The Impact of Familiarization on Pressure and Heat Pain Scores

Original Research

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Abstract

Introduction: Quantitative sensory testing (QST) provides an effective means to better understand the pain process; however, inherent variability exists depending on how QST methods are implemented. The current study sought to investigate the impact of pain testing familiarization on pain pressure testing (PPT) and heat pain testing during QST in young, healthy participants.

Methods: 25 participants (13(m)/12(f); 22.5 ± 2.5 yrs) underwent 4 separate testing sessions of pressure pain threshold (PPT) and pressure pain supra-threshold (PPTs) and heat pain threshold (HT) and 50/100 Visual Analogue Scale (H50), which included pain familiarization.

Results: No significant effects were seen across session for PPT ($F(3,184) = 1.205$, $p = 0.309$) or PPTs ($F(3,184) = 0.227$, $p = 0.8774$) and trial type for PPT ($F(1,184) = 0.12$, $p = 0.722$) or PPTs ($F(1,184) = 0.743$, $p = 0.390$). A significant main effect for the independent variable of trial was found for the dependent variable of H50 ($F(1,184) = 109.42$, $p = < 0.000$) with the experimental trial values lower than familiarization values. This was not seen within the HT ($F(1,184) = 3.374$, $p = 0.068$) values.

Conclusions: When testing for moderate levels of heat pain, familiarization should be considered. Additional research is still needed to support or deny the need for familiarization to be included in pain testing research to increase the accuracy of future research studies.

Key Words: pain familiarization, pain testing, pain variability

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Introduction

Chronic pain is a major issue worldwide affecting over a pooled estimate of 31% of the worldwide population and 20.9% of adults in the United States as of 2021.[1,2] The issue of chronic pain presents a massive burden as it is linked to decreases in quality of life potentially leading to issues such as depression[3], dementia[4], higher suicide rates[5], and substance use[6]. This has resulted in an estimated cost of $560 to $635 billion U.S. dollars per year. The burden, rightfully, has provided a strong incentive towards developing and testing more effective therapies and interventions. Of which, require standardized methods of pain testing to ensure these therapies optimize their effectiveness and reproducibility. A common translational tool used in pain research is quantitative sensory testing (QST). Quantitative sensory testing is the administration of standardized and quantifiable sensory stimuli (e.g., thermal, mechanical, vibration, and pressure) in both static and dynamic capacities to the body with the subsequent perceptual responses recorded. A significant body of research has used QST, specifically through heat and pressure stimuli, to develop somatosensory profiles of

chronic pain patients, predict treatment response, and understand the hypoalgesic effects of pain therapies in pain-free and chronic pain populations.[7–10] However, investigations into pain testing procedures often lead to inconsistent results across studies, demonstrating large variability within pain response results[11–17]. This variability arises from many potential factors. The potential value of QST as research and clinical tools necessitates that measurement error be minimized during administration of these tests allowing for better comparison across studies.

A host of factors have been associated with altered pain responses during pain testing. Factors such as gender[18–20], age[19], anxiety[21], cognition[19], and even the gender of the pain assessor[22] have all been shown to have an effect on the pain response during QST. This influence shows the incredible complexity associated with the human pain response indicating the need for procedures to minimize the potential effect these factors may have on the pain response. For example, if pain testing anxiety is shown to influence the pain response during testing, pain testing familiarization prior to collecting data may reduce its influence on the pain response. Theoretically, pain testing familiarization may effectively provide a better indicator of the individual's pain response during experimental trials, reducing some of the variability seen within the pain testing literature. The impact of familiarization has been demonstrated within animal models; however, this remains to be clearly demonstrated within human participants.[23]

The purpose of the current study was to investigate the impact of pain testing familiarization on the pain response during QST. Specifically, the study sought to investigate whether familiarization of pain testing procedures for both pain pressure testing (PPT) and heat pain testing lead to a difference in the pain response of young, healthy participants during experimental trials. The authors hypothesized that the use of familiarization of pain testing procedures would lead to a reduced sensitivity to both heat and pressure pain. These results may help inform investigators of the potential use and benefits of pain testing familiarization, leading to greater standardization of pain testing. This standardization in return may lead to a reduction in pain score variability and allow for stronger comparisons across pain studies leading to better overall evidence-based pain reduction therapies.

