Case-Control Study

Event-Related Potentials Following Cutaneous Electrical Stimulation in Patients With Chronic Whiplash-Associated Disorders

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Background: Whiplash injuries typically occur from a motor vehicle collision and lead to chronic whiplash-associated disorders (CWAD) in 20% to 50% of cases. Changes in neurotransmission, metabolism, and networks seem to play a role in the pathogenic mechanism of CWAD.

Objectives: To further elucidate the functional brain alterations, a neurophysiological study was performed to investigate the somatosensory processing of CWAD patients by comparing the event-related potentials (ERPs) resulting from electrical nociceptive stimulation between patients suffering from CWAD and healthy controls (HC).

Study Design: Case-control study.

Setting: University Hospital in Ghent.

Methods: In this case-control study (CWAD patients/HC: 50/50), ankle and wrist electrical pain thresholds (EPT), and amplitude and latency of the event-related potentials (ERPs) resulting from 20 electrical stimuli were investigated. Correlations between the ERP characteristics, EPT, self-reported pain, disability, pain catastrophizing, and self-reported symptoms of central sensitization were investigated.

Results: Only the latency of the P3 component after left wrist stimulation (t = -2.283; $P = 0.023$) differed between both groups. In CWAD patients, the ankle EPT correlated with the amplitude of the corresponding P1 ($\rho s = 0.293$; $P = 0.044$) and P3 ($\rho s = 0.306$; $P = 0.033$), as well as with the amplitude of the P3 to left wrist stimulation ($\rho s = 0.343$; $P = 0.017$). Self-reported symptoms of CS correlated with right wrist P3 amplitude ($\rho s = 0.308$; $P = 0.030$) and latency ($\rho s = -0.341$; $P = 0.015$), and the worst pain reported during the past week was correlated with left wrist P1 latency ($\rho s = 0.319$; $P = 0.029$).

Limitations: Although the inclusion criteria stated that CWAD patients had to report a moderate-to-severe pain-related disability, 8 of the included CWAD patients (that scored above this threshold in the inclusion questionnaire), scored below the required cutoff at baseline.

Conclusions: The CWAD patients did not show signs of hypersensitivity, but their ERP characteristics were related to the intensity of the applied stimulus, self-reported symptoms of CS, and the worst pain reported during the past week.

Key words: Chronic whiplash-associated disorders, electro-encephalography, nociceptive stimulation, event-related potentials

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A whiplash injury refers to a typical acceleration-deceleration energy transfer to the neck that usually occurs during a motor vehicle collision (1-3). Although motor vehicle collisions are the most frequent cause of such injuries, these can also occur as a result of diving or other mishaps (1). The incidence of (acute) whiplash injuries (6,14) is estimated to be as high as 677 per 100,000 inhabitants, but varies across countries (4). Recovery of this condition is usually characterized by a benign and self-limiting course with quickly fading pain and symptoms (5,6). However, 20% to 50% of the patients (2) will continue to experience symptoms and will develop a complex array of persistent physiologic and psychological sequelae, collectively known as chronic whiplash-associated disorders (CWAD) (7,8). These patients may exhibit decreased neuropsychological functioning, such as troubles with attention and working memory, in addition to their neck pain, headache, limited neck range of motion, and/or bodily pain (1,9,10). Moreover, about 10% of these patients (11) will report constant severe pain. In Europe, this results in an important economic impact of whiplash injuries estimated to reach 10 billion euro per year (12), mostly caused by the chronic patients.

The pathogenic mechanisms underlying CWAD remain to be fully identified, and no single structural lesion can explain the heterogeneous signs and symptoms (13-18). Neuroimaging studies (13,18,19) in CWAD have led to diverse findings, but seem to indicate the existence of functional brain alterations, such as disturbed neurotransmission, metabolism, and network properties. Based on quantitative sensory testing (QST), an enhanced excitability and responsiveness of the neurons within the central nervous system has been observed in CWAD patients (20). The QST assesses the sensitivity of certain structures to specific stimulus modalities by applying standardized (painful) stimuli to cutaneous and musculoskeletal structures (21,22). Local and distant decreased pain thresholds have been reported in CWAD patients in response to several stimuli, indicating the presence of local and distant hyperalgesia (20). The cerebral response to such nociceptive stimulation has already been investigated in different chronic pain patients (23-26), but only very limited in CWAD patients (27,28). The results of these studies differed per patient population, but all indicated that differences in specific brain region activity can be observed in response to painful stimulation when compared to healthy controls (HC). Possibly, these alterations are mostly present in those patients suffering from chronic neuropathic pain or in cases involving nerve fiber dysfunction (26). Although some of these studies (23-25) were based on magnetic resonance imaging, the use of electroencephalography (EEG) has several advantages when examining the cerebral response to nociceptive stimulation. Apart from being noninvasive, low cost, and easy to use, it also captures the electrical activity of neuronal cell assemblies on a submillisecond time scale, giving it an extremely high temporal resolution (29,30). Therefore, it is an ideal method to investigate cortical processes during experimental nociceptive stimulation paradigms.

Given the limited amount of research into cerebral responses to nociceptive stimulation in patients with CWAD, the aim of this study was to investigate the somatosensory processing of CWAD patients by comparing the event-related potentials (ERPs) resulting from electrical nociceptive stimulation between patients suffering from CWAD and HC.

Methods

Patients

Fifty patients with CWAD and 50 age- and gender-matched HC were included in this case-control study.

