Psychophysical and electrophysiological evidence for nociceptive dysfunction in complex regional pain syndrome

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ABSTRACT

The aim of this study was to assess the function of the thermo-nociceptive system in 25 patients with long-lasting, medium-to-severe refractory complex regional pain syndrome (CRPS)-1 using behavioral (detection rates and reaction times) and electrophysiological (event-related brain potentials) responses to brief (50 milliseconds) and intense (suprathreshold for Aδ-nociceptors) carbon dioxide laser stimuli delivered to the affected and contralateral limbs, and by comparing these responses to the responses obtained in the left and right limbs of age- and sex-matched healthy controls. Compared with healthy controls and compared with the contralateral limb, the detection rate of pricking pain related to the activation of Aδ-fibers was markedly reduced at the affected limb. Furthermore, reaction times were substantially prolonged (>100 milliseconds in 84% of patients and >300 milliseconds in 50% of patients). Finally, the N2 and P2 waves of laser-evoked brain potentials were significantly reduced in amplitude, and their latencies were significantly increased. Taken together, our results show that in the majority of patients with chronic CRPS-1, thermo-nociceptive pathways are dysfunctional. A number of pathological mechanisms involving the peripheral nervous system and/or the central nervous system could explain our results. However, the primary or secondary nature of these observed changes remains an open question.

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1. Introduction

The symptoms of complex regional pain syndrome (CRPS) cluster into four distinct categories: (1) abnormal pain, (2) vasomotor and temperature changes, (3) sudomotor changes and edema, and (4) motor dysfunction and trophic changes [13]. Two subtypes of CRPS are defined according to the absence (CRPS-1) or presence (CRPS-2) of an unequivocal nerve lesion. Although the absence of CRPS are defined according to the absence (CRPS-1) or presence (CRPS-2) of an unequivocal nerve lesion. Although the absence of nerve lesion questions whether CRPS-1 is a true neuropathic pain syndrome. PAIN © (2013), http://dx.doi.org/10.1016/j.pain.2013.07.038

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to brief infrared laser stimuli delivered to the affected vs contralateral limb. Indeed, laser-evoked brain potentials (LEPs) are currently recognized as the most reliable diagnostic tool to assess the function of the spinothalamic system in humans [12,52,54].

2. Methods

2.1. Subjects

Twenty-five patients diagnosed with CRPS-1 were recruited from the multidisciplinary Pain Clinic (Cliniques Universitaires Saint-Luc, Brussels, Belgium). Diagnosis was based on the Budapest criteria [14]. Study inclusion was conditioned by the availability of medical records, including detailed clinical examination and medical history, in order to compute a CRPS severity score [13]. Exclusion criteria were history of a major psychiatric disorder or the inability to understand the testing procedures.

Data of healthy volunteer participants were extracted from a large database of our laboratory in order to match, as closely as possible, the age and gender ratio of the patient group. These participants had no clinical history, symptoms or signs of PNS or CNS disorder, and were not taking any medication at the time of testing or in the month before testing. As the main objective of the present investigation was to study the responses to brief and supraliminal laser stimuli directed to the affected and asymptomatic side in unilateral CRPS-1, we examined the responses from left and right limbs obtained in healthy controls with a strictly similar protocol. Informed consent was obtained from all volunteers. The study was approved by the local ethics committee and conducted in accordance with the principles of the Helsinki declaration.

2.2. Stimulus

Cutaneous heat stimuli were delivered using a carbon dioxide (CO₂) laser (Université Catholique de Louvain, Louvain-la-Neuve, Belgium). Stimulus duration was 50 milliseconds and beam diameter at target was 10 mm. The energy density of the laser stimulus was adjusted individually on the asymptomatic limb or on the left hand in healthy controls to be clearly supraliminal for Aδ-nociceptor activation (9.5 ± 2.3 mJ/mm²). We did not assess thresholds on the affected side, as we expected that these thresholds would be potentially biased by emotional and cognitive factors.

