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# The effect of stress on pain sensitivity in healthy adults

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**THE EFFECT OF STRESS ON PAIN SENSITIVITY IN HEALTHY ADULTS**

by

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Submitted in partial fulfillment of the  
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# **THE EFFECT OF STRESS ON PAIN SENSITIVITY IN HEALTHY ADULTS**

**EMILY MOSHER**

## **ABSTRACT**

Stress can have influence on pain sensitivity, but the direction of its effects remains unclear. Previous research has reported both increased and decreased pain sensitivities under stress with different sensory tasks. The aim of the current study was to investigate the effect of stress on pain sensitivity using multiple psychological stressors in a relatively large sample of young men and women. Sixty-two participants were included, and pain thresholds, tolerance, and temporal summation were tested using thermal, mechanical, and dynamic tasks before and after stress. A condition of stress was induced by the Stroop task and a mental arithmetic task.

On average, there were no significant differences between stress and no stress conditions. Although not significant, pressure thresholds and tolerance had a tendency to decrease under stress conditions, and thermal thresholds and tolerance had a tendency to increase under stress conditions. Temporal summation did not change regardless of condition. These findings suggest that individual differences in response to stress and type of task being completed may play a role in how stress affects pain sensitivity.

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## LIST OF ABBREVIATIONS

ANOVA.....	Analysis of Variance
BPM.....	Beats per Minute
BWH.....	Brigham and Women’s Hospital
CBT.....	Cognitive Behavioral Therapy
CPA.....	Cuff Pressure Algotometry
CPM.....	Conditioned Pain Modulation
CPT.....	Cold Pressor Task
HF.....	High Frequency
HPA.....	Hypothalamic-Pituitary-Adrenocortical Axis
HPT.....	Heat-Pain Threshold
HRV.....	Heart Rate Variability
LF.....	Low Frequency
MAT.....	Mental Arithmetic Task
MDT.....	Mechanical Detection Threshold
NCS.....	Nerve Conduction Study
PAG.....	Periaqueductal Grey
PPT.....	Pressure-Pain Threshold
QST.....	Quantitative Sensory Testing
QST 1.....	Quantitative Sensory Testing Baseline Session
QST 2.....	Quantitative Sensory Testing Second Session
RMSSD.....	Root Mean Square of Successive Differences

RVM..... Rostral Ventromedial Medulla  
SAM ..... Sympathetic-Adrenal-Medullary System  
SCWT..... Stroop Color and Word Task  
SD..... Standard Deviation  
TS ..... Temporal Summation

## INTRODUCTION

### **Chronic and Acute Pain**

Chronic pain is a serious public health issue affecting over 20% of all adults in the United States (Dahlhamer et al., 2018). Some conditions, such as back pain, can affect up to 70%-85% of adults at some point in the course of their lives (Apkarian, Baliki, & Geha, 2009). Despite being such a common issue, there are few effective treatment options with favorable outcomes for those who do suffer from chronic pain. Treatment options include psychological intervention, opioid intervention, or a multidisciplinary approach to intervention (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006; Hoffman, Papas, Chatkoff, & Kerns, 2007). Hoffman and colleagues (2007) completed a meta-analysis that looked at psychological treatments. Psychological interventions commonly used involve cognitive behavioral therapy (CBT), self-regulatory therapy, and multidisciplinary treatments (Hoffman et al., 2007). Past research has shown that these therapies help to decrease pain intensity, pain interference, and health-related quality of life compared with individuals who do not participate in therapy (Hoffman et al., 2007). However, most treatments did not help to decrease feelings of depression, and after the treatment was completed, only the health-related quality of life of these individuals remained superior to other active individuals who did not participate in therapy (Hoffman et al., 2007).

Opioids are commonly prescribed to treat chronic pain. One study showed that of the 33.4% of patients who used prescription medication as treatment, over 45% took

opioid medication (Toblin, Mack, Perveen, & Paulozzi, 2011). However, a meta-analysis looking at opioid treatments for chronic pain found that only strong opioids worked for pain relief and that even then other drugs produced better functional outcomes (Furlan et al., 2006). Patients also had a large dropout rate despite the longest study lasting only 16 weeks. Because of these dismal outcomes, individuals with chronic pain are more likely to be restricted in their day-to-day activities (Gureje, Korff, Simon, & Gater, 1998), be dependent on opioids (Simon, 2012), suffer from anxiety and depression (Smith et al., 2001), and have a lower overall quality of life (Gureje et al., 1998; Hart, Martelli, & Zasler, 2000; Smith et al., 2001).

Pain itself is a dynamic phenomenon that involves a physiological sensation of hurt caused by activation of nociceptive pathways from noxious stimuli (Latremoliere & Woolf, 2009). This is a protective process for the body which can help prevent injury by producing such a negative sensation that individuals try hard to avoid further contact with the stimuli.

Nociception is affected and controlled through many excitatory and inhibitory endogenous control mechanisms. These mechanisms include ascending excitatory, descending inhibitory, and spinal cord control pathways. Within the ascending pathways, the spinothalamic and spinoreticular tracts both carry nociceptive signals to higher centers in the brain from the spinal cord (Aitkenhead, Thompson, Rowbotham, & Moppett, 2013). The spinothalamic tract has secondary afferent neurons that intersect one another as they enter the spinal cord and carry signals to nuclei in the thalamus of the brain (Aitkenhead et al., 2013). This tract is important for pain localization. The

spinoreticular tract also has neurons that intersect one another before ascending the spinal cord to reach the brainstem reticular formation and continuing onto the thalamus and hypothalamus in the brain (Aitkenhead et al., 2013). This tract is important for the emotional aspects that go along with pain.

In the descending pathways, the periaqueductal grey (PAG) area in the midbrain and the rostral ventromedial medulla (RVM) are involved in pain inhibition and modulation (Serpell, 2006). The pathways from these areas in the brain descend the spinal cord and project onto the dorsal horn, which in turn inhibits pain transmission when activated (Serpell, 2006). At the spinal cord level, the gate control theory of pain posits that when A-beta fibers are activated through tactile, non-noxious stimuli, the inhibitory interneurons in the dorsal horn also activate, leading to pain inhibition (Macintyre, Walker, Power, & Schug, 2006). When one of these mechanisms goes awry, the pain that results can usually be categorized through identification of increased activity of the facilitating pain mechanisms or decreased activity of the pain inhibitory mechanisms (Teles et al., 2018). When these mechanistic issues persist and continue to cause pain after the healing phase of an injury, chronic pain ensues (Merskey and Bogduk, 1994). The amount of time considered as past healing is dependent on the area and type of pain, but often this period must continue longer than 3 months. The average duration of pain in chronic pain patients is 7 years (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

During this time period of chronic pain, individuals may experience central sensitization (Latremoliere & Woolf, 2009). This sensitization occurs when a noxious

stimulus is particularly intense or repeats multiple times, causing a decrease in the amount of stimulation needed for activation of the system which amplifies the response (Latremoliere & Woolf, 2009). This sensitization allows the nociceptive system to be highly alert to any potential risk that would cause further damage to the body. In a healthy individual, once there is no longer ongoing tissue injury, the activation threshold returns to baseline; the sensitization is not permanent (Latremoliere & Woolf, 2009). However, in an individual with chronic pain, the sensitization persists and is not considered protective. This may result in pain being elicited from normally innocuous stimuli (allodynia), exaggerated or prolonged pain when a noxious stimulus is applied (hyperalgesia), and/or the spread of pain beyond the site of injury to other parts of the body (secondary hyperalgesia). Quantitative sensory testing (QST) is one method used to assess and quantify these abnormalities seen in chronic pain patients (Rolke, Baron, et al., 2006; Rolke, Magerl, et al., 2006; Shy et al., 2003; Zaslansky & Yarnitsky, 1998).

### **Quantitative Sensory Testing**

Quantitative sensory testing is a protocol initially developed to assess and quantify abnormal sensory function in clinical practice (Fruhstorfer, Lindblom, & Schmidt, 1976). Since its implementation, QST has been utilized to assess pain sensitivity in individuals with a myriad of diagnoses as well as healthy individuals (Zaslansky & Yarnitsky, 1998). Testing is based on various stimulus properties (modality, intensity, spatial location, and timing) that analyze the quality of evoked sensation and quantify its intensity (Hansson, Backonja, & Bouhassira, 2007). Thermal, mechanical, ischemic, and

electrical stimuli excite various senses that engage different pathways in both the peripheral and central nervous systems (Reinhardt, Kleindienst, Treede, Bohus, & Schmahl, 2013).

Before the inception of QST, the major form of nervous system investigation was through nerve conduction studies (NCSs). NCSs evaluate the peripheral nervous system through detecting physiological properties of the nerves under investigation (Zaslansky & Yarnitsky, 1998). This type of testing requires highly trained personnel, is quite painful, and cannot be readily done in the field. QST was then developed as a quick, relatively noninvasive way to assess the nervous system. It can be easily used in the field to evaluate the functional properties of the entire sensory axis. QST is the only quantitative assessment of small nerve fibers that cannot be detected through routine electrophysiological techniques (Zaslansky & Yarnitsky, 1998). One of the major differences between QST and NCSs is the subjectivity of QST compared with the objectivity of NCSs. The sensory stimulus elicited from a particular test is an objective physical event, but the response is based on a subjective report from the participant (Shy et al., 2003). Because of this nature of QST, only results from a fully cooperative participant can be considered valid.

Quantitative sensory testing generally utilizes two different methodologies within a protocol: the method of limits and the method of levels. The method of limits increases or decreases the intensity of a certain stimulus until the participant perceives the stimulus (threshold) or perceives the stimulus as painful (pain detection threshold). The thresholds are calculated based on values from a series of the same tests, and all values are

dependent on reaction time (Hansson et al., 2007). An example of this style of testing is the determination of the heat pain threshold. In this test, the temperature slowly increases, and individuals identify when the stimulus first becomes painful by clicking a mouse. This dependency on reaction time can lead to small errors in measurement because each participant must perceive the stimulus, process the information gathered, and generate an action to give a response (Shy et al., 2003).