The CWAD patients and HC were recruited through flyers and posters on social media and in public places, through university college staff, family members, and acquaintances of the researchers. Additionally, patients were recruited: by distribution of flyers through general practitioners, physiotherapists, hospitals, and pharmacies; through advertisements on the radio and in local newspapers; and through publications and lectures in patient-support groups (eg, vzw Whiplash and Vlaamse Pijnliga) and symposia. Patients or HC had to

be Dutch-speaking male or female patients between 18 and 65 years old. Moreover, they had to continue their usual care throughout the study duration and were not allowed to start new treatments or medication 6 weeks prior to study participation (to obtain a steady state).

Patients with CWAD were included if they had undergone a whiplash trauma (ie, neck pain resulting from a motor vehicle crash or traumatic event), which was diagnosed by a physician (grades II to III as defined by the Quebec Task Force scale [1,31]), which caused pain for at least 3 months with a mean pain frequency of 3 days per week or more, and with self-reported moderate-to-severe pain-related disability, established by a score of ≥ 15/50 on the Neck Disability Index (NDI) (32).

Patients were excluded if they had a history of specific spinal surgery (ie, surgery for spinal stenosis), history of neck or shoulder surgery in the past 3 years, or if they suffered from epilepsy, a rheumatic, endocrinological, psychiatric, or cardiovascular disorder, or if they had neuropathic pain based on evidence of neurological damage in combination with a score of ≥ 12/24 on the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale, and a score of ≥ 4/10 on the Douleur Neuropathique 4 questionnaire. If patients were pregnant, or if they gave birth during the year before enrollment, they could not participate either (28).

The HC were excluded if they had ever been diagnosed with chronic widespread pain as defined by the 1990/2010 American College of Rheumatology criteria (33,34), but CWAD patients were only excluded if the diagnosis of fibromyalgia or chronic fatigue syndrome was made before the whiplash diagnosis. The HC were also excluded if they had ever experienced a whiplash trauma; if they had consulted a physician for neck/shoulder/arm pain during the past 12 months; if they had experienced pain with an intensity higher than 2/10 on a Numeric Rating Scale (NRS-11) (49) in the neck, shoulder, or arm region for more than 8 consecutive days during the last year; or if they experienced pain on the day of the experimental assessments (NRS-11 > 2/10).

All patients were asked to refrain from undertaking physical exercise (> 3 metabolic equivalents) on the day before the experimental assessments; from non-opioid analgesics in the previous 48 hours of the experimental assessments; and from caffeine, alcohol, and nicotine in the previous 24 hours of the experimental assessments (28,35).

All patients provided written informed consent before participation. The study was conducted according to the revised Declaration of Helsinki (1998). The study protocol was approved by the ethics committee of the University Hospital of Ghent (2017/0850) and by the ethics eommittee of "Vrije Universiteit Brussel" (2016/388). The clinical trial was registered with the number NCT04204525 (https://register.clinicaltrials.gov/).

Procedure

Study participation required one visit to the lab, situated on the site of the university hospital in Ghent, during which pain thresholds and ERPs were measured. Prior to the experimental assessment, patients were asked to fill out 2 online questionnaires. The first one consisted of questions to determine whether a person fulfilled the selection criteria. The second one had to be filled out during the 2 weeks before the experimental assessment and included the NDI, the Central Sensitization Inventory (CSI) (40), an NRS-11 to score their mean and worst pain during the past week and the Pain Catastrophizing Scale (PCS) (45). On the day of the experimental assessment, patients were asked to fill out a pain drawing, and to indicate whether they had consumed alcohol, caffeine, or nicotine during the last 24 hours, as well as if they took any medication in the last 48 hours, or if they had performed physical exercise during the last 24 hours. Next, the electrical pain thresholds (EPTs) were measured at the median nerve of both wrists and at the sural nerve of the ankle unilaterally (symptomatic side in case of unilateral neck pain complaints, hand dominant side in case of bilateral neck pain complaints, or in HC).

Next, EEG was recorded during the administration of 20 stimuli at the intensity of 1,4 times the EPT at the median nerve bilateral and at the sural nerve (same side as during the EPT assessment) (35). After the application of the 20 stimuli, patients were asked to score the overall experience of the electrical stimuli on an NRS-11 scale from 0 (no pain) to 10 (worst possible pain).

Questionnaires

The Dutch version of the NDI was used as a measure for self-reported pain-related disability levels (ranging from 0 to 50) (32). The NDI is the most commonly used self-report outcome measure for neck pain, and higher scores represent higher levels of pain-related disability (36). The Dutch version of the NDI has been shown to be valid, sensitive, and reliable to assess self-reported disability (37-39).

The (Dutch version of the) CSI uses 25 statements scored on a 5-point Likert scale (42) ranging from 0 to 4 to measure self-reported symptoms indicative of central sensitization (CS) and its overlapping symptoms in people with chronic pain (ranging from 0 to 100). CSI scores of ≥ 40/100 have been shown to distinguish best between a group of patients who had a central sensitivity syndrome and a group of patients who did not have a central sensitivity syndrome (40). The (Dutch) CSI has good psychometric strength (40-44), as well as good discriminative power and internal consistency, and excellent test-retest reliability (42).

The PCS assesses catastrophic thoughts and feelings about pain by generating a general score, as well as scores on 3 subscales (ie, helplessness, magnification, and rumination) (45). The Dutch version of the PCS has good psychometric quality, and higher scores are indicative of more severe catastrophic thoughts and feelings regarding pain (46,47).

