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INCREASED PAIN SENSITIVITY IN ACCIDENT-RELATED CHRONIC PAIN PATIENTS WITH COMORBID POSTTRAUMATIC STRESS

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ABSTRACT

Objectives: Posttraumatic stress disorder (PTSD) is prevalent in chronic pain, and associated with increased pain, hyperalgesia and psychological distress. This study aimed to investigate anti-nociceptive and pro-nociceptive pain mechanisms, pain intensity, and psychological distress (depression, anxiety, pain catastrophizing, and fear of movement) in patients with accident-related chronic spinal pain with (N=44) and without (N=64) comorbid PTSD characteristics.

Methods: Cuff algometry was performed on lower legs to assess pressure pain threshold (cPPT), tolerance (cPTT), temporal summation of pain (TSP: increase in pain scores to ten repeated stimulations), and conditioning pain modulation (CPM: increase in cPPT during cuff pain conditioning on the contralateral leg). Warmth detection threshold (WDT) and heat pain threshold (HPT) at the hand were also assessed. Clinical pain intensity (numerical rating scale), psychological distress, and PTSD symptomatology (ICD-11) were assessed with questionnaires. Mediation analyses were performed to investigate possible psychological mediators in the associations between PTSD and pain (intensity and mechanisms).

Results: Patients with PTSD demonstrated increased pain intensity, and psychological distress as well as reduced WDT and cPTT compared with patients without PTSD ($P < 0.05$). No significant differences in cPPT, HPT, TSP and CPM were found. The association between PTSD and pain intensity was mediated by pain catastrophizing, and fear of movement mediated the association with cPTT.

Discussion: The association between PTSD and pain intensity is in accordance with the mutual-maintenance and fear-avoidance models. Future studies should investigate changes in pain intensity and mechanisms after treatment targeting comorbid PTSD in chronic pain patients.

Keywords: PTSD, experimental pain sensitivity, clinical pain, trauma, cuff algometry

1. INTRODUCTION

Chronic pain following trauma is the second most prevalent chronic pain condition after musculoskeletal pain [1]. Specifically the involvement in a motor vehicle accident confers an increased risk of chronic pain [2]. In addition to chronic pain, individuals are at increased risk for developing posttraumatic stress disorder (PTSD) [3, 4], and motor vehicle accidents have been estimated as the single most significant cause of PTSD [5]. Although estimated prevalence rates of PTSD in chronic pain patients may vary across studies, prevalence rates are found to be considerably higher [6-8] compared with the general population [9]. This suggests that chronic pain and PTSD may be intrinsically linked, and interact in a way that negatively impacts the course of either condition.

Chronic pain patients with co-morbid PTSD report higher levels of pain, psychological distress, and functional disability compared with chronic pain patients without PTSD [10-13]. Although it is difficult to determine a causal relationship between PTSD and chronic pain, both cognitive and sensitized pain mechanisms have been suggested to be important factors in the development and maintenance of chronic pain [14]. The mutual maintenance model [15] outlines how PTSD and pain may be mutually maintained by attention bias, anxiety, negative affect, and avoidance behaviours. Furthermore, it was recently demonstrated that the association between PTSD and pain in whiplash patients was mediated by pain catastrophizing and fear of movement [16] which are the key cognitive elements in the fear-avoidance model [17]. Moreover, a previous study demonstrated that whiplash patients with moderate to severe persistent pain and disability at 6 months post-injury were characterised by a complex clinical profile involving widespread hyperalgesia, high levels of post-traumatic stress symptoms, and generalised psychological distress [18]. Importantly, symptoms were present within one month post-injury and remained unchanged at 2-3 years follow up [18]. Furthermore, longitudinal studies using cross-lagged panel analyses have

demonstrated a significant influence of PTSD symptoms on pain intensity and vice versa within the first 6 months after traumatic injury, while PTSD symptoms significantly influenced pain intensity and not the other way around after 6 months post-injury [19, 20]. In line with this, Andersen et al. demonstrated that hypersensitivity to cold and hyposensitivity to brush stimulations were significantly correlated with PTSD severity in a sample of chronic pain patients [21]. Finally, research suggests that patients with chronic combat-related and terror-related PTSD display a unique experimental sensory profile of hyposensitivity to heat pain and hypersensitivity to pain above the pain threshold [22]. Thus, chronic pain patients with comorbid PTSD may have altered sensory perception, albeit the nature of sensory abnormalities remains unclear. In addition, central pain mechanisms like temporal summation of pain (TSP) and conditioned pain modulation (CPM) in patients with accident-related chronic pain with and without comorbid PTSD have not previously been investigated.

