|\text{recorded heartbeats} - \text{counted heartbeats}|}{\text{recorded heartbeats}}$$

HBC score (Tsakiris et al., 2011) ranges from 0 to 1, with higher scores indicating smaller differences between real and perceived heartbeats (i.e. better heartbeat perception). We tested in both experiments significant differences between patients and healthy control using two-sample *t*-test.

2.4. EEG analysis (experiment 3)

For the participants of experiment 2, we also measured the HEP as a cortical marker of interoceptive signals (Gray et al., 2007; Park and Blanke, 2019a, 2019b; Park et al., 2014, 2016; Pollatos and Schandry, 2004). Five minutes of resting state, eyes open, were recorded for the HEP analysis before the HBC task was. Subjects were instructed to relax and visually fixate a centrally presented fixation cross while avoiding to focus on specific thoughts. They were neither aware of the goal of the experiments nor that the upcoming part of the experiment was about interoception. The detailed steps of EEG and ECG processing for the HEP have been described previously (Park et al., 2016). In brief, we recorded continuous electroencephalography (EEG) at a sampling rate of 2048 Hz using a 64-channel Biosemi Active Two EEG system (Biosemi B.V., Amsterdam, Netherlands) referenced to the common mode sense (CMS;

active electrode) and online low-pass filtered at 400 Hz. We used two additional electrodes placed over the top of the right shoulder and the bottom of the left side of the abdomen to measure the ECG. Offline EEG preprocessing were performed in Matlab with the EEGLAB toolbox (Delorme and Makeig, 2004). After re-referencing to the average reference, data were down-sampled to 512 Hz and offline filtered between 1 and 40 Hz. EEG signals of malfunctioning electrodes (median: 1, range: 0–3 electrodes) were interpolated by computing average of neighboring electrodes. We then divided the row data in 800 ms epochs, (−200–600 ms regarding the detected R-peak onset) and rejected trials if several channels showed non-stereotypical artifacts on visual inspection. We applied independent component analysis (ICA) to the remaining trials. ICA components reflecting eye blinks, the cardiac-field artifact, saccades or noise were identified and removed using SASICA toolbox (Chaumon et al., 2015). Then, we inspected again all epochs and rejected those containing remaining ambient noise not removed by the ICA. A baseline correction was performed using the pre-stimulus interval (−200 to 0 ms regarding R-peak onset). For the primary objective of comparing patients and controls, we subtracted for each subject independently the mean across all trials and divided by the standard deviation (z-scores). Normalized epochs (356 ± 6 in controls and 360 ± 7 in patients (mean ± SEM), t(24)=0.37, p=.71) were averaged to compute HEP and compared between groups. Difference in HEPs between chronic pain patients and heathy controls was tested using a cluster based permutation *t*-test as implemented in the Fieldtrip toolbox (Maris and Oostenveld, 2007; Oostenveld et al., 2011) and controlled for multiple comparisons using a non-parametric Monte-Carlo randomization test. Based on the HEP time-window reported in former studies (Schandry et al., 1986; Montoya et al., 1993; Pollatos and Schandry, 2004; Canales-Johnson et al., 2015; Park et al., 2016) this procedure was applied at the sensor level in the time window from 200 to 400 ms after the R-peaks. Significant electrodes and time point were averaged for each patient to compute averaged HEP amplitude used for correlation analysis (see below).

Similar cluster based permutation test was applied to the ECG signals (cluster based on temporal dimension only) to control for differences between groups in the cardiac signals.

2.5. Correlation analysis (experiments 1, 2 & 3)

To test whether interoceptive measures were related to clinical characteristics of the CRPS patients, we first performed post hoc Pearson correlation between the HBC score (pooled data from Experiments 1 & 2) and 1) pain intensity, 2) time since the beginning of the disease, and 3) motor impairment. P-values were adjusted for multiple comparisons using Bonferroni correction. In Experiment 3, we also used cluster averaged HEP to investigate if the HEP amplitudes correlate with the same three clinical variables (i.e. pain intensity, duration of the disease and motor impairment) p-values were again adjusted for multiple comparisons using Bonferroni correction. Finally, we controlled for the well-established relation between HBC score and averaged HEP amplitude (e.g. Pollatos and Schandry, 2004; Pollatos et al., 2005) using Pearson correlation analysis in patients and controls data.