The stimuli elicited a clear pricking and burning sensation in the asymptomatic limb of patients and in both limbs of healthy participants. This sensation was always detected with RTs <650 milliseconds when stimulating the hand and with RTs <750 milliseconds when stimulating the foot (ie, RTs compatible with the conduction velocity of myelinated Aδ-fibers). The same energy density was used at both sites within each subject. The laser beam was slightly shifted between each trial to avoid skin overheating and to minimize nociceptor sensitization or habituation.

2.3. Electroencephalogram recording

At least 30 stimuli were delivered at each stimulation site, in blocks of 10 trials separated by a short resting period lasting approximately 1 minute. The inter-stimulus interval varied between 8 and 15 seconds. The electroencephalogram (EEG) was recorded from 19 silver–silver chloride electrodes evenly placed on the scalp according to the International 10–20 system referenced to linked earlobes. In addition, the electro-oculogram was recorded from two surface electrodes: one placed below the right lower eyelid and the other placed lateral to the outer canthus of the right eye. Signals were amplified and digitized (gain: 1000; filter: 0.06–75.00 Hz, sampling rate: 167 cps) using a PL-EEG recorder (Walter Graephek, Lübeck, Germany).

2.4. RTs and detection rates

For each trial, participants were asked to press a button as soon as any type of sensation was perceived at the stimulation site. RTs were used to distinguish between detection mediated by C-fiber input and detection mediated by Aδ-fiber input. Specifically, RTs <650 milliseconds when stimulating the upper limbs and RTs <750 milliseconds when stimulating the lower limbs were considered as related to the detection of Aδ-fiber input, whereas RTs ≥650 or >750 milliseconds were considered as related to the detection of C-fiber input (and, hence, to the absence of detection of Aδ-fiber input) [15]. In previous studies, we have shown that, at least in healthy individuals, RTs can be used to distinguish between detections triggered by Aδ- and C-fiber input because of the great difference between the nerve conduction velocities of Aδ- and C-fibers [3]. RTs exceeding 2500 milliseconds were considered as undetected. For each subject and stimulation site, two detection rates were computed: first, the absolute detection rate, corresponding to the proportion of detected trials regardless of RT; second, the rate of detections with RTs <650 milliseconds (upper limb) and <750 milliseconds (lower limb), corresponding to the proportion of trials detected with RTs compatible with Aδ-fiber activation.

2.5. Analysis of EEG data

The EEG data were processed offline using BrainVision Analyzer (Brain Products, Gilching, Germany) and Letswave 5 (http://lets-wave.webnode.com). The EEG was band-pass filtered (0.1–20.0 Hz) using a zero-lag Butterworth filter, segmented into epochs extending from −0.5 to +2.5 seconds relative to stimulus onset (512 bins) and baseline-corrected (reference interval −0.5 to 0 seconds). Epochs contaminated by eye blinks were rejected by visual inspection. Average waveforms were then computed for each participant and stimulation site. Based on their peak latency and scalp topography as originally defined by Treede et al. [51], three distinct peaks (N1, N2, P2) were characterized in the LEP waveforms obtained following stimulation of the hands, whereas two distinct peaks (N2, P2) were characterized in the LEP waveforms obtained following stimulation of the foot. The N1 latency and amplitude were measured at the temporal electrode contralateral (Tc) to the stimulated hand, referenced to electrode Fz, following the recommendations of Valentini et al. [53]. The N2 latencies and amplitudes were measured at the vertex electrode Cz referenced to linked earlobes A1A2.

2.6. Single trial analysis: Relating LEP amplitude and RT latency

For each electrode and each time bin of the LEP waveform, the relationship between LEP amplitude and RT was assessed using linear mixed models [27,47] as follows:

\[ y = a \times x + b + u + e \]

The dependent variable \( y \) represents single-trial LEP amplitudes. The independent variable \( x \) represents RTs with \( a \times x \) as the fixed effect. The quantity \( b + u \) represents the random effect taking into account variability between patients and stimulation sites. The term \( e \) represents the residual error. This procedure yielded time-courses of T-value, representing the strength of the relationship between LEP signal amplitude and RTs. To address the problem of multiple comparisons, the significance level (P-value) was corrected using a false discovery rate procedure [10].