The method of levels involves a series of predefined stimuli. For each stimulus, the participant must determine whether the stimulus is perceived and whether it is painful (Hansson et al., 2007). Based on the participant's response, the intensity of the next stimulus can be systematically increased or decreased. An example of this style of testing occurs during light-touch detection tasks. An individual is touched with filaments of different sizes and identifies whether the touch is perceived. Based on the participant's response, the size of the filament is increased or decreased. This methodology does not depend on reaction time but can be very time-consuming when completing a full battery of tests. The increased time can lead to susceptible errors from decreased attention as testing progresses (Shy et al., 2003).

The common battery of tests for quantitative sensory testing usually includes thermal detection and pain thresholds, mechanical and pressure detection and pain thresholds, and dynamic thermal and mechanical examinations (Rolke, Baron, et al., 2006). Thermal testing investigates the function of small A-gamma fibers (cold) and C fibers (warmth). Detection can be examined through identification of when a stimulus changes in temperature. Thermal pain threshold can be determined through a participant

identifying when a temperature, either hot or cold, becomes painful. Within mechanical detection, light-touch testing utilizes the method of limits to determine detection. This assessment is known to activate the large myelinated A-alpha and A-beta sensory fibers (Chong & Cros, 2004). Mechanical threshold also utilizes the method of limits to assess fast A-beta sensory fibers and can be done through pressure testing or pinprick stimuli.

Dynamic thermal testing consists of examining conditioned pain modulation. Conditioned pain modulation (CPM) is a quantitative measurement of an individual's ability to inhibit pain and is used to investigate the efficacy of the diffuse noxious inhibitory control system in the body (Geva & Defrin, 2018; Teles et al., 2018). When the nociceptive system is functioning normally, the amount of pain perceived after the application of a conditioning pain stimulus decreases in comparison with the amount of pain perceived before the application of the conditioning pain stimulus; an individual's pain threshold increases. This can be tested through using cold water as a conditioning stimulus and pressure as a threshold measurement. An individual has a higher pressure-pain threshold when his or her hand is in cold water (conditioning pain stimulus) than when the pressure is added alone.

Dynamic mechanical testing involves examining a perceived increase in pain intensity (wind-up) through temporal summation in a specific area of the body. The test of summation is used to determine central pain-facilitatory processes through the method of limits and the method of levels. A painful stimulus can be identified utilizing the method of levels prior to the temporal summation task that uses the method of limits. A way to test temporal summation is with pinprick probes. A probe is repeatedly applied to

an area in an individual's body, and the individual reports pain scores as the pricks are repeated. This test outcome is normally characterized by a progressive increase of perceived pain as the pain stimulus is applied repetitively (Reinhardt et al., 2013).

All of these tests combined create a well-rounded assessment of pain sensitivity in healthy individuals and those with chronic pain (Rolke, Magerl, et al., 2006; Vachon-Preseau et al., 2013). These QST protocols are used not only clinically but also in a research context (Meh & Denišlić, 1994; Rolke, Magerl, et al., 2006; Shy et al., 2003). Indeed, a common use is to identify factors that are associated with increased pain sensitivity, such as stress (Dickerson & Kemeny, 2004; Geva, Pruessner, & Defrin, 2014).

## **Stress**

Stress, more specifically psychological stress, occurs when individuals perceive their environment to be taxing on their adaptive capacity (Cohen, Janicki-Deverts, & Miller, 2007). Past research has shown that stressful events can influence the pathology of various diseases through creating negative affective states, such as anxiety or depression. These negative affective states can impact biological processes and behavioral patterns that influence poorer health (Cohen, Kessler, & Gordon, 1997).

The stressor-elicited endocrine response can provide insight into this connection between psychological stress and physical disease. The hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenal-medullary (SAM) system are particularly susceptible to psychological stress (McEwen, 1998). The HPA uses cortisol

as its primary effector, which regulates many physiological and anti-inflammatory responses. The SAM uses catecholamines as its primary effector, which works with the autonomic nervous system to provide many regulatory effects on body systems. When these systems are activated repeatedly or for a prolonged time period because of stress, their control of other physiological systems can be disrupted. This prolonged activation of SAM through chronic stress has also been linked with cardiovascular disease (Rozanski, Blumenthal, & Kaplan, 1999) and impaired vagal tone (Porges, 1995).

### **Stress and Pain Sensitivity**

Pain research has found that chronic stress can exacerbate chronic pain conditions and is associated with increased pain sensitivity (Li et al., 2017; Moeller-Bertram et al., 2014). Individuals who have experienced chronic stress in their childhood have an increased incidence of chronic pain later in life (Afari et al., 2014; Barreau, Ferrier, Fioramonti, & Bueno, 2007; Fillingim & Edwards, 2005; Low & Schweinhardt, 2012). One mechanism for this relationship involves the dysfunction of the HPA axis (Brummelte et al., 2015). The dysfunction of this axis potentiated by chronic stress can cause increased cortisol release which has been linked with chronic pain disorders such as fibromyalgia, chronic back pain, and rheumatoid arthritis (Catley, Kaell, Kirschbaum, & Stone, 2000; Riva, Mork, Westgaard, Rø, & Lundberg, 2010; Vachon-Preseau et al., 2013).

The neurophysiological mechanisms that regulate pain perception are not just activated by chronic stressors but can be influenced by an acute stress response as well

(Vachon-Preseau et al., 2013). However, there has been limited research on how acute stress can affect pain perception, and the results in the literature have shown contradictory findings.

Some research studies have found that acute stress can inhibit the pain system in rodents (Madden, Akil, Patrick, & Barchas, 1977; Willer, Dehen, & Cambier, 1981). This is due in part to the descending inhibition of the spinal cord (Butler & Finn, 2009; Hohmann et al., 2005). This inhibition would be expected to reduce the activation of the ascending pain pathways lowering pain response. This mechanism could be an evolutionary adaptation to reduce pain during the fight-or-flight response (Millan, 2002).

Geva et al. (2014) examined the effect of acute stress on pain perception in a sample of 29 healthy men. Participants underwent two sessions of quantitative sensory testing with thermal and mechanical measures and an acute stress task completed in between the sessions. This study showed that stress had no impact on pain threshold and tolerance. Stress caused an increased response in temporal summation in individuals who were not stressed by the stress task and a decreased response in temporal summation in individuals who were highly stressed by the stress task. This result suggests that acute psychosocial stress has little effect on static pain sensitivity but significantly decreases an individual's ability to facilitate pain (Geva et al., 2014).

However, other studies showed opposite results. Caceres and Burns (1997) found that cold-pain threshold and tolerance were lower following an acute stressor compared with an application of no stress. Another study explored the impact of stress on pain sensitivity in a sample of 80 healthy females in which significant differences in pain

thresholds between the stress and nonstress conditions were found (Reinhardt et al., 2013). These results suggest an evolutionary adaptation increasing vigilance to potential harm with higher pain sensitivity.

Overall, the variability in results may be related to individual variability in stress responding. Studies measuring cortisol have found that individuals with the largest reactive cortisol response reported less pain unpleasantness during scanning (Vachon-Presseau et al., 2013; Wang et al., 2005).

### **Heart Rate Variability**

Heart rate variability (HRV) is a noninvasive technique that measures the amount of fluctuation around an individual's heart rate in order to examine the autonomic nervous system (Rajendra Acharya, Paul Joseph, Kannathal, Lim, & Suri, 2006). Thus, heart rate variability can be a proxy for measuring autonomic nervous system activation as a result of stress (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). Heart rate variability can be measured through frequency domains and time domains. Within the frequency domain, there are high-frequency (HF) oscillations that represent vagal activity and are between 0.15 and 0.4 Hz (Castaldo et al., 2015) and low-frequency (LF) oscillations that represent either sympathetic modulation or a combination of sympathetic and vagal influences and are between 0.04 and 0.15 Hz (Castaldo et al., 2015; Malik, 1996). The ratio of high-frequency oscillations to low-frequency oscillations (HF/LF) is a marker of the relative balance between sympathetic and vagal control (Malliani, Lombardi, & Pagani, 1994). The main measurement through the time domain involves

looking at the interval between heartbeats (R-R interval). An R-R interval measures the amount of time between the peaks of two consecutive QRS complexes (Singh, Vinod, & Saxena, 2004). A QRS complex represents the depolarization of the cardiac ventricles following ventricular contraction. The root mean square of successive differences (RMSSD) of R-R intervals can be calculated from these measurements and is considered a marker of vagal function that can correlate with high-frequency oscillations (Malik, 1996).

Heart rate variability can be affected by numerous conditions and is most reliable when used for a healthy individual at rest (Sandercock, Bromley, & Brodie, 2005). In order to help measure an individual's physiological reaction to stress, past research has looked into the values of HF, LF, HF/LF, and RMSSD (Castaldo et al., 2015). When acute stress was induced, the HF and RMSSD measurements decreased compared with the HRV measurements taken during a resting state (Castaldo et al., 2015). In contrast to these results, the ratio between HF and LF was found to increase during a stressful event compared with a resting state (Castaldo et al., 2015).

### **Purpose of Research**

Because of the unclear findings currently in research, the present study looks to extend previous work by examining the effects of acute stress on pain sensitivity in a large sample of both males and females using a within-groups experimental design. The study implements a QST protocol with static and dynamic measures across multiple modalities (pressure, heat, and cold) and uses HRV as a manipulation check to verify the

effects of the experimental stress task for inducing acute stress. The hypothesis of the work is that individuals who are exposed to an acute stressor will experience an increase in pain sensitivity compared with those who are not exposed to acute stress.

## METHODS

Ethical approval was obtained prior to recruitment for the study from the Institutional Review Board at Brigham and Women's Hospital (BWH).

