THE IMPACT OF TONIC PAIN ON IMPULSIVE DECISION-MAKING

A Thesis

by

FENAN SAMSON RASSU

Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Chair of Committee,	Mary Meagher
Committee Members,	Sherecce Fields
	Louis Tassinary
	Darrell Worthy
Head of Department,	Heather Lench

December 2016

Major Subject: Psychology

ABSTRACT

Pain impairs self-regulation and cognitive abilities related to decision-making. Additionally, clinical chronic pain patients have demonstrated impaired performance on risky decision-making tasks, often choosing immediate rewards at the cost of future consequences. Based on this literature, experiencing pain may lead to an increase in impulsive decision-making by demonstrating an increased preference for immediate rewards at the cost of delayed rewards on a measure of delay discounting (DD). Using a mixed between-group (no pain vs. pain)/within-subjects repeated measures design (DD before and during the manipulation), participants' delay discounting rates were assessed before and while experiencing either a no pain control (n = 38) or a painful, inflammatory heat stimulus (n = 38). Contrary to the hypothesis, participants in the pain demonstrated a shift in preference towards larger, delayed rewards over time (p = .024). The no pain control group did not experience a significant shift in preference over time (p = .051).

The results indicate that those that experienced pain displayed a reduction in impulsive decision-making. This shift towards larger, delayed rewards is in accordance with literature on experimental stressors and risky decision-making. This shift in reward preference may be due to a decrease in reward sensitivity.

ACKNOWLEDGEMENTS

I would like to thank my committee chair and advisor, Dr. Meagher, for all of her support and guidance throughout this process and over the course of the last few years. From undergraduate research assistant, to lab technician, and now graduate student, you've provided so many opportunities for me to grow, and I am eternally grateful.

To my committee members for all of their support and time, I greatly appreciate it. Also, thank you to the Psychology Department for all the support and encouragement they have expressed over the past few years.

Finally, to my wonderful family, thank you for the unconditional love, care, and support.

NOMENCLATURE

ACC	Anterior Cingulate Cortex
AUC	Area Under the Curve
BPM	Beats Per Minute
COMT	Catechol-O-Methyltransferase
DD	Delay Discounting
DDQ	Delay Discounting Questionnaire
DLPFC	Dorsolateral Prefrontal Cortex
FIR	Finite Impulse Response Filter
HR	Heart Rate
IGT	Iowa Gambling Task
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
SAM	Self-Assessment Manikin
SCL	Skin Conductance Level
TSST	Trier Social Stress Test
TRPV1	Vanilloid Transient Receptor Potential 1
VAS	Visual Analogue Scale
VMPFC	Ventromedial Prefrontal Cortex

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

Page

TABLE

1. INTRODUCTION

When faced with two values available at different time points, does one's preference remain consistent? Or do we adapt our choice to the context, or challenge, at hand? And if we do adapt, which option do we choose and why?

Goal-directed decision-making posits that pursuing a reward is dependent on the value of the difference between the outcome and the associated costs of that choice.[1] In the context of pain, an organism balances the value associated with a particular action (e.g. going for an enjoyable jog while in pain) against the consequence of said action (e.g. experiencing immediate pain). However, additional dimensions, including temporal factors related to reward availability, complicate this simple framework. In instances of chronic pain, for example, the immediate pain relief attained from consuming analgesics must be weighed against the long-term consequences of side effects.[2]

Pain motivates and drives organisms to act, or inhibit, particular behaviors. By its very nature, pain enhances survival by signaling potential or perceived harm and modifying behavior accordingly.[2,3] Due to its biological relevance, the brain's salience and cognitive control networks prioritize pain processing over concurrent information resulting in the disruption of ongoing cognitive processes.[4]

In the context of risky decision-making, an increase in risky choices has been reported in healthy individuals exposed to persistent pain[5] and in clinical patients experiencing chronic pain.[6–10] A possible explanation for why individuals in pain tend to act more impulsively is that due to pain leading to increased perseveration of choices and choosing outcomes that yielded high immediate gains despite higher losses in the

future.[11] However, the effect of pain on increasing risky decision-making is not always consistent.[12]

An alternative explanation through which pain may result in increased risky decision-making is that it may increase one's predisposition for making impulsive decisions. Impulsivity is a multidimensional construct that includes the inability to wait or inhibit a behavior, preference for immediate over delayed rewards, insensitivity to consequences, tendency to engage in risky behaviors, and having a limited attention span.[13,14] However, impulsive decision-making is most relevant to risky decision-making as it refers to preference for immediate rewards without adequate regard for future values or consequences.[15] In impulsive decision-making, the subjective value of a reward decreases as a function of delay to its delivery, put another way, a reward becomes less valued as it occurs later and later, a phenomenon known as delay discounting (DD).[16]

While there has been extensive research on the effect of pain on cognitive impairments (e.g. attention, learning, memory)[4,17] and self-regulation[18–20], the effect of pain on impulsive decision-making has been overlooked.