The primary aim of this study was to investigate the clinical pain profile, anti-nociceptive and pro-nociceptive pain mechanisms, and psychological distress in patients with accident related chronic spinal pain with and without comorbid PTSD. Secondary aim was to explore whether significant associations between PTSD and pain (intensity and mechanisms) in fact were explained or mediated by psychological factors, as indicated by the mutual-maintenance model and the fear-avoidance model. It was hypothesized that chronic pain patients with comorbid PTSD compared with patients without PTSD demonstrated 1) increased pain intensity and psychological distress, 2) increased pain sensitivity, facilitated temporal pain summation and impaired conditioning pain modulation, and 3) that the significant associations between PTSD and pain (intensity and mechanisms) were mediated by depression, anxiety, pain catastrophizing and fear of movement.

2. MATERIALS AND METHODS

2.1 Patients

This cross-sectional study included 108 patients (mean age: 45.7 years [range: 20-81]; 58 women) whom were referred to interdisciplinary pain treatment due to accident-related chronic spinal pain. Inclusion criteria were 1) Danish speaking women (non-pregnant) and men who 2) reported pain primarily located in the spine (lumbar, thoracic or cervical) for a minimum of 6 months following a traffic accident, and 3) reported that the onset of pain was associated with the traffic accident. Patients were specifically asked whether the current pain condition was related to the accident, and only patients who indicated a direct relationship was included in the study. The study was approved by the local ethical committee (S-20140010), all patients provided written informed consent and all procedures followed the Helsinki declaration. Approximately one third of patients included in this study were included in a previous study [23] investigating subgroups based on pain modulatory phenotypes in patients with chronic pain.

2.2 Procedure

After referral to the pain clinic, pain sensitivity was assessed in all patients by the same experienced male assessor. Assessments of pressure pain sensitivity, TSP and CPM were performed on the lower leg, and assessment of heat pain sensitivity was performed on the left hand. The same order was used for all patients (Fig. 1). Prior to assessments; patients were thoroughly introduced to the pain testing procedures by illustrations as well as verbal instructions. The pain sensitivity assessments lasted between 20 and 30 minutes and were performed with the patient seated with arms resting on the thighs.

Demographics including age, gender, and body mass index (BMI), as well as clinical pain manifestations were collected via an electronic software system (PainData, Denmark). The following pain related data was collected: Duration of pain, use of analgesics, pain intensity for

average clinical pain on a 0-10 numerical rating scale (NRS) with 0 defined as “no pain” and 10 “as worst imaginable pain” during the previous 24 hours [24]. Moreover, levels of psychological distress was recorded: anxiety (Generalized Anxiety Disorder, GAD-7) [25], depression (Patient Health Questionnaire, PHQ9) [26], pain catastrophizing (Pain Catastrophizing Scale (PCS) [27], and fear of movement (Tampa Scale of Kinesiophobia, TSK) [28].

2.3. Subgrouping based on PTSD symptomatology

Patients were divided into two groups (Pain/PTSD and Pain/No-PTSD) depending on whether or not they met the criteria for PTSD in relation to the accident-related trauma. PTSD was assessed using the ICD-11 Trauma Questionnaire, Part 1 [29]. The questionnaire includes 7 items relating to the core clusters of PTSD as outlined by the ICD-11 model; re-experiencing (3 items), avoidance (2 items), and sense of threat (2 items). Using a 5-point Likert scale, ranging from 0 (“not at all”) to 4 (“extremely”) each item is assessed in relation to how much the patient has been bothered by that item during the last month. The ICD-11 criteria of PTSD is met if patients endorse at least one symptom within each of the three clusters, as indicated by scores ≥2. An a priori power analysis determined that 45 participants per group were required to examine a potential difference in pain intensity and pain mechanisms between the two groups with a power of 0.80, alpha ≤ 0.05 and a moderate to large effect size (d = 0.60).

Recently, the validity of the ICD-11 model has been assessed across seven different trauma samples in Denmark demonstrating that the factor structure was valid across multiple trauma types and possessed good concurrent validity [30]. Additionally, the ICD-11 model provided an excellent model of fit in six of the seven trauma samples. Previous studies have demonstrated that the use of self-report measures and clinical interviews may be comparable when identifying the presence of PTSD in patients following motor vehicle accidents [31].