Methods

Participants

Twenty-five healthy adults (13 males; 12 females) between the ages of 18 and 32 years (mean = 23 years, SD = 2 years) were recruited via word of mouth as part of a larger study investigating the influence of aerobic-based exercise on pain perception. The data of which provided the opportunity to investigate the influence of the familiarization protocol on subsequent pain experimental trials prior to engaging in exercise. Exclusion criteria for the study included the inability to reliably rate pain intensity, uncontrolled hypertension defined as resting blood pressure >150/99 mmHg, any systemic disease that restricts normal daily activities, neurological disorders relating to changes within somatosensory perception, any uncontrolled psychiatric conditions, or daily narcotic medication use.[24] Additionally, any participants that self-reported a history of metabolic, pulmonary, cardiovascular disease, or an orthopedic related injury were also excluded from participation. The university institutional review board approved the protocol utilized in the study in accordance with the Declaration of Helsinki. Participants of the study were provided information about the procedures and privacy information after which they reviewed and signed an informed consent form. Participant eligibility was then determined once they completed a health history questionnaire supplemented by any questions and blood pressure measurement.

Protocol

All participants were tested in the Human Movement Laboratory of the university in an open isolated, climate-controlled room under the supervision of trained pain investigators. Participants were seated upright on a treatment table and tested via pressure and thermal heat modalities. A visual analog pain scale (VAS) placed in front of the subject for ease of pain response reporting. The VAS pain scale was a 0-100 scale with the left endpoint defined as "no pain" and the right endpoint as "highest tolerable pain". Additional hash marks in increments of 10 were provided to simulate a 0-100 numerical rating scale.[25]

Pressure stimuli were delivered to the mid-thigh using a digital handheld clinical grade pressure algometer with a 1 cm^2 probe (Wagner FPX, Greenwich, CT).[26] Participants were tested for both their pressure pain threshold (PPT) and supra-threshold pressure pain (PPTs). For PPT, participants were instructed to verbally say "pain" to the investigator when the increase in pressure first began to become painful. For PPTs, participants were instructed to say "pain" to the investigator when they could no longer tolerate an increase in pressure.

Thermal heat stimuli were delivered to the mid-thigh using a computer-controlled Medoc Q-Sense CPM System (Ramat Yishai, Israel) using a 30 x 30 mm thermode with baseline temperature set at 28°C with a rate of increase of 1°C/s. Participants were instructed to click a participant response device, in real-time, to indicate thermal temperatures that were associated with the following terms: 1) warm temperature crossed over into "pain" known as heat pain threshold (HT); 2) when they perceived the heat pain as a rating of "50" on the 0-100 VAS pain scale known as heat temperature at a VAS of 50 (H50); 3) when they perceived the heat pain as a rating of "100" on the 0-100 VAS pain scale known as heat tolerance (HTol). All testing was conducted with the participant seated upright on a therapy table.

Upon signing of the informed consent, participants were provided with an orientation of the testing equipment being utilized and the VAS scale. Specific instructions for each testing modality and pain "level" (i.e., thresholds vs supra-threshold vs tolerance) were then given and testing began. Participants were exposed to three separate testing trials for each pressure and thermal heat test. The three trials consisted of a familiarization trial, experimental trial 1, and experimental trial 2. The familiarization trials were implemented on the midthigh of the non-dominant side, as determined by asking the participant, and included the following tests in the following order: PPT, PPTs, HT, HTol, and H50. Upon completion of the familiarization trial, after 5 minutes of rest, participants then completed the experimental trials which, once again, took place on the mid-thigh, however the limb side was randomized and counterbalanced.[24] Also, the exact location on the mid-thigh for each trial was slightly altered between trials by moving the testing thermode or pressure tip approximately 1-1.5cm from the previously testing spot. The same tests as the familiarization trials were repeated except for the HTol test. This was excluded to eliminate any potential undue heat sensitization within the limb. The experimental trials were completed two times (i.e., experimental trial 1 and experimental trial 2) with 2-3 minutes between each testing period. This process was completed over the course of 4 total testing sessions, each of which was separated by a minimum of 48 hours. All tests were completed on the same limb as the participant's previous session.