1.1 Intertemporal Choice and the Potential Effect of Pain

At one point, economists endorsed the belief that intertemporal choices, or rather, decisions involving alternatives whose costs and benefits are distributed over time, were consistent.[21] To better understand how people make decisions between these proximal and distal values, economists proposed a discounted utility model, a way of conceptualizing how people made decisions about immediate rewards against delayed

rewards.[21] The model proposed that individuals make decisions in an exponential manner; delayed values were discounted the further they were from the present in a time-consistent fashion. Under this conceptualization, a delay would lead to the same amount of discounting, regardless of the time in which the decision was made. This paradigm would suggest that delaying the delivery of a product by one day would lead to the same amount of time discounting regardless of whether the options occurred, for example, 1) between consuming the product tomorrow rather than today or 2) in a year and a day rather than in just a year.[22]

However, evidence to the contrary suggests that people do not discount future rewards at a constant rate. That is, options posed at times that are closer to the present are more salient than options that are presented further away.[23] For example, choosing between a) one dollar in one year and two dollars in one year and a day would seem less significant to an individual than choosing between b) one dollar today and two dollars tomorrow, even though the delays between both delay periods is one day. This time-inconsistent model of temporal discounting is known as hyperbolic discounting and suggests that individuals are biased to the present.[24]

While the predictive power of the hyperbolic discounting model has been well established[25], the hyperbolic discount function still provides only a limited explanation of intertemporal preferences.[21,26] Once thought of only as a trait-like variable[27,28], evidence for the plasticity of intertemporal choice is well documented.[29] Indeed, the activation of visceral drive states such as sexual arousal can lead greater discounting.[30] In an addiction population, opiate deprivation of heroin-dependent individuals leads to

greater discounting.[31] Similarly, nicotine deprivation for smokers produces greater discounting as well.[32–34]

Visceral influences contribute to manifestation of particular emotions that relate to changes in motivational drive states.[21,35] Visceral influences are generated by biological needs (e.g. thirst, hunger, sexual arousal, fatigue, pain, fear). These visceral influences often overtake competing goals and lead to short-sighted, immediate behaviors.[35] This assumption has also been embraced in a two-state decision-making model, which proposes that our preference for immediate rewards is related to "hot" emotional responses, while patience or delay of gratification emerges from more deliberative, "cold" reasoning.[36,37] An emotionally arousing experience, such as pain, would then be predicted to elicit "hot" emotional responses that increase impulsive decision-making and delay discounting. However, despite theories regarding the influence of visceral factors related to motivation and impulsivity, the effect of pain on delay discounting has not been examined.

1.2 Neural Mechanisms Underlying Pain and Impulsive Decision-Making

Numerous studies have established that decision-making mechanisms are disrupted during chronic pain conditions in both humans and animal models.[7,38–42] In animal studies, an inflammatory model of chronic pain in rats led to preference for high-risk options in a risky decision-making task.[38,41] Rats in the pain group demonstrated reduced tonic levels of dopamine, DOPAC (3,4-hydroxyphenylacetic acid; dopamine metabolite) and 5-HIAA (5-hydroxyindole-3-acetic acid; serotonin metabolite) in the OFC.[41] A follow-up study found that pain disrupted the ability of OFC neurons to

encode reward magnitude, thereby leading to impairment in the estimate of reward magnitude.[38]

Evidence from clinical and preclinical human studies demonstrate a central role for dopaminergic neurotransmission in modifying pain perception and analgesia.[43,44] Positron emission tomography (PET) studies have shown that dopamine transmission in the striatum increases during noxious stimulation in healthy participants, and was shown to be related to sensory and affective qualities of the pain, as well as emotional responses to the stimulation.[45] However, the extent to which experimental noxious stimulation affects dopaminergic activity in the prefrontal cortex, and therefore how this activity could lead to reduced prefrontal regulation, remains to be determined.

Human experimental pain models are utilized to model acute nociception and neuronal sensitization without producing nerve injury.[46] Inflammatory based experimental pain application activates several underlying mechanisms that contribute to neuropathic pain states.[47,48] Spontaneous burning pain, mediated in part by nociceptor sensitization, is elicited at the site of application, while central sensitization, a process that contributes to the development and maintenance of persistent pain, occurs in the nociceptors of the dorsal horn of the spinal cord. The use of inflammatory based experimental pain may then lend itself to studies of intertemporal decision-making as this modality of pain has been shown to activate cortical areas associated with executive and emotional functioning including the OFC, vmPFC, dlPFC, and anterior insula.[49]

While there aren't available studies that have tested the direct effect of pain on delay discounting, it has been established that dopamine levels in the prefrontal cortex

modulate impulsivity.[50,51] Administering a single 20mg dose of D-amphetamine to healthy human participants led to a reduction in delay discounting (reduced impulsivity).[52] This reduction in a bias towards closer temporal events is then believed to be due to the increase in dopamine due to the stimulant. Additionally, the presence of the Val158Met allele of the catechol-O-methyltransferase (COMT) gene correlates positively with impulsive choice. This occurs through degradation of dopamine via COMT in the frontal cortex, which leads to increased impulsivity.[53]

Taken together, these findings may suggest that tonic, inflammatory pain may also lead to reductions in dopaminergic activity in the frontal cortex, and subsequently greater discounting.