2.4 Assessment of pressure pain thresholds and tolerance

Pressure pain threshold (cPPT) and pressure pain tolerance (cPTT) on the left lower leg was assessed by computer-controlled cuff algometry (Nocitech, Denmark and Aalborg University, Denmark) [32]. A 13-cm wide silicone tourniquet cuff (VBM, Sulz, Germany) was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The rate of the cuff pressure increase was 1 kPa/s and the maximal pressure was 100 kPa. Air was supplied from an external air tank to avoid loud noises from the cuff system during assessment. Patients were instructed to continuously rate their pressure-induced pain intensity via an electronic visual analogue scale (VAS) from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was perceived as intolerable. Zero and 10 cm extremes on the VAS were defined as "no pain" and as "maximal pain", respectively. The pressure value, when the patient rated the sensation of pain as 1 cm on the VAS was defined as cPPT, and when the patient terminated the pressure inflation, the pressure value was defined as the cPTT. The VAS score of the pain intensity when patients terminated the pressure inflation was also extracted (VAScPTT). Pressure pain assessments were repeated twice and the averages of cPPT and cPTT, respectively, were calculated. Computer-controlled cuff algometry has previously demonstrated good test-retest reliability in patients with chronic pain [33] and healthy subjects [34, 35].

2.5 Assessment of temporal summation of pressure pain

Temporal summation of pain (TSP) was assessed 1 min after the first assessment of cPPT and cPTT. Ten repeated cuff pressure stimulations with an intensity equivalent to the cPTT and with duration of 1 s were delivered. This intensity was chosen to ensure that the first stimulation was perceived as painful although not extremely painful due to the short stimulation time. In the period between stimuli (1 s) a constant non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. During the sequential stimulation, patients rated their pressure pain intensity on the

electronic VAS without returning it to zero between stimulations. The VAS score immediately after each stimulus was extracted and the mean VAS scores were calculated for stimulation 1-4 (VAS-I), stimulations 5-7 (VAS-II), and stimulations 8-10 (VAS-III). TSP was calculated as the ratio between VAS-III and VAS-I, with values above 1 indicating an increase in VAS score during the sequential stimulation. This method has previously demonstrated good test-retest reliability in patients with chronic pain [33] and in healthy subjects [35].

2.6 Assessment of conditioned pain modulation

Conditioned pain modulation (CPM) was assessed 3 min after the second assessment of cPPT and cPTT. The conditioning stimulus was delivered by a 7.5 cm wide silicone tourniquet cuff (VBM, Sulz, Germany) wrapped around the right lower leg. This cuff was mounted 8 cm below the tibial tuberosity. The cuff was inflated to 30 kPa within 1 s and the pressure was kept constant throughout the CPM protocol for a maximum of 100 s. This intensity was chosen to ensure that the conditioning intensity was above cPPT and thus would be perceived as moderately painful as recommended [41]. Five seconds after the conditioning stimulation began, the test stimulus cuff on the left leg was inflated with a rate of 1 kPa/s as described above and the cPPT and cPTT were reassessed. Patients were instructed that the conditioning would be moderately painful and that they should focus their attention on the test stimulus on the left leg. The CPM response was defined as the percentage change in test stimulus (cPPT) recorded during conditioning compared with baseline assessments of cPPT with positive values indicating a hypoalgesic response.

2.7 Assessment of warmth detection and heat pain thresholds

Warmth detection threshold (WDT) and heat pain threshold (HPT) at the thenar eminence of the left hand was assessed by a computer-controlled contact thermal stimulator (MSA Thermal Stimulator, SENSELab, Somedic Sales AB, Hörby, Sweden) with a thermode covering a 25x50 mm skin area. The baseline temperature was 32°C and increased by 1.0°C/s to a maximum of 50°C. Patients were

instructed to press a handheld switch as soon as they detected a change in warmth sensation (WDT). After assessment of WDT, HPT was assessed. Patients were instructed to press the handheld switch as soon as the heat sensation was defined as the first sensation of pain. The peak temperature was stored and the thermode decreased its temperature (3.0°C/s) to the baseline temperature. Test stimuli were repeated three times and the averages of WDT and HPT, respectively, were calculated.

2.8 Statistics

Data are reported as means and standard deviations (SD). All statistical analyses were run in SPSS Statistics (Version 21; IBM, Armonk, NY, USA). First, the proportion of gender and use of analgesics (yes/no) between the two groups (Pain/PTSD and Pain/No-PTSD) were analyzed by Chi-square test. No significant difference in distribution of women and men between the groups was found. However, due to significant differences between women and men in several pain related variables [23], all variables were gender-adjusted by z-transformation by subtraction of the mean values divided by the standard deviation (SD) for women and men, respectively. Potential differences in demographics, clinical pain intensity (NRS scores), pain mechanisms (cPPT, cPTT, TSP, CPM), and psychological distress between groups (with and without PTSD) was analyzed by independent t-test. *P*-values less than 0.05 were considered significant. Effect sizes of the group differences were calculated based on Hedges' g, due to dissimilar group sizes. Effects sizes were evaluated as small (g = 0.20), medium (g = 0.50), and large (g = 0.80). Pearson's correlations were used to determine the relationship between the z-scores of pain intensity, pain mechanisms and psychological distress. Due to multiple correlational analyses, P-values equal to or less than 0.001 (0.05 / 34) were considered significant for the correlations.

