Journal of Behavioral and Brain Science, 2022, 12, 359-379
https://www.scirp.org/journal/jbbs
ISSN Online: 2160-5874
ISSN Print: 2160-5866

The Differing Effects of Nociception and Pain Memory on Pain Thresholds in Participants with and without a History of Injury: A Pretest-Posttest Quasi Experimental Study

Derrick G. Sueki[1*], Kim Dunleavy[2], Emilio J. Puentedura[3], Lindsey Heard[4], Peter Van der Heide[5], Ming-Shun Cheng[6]

[1]Department of Physical Therapy, Azusa Pacific University, Azusa, USA
[2]Department of Physical Therapy, University of Florida, Gainesville, USA
[3]Department of Physical Therapy, Baylor University, Waco, USA
[4]Scripps Memorial Hospital, Encinitas, USA
[5]Amigo Baby, Oxnard, USA
[6]Department of Physical Therapy, Nova Southeastern University, Fort Lauderdale, USA
Email: *dsueki@apu.edu

How to cite this paper: Sueki, D.G., Dunleavy, K., Puentedura, E.J., Heard, L., Van der Heide, P. and Cheng, M.-S. (2022) The Differing Effects of Nociception and Pain Memory on Pain Thresholds in Participants with and without a History of Injury: A Pretest-Posttest Quasi Experimental Study. *Journal of Behavioral and Brain Science*, **12**, 359-379.
https://doi.org/10.4236/jbbs.2022.128021

Received: June 20, 2022
Accepted: August 7, 2022
Published: August 10, 2022

Abstract

Purpose: Memory has been identified as an important protective feature to prevent future injury, but its role has yet to be ascertained. The current study aimed to determine whether there was a difference in pressure pain threshold (PPT) responses between participants with a prior history of injury of lower extremity injury (PSI) and those without (NPSI) when exposed to 1) experimental mechanical pain, 2) short-term memory recall of a painful stimulus, or 3) long-term memory of the pain associated with a prior injury. Subjects and Methods: The study used a pretest-posttest quasi-experimental design. A convenience sample of 59 pain-free participants was recruited from an urban university. Twenty-nine PSI and 30 NPSI were stratified into two groups based on their injury history with PPT values measured at baseline and immediately following each of the three experimental conditions. A repeated measure ANCOVA analysis was conducted for each condition to determine whether there was a difference in PPT responses between the two groups. Results: There was a statistically significant difference in PPT values between the two groups when exposed to experimental pain, $F(1,57) = 6.010$, $p = 0.017$, partial $\eta^2 = 0.095$ and with long-term pain memory, $F(1,57) = 4.886$, $p = 0.031$, partial $\eta^2 = 0.079$. There was no statistically significant difference between groups with short-term pain memory, $F(1,57) = 3.925$, $p = 0.052$,

partial η^2 = 0.064. Conclusions: These findings suggest that pain processing may be altered by pain memory, highlighting the role of experience and memory in the rehabilitation process.

Keywords

Pain Memory, Nociception, Pressure Pain Threshold, Pain Perception, Pain Learning

1. Introduction

Pain is a behavioral mechanism designed to warn of actual or perceived damage [1] [2]. It is a personal sensory experience learned through life events and warns of actual or perceived injury or tissue damage [3] [4]. Ingrained in this definition is recognizing pain as both a reactive response and a predictive mechanism designed to shape current and future protective reactions [5] [6]. Pain memory, or the memory that individuals store about past painful events, is an essential component of the ability to protect, predict and warn of potential danger, threat, or damage. It guides future responses when conditions are comparable to those present during the original injury or instance.

Prior injuries and exposure to pain can alter subsequent pain responses, with pain memory being identified as a factor in the modulation of pain perceptions [7] [8] [9] and a potential contributor to pain chronicity [10] [11]. The recognition that pain functions as a predictive protective response suggest that pain perception involves learning. This learning is complex and can occur both peripherally and centrally mechanisms for when tissue is injured, damaged, or threatened, nociceptive input is processed at multiple sites in the brain and body, but processing is not limited to nociception; sensory, interoceptive, contextual, and emotional information are all appraised along with nociception and compared with prior experience [12] [13]. Peripherally, changes can occur in synapses and neuronal transmission after a nociceptive stimulus. The long-term potentiation, hyperalgesia, and neuronal sensitization experienced after exposure to pain can be long-lasting, with researchers arguing that these neurophysiological changes represent forms of learning [14] [15]. Plastic changes occur in multiple brain regions, where initial physiological responses are cortically and subcortically reconciled with prior learned pain responses [16] [17]. These findings have led authors to suggest that pain memory and emotional learning are important factors in pain chronicity [7] [16] [17] [18]. Pain memories are used to adjust initial responses, and these responses are then encoded and stored for future reference. Pain perception relies on recalling these memories, reconciling experience with the current input, and responding conducive to the situation [2]. The neurophysiological responses associated with pain are shaped by peripheral factors, but research is increasingly demonstrating that they can be influ-

enced by conscious and subconscious cognitive, emotional, and environmental factors [19]-[26]. In this regard, pain is more than a simple reactive sensorial experience; instead, pain is predictive and is shaped by memories and learning from prior pain experiences.