Electrical Pain Thresholds

For the stimulation of the sural nerve, felt pad electrodes were placed 2 cm posterior to the lateral malleolus in the innervation area of the sural nerve (48,49). For median nerve stimulation, the electrodes were placed on the skin overlying the median nerve. The cathode of this bipolar electrode was placed 5 cm proximally from the wrist, while the anodal electrode was placed 3 cm distally from the cathode (50). The order for exploring the test locations was randomized in each individual. A Digitimer DSA7 constant current stimulator (Digitimer, Hertfordshire, United Kingdom) was used to deliver the stimuli. Each stimulus consisted of a constant current rectangular pulse train consisting of 5 pulses (51) delivered at a frequency of 250 Hz, each lasting 0.5 ms (52,53) (interstimulus interval = 3.5 ms, total duration of 5 pulse train = 20 ms). The intensity of the stimuli started at 0 miliampere (mA) and was gradually increased by steps of 0.5 mA (54,55) until the patient indicated that the experience became unpleasant (= EPT) (35). Three consecutive measurements were taken at a 30 seconds interval on each site to compute an average EPT. The use of EPTs has proven reliable to evaluate the sensitivity of the spinal nociceptive pathways in people with chronic pain (56).

Event-Related Potentials

During the EEG measurement, 20 stimuli (250 Hz, train of 5), with a variable interstimulus interval of 8-12 seconds, were administered successively at 1,4 times EPT (57) to the right and left median nerve, as well as the sural nerve (same side as during the EPT assessment) (35). Patients were seated comfortably on a chair, with their eyes closed, while the EEG was measured with a 32-channel eego sports system (ANT Neuro, Enschede, The Netherlands) at a sampling frequency of 2000 Hz using active surface Sn electrodes in a headcap with unipolar montage following the standard 10/20 recording system. Electrode impedance was kept as low as possible (< 20 kΩ), and was evaluated before and after each recording.

Data Analysis

Preprocessing

Preprocessing was performed with BrainVision Analyzer 2.2 software (Brain Products GmbH, Gilching, Germany). All EEG signals were band-pass filtered between 0.5 and 100 Hz, and referenced to the average of all scalp electrodes. To increase the signal:noise ratio and to remove (movement and eye) artifacts, independent-component analysis was performed. Epochs were selected as time windows from -100 milliseconds to 900 milliseconds poststimulus. Baseline correction of the epochs was performed by subtracting the average of the first 100 milliseconds prestimulus of the epoch (-100 to 0 milliseconds). The remaining epochs were averaged per patient and per condition. Based on the publication of Goudman et al (35), the evoked potentials were expected to correspond to 2 components, each distributed over several electrodes. The 100 millisecond component (P1) gathered the signals Fp1, Fpz, and Fp2 (referred to the common average), thus ([Fp1(t) + Fpz(t) + Fp2(t)] / 3); whereas, the 300 millisecond component (P3) corresponded to the average of M1, T7, T8, and M2 subtracted from the average of Cp1, Cz, and Cp2 ([(Cp1(t) + Cz(t) + CP2(t)) / 3] - [(M1(t) + T7(t) + T8(t) + M2(t)) /4]). In order to further reduce noise and variability, the corresponding averaged signals were pooled with Python 3.7 software (STX NEXT, Poznań, Poland) and the MNE-package (58). This same software was used to measure the latency and amplitude of these ERP components. The amplitude was defined as the maximal value poststimulus relative to the average of the signal amplitude during the 100 milliseconds prestimulus. The latency was defined as the time between stimulus administration (0 milliseconds) and the poststimulus peak (maximal value).

Statistical Analysis

All analyses were performed with R version 4.0.2 (2020-06-22). Normality of each outcome within each group (CWAD or HC) was evaluated by visual inspection of histograms and QQ-plots, together with a Shapiro-Wilk test. Statistical significance was set at $\alpha < 0.05$.

Electrical Pain Thresholds

For each outcome, a linear mixed effect model was built including pain thresholds as dependent outcome variable, and group (CWAD vs HC) and region (left and right wrist, and ankle) as independent variables. Patients were used as random intercepts in the model to account for within-patient correlations. An interaction term (group*region) was included in the model to estimate post hoc pairwise differences in EPT between CWAD patients and HC stratified by region. Model assumptions of linearity, normality of residuals, and homoscedasticity of variance were consecutively checked to evaluate the model validity.

Latency and Amplitude of ERP

For each outcome, a linear mixed effect model was built, including latency and amplitude of the ERP as the dependent outcome variable, and group (CWAD vs HC), region (left and right wrist, and ankle) and time (P1 vs P3) as independent variables. Patients were used as random intercepts in the model to account for within-patient correlations. An interaction term (group*region*time) with its respective suborder interaction terms were included in the model to estimate post hoc pairwise differences in latency and amplitude between CWAD patients and HC stratified by time and region. Model assumptions of linearity, normality of residuals, and homoscedasticity of variance were consecutively checked to evaluate the model validity.

Correlations

Correlations between the latency and amplitude of the P1 and P3 at the ankle, right wrist, and left wrist, on the one hand, and the EPTs, NDI, CSI, PCS, worst pain last week (NRS-11), mean pain last week (NRS-11), and pain score of the applied stimuli (NRS-11), on the other hand, were determined by calculating the pairwise Spearman (ρs) correlation among all included variables. Correlation coefficients were considered to represent negligible correlation for values ≤ 0.1; weak correlations for values between 0.1 and 0.35; moderate for values between 0.36 and 0.67; strong for values between 0.68 and 0.89; and very strong for values ≥ 0.90 (59,60).