2.7. Statistical analysis

All data are expressed as means ± SD. The analyses were performed separately for the lower and upper limb groups. A two-way mixed analysis of variance (ANOVA), with stimulated “limb” (affected vs asymptomatic limb for CRPS-1 patients; left vs right limb for healthy controls) as the within-subject variable and gender as the between-subject variable, was used for analysis of the LEP waveforms.
limb for healthy participants) as the within-subject factor and “group” (CRPS-1 patients vs healthy participants) as the between-subject factor was used for the analysis of psychophysical and LEP data. When appropriate, Greenhouse-Geisser correction of degrees of freedom and contrast analyses were used. The Bonferroni-Dunn test adjusted for pairwise comparisons according to the number of paired comparisons to be performed. Significance level was set at $P < .05$. The statistical analyses were performed using Aabel 3 (Gigawiz Ltd. Co. 2010) and Matlab R2006b (The Math-Works, Natick, MA, USA).

3. Results

3.1. Study population

Characteristics of patients and healthy participants are reported in Table 1. Most patients were middle-aged but two female patients were adolescents with CRPS-1 in the lower limb. There was no significant difference in age and gender between the patient/control and lower/upper limb groups. As in most previous studies on CRPS (review in [34]), females were over-represented (72%) and the lower limbs were most often involved (72%). The frequency distribution of the CRPS severity scores (CSS; [13]), showed two peaks: a first peak at medium scores (0.5–0.6; 36% of patients) and a second peak at high scores (0.8–1.0; 45% of patients).

3.2. Psychophysical data

Psychophysical data of healthy subjects and patients are summarized in Table 2. In the lower-limb group, comparison of the total detection rate showed a significant interaction between the factors “group” and “limb” (main effect of “group”: F = 3.675, $P = .0064$; main effect of “limb”: $F = 13.387, P = .0009$; interaction: $F = 12.655, P = .0011$). Comparison of the detection rate with RT <750 milliseconds (Aβ-fiber detections showed a similar interaction between the factors “group” and “limb” (main effect of “group”: $F = 10.413, P = .003$; main effect of “limb”: $F = 38.812, P < .0001$; interaction: $F = 21.011, P < .0001$). Finally, comparison of RT also showed an interaction between the factors “group” and “limb” (main effect of “group”: $F = 8.368, P = .007$; main effect of “limb”: $F = 29.835, P < .0002$; interaction: $F = 14.714, P = .0005$). Post-hoc comparisons revealed that, in CRPS patients, the total detection rate was significantly decreased ($-29%$; $T = 3.691, P < .001$), the detection rate with RT < 750 milliseconds was even further decreased ($-52%$; $T = 6.337, P < .001$), and the average RTs were significantly increased (+69%; $T = 4.729, P < .001$).

In the upper-limb group, the total detection rate in CRPS patients differed significantly from the total detection rate in healthy controls (main effect of “group”: $F = 7.452, P = .018$). There was no main effect of stimulated “limb” ($F = 7.646, P = .171$) and no interaction between the two factors ($F = 8.129, P = .334$), indicating that the total detection rates were reduced in the patient group, regardless of the stimulated limb. The detection rate with RT <650 milliseconds showed a main effect of “group” ($F = 14.899, P = .002$), a main effect of the factor “limb” ($F = 46.667, P < .0001$), and an interaction between the two factors ($F = 46.667, P < .0001$). Similarly, RT showed a main effect of “group” ($F = 14.173, P = .003$), a main effect of “limb” ($F = 27.537, P = .0002$), and an interaction between the two factors ($F = 29.976, P = .0001$). Post-hoc comparisons revealed that, in CRPS-1 patients, the detection rate with RT <650 milliseconds was significantly decreased ($-31%$; $T = 2.811, P = .014$) and that the RT were significantly increased (+78%; $T = 6.831, P < .001$) when stimulating the affected vs the unaffected contralateral limb.