To assess possible psychological mediators in the associations between PTSD and pain (intensity and mechanisms), significant group differences (PTSD vs. no PTSD) in pain intensity and mechanisms parameters were further assessed by mediation analyses. Multiple

mediation models were specified and estimated using the Preacher and Hayes macro process (model 4) for SPSS based on maximum likelihood estimation and 5000 bootstrap draws [36]. The analyses estimated the direct effect of PTSD on pain (intensity and mechanisms) and the indirect effect mediated by levels of depression, anxiety, pain catastrophizing, and fear of movement (Fig. 2). Moreover, due to significant difference in pain intensity between groups and the potential relationship between pain intensity and pain mechanisms [23], clinical pain intensity was included as a covariate in the multiple mediation model estimating the direct effect of PTSD on pain mechanisms. The following terms were used for the different pathways: path "A" was the effect of the independent variable (IV) on the mediators (MedVs); path "B" was the effect of the mediators on the dependent variable (DV), controlling for the independent variable (MedVs to DV, controlling for IV); the "total effect" (path C) was the relationship between PTSD and pain (intensity and mechanisms); the "indirect effect" (A*B) was the effect of PTSD on pain (intensity and mechanisms) via the mediators; the "direct effect" (C') was the effect of PTSD on pain intensity/mechanisms adjusted for the mediators. Full mediation was evident when 1) path A and path B was significant, 2) path C was statistically significant, but become non-significant after adjusting for the mediator (C'), and 3) the indirect effect (A*B) was significant represented as the 95% confidence interval not including zero. The strength of the mediation was represented as the difference in the estimated path C and path C', and the percentage mediated by the mediators was calculated as 1 - (C'/C). Findings from the mediation analyses were reported as unstandardized regression coefficients.

3. RESULTS

3.1 Group demographics

In total, 108 patients with accident-related chronic spinal pain were assessed and further classified with comorbid PTSD (n=44) and without PTSD (n=64). Table 1 illustrates demographics in the two

groups. No significant difference was found in distribution of women and men between groups ($X^{(1)}$ = 0.061, P = 0.81). Furthermore, no significant differences were found for age (t-test: P = 0.35) or BMI (t-test: P = 0.28) between groups.

3.2 Clinical pain characteristics

There was a significant difference in pain intensity between groups with higher pain intensity scores in the PTSD group compared with the non-PTSD group (Table 1; t-test: P = 0.03). Pain duration was not significantly different between groups (t-test: P = 0.57), and no significant differences in use of analgesics were found ($X^{(1)} < 2.1$, P > 0.14).

3.3 Psychological distress

Patients with PTSD had significantly higher scores of depression, anxiety, pain catastrophizing, and fear of movement compared with patients without PTSD (Table 1; t-test; P < 0.02).

3.4 Experimental pain sensitivity

All patients tolerated and completed the pain sensitivity assessments. There was a significant difference in cPTT between groups with lower pressure pain tolerance in the PTSD group compared with the non-PTSD group (Table 1; t-test: P = 0.02). The cPPT had a tendency for being decreased in the PTSD group compared with the non-PTSD group (t-test: P = 0.07). Moreover, the WDT was significantly increased in the PTSD group compared with the non-PTSD group (t-test: P = 0.02). No significant differences were found for the heat pain threshold (HPT), TSP, and CPM (t-test: P > 0.3) between the PTSD and non-PTSD groups.

3.5 Associations between pain intensity, pain mechanisms, and psychological distress

Associations between pain intensity, pain mechanisms, and the psychological variables are presented in Table 2. Significant positive correlations were found between pain intensity and pain catastrophizing (r = 0.36, P < 0.001), and between pain intensity and fear of movement (r = 0.37, P < 0.001), indicating that patients with higher levels of maladaptive pain beliefs reported higher

levels of clinical pain. A significant negative correlation was also found between pain intensity and HPT (r = -0.31, P = 0.001), indicating that patients with higher levels of clinical pain had reduced heat pain threshold.