It is well established that actual pain or nociception can alter pain thresholds [5] [6]. Pressure pain threshold (PPT) is a standard measure to assess pain perception changes for many pain conditions and interventions [27] [28] [29]. It represents the point at which a pressure stimulus changes from pressure to pain. When PPT decreases, pain can be felt with less pressure. The opposite is true; when PPT increases, pain perception diminishes. The modulation of pain in response to pain has been termed conditioned pain modulation (CPM) [30]. The literature suggests that CPM may indicate a physiological protective response [5] [6]. While varied responses occur, pain intensity will typically decrease and PPT increases during or after exposure to a painful stimulus [31] [32]. Prior research has used PPT to measure changes in pain perception for conditions such as osteoarthritis, [27] rheumatoid arthritis, [33] complex regional pain syndrome, [34] fibromyalgia, [35] low back pain, [28] shoulder pain, [29] headaches, [36] and whiplash injury [37]. The composite picture of these studies suggests that PPT can be used as a reliable and valid measure of pain perception and can measure differences between healthy subjects and those with pathology [38] [39] [40].

Despite the increasing recognition that pain extends beyond biological considerations and involves responses learned from prior experience, understanding the relationship between memory and pain perception continues to evolve [41] [42]. Growing evidence supports the role of learning in pain modulation [43] [44] [45]. In these studies, neutral stimuli were paired with pain. When the participants were re-exposed to the stimulus, higher pain levels were reported. Pain conditioning studies also suggest that implicit mechanisms are involved in pain modulation as stimulus introduced at subconscious levels of awareness can also produce changes in reported pain levels and pain threshold [46] [47]. Together, these findings indicate that learning and prior pain-related learning and memories can impact pain perception, where the pain is seen as an innate response to nociception [22]. Thereafter, associations are created between a stimulus and a pain-producing nociceptive event where the pain is a learned response that has become linked with the stimulus present at the time of pain.

The purpose of this study was, therefore, to investigate whether there was a difference in PPT responses between participants with or without a prior history of injury when exposed to experimental mechanical pain, short-term memory recall of the painful stimulus, or long-term memory of a prior painful lower extremity musculoskeletal injury. The research hypothesis is that both nociception and pain memories would result in anticipatory reductions in PPT and that individuals with a prior history of injury in an area would have a greater change in PPT than those with no history of injury in that area.

2. Materials and Methods

2.1. Research Design and Groupings

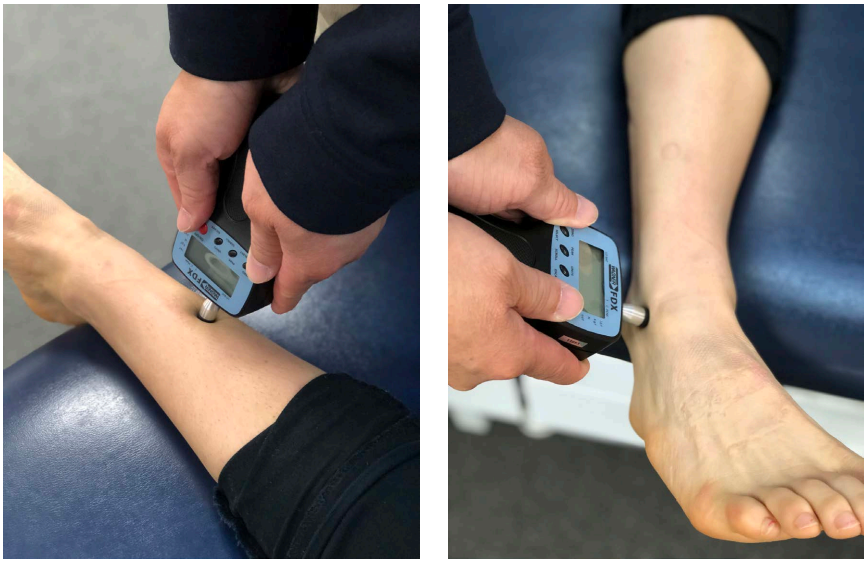
The Institutional Review Boards of Nova Southeastern and Mount Saint Mary's Universities approved the study and was conducted according to the Declaration of Helsinki. The results of the current article are part of a larger study that was registered with ClinicalTrials.org (#NCT02269384). Other aspects of the study will be reported in subsequent writings. The current study used a pretest-posttest quasi-experimental design structured to contrast individuals with 1) a history of prior substantial lower extremity injury (PSI) and 2) no history of substantial lower extremity injury (NPSI) allowing for a comparison of the responses of the two groups. There were two independent variables (IVs) and two dependent variables (DVs). The IVs were the history of injury and the experimental condition, and the DVs were time and PPT values. Participants in the PSI group experienced a severe injury in the lower extremity at least six months priorly (*i.e.*, fracture, ligament strain, surgery, trauma) that resulted in not walking or being required to use crutches for at least two weeks. These participants were matched for age and gender with participants from the NPSI group. Informed consent was obtained from all eligible and interested participants. Participants were informed of the study's purpose and objectives as part of the consent process.