Finally, in CRPS patients, the temperature of the skin at the affected site was, on average, cooler than the temperature of the skin at the contralateral site by 2.0 ± 1.1 °C (range +0.2 °C to −4.8 °C; n = 23).

3.3. LEP

Figure 1 shows the average LEP waveforms obtained from a typical CRPS-1 patient. The patient is 30-year-old woman with a severe CRPS-1 (CSS: 0.82) of the right foot following a Hemicastrating ligamentoplasty for the treatment of chronic lateral instability of the right ankle, 2.8 years before the evaluation. Laser stimuli directed to the left asymptomatic foot dorsum were always detected, and detected with a RT <750 milliseconds in 84% of trials. The average RT was 497 milliseconds. In contrast, only 83% of laser stimuli directed to the right symptomatic foot dorsum were detected and only one of these stimuli was perceived with a RT <750 milliseconds. The mean RT was 1191 milliseconds, that is more than twice the latency following stimulation of the unaffected foot. Comparison of the LEP waveforms obtained following stimulation of the affected and unaffected foot shows that the latency of the N2 and P2 peaks is markedly increased following stimulation of the affected limb ($\Delta N2 = 30$ milliseconds; $\Delta P2 = 42$ milliseconds) and that the amplitude of the N2–P2 is markedly reduced ($\Delta N2–P2 = -14 \mu V$; −50%).

In the lower-limb groups, a N2–P2 complex with latencies compatible with the conduction velocity of Aβ-fibers was identified visually in all waveforms recorded in the healthy controls. In lower-limb CRPS-1 patients, the N2–P2 complex was identified in all waves obtained from the unaffected limb and in 16/18 waveforms obtained from the affected limb (Fig. 2, upper panels). Comparison of N2 latencies showed a significant interaction between the factors “group” and “limb” (main effect of “group”: $F = 1.675, P = .0206$; main effect of “limb”: $F = 3.350, P = .007$; interaction: $F = 9.787, P = .004$). Comparison of P2 latencies (main effect of “group”: $F = 1.147, P = .5$; main effect of “limb”: $F = 5.044, P = .032$; interaction: $F = 5.755, P = .023$) and N2–P2 amplitudes (main effect of “group”: $F = 3.81, P = .5$; main effect of “limb”: $F = 3.845, P = .059$; interaction: $F = 6.147, P = .019$) revealed the same interaction. Post-hoc comparisons showed that, in CRPS-1 patients, N2 (+11%; $T = 2.912, P = .006$) and P2 amplitudes (+8%; $T = 5.755, P = .023$) were significantly increased when stimulating the affected limb, whereas the N2–P2 amplitude was significantly decreased ($-30%$; $T = 2.941, P = .006$).

In the upper-limb groups, an N2–P2 complex was identified visually in all waveforms recorded in the healthy controls and all
wavesforms recorded in patients (Fig. 2, lower panels). The N2–P2 complex was preceded by an earlier N1 wave, maximal over central-parietal leads of the hemisphere contralateral to the stimulated side [53]. Of note, this lateralized N1 wave was not visible when stimulating the foot dorsum. The two-way mixed model analysis of variance (ANOVA) revealed no main effect of “group” (N1 latency: F = 336, P > .5; N1 amplitude: F = 2.806, P = .120), no main effect of “limb” (N1 latency: F = 1.083, P = .318; N1 amplitude: F = 4.168, P = .064), and no interaction between the two factors (N1 latency: F = 1.326, P = .272; N1 amplitude: F = 1.382, P = .263). Similarly, the two-way mixed model ANOVA revealed that the latency of the N2 wave did not significantly differ across conditions (main effect of “group”: F = 1.340, P = .270; main effect of “limb”: F = 1.720, P = .214; interaction: F = 1.83, P > .5) and that the latency of the P2 wave differed only marginally (main effect of “group”: F = 1.088, P = .047; main effect of “limb”: F = 4.935, P = .046; interaction: F = 2.907, P = .114). In contrast, comparison of N2–P2 amplitudes revealed a significant interaction (main effect of “group”: F = .088, P > .5; main effect of “limb”: F = 3.829, P = .074; interaction: F = 6.443, P = .026). Post-hoc comparisons showed that, in CRPS patients, the latency of the P2 wave was significantly increased (+10%; T = 2.669, P = .018) and the N2–P2 amplitude was significantly decreased (−34%; T = 2.850, P = .013) following stimulation of the affected limb.