All participants completed 4 sessions of testing that included the result of familiarization trials and an average of experimental trials for each session for each variable of interest. Within the data, 9 data points were found to qualify as outliers (± 3 standard deviations away from the mean). However, upon further investigation, the removal of these outliers did not influence the results of the data and, due to the nature of the data, were left in for final analysis. All data was collected via pen and paper and logged into Microsoft Excel (Redmond, WA) by trained investigators. This data was then organized and prepared for subsequent statistical analysis by the primary investigators.

Statistical Analysis

The primary aim of this study was to investigate the influence that pain testing familiarization may have on subsequent testing of both pressure and heat pain in young, healthy adults. Power analysis indicated the need for 25 participants (power = 0.80, alpha = 0.05). An assumption check resulted in a Shapiro-Wilks violation of normality at a p-value <0.000 for PPT (W = 0.903), PPTs (W = 0.905), HT (W = 0.976), and H50 (W = 0.984).[27] Therefore, non-parametric Aligned Rank Transform Contrasts were performed.[28–37] Independent variables consisted of participant sex, session number, and trial (e.g., familiarization or testing trial average) with the dependent variables consisting of PPT, PPTs, HT, and H50. All statistical analyses were completed via the software 'R' version 4.4.0.[33]

Secondarily, it was hypothesized that the one of the benefits of familiarization would be that the data would be more reliable between experimental trials. Therefore, intraclass correlations (ICCs) and intraindividual stability coefficients (ISCs) were calculated for the familiarization, experimental trial 1, and experimental trial 2 across all sessions for the dependent variables. Intraclass correlations coefficients range between 0 and 1.0, with values less than 0.50 indicating poor reliability, values between 0.50 and 0.75 indicating moderate reliability, values between 0.76 to 0.90 indicating good reliability, and above 0.90 indicating excellent stability/reliability.[38] The ICCs allowed us to observe whether relative stability was higher when a familiarization trial was present (ICC for familiarization trial and experimental trial 1 vs. experimental trial 1 and experimental trial 2). Similar to previous studies, intraindividual stability coefficients (ISC) were computed to examine intraindividual QST stability.[39] First, the QST test scores for each session and trial were standardized across the whole sample. We then calculated a change score by subtracting the experimental trial 1 standardized score from the Familiarization trial standardized score. Next, we calculated an ISC for each QST score for each session using the following formula: $IS_{xy} = 1 - ([Z_x - Z_y]^2/2)$, where Z_x and Z_y represent standardized scores across the sample and session at experimental trial 1 (X) and familiarization trial (Y), respectively. Using the same procedure, ISC scores were also calculated for experimental trials 1 (Y) and 2 (X). The ISCs for each QST test were averaged across sessions. Because QST scores are standardized within each session, ISCs are not associated to mean-level changes happening at the group level. Therefore, ISCs offer an approach to control for some potential

confounding effects, such as regression to the mean. Similar to ICCs, higher ISCs represent greater stability of the outcome measures, whereas lower ISCs represent lower stability. Shapiro-Wilk's test of normality indicated that the ISCs for all the variables were not normally distributed, thus Mann-Whitney U tests were conducted to determine if these variables differed between leg of testing. None of the ISCs differed based on leg of testing ($p > 0.05$) and thus, this was not considered a variable in the final analyses. Related samples Wilcoxon signed Rank tests were used to determine whether ISCs for each QST test differed by trial comparison [ISC for familiarization trial and experimental trial 1 (Fam-T1) vs. experimental trial 1 and experimental trial 2 (T1-T2)].