### Participants

There were 62 participants (20 males, 42 females) aged 18-35 years (mean = 23.9, SD = 3.7) recruited by means of the Partners Healthcare Clinical Trials website (<http://clinicaltrials.partners.org>), fliers posted in BWH clinics, or word of mouth. Potential participants provided their names and contact information through either the Clinical Trials website or direct contact with the research team. Research staff then screened and scheduled potential participants using email. Participants were enrolled in the study after providing informed consent. Inclusion criteria consisted of the ability to read English at an eighth-grade level or above. Exclusion criteria consisted of the inability to read English at an eighth-grade level. Potential participants were also excluded for pregnancy, severe cognitive impairment, Raynaud's disease, sickle cell anemia, documented neuropathy, myocardial infarction within the past year, and cancer.

## **Measures**

### Pain Rating

Patients were asked to provide their current pain rating, if any, and location of pain on a standard 11-point numeric rating scale from 0 (no pain) to 10 (worst pain imaginable) (von Baeyer et al., 2009).

### Heart Rate Variability

Throughout the entire session, heart rate variability (HRV) was measured using the emWave® Pro system (HeartMath, USA) for 2 minutes a measurement to determine how HRV fluctuated during QST and the experimental conditions. Measurements were taken during the baseline and second QST protocol as well as after the stress tasks in the experimental condition. Specifically, the mean heart rate, high frequency (HF), high frequency/low frequency (HF/LF) ratio, and the root mean square of successive differences (RMSSD) of R-R intervals were measured during each HRV session. The HRV measurements were averaged to create baseline (measurements taken during baseline QST protocol), Stroop task (measurements taken after the Stroop task and before the mental arithmetic task), and mental arithmetic task (measurements taken after the mental arithmetic task) groups for analysis.

## **Acute Psychosocial Stressors**

### Stroop Color and Word Test

The Stroop Color and Word Test (SCWT) was designed to evaluate an individual's ability to inhibit cognitive interference (Stroop, 1935). A modified version of

this test was used to induce stress (Keinan, Friedland, Kahneman, & Roth, 1999; Renaud & Blondin, 1997). There were three trials included in the task in which participants were asked to read as quickly as possible without making any mistakes. Two of the trials had the congruous condition, and one had the incongruent condition. In the first congruous condition, participants read aloud the names of colors in black ink. In the second congruous condition, participants identified aloud the color of the ink printed on a row of X's. In the incongruent condition, participants were presented with names of colors (color-words) in conflicting ink colors and were asked to identify aloud the color of the ink instead of reading the word. For all trials, participants were timed. If they made any errors or took longer than 5 seconds to answer, they were required to restart from the beginning of the table. Results were recorded for the total time to complete each trial, the number of errors made, and the number of times the participant was required to start over.

#### Mental Arithmetic Task

In the mental arithmetic task (MAT), participants were required to count backward by 7's from 762 to 496 as fast as possible without errors. However, the participants were not told that they would be stopped at 496, and they did not know when the task would be terminated. Participants were asked to restart from 762 if they made an error or took longer than 5 seconds to provide the next value. Previous studies had found this task to cause acute stress (Castaldo et al., 2015; Keinan et al., 1999). Results were recorded for total time to complete each trial, the number of errors made, and the number of times the participant was required to start over.

## **Quantitative Sensory Testing**

Training of experimenters and standardization of all verbal instructions occurred prior to the start of the study. Participants completed seven different tests allowing for a comprehensive profile of somatosensory functions assessed with both thermal and mechanical procedures.

### Light-Touch Detection

The touch test was to determine mechanical detection threshold (MDT) as well as any sensation abnormalities in participants. A kit consisting of 20 nylon von Frey monofilaments (Semmes-Weinstein Monofilaments, Stoelting Co., Wood Dale, IL, USA) with increasing filament diameters (evaluator sizes 1.65-6.65) was used. The monofilaments were successively applied in increasing thickness on the skin over the dominant deltoid until a sensory threshold was detected. Participants were asked to keep their eyes closed during testing to avoid visual feedback concerning the stimuli, and they were also asked to verbally signal when a stimulus was perceived. Two trials were completed—one trial with the filaments ascending in size and another trial with the filaments descending in size. All data were reported in evaluator size and the average of both trials was used in the analysis (see Table 1).

### Pressure-Pain Sensation

Pressure-pain threshold (PPT) and pressure-pain tolerance were assessed using a pressure algometer (Somedic, Hörby, Sweden). The pressure algometer delivered a firm and quantifiable pressure through a flat base applied to the skin. The pressure applied through the base was transduced, amplified, and converted to an electrical reading on a

digital display in units of kilopascal (kPa). Testing was completed on the first knuckle of the thumb on the participant's dominant hand and on the dominant trapezius. The tests were performed twice in both areas for threshold and tolerance for a total of eight measurements. For the determination of PPT, participants were asked to verbally signal when they started to feel pain/discomfort in the affected region. For the determination of pressure-pain tolerance, participants were asked to verbally signal when they could no longer tolerate the pain in the affected region. Immediately after each measurement, participants scored their pain from 0 to 100, with 0 being no pain at all and 100 being the worst pain imaginable. The averages of the trials for thumb threshold and tolerance as well as the averages of the trials for trapezius threshold and tolerance were used in the analysis (see Table 1).

Response to deep pressure pain was measured by cuff pressure algometry (CPA). Deep-tissue mechanical stimulation was applied using a Hokanson rapid cuff inflator (D. E. Hokanson, Inc., Bellevue, WA, USA) and a standard blood pressure cuff wrapped around the dominant gastrocnemius muscle. Starting at 60 mmHg of pressure when the cuff was inflated, the pressure was increased by approximately 5 mmHg/s. Participants provided pain ratings after every pressure increase of 20 mmHg until a pain score of 40/100 was reached (P40), at which point the cuff was deflated. After a delay, the cuff was reinflated to the P40 pressure and was maintained for 3 minutes. Participants provided pain ratings every 30 seconds for the entire 3 minutes as well as a rating for any painful aftersensations 15 seconds following cuff deflation. The mean pain intensity rating was calculated by averaging the pain ratings from the 30-, 60-, 90-, 120-, 150-, and

180-second marks. The pain rating at the 180-second mark of inflation was subtracted from the initial pain rating of inflation to determine the value for pressure temporal summation (see Table 1).

### Mechanical Pain Sensitivity

Punctuate mechanical stimulation was applied using pinprick probes. The probe for temporal summation (TS) was determined by applying three different probes to the middle of the middle finger on the nondominant hand one time each, with participants providing pain ratings (0-100). The test of summation was used to determine central pain-facilitatory processes. The probe that received a pain rating greater than 10/100 was selected for the summation test. If all three probes were rated below 10/100 pain, the heaviest probe was used for the test. During the summation test, the stimuli were applied 10 times, and the participant was asked to provide pain intensity ratings (0-100) after the first, fifth, and tenth stimulus. This task was then repeated following the same procedure. The average of all three probe pain ratings was used to determine the average pain intensity of the probe. Temporal summation was calculated by subtracting the pain rating of the first stimulus from that of the tenth. The values of the two temporal summation trials were then averaged to find the mean temporal summation effect (see Table 1).

### Thermal Pain Sensitivity

#### *Heat-Pain Threshold*

Thermal thresholds were measured using a calibrated warm contact thermode (30 x 30 mm) connected to a Q-Sense apparatus (Medoc Advanced Medical Systems, Ramat Yishai, Israel) and were reported in degree Celsius (°C). The function of the apparatus

was based on the Peltier principle in which the direction and intensity of a specific current flow controls the surface temperature of the thermode throughout the duration of testing (Keinan et al., 1999; Renaud & Blondin, 1997). Two heat-pain threshold (HPT) trials were conducted on the skin of the nondominant forearm. Beginning at a baseline of 32 °C, the thermode increased in temperature using a rate of rise of 0.5 °C/s. Participants were instructed to press a button when the thermal stimulation became painful. The temperature at threshold was averaged across trials (see Table 1).

#### *Cold-Pain Assessment*

Responses to noxious cold were determined using a cold pressor task (CPT). Each participant immersed his or her dominant hand in a circulating water bath (Neslab RTE17, Thermo, Newington, NH, USA) at a temperature of 5 °C until the participant reached pain tolerance or a 3-minute maximum. Participants rated the pain intensity (0-100) from the cold every 15 seconds. These pain ratings were averaged across trials to find the mean pain intensity. The value used in the analysis for this task was the time in seconds until withdrawal (see Table 1).

#### *Cold Pain and Conditioned Pain Modulation*

Before measurement of conditioned pain modulation (CPM), the baseline PPT for the task was first assessed on the nondominant trapezius using the pressure algometer. The participants then completed a brief cold pressor task in which they immersed their hands in cold water (5 °C) for 15 seconds in the circulating water bath and provided a pain intensity rating (0-100). The PPT was then reassessed at the nondominant trapezius while the participant's hand remained in the noxiously cold water. Participants were told

to keep their hands in the water for the duration of the procedure. The CPM index was calculated from the baseline PPT and the PPT with the conditioning stimulus (see Table 1).

**Table 1. Outcomes With Corresponding Measures and Calculations<sup>a</sup>**

<b>Outcome</b>	<b>Measurement</b>	<b>Calculation</b>
Pain	Pain ratings	Average
Stress	HRV	Average
MDT	Light-touch detection	Average
Pressure-pain sensitivity	PPT; tolerance	Average
Deep pressure pain	CPA over 180 seconds	Average
TS	CPA; pinprick probes	Final rating - Initial rating
Punctuate mechanical stimulation	Pinprick probe rating	Average
HPT	Threshold temperature	Average
CPT	Seconds until withdrawal	Average
CPM	PPT; cold pressor task	(Final/Initial)*100

<sup>a</sup>This table summarizes the measurements and calculations that were done to determine the outcome values in the analysis. CPA = cuff pressure algometry; CPM = conditioned pain modulation; CPT = cold pressor task; HPT = heat-pain threshold; HRV = heart rate variability; MDT = mechanical detection threshold; PPT = pressure-pain threshold; TS = temporal summation.