2.2. Participants

A convenience sample of students and acquaintances was recruited from an urban university utilizing email, posted signage, and personal contacts. Inclusion criteria included healthy adults between 18 - 60 years old who were not experiencing any pain at the time of testing. A healthy adult in this study is defined as an individual with no self-reports of pain or functional limitations at the testing time. Exclusion criteria included acute injuries in the lower extremity occurring less than six months before the study, chronic pain in any body region, lower extremity open wounds, decreased sensation, or cognitive impairments. Participants with chronic pain were intentionally excluded from this study because this study sought to determine responses in participants that had a prior injury but no long reported pain.

2.3. Experimental Conditions and Outcome Measures

Three experimental conditions were applied to both groups: 1) experimental mechanical pressure pain (EMP) (**Figure 1(a)**), 2) short-term memory of the experimental mechanical pressure pain (STPM), and 3) long-term memory of the pain associated with a substantial prior injury (LTPM). Pressure pain threshold measured at the anterior talofibular (ATF) ligament was used as the outcome measure to determine the change in pain perception following each experimental condition. (**Figure 1(b)**) Testing PPT is a valid [38] measure of pain perception with a high test-retest reliability in musculoskeletal pain subjects



(a) (b)

Figure 1. (a) Application of experimental mechanical pressure pain stimulus. Pressure was placed at site of injury or a predesignated location until maximum tolerable level of pain was reached. Pressure was held for 10 seconds; (b) Testing of pressure pain threshold (PPT). PPT was tested at the anterior talofibular ligament of the involved leg immediately following intervention.

[39] [40]. The minimal detectable change (MDC) for PPT testing is 86.3 kPa (8.63 N/cm^2) [39] [40].

2.4. Study Procedures and Data Collection

Participants were stratified by the principal investigator into two groups based upon injury history: 1) PSI group or 2) NPSI group. A second investigator who was not involved in the testing procedure was tasked with measuring or recording outcome measures, and a third investigator was responsible for administering each experimental condition. Both the second and third investigators were blinded to the subject grouping. Before data collection, high test-retest reliability for the third investigator was established at the ATF ligament on five healthy participants not included in the final experimental data (ICC = 0.93, 0.46 - 0.99 95% CI).

Participants were positioned supine on a treatment table in a temperature-controlled lab room at an urban university. Two points were located and marked on each participant. The principal investigator palpated the prior substantially injured area locating and marking the most tender point in this area. The investigator also located and marked the ATF ligament on the side of the previous injury. In the NPSI group, a site corresponding with the location and side in the PSI group was predetermined. The most tender point was located and marked along with the ATF ligament within the identified area. At this point, the remaining two investigators entered the testing room, blinded to the participant grouping.

A baseline PPT value was collected at the ATF ligament for comparative purposes. To assess PPT, the 1-cm^2 tip of the Wagner Force Ten^{TM} FDX Pain Algometer was placed at a pre-marked anterior talofibular (ATF) ligament. (Figure 2) The pressure was slowly applied perpendicular to the ATF ligament at a rate of 50 kPa (5.0 N/cm^2) per second until the subject reported the initial onset of pain. This process was repeated two additional times with three minutes between tests. The mean value of the three responses was used as the baseline value. After collecting baseline data, participants were instructed to lie quietly for five minutes, after which they were exposed to each of the three experimental conditions. To assess PPT responses to acute experimental mechanical pressure pain (EMP), the 1-cm^2 tip of the Wagner Algometer was placed upon the prior injury area or the matched area of the control group. The participant was instructed to close their eyes and a maximum tolerable pressure pain was placed upon the area and held for 10 seconds. After 10 seconds, the stimulus was removed and PPT was assessed (Figure 1). To assess PPT responses to the short-term memory

