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Case-Control Study

# Autonomic Response to Pain in Patients with Chronic Whiplash Associated Disorders

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**Background:** Patients with chronic whiplash associated disorders (WAD) demonstrate altered central pain processing and impaired endogenous analgesia. In addition, previous research reported disturbances in the autonomic nervous system and the presence of post-traumatic stress reaction in patients with chronic WAD. The autonomic nervous system, in particular the autonomic stress response, might modulate central pain processing in this population.

**Objectives:** The goal of this study was to compare the autonomic response to acute painful stimuli in patients with chronic WAD and healthy controls and to look for associations between endogenous analgesia and autonomic parameters.

**Study design:** Case-control study.

**Methods:** Thirty patients with chronic WAD and 31 healthy controls were subjected to an experiment evaluating the autonomic nervous system at rest and during experimental painful stimuli. Skin conductance, heart rate, and heart rate variability parameters were monitored continuously during the evaluation of conditioned pain modulation. The paradigm of heterotopic noxious conditioning stimulation was used to assess this conditioned pain modulation effect.

**Results:** The data revealed no difference in autonomic response to pain between chronic WAD and healthy controls. The autonomic response was unrelated to pressure pain thresholds or the effect of conditioned pain modulation in either group.

**Limitations:** The present study only investigates the autonomic response to a stress caused by pain.

**Conclusion:** Results of this study refute autonomic dysfunction in response to pain in patients with chronic WAD. The autonomic nervous system activity or reactivity to acute pain appears unrelated to either pain thresholds or endogenous analgesia in patients with chronic WAD.

**Key words:** chronic whiplash associated disorders, central sensitization, pain modulation; posttraumatic stress disorder ,sympathetic, heart rate variability

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Chronic Whiplash-Associated Disorder (WAD) is a debilitating and costly condition of at least 6 months duration and is characterized by multiple symptoms such as chronic neck pain, fatigue, dizziness, concentration difficulties, and headaches (1). Some patients recover within the first 3 months after a whiplash injury (2). However, up to 50% of the patients suffering from whiplash injuries develop chronic pain and pain-related disability (3-7).

Recent scientific research provided new insights into the development of chronic WAD after a whiplash trauma. Radiological findings do not account for the development of chronic WAD (8), and treatment approaches focusing on local cervical dysfunctions appear to have limited results (9,10). Instead, there is consistent evidence for altered central pain processing

and central sensitization in people with chronic WAD (11-15), providing a rationale for studying chronic WAD from a central neurologic perspective.

### Central Sensitization Is Present in Chronic WAD

Central sensitization or hyperexcitability of the central nervous system is present in patients with chronic WAD (16). Central sensitization encompasses altered sensory processing in the brain (17), malfunctioning of descending pain inhibitory mechanisms (18), increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up (17,19), and long-term potentiation of neuronal synapses in the anterior cingulate cortex (20). Clinically, central sensitization results in an increased responsiveness to a variety of peripheral stimuli (21). This widespread hypersensitivity has been documented in patients with chronic WAD (11,12,15,22) as well as the malfunctioning of descending pain inhibitory pathways (23). These pathways separate relevant from irrelevant stimuli in order to enhance the biologically valuable pain signal. The function of the descending pain inhibitory pathways can be examined by using the method of Conditioned Pain Modulation (CPM) (24). Following the recommendations of Yarnitsky et al (25), the term CPM is used instead of diffuse noxious inhibitory control. During CPM nociceptive neurons in spinal and trigeminal dorsal horns are inhibited by noxious stimulation from the neurons excitatory receptive field (26). Inefficient CPM has been found in multiple chronic pain syndromes like fibromyalgia (27,28), chronic fatigue syndrome (18), and chronic tension headache (29), but not in chronic low back pain (27). Recently our group demonstrated impaired CPM in patients with chronic WAD (23).

### Stress and the Stress Response System

Chronic WAD is associated with physical and psychological stress that involves sympathetic nervous system (SNS) activation (30-32). Given the traumatic nature of a car accident, patients with a whiplash injury may experience a post-traumatic stress reaction (PTSR). The presence of PTSR is associated with a poor long-term recovery (33) and is found to be related with SNS disturbances in patients with acute and chronic WAD (32). Sympathetic activation is a factor in pain maintenance, and pain itself is a stressor that may further enhance the sympathetic outflow leading to a vicious cycle. Still, only few studies have examined the SNS in patients with WAD (32,34,35).