3.4. Single-trial analysis of the relationship between LEP amplitude and RT latency

Conventional analysis of the latencies and amplitudes of LEP peaks obtained in the average waveforms showed that in the affected limb of CRPS-1 patients, the latency of the N2 and P2 waves was significantly increased, and the amplitude of the N2–P2 complex was significantly decreased. Parallel to these changes, the RT to stimuli delivered to the affected limb was significantly increased. For this reason, we conducted a supplementary analysis aimed at specifying the relationship between the amplitude of LEP waveforms and RT at the level of single trials [16,18]. The analysis was performed on the 21 patient EEG recordings for which we possessed complete original data files.

The results of this analysis are reported in Fig. 3. A significant negative relationship between LEP amplitude and RT was observed maximally at P2 between 365 and 533 milliseconds after stimulus onset, corresponding to the latency of the P2 wave. This relationship indicates that trials in which the stimulus elicited P2 waves of smaller amplitude were also trials in which the stimuli were detected with later RT.

3.5. Ultra-late C-fiber related LEPs

In two patients with lower limb CRPS-1, laser stimuli delivered to the affected limb did not elicit a clearly identifiable LEP at latencies compatible with the conduction velocities of Aβ-fibers. Interestingly, in these two patients, the stimulus elicited a later negative–positive complex at latencies compatible with the conduction of C-fibers (Fig. 4).

The first patient was a 57-year-old woman presenting with severe CRPS-1 (CSS: 0.88) at the right lower limb for 12.7 years, following a Maquet osteotomy of the right knee. Stimulation of the unaffected left foot dorsum clearly elicited LEPs compatible with the conduction velocity of Aβ-fibers (N2 latency: 263 milliseconds; P2 latency: 449 milliseconds). However, this response was followed by a later negative–positive complex whose latency (N2: 1006 milliseconds; P2: 1365 milliseconds) was compatible with the expected latency of C-fiber LEPs. Furthermore, stimulation of the affected right foot dorsum did not elicit an identifiable LEP compatible with the conduction velocity of Aβ-fibers, but did elicit a LEP compatible with the conduction velocity of Aδ-fibers, but did elicit a LEP compatible with the conduction velocity of C-fibers (N2: 1156 milliseconds; P2: 1341 milliseconds). Like the scalp topography of Aδ-fiber related LEPs, the C-fiber related N2′ and P2′ waves were symmetrically distributed over the two hemispheres and maximal at the scalp vertex. As shown in the lower part of Fig. 4, the frequency distributions of RTs were bimodal when stimulating the unaffected limb (with a first peak of RTs around 400 milliseconds compatible with the detection of Aβ-fiber input and a second peak of RTs around 1200 milliseconds compatible with the detection of C-fiber input). In contrast, almost all RTs obtained when stimulating the affected limb were compatible with the conduction of C-fiber input. However, one should be cautious when interpreting these results, as RTs are not only dependent on the time required to conduct and process the sensory input, but also on the time required for sensorimotor integration and the production of motor output. Therefore, one cannot exclude that the observed increase in RTs observed in these patients was due to an abnormal increase in the time required for sensorimotor integration and motor output. However, it seems unlikely that this could lead to an increase in the latency of the elicited responses of several hundreds of milliseconds.