1.3 Current Study

The purpose of the present study was to determine the effect of pain on impulsive decision-making in healthy subjects. First, participants participated in a baseline delay discounting task. Next, they were randomly assigned to either the pain or control condition. Finally, they participated in an additional delay discounting task. A mixed between/within-subjects design was used to 1) assess individual delay discounting before and after exposure to either a pain or control manipulation and 2) assess change between the groups. To accomplish these purposes, a standardized acute, inflammatory pain stimulus was used to elicit tonic pain and individual discounting rates were assessed before and during exposure to the either pain or control manipulation.

Based on with past findings between pain and risky decision-making, the current study's hypothesis is that 1) individuals in the pain group will display greater delay

discounting (i.e. be more impulsive) when compared to the control group and 2) individuals in the pain group will display greater delay discounting (i.e. be more impulsive) after the pain manipulation, while those in the control group will not display a change over time.

2. MATERIALS AND METHODS

2.1 Participants

Healthy, pain-free college students of both sexes were eligible for study enrollment. Relative to studies using a clinical sample, the use of healthy, pain-free participants in the current study removes potential confounding variables such as pre-existing alterations in pain sensitivity that may affect neuroendocrine function and decision-making.

Individuals were unable to participate if they met any of the following criteria: (a) age less than 18; (b) ongoing chronic pain problems; (c) diagnosed with hypertension or taking medication for blood pressure; (d) circulatory disorders; (e) history of cardiac events; (f) history of metabolic disease or neuropathy; (g) pregnant; (h) use of nicotine, (i) use of prescription medication (e.g., analgesics, tranquilizers, antidepressants, corticosteroids, oral contraceptives, or ADHD medication); (j) neurological or psychiatric, or (k) chronic or acute health problems that affect the neuroendocrine system. Individuals were also asked to refrain from use of: (a) over-the-counter pain and allergy medication within 3 days of the study, (b) alcohol within 12 hours the experiment, and (c) caffeine within 4 hours of the experiment.

A total of 103 volunteers participated in the study, of which 2 were excluded for equipment malfunction. An additional 4 were excluded from analyses upon discovering they met exclusion criteria. A final 16 were excluded due to non-systematic presentation on the decision-making task after assessing for orderliness of the data.[54] The final

sample consisted of 81 healthy participants [33 male, 48 female, aged 18-21 years, M = 18.74 years, standard deviation (SD) =.91 years].

The study complied with the revised Declaration of Helsinki (2008) and was approved by Texas A&M University's Institutional Review Board. Informed consent was obtained from each participant at the beginning of the experiment. Participants received course credits for their participation and were informed that they could withdraw from the study at any time without forfeiting the credits.

2.2 Delay Discounting Questionnaire

The Delay Discounting Questionnaire (DDQ) was used to measure the effect of pain on preferences for immediate vs. delayed rewards.[55] The DDQ has been used to investigate impulsive decision-making related to addiction, risk behaviors, stress and psychiatric illness.[56–58] Participants were presented with choices between $10 available after a specified delay (i.e., 1, 2, 30, 180, or 365 days) and a smaller amount available immediately (e.g., "would you rather have $10 in 30 days or $2 now?"). This task used an adjusting amount process (adjusting the immediate amount in increments of ± $0.50) to determine indifference points between the delayed standard and immediate adjusting options for each of the five delays assessed. An indifference point reflected the smallest amount of money an individual chose to receive immediately instead of the delayed standard amount ($10) at the specific delay. The choice questions were presented in a randomized order determined by the computer program. Participants were told to pay attention to each scenario and to perform the task as if they were dealing with actual money. Previous work comparing real and hypothetical money rewards - using both

between and within-subjects designs - demonstrated that choices made in response to hypothetical rewards are similar to real rewards and can act as a proxy for real reward choices in delay discounting research.[59–61]

The choice questions were presented using a titration procedure that was determined by participant choices, with each participant making a total of approximately 60 choices. Indifference points across the different delays were characterized with an area under the curve (AUC) method with smaller area values indicating greater discounting by delay.[62] Greater preference for immediate reward is indicative of greater discounting of delayed reward and greater impulsivity.

To assess orderliness of delay discounting data, the Johnson and Bickel (2008) algorithm was used.[54] These criteria flag participants for whom either (1) the earliest indifference point is not greater than the latest indifference point by at least 10% of the delayed reward, or (2) any indifference point (starting with the second delay) exceeds the preceding indifference point by a magnitude greater than 20% of the delayed reward amount. These flexible criteria were developed to be used to identify participants who discount according to unexpected or atypical patterns.