Stress, negative emotions, thoughts, attention, etc. can modulate the activity in the descending pathways, facilitating pain and resulting in cognitive emotional sensitization (36). There is evidence for the presence of these maladaptive cognitions in chronic WAD (2,37-39). However psychological factors such as depressive thoughts, catastrophic thinking, and hypervigilance to pain did not influence the CPM-effect in chronic WAD (23). There is a lack of knowledge about the SNS and its influence on pain mechanisms in chronic WAD. Hence, studying the autonomic responses to pain and its relation with pain modulation seems warranted.

The present study aimed at examining the autonomic response (i.e., skin conductance, heart rate, heart rate variability) to a physical stressor (i.e., painful stimuli) in patients with chronic WAD. First, it is hypothesized that the autonomic response to painful stimuli differs between patients with chronic WAD and healthy controls. More specifically, a stronger activation of the sympathetic branch of the autonomic nervous system (and concomitant decreased parasympathetic activity) in response to acute pain is anticipated in the chronic WAD group. Second, the study aimed at examining the association between the autonomic response to acute pain and impaired pain inhibition in patients with chronic WAD. We expected that a stronger sympathetic activation would be associated with a greater impairment in pain inhibition. Finally, this study aimed at exploring the influence of PTSR on the autonomic responses in a WAD population.

## Methods

### Patients

Patients were recruited from the medical database of a local medical care unit. The inclusion criteria were experiencing chronic symptoms of a whiplash trauma and fulfilling diagnostic criteria of WAD I to III of the Quebec Task Force classification (3). Chronic symptoms were defined as symptoms persisting for at least 3 months. Patients were excluded if they were classified as WAD grade IV (3).

Healthy control patients were recruited through the local university staff, and through family and acquaintances of the researchers. The control patients had no previous knowledge about the research topic and the possible hypotheses. They were not allowed to participate if they ever had experienced a whiplash trauma or suffered from pain or neck-shoulder-arm symptoms. Further, persons suffering from severe

chronic disease, chronic pain conditions, or psychiatric disorders were excluded from study participation.

Patients were asked to discontinue analgesic and anti-inflammatory drugs 48 hours before testing and all patients were instructed to avoid physical exertion and to refrain from consuming nicotine, alcohol, and caffeine 24 hours before testing. Further exclusion criteria were pregnancy, cardiovascular disease, or neurological disease. An a priori power analysis determined that at least 30 patients per group were required to examine the effect of CPM on temporal summation of pressure pain, with a Power of 0.80 and $\alpha \leq 0.050$. The power was calculated based on outcomes of CPM. The control group was recruited, age- and gender-matched to the chronic WAD-group.

## Procedure

Before study participation, patients were asked to read an information leaflet and to sign the informed consent. The study protocol, information leaflet, and informed consent were approved by the Human Research Ethics Committee of the Antwerp University Hospital. A standardized questionnaire was used to collect personal characteristics and accident- and health-related information. Afterwards, patients filled out a battery of questionnaires. Next, they were subjected to an experiment to evaluate the CPM-mechanism. Simultaneously with this pain measurement, autonomic functions were continuously registered, to measure the autonomic response to acute pain.

## Measurements

### *Self-reported Questionnaires*

Self-reported questionnaires were used to assess pain, disability, psychosocial factors, pain cognition, and post-traumatic stress. A score for post-traumatic stress was obtained by the Impact of Event Scale (IES). It has been validated for the measure of stress reactions after a traumatic experience (40) and has been used in previous studies regarding whiplash patients (32,41). The IES-score was dichotomized into "no-mild PTSR" (IES < 26) and "moderate-severe PTSR" (IES ≥ 26) (42). Other questionnaires were the Neck Disability Index (43), Pain Catastrophizing Scale (44), Pain Vigilance Awareness Questionnaire (45), and the Beck Depression Inventory (46).