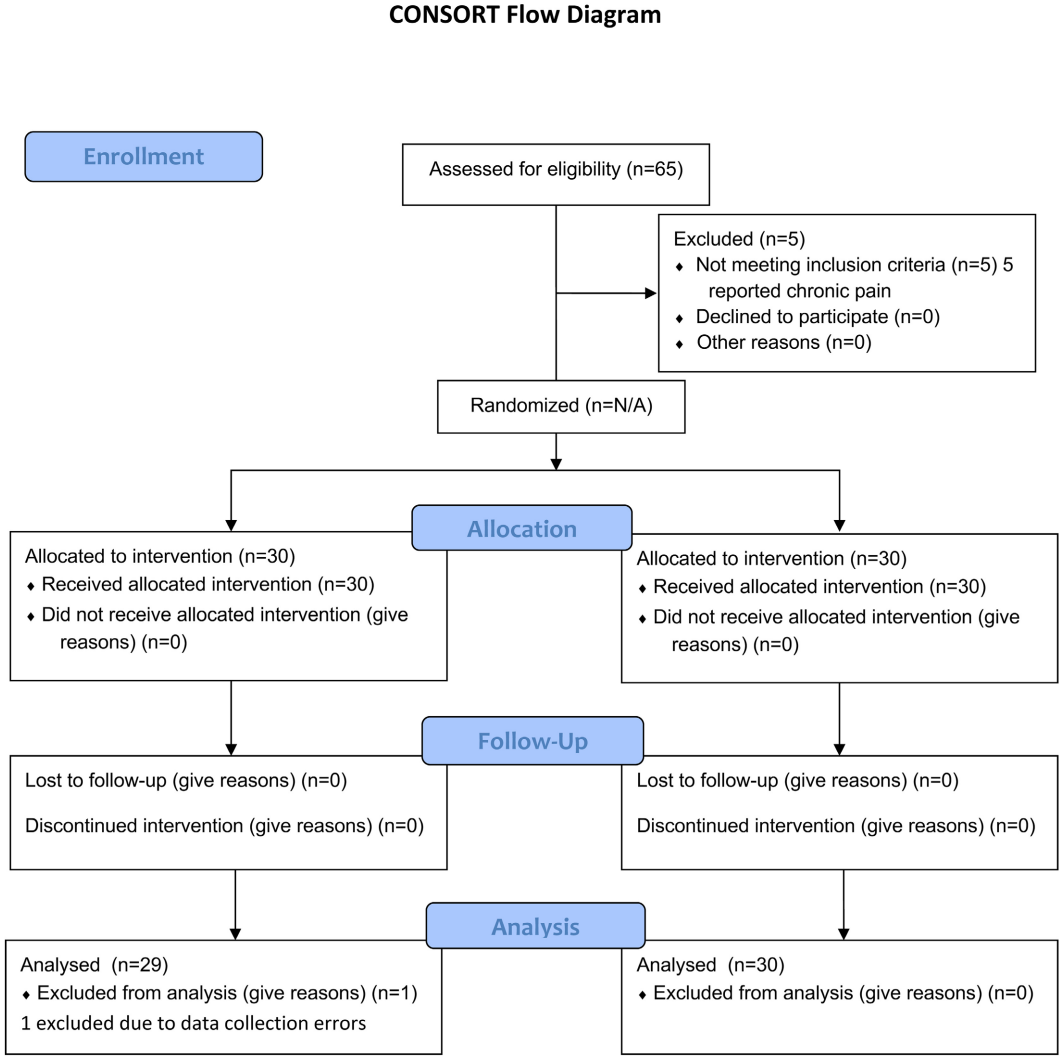


Figure 2. CONSORT flow diagram.

of the experimental mechanical pressure pain (STPM), the participants were asked to close their eyes for 10 seconds and envision the pain related to the mechanical pressure that had been just priorly placed upon their lower extremity. After 10 seconds, PPT was assessed. Finally, to assess PPT responses to the long-term memory of pain, participants with a prior history of injury were asked to close their eyes and visualize their prior injury and the pain associated with it for 10 seconds, while the control group with no prior history of injury were asked to close their eyes for 10 seconds and visualize a predetermined region of their lower extremity. At the end of the 10-second visualization period, PPT was assessed.

All three experimental conditions were conducted three times with three minutes between testing before moving to the succeeding condition. Five-minute normalization periods were allotted before commencing the testing of each new condition. The mean value of the three tests was utilized to analyze each condition.

2.5. Sequencing of Testing Order

The testing order was randomized to limit confounding effects due to test sequencing. Baseline measures were assessed before testing any experimental conditions, and short-term pain memory was always clustered to follow experimental mechanical pain testing immediately (Table 1). Besides those two criteria, the order of testing experimental mechanical pain/short-term pain memory and long-term pain memory were randomized. The testing sequencing was determined through computer-generated randomization tables and pre-assigned to a participant number in all cases.

2.6. Data Analysis

SPSS Statistics Version 27.0 (Armonk, NY) was utilized for all data analysis. Descriptive statistical analysis determined the means and standard deviations of demographic information collected in the participant intake forms. Additionally, descriptive analysis was conducted to determine the normality and skewness of data. A mixed model repeated measure ANCOVA analysis was performed for

Table 1. Sequencing of interventions. Intervention order was randomized and randomization was predeteremined using a computer-generated randomization table.

Baseline	Experimental Mechanical Nociceptive Pressure Stimulus	Short Term Pain Memory	Long Term Pain Memory or Visualization
Quiet supine resting (both groups)	Maximum tolerable mechanical pressure pain (both groups)	Memory of maximum tolerable pressure pain (both groups)	Memory of previous substantial injury or visualization of lower extremity
	Clustered. Mechanical nociceptive pressure pain always preceded short term pain memory		
Randomized order	Randomized order		Randomized order

each condition to determine whether there was a difference in PPT responses between those with and without a substantial prior injury. For each condition, time (baseline and postcondition) and the condition (acute experimental mechanical pain, short-term pain memory, and long-term pain memory) were used as the within-subject factors. The substantial prior injury history was the between-subject factor, and gender was used as a covariate to account for its impact as a confounding factor. A follow-up repeated measure ANCOVA analysis was conducted on data split for injury history to determine PPT responses to each condition for each study group. An a priori alpha value of 0.05 was used to establish significance in all analyses.