2.6. Control analysis regarding potential confounding factors influencing interoception

We confirm that our results were not related to differences in cardiac parameters and compared heart rate and heart rate variability (HRV) between groups. To confirm the absence of differences (i.e. confirm the null hypothesis) we used a Bayesian approach with default prior scales so that a Bayes factor (B)<0.33 implies substantial evidence for the null hypothesis (Morey and Rouder, 2011). For HRV, we collected inter-beat intervals, defined as the time between two successive R spikes, and then calculated the square root of the mean squared differences of successive beats intervals (RMSSD). Moreover, to exclude any potential role of medication on interoception, we compared HBC scores between patients under medication (gabapentin or corticosteroids) and patients without any medication.

3. Results

3.1. Heartbeat counting task (experiments 1 and 2)

We tested the hypothesis that perceptual changes in somatosensory processing occurring in CRPS (Birklein, 2005; Förderreuther et al., 2004; Lewis et al., 2007, 2010; McCabe et al., 2003; Moseley, 2004, 2005) also apply to processing of internal bodily cues and apply to interoceptive processing. As predicted, results of Experiment 1 showed that CRPS patients' HBC performance task (mean = 0.52, SD = 0.20) was lower compared to age-matched healthy controls (mean = 0.74, SD = 0.16) (t(44) = -4.10, $p < 0.001$, Cohen's d = 1.19) (Fig. 1A). To corroborate this first result, we tested HBC performance in another, completely independent, group of CRPS patients. During this second experiment (Experiment 2) we excluded one patient, who reported to not feel any heartbeat and therefore performed zero in the HBCscore. Patients again showed decreased HBC performance (mean=0.61, SD=0.14) compared to controls (mean = 0.75, SD = 0.17) (t(24) = -2.24, p = 0.03, Cohen's d = 0.82) (Fig. 1B). Assessing whether interoceptive performance in the HBC task relates to clinical characteristic we found a significant negative correlation between HBC scores and motor impairment (t(33) = −3.05, r = − 0.49, p = 0.01, Bonferonni corrected), that is the more grip strength was diminished, the lower was the patient's ability in detecting their heartbeat (Fig. 1C). No significant correlations were observed between HBC scores and other variables (i.e. pain intensity; time since the beginning of the disease: t(33) = -0.04, r = − 0.01, p = 0.96; t(33) = -0.41, r = − 0.07, p = 0.68 respectively, uncorrected).

3.2. Heartbeat evoked potentials (experiment 3)

We compared the HEP amplitude between groups employing a non-parametric cluster permutation test, which revealed the presence of a significant cluster (cluster-level p = 0.03, corrected for multiple comparisons) (Fig. 2A). This significant difference was observed over the central scalp regions and, as predicted, only in the 200–330 ms post-R-peak period (Park et al., 2016). HEP amplitude was reduced in CRPS patients (less negative) versus control participants (Fig. 2B). Importantly, there was no significant difference in the ECG signals between groups (Fig. 2C) (all $p > 0.41$), ruling out the possibility that the observed effect on HEP was due to mere peripheral cardiac difference between groups.

Correlation analysis revealed a significant relation between HEP amplitude and HBC performance, that is, the better participants were able to perceived their heartbeat as assessed by the HBC task, the more negative was the HEP amplitude (t(27)= -2.67, r=- 0.45, p=0.03, Bonferroni corrected) (Fig. 3). Concerning clinical data, we found that the HEP amplitude in CRPS patients correlated with the time since the beginning of the disease, that is, the longer the patients experienced chronic pain, the more HEP was reduced compared to healthy controls (i.e. less negative) (t(10) = 2.42, r = 0.6, p = 0.03, uncorrected), however, this did not survive Bonferroni correction for multiple comparison (p=0.12). No relation between HEP amplitude and pain intensity or motor impairment was observed (t(10) = -0.01, r = − 0.003, p = 0.99 and (t(9) = 1.36, r = 0.4, p = 0.21 respectively, uncorrected).