## **Procedure**

Testing took place in a private room for a 2.5-hour period during a single study visit. The participants were instructed to refrain from caffeine and nicotine for 2 hours before testing. After giving informed consent, participants completed a series of questionnaires (as part of a larger study), including demographic information. They then completed HRV assessment. Following the first HRV assessment, all participants underwent baseline QST (QST 1) based on the procedure used previously in stress

studies (Meints, Wang, & Edwards, 2018). Using an online randomization tool, participants were randomized into one of two groups (high stress; no stress/control). In the high-stress condition, participants completed a modified Stroop test before starting the second round of QST, and they completed a mental arithmetic task (MAT) halfway through the second round of QST. In the control condition, participants were not exposed to psychological stressors and were instead given breaks before starting the second round of QST and halfway through the second round of QST. The second round of QST (QST 2) had the sensory tasks in a different order than the first round of QST. Throughout the entire session, HRV and stress were assessed intermittently. Figure 1 shows the timeline for the experiment.

<b>QST 1</b>	HRV	1. Touch Detection	2. PPT	3. CPA	HRV	4. TS	5. HPT	6. CPM	7. CPT
<b>Stress Task</b>	SCWT/Control								
<b>QST 2 Part 1</b>	HRV	1. TS	2. PPT	3. HPT					
<b>Stress Task</b>	MAT/Control								
<b>QST 2 Part 2</b>	HRV	4. CPM	HRV	5. CPA	HRV	6. CPT	HRV	7. Touch Detection	HRV

**Figure 1. Timeline for the experiment.** This figure shows the timeline of the experiment with each task shown and numbered in the order that it was completed in the baseline QST (QST 1) and the second QST session (QST 2). CPA = cuff pressure algometry; CPM = conditioned pain modulation; CPT = cold pressor task; HPT = heat-pain threshold; HRV = heart rate variability; MAT = mental arithmetic task; PPT = pressure-pain threshold; QST = quantitative sensory testing; SCWT = modified Stroop Color and Word Test; TS = temporal summation.

## **Data Analysis**

Data were analyzed using IBM SPSS Statistics software (IBM Corporation, Armonk, NY, USA) with a significance threshold of  $p < 0.05$ . The data underwent analysis for skewness and kurtosis along with visual inspection of normality using boxplots and histograms (Ghasemi & Zahediasl, 2012). All data, except the mean heart rate, pressure-pain tolerance of the thumb, HPT, and CPM indices, were transformed logarithmically before statistical analysis (Rolke, Magerl, et al., 2006). Nine of the QST tests were non-normal, and outliers more than two standard deviations from the mean were winsorized (Ghasemi & Zahediasl, 2012). All data of log-transformed QST parameters were retransformed to values representing the original units after analyses. To determine whether stress tasks were effective in inducing acute stress, 2 (stress: stress vs. no stress) x 3 (time: baseline vs. Stroop vs. MAT) repeated measures analysis of variance (ANOVA) tests were conducted for HRV outcomes and self-reported stress levels. This was followed by 2 (stress: stress vs. no stress) x 2 (time: QST 1 vs. QST 2) repeated measures ANOVAs for each QST outcome. Results were reported as the F-score, the p-value, and the effect size ( $\eta^2$ ). Post-hoc comparisons were used to assess group differences for all significant omnibus ANOVAs using a Bonferroni correction.

To determine how individual variation in the stress response impacted pain sensitivity, Spearman correlations between stress outcomes (i.e., HRV and stress ratings) and QST outcomes were completed. Results were reported as the Spearman's correlation coefficient ( $\rho$ ) and the p-value.

## RESULTS

### Stress Manipulation Check

Spearman correlations between the stress measurements including HRV and perceived stress after the Stroop task (Table 2) showed a positive correlation between HF and RMSSD ( $\rho = 0.89$ ,  $p < 0.01$ ). Spearman correlations between the stress measurements after the MAT (Table 3) also showed a positive correlation between HF and RMSSD ( $\rho = 0.84$ ,  $p < 0.01$ ). These correlations from both stress tasks suggest that the frequency domain and the time domain of the HRV measurements were correlated as expected.

**Table 2. Stroop Stress Measurement Correlations<sup>a</sup>**

Measure After Stroop Task	Spearman's Correlation Coefficient ( $\rho$ )		
	Stress Rating	RMSSD	HF
Stress Rating	-	-	-
RMSSD	-0.158	-	-
HF	0.013	0.891**	-
HF/LF	0.101	0.034	-0.08

<sup>a</sup>This table shows the Spearman correlations between the Stroop perceived stress ratings and HRV measurements (RMSSD, HF, and HF/LF). N = 62 participants. HF = high-frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations, RMSSD = root mean square of successive differences; Stroop = modified Stroop Color and Word Test (SCWT)

\*\* A significant correlation ( $p < 0.01$ ).

**Table 3. MAT Stress Measurement Correlations<sup>a</sup>**

Measure After MAT	Spearman's Correlation Coefficient ( $\rho$ )		
	Stress Rating	RMSSD	HF
Stress Rating	-	-	-
RMSSD	0.042	-	-
HF	0.063	0.84**	-
HF/LF	-0.049	-0.179	-0.086

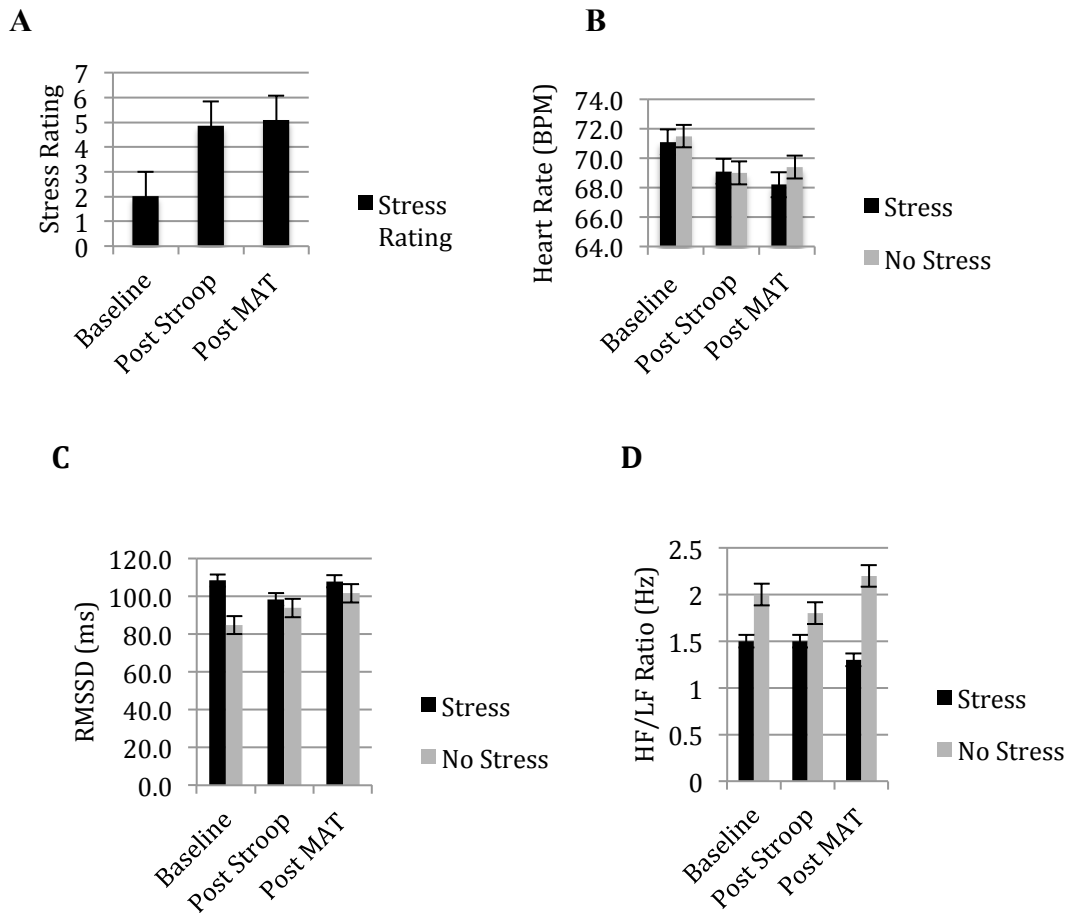
<sup>a</sup>This table shows the Spearman correlations between the MAT perceived stress ratings and HRV measurements (RMSSD, HF, and HF/LF). N = 62 participants. HF = high-frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations, RMSSD = root mean square of successive differences; MAT = mental arithmetic task.

\*\* A significant correlation ( $p < 0.01$ ).

Results of a series of 2 (stress group) x 3 (time) repeated measures ANOVAs indicated that there was a significant increase in perceived stress after the stress tasks were induced ( $F = 32.93$ ,  $p < 0.01$ ,  $\eta^2 = 0.71$ ). Figure 2A shows an average increase of 3 points (out of 10) after each stress task was completed by the stress group.

In Figure 2B, there was a main effect of time for heart rate ( $F = 17.60$ ,  $p < 0.01$ ,  $\eta^2 = 0.23$ ) in which the heart rate for participants significantly decreased between baseline (stress:  $71.1 \pm 9.8$ , no stress:  $71.5 \pm 9.9$ ), the Stroop task (stress:  $69.1 \pm 9.1$ , no stress:  $69.0 \pm 9.8$ ), and the MAT (stress:  $68.2 \pm 9.5$ , no stress:  $69.4 \pm 9.2$ ). In Figure 2D, the results indicated a main effect for stress for HF/LF ratio ( $F = 9.00$ ,  $p < 0.01$ ,  $\eta^2 = 0.13$ ) in which the stress group had lower ratios for baseline ( $1.5 \pm 2.0$ ), after the Stroop task ( $1.5 \pm 1.4$ ), and after the MAT ( $1.3 \pm 2.1$ ) compared with the no stress group at baseline ( $2.0 \pm 2.2$ ), after the Stroop task ( $1.8 \pm 1.6$ ), and after the MAT ( $2.2 \pm 1.8$ ).