Results

Descriptives

Between-group differences in descriptives were evaluated with an independent samples Mann-Whitney U test for continuous variables, and an X^2 was applied to categorical data. Gender, age, and body mass index did not differ between both groups. However, CWAD patients reported significantly higher pain intensity on the day of testing, a larger painful body area, and higher scores on the NDI, CSI, and PCS than HC, as shown in Table 1. Although not all patients complied with the restriction of exertion of physical exercise, and intake of caffeine, alcohol, nicotine, and medication, these activities or intakes did not differ (significantly) between both groups.

Electrical Pain Thresholds

For each location, a linear mixed model was constructed to determine the location specific group effect, but between-group differences in EPT were not significant for any of the 3 locations. Results of these analyses are presented in Table 2.

Latency and Amplitude of ERP

In patients suffering from CWAD, the mean latency of the P1 component was 122.01 milliseconds (± 27.013) for the ankle stimulation, 116.41 milliseconds (± 28.238) for the right wrist, and 116.81 milliseconds (± 25.711) for the left wrist. The mean amplitude reached 7.61 µV (± 7.029) with ankle stimulation, 15.41 µV (± 18.24) for the right wrist, and 10.41 µV (± 9.729) for the left wrist. In HC, the mean latency of the P1 component was 122.48 milliseconds (± 24.956) for the ankle stimulation, 110.60 milliseconds (± 22.426) for the right wrist, and 118.24 milliseconds (± 25.327) for the left wrist. The mean amplitude was 9.52 µV (± 10.793) on ankle stimulation, 12.07 µV (± 8.371) for the right wrist, and 12.28 µV (± 12.76) for the left wrist (Table 3).

The mean latency of the P3 component was 281.541 milliseconds (± 41.273) after ankle stimulation, 261.68 milliseconds (± 34.783) for the right wrist, and 257.62 milliseconds (± 36.658) for the left wrist in CWAD patients. The mean amplitude reached 15.14 µV (± 6.106) on ankle, 18.38 µV (± 8.880) for the right wrist, and 18.05 µV (± 7.216) for the left wrist. The latency of the P3 component in the HC group was 280.55 milliseconds (± 43.602) after ankle stimulation, 250.62 milliseconds (± 36.009) for the right wrist, and 243.27 milliseconds (± 31.169) for the left wrist. The amplitude was 16.85 µV (± 8.323)

Table 1. *Descriptives*.

	CWAD (n = 50)			HC (n = 50)			*P* value
Gender	Men: n = 12 (24%) Women: n = 38 (76%)			Men: n = 12 (24%) Women: n = 38 (76%)			0.999
Symptomatic Side	Bilateral Pain: n = 23 (46%) Unilateral Pain: n = 27 (54%)			NA			
	Right Side: n = 15 (30%) Left Side: n = 12 (24%)						
Total Number of Whiplash Injuries	Single Event: n = 35 (70%) 2 Events: = 10 (20%) 3 or More Events: n = 5 (10%)						
	Mean (± SD)	**Median (IQR)**	**Range**	**Mean (± SD)**	**Median (IQR)**	**Range**	***P* value**
Age (y)	40.88 (10.316)	39.56 (32.8 - 49.0)	23 - 62	40.93 (10.06)	39.67 (33.6 -47.3)	22 - 64	0.885
Pain Drawing (% of Total Body Area)	4.52 (3.76)	3.02 (2.09 - 5.54)	0.49 19.24	0.14 (0.519)	0.00 (0.00 - 0.00)	0.00 - 2.91	< 0.001*
BMI (kg/m^2)	24.83 (4.135)	24.03 (21.2 - 27.9)	18.78 - 35.51	23.87 (4.207)	22.79 (21.2 - 25.6)	16.60 - 39.67	0.243
NDI (/50)	18.48 (4.824)	17.50 (15.0 - 21.8)	10 - 35	1.88 (1.870)	1.00 (1.0 - 3.0)	0 - 9	< 0.001*
CSI (/100)	46.96 (13.751)	47.50 (35.0 - 56.0)	19 - 73	16.28 (8.713)	16.50 (10.0 - 22.5)	1 - 34	< 0.001*
PCS	25.24 (10.856)	25.00 (16.0 - 34.0)	4 - 47	1.74 (3.630)	0.00 (0.0 - 2.00)	0 - 17	< 0.001*
Pain on Testing Day (NRS-11)	6.01 (1.698)	6.00 (5.0 - 7.0)	2 - 9	0.170 (0.470)	0.00 (0.00 - 0.00)	0 - 2	< 0.001*
Mean Neck Pain Past Month (NRS-11)	6.38 (1.665)	7.00 (6.0 - 7.0)	2 - 10	NA			
Worst Pain Past Week (NRS-11)	7.12 (1.304)	7.00 (6.0 - 8.0)	4 - 9				
Mean Pain Past Week (NRS-11)	5.30 (1.568)	6.00 (4.0 - 6.0)	1 - 8				
Time Since Last Whiplash Injury (y)	5.93 (7.601)	2.78 (1.6 - 8.3)	0.48 - 45.00				

Abbreviations: BMI, body mass index; CSI, central sensitization inventory; CWAD, chronic whiplash associated disorders; HC, healthy controls; IQR, interquartile range; kg, kilogram; m, meter; n, number; NA, not applicable; NDI, neck disability index; NRS-11, numeric rating scale; PCS, pain catastrophizing scale; SD, standard deviation. *Significant values are represented in bold.