2.3 Experimental Conditions

Participants were tested in one experimental session. To get a baseline measure of delay discounting, everyone participated in the first DDQ prior to any experimental manipulation. Afterwards, participants were randomly assigned to either the painful or the non-painful active control condition. Participants were blinded to which condition

they were assigned to; during the consenting processes, they were informed that they may or may not receive the painful treatment.

2.3.1 Pain Condition

For the painful condition, 0.3 mL of a 10% topical capsaicin solution (one-gram of capsaicin in 10 ml of 50% ethanol, 50% water) was topically applied to the center of the participant's non-dominant volar forearm via a circular filter paper with a diameter of 1.9-cm.[63] The filter paper was then covered by Tegaderm transparent dressing (3M Health Care, St. Paul, MN, USA). Then, a tonic thermal stimulus was applied to the area capsaicin using an electrical heating pad with a surface area of 35.56cm X 35.56cm (ZHP1414, BodyMed, Hudson, OH, USA). The heating pad was wrapped around the forearm to raise the skin temperature to a constant 37 °C. The capsaicin and heat combination was kept on the forearm for the rest of the experiment.

Capsaicin is the active ingredient of chili peppers. When coupled with heat, it induces heat sensitization by activating temperature-dependent TRPV1 receptor (vanilloid transient receptor potential 1) ion channels.[64] The combination of 10% topical capsaicin with heat has previously been shown to reach peak intensity at approximately 15 min and induce a stable level of pain intensity for approximately 1 hr. [63,65,66]

2.3.2 Control Condition

Participants in the control condition were treated with 0.3mL of a vehicle solution (50% ethanol, 50% water). Thermal stimulation procedures and pain rating procedures were the same as the painful condition.

2.4 Manipulation Checks

Subjective pain responses and physiological measures were recorded to confirm whether the painful condition was more arousing than the control condition.

2.4.1 Subjective Responses to Pain

Participants were trained to make pain ratings prior to capsaicin application. They were also given time to practice rating until they were confident with their abilities. A computerized 10-point visual analogue scale (VAS) was used to rate pain intensity and unpleasantness.[67] The VAS consisted of a horizontal bar on a computer screen that ranged from 0 to 10, with 0 signifying "no pain intensity/unpleasantness" and 10 representing "the most intense/unpleasant pain imaginable".

To measure subjective emotional reaction to the painful stimulus, each VAS rating was followed by a rating on a computerized version of the Self-Assessment Manikin (SAM).[68] The SAM is a three-item questionnaire that yields valence (sad to happy), arousal (calm to excited), and dominance ratings (no control to complete control) that range from 1 to 9. Higher scores indicate greater valence, arousal, and dominance. Participants responded by clicking on any of the nine pictographs individually for each of the 3 subscales. The SAM provides a valid and reliable measure to assess emotional responses to stimulation. The split-half coefficients for the valence and arousal dimensions have been shown to be highly reliable, with coefficients for valence and arousal being $r = .94$ and $r = .94$, respectively.[69] It has also been previously used to measure emotional responses to capsaicin.[68,70,71]

2.4.2 Physiological Measurement

Psychophysiology was recorded using a Biopac MP150 system (BIOPAC Systems Inc., Goleta, CA, USA). Recordings were sampled at 1000hz. Skin temperature was measured with a Biopac SKT100C amplifier and a stainless steel skin thermistor applied on the volar forearm, two cm distal to the site of capsaicin application. ECG was recorded with a Biopac ECG100C amplifier and two disposable Ag-AgCl electrodes, positioned in a modified lead-2 placement. The peak of the R- waves was used for the calculation of heart rate (HR) in beats per minute (BPM). Skin conductance level (SCL) were measured with a Biopac GSR100C amplifier via two electrodes attached on the volar surfaces of the medial phalanx of the index and middle fingers. All the recordings were reduced and analyzed offline using AcqKnowledge 4.2 (BIOPAC Systems Inc., Goleta, CA, USA). A band-pass finite impulse response (FIR) filter (35.0-0.5Hz) was used to remove noise for heart rate data and low-pass FIR filter (1Hz) was use for skin conductance data.

2.5 Procedure

All participants were tested between the hours of 2 pm and 8 pm in order to minimize circadian variation in cortisol. The experiments were conducted in a sound attenuated and temperature controlled room. The DDQ, self-report ratings, and physiological data collection were administered via computer with dual monitor capability. The control room contained one computer monitor for the experimenter to observe physiological signals and direct the experiment, while a second monitor in the participant's room was used to answer questionnaires, make pain ratings, and perform

the DDQ. Participants were monitored from the adjacent control room via a video camera.

Figure 1 illustrates the timeline of experimental procedures. All participants were provided an overview of the experiment before informed consent was obtained. Demographics, health status, and psychological measures were then assessed during baseline questionnaires. Participants were then familiarized with the VAS and practiced making ratings until they felt comfortable.

Next, the experimenter attached electrodes to the participant, then left the room while a 10 min baseline physiological recording occurred, with the instructions that the participant remain as still as possible during the recording. At the end of the recording, the experimenter returned to the room and explained the instructions for the DDQ. The participant was then left alone in the room while the participant answered the DDQ.