### *Conditioned Pain Modulation*

Pressure pain thresholds were measured at the right trapezius belly (middle between processus spinosus of T1 and lateral part of the acromion) and at the right quadriceps belly (middle between groin and proximal part of the patella) with an analogue Fisher algometer (Force Dial model FDK 40 Push Pull Force Gage, Wagner Instruments, P.O.B. 1217, Greenwich, CT 06836). In order to determine pressure pain thresholds at each location, pressure was gradually increased at a rate of one kg/s until the subject reported first onset of pain. The threshold was taken as the mean of 2 consecutive (30 seconds in between) measurements. The pressure pain threshold technique was found to be reliable (47). At each location, temporal summation was provoked by means of 10 consecutive (one second in between) pressure pulses at the previously determined pressure pain threshold. Pressure was gradually increased at a rate of 2 kg/s to the determined pressure pain threshold and maintained to that point for one second before being released. The patients rated the intensity and unpleasantness of the pain of the first, fifth, and tenth pulse on a verbal numerical rating scale (0 = no pain to 10 = worst possible pain). Afterwards, a rest period of 5 minutes was allowed before investigating the CPM-mechanism. This CPM-mechanism was induced by inflating an occlusion cuff at the patient's left arm to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mmHg/s until "the first sensation of pain" was reported and maintained for 30 seconds. Afterwards, the patient was asked to rate the pain intensity of the cuff inflation on a verbal numerical rating scale. Next, the cuff inflation was increased or decreased until pain intensity at the left arm was rated as 3/10 on the verbal rating scale. The previous described temporal summation assessment was then repeated during maintenance of this cuff inflation. The difference in increase in pain intensity from the first to tenth pulse is used as a measure for temporal summation and the difference in temporal summation with and without cuff inflation as a measure for CPM-effect in further statistical analysis. The test-retest reliability of the experimental noxious protocol was described elsewhere (26).

## Autonomic Function Measurements

### *Recording Equipment*

Continuous recordings of skin conductance and cardiovascular parameters were obtained using the Nexus 10 device with blood volume pulse and skin conductance sensors (NeXus 10, Mind Media BV, The Netherlands). The recorded data were processed using

the Bio Trace+ software version V2010A (Mind Media BV). All sensors were attached at the patient's right hand. The skin conductance sensor uses 2 Ag-AgCL electrodes that are secured to the tip of the index and ring finger using velcro straps. The sensor is sensitive to very small (1/1000 microsiemens) relative changes in skin conductance. The blood volume pulse sensor uses fingertip photoplethysmography to measure heart rate and monitor relative blood flow. Heart rate variability (HRV) can be acquired through this sensor and generates reliable data (48). The blood volume pulse sensor was placed on the little finger. For artefact removal in the HRV recordings, a prolonged inter-beat-interval was defined as being either longer than 1,400 ms or longer than 150% of the value of the preceding inter-beat-interval. A short inter-beat-interval was defined as being either shorter than 400 ms or shorter than 50% of the value of the preceding inter-beat-interval.

### Data Processing

HRV measures in time domain included standard deviation of inter-beat intervals (SDNN) and root mean square of successive differences between NN intervals (RMSSD). In addition, power spectra of the P-intervals (the time interval between 2 consecutive pulses) were derived by Fast Fourier transformation using Kubios HRV 2.0. It is suggested that low frequency (LF) (0.04 – 0.15Hz) power of HRV is mediated by both sympathetic and parasympathetic modulations (49). High frequency (HF) (0.15 – 0.4Hz) power of HRV is mainly under control of the vagus nerve (49). The LF/HF ratio is an indicator of cardiac sympathetic modulation and sympathovagal balance (49). Measures of total spectral power and very low frequency from short recordings are physiologically ambiguous and for this reason their use is not recommended by the task force (49). For all parameters mean values in each experimental stage were calculated.

### Statistical Analysis

Statistical analysis was performed in SPSS 20.0 (SPSS Inc.). All data were checked for normal distribution according to the Kolmogorov-Smirnov test. HRV parameters in the frequency domain – LF, HF, LF/HF – were not normally distributed and were logarithmically transformed (Ln). A 2 X 3 (GROUPxTIME) analysis of variance with repeated measures was used. Main effect of group (chronic WAD and healthy controls), main effect of time (rest, phase one, and phase 2), and GROUPxTIME interaction were evaluated for all dependent variables (skin conductance, heart rate, SDNN, RMSSD, LF, HF, LF/HF). Greenhouse-Geisser was used to correct for repeated measures. A Pearson correlation analysis was used to assess the relation between the dependent variables and CPM, and for the associations with pressure pain thresholds. The significance level for correlations was set to 0.01 to correct for type I errors. The IES-score was dichotomized into "no-mild PTSR" (IES < 26) and "moderate-severe PTSR" (IES ≥ 26) (42) in the analyses to compare chronic WAD with and without PTSR with a Mann-Whitney U-test.