3. Results

3.1. Demographic Analysis

A total of 65 individuals were eligible for the study, with five excluded because they did not meet the inclusion or exclusion criteria (Figure 2). Based on the desired power of 0.80, and an effect size of 0.50, an 18.2 standard deviation, and a confidence level of 95%, it was estimated that a sample size of 58, 29 for each group, was required to yield statistically significant results. From October 2014 to April 2015, 60 individuals participated in the study. Data collection concluded once the required number of participants was reached. The data of one individual in the NPSI group was excluded because of errors occurring during data collection. The final analysis included the data of 59 subjects. Of the participants, 29 were included in the PSI group, and the NPSI group included 30 participants. In total, 25 males and 34 females participated in the study. There was no significant difference in age or gender between the PSI and NPSI groups (Table 2).

3.2. Normality of Data

An analysis of the studentized residuals found no outliers greater than +3, so the data required no adjustments. A Shapiro-Wilk analysis was conducted on each condition's data to determine the distribution's normality. The initial investigation found moderately positively skewed data for each condition (p between +0.5 and

Table 2. Participant demographic information.

	Total Sample	PSI	NSPI	Male Total Sample	Male PSI	Male NPSI	Female Total Sample	Female PSI	Female NPSI
Number	59	29	30	25	13	12	34	17	17
Mean Age Yrs. (SD)	28.06 (5.66)	28.07 (3.98)	28.06 (6.94)	27.42 (5.78)	28.56 (5.60)	27.42 (2.78)	27.43 (7.60)	28.53 (4.69)	26.54 (6.54)
Max Age Yrs.	52	40	52	52	52	33	52	40	52
Min Age Yrs.	23	24	23	23	24	24	23	24	24
Time Since Injury Yrs. (SD)	4.88 (5.79)	10.10 (4.01)	NA	4.92 (6.16)	4.85 (5.59)	10.67 (4.42)	NA	9.71 (3.79)	NA

Abbreviations: Yrs., years; SD, standard deviation; PSI, prior substantial injury; NPSI, no prior substantial injury.

+1.0). The data was subsequently transformed using a square root transformation applied to the mean values for each condition. Following the transformation, there was homogeneity of variances ($p > 0.05$) and covariance ($p > 0.001$) for all data as assessed by Levene's test of homogeneity of variance. After transformation, all data were normally distributed as assessed by Shapiro-Wilk's test of normality ($p < 0.05$).

3.3. Experimental Mechanical Pressure Pain

There was a statistically significant difference in PPT values between the PSI and NPSI groups exposed to experimental mechanical pain, $F(1,57) = 6.010$, $p = 0.017$. Injury history had a medium to large effect on PPT values accounting for 9.5% of the total variance (partial $\eta^2 = 0.095$). Participants in the PSI group experienced a significant 37.6 kPa or 9.7% (95% CI, −0.684 to 6.777) reduction in PPT ($F(1,28) = 4.532$, $p = 0.042$ with a medium to large effect size. Of the total variance, 8.8% was accounted for by experimental pressure pain (partial $\eta^2 = 0.088$). The NPSI group experienced a mean increase of 43.3 kPa or 12.7% (95% CI, −4.312 to 1.663) in PPT but this difference was not significant, ($F(1,29) = 2.174$, $p = 0.151$. There was a small to medium effect size (partial $\eta^2 = 0.029$ or 2.9% of the total variance) (Table 3 and Figure 3).

3.4. Short-Term Pain Memory Recall

There was no statistically significant difference in PPT values between the PSI and NPSI groups as both groups experienced a similar reduction in PPT when participants were asked to recall the recently experienced painful stimulus, $F(1,57) = 3.925$, $p = 0.052$. The PSI group experienced a 108.8 kPa or 28.1% decrease in PPT ($F(1,28) = 36.13$, $p < 0.001$), while the NPSI group also experienced a 36.0 kPa or 10.6% decrease ($F(1,29) = 9.513$, $p = 0.004$). Although the ANCOVA showed no statistical difference between the two groups, there was a medium effect size with a history of injury accounting for 6.4% of the total variance (partial $\eta^2 = 0.064$) (Table 3 and Figure 4).

Table 3. Results of the mixed methods ANCOVA.

	Baseline (kPa)	Experimental Pressure Pain (kPa)	Change: Pain vs. Baseline (kPa)	Short Term Pain Memory (kPa)	Change: Short Term Pain Memory vs. Baseline (kPa)	Long Term Pain Memory (kPa)	Change: Long Term Pain Memory vs. Baseline (kPa)
Prior history of substantial injury	M = 387.0 SD = 153.5	M = 349.4 SD = 153.2	−37.6 (9.7%) p = 0.042[a]	M = 278.2 SD = 115.1	−108.8 (28.1%) p < 0.001[a]	M = 271.7 SD = 107.1	−115.3 (29.8%) p < 0.001[a]
No prior injury	M = 338.1 SD = 139.2	M = 381.4 SD = 191.9	+43.3 (12.7%) p = 0.151	M = 302.1 SD = 206.5	−36.0 (10.6%) p = 0.004[a]	M = 290.5 SD = 148.4	−47.6 (14.1%) p = 0.006[a]
Total sample	M = 361.7 SD = 147.1	M = 360.7 SD = 173.2	−1.0 (0.3%) p = 0.014[a]	M = 290.6 SD = 167.7	−71.1 (19.7%) p = 0.076	M = 281.4 SD = 129.4	−80.3 (22.2%) p = 0.050[a]

Abbreviations: M, mean; SD, standard deviation; kPa, kilopascals; [a], indicates significant findings ($p < 0.05$).