The second patient was a 62-year-old man presenting with severe CRPS-1 (CSS: 0.88) after an ankle sprain about 6.1 years before evaluation. In this patient, an Aδ-fiber LEP was identified when stimulating the unaffected limb (N2 latency: 258 milliseconds; P2 latency: 508 milliseconds; N2–P2 amplitude: 23.8 μV) but not when stimulating the affected limb. Instead, a C-fiber LEP was

| Table 2
| Psychophysical and laser-evoked brain potential (LEP) data (mean ± SD). |
|---------------------------------|------------------|------------------|------------------|
|                                 | Healthy participants (n = 25) | Upper limb CRPS (n = 7) | Lower limb CRPS (n = 18) |
| Skintemperature (°C)            | Upper limb CRS limb | Unaffected limb | CRPS limb | Paired difference | Unaffected limb | CRPS limb | Paired difference |
| Skin temperature (°C)           | 32.5 ± 2.2         | 30.2 ± 2.0       | 28.8 ± 2.1 | −1.4 ± 1.1       | 30.0 ± 2.1       | 28.1 ± 1.9 | −2.1 ± 1.2**    |
| Physiological data              |                    |                  |            |                |                  |            |                |
| Total detection rate (%)        | 100 ± 1            | 99 ± 2           | 71 ± 2.8   | −28 ± 26**     | 97 ± 6           | 75 ± 28    | −24 ± 28***    |
| Detection rate with RT >650 ms (%,Aβ-related) | 85 ± 16 | 81 ± 16 | 30 ± 32 | −51 ± 20** | 81 ± 17 | 41 ± 36 | −42 ± 29*** |
| Reaction time (ms)              | 414 ± 84           | 471 ± 107        | 889 ± 298  | +147 ± 204*** | 551 ± 178        | 829 ± 312  | +382 ± 426**   |
| LEP data                        |                    |                  |            |                |                  |            |                |
| N2 latency (ms)                 | 253 ± 29           | 223 ± 32         | 239 ± 18   | +5 ± 17        | 279 ± 34         | 303 ± 44   | +32 ± 43**     |
| P2 latency (ms)                 | 395 ± 60           | 328 ± 52         | 353 ± 48   | +33 ± 32       | 424 ± 46         | 461 ± 51   | +32 ± 60**     |
| N2–P2 amplitude (μV)            | 29 ± 16            | 34 ± 27          | 26 ± 21    | −11 ± 14       | 26 ± 9           | 18 ± 6     | −8 ± 10        |

Note. CRPS = complex regional pain syndrome; RT = reaction time.

* P < .05.
** P < .01.
*** P < .001.
clearly visible (N2 latency: 1060 milliseconds; P2 latency: 1458 milliseconds; N2–P2 amplitude: 23.8 μV). The total detection rate was 82% for both limbs. However, the detection rate with RTs <750 milliseconds was 70% when stimulating the unaffected limb, and only 2% when stimulating the affected limb.

4. Discussion

In contrast to the healthy volunteers, we found that in patients with CRPS-1 (1) the total detection rate of laser stimuli and (2) the rate of detections with RTs compatible with the conduction velocity of A-d-fibers were both significantly reduced at the pathological limb compared with the asymptomatic limb. Likewise, we found that RTs were substantially prolonged in patients vs controls (increased by more than 300 milliseconds in 50% of patients). Analysis of the LEP waveforms showed that the latency of the N2 and P2 waves obtained from the pathological limb were significantly increased. Furthermore, the amplitude of the N2–P2 complex was significantly decreased in patients vs controls. Taken together, these results indicate a dysfunction of thermo-nociceptive pathways in CRPS-1. In the following paragraphs, we discuss whether this dysfunction results from changes at the level of the PNS, the CNS, or both.

4.1. Biophysical properties of the skin

The chronic inflammatory state in the upper skin layers held responsible for edema and trophic changes could have altered...
the thermophysical properties of the skin in such a way that absorption and transmission of the CO₂ laser radiation are reduced at the affected limb. Although we used stimuli that were clearly supra-threshold for type II A-fiber mechanohot nociceptors (AMH-2) in the hairy skin of healthy individuals (i.e., the Aδ-fiber-related LEPs), changes in biophysical properties of the affected skin cannot be ruled out entirely.