Table 2. *Between-group differences in EPT.*

	CWAD (n = 50)			HC (n = 50)			Linear Mixed Models				
	Mean (± SD)	**Median (IQR)**	**Range**	**Mean (± SD)**	**Median (IQR)**	**Range**	**Test Statistic**	**MD**	**SE**	**df**	***P* value**
EPT Ankle (mA)	7.66 (4.148)	6.50 (4.79 - 10.71)	1.83 - 18.67	8.55 (5.204)	6.50 (4.92 - 12.71)	1.50 - 24.33	1.138	0.893	0.785	146.630	0.257
EPT Left Wrist (mA)	4.82 (3.034)	3.83 (2.96 - 5.50)	1.50 - 17.00	5.90 (3.494)	5.08 (3.54 - 7.88)	1.00 - 19.00	1.376	1.080	0.785	146.630	0.171
EPT Right Wrist (mA)	5.09 (2.775)	4.67 (3.16 - 6.17)	1.00 - 15.33	6.18 (4.357)	5.00 (2.96 - 8.25)	1.00 - 21.33	1.847	1.087	0.785	146.630	0.168

Abbreviations: CWAD, chronic whiplash-associated disorders; df, degrees of freedom; EPT, electrical pain threshold; HC, healthy controls; IQR, interquartile range; mA, miliampere; MD, mean difference; n, number; SD, standard deviation; SE, standard error.

on ankle stimulation, 17.37 μV (± 8.349) for the right wrist, and 18.28 μV (± 9.522) for the left wrist (Table 3).

Linear mixed models only revealed a significant difference between CWAD patients and HC in the latency of the P3 component induced by the left wrist stimulation (t = -2.283; *P* = 0.023). The latency of the P1, as well as the amplitude of the P1 and P3, did not differ significantly between both groups.

Descriptives of the latencies and amplitudes of the

Table 3. *Descriptives of latency and amplitude of the P1 and P3 components.*

	CWAD				HC				Linear mixed models				
	n	Mean (± SD)	Median (IQR)	Range	n	Mean (± SD)	Median (IQR)	Range	Test statistic	MD	SE	df	*P* value
P1 Ankle Latency (ms)	48	122.01 (27.013)	118.75 (109.25 - 132.38)	50.50 - 199.50	49	122.48 (24.956)	121.00 (114.50 - 131.50)	50.50 -185.50	<0.001	0.005	0.007	542.339	0.999
P1 Ankle Amplitude (μV)	48	7.61 (7.029)	6.06 (2.97 - 9.98)	0.44 - 35.00	49	9.52 (10.793)	6.96 (3.81 - 12.08)	0.42 - 72.19	1.040	2.129	2.047	448.107	0.299
P3 Ankle Latency (ms)	49	281.541 (41.273)	279.00 (258.00 - 304.50)	182.50 - 365.50	48	280.55 (43.602)	277.50 (243.63 - 310.63)	200.50 - 373.00	-0.186	-1.215	0.007	542.340	0.852
P3 Ankle Amplitude (μV)	49	15.14 (6.106)	15.52 (10.63 - 18.32)	5.29 - 34.57	48	16.85 (8.323)	15.95 (10.48 - 22.95)	2.66 - 43.18	0.850	1.740	2.047	448.108	0.396
P1 Right Wrist Latency (ms)	49	116.41 (28.238)	112.00 (102.00 - 123.50)	73.00 - 199.50	49	110.60 (22.426)	109.50 (100.00 - 120.50)	52.50 –-199.50	-0.904	-5.860	0.006	540.801	0.367
P1 Right Wrist Amplitude (μV)	49	15.41 (18.239)	9.18 (5.39 - 17.96)	0.54 - 92.22	49	12.07 (8.371)	11.45 (4.79 - 15.83)	0.22 - 35.34	-1.600	-3.261	2.038	445.274	0.110
P3 Right Wrist Latency (ms)	50	261.68 (34.783)	265.25 (236.50 - 285.88)	200.00 - 347.00	50	250.62 (36.009)	249.25 (222.75 - 267.25)	200.50 - 351.500	-1.721	-11.060	0.006	537.455	0.086
P3 Right Wrist Amplitude (μV)	50	18.38 (8.880)	17.80 (14.13 - 21.45)	1.04 - 61.97	50	17.37 (8.349)	15.27 (11.63 - 22.82)	0.26 - 42.81	-0.498	-1.007	2.021	439.496	0.619
P1 Left Wrist Latency (ms)	47	116.81 (25.711)	111.00 (99.50 -12.75)	72.00 - 199.50	50	118.24 (25.327)	113.75 (103.75 - 125.75)	82.50 - 199.50	0.131	0.856	0.007	542.337	0.896
P1 Left Wrist Amplitude (μV)	47	10.41 (9.729)	7.34 (3.63 - 13.90)	0.22 - 36.76	50	12.28 (12.756)	8.18 (4.73 - 16.00)	0.34 - 66.37	0.966	1.979	2.048	448.240	0.334
P3 Left Wrist Latency (ms)	48	257.62 (36.658)	256.50 (224.38 - 283.88)	200.50 -337.50	50	243.27 (31.169)	239.25 (219.63 - 260.63)	200.50 - 335.50	-2.283	-14.810	0.006	540.595	0.023*
P3 Left Wrist Amplitude (μV)	48	18.05 (7.216)	17.04 (13.60 - 22.11)	3.61 - 44.01	50	18.28 (9.522)	17.97 (12.46 - 22.29)	0.80 - 62.57	0.123	0.251	2.038	445.181	0.902

Abbreviations: CWAD, chronic whiplash-associated disorders; df, degrees of freedom; HC, healthy controls; IQR, interquartile range; MD, mean difference; ms, milliseconds; n, number; SD, standard deviation; SE, standard error; μV, microvolt.
*Significant values represented in bold.

P1 and P3 components and results of the linear mixed models can be found in Table 3.