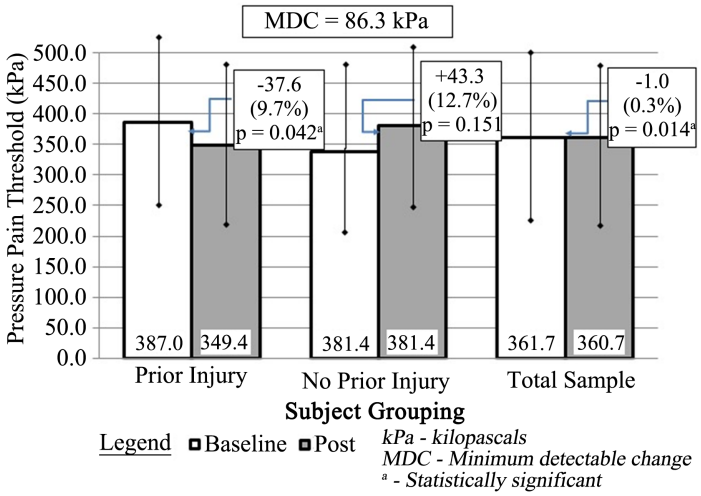


Figure 3. Experimental mechanical nociceptive pressure pain application. Comparison of baseline values and values taken following exposure to experimental mechanical pressure pain.

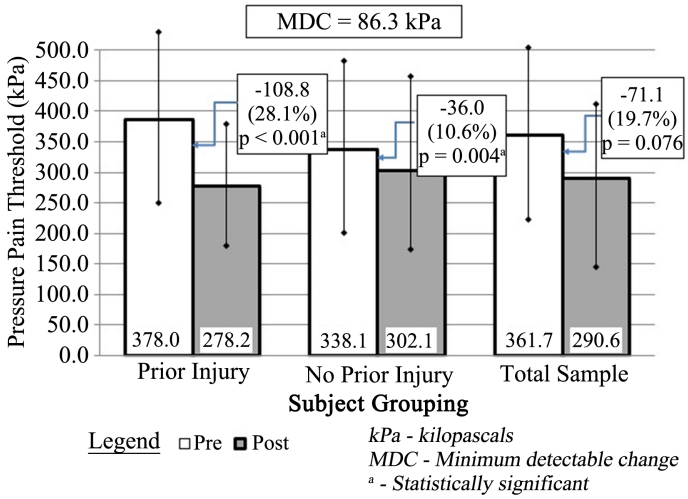


Figure 4. Short-term pain memory recall. Comparison of baseline values and values taken immediately after the recall of the experimental mechanical pressure pain.

3.5. Long-Term Pain Memory Recall

There was a statistically significant difference in PPT values between the PSI and NPSI groups when participants were asked to recall a prior painful injury, $F(1,57) = 4.886$, $p = 0.031$. History of injury had a medium to large effect on PPT values accounting for 7.9% of the total variance (partial $\eta^2 = 0.079$). Participants in the PSI group experienced a significant 115.3 kPa or 29.8% (95% CI, 7.452 to 16.214) reduction in PPT ($F(1,28) = 33.92$, $p < 0.001$). Long-term pain memory had a large effect on PPT values accounting for 51.3% of the total variance (partial $\eta^2 = 0.513$). Participants in the NPSI group experienced a significant 47.6 kPa or 14.1% (95% CI, 1.211 to 8.375) reduction in PPT ($F(1,29) = 8.622$, $p = 0.006$). Visualizing a lower extremity region had a large effect on PPT, accounting for 21.2% of the total variance (partial $\eta^2 = 0.212$) (Table 3 and Figure 5).

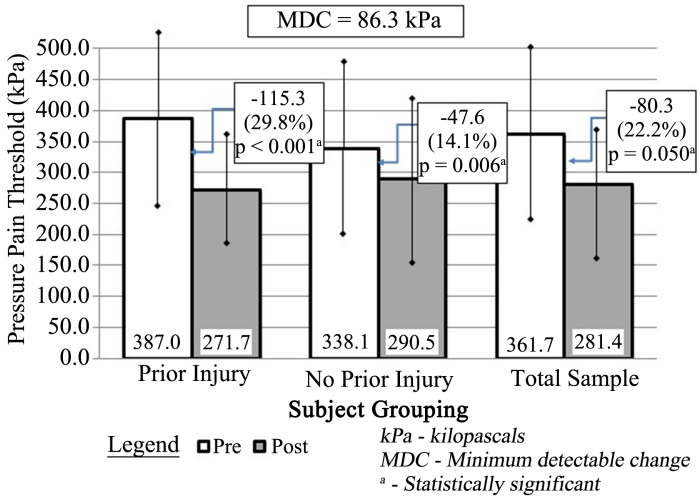


Figure 5. Long-term pain memory recall. Comparison of baseline values and values taken after recall of the pain of a past injury or visualization of the lower extremity.