3.6 Mediation of psychological factors on the association between PTSD and pain intensity

The total effect (C) of PTSD on pain intensity was significant (Table 3). When the effects of the mediators were included in the model, the direct path (C') turned non-significant, indicating full mediation. However, only pain catastrophizing was significant and accounted for 70.5% of the total effect. Depression, anxiety and fear of movement did not significantly mediate the association between PTSD and pain intensity.

3.7 Mediation of psychological factors on the association between PTSD and pain mechanisms

The total effect (C) of PTSD on cPTT was significant (Table 4). When adjusting for clinical pain intensity, the association between PTSD and cPTT was fully mediated by fear of movement, which accounted for 45.0% of the total effect. Pain intensity, depression, anxiety, and pain catastrophization did not significantly mediate the effect of PTSD on cPTT. No mediation was found in relation to WDT.

4. DISCUSSION

This study is the first to explore pain intensity, pain sensitivity, and pain facilitatory and inhibitory modulatory mechanisms in a cohort of accident-related chronic spinal pain patients with and without comorbid PTSD where the chronic pain condition and PTSD is related to the same traumatic event. Pain intensity and psychological distress was increased in patients with comorbid PTSD, and the association between PTSD and pain intensity was mediated by pain catastrophizing, which could suggest that the effects of PTSD on pain intensity are partly attributed to the way patients with PTSD cognitively interpret and respond to their clinical pain.

Pressure pain tolerance was reduced in patients with comorbid PTSD, however, despite increased pain intensity and psychological distress, the association between PTSD and pain tolerance was only mediated by fear of movement. Moreover, warmth detection threshold was increased in patients with PTSD, and no significant mediation by pain intensity and the psychological factors tested was found potentially indicating a more direct link between PTSD and non-noxious heat stimulation. Finally, no significant differences were found for TSP and CPM. Moreover, to our knowledge, the present study is the first study testing potential mediators related to both clinical and experimental pain sensitivity in the same sample. The finding that only clinical pain intensity is mediated by pain catastrophizing, indicate that facilitated pain sensitivity may be more related to the avoidance cluster of PTSD, which adds important knowledge about the association between PTSD, pain intensity and pain mechanisms in the context of chronic pain rehabilitation.

4.1 Clinical pain intensity

Clinical pain intensity and psychological distress was increased in patients with PTSD. These findings are in agreement with previous studies demonstrating higher levels of pain and psychological distress in pain patients with comorbid PTSD [10-13]. The association between PTSD and pain intensity was mediated by pain catastrophizing. These results are in agreement with recent studies [16, 37] and in support of PTSD as an important mechanism in the fear-avoidance model for patients with accident-related pain. The mediating role of the cognitive elements of the fear-avoidance model could indicate that the effect of PTSD on pain intensity to some extend is explained by similar cognitive mechanisms of PTSD, such as avoidance of reminders of the trauma. Also, when pain and PTSD is the result of the same traumatic event, trauma reminders, whether related to pain or the traumatic event may fuel catastrophic thinking and thereby negatively affect both conditions [38]. Although no information was collected on previous trauma history or other

chronic pain conditions, patients were specifically asked to indicate whether the onset of their current pain was related to the motor vehicle accident and the questions in the ICD-11 was specifically asked in relation to that accident suggesting that pain and PTSD was related to the same traumatic event in this sample. Mechanisms related to hyperarousal may also negatively affect both clinical and experimental pain sensitivity. For instance, the perceptual avoidance model outlines how PTSD re-experiencing triggers hyperarousal, which in turn exacerbate pain through muscle tension and avoidance behaviours [38]. The finding that depression and anxiety did not mediate the effect of PTSD on pain intensity might suggest that the present effect is more related to the phenomenology of PTSD than general distress.

The results from this study suggest that chronic pain and comorbid PTSD may be targeted by multidisciplinary pain rehabilitation that often aims to reduce catastrophic thinking. However, more studies are needed to establish whether standard pain rehabilitation programs, endorsing relaxation techniques, mindfulness, cognitive restructuring and activity regulation, are sufficient in treating chronic pain and comorbid PTSD [39].