At the end of the decision-making task, the experimenter re-entered the room to apply either the capsaicin or vehicle solution and heating pad to the forearm. The participant was reminded that they could receive either compound and that once applied, they would begin to make ratings of the sensation at 2 min intervals. The experimenter then left the room while physiological recordings and pain ratings took place.

After approximately 15 min, the experimenter entered the room and re-read the instructions for the DDQ to the participant. The participant was again left alone in the room and answered the DDQ while also continuing to experience the painful or control stimulus.

At the conclusion of the second DDQ, participants filled out the exit questionnaires. Participants were then debriefed and provided course credit. Each experiment took approximately 2.5 hrs to run.

2.6 Statistical Analyses

Prior to data analysis, all variables were examined for missing values, outliers, normality of distribution, and homogeneity of variance and covariance.

To test our main hypothesis - the influence of pain on impulsive decision-making - a mixed ANOVA was calculated with condition as the between-subjects factor and pre/post DDQ scores as the within-subjects factor. To test the second hypothesis of comparing changes between two time points within a group, paired samples *t*-tests were conducted. Effect sizes were calculated as Cohen's *d*.

Following significant interaction effects of the ANOVAs, post hoc simple main effects were conducted to compare mean values between conditions. Effect sizes were calculated as partial eta squared (partial η^2).

To assess the effect of capsaicin and heat on pain and affect responses relative to individuals in the control, heat alone condition, two-way mixed analysis of variances (ANOVAs) for pain intensity, pain unpleasantness, and SAM responses were conducted.

To evaluate the whether the two conditions differentially influenced autonomic responses, mixed analyses of covariance (ANCOVAs) were conducted for HR and SCL during the stimulation period with condition (capsaicin + heat or heat alone) as the between-subjects factor and time at one min increments as the within-subjects factor. The last five mins of the baseline physiological recording served as the covariate.[72]

The Greenhouse-Geisser correction was applied to the degrees of freedom when needed for violations of sphericity.[73] Each analysis was a 2-tailed test with a *p*-value of < 0.05 considered significant, unless otherwise indicated. All statistical analyses were performed using SPSS, version 20 (IBM, Chicago, IL, USA).

2.6.1 Handling Missing Values and Outliers

When there were missing values for physiological data due to excess artifacts during the recordings that could not be appropriately reduced, listwise deletion was used to exclude those participants from physiological analyses.[74] Based on this criteria, 21 participants were excluded from physiological analysis.

Outliers were assessed with inspection of boxplots, studentized residuals > ±3 standard deviations, and visual inspection of QQ plots for normality of studentized residuals. Based on these methods of inspection, there were a few outliers for pain intensity and unpleasantness at different time points, and one outlier for SAM valence. Additionally, there were a few outliers for the physiological data. After the data was inspected for abnormalities, it was kept in for analysis.

2.6.2 Assumptions For Statistical Analyses

Shapiro-Wilk's test was performed to check normality after outliers were addressed. When the assumption of normality was violated, skew and kurtosis were examined. Skew and kurtosis values were used to conduct a z-test by dividing the skew or kurtosis values by their standard errors. A score within the ±2.5 range is considered normally distributed at a statistical significance level of .01.[75]

Pain intensity and unpleasantness ratings were not consistently normally distributed at each time point. Logarithmic transformation did not consistently fix normality, so data was left untransformed.

Using the prior criteria, the assumption of normality was not violated for most psychological and physiological data. However, even when normality could not be assumed for some measures (e.g. pain ratings), robustness was expected in this sample because of equal samples in groups, two-tailed tests, and greater than 20 degrees of freedom for error.[73]

Levene's test was used to assess homogeneity of variances between groups for the dependent variable. The test indicated equal variances for physiological and most SAM data (p's $> .05$). However, the assumption was violated for pain intensity and unpleasantness, as well as SAM Arousal ratings.

Box's M was used to assess homogeneity of covariances when running mixed ANOVAs. All data violated this assumption (p's $< .05$).

3. RESULTS

3.1 The Impact of Pain on Delay Discounting

During the baseline DDQ, there was no difference in the average delay discounting between the pain 0.48 (*SD* = 0.27) and control 0.52 (*SD* = 0.26) groups, $F(1,74) = 1.301$ $p = .258$, partial $\eta^2 = .017$. This suggests that any differences between groups in their DDQ scores would likely be due to the pain manipulation and not pre-existing differences.

To test the hypothesis that pain would lead to an increase in discounting rate, a one-way ANOVA was conducted to examine the effect of the condition on delay discounting AUC. The initial analysis revealed no significant difference between groups post manipulation, $F(1, 76) = 1.125$, $p = .292$, partial $\eta^2 = .015$. Next, an ANCOVA was conducted with post manipulation DDQ AUC as the dependent variable and baseline DDQ AUC as the covariate. This analysis also revealed no significant difference between the groups, $F(1, 74) = 0.005$, $p = .944$, partial $\eta^2 = .000$.