## Results

### Group Characteristics

Thirty patients with chronic WAD (24 women and 6 men) and 31 healthy controls (24 women and 7 men) volunteered for the study. The mean age was 43.6 (± 9.44 SD) years for the experimental group and 43.45 (± 15.87 SD) years for the control group. Both groups were comparable for age and gender distribution, educational level, and socio-economic status ($P > 0.05$). Mean scores for neck disability, depression, pain catastrophizing, pain vigilance and awareness, and PTSR for both groups are presented in Table 1. Mean scores of all these questionnaires were significantly different between patients with chronic WAD and healthy controls ($P \leq 0.05$). In the chronic WAD group, one participant reported mild pain and disability (Neck Disability Index score between 10 and 28), and 29 patients were classified as having moderate/severe pain and disability (Neck Disability Index score ≥ 30).

### Pressure Pain Thresholds and CPM

Mean pressure pain thresholds at the shoulder and thigh were respectively 3.26 (± 1.38 SD) kg/cm$^2$ and 5.25 (± 2.5 SD) kg/cm$^2$ for the chronic WAD group, and 4.94

*Table 1. Mean scores of self-reported measurments in chronic WAD and control participants.*

| | NDI | BDI | PCS | PVA | IES |
|---|---|---|---|---|---|
| Chronic WAD (n = 30) | 44.27 (±13.39 SD) | 15.47 (±9.41 SD) | 17.17 (±12.01 SD) | 34.38 (±12.73 SD) | 20.37 (±16.57 SD) |
| Controls (N = 31) | 3.48 (±4.19 SD) | 2.68 (±2.63 SD)* | 8.57 (±8.87 SD)* | 23.70 (±12.17 SD)* | |

NDI: Neck Disability Index; BDI: Beck Depression inventory; PCS: Pain Catastrophizing scale; PVAQ: Pain Vigiliance and Awareness Questionnaire; IES: Impact of Event Scale. *$P \leq 0.05$

(± 1.53 SD) kg/cm$^2$ and 6.7 (± 2.44 SD) kg/cm$^2$ for the healthy control group. The chronic WAD group demonstrated a dysfunctional CPM-effect compared with the control group. Following cuff inflation, the temporal summation effect was depleted among the healthy controls. In contrast, the increase in pain intensity from the first to tenth pulse was quite similar before and during cuff inflation in the chronic WAD group. The report of the pain measurements can be found in Daenen et al (23).

## Autonomic Function: Comparison Between Patients and Controls

### *Autonomic Response to an Acute Painful Stimulus*

At rest, there were no significant differences for any of the autonomic function parameters between chronic WAD patients and healthy controls ($P > 0.05$). Both the chronic WAD group and control group reacted to painful stimuli with a significant increase in skin conductance (F = 103.462; $P < 0.001$) and a significant decrease in SDNN (F = 18.259; $P < 0.001$), RMSSD (F = 4.316; $P = 0.017$), and LF power (F = 4.205; $P = 0.018$) as compared to rest (TIME effect) (Fig. 1). There was no significant GROUP effect for any of the variables and there were no significant GROUPxTIME interaction effects. This indicates that chronic WAD patients and healthy controls show similar patterns of sympathetic response to a painful stimulus.

### *Correlation of Autonomic Measurements with Pressure Pain Thresholds and CPM*

The associations between the autonomic measurements and the pressure pain thresholds were analysed in the chronic WAD group and in the control group separately. For this analysis the transformed data were used in a Pearson correlation analysis. The pressure pain thresholds appeared unrelated to any of the autonomic measurements in either groups ($P > 0.01$). Likewise, no significant associations between the autonomic parameters and CPM data were found in either group ($P > 0.01$).

## Post-traumatic Stress Reaction

The chronic WAD group was divided in 2 subgroups depending on the IES score (i.e., patients with and without a moderate PTSR) (42). Ten patients with chronic WAD – all women – were classified in the PTSR group (mean IES score of 40 ± 10.44). Twenty patients were classified as having mild to no PTSR (6 men and 14 women; mean IES score of 10.7 ± 8.52 SD). There