Correlations

Correlations were determined between the ERP characteristics (namely the latency and amplitude of the P1 and P3 at the ankle, right wrist, and left wrist) on one hand, and the EPTs, NDI, CSI, PCS, worst pain last week (NRS-11), mean pain last week (NRS-11), and pain score of the applied stimuli (NRS-11) on the other hand (Table 4).

The EPT at the ankle showed a significant positive weak correlation with the amplitude of the P1 ($\rho s = 0.293$; $P = 0.044$) and P3 ($\rho s = 0.306$; $P = 0.033$) on stimulation of the same location, as well as with the amplitude of the P3 on left wrist stimulation ($\rho s = 0.343$; $P = 0.017$) (Table 4). The EPTs of the left and right wrist did not correlate significantly with the amplitude

or latency of the corresponding P1 or P3, and neither did the pain score (NRS-11) for the received stimuli (respectively at the ankle, left wrist, or right wrist).

Concerning the questionnaires, the NDI, PCS, and mean pain last week (NRS-11) did not correlate with the amplitude or latency of the P1 or P3. The CSI did, however, show a significant weak positive correlation with the P3 amplitude ($\rho s = 0.308$; $P = 0.030$) and latency ($\rho s = -0.341$,; $P = 0.015$) of the responses to right wrist stimulation, and the worst pain last week (NRS-11) was weakly and positively correlated with the P1 latency of the left wrist ($\rho s = 0.319$; $P = 0.029$). All calculated correlations can be found in Table 4.

Discussion

The purpose of this study was to investigate the somatosensory processing of CWAD patients by comparing the ERPs resulting from electrical nociceptive stimulation between patients suffering from CWAD and HC (26). As the pain threshold did not differ significantly between both groups, stimuli were administered to both CWAD patients and HC at a similar intensity. Linear mixed models only revealed significant differences between CWAD patients and HC in the latency of the P3 component induced by left wrist stimulation. The latency of the P1, as well as amplitude of the P1 and P3, did not differ significantly between both groups (Table 3).

As a secondary outcome measurement, correlations between parameter pairs were examined in the CWAD patients. This involved latency and amplitude of the ERP components, on the one hand, and pain thresholds, self-reported pain, symptoms of CS, pain catastrophizing, and disability, on the other hand. A positive correlation was found between the EPT at the ankle, and the amplitude of the P1 on ankle stimulation, and P3 on ankle and left wrist stimulation (Table 4). Neither the EPTs of the left and right wrist, nor the pain score (NRS-11) attributed to the received stimuli correlated significantly with the amplitude or latency of the ERP components. These findings are, however, in line with previous research, using laser-evoked potentials, stating that EEG responses are not determined by the perception of pain per se, but that they are mainly determined by the saliency of the eliciting nociceptive stimulus (61,62).

The CSI was positively correlated with the P3 amplitude and negatively correlated with the P3 latency on right wrist stimulation; whereas, the worst pain last week (NRS-11) was positively correlated with the P1 latency of the left wrist. The NDI, PCS, and mean pain last week (NRS-11) did not correlate with the amplitude or latency of the P1 or P3 (Table 4). However, it must be stated that all of these correlations were significant at the level of $a < 0.05$; whereas, it could be argued that a stricter significance threshold should be applied due to multiple comparisons. Due to the comparison of 5 categories of outcomes (i.e., ERP characteristics, pain reports, self-reported disability assessed with the NDI, symptoms of CS investigated with the CSI, and psychological symptoms measured with the PCS), a threshold of $a < 0.01$ could be seen as more appropriate. Additionally, since the obtained correlations were merely weak, this raises questions about the statistical significance and clinical relevance of these findings.

Although previous studies (20,63-67) have extensively reported local and widespread hypersensitivity in CWAD patients based on the observations of lower cold, heat, and pressure pain thresholds, and occurrence of a nociceptive withdrawal reflex at a lower electrical stimulation intensity, the current study did not reveal significant differences in EPTs between the included CWAD patients and HC. It must, however, be stated that a trend of lower EPTs could be observed in the patients suffering from CWAD, but that this difference did not reach significance. The presence of such hypersensitivity has been hypothesized to be dependent on the severity of (self-reported) pain, disability, quality of life, and psychological symptoms (67,68). Self-reported pain, disability, pain catastrophizing, and self-reported symptoms of CS did differ significantly between the included CWAD patients and HC. Sterling et al (68) reported hypersensitivity to be present in patients suffering from CWAD with an NDI higher than 30%. Although, in our study, the majority of the included CWAD patients had a score above this disability cutoff (interquartile range: 15/50 to 21,8/50) and, therefore, reported moderate-to-severe disability, the reported baseline NDI score of included patients ranged from 10/50 to 35/50. Of the included CWAD patients, 5 reported a baseline NDI of 14/50, 2 obtained a total score of 11/50, and 1 patient scored 10/50. Sterling et al (68) reported that CWAD patients with mild disability did not show hypersensitivity in the form of a decreased nociceptive withdrawal reflex, and this could explain why lower EPTs were not obtained in the CWAD patients included in the current study. Patients with an NDI below 15/50 at baseline were included in the study as the NDI was questioned twice, once in the inclusion questionnaire and once in the baseline questionnaire.