A follow-up mixed 2 (Pain vs. control) X 2 (Pre and Post DDQ AUC) ANOVA revealed no significant interaction or main effect of group (p's > .100), however there was a significant main effect of time, $F(1,74) = 9.366$, $p = .003$, partial $\eta^2 = .112$. This time effect indicates that discounting increased after the manipulation relative to baseline discounting (Figure 2).

While no significant interaction occurred, follow-up paired samples *t*-tests were conducted to determine which group was driving the main effect of time. *T*-tests revealed that the pain group showed a significant increase in DDQ values, $t(37) = 2.35$, p

= .024, d = .36, after the manipulation (M = .45, SD = .28) relative their baseline DDQ performance (M = .41, SD = .23). However, the control groups did not show a significant change DDQ values after pain (p = .051).

Interestingly, the change from lower to higher AUC values in the pain group indicates that participants shifted their preferences towards larger, delayed rewards, suggesting that participants in the pain condition made less impulsive decisions after the painful stimulation. Participants in the control group, however, did not display a significant shift in preferences between the two trials.

3.2 Manipulation Checks

3.2.1 Pain Ratings

To determine if the capsaicin + heat produced a painful sensation above heat alone, a mixed 2 (pain vs. control group) by 8 (time points) ANOVA was conducted. Analysis revealed a Group X Time interaction for pain intensity, $F(1.866, 3.170) = 21.847$, $p < .0001$, partial $\eta^2 = .219$, and pain unpleasantness, $F(2.197, 3.294) = 18.021$, $p < .0001$, partial $\eta^2 = .188$.

Participants in the pain group (capsaicin + heat) reported greater pain intensity and unpleasantness within the first two mins (intensity M = 0.2, SD = 0.38; unpleasantness M = 0.4, SD = 0.73) when compared to the control (heat alone) group (intensity M = 0, SD = 0.01; unpleasantness M = 0.1, SD = 0.05) (See Table 1 for pain ratings).

Figure 3 shows that participants in the pain condition steadily increased their ratings over time, then plateaued towards the tail end of the 15-min period. The pain

group also reported significantly greater ratings than the control group throughout the 15-min period.

3.2.2 SAM Ratings

Measures of affective valence, arousal, and dominance were expected to significantly change from baseline during the 15-min stimulation period for both groups, with the pain condition then demonstrating a significant decrease in valence and dominance, and a significant increase in arousal, relative to the control group during the 15-min stimulation period.

Supporting this, a two-way mixed ANOVA indicated that there was a statistically significant interaction between the group and time for each affective dimension, valence: $F(3.026, 236.011) = 8.998$, $p < .0001$, partial $\eta^2 = .103$; arousal: $F(3.150, 245.678) = 7.913$, $p < .0001$, partial $\eta^2 = .092$; dominance: $F(2.647, 238.252) = 5.295$, $p = .003$, partial $\eta^2 = .63$.

Figure 4 shows that participants in the painful condition experienced lower valence and greater arousal at 2 mins into the stimulation period when compared to the control group (See Table 2 for SAM ratings). At 6 mins, the painful condition began to report significantly lower dominance scores than the control group. These differences between groups continued through the rest of the stimulation period, with the exception of 10 mins for dominance scores in which no difference was seen, $F(1, 79) = 3.912$, $p = .05$, partial $\eta^2 = .047$.

Taken together, participants in the pain group experienced greater subjective stress during the stimulation period relative to the control group.

3.2.3 Psychophysiology

Prior work has demonstrated a significant difference between participants experiencing capsaicin + heat vs. heat alone control group on measures of physiological response.[76] As such, autonomic activity, as indexed by heart rate and skin conductance level, were expected between the Pain and control conditions. A two-way mixed ANCOVA indicated that there was not a statistically significant main effect of group, nor was there a Time X Group interaction (p's > .100) for heart rate and skin conductance levels.

Figure 5 shows heart rate and skin conductance values during the stimulation period (See Table 3 for physiological values). After controlling for baseline physiology, no significant differences emerged at any of the 15-min time points between the two groups. Paired samples t-test showed that participants in the painful condition experienced a statistically significant mean decrease of 2.99 BPM from baseline to the first 1 min of recording, 95% CI [1.91, 4.06], $t(29) = 5.676$, $p < .0001$, $d = 1.04$. However, participants in the control group experienced a similarly significant mean deceleration of 3.56 BPM, 95% CI [2.16, 4.95], $t(29) = 5.217$, $p < .0001$, $d = .95$. Relative to baseline, participants' SCL in the pain condition significantly increased by 3.24 μS, 95% CI [2.38, 4.10], $t(29) = 7.70$, $p < .0001$, $d = 1.41$. Participants in the control group also experienced a similarly significant mean increase of 3.03 μS relative to baseline, 95% CI [2.17, 3.89], $t(29) = 7.23$, $p < .0001$, $d = 1.31$. These data would suggest that changes from baseline to the start of the stimulation are similar for both groups, and that the capsaicin + heat is not producing a change beyond heat alone.