There was also an interaction (Figure 2C) in which stress participants showed an increase in RMSSD after stress induction while no stress participants had decreases in RMSSD trending toward significance ( $F = 2.26, p = 0.071, \eta^2 = 0.04$ ). The HF and HF/LF ratio did not show significant differences between groups (Table 4).



**Figure 2. Stress measurements between experimental groups.** This figure shows the change in stress rating (A), heart rate (B), RMSSD (C), and HF/LF ratio (D) between baseline measurements, after the Stroop task, and after the MAT in stress and no stress groups. Data are plotted as means and standard deviations. N = 62 participants (29 stress condition, 33 no stress condition). HF/LF = ratio of high-frequency oscillations to low-frequency oscillations; MAT = mental arithmetic task; RMSSD = root mean square of successive differences; Stroop = modified Stroop color and word task (SCWT).

**Table 4. HRV Outcomes Between Experimental Groups<sup>a</sup>**

HRV Outcome	Condition	Baseline	Post Stroop	Post MAT
HR	No stress	71.5 ± 9.9	69.0 ± 9.8	69.4 ± 9.2
	Stress	71.1 ± 9.8	69.1 ± 9.1	68.2 ± 9.5
RMSSD	No stress	108.4 ± 1.8	98.4 ± 1.8	107.9 ± 1.6
	Stress	84.9 ± 1.7	93.8 ± 1.7	101.6 ± 1.5
HF	No stress	523.6 ± 3.2	467.7 ± 3.2	605.3 ± 2.9
	Stress	391.7 ± 2.8	405.5 ± 2.6	417.8 ± 2.7
HF/LF	No stress	2.0 ± 2.2	1.8 ± 1.6	2.2 ± 1.8
	Stress	1.5 ± 2.0	1.5 ± 1.4	1.3 ± 2.1

<sup>a</sup>This table shows the means and standard deviations for heart rate variability (HRV) measurements (RMSSD, HF, and HF/LF) under stress and no stress conditions at the baseline reading, after Stroop, and after MAT. N = 62 participants. HR = mean heart rate; HF = high frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations, RMSSD = root mean square of successive differences; Stroop = modified Stroop and Color Word Task (SCWT); MAT = mental arithmetic task.

### **Pain Sensitivity and Stress**

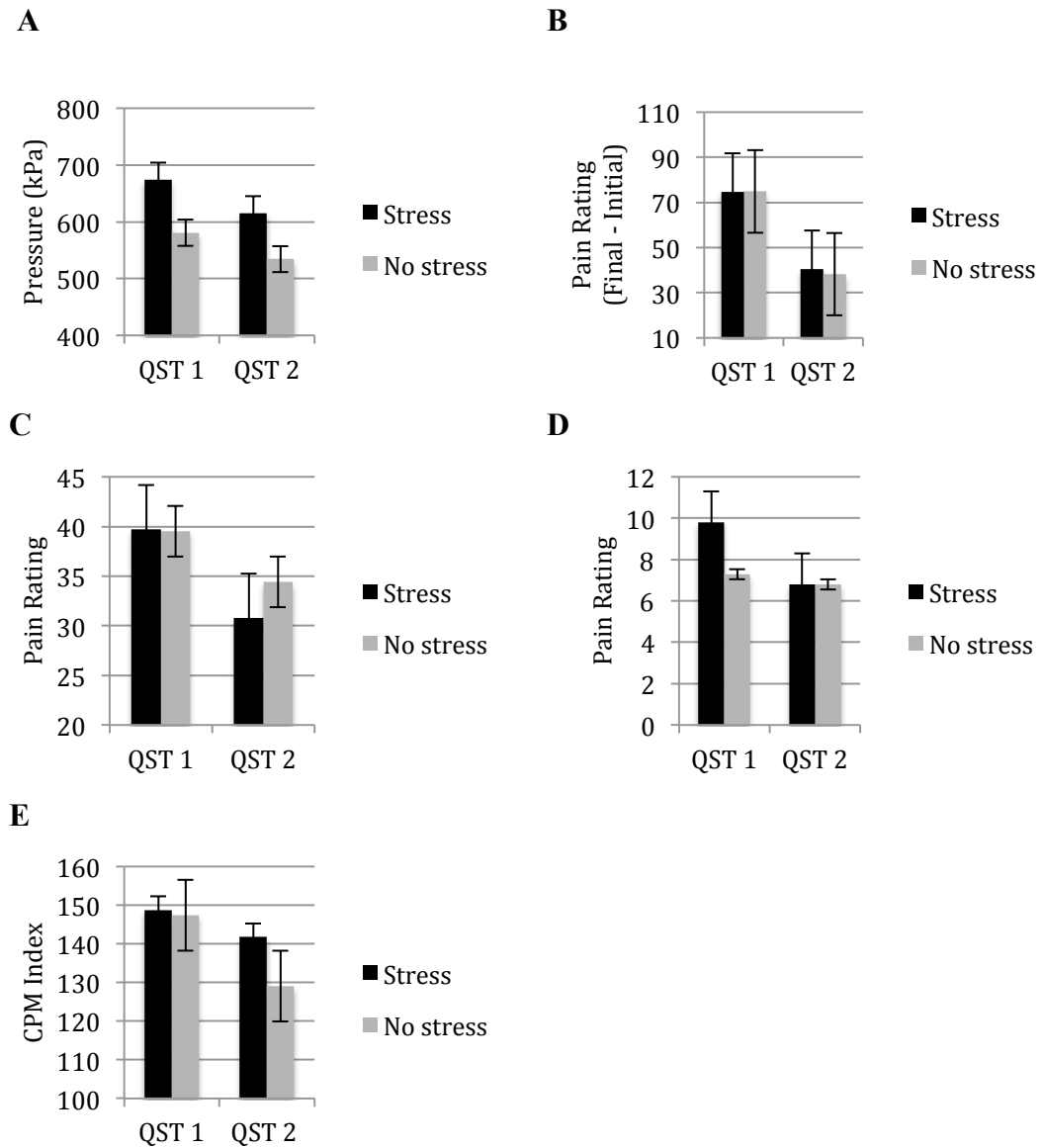
Table 5 shows the QST measurements for the two experimental groups. Results of a series of 2 (stress group) x 2 (time) repeated measures ANOVAs indicated a main effect of time for trapezius pressure-pain tolerance ( $F = 7.32, p < 0.01, \eta^2 = 0.11$ ), average cuff pain ratings ( $F = 10.54, p < 0.01, \eta^2 = 0.15$ ), temporal summation with the cuff ( $F = 122.75, p < 0.01, \eta^2 = 0.67$ ), average punctuate probe pain ratings ( $F = 14.39, p = 0.000, \eta^2 = 0.19$ ), and CPM index ( $F = 8.03, p < 0.01, \eta^2 = 0.13$ ). There were no main effects for time for other QST variables. All of the tests with a main effect for time had higher ratings during QST 1 than during QST 2. The trapezius pressure-pain tolerance (Figure 3A) was greater for QST 1 (stress:  $674.5 \pm 1.4$ , no stress:  $580.8 \pm 1.5$ ) than for QST 2 (stress:  $615.2 \pm 1.6$ , no stress:  $534.6 \pm 1.6$ ). The average cuff pain ratings (Figure 3C)

were higher for QST 1 (stress:  $39.7 \pm 1.5$ , no stress:  $39.5 \pm 1.5$ ) than for QST 2 (stress:  $30.8 \pm 1.7$ , no stress:  $34.4 \pm 1.6$ ). The temporal summation effect from the cuff (Figure 3B) was higher for QST 1 (stress:  $74.8 \pm 1.4$ , no stress:  $74.9 \pm 1.4$ ) than for QST 2 (stress:  $40.6 \pm 1.7$ , no stress:  $38.3 \pm 1.8$ ). The average punctuate probe ratings (Figure 3D) were higher for QST 1 (stress:  $7.3 \pm 2.2$ , no stress:  $9.8 \pm 1.9$ ) than for QST 2 (stress:  $6.8 \pm 2.5$ , no stress:  $6.8 \pm 2.4$ ). The CPM index was greater for QST 1 (stress:  $148.8 \pm 29.5$ , no stress:  $147.4 \pm 29.5$ ) than for QST 2 (stress:  $141.8 \pm 25.7$ , no stress:  $129.1 \pm 20.2$ ) (Figure 3E).