"Control analysis regarding cardiac parameters and medications

No differences in heart rate between patients (mean = 70.9, SD = 10.1) and controls (mean = 71.4, SD = 7.6) was observed (Bf = 0.23). As expected from the literature (Terkelsen et al., 2012; Tracy et al., 2016) HRV was reduced in CRPS patients (mean = 35.9 ms, SD = 16.8) compared to the control group (mean = 46.47 ms, SD = 18.13) (Bf = 4.4). However, linear correlation (Jeffrey and Rouder, 2011) excluded relation between HRV and HBC score (Bf = 0.26), excluding any relation

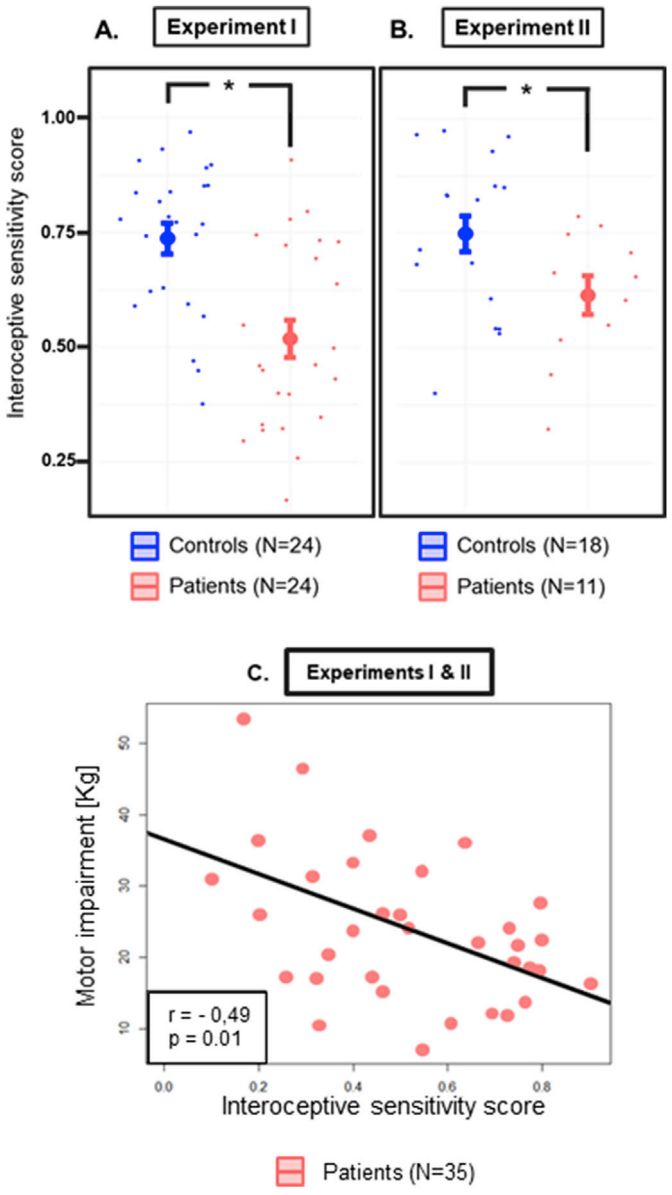

Fig. 1. Heart beat counting task: HBC performance differs between CRPS patients and controls.
(A) & (B) In two independent experiments CRPS patients' performance in the heartbeat counting task was lower compared to healthy control participants (Error bars represent standard error of the mean). Note the comparable performance levels between both experiments across groups. (C) Interoceptive counting task score and were negatively correlated, that is the more grip strength was diminished with respect to the healthy hand, the lower was patient's ability in detecting their heartbeat.

between performance at the HBC task and HRV. Finally, no differences in HBC scores were found between patients taking medication (N = 19, mean = 0.54, SD = 0.22) and patients without any medication (N = 17, mean = 0.53, SD = 0.20) (Bf = 0.32). Bring together, these results rule out the possibility that different cardiac parameters or medication intake cause differences in HBC performance"