4. DISCUSSION AND CONCLUSIONS

By its nature, pain is an experience that demands attention and orients individuals to the immediate threat. One would expect then, that experiencing a painful stimulus would lead to preference for immediate over delayed rewards. Indeed, both clinical and preclinical evidence has shown that experiencing pain tends to produce risk-prone choice patterns that favor immediate, large gains at the cost of even larger losses.[11,41,77]

The primary objective of the current study, then, was to test the hypothesis that experimental pain would cause individuals to discount delayed rewards for immediate rewards. This hypothesis, however, was not supported by evidence from the study. Using a delay discounting questionnaire to measure discounting rates before and after a pain manipulation, the data suggests the contrary. Individuals in the pain group discounted delays less (i.e. AUC value was higher) than they did prior to the pain manipulation. While individuals in the control group trended towards less delay discounting, the difference before and after the active control manipulation was not significant.

4.1 Pain and Impulsive Decision-Making Studies

This is the first study to investigate the effect of experimental pain on intertemporal decision-making in healthy individuals. The finding that pain leads to a shift towards less impulsive choices on the DDQ is in line with a growing body of work that suggests that painful, physical stressors can lead to less risky decision-making. For example, Porcelli & Delgado (2009) found that a stress-inducing cold-pressor task led to individuals making fewer risky choices (stronger risk aversion behavior) in the domain

of gains when compared to the no stress group during a probability based financial decision-making task.[78] Additionally, Lighthall et al. (2009) found that after a cold-pressor task, women made less risky decisions on a measure of risky decision-making involving monetary rewards compared to the control group.[79] However, men made more risky choices relative to their controls. These contrasting results of sex were mediated by a differential cortisol response to the stimulus: women produced a greater cortisol response to the stressor relative to baseline whereas men did not.

An important difference in these two cold-pressor studies is the interval of time between when the cold-pressor stressor was administered and when the decision-making task was introduced. Cold-pressor studies that administer the stressor approximately 15 mins prior to presentation typically do so with the goal of inducing HPA axis activation and peak levels of cortisol release.[80] This is in contrast to activation of sympathoadrenal axes at the onset of a stressor, which is associated with an immediate release of norepinephrine and epinephrine.[81] While Lighthall et al. (2009) utilized a 15 min interval during their study, Porcelli & Delgado (2009) introduced their financial task immediately after the stressor, potentially capturing effects of sympathetic-adrenal activation as opposed to the HPA axis. However, both studies observed a reduction in risky choices, regardless of timing.

Although the current study did not observe significant differences in autonomic activity through objective measures of HR and SCL, there were significant differences in subjective distress (e.g. valence, arousal, and dominance/control) to the manipulation, indicating that a mild distress response was produced (See Table 2 for SAM ratings).

Taken together, the findings from these studies suggest that multiple factors related to the nature and timing of pain, including affective and neuroendocrine responses, may influence reward related decision-making.

However, despite prior evidence from our laboratory that the capsaicin + heat pain manipulation led to poorer performance and greater immediate reward responsiveness on a separate risky decision-making task[5], participants who experienced the pain in the current study displayed less impulsive decision-making. This may be attributable to the nature of the risky decision-making task utilized in the past study, the Iowa Gambling Task (IGT). The IGT is dissimilar from the DDQ used in the current study in that the IGT does not directly present options that are more immediately rewarding against options that are more rewarding in the future, but rather is built on risk (i.e. gain and loss). Looking at similar work, individuals that experienced an acute pain stressor displayed greater risky choices (less risk aversion behavior) in the domain of losses when compared to the no stress group during a probability based financial decision-making task (although it did not reach significance [$p < .10$]).[78] It is possible that individuals experiencing acute pain and stress may react differently in situations where the context is more risk-oriented due to the inclusion of loss in the decision-framework.

4.2 Stress and Delay Discounting Studies

While no other study has examined the effect of experimental pain on delay discounting, laboratory psychosocial stressors have been utilized to study the effect of stress on delay discounting.[82–84] However, the results of these studies are inconsistent.

For instance, a study by Kimura et al. (2013) found that participants did not differ in discounting rates prior to and after a Trier Social Stress Test (TSST).[82] However, they did notice a shift towards increased discounting of delayed rewards (preference for immediate rewards) when they compared a subset of participants grouped as responders and non-responders to the stressor (highest vs. lowest quartile in cortisol response). The shift in discounting towards immediate rewards was in the opposite direction from the current study. These opposing findings may be attributable to the difference in stress response magnitude produced between the TSST and the capsaicin + heat used in the current study. Although the two tasks' stress responses have not been compared within one study, the TSST produces greater HPA response than the cold pressor test, a commonly used experimental pain task.[85]