An additional factor that could have contributed to the increase in RT and LEP latencies at the affected limb was the average reduction in skin temperature of 2.0 ± 1.1°C at the affected vs contralateral limb. However, it seems unlikely as the latency and amplitude of the early N1 wave of LEPs elicited by stimulation of the upper limbs was not significantly different between affected and unaffected sides in CRPS-1 patients.

4.2. Peripheral neuropathy

Given the well-characterized clinical signs and laboratory tests demonstrating autonomic and vasomotor dysfunction in the skin of the affected limb of CRPS-1 patients, one could expect to find an associated dysfunction of peripheral nociceptive fibers (for a review see [36]). However, the multiple interactions between autonomic and nociceptive systems make it very difficult to define a causal direction, and disentangle primary and secondary mechanisms.

Our finding that, following stimulation of the affected limb, the latency of the N2 and P2 waves was significantly increased, and the amplitude of the N2–P2 complex was significantly reduced is compatible with an increased trial-to-trial jitter of response latencies [42]. However, it seems unlikely that this mechanism could have played a significant role as the latency and amplitude of the earlier N1 wave was not significantly different between groups and between sides in CRPS-1 patients. Furthermore, the SDs for N2–P2 amplitudes and latencies were not different between the patient and control groups, and between the affected and unaffected sides in CRPS-1 patients (Table 2).

In many neuralgic conditions, intra-epidermal nerve fiber (IENF) density is reduced [17,26]. This might conceivably be the most prominent feature that explains all the phenomena we observed in CRPS-1. Indeed, a reduction in IENF density may explain the drop in total detection rate, the reduction in the Aδ-nociceptor-related detection rate [35,41], and the reduction in

Fig. 3. Group-level average laser-evoked brain potential (LEP) waveform and topographic maps at Cz (blue) and Pz (red) of all patients (left panel). Right panel. The statistic T-value, revealed by the linear mixed model, shows an inverse and significant relationship between LEP amplitude and reaction times, with the maximum at Pz between 365 ms and 533 ms (gray area in both panels). On average, trials with larger P2 amplitudes were also trials with shorter reaction times. In contrast, the amplitude of the N1 and N2 components was not significantly correlated with the reaction times (RTs). This may indicate that the variability of RTs could be mainly caused by cognitive influences.

Fig. 4. Average laser-evoked brain potential (LEP) waveforms recorded at the vertex (Cz, vs. A1–A2) after stimulation of the right and left foot dorsum of a 57-year-old woman presenting with complex regional pain syndrome (CRPS) at the right limb for 12.7 years (severity score of 0.88). Stimulation of the asymptomatic left foot (gray waveform) clearly elicited two distinct negative–positive waves, the first with a latency compatible with the conduction velocity of Aδ-fibers, the second with a latency compatible with the conduction velocity of C-fibers. Stimulation of the affected right foot evoked only elicited a LEP at a latency compatible with the conduction velocity of C-fibers. As shown by the scalp topographies of the N2 and P2 peaks, the topographical distribution of the C-fiber-related LEP was well structured with a maximum at Cz–Pz. The lower part of the figure shows the time–frequency representation of LEP amplitude averaged across trials.
In contrast, Albrecht et al. [1] found evidence of widespread cutaneous neuropathological changes, including a marked decrease in epidermal innervation in skin samples from the amputated upper and lower extremity of two patients with CRPS-1. To our knowledge, there are only two studies reporting on IENF density in CRPS-1 using skin punch biopsies stained with the pan-axonal marker PGP 9.5, a validated technique for diagnosing small-fiber neuropathies [6]. The first study [37] included 18 CRPS-1 patients and reported a 30% median reduction of IENF density compared with the contralateral limb. As pointed out by Jäning and Baron [20], in patients with diabetic and other peripheral neuropathies, a 30% reduction of IENF density does not normally lead to clinically detectable changes of thermal and nociceptive sensations. The second study [23] showed that the IENF density in the affected limb of 43 CRPS-1 patients was not significantly different from the IENF density at the thigh or at the calf, or the IENF density assessed in healthy controls. Furthermore, there was no significant difference in the mean IENF density between patients with normal and abnormal sensory thresholds for warm, cold, heat pain, and cold pain. Thus, there is no clear evidence for a structural reduction in IENF density and, hence, for a structural alteration of the PNS.