4. Discussion

The current study results differed in how previously injured and non-injured participants responded to a noxious stimulus. Participants with a history of injury experienced pain with less pressure following exposure to a noxious stimulus than their non-injured counterparts. These findings appear to align with the growing body of research demonstrating that prior experiences with pain shape future pain responses [8] [9] [19] [24] [26] [45] [47] [48]. Studies pairing stimulus, both conscious and subconscious, with nociceptive stimulus consistently show that the paired stimulus has the potential to alter subsequent responses to a noxious stimulus [22] [45] [46] [49] [50] [51]. These forms of stimulus conditioning are examples of associative learning and represent the conditioning and learning that can occur in response to a pain-producing event.

Prior studies exploring how exposure to a painful stimulus impacts subsequent pain thresholds found that PPT responses to a noxious stimulus are not uniform; some studies found an increase in pain threshold, and others found the opposite [52] [53] [54] [55] [56]. This variability differs from the responses typically found in animal studies. In animal studies, the overriding finding is that applying a noxious stimulus increases the pain threshold [57]. The physiological rationale for this variability is not entirely understood, but authors speculate that top-down descending modulation likely plays a prominent role in the variability seen in humans [58] [59]. The variability provides mechanisms to adapt pain responses to the particular needs and demands of a situation.

While the mechanisms and purpose of this modulatory variability are not entirely understood, the evidence indicates that animal and human cognitive processing are not identical. When a noxious stimulus is encountered in animals, the programmed response is to survive. As mentioned prior, part of this survival mechanism involves increasing pain thresholds to facilitate survival; this response is known as diffuse noxious inhibitory control (DNIC). With DNIC,

pain thresholds are increased to allow for more pain to be tolerated allowing escape [60] [61]. Conditioned pain modulation is the human equivalent to DNIC. But in humans, CPM does not always occur as more varied responses are possible, and these initial survival-based escape responses can be inhibited or enhanced in reaction to other factors such as potential damage or threat [25] [62] [63] [64]. In line with this view, studies by Madden, Harvie, Koban, and Meulders all demonstrate that pain conditioning is not uniform but varies from individual to individual and circumstance to circumstance [22] [45] [46] [49] [50] [51]. Several attributes have been proposed as factors that influence these responses. Jepma and Wager found that higher pain intensity was a factor in the conditioning of neutral stimulus, and Meulders suggests that the presence of fear was a key element in future responses to neutral movement cues, both suggesting that perceived threat may be a factor in determining when pain thresholds are enhanced or diminished [24] [65]. In the current study, we speculate that the group with a history of significant injury and having experienced prior pain had stored memories of the experience. When the pain was presented, pain thresholds were reduced as a pre-encoded learned response functioning to provide quicker warning and avoidance of re-injury. By comparison, participants without a prior history of pain in the area did not experience anticipatory reductions in pain threshold because no pre-encoded memory response had been developed. Instead, those with no history of injury experienced an increased pain threshold allowing escape from the painful stimulus.

The second component of the study explored responses to short-term pain memory. When asked to recall the painful stimulus from minutes prior, regardless of past injury history, both groups of participants experienced a reduction in pain threshold. These findings suggest that both groups, having previously experienced pain, had developed a short-term memory of pain, eliciting an anticipatory protective reduction in the pain threshold. Previous research that explored sequential exposure to noxious stimulation found that pain thresholds generally increased with repetitive noxious stimulation [31] [32]. Typically, these CPM responses could last for as long as 10 minutes following noxious stimulation and are considered a normal physiological response [66]. In the current study, the normal increases in PPT associated with CPM seem overridden by conscious short-term pain recall. Researchers speculate that this ability to modulate PPT allows for shaping the pain threshold in response to personal and environmental factors where experience and memory are utilized to shape responses [67] [68]. Just as prior research found that subconscious memory cues that have been conditionally paired with a noxious stimulus could modulate pain thresholds and pain reports, the current findings suggest that the conscious recall of pain can modulate pain perception as well.

Lastly, the current study also explored whether the long-term memory of pain could alter the pain threshold and found that long-term pain memory also appears to produce an anticipatory reduction in the pain threshold. These findings, like those seen in response to the short-term recall of pain, suggest that individ-

uals who experienced a painful event in the past retain protective anticipatory responses, even when fully recovered and no longer experiencing pain or functional limitations due to the injury. Meulders and Vlaeyen found that imagining a painful movement could activate the memory representation of pain and a conditioned fear response [51]. Moseley found that motor imagery could increase pain and swelling in individuals with Complex Regional Pain Syndrome [24] [51] [69]. While no prior research has looked directly at the impact of long-term pain recall on pain thresholds; the literature suggests that PPT reductions in individuals with a prior pain history are part of a pre-programmed protective response that can be recalled where the pain is perceived with less stimulus [47] [70] [71]. As a comparative intervention, participants with no prior history of injury were asked to visualize a region of their lower extremity. While this is not a completely comparable task, the intent was to determine whether the changes experienced in PPT were due to visualization of pain or due to a competing cognitive task. The visualization produced a reduction in PPT, suggesting that the cognitive task played a role in PPT responses, but the magnitude of the response was significantly greater with the visualization of pain than it was with neutral visualization. This finding aligns with prior studies showing that fear, anxiety, positive and negative cues have different effects on pain responses and demonstrate the potential role that pain experience and pain memory have upon pain responses [25] [72] [73].