4. Discussion

Treatment of patients with CRPS remains extremely challenging for physicians as little agreement exists on its etiology, pathophysiology, involved neural systems, and treatment (Marinus et al., 2011; Sebastin, 2011). Recent work has elucidated that - next to the disabling and persistent pain - CRPS is also characterized by perceptual changes in tactile and proprioceptive processing, as well as the presence of illusory own body perceptions (Förderreuther et al., 2004; Lewis et al., 2007, 2010; McCabe et al., 2003; Moseley, 2004, 2005). It has been proposed that these perceptual changes are the consequence of the sensory-motor reorganization observed in the related brain systems (Bekrater-Bodmann et al., 2015; Maihöfner et al., 2003, 2004; Mercier and Léonard, 2011), leading to new therapeutic solutions targeting these cortical changes (Moseley and Wiech, 2009; Moseley et al., 2008; Schmid et al., 2017). While previous studies have focused on changes in bodily cues involving exteroceptive (i.e. visual, tactile), motor, or proprioceptive information, the present work adds behavioral and EEG evidence in favour of the hypothesis that such deficits in bodily perception in CRPS also include abnormalities in how interoceptive cues are perceived and processed.

This was shown at the behavioral level in a first group of 24 patients and 24 aged-matched healthy controls using the HBC task (Experiment 1) (Schandry, 1981). Our HBC findings confirm earlier observations in patients across different chronic pain conditions (Duschek et al., 2015, 2017; Pollatos et al., 2011; Weiss et al., 2014) and extend them to CRPS. The magnitude of the deficit in HBC performance in the present CRPS patients is consistent with the previous deficits reported in patients with fibromyalgia (score: 0.53) (Duschek et al., 2015) and somatoform disorders (score: 0.50) (Pollatos et al., 2011; Weiss et al., 2014). Although the HBC task is the most commonly used behavioral interoceptive measure, it has been recently criticized because it is strongly modulated by the influence of individual factors independent of interoceptive abilities such as beliefs about the heart rate and subjective threshold in reporting counted heartbeats (Desmedt et al., 2018; Ring and Brener, 2018; Zamariola et al., 2018). Because most of these factors are presumably not affected by chronic pain, we carried out a replication study in a completely independent sample of patients and controls. This study confirmed again the HBC decrease of similar magnitude in CRPS patients (Experiment 2). Thus, the reduction of interoceptive perception is robust and extends to CRPS patients and is similar in amplitude across different chronic pain disorders, suggesting a general link between chronic pain and abnormalities in interoception, at least cardiac perception.

We note that, although we control for medication and different cardiac parameters, it is possible that other factors, unrelated to interoception and influencing HBC performance may differ between CRPS and heathy subjects such as attention (Moore et al., 2019) or time perception (Rey et al., 2017). Thus, to provide more objective evidence and to investigate whether cortical processing of interoceptive cues is altered in chronic pain, we also analyzed the neural response to heartbeats in CRPS patients, which is an orthogonal measure to those possible confounding factors. We report, as hypothesized, a significant suppression of the HEP in CRPS patients compared to heathy controls. This finding is consistent with the existing literature, as we observed the HEP change in CRPS patients at the predicted location (over central scalp regions) and in the specific time window that is classically described in HEP studies in healthy participants and other populations (Schandry et al., 1986; Montoya et al., 1993; Pollatos and Schandry, 2004; Park et al., 2014, 2016; Canales-Johnson et al., 2015). Moreover, the amplitude of the HEP correlated with the performance in the HBC task (as reported previously in several studies in healthy subjects (e.g. Pollatos and Schandry, 2004)), providing further evidence for the use of HEP as a neurophysiological signature and possible neural marker of interoceptive ability. The suppression of the HEP in CRPS patients observed here points to changes in the cortical network responsible of cardiac and HEP processing, which primarily involves the insula, the cingulate cortex, the somatosensory cortex, the amygdala and the medial prefrontal cortex (Craig, 2009; Critchley and Harrison, 2013; Damasio and Carvalho, 2013; Park and Blanke, 2019a, 2019b; Park et al., 2018). Interestingly, we observed that the more the HEP was reduced (compared to healthy controls), the longer our patients had already experienced chronic pain, suggesting that HEP relates to duration and chronification of pain in CRPS. Although this exploratory finding in a small sample of patients did not survive