To account for our results, two possibilities should be considered at the peripheral level. First, CRPS-1 could be related to changes in the function of peripheral nociceptors without any visible change in their structure. The persistent inflammatory state of the skin could modify the normal functioning of IENF [25]. Furthermore, CRPS-induced vasoconstriction may induce hypoxia, lactate increase, and acidosis, which could also contribute to nociceptor dysfunction [22,44,45]. Second, CRPS-1 could be related primarily to changes in the function of Aβ-nociceptors, with a relative preservation of C-fiber nociceptors. Indeed, the present study showed a marked reduction of detection rates compatible with the conduction velocity of Aβ-fibers, and a marked alteration of the LEPs related to the activation of Aβ-fibers. Furthermore, in some patients, the disappearance of the Aβ-fiber-related LEP led to the appearance of a later C-fiber-related LEP, suggesting that the dysfunction affected Aβ-fibers, but not C-fibers (see [58] for a case reporting a similar finding). Importantly, because the number of C-fibers is thought to greatly exceed the number of Aβ-fibers [39,46], a selective structural alteration of Aβ-fiber IENFs could go largely unnoticed using currently available histological techniques to analyze skin biopsies, which only assess the total IENF density, as these are unable to distinguish between C- and Aβ-fiber-free nerve endings. This interpretation is also compatible with the results of Gierthmühlen et al. [11], who showed no impairment of thermal thresholds in approximately 60% of 298 patients with upper-limb CRPS-1. Indeed, because these thresholds were assessed using a large (900 mm²) Peltier thermode and slow heating ramps, these thresholds were likely to mainly reflect the function of C-fibers [22,59].

4.3. CNS dysfunction

There is accumulating evidence that the CNS plays an important role in the maintenance and, possibly, in the initiation of the symptoms associated with CRPS-1 [33,50]. At the spinal level, Del Valle et al. [4] found microglial and astrocytic activation, as well as significant posterior horn cell loss in autopsy tissue from the cervical, thoracic, and lumbar spinal cord of a patient with longstanding CRPS-1. Using magnetoencephalography, Walton et al. [57] reported changes in the power spectrum of the recorded signals interpreted as reflecting a neurological “disconnection syndrome” resulting from a disturbance in thalamocortical interplay. An involvement of the CNS is also suggested by a number of neuropsychological symptoms associated with CRPS-1-like glove stocking sensory loss, trend to asomatognosia, referred sensations, impaired representation, and discriminative abilities of the pathological limb and intentioned motor dysfunction [28,33,43,44].

Impaired perception and utilization of the affected limb in CRPS is consistent with studies showing abnormal reorganization of the cortical activity in areas involved in sensory motor functions [21,31,32,40,56]. Importantly, such changes could have contributed to the results of the present study, as these would predict an increased latency and decreased amplitude of the responses to nociceptive stimuli. For instance, the observed reduction in the somatotopic map of the affected limb could, of course, result from reduced afferent input (as observed in amputees with phantom limb pain [7]) or pain-induced reduction in responsiveness of neurons in somatosensory pathways [11]. Importantly, such a reduction in neuron responsiveness could be related to the fact that CRPS patients tend to ignore the affected limb and attentional effort is needed to move it [8]. Several studies have shown that, in healthy volunteers, LEPs elicited by stimulation of the attended limb are enhanced compared with LEPs elicited by stimulation of the unattended limb [9,29,50], as observed in our CRPS patients. However, such an interpretation would not account for the dissociation between a marked alteration of the responses to Aβ-fiber input and a relative preservation of the responses to C-fiber input, possibly even leading to an “unmasking” of C-fiber LEPs in some patients.

In summary, the present results show that in most patients with chronic CRPS-1, the thermo-nociceptive system is markedly dysfunctional. Whether the observed dysfunction results from pathological mechanisms involving the PNS, the CNS, or both remains an open question.

Conflict of interest

None.

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