**Table 5. QST Outcomes Between Experimental Groups<sup>a</sup>**

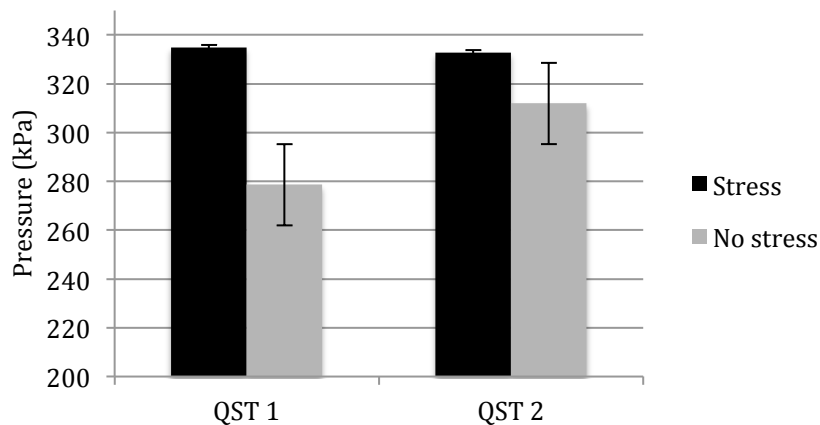
QST Outcome	Condition	QST 1	QST 2
Light-touch detection	No stress	3.3 ± 0.4	3.4 ± 0.4
	Stress	3.3 ± 0.4	3.2 ± 0.4
Pressure-pain threshold (thumb)	No stress	278.6 ± 1.3	311.9 ± 1.5
	Stress	334.9 ± 1.4	332.7 ± 1.4
Pressure-pain threshold (trapezius)	No stress	285.1 ± 1.5	285.8 ± 1.5
	Stress	358.1 ± 1.5	342.0 ± 1.5
Pressure-pain tolerance (thumb)	No stress	594.8 ± 169.1	612.7 ± 243.4
	Stress	613.9 ± 156.5	613.9 ± 217.5
Pain rating at tolerance (thumb)	No stress	46.0 ± 1.7	42.8 ± 1.9
	Stress	43.9 ± 1.9	41.4 ± 2.0
Pressure-pain tolerance (trapezius)	No stress	580.8 ± 1.5	534.6 ± 1.6
	Stress	674.5 ± 1.4	615.2 ± 1.6
Pain rating at tolerance (trapezius)	No stress	44.7 ± 1.9	44.2 ± 1.9
	Stress	46.5 ± 1.8	43.4 ± 1.9
Average cuff pain rating	No stress	39.5 ± 1.5	34.4 ± 1.6
	Stress	39.7 ± 1.5	30.8 ± 1.7
Temporal summation using cuff	No stress	74.9 ± 1.4	38.3 ± 1.8
	Stress	74.8 ± 1.4	40.6 ± 1.7
Cuff residual pain	No stress	2.0 ± 3.2	1.9 ± 3.1
	Stress	2.3 ± 3.3	2.1 ± 3.1
Punctuate probe pain rating	No stress	7.3 ± 2.2	6.8 ± 2.5
	Stress	9.8 ± 1.9	6.8 ± 2.4
Temporal summation using punctuate probe	No stress	8.4 ± 2.6	6.9 ± 3.1
	Stress	9.8 ± 2.7	10.1 ± 2.3
HPT	No stress	41.0 ± 2.9	40.7 ± 3.6
	Stress	41.6 ± 3.3	41.8 ± 3.2
CPM index	No stress	147.4 ± 29.5	129.1 ± 20.2
	Stress	148.8 ± 35.8	141.8 ± 25.7
Average pain rating during CPT	No stress	30.3 ± 2.0	30.1 ± 2.2
	Stress	24.9 ± 1.9	25.0 ± 2.0
CPT pain tolerance time	No stress	41.8 ± 2.6	43.2 ± 2.6
	Stress	45.3 ± 2.1	43.5 ± 2.1
Pain rating at CPT tolerance	No stress	17.9 ± 3.1	19.6 ± 3.1
	Stress	12.9 ± 3.3	15.5 ± 3.0

<sup>a</sup>This table shows the means and standard deviations for the QST measurements under stress and no stress conditions at the baseline QST (QST 1) and at the second QST session (QST 2). N = 62 participants. Light-touch detection measured in filament size. Pressure-pain threshold and tolerance measured in kPa. Cuff algometry measured in mmHg. Heat-pain threshold (HPT) and cold pressor task (CPT) measured in degrees Celsius. CPM = conditioned pain modulation.



**Figure 3. QST outcomes with significant main effect of time.** This figure shows the change in pain sensitivity between QST 1 and QST 2 in trapezius pressure-pain tolerance (A), cuff temporal summation (B), cuff pain rating (C), punctuate probe pain rating (D), and CPM index (E) for stress and no stress groups. Data are plotted as means and standard deviations. N = 62 participants (29 stress condition, 33 no stress condition). CPM = conditioned pain modulation; QST 1 = baseline QST; QST 2 = second QST session.

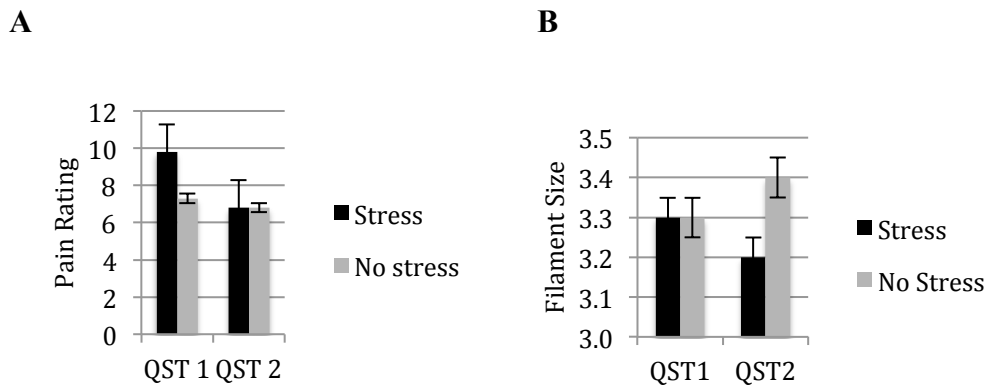
The results also indicated a main effect of stress for the thumb pressure-pain threshold ( $F = 4.51, p < 0.05, \eta^2 = 0.07$ ), with the pressure-pain threshold being higher for the stress group (QST 1:  $334.9 \pm 1.4$ , QST 2:  $332.7 \pm 1.4$ ) than for the no stress group (QST 1:  $278.6 \pm 1.3$ , QST 2:  $311.9 \pm 1.5$ ) (Figure 4).



**Figure 4. QST outcome with significant main effect of stress.** This figure shows the change in pain sensitivity between QST 1 and QST 2 in thumb pressure-pain threshold for stress and no stress groups. Data are plotted as means and standard deviations.  $N = 62$  participants (29 stress condition, 33 no stress condition). kPa = kilopascal; QST 1 = baseline QST; QST 2 = second QST session.

Figure 5 shows two interactions in the results between stress and time for the punctuate probe pain ratings ( $F = 6.499, p < 0.05, \eta^2 = 0.098$ ) and for light-touch detection ( $F = 4.075, p < 0.05, \eta^2 = 0.064$ ). For the average punctuate probe ratings (Figure 5A), the results of the stress group significantly decreased between QST 1 ( $9.8 \pm 1.9$ ) and QST 2 ( $6.8 \pm 2.4$ ), whereas the no stress group had less of a decrease in ratings

between QST 1 ( $7.3 \pm 2.2$ ) and QST 2 ( $6.8 \pm 2.5$ ). This task had both a main effect of time and a significant reaction between experimental groups. For light-touch detection (Figure 5B), the stress group became more sensitive to the filaments between QST 1 ( $3.3 \pm 0.4$ ) and QST 2 ( $3.2 \pm 0.4$ ), but the no stress group became less sensitive to the filaments between QST 1 ( $3.3 \pm 0.4$ ) and QST 2 ( $3.4 \pm 0.4$ ).



**Figure 5. Significant interactions between experimental condition and QST session.** This figure shows the change in pain sensitivity between QST 1 and QST 2 in punctuate probe pain rating (A) and light-touch detection (B) for stress and no stress groups. Data are plotted as means and standard deviations. N = 62 participants (29 stress condition, 33 no stress condition). QST 1 = baseline QST; QST 2 = second QST session.

### Correlation Between Stress Measures and QST Outcomes

Spearman correlations between the perceived stress ratings, HRV, and QST outcomes after the Stroop task (Tables 6 and 7) revealed a significant negative correlation between RMSSD and thumb pain tolerance ( $\rho = -0.322$ ,  $p < 0.05$ ) and between RMSSD and trapezius pain tolerance ( $\rho = -0.363$ ,  $p < 0.01$ ). There was another significant negative correlation between HF and thumb pain tolerance ( $\rho = -0.268$ ,  $p < 0.05$ ) and between HF

and trapezius pain tolerance ( $\rho = -0.331, p < 0.01$ ). There was also a significant positive correlation between HF and trapezius threshold ( $\rho = 0.264, p < 0.05$ ) and between HF and HPT ( $\rho = 0.282, p < 0.05$ ).

**Table 6. Stroop Stress and QST Outcome Correlations<sup>a</sup>**

Measure After Stroop Task	Spearman's Correlation Coefficient ( $\rho$ )					
	Thumb Threshold	Trapezius Threshold	Thumb Tolerance	Trapezius Tolerance	Thumb Pain Tolerance	Trapezius Pain Tolerance
Stress Rating	-0.004	-0.043	-0.003	-0.289	0.210	0.271
RMSSD	0.162	0.229	0.031	0.078	-0.322*	-0.363*
HF	0.189	0.264*	-0.007	0.079	-0.268*	-0.331*
HF/LF	-0.216	-0.082	-0.183	-0.081	-0.033	-0.030

<sup>a</sup>This table shows the Spearman correlations between the Stroop perceived stress ratings, HRV measurements (RMSSD, HF, and HF/LF), and the pressure QST measures that were completed after the Stroop task but before the mental arithmetic task. N = 62 participants. HF = high-frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations; RMSSD = root mean square of successive differences; Stroop = modified Stroop Color and Word Test (SCWT).

\* A significant correlation ( $p < 0.05$ ).

**Table 7. Stroop Stress and QST Outcome Correlations Continued<sup>a</sup>**

<b>Measure After Stroop Task</b>	<b>Spearman's Correlation Coefficient (<math>\rho</math>)</b>		
	Probe Pain	Probe TS	HPT
Stress Rating	0.206	0.023	0.113
RMSSD	0.028	-0.094	0.082
HF	0.049	-0.038	0.282*
HF/LF	-0.023	-0.360*	-0.148

<sup>a</sup>This table shows the Spearman correlations between the Stroop perceived stress ratings, HRV measurements (RMSSD, HF, and HF/LF), and QST measures that were completed after the Stroop task but before the mental arithmetic task. N = 62 participants. HF = high-frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations; RMSSD = root mean square of successive differences; Stroop = modified Stroop Color and Word Test (SCWT); TS = temporal summation; HPT = heat-pain threshold.

\* A significant correlation ( $p < 0.05$ ).

Spearman correlations between the HF/LF ratio and QST tests after the MAT test showed a significant positive correlation between the HF/LF ratio and the light-touch detection task (0.271,  $p < 0.05$ ) (Table 8). This positive correlation suggests that as the HF/LF ratio increased, the sensitivity to the filaments also increased.