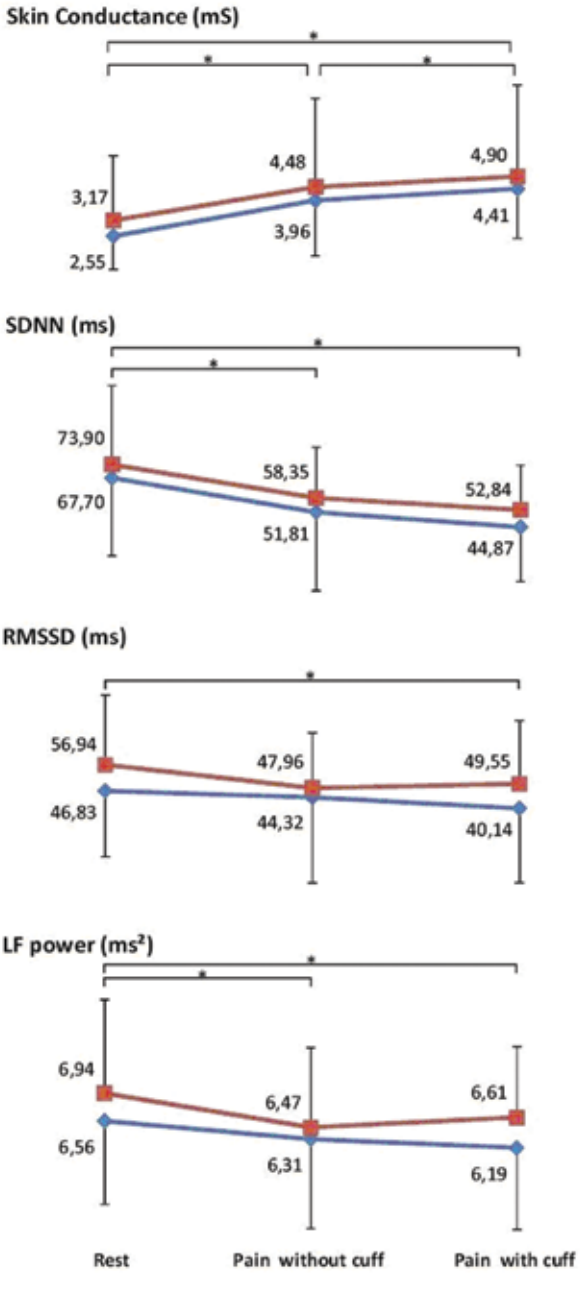


Fig. 1. *A significant TIME effect is present for 4 of the autonomic parameters, namely skin conductance, SDNN (standard deviation of normal intervals), RMSSD (root mean square of successive differences between NN intervals), and LF (Low Frequency band power). LF values are logarithmically transformed. Repeated measures anova, mean values for each phase SD. * = $P < 0.05$.*

was a significant difference between the distribution across patients with and without PTSR for SDNN and RMSSD during phase 2 (Table 2). There was no difference in Neck Disability Index score between chronic WAD groups with and without PTSR, suggesting that the presence of PTSR is independent from levels of pain and disability.

## Discussion

The present study aimed at examining the autonomic response to pain in patients with chronic WAD. The results demonstrate a similar autonomic response to acute pain in patients with chronic WAD and healthy controls. The dysfunctional endogenous analgesia (i.e., CPM) in patients with chronic WAD was found to be unrelated to autonomic nervous system parameters.

### Autonomic Response to Acute Pain

Enhanced sympathetic activation affects muscle microcirculation, muscle spindle function, and muscle contractile properties, and can lead to central sensitization, contributing to the development of chronic pain (31). In the present study, a significant reaction to acute pain was found for skin conductance, SDNN, RMSSD, and LF power, indicating that the painful stimuli were able to activate the sympathetic branch of the autonomic nervous system. Both groups demonstrated a similar autonomic response to pain. Hence, these findings refute the hypothesis of a stronger sympathetic response to acute pain in chronic WAD patients. In addition, autonomic nervous system activity at rest in acute WAD patients did not differ from healthy controls, suggesting normal autonomic activity at rest in patients with chronic WAD.

Previous research on the autonomic nervous system in chronic WAD patients found a stronger autonomic response (heart rate measurements) to a dynamic loading of the jaw-neck motor system (34). However, no difference in HRV reactivity was found (34), which is in line with the results of the present study. In fibromyalgia, another chronic pain condition sharing aspects with chronic WAD, studies have indicated the involvement of the autonomic nervous system in terms of changes in cardiovascular neural control, namely enhanced activity of the sympathetic system (50,51). In fibromyalgia, reduced HRV and increased LF/HF ratio have been repeatedly observed (50,51) and interpreted as increased sympathetic cardiac control. Although chronic WAD and fibromyalgia share some clinical features, the disturbances in autonomic reaction found in fibromyalgia were not present in the chronic WAD patients in the current study.