4.2 Experimental pain sensitivity

PTSD patients demonstrated increased warmth detection threshold (hypoesthesia) compared with patients without PTSD, which is in accordance with a previous study on chronic pain patients with comorbid PTSD [22]. The increased warmth detection threshold in patients with possible PTSD could be related to dissociation such as depersonalization, which is a central defence mechanism of PTSD acting as an escape from the external environment and internal distress or arousal [40]. Also poor concentration [41] may have affected the response time during assessment with heat stimulus. Furthermore, PTSD patients showed reduced pressure pain tolerance (increased pain sensitivity) indicating a combination of reduced and increased sensory perception in pain patients with pain and PTSD. The results of the mediation model indicate that patients with PTSD are avoidant and that

the avoidance is causally related to the increased pain sensitivity. In line with the fear-avoidance model, avoidance behaviours may lead to increased pain sensitivity. Surprisingly, the association between changes in sensory perception and PTSD was not mediated by pain intensity or any other psychological factors. As no significant differences in pressure or heat pain thresholds were found, the increased pain sensitivity in patients with comorbid PTSD does not appear to be related to peripheral sensitization. Since no significant differences in pain thresholds for the deeper tissues (pressure) and the skin (heat) were demonstrated, these findings indicate that the mechanisms underlying the influence of PTSD on pain perception and vice versa could be related to differences in pain perception above the pain threshold. This is supported by the significant difference in pain tolerance which is manifested with more painful stimuli and the pain tolerance measure could be more related to pain coping strategy than nociception. In addition, despite different pain tolerances between group, no significant differences in pain modulatory characteristics derived based on the TSP-ratio and the CPM-response were found, suggesting that assessment of these central anti-nociceptive and pro-nociceptive mechanisms by cuff algometry are robust and not significantly influenced by PTSD or psychological distress in this cohort. This could indicate that PTSD in addition to chronic pain does not further facilitate central pain mechanisms, which is in agreement with the findings from Defrin and colleagues [22]. Similarly, the CPM protocol demonstrated robust increases in pressure pain threshold in both groups compared with previous findings [23, 34], suggesting that PTSD in addition to chronic pain does not further impair descending pain inhibitory mechanisms. The CPM response has not previously been studied in patients with chronic pain and comorbid PTSD.

4.3 Limitations

Several limitations should be considered in the interpretation of the results. First, the cross-sectional design is a major limitation, as judgement on causality and definite directions of the associations

cannot be made. It may be that increased pain intensity and pain-related cognitions (pain catastrophizing and fear of movement) influences patterns of thinking and behaviour potentially increasing the presence of the core clusters of PTSD. However, the mediation analysis, driven by sound theoretical models allow for some inferences about causality. Moreover, the absence of a structured clinical interview for PTSD was a limitation in the current study. A healthy control group was not included since significant differences could be expected in experimental pain sensitivity due to on-going clinical pain, and psychological distress by itself. Further research in this area is warranted, taking differences in ongoing pain and psychological distress between patients with chronic pain and healthy controls into account. No information was collected on previous trauma history (e.g. childhood trauma) or other chronic pain conditions prior to the motor vehicle accident and it was not assessed whether patients did have experience with any previous chronic pain episodes prior to the current condition, which could influence future development of mood disorders and maladaptive cognitions. Finally, the results could be limited by the relative small group sample sizes potentially affecting statistical power and based on the cross-sectional explorative approach of this study the multiple t-tests between groups may induce a risk of false positive results. Larger studies should confirm the findings of this study.

4.4 Conclusion

Patients with pain and PTSD demonstrated increased clinical pain intensity and psychological distress as well as reduced pressure pain tolerance compared with pain patients without comorbid PTSD. The association between PTSD and pain intensity was mediated by pain catastrophizing whereas the associations between PTSD and pressure pain tolerance was mediated by fear of movement. Future studies should investigate changes in pain intensity and mechanisms after treatment targeting comorbid PTSD in patients with chronic pain.

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Figure Legends

Fig. 1: Experimental procedure. Cuff pressure pain threshold (cPPT), pressure pain tolerance (cPTT), temporal summation of pressure pain (TSP) and conditioned pain modulation (CPM) were assessed with cuff algometry on the left lower leg. Warmth detection threshold (WDT) and heat pain threshold (HPT) was assessed on the left hand.

Fig 2: Multiple mediator model, where the variable 'C path' illustrates the relationship between PTSD and pain (intensity and mechanisms); the variable 'A path' illustrates the relationship between PTSD and the mediators, and the variable 'B path' illustrates the relationship between the mediators and pain (intensity and mechanisms). The "indirect effect" (A*B) was the effect of PTSD on pain (intensity and mechanisms) via the mediators; the "direct effect" (C') was the effect of PTSD on pain intensity/mechanisms adjusted for the mediators. Full mediation was evident when 1) 'A path' and 'B path' was significant, 2) 'C path' was statistically significant, but became non-significant after adjusting for the mediator (C'), and 3) the indirect effect (A*B) was significant represented as the 95% confidence interval not including zero. The strength of the mediation was represented as the difference in the estimated 'C path' and 'C' path', and the percentage mediated by the mediators was calculated as 1 - (C'/C).