Table 4. *Correlations between event-related potentials, quantitative sensory testing, and self-reported outcome measures.*

	EPT Ankle		EPT Left Wrist		EPT Right Wrist		NDI		CSI	
	ρs	*P* value	ρs	*P* value	ρs	*P* value	ρs	*P* value	ρs	*P* value
P1 Ankle Latency (n = 48)	0.118	0.425	0.200	0.172	0.270	0.064	0.022	0.880	0.021	0.886
P1 Ankle Amplitude (n = 48)	0.293*	0.044*	0.095	0.519	0.251	0.085	-0.165	0.262	-0.036	0.808
P3 Ankle Latency (n = 49)	0.132	0.365	0.094	0.523	0.113	0.440	-0.254	0.078	-0.126	0.390
P3 Ankle Amplitude (n = 49)	0.306*	0.033*	0.091	0.535	0.111	0.448	-0.151	0.300	0.034	0.819
P1 Right Wrist Latency (n = 49)	0.215	0.137	0.134	0.359	0.125	0.393	0.125	0.392	0.190	0.191
P1 Right Wrist Amplitude (n = 49)	0.063	0.666	-0.035	0.813	-0.042	0.774	0.171	0.240	0.098	0.501
P3 Right Wrist Latency (n = 50)	-0.123	0.397	-0.062	0.667	-0.110	0.448	0.065	0.654	-0.341*	0.015*
P3 Right Wrist Amplitude (n = 50)	0.155	0.284	0.051	0.723	0.063	0.661	0.121	0.402	0.308*	0.030*
P1 Left Wrist Latency (n = 47)	-0.105	0.481	-0.068	0.649	-0.022	0.883	0.116	0.439	0.256	0.082
P1 Left Wrist Amplitude (n = 47)	0.241	0.103	0.139	0.352	0.162	0.277	-0.029	0.845	0.029	0.849
P3 Left Wrist Latency (n = 48)	0.026	0.859	0.065	0.660	0.008	0.957	0.012	0.935	-0.184	0.210
P3 Left Wrist Amplitude (n = 48)	0.343*	0.017*	0.129	0.381	0.053	0.719	-0.154	0.297	-0.005	0.975

	PCS Total Score		Worst Pain Past Week (NRS-11)		Mean Pain Past Week (NRS-11)		Pain Score Stimuli Ankle (NRS-11)		Pain Score Stimuli Left Wrist (NRS-11)		Pain Score Stimuli Right Wrist (NRS-11)	
	ρs	*P* value	ρs	*P* value	ρs	*P* value	ρs	*P* value	ρs	*P* value	ρs	*P* value
P1 Ankle Latency (n = 48)	0.025	0.865	0.062	0.676	-0.170	0.249	-0.060	0.687	-0.105	0.478	0.043	0.772
P1 Ankle Amplitude (n = 48)	0.104	0.480	-0.212	0.147	-0.161	0.275	0.119	0.419	-0.059	0.692	0.045	0.759
P3 Ankle Latency (n = 49)	-0.264	0.067	0.118	0.418	-0.041	0.782	0.077	0.601	-0.069	0.639	0.055	0.710
P3 Ankle Amplitude (n = 49)	0.116	0.426	-0.068	0.641	0.079	0.589	0.261	0.070	0.033	0.822	0.022	0.878
P1 Right Wrist Latency (n = 49)	0.015	0.918	0.054	0.713	0.056	0.701	0.094	0.520	-0.132	0.365	-0.005	0.973
P1 Right Wrist Amplitude (n = 49)	0.172	0.236	-0.017	0.908	0.012	0.937	-0.175	0.228	-0.134	0.357	0.022	0.880
P3 Right Wrist Latency (n = 50)	-0.046	0.749	-0.037	0.798	-0.203	0.157	-0.073	0.617	-0.220	0.124	-0.102	0.480
P3 Right Wrist Amplitude (n = 50)	-0.149	0.303	0.040	0.785	0.163	0.257	0.009	0.950	-0.053	0.716	0.138	0.341
P1 Left Wrist Latency (n = 47)	-0.001	0.997	0.319*	0.029*	0.265	0.072	0.090	0.547	-0.032	0.833	0.258	0.080
P1 Left Wrist Amplitude (n = 47)	0.238	0.108	-0.108	0.469	-0.065	0.663	0.168	0.260	0.201	0.175	0.150	0.314
P3 Left Wrist Latency (n = 48)	-0.089	0.547	0.073	0.623	0.027	0.853	-0.001	0.997	-0.020	0.893	-0.098	0.510
P3 Left Wrist Amplitude (n = 48)	-0.207	0.158	-0.119	0.421	-0.023	0.875	0.125	0.397	0.085	0.567	0.051	0.732

Abbreviations: CSI, central sensitization inventory; EPT, electrical pain threshold; NDI, neck disability index; PCS, pain catastrophizing scale; n, number; NRS-11, numeric rating scale; ρs, Spearman correlation coefficient
*Significant values are represented in bold.

Patients reporting mild disability on the baseline NDI (which was used for the analyses) did, however, obtain a total minimal score of 15/50 on the inclusion questionnaire and were, therefore, included. Moreover, EPTs were based on self-report by the patient; whereas, the nociceptive withdrawal reflex is regarded as an objective physiologic correlate of nociception as it does not require a cognitive patient response (48). Although differences in the nociceptive withdrawal reflex were observed by Sterling et al (69), reported pain at this threshold was no different from HC, which has been suggested to be an indication that reflex responses are more sensitive than pain responses in detecting central hyperexcitability (55).

Given the fact that pain threshold determinations merely refer to the quality of the perception by the patient (70), the evaluation of ERPs in response to (electrical) nociceptive stimuli can add valuable information by providing a quantitative evaluation of pain perception (70,71). Applying this technique can aid to detect, chronic pain state specific, alterations in cerebral responses, which are characterized by an amplification and prolongation of a pain signal at a central level (72). Secondary processing of nociceptive input, immediately enhanced by attention caused by the compelling sensation of pain is thought to be reflected in the nociceptive-evoked response (73,74).