### Relation of Autonomic Measurements with Pressure Pain Thresholds and CPM

Patients suffering from chronic WAD showed lower pressure pain thresholds than healthy controls. Still, as discussed by Shah et al (52) there is an overlap between patients and controls for the pressure pain thresholds results, in such that group allocation based on pressure pain thresholds results is not possible. Beside these lower pain thresholds, chronic WAD patients showed a dysfunctional pain inhibition, indicating impaired descending pain inhibitory pathways. Autonomic sympathetic activation may lead towards lower sensory and pain thresholds (53). In addition, McLean et al (54) suggested the relationship between stress response systems and deregulation of descending pain modulating pathways in post-stress pain states, like WAD. The present study examined this interaction for the first time. However, the endogenous analgesia (i.e., CPM) seems to be unrelated to the activity of the autonomic nervous system in patients with chronic WAD. Although pain pressure thresholds were significantly lower in chronic WAD patients, the pain pressure thresholds were not correlated to any of the autonomic measurements. Similar for CPM-effect, no significant correlations of autonomic parameters with CPM-effect were found in any of the groups. This indicates that pressure pain thresholds and functioning of descending pain inhibitory pathways are independent of sympathetic activation at rest and sympathetic reactivity to painful stimuli. In addition, the present study indicates that patients with chronic WAD do not present an aberrant autonomic pattern compared to healthy controls.

Table 2. *SDNN and RMSSD during pain measurement without cuff inflation in chronic WAD with (IES > 26) and without (IES ≤26) post traumatic stress reaction.*

| | IES ≤26 | IES >26 | *P*-value |
|---|---|---|---|
| SDNN | 46.10 (±39.02 SD) | 65.14 (±27.07 SD) | 0.044 |
| RMSSD | 35.68 (±25.28 SD) | 64.48 (±41.21 SD)* | 0.049 |

IES = impact of event scale; SDNN = standard deviation of RR intervals; RMSSD = root mean square of successive differences between NN intervals.

### Presence of PTSR in Patients with Chronic WAD

In the current study 33% (10 out of 30) of the patients with chronic WAD experienced a moderate to severe PTSR. This is a higher prevalence than previously reported. Sterling and Kenardy (32) found that 13% of patients continued to manifest a moderate reaction at 6 months post injury, and Buitenhuis et al (55) reported prevalence rates of 16% and 11% at 6 months and one year post injury respectively. The difference might be due to the limited number of patients in this study, and the difference in duration since the whiplash injury. Taken together, an increasing number of studies found evidence favoring a significant proportion of chronic WAD sufferers experiencing PTSR. Moreover, several studies provide evidence for a close association between post-traumatic stress symptoms and pain after whiplash injury (41,56,57), an association absent in this present study.

Levels of pain and disability did not differ between those with and without PTSR. In contrast, previous reports found greater levels of disability in patients with moderate PTSR compared to those without PTSR, and the group with PTSR showed lower pain thresholds compared to those without PTSR (32). We did find a difference in HRV parameters: chronic WAD patients with PTSR demonstrated higher levels of SDNN and RMSSD during phase one. Since the current study was not designed to test if PTSR in patients with WAD affects response to painful stimuli, further conclusions cannot be drawn out of these results. Still, the presented data indicate that a study designed to examine this phenomenon is warranted.

It should be noted that the present study used fingertip photoplethysmography to obtain HRV data. Although this technique generates reliable data (48), it is sensitive to movement artifacts. Therefore similar research using electrocardiogram to assess HRV is warranted to further explore the role of the autonomic nervous system in patients with chronic WAD. Further the present study investigated the autonomic response to a stress caused by pain. Further exploration of autonomic nervous system reactivity by a wide range of stress stimuli in combination with a focus on post-traumatic stress might present interesting insight into the complex mechanisms of chronic WAD.

## Conclusion

In conclusion, the autonomic response to painful stimuli does not differ between patients with chronic WAD and healthy controls. The autonomic nervous system activity or reactivity to acute pain appears unrelated to either pain thresholds or endogenous analgesia in patients with chronic WAD. Further research is warranted to study in depth the preliminary findings of reduced sympathetic reactivity to pain in the subgroup of patients with chronic WAD suffering from moderate and severe PTSR.

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