Results

Data Reliability and Stability

ICCs. The data demonstrated good reliability across trials regardless of whether it is comparing reliability between familiarization trial and experimental trial 1 (Fam-T1) or experimental trial 1 and experimental trial 2 (T1-T2) for the dependent variables of PPT (Fam-T1: ICC = .88, p <.001, 95% CI =.82-.92; T1-T2: ICC = .89, p <.001, 95% CI .84-.93), PPTs (Fam-T1: ICC = .87, p <.001, 95% CI =.81-.91; T1-T2: ICC = .88, p<.001, 95% CI .82-.92) , and HT (Fam-T1: ICC = .79, p <.001, 95% CI =.70-.85; T1-T2: ICC = .77, p<.001, 95% CI .60-.86). The dependent variable of H50 however, demonstrated poor reliability for the familiarization trial and experimental trial 1 comparison (ICC = .28, p <.001, 95% CI =-.10, .60) but did show good reliability for experimental trial 1 and experimental trial 2 (ICC = .81, p <.001, 95% CI =.68-.88).

ISCs. The Wilcoxon signed rank test conducted on the H50 test indicated that intra-individual stability for T1-T2 comparison (ISC = .85, 95% CI .78-.91) was significantly higher compared to the Fam-T1 comparison (ISC = .68, 95% CI .56-.80), p=.005. No significant differences in ISCs were found for the PPT test (Fam-T1: ISC = .87, 95% CI =.81-.92; T1-T2: ISC = .90, 95% CI .85-.95; p=.242), PPTs test (Fam-T1: ISC = .85, 95% CI =.77-.92; T1-T2: ISC = .89, 95% CI .85-.94; p=.264), and HT test (Fam-T1: ISC = .71, 95% CI =.55-.87; T1-T2: ISC = .81, 95% CI .74-.88; p=.427).

Pressure Pain Tests

Descriptive data on the 25 subjects for each of the dependent variables are presented in Table 1 averaged across sessions. No significant differences were found between the experimental trials (i.e., experimental trial 1 vs 2); therefore, the experimental trials are presented as an average of the two trials and labeled as experimental trial. Analysis of the transformed data demonstrated a significant main effect for the independent variable of sex for both the dependent variables PPT ($F(1,184) = 52.68$, $p < 0.000$, $\eta^2 = 0.22$) and PPTs ($F(1,184) = 43.154$, $p < 0.000$, $\eta^2 = 0.19$). On average, men were found to have significantly higher PPT and PPTs scores when compared to women within every session and trial. This was apart from the PPT familiarization trial for session 3, PPTs experimental trial for session 2, and PPTs familiarization trial for session 4. No significant effects were seen for the independent variables of session for PPT ($F(3,184) = 1.205$, $p = 0.309$, $\eta^2 = 0.02$) or PPTs ($F(3,184) = 0.227$, $p = 0.8774$, $\eta^2 < 0.00$) and trial type for PPT ($F(1,184) = 0.12$, $p = 0.722$, $\eta^2 < 0.00$) or PPTs ($F(1,184) = 0.743$, $p = 0.390$, $\eta^2 < 0.00$). Additionally, no interaction effects at any level were seen for either PPT or PPTs (see Figures 1 & 2).

Table 1. Average pressure pain across trials for men and women.

	PPT (lbf)			PPTs (lbf)		
	Fam	T1	T2	Fam	T1	T2
Male	25.4± 12.2	25.5± 12.0	25.2± 11.8	46.5± 21.0	43.4± 19.3	40.4± 17.5
Female	15.5± 6.3	15.5± 7.4	14.9± 7.1	28.9± 11.6	28.8± 10.7	27.7± 10.9

Table depicting the average scores (across sessions) ± standard deviation for both men and women for pressure pain testing.

Table 2. Average heat pain across trials for men and women.

	HT (^{0}C)			H50 (^{0}C)			HTOL (^{0}C)
	Fam	T1	T2	Fam	T1	T2	Fam
Male	38.6± 2.6	38.9± 3.0	40.0± 2.9	45.9± 2.1	42.3± 2.6	43.0± 2.3	45.9± 2.1
Female	37.3± 3.7	37.5± 3.7	38.5± 3.9	45.1± 2.0	41.2± 3.1	42.0± 3.1	45.1± 2.0

Table depicting the average scores (across sessions) ± standard deviation for both men and women for thermal pain testing.