The capacity to override initial responses suggests that the meaning of the noxious stimulus may play a role in an individual's behavioral responses [59]. The more stressful [74] or threatening the perception of the stimulus [75] [76], the more likely the response will be modulated and shaped by experience. Noel *et al.* [77] synthesized data and explored how exposure to a painful stimulus impacted future pain responses in children. The authors found that painful memories were not uniform. Research indicates that two factors may influence pain conditioning and memory formation [65]. Firstly, multiple authors have found that the intensity or magnitude of pain experienced impacts pain learning [19] [78] [79]. Pain responses to contextual cues are larger when paired with conditioned with high pain intensities than with lower intensities of pain. Secondly, research suggests that threat and expectation play a role in the memory of pain and subsequent responses [65]. When pain is perceived as threatening, physiological mechanisms that function to protect will be engaged; conversely, when no threat is perceived, these mechanisms are not engaged [24]. Multiple studies have linked fear and anxiety to pain learning and pain conditioning. Tesarz *et al.* [80] found that combat-related PTSD was associated with increased PPT, and accident-related PTSD was associated with decreases. These authors have suggested that fear-linked experiences increase PPT, allowing for escape from threats. In contrast, anxiety-producing experiences decrease PPT, providing a mechanism for early threat detection. Authors have speculated that fear is an emotion that has been linked to threat and survival. The presence of fear with pain increases contextual cueing, associative learning, and the storage of pain-related

responses. In these instances, the meaning associated with pain present at the time of injury is an important factor in how the memory is stored and the future responses associated with the event.

Together, the findings of the current study suggest that pain history matters. Individuals with a prior history of injury have greater reductions in pain threshold when exposed to a noxious stimulus in the area of an injury and when asked to recall short-term and long-term pain. Clinically, this is relevant as these findings suggest that beyond biology, pain memory and the recall of painful memories may impact a patient's pain perception and responses to treatment and should be a consideration in the management of patients. Past experiences with pain influence future responses to pain. Nocebo is a term used to describe the relationship between negative expectations and negative pain outcomes. Clinically, negative expectations and negative recall can increase pain-related behavior [81]. The recall of pain history or the disclosure of negative information about pain can produce enhanced pain responses and should be a consideration in clinical practice [82] [83] [84]. While current management tends to focus on correcting the physiological responses associated with pain, increasingly, there is a recognition that it is also important to address the psychological, contextual, and social factors driving the physiology [85] [86]. While still in its infancy, interventions that target the formation of trauma, injury, and pain-related memories and those that strive to reduce the fear, anxiety, and negative expectations and responses that have been stored in memory have been shown to be effective in the management of pain [87] [88] [89].

Limitations and Future Directions

The selected sample consisted primarily of students and faculty, which biased our selection to young, healthy, educated individuals. Additionally, it is important to note that while many of the results were statistically significant, many failed to reach the level of clinical detectability. Pain is multifactorial; while the study focused on pain memory, other factors may have contributed to the results. The participant's stress, anxiety state, and history of PTSD at the testing time were not assessed as part of the study and may influence pain perception. While the authors acknowledge the limitations of a quasi-experimental research design and its inherent threat to internal validity, complete randomization was not possible when comparing participants with and without prior injury history. Sequencing of testing conditions may have also factored into the results as the short-term recall of pain sequenced prior to the long-term recall may have primed responses and this is an acknowledged limitation of the study. Creating a memory task compared to the long-term pain memory was a challenge of this study design and is acknowledged as a limitation. While the reductions in PPT experienced with the recall of a painful stimulus were significantly greater than those experienced with visualization, caution should be used in ascribing the reduction solely to the recall of pain memory. Follow-up studies should increase this study's sample size and breadth to strengthen the findings. Future studies

should also include participants with greater levels of pain chronicity to determine whether differences exist in how pain and memory are processed in this population.

5. Conclusions

Developing lines of research point to the predictive role of experience, learning, and memory formation on the pain experience. The memory of pain and the meaning and context surrounding the event allows information about an injury to be stored for future use as a top-down protective mechanism, with threat and contextual cues acting as prompts for recalling anticipatory pain responses stored in memory. The current study shows a difference in the processing after a substantial injury and reinforces the thought that experience and memory shape pain perception. The findings suggest that once an area is injured, the processing of future pain in the area may be altered. Traditional rehabilitation paradigms rely heavily upon biological principles; rehabilitation and future research may need to expand beyond the management of biomedical factors to address the learned and stored pain responses that may shape pain.

Acknowledgements

We would like to acknowledge Neil Spielholz PT, Ph.D., for his expertise and assistance throughout the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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