Table 1. Demographics, clinical pain profile, psychological distress, and experimental pain sensitivity in chronic trauma-related spinal pain patients with and without comorbid PTSD. P-values from independent t-tests are based on gender-adjusted (z-transformed) values. 'BMI': Body Mass Index. 'NRS': Numerical Rating Scale. 'GAD7': Generalized anxiety disorder. 'PHQ9': Patient health questionnaire. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia. 'WDT': Warmth Detection Threshold. 'HPT': Heat Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance. 'VAScPTT': VAS score at cPTT. 'TSP': Temporal summation of pressure pain. 'CPM': Conditioned pain modulation.

Domain	Variable	Total (n=108)	Spinal pain with PTSD (n=44)	Spinal pain without PTSD (n=64)	P-value	Effect size (Hedge's g)
Demographics	Gender (Women/Men)	58/50	23/21	35/29	0.81	-
	Age (years)	45.7±11.6	44.5±11.5	46.±11.7	0.35	-
	BMI (kg/m^2)	27.1±5.0	27.9±6.3	26.7±4.0	0.28	-
Clinical pain	Pain duration (years)	7.5±9.1	6.9±8.0	8.0±9.9	0.57	0.12
	Clinical pain intensity (NRS: 0-10)	6.7±1.6	7.1±1.9	6.4±1.2	0.026	0.46
	Opioid users (Y/N)	52/56 (48.1%)	21/23 (47.7%)	31/33 (48.4%)	0.94	-
	Antidepressant users (Y/N)	26/82 (24.1%)	11/33 (25.0%)	15/49 (23.4%)	0.85	-
	Anticonvulsive users (Y/N)	25/83 (23.1%)	13/31 (29.5%)	12/52 (18.8%)	0.19	-
	NSAID users (Y/N)	23/85 (21.3%)	8/36 (18.2%)	15/49 (23.4%)	0.51	-
	Paracetamol users (Y/N)	74/34 (68.5%)	26/18 (59.1%)	48/16 (75.0%)	0.08	-
	Muscle relaxants (Y/N)	26/82 (24.1%)	11/33 (25.0%)	15/49 (23.4%)	0.85	-
Psychological distress	Anxiety (GAD7: 0-21)	7.8±5.1	10.9±5.0	5.8±4.0	<0.001	1.20
	Depression (PHQ9: 0-27)	10.5±5.8	12.2±6.0	9.3±5.4	0.011	0.65
	Pain Catastrophizing (PCS: 0-52)	25.4±10.5	31.8±9.8	21.0±8.6	<0.001	1.18
	Fear of movement (TSK: 17-68)	42.1±8.4	46.2±9.2	39.6±6.8	<0.001	0.83
Experimental pain sensitivity	WDT Hand (32-50°C)	34.9±1.3	35.3±1.5	34.7±1.1	0.017	0.46
	HPT Hand (32-50°C)	43.0±3.9	42.6±4.2	43.3±3.8	0.33	0.18
	cPPT (0-100 kPa)	23.1±11.4	21.1±9.7	24.5±12.2	0.07	0.30
	cPTT (0-100 kPa)	51.3±21.4	46.7±19.9	54.4±21.9	0.024	0.36
	VAScPTT (VAS: 0-10 cm)	8.8±1.9	8.8±1.9	8.8±1.8	0.97	0.00
	TSP (ratio VAS-III / VAS-I)	2.3±1.5	2.3±1.4	2.3±1.5	0.99	0.00
	CPM (% increase in cPTT)	24.5±37.3	21.6±43.4	26.5±32.7	0.45	0.13

Table 2: Pearson's correlations between pain intensity, pain mechanisms, and psychological distress. Due to multiple correlational analyses, P-values equal to or less than 0.001 (0.05 / 34) were considered significant. 'PHQ9': Patient health questionnaire. 'GAD7': Generalized anxiety disorder. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia. 'WDT': Warmth Detection Threshold. 'HPT': Heat Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance. 'TSP': Temporal summation of pressure pain. 'CPM': Conditioned pain modulation.