Amplitude and latency of the P1 and P3 components did not differ significantly between CWAD patients and HC, with the exception of the latency of the P3 component measured at the left wrist, which was longer in patients suffering from CWAD (256,50 milliseconds) than in HC (243,27 milliseconds) (Table 3). Although most previous studies did not find any differences in ERP components in other chronic pain populations, some studies reported a prolonged latency of the N1 in fibromyalgia patients (75), of the N9 in chronic low back pain (76), and of the N2 and P2 in patients suffering from complex regional pain syndrome (26,77). Findings of prolonged latencies have been hypothesized to be related to dysfunctions of the central nervous system (with pain-induced reduction of responsiveness of neurons in the somatosensory pathways) (77,78), dysfunction of the nociceptive pathway, or impairment of small nerve fiber function (75). Similar research in CWAD patients is very limited, but 2 recent studies (27,28) on laser-evoked potentials in CWAD patients reported an absence of differences in the amplitudes and latencies of the N1, N2, and P2 components, when compared to HC. However, changes in ERP characteristics were hypothesized due to the combined evidence from previous studies (20) for the significant role of hypersensitivity of the central nervous system in CWAD, and such CS has been linked to the occurrence of decreased latencies or increased amplitudes of ERPs (27,79-82). Since the current study only found an increased latency, its results do not substantiate this stated importance of CS and rather point in the direction of involvement of small fiber dysfunction or dysfunction of the nociceptive pathway. This is in line with previous findings (70,77,83) that mostly indicate differences in ERP components in patient populations with a neurological lesion or small fiber dysfunction. A recent study (84) has, however, provided structural and functional evidence of a small fiber pathology in people with CWAD, which also led to the expectation of finding differences in ERP components. From a clinical point of view, the obtained findings of prolonged latency of the P3 component would suggest the importance of a neurological approach rather than approaches that aim to resolve a clinical picture dominated by CS (including treatment approaches that are often applied to patients suffering from CS, such as pain neuroscience education, or cognitive behavioural therapy) (85-90). However, since a trend of lower pain thresholds in CWAD patients was observed, and only the latency of one component was altered, these results do not suffice to make such strong recommendations, and differential diagnosis between CWAD patients with or without neurological involvement remains essential. Therefore, future studies should evaluate nerve fiber function in CWAD patients and compare ERP components between those with and without small fiber pathology.

Analyses of the correlations revealed that higher EPTs at the ankle correlated weakly with higher amplitudes of the P1 (of the ankle) and P3 (of the ankle and wrist). Moreover, more severe self-reported symptoms of CS correlated weakly with higher P3 amplitude and with shorter P3 latency (of the right wrist). Lastly, higher reports of experienced worst pain during the last week correlated weakly with higher P1 latency of the left wrist. Differences between both components could be expected as earlier components originate from the suprasylvian region and are devoted to the discriminative component of pain; whereas, the later components arise from the anterior cingulate cortex and play a role in the attentive and emotive features of pain (91).

Correlations between the latency and amplitude of the ERP components and the pain rating of the re-

ceived stimuli were not obtained, which contradicts the findings of studies in HC (92-95), but are in line with the conviction that EEG responses are not determined by the perception of pain per se, but by the saliency of the eliciting nociceptive stimulus (61,62).

Limitations and Strengths

Although the inclusion criteria stated that CWAD patients had to report ≥ 15/50 on the NDI, self-reported disability had changed between time of inclusion and time of baseline assessment, resulting in the inclusion of 8 CWAD patients with an NDI score of < 15/50 at baseline.

The EEG is particularly useful as a result of its high temporal resolution, low cost, portable device, which enables patients to be in any position required for the assessment, and is not restricted by metallic implants in the body or claustrophobia (29,96,97). However, the high temporal resolution comes at a cost of low accuracy concerning structural identification in deep brain structures, in particular, but also in the brain, in general (97,98).

Electrical stimulation bypasses peripheral receptors and concurrently activates non-nociceptive β-fibers along with Aδ and C fibers (unless intraepidermal electrical stimulation is used with a maximum stimulus intensity of twice the perceptual threshold) (99). Electrical stimuli have shown among the best discriminative abilities (20,100), and provide evidence of involvement of central pain mechanisms when pain hypersensitivity is observed after stimulation of uninjured body parts (101).

Methodological quality of the paper was increased by matching CWAD patients and HC on gender and on age, and (eye blink) artifacts were minimalized by performing the assessments in a steady seated position with eyes closed. In addition, the clinical trial was officially registered before the publication of the results.

Recommendations for Future Research

Future studies should assess laser-evoked potentials in CWAD patients, as these are currently regarded as the most reliable tool to assess the function of the spinothalamic system in humans (27), and should combine this with small fiber impairment tests, to determine whether evoked potentials findings differ between CWAD patients with or without such impairment, and to compare the results to previous studies.

Conclusions

EPTs, as well as latency and amplitude of the P1 and P3 ERPs in response to electrical stimuli, did not differ between patients with CWAD and HC, with the exception of a prolonged latency of the P3 component in CWAD patients measured at the left wrist. Therefore, these findings do not provide evidence for the presence of hypersensitivity, but indicate a possible involvement of suggestive for dysfunctions of the central nervous system, dysfunction of the nociceptive pathway, or impairment of small fiber function. The ERP characteristics did not correlate with the reported pain induced by the stimuli, but they did seem to be influenced by the intensity of the applied stimulus, the severity of self-reported symptoms of CS, and the intensity of the worst pain reported during the past week. However, these relationships were based on weak correlations, causing their clinical relevance to be questionable.

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