**Table 8. MAT and QST Outcome Correlations<sup>a</sup>**

<b>Measure After MAT</b>	<b>Spearman's Correlation Coefficient (<math>\rho</math>)</b>							
	Light Touch	CPT Pain Rating	CPT Tolerance Time	CPT Pain Tolerance	Cuff Pain	Cuff TS	Cuff Residual Pain	CPM Index
Stress Rating	0.188	-0.096	-0.082	-0.106	-0.096	0.337	0.171	-0.146
RMSSD	-0.073	0.056	-0.031	0.083	0.056	-0.155	-0.066	0.176
HF	-0.091	0.069	-0.096	0.088	-0.227	-0.074	0.002	-0.104
HF/LF	0.271*	-0.005	0.153	-0.073	0.114	0.057	-0.078	-0.068

<sup>a</sup>This table shows the Spearman correlations between the mental arithmetic task (MAT) perceived stress ratings, HRV measurements (RMSSD, HF, and HF/LF), and the pressure QST measures that were completed after the MAT. N = 62 participants. HF = high-frequency oscillations; HF/LF = ratio of high-frequency oscillations to low-frequency oscillations, RMSSD = root mean square of successive differences; MAT = mental arithmetic task; CPT = cold pressor task; TS = temporal summation; CPM = conditioned pain modulation.

\* A significant correlation ( $p < 0.05$ ).

## **DISCUSSION**

This study investigated the changes in pain sensitivity as a result of experimental stress in a sample of 62 healthy individuals. Pain thresholds, pain tolerance, temporal summation, and conditioned pain modulation were assessed before and after stress induced by the Stroop task and a mental arithmetic task (MAT).

### **Reproducibility of Pain Measurements**

As demonstrated by the means and standard deviations between the first and second QST sessions, most pain measurements showed good intersession reproducibility, indicating stability over time. This finding is consistent with Reinhardt et al. (2013) and Geva and Defrin (2018) who also showed good reproducibility of thermal and pressure-pain measurements over time. This result continues to demonstrate that QST is a good, reliable measure of pain sensitivity that can be used to assess an individual's sensitivity over time.

### **Change of Pain Sensitivity Under Stress Conditions**

The effect of stress on pain thresholds was small and variable. For light-touch detection, individuals under the stress condition became more sensitive to the filaments after stress was induced, showing greater non-nociceptive sensory perception. The opposite trend was observed in punctuate mechanical stimulation with the pinprick probes. Individuals under stress reported lower pain ratings representing a lower pain

sensitivity after the stress tasks with lower nociception. Although not significant, pressure-pain threshold and tolerance decreased after stress induction. For descriptive analyses, the PPT tasks, pressure-pain tolerance tasks, average pain ratings during cuff algometry, and temporal summation using the cuff all had a tendency to decrease between QST 1 and QST 2 for individuals in the stress condition. In the no stress condition, most pressure tasks remained the same (trapezius pressure-pain threshold, thumb pain tolerance rating, trapezius pain tolerance rating, and average pain rating from cuff algometry) or increased (thumb pressure-pain threshold and thumb pressure-pain tolerance) between QST 1 and QST 2. Despite the lack of significance, this trend is consistent with the findings of Caceres and Burns (1997) and Reinhardt et al. (2013), suggesting that acute stress is associated with decreased pain sensitivity.

This relation between acute stress and decreased pain sensitivity means that stress potentially plays a role in descending inhibition of the spinal cord, reducing the activation of ascending pain pathways lowering the pain response (Butler & Finn, 2009). This effect could be an evolutionary adaptation to reduce pain when the sympathetic nervous system is activated during the fight-or-flight response (Millan, 2002). This finding could help explain why individuals under high-stress situations, such as an accident, may not feel as much pain from an injury as they would in everyday life. Clinical implications of this finding include when an individual goes into surgery. Previous research has shown that individuals get stressed prior to surgery (Broadbent, Petrie, Alley, & Booth, 2003; Spielberger, Auerbach, Wadsworth, Dunn, & Taulbee, 1973) and that this stress can impair healing (Broadbent et al., 2003) and have a negative effect on health-related

quality of life outcomes (Schelling et al., 2003). This stress may also impede an individual's ability to accurately rate pain, potentially affecting rehabilitation plans and health outcomes.

The QST measurements involving temperature showed that individuals in the stress condition either did not change from QST 1 to QST 2 or had a tendency to increase in pain ratings, indicating an increase in pain sensitivity after a stressful task. This result differed from the individuals in the no stress group who had a tendency to decrease their pain ratings and increase the amount of time in the cold water during the cold pressor task. These findings regarding temperature follow the results that Geva et al. (2014) and Millan (2002) reported previously.

This temperature relation means that stress could potentially play a role in heightening the sympathetic nervous system as an evolutionary mechanism to increase vigilance toward potential harm by causing increased pain (Reinhardt et al., 2013). Increased pain sensitivity under acute stress could be an extension of the previous finding that chronic stress can increase pain sensitivity, especially in chronic pain populations (Moeller-Bertram et al., 2014). These results could affect individuals who become stressed before going to see a physician. Previous research has shown that individuals can get stressed visiting a physician and that this can create negative emotions (Hyson, 1983) and negative interactions (Weitzman & Weitzman, 2003) between physicians and patients. If acute stress increases pain sensitivity, individuals may not be as accurate in judging their pain at an appointment as they would be in everyday life, leading to incorrect treatment of an ailment. This effect may have even higher implications if the

same phenomena are seen in chronic pain populations where opioid use is high (Furlan et al., 2006) and health-related quality of life is low (Hart et al., 2000; Smith et al., 2001).

These differing results could indicate that multiple evolutionary mechanisms are at play when stress is induced. Pain caused by temperature activates the small A-gamma fibers and small C fibers, whereas pain from pressure involves fast A-beta fibers (Chong & Cros, 2004). Because of these differences in nervous system activation, stimuli type could alter the effect that stress has on an individual.

For the cuff algometry temporal summation task, less temporal summation was found in the second round of QST compared with the first round, regardless of stress condition. Individuals could have had an expectation of pain going into the task, which is known to produce increased pain sensitivity (Keltner et al., 2006). The second time individuals completed the task was after the conditioned pain modulation task with the cold water bath. This could have caused individuals to have a lower expectation of pain for the cuff compared with the cold water bath, resulting in decreased pain sensitivity. Previous studies have shown that counterbalancing QST tasks across participants can avoid potential order and carryover effects (Bartley et al., 2016; Kosek & Ordeberg, 2000). However, the current study was not counterbalanced so as to help maximize the effect of stress in a uniform way. Future studies should counterbalance the protocol with the stress tasks to see if this changes the main effects of time seen in this study.

The pinprick probe temporal summation had almost the same scores for QST 1 and QST 2 in both conditions. In the two QST sessions, individuals showed summation, but stress did not lead to greater summation. Temporal summation is not a static pain

measurement but rather a dynamic measure of central pain sensitization. Because of this difference, it is possible that this task shows very different outcomes than the static measures such as threshold and tolerance. The temporal summation task is also well documented (Reinhardt et al., 2013; Rolke et al., 2006; Shy et al., 2003), and acute stress may not be enough to affect an individual's central sensitization. Reinhardt et al. (2013) did not find significant results for the effect of stress on a temporal summation task, and these results support the findings in this study.

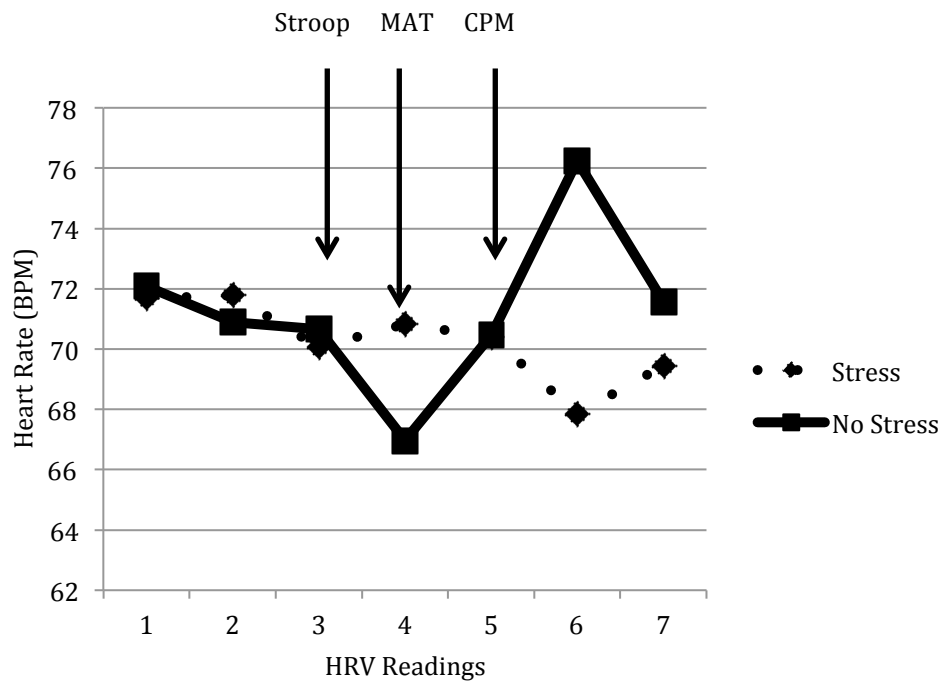
### **Physiological Responses to Stress**

The heart rate variability measurements throughout the study had mixed results. The decrease in heart rate and increase in RMSSD and HF from baseline to after the stress inductions are contrary to previous findings (Castaldo et al., 2015). The heart rate in the no stress condition increased after the CPM task, suggesting it may have been perceived as stressful or distressing (Figure 6). By contrast, the stress group demonstrated a decrease in heart rate after CPM. Together, these results suggest that although the CPM task was stressful or distressing, it may have been less stressful compared with the MAT and resulted in the decrease in heart rate.