Figure 1. Pressure pain thresholds differences across sessions. Sex differences in PPT across all trials (*$p \leq 0.05$). Boxplots show medians, IQRs, and 1.5x IQR whiskers; individual data points and outliers are included.

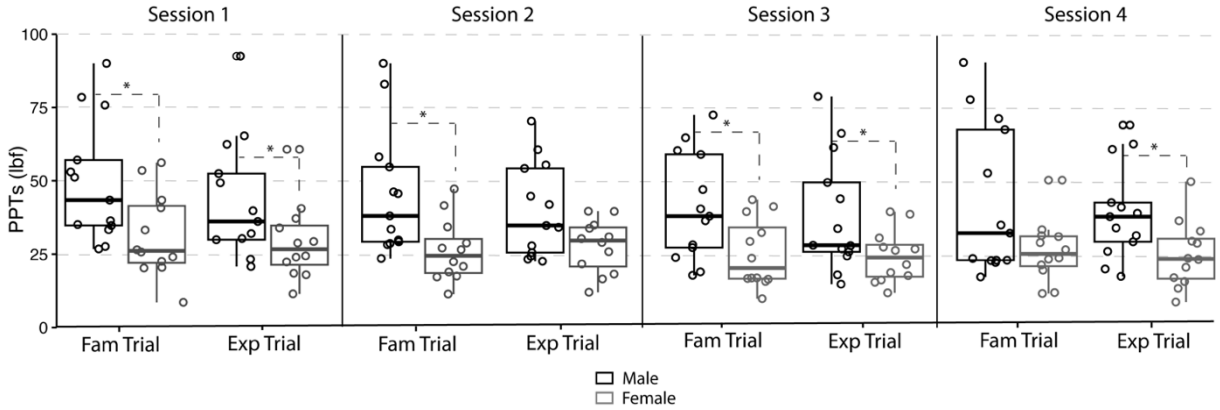

Figure 2. Pressure pain supra-thresholds differences across sessions**.** Sex differences in PPTs across all trials (*$p \leq 0.05$). Boxplots show medians, IQRs, and 1.5x IQR whiskers; individual data points and outliers are included.

Heat Pain Tests

Significant main effects were found for the independent variable of sex, for the dependent variables of HT ($F(1,184) = 8.36$, $p < 0.004$, $\eta^2 = 0.04$) and H50 ($F(1,184) = 9.701$, $p < 0.0214$, $\eta^2 = 0.05$). On average HT and H50 were higher for men when compared to women both within and across sessions. Tukey's post-hoc demonstrated a difference in the H50 variable only, showing a significant decrease in temperature consistently across all sessions for both men and women. Additionally, a significant main effect for the independent variable of trial was found for the dependent variable of H50 ($F(1,184) = 109.42$, $p = < 0.000$, $\eta^2 = 0.37$) while this was not the case of HT ($F(1,184) = 3.374$, $p = 0.068$, $\eta^2 = 0.02$). No significant main effect was found for the independent variable of session for the dependent variable of H50 ($F(3,184) = 2.025$, $p = 0.112$, $\eta^2 = 0.03$). A significant main effect was found for HT ($F(1,184) = 109.42$, $p = < 0.000$, $\eta^2 = 0.01$); however, upon further inspection, post-hoc analysis failed to demonstrate a statistically significant difference. Once again, no interaction effects at any level were demonstrated for either HT or H50 (see Figures 3 & 4).

Discussion

The current study sought to investigate the impact of pain testing familiarization on the pain response during QST in young, healthy adults. Subjects, after exposure to familiarization, demonstrated lower heat temperatures that elicited a pain score of 50 out of 100 for the subsequent experimental trials, for both men and women. Surprisingly, a similar result was not seen within the pressure pain or heat pain threshold data suggesting that familiarization may have a greater impact within dynamic heat pain testing modalities when compared to pressure pain testing modalities and cannot be generalized across other pain testing modalities[40–43]. Care should be taken with this interpretation, however, as the data fail to provide direct evidence as to why this result could take place due to the design of the study. The study results do demonstrate that familiarization may provide a means to help reduce elevated heat pain scores that may be found with initial suprathreshold heat QST trials.