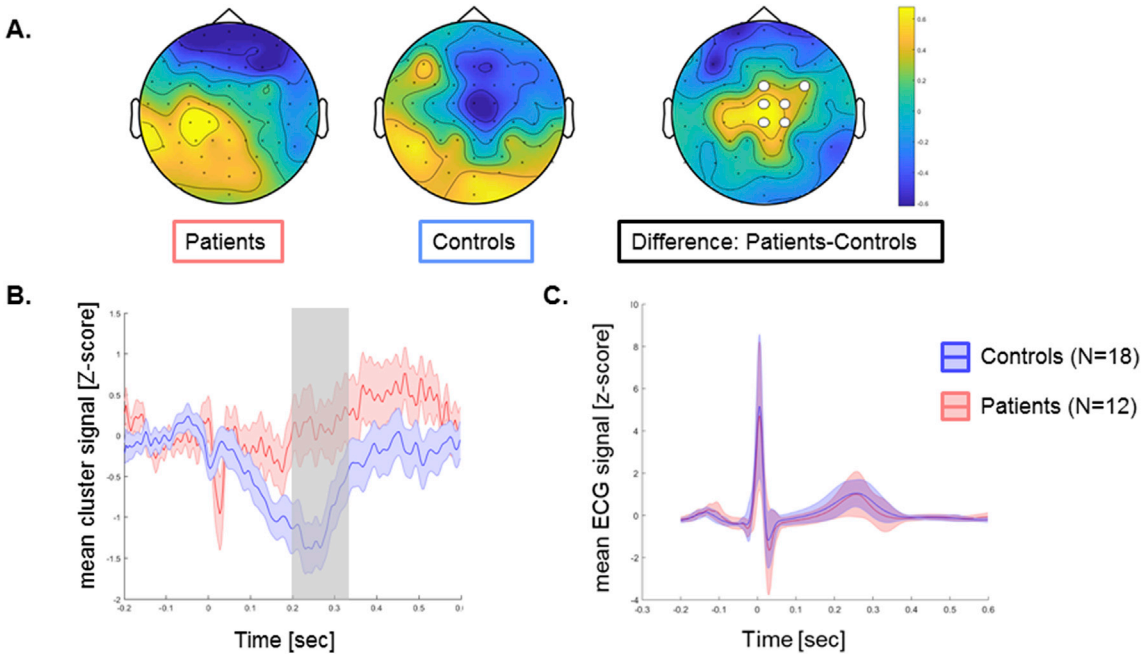

Fig. 2. HEP differs between CRPS patients and controls
A. Comparison of the HEP between groups employing a non-parametric cluster permutation test, revealed the presence of a significant cluster over central region (cluster-level $p < 0.05$, corrected for multiple comparisons). Larger white dots indicate the electrodes contributing to the significant cluster. B. Cluster signal (significant electrodes showed in (A)) show significant difference in the 200–330 ms post-R-peak period was found (i.e. amplitudes were on average suppressed in chronic pain patients (less negative) than control). The gray shaded area highlights the time window in which a significant difference is observed whereas shaded areas of the time course represent standard error of the mean. C. No significant differences were found in the ECG signals between groups.

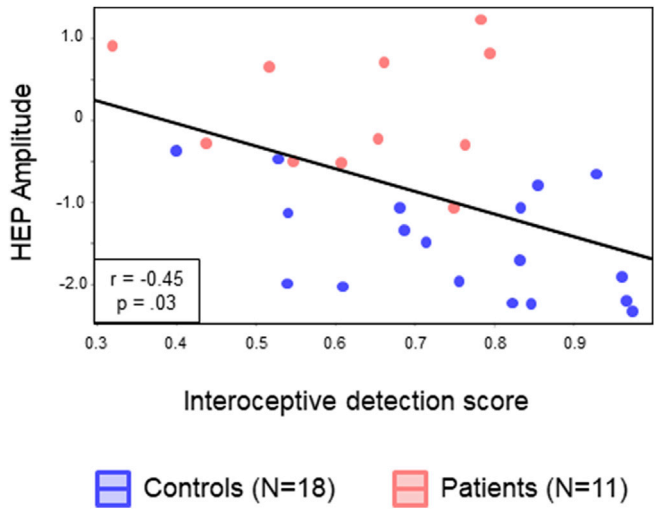

Fig. 3. HEP amplitude correlates with interoceptive sensitivity.
Correlation analysis revealed a significant relation between HEP amplitude and interoceptive counting score, this is higher HEP (more negative) in subjects with better performance at the heartbeat counting task. Note the overall reduced HEP in patients (red) compared to Controls (blue).

correction for multiple comparisons, it extends former studies showing that the level of cortical reorganization occurring in chronic pain correlates with pain duration and intensity (e.g. Apkarian et al., 2004; Juottonen et al., 2002; Flor, 2003; Maihöfner et al., 2003, 2004), but needs to be investigated in future studies involving a larger population.