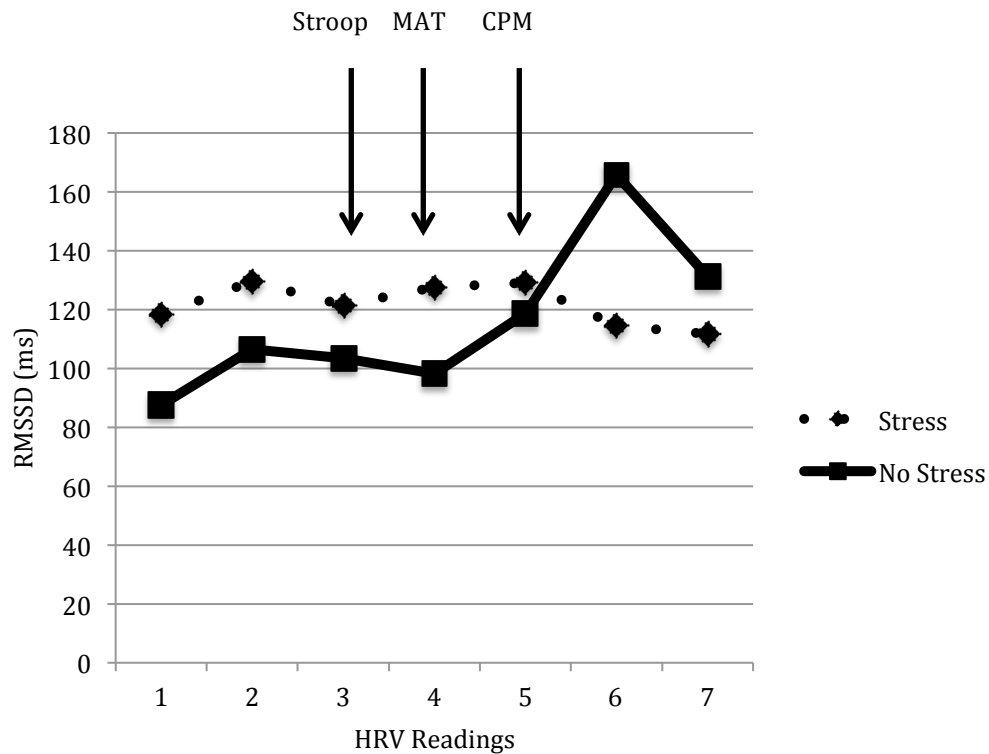
In the stress condition, the RMSSD remained relatively constant, while the no stress participants demonstrated increased measurements in the second QST (Figure 7), consistent with a relaxation response. It is possible that participants were worried (i.e., experiencing stress) about the upcoming sensory testing. Then, when asked to repeat the tasks, the knowledge of what to expect lowered that stress level. On the other hand, the

stress tasks, although not creating increased stress, kept stress levels from decreasing compared with those participants who did not experience the stress task.

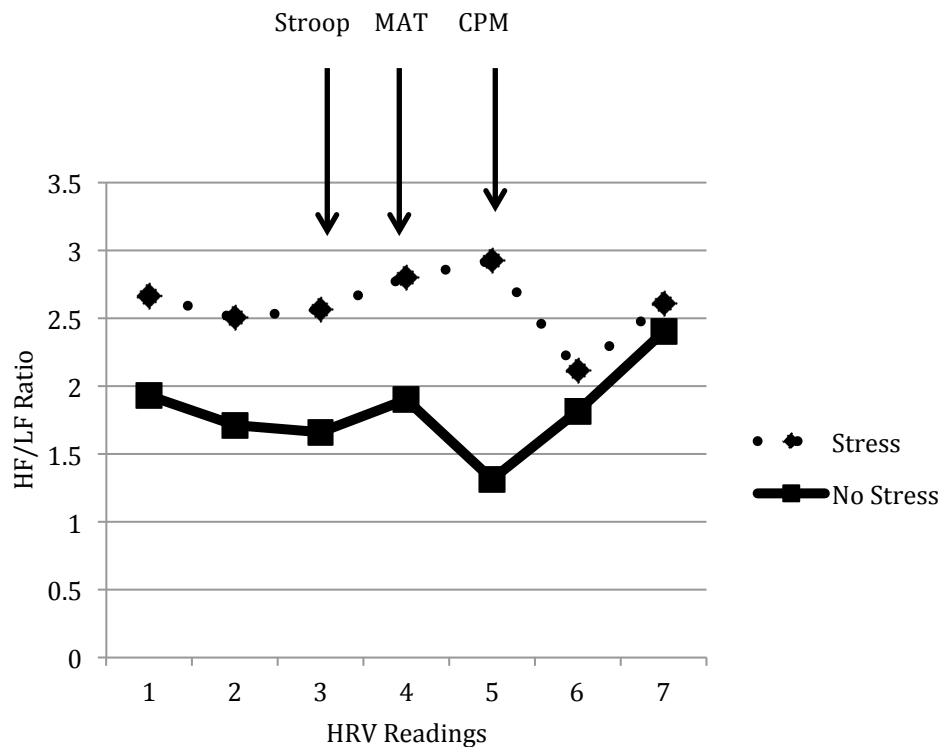
The HF/LF ratio decreased during the stress tasks but increased after CPM (Figure 8). This response supports the idea that compared with psychological stressors, the physical stress caused by the CPM task may have more of an effect on the physiological measurements of stress. An earlier study using CPM and acute stress found less inhibitory pain modulation (Geva et al., 2014), but the study did not include physiological measures of stress. Although the current study is novel in using HRV to measure stress, it is outside the scope of this work to determine differential effects of physiological stress (i.e., pain) and psychological stress on physiological stress measures. Thus, this aspect of the work should be examined in future research.



**Figure 6. Heart rate readings taken during QST 1 and QST 2.** Heart rate readings were taken in beats per minute (BPM) at seven time points for heart rate variability (HRV) during the study protocol. Time points 1 and 2 were completed during QST 1, time point 3 was immediately after the Stroop task, time point 4 was immediately after the mental arithmetic task (MAT), time point 5 was after conditioned pain modulation (CPM), and time points 6 and 7 were in the last portion of QST 2. N = 62 participants (29 stress condition, 33 no stress condition). Stroop = modified Stroop and Color Word Task (SCWT); MAT = mental arithmetic task; CPM = conditioned pain modulation; QST 1 = baseline QST; QST 2 = second QST session.



**Figure 7. RMSSD readings taken during QST 1 and QST 2.** RMSSD readings were taken at seven time points for heart rate variability (HRV) during the study protocol. Time points 1 and 2 were completed during QST 1, time point 3 was immediately after the Stroop task, time point 4 was immediately after the mental arithmetic task (MAT), time point 5 was after conditioned pain modulation (CPM), and time points 6 and 7 were in the last portion of QST 2. N = 62 participants (29 stress condition, 33 no stress condition. QST 1 = baseline QST; QST 2 = second QST session; RMSSD = root mean square of successive differences; Stroop task = modified Stroop and Color Word task (SCWT).



**Figure 8. High frequency/low frequency readings taken during QST 1 and QST 2.** High-frequency oscillations/low-frequency oscillations (HF/LF) readings were taken at seven time points for heart rate variability (HRV) during the study protocol. Time points 1 and 2 were completed during QST 1, time point 3 was immediately after the Stroop task, time point 4 was immediately after the mental arithmetic task (MAT), time point 5 was after conditioned pain modulation (CPM), and time points 6 and 7 were in the last portion of QST 2. N = 62 participants (29 stress condition, 33 no stress condition). QST 1 = baseline QST; QST 2 = second QST session; Stroop task = modified Stroop and Color Word Task (SCWT).

The HRV measures for this study contradict the perceived stress ratings that were found to be significant for the individuals in the stress condition. This could be due to the HRV measurements being inaccurate. Previous research on HRV suggested making measurements for a minimum of 5 minutes to get the most accurate reading (Sinnreich, Kark, Friedlander, Sapoznikov, & Luria, 1998). HRV readings could also vary based on age and sex (Malik, 1996; Rajendra Acharya et al., 2006; Sinnreich et al., 1998). Future studies should take these differences into account during analyses to see if results change based on age, sex, and length of the HRV measurement.

### **Limitations of Present Study**

There are several limitations in the present study. First, there were considerable individual differences in responses to the stressful tasks (both in self-rating and HRV), making it difficult to reliably determine whether the stress tasks were sufficient in producing a stress response. If stress induction was not sufficient, the study could not reliably determine the effect of acute stress on pain sensitivity. Future studies should focus more on individuals who have reported high ratings of perceived stress and who have shown physiological changes in response to stress.

Second, although there was fairly high test-retest reliability, there were still some tasks with a main effect of time. This could be potentially prevented in the future by randomizing the order of tests in each block. The length of the battery was also quite long. No other studies had their participants complete as many tasks in their batteries, and

the length of the protocol alone could have caused individuals to get impatient and try to finish tasks quicker. Also, the effects of the stress tasks may not have lasted the entire battery.

Third, pain sensitivity was investigated in a healthy, young sample. It can be expected that patients with chronic pain may differ from healthy participants in experiencing pain under baseline and stress conditions. Future studies should investigate whether the outcome findings of this study can extrapolate to these patient groups.

Fourth, predictors of stress-related change, such as demographic factors, trauma history, depression, and other psychosocial factors, were not tested. Because these factors may be associated with the experience of stress as well as pain, these aspects should be examined in future studies.

Finally, acute experimental stressors (the Stroop task and the MAT) were used for investigating changes in pain sensitivity under stressful conditions. These stress tasks do not necessarily mimic real-life stressors. However, they have been demonstrated to effectively introduce acute stress (Renaud & Blondin, 1997; von Baeyer et al., 2009) and are advantageous because they are systematic and thus reduce confounding and bias present in the simple measurement of real-life stressors.

## **Summary and Outlook**

This study revealed a tendency toward individuals having lower pain sensitivity after stressful conditions. However, strong variations based on task type and individual changes in pain sensitivity were observed. Future studies should investigate the effects of

stress on pain in chronic pain populations as well as the differences between sex, socioeconomic status, and other demographic and psychosocial factors.

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## CURRICULUM VITAE