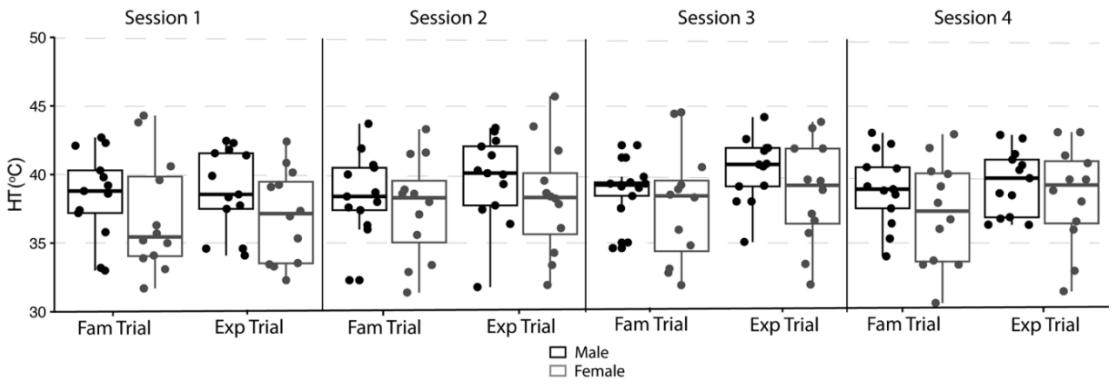

Figure 3. Heat threshold pain differences across sessions**.** Sex differences in HT across all trials (*$p \leq 0.05$). Boxplots show medians, IQRs, and 1.5x IQR whiskers; individual data points and outliers are included.

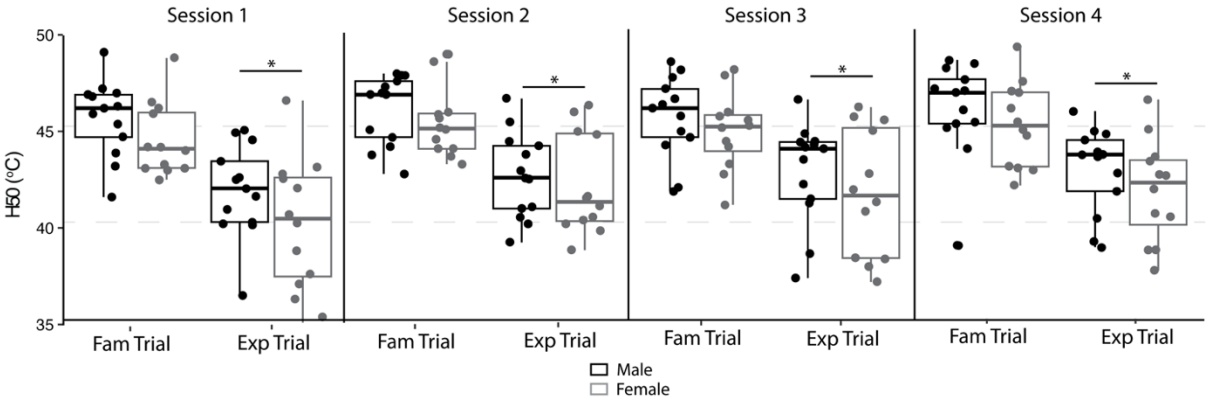

Figure 4. Heat pain at a score of 50/100 on the visual analogue scale differences across sessions**.** Sex differences in H50 (50/100 VAS) across all trials (*$p \leq 0.05$). Boxplots show medians, IQRs, and 1.5x IQR whiskers; individual data points and outliers are included.