Collectively, these behavioral and electrophysiological findings demonstrate an impaired ability in patients suffering from chronic pain in correctly detecting and processing internal bodily states. As the brain's body representation is largely derived and based on multisensory processing of bodily stimuli (e.g., somatosensory, visual, interoceptive signals), we suggest that the altered sensory processing we observed for interoceptive cardiac signals contributes to the distortion of own body representation in CRPS patients. This hypothesis is in line with earlier work showing that reduced interoception and HEPs in particular are objective markers of altered body perception in depressed patients (Terhaar et al., 2012). How do cardiac representations interact with limb representations in healthy participants and in the case of CRPS? The so-called clinical sign or phenomenon of 'Head's zones' (after Henry Head) may provide a good example. The sign refers to the projection zone of visceral pain to circumscribed skin regions, such as cardiac pain to the chest/left shoulder or gastric pain to the region of the sternum (Arendt-Nielsen et al., 2008; Van Gelderen, 1948) and is compatible with neural co-representation of extero- and interoceptive processes. Similarly, reduced interoceptive abilities have been observed in patients with eating disorder, also characterized by distorted body representation (Eshkevari et al., 2012; **Pollatos et al., 2008**). In addition, past research has shown that interoceptive stimulations can lead to changes in the body representation (Aspell et al., 2013) and limb representations (Suzuki et al., 2013) as well as perceptual changes in how participants perceive multisensory exteroceptive stimuli (Aspell et al., 2013; Heydrich et al., 2018). Moreover, such cardio-visual stimulations have been shown to reduce pain in CRPS (Solcà et al., 2018). Accordingly, we suggest that the altered cardiac processing observed here behaviorally and at the level of the HEP in CRPS patients is related to changes such a common (likely distributed) neural system that integrates interoceptive and exteroceptive signals (for review see; Park and Blanke, 2019a). Consistently, we also observed significant correlations between interoceptive HBC performance and limb motor impairment, that is the more grip strength was diminished, the lower was the patient's HBC performance. Studies in CRPS patients have shown that the impairment of the motor function is not simply a limitation due to pain but also reflects the level of distorted central body representation (Bultitude and Rafal, 2010). Moreover, the prevalence of motor dysfunction increases as the disease duration lengthens (van Rijn et al., 2007; Veldman et al., 1993) and longer

duration of the symptoms induces stronger body representation disturbance in CRPS (Moseley, 2004).

We speculate that the present data are also of therapeutic relevance. The relation between altered feedback signals from the body and clinical symptoms motivated the development of new therapeutic approaches for chronic pain in the past, targeting disturbed body perception in order to reduce painful symptoms (Bolognini et al., 2015; Lotze and Moseley, 2007; Moseley and Flor, 2012; Pozeg et al., 2017; Rognini et al., 2018). Compatible with the present findings, manipulation of interoceptive signals during rehabilitation procedures seems to be an additional promising avenue. Thus, Schaefer and colleagues used an interoceptive training task aiming at improving HBC in somatoform pain disorders and observed significant symptoms reduction (Schaefer et al., 2014). Similarly, an immersive VR therapy has been developed and tested that integrates online detected cardiac signals and multisensory stimulation with and was able to alleviated CRPS, improve motor function, and pain markers in CRPS (Solcà et al., 2018). Future work is needed to investigate interoceptive function in patients with chronic pain (such as respiratory and gastric function; i.e. Adler et al., 2014; Allard et al., 2017; Richter et al., 2017) and related cortical representations and systematically explore the potential analgesic benefits of cardiac/respiratory rehabilitation using automatized immersive VR feedback of such signals.

Collectively, the behavioral and neurophysiological results of the present three experiments support the idea that the perceptual and cortical changes occurring in chronic pain include signals originating from internal organs, providing empirical clinical evidence for a shared neural body representation system that integrating exteroceptive and interoceptive signals (Park and Blanke, 2019a).

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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