Variables	Correlation	Pain intensity	PHQ9	GAD7	PCS	TSK
Pain intensity	R P-value	-	0.17 0.08	0.16 0.10	0.36 <0.001	0.37 <0.001
PHQ9	R P-value	0.17 0.08	-	0.71 <0.001	0.68 <0.001	0.40 0.001
GAD7	R P-value	0.16 0.10	0.71 <0.001	-	0.75 <0.001	0.47 <0.001
PCS	R P-value	0.36 <0.001	0.68 <0.001	0.75 <0.001	-	0.54 <0.001
TSK	R P-value	0.37 <0.001	0.40 0.001	0.47 <0.001	0.54 <0.001	-
WDT	R P-value	0.03 0.74	0.08 0.45	0.22 0.03	-0.01 0.97	0.08 0.44
HPT	R P-value	-0.31 0.001	-0.13 0.21	-0.07 0.48	-0.19 0.06	-0.23 0.02
cPPT	R P-value	-0.06 0.54	0.09 0.37	-0.04 0.68	-0.08 0.46	-0.12 0.25
cPTT	R P-value	-0.11 0.26	<0.001 1.0	-0.07 0.46	-0.11 0.26	-0.26 0.01
TSP	R P-value	0.07 0.48	0.02 0.87	-0.12 0.24	-0.05 0.59	-0.06 0.58
CPM	R P-value	-0.03 0.75	-0.06 0.53	-0.03 0.79	-0.05 0.64	0.01 0.98

Table 3: Direct and indirect effects of PTSD on pain intensity (NRS: 0-10) mediated by depression, anxiety, pain catastrophizing, and fear of movement. 'Ratio': Percentage mediated by the significant mediators calculated as 1-(C'/C). 'NRS': Numerical Rating Scale. 'PHQ9': Patient Health Questionnaire. 'GAD7': Generalized Anxiety Disorder. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia.

Effect	Independent	Dependent	Standardized	*P*	R^2	Ratio
C path (total)	PTSD	Pain (NRS)	0.536	0.011	0.07	
Direct (*C'*)	PTSD (mediators)		0.296	0.227		45%
	(PHQ9)					
	(GAD7)					
	(PCS)					
	(TSK)					
A path	PTSD	PHQ-9	0.621	0.005	0.09	
B path	PHQ-9	Pain (NRS)	0.004	0.978		
Indirect (*A*B)*	PTSD-PHQ-9		0.002 [95% CI: -0.16:0.18]			
A path	PTSD	GAD-7	1.049	<0.001	0.26	
B path	GAD-7	Pain (NRS)	-0.276	0.057		
Indirect (*A*B)*	PTSD-GAD-7		-0.281 [95% CI: -0.72:-0.02]			
A path	PTSD	PCS	1.056	<0.001	0.26	
B path	PCS	Pain (NRS)	0.358	0.038		71%
Indirect (*A*B)*	PTSD-PCS		0.378 [95% CI: 0.09:0.78]			
A path	PTSD	TSK	0.792	<0.001	0.15	
B path	TSK	Pain (NRS)	0.188	0.120		
Indirect (*A*B)*	PTSD-TSK		0.149 [95% CI: -0.02:0.37]			

Table 4: Direct and indirect effects of PTSD on cPTT mediated by depression, anxiety, pain catastrophizing, and fear of movement. Clinical pain intensity was included as a covariate. 'Ratio': Percentage mediated by the significant mediators calculated as 1- (C'/C). 'NRS': Numerical Rating Scale. 'PHQ9': Patient Health Questionnaire. 'GAD7': Generalized Anxiety Disorder. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia.

Effect	Independent	Dependent	Standardized	*P*	R^2	Ratio
C path (total)	PTSD	Pain (cPTT)	-0.499	0.028	0.07	
Direct (*C'*)	PTSD (mediators)		-0.380	0.153		24%
	(PHQ9)					
	(GAD7)					
	(PCS)					
	(TSK)					
A path	PTSD	PHQ-9	0.538	0.019	0.11	
B path	PHQ-9	Pain (cPTT)	0.211	0.158		
Indirect (*A*B)*	PTSD-PHQ-9		0.113 [95% CI: -0.01:0.40]			
A path	PTSD	GAD-7	1.050	<0.001	0.25	
B path	GAD-7	Pain (cPTT)	-0.080	0.611		
Indirect (*A*B)*	PTSD-GAD-7		-0.083 [95% CI: -0.60:0.28]			
A path	PTSD	PCS	0.944	<0.001	0.31	
B path	PCS	Pain (cPTT)	0.082	0.662		
Indirect (*A*B)*	PTSD-PCS		0.077 [95% CI: -0.28:0.49]			
A path	PTSD	TSK	0.681	<0.001	0.22	
B path	TSK	Pain (cPTT)	-0.332	0.013		45%
Indirect (*A*B)*	PTSD-TSK		-0.226 [95% CI: -0.50:-0.06]