The role of familiarization is theorized to help reduce elevations in pain scores during QST due to various factors outside of the actual pain testing. While not directly measured in this study, issues such as anxiety and uncertainty about the pain testing have been shown to influence the pain testing response, generally elevating pain scores[44–48]. In theory, exposing an individual to the pain testing methods prior to the actual "testing trials" would alleviate some of the inflated pain response. This study design however, can only speculate as to why heat pain temperatures were reduced following familiarization. In contrast, other studies have suggested that such a reduction may be a result of peripheral fatigue of the nociceptive pathways.[49] However, within the current study design this is unlikely due to the minimal nature of testing type, layout, and amount of stimulation utilized. The results of this study do however suggest that including familiarization trials may help individuals better rate their pain experience in a more consistent manner during laboratory evoked heat pain testing procedures. There was not a consistent reduction across modalities, however, which may suggest a modality specific nature to the familiarization. There may be several reasons for this discrepancy, including but not limited to the site being tested[50–53] as well as the existence of the minimal use of heat tolerance testing during familiarization. Additionally, previous literature has demonstrated lower variation in day-to-day testing within static measures of pain (e.g., pressure and heat thresholds) when compared to those of dynamic measures of pain (e.g., temporal summation and conditioned pain modulation).[40–43] This discrepancy between static and dynamic measures of pain may explain why the results only demonstrated significant differences within the heat temperatures at a pain score of 50 out of 100 as it more closely relates to a dynamic measure. The use of the midthigh for testing may also have led to a lack of differences within pressure pain testing when compared to heat pain testing as higher pressures were necessary to elicit a threshold response in the midthigh area. Thus, before any hard conclusions

can be drawn, it would be necessary to repeat the experiment on additional sites to confirm or deny the results of the current study. Additionally, while the use of heat tolerance testing during familiarization may provide participants with a better reference scale for their level of pain experienced, it may also introduce the potential for alterations in pain sensitivity at both spinal and supraspinal levels directly affecting sensitivity to heat pain testing.[54] In the current study, however, heat pain tolerance testing was kept at a minimum with only one heat tolerance testing per session with adequate recovery and was randomized and counterbalanced with the testing limb. If an alteration in sensitivity were to be seen it would likely be seen as an increase in heat pain sensitivity, not a decrease. Regardless, the results of the current study should provide enough evidence for pain researchers to strongly consider the use of familiarization testing, particularly with heat trials, within their study protocols if they don't already. Replication of the presented results is needed in order to draw strong conclusions as to the modality specific effects of familiarization providing a solid basis for standardization within QST protocols.

Several limitations must be considered when interpreting the current study results. The current study only employed the use of young, healthy, college-aged participants. This was done purposefully, as it was speculated that any differences in results seen in this population would likely also be seen in clinical populations, possibly to a greater degree. However, it must be stressed that this is speculatory and would need to be confirmed directly by testing different clinical populations. Additionally, previous investigations clearly demonstrate that testing site matters.[24,55] It remains possible that the differences seen across pain testing modalities are a product of the site tested. Therefore, the results of the current study need to be replicated across multiple testing sites, within multiple populations, and compared with data sets that do not include a familiarization trial. This additional data would then allow for a greater comparison of the usefulness of familiarization techniques across modalities, sites, and populations. While previous studies have demonstrated the impact of various factors (i.e., anxiety, uncertainty, cognition, etc..)[18–21] on pain testing scores, this study did not specifically address these potential mechanisms. Rather, this study provides a first step towards investigating the value of familiarization within pain testing studies and care should be taken when extrapolating any mechanistic basis from this data.

Conclusions

The current study demonstrated that the use of familiarization may be warranted for use within investigations utilizing experimentally evoked pain. More specifically, studies employing the use of evoked thermal heat pain may benefit from the use of heat pain familiarization to gain a clearer picture of heat pain scores. Additional studies are required to solidify the use of familiarization within studies, specifically those focused on clinical populations as well as different testing sites. At a minimum, the authors recommend that the use of familiarization should be strongly considered when employing the use of heat evoked pain.

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Conflict of Interest

The authors declare no conflicts of interest.

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