Based on the results from Kimura et al. (2013), our lab (Rassu et al. [2016]), examined the effects of a painful cold-pressor manipulation on delay discounting rates in individuals with high perceived stress.[86] The goal was to utilize a painful stressor that could mimic the intense physiological stress response that the Kimura group observed with their psychosocial stressor. Relative to controls, the manipulation checks indicated that the pain group experienced significantly greater SAM subjective arousal (M = 6.57, SD = 2.13) and sympathetic activation, as indexed by skin conductance levels (M = 5.77, SD = 2.46). After adjustment for pain tolerance time and perceived stress on the day of the experiment, the pain group displayed greater delay discounting AUC values relative to the high perceived stress control group, suggesting that pain led to significantly less discounting, or reduced impulsivity, compared to the no pain group. This decrease in

delay discounting from Rassu et al. (2016) is in line with another study reporting that participants with high perceived stress discounted rewards at a lower rate when challenged with an anticipatory psychosocial stressor relative to high stressed individuals who did not receive the laboratory stressor.[83]

The findings from these previous delay discounting studies[82,83,86] and the present study suggest that the context in which an acute stressor is presented can produce varied effects on intertemporal choice; they reveal an important interaction between 1) basal stress levels and 2) the magnitude of stress reactivity to acute stressors on delay discounting. While the current study did not observe increases in subjective or autonomic arousal levels (See Table 2 for SAM ratings, Tables 3 and 4 for physiological responses) as high as observed in Rassu et al. (2016), a similar shift in direction for arousal levels and discounting rate were observed. However, the lack of an observed significant interaction effect in the current study between the manipulation condition and time for delay discounting may be explained by the relatively smaller physiological stress response produced.

4.3 Possible Mechanism

A possible reason for the shift towards choosing larger, delayed rewards in the current study may be due to the effect of pain on reward sensitivity. In other words, the painful stressor may be producing a stress-induced anhedonia that could alter the value placed on rewards at different time points. To understand why this is relevant, consider that the value of a reward typically decreases as the distance in time increases. As such, individuals generally prefer immediate rewards to delayed rewards. However, if the

value of the immediate reward is reduced due to a lack of pleasure that the reward elicits, an individual may be more inclined to choose a larger, delayed reward.

Evidence for shifts in discounting rates due to reduced reward responsiveness comes from a study that observed that anhedonia was negatively associated with discounting rates, suggesting that individuals displaying anhedonia chose larger, delayed rewards.[58] The authors interpreted this finding to mean that these individuals were less biased to immediate rewards due to their lack of reward responsivity.

Further evidence for why pain may affect reward sensitivity lies in the fact that pain and reward processing share overlapping brain circuitry (e.g. anterior and posterior insula, amygdala, anterior cingulate cortex (ACC), dorsal and ventral striatum, and the orbitofrontal cortex). [87–89] Clinically, chronic pain patients display increased levels of anhedonia and lower levels of self-report reward responsiveness when compared to healthy controls.[90,91] This reduction is also correlated with diminished nucleus accumbens volume, suggesting that pain the may lead to morphological changes in reward brain regions.[92]

Shifting focus to pre-clinical research, a study by Berghorst et al. (2013) found that individuals who were high stress responders to a threat-of-shock stimulus, with regards to cortisol and negative affect, demonstrated reduced reward sensitivity relative to participants in the no stress group on a probability based decision-making task.[93] Similarly, a study by Bogdan and Pizzagalli (2006) found that participants in the threat-of-shock condition displayed less response bias (reward responsivity) when compared to a no stress control group.[94]

Work with animals has also indicated that acutely injured adult rats displayed increased motivation to remain at the center of open field arena where rewarding food pellets were present, when compared with uninjured controls.[95] However, the same injured rats did not eat more food than the control group. This would suggest that pain did not increase the rewarding properties of food, as evidenced by unaltered eating behavior between the groups. Similarly, a study by Gandhi et al. (2013) found that human participants who experienced a tonic painful capsaicin + heat stimulus displayed increased motivation behavior for larger monetary rewards, but did not experience increased liking, or reward responsiveness.[76] In other words, winning a larger amount of money was valued the same during both the pain and no pain conditions. Although anhedonia was not measured in the current study, it did utilize a similar pain stimulus to Gandhi et al. (2013), and as such, may also be affecting reward responsiveness in participants to a similar degree.

While it is evident from the aforementioned studies that stressors are able to produce a reduced reward response on several monetary decision-making tasks, would a reduction in reward responsivity affect delay discounting as well? To answer this, one could observe underlying reward related brain circuitry affected by stressful stimuli that are necessary for delay discounting. As such, a recent neuroimaging study determined that a reduction in reward responsiveness to monetary values was associated with stress induced reductions in activation of the striatum during the consumatory phase of a monetary choice task.[96]

This finding is also mirrored when using acute, painful stimuli; a cold-pressor administered immediately prior to a reward paradigm led to reduced activity in brain regions involved in reward processing, including the orbitofrontal cortex and dorsal striatum.[97] Considering the involvement of these brain regions for intertemporal choice [98,99], this lack of activation of the orbitofrontal cortex and striatum due to stress may then contribute to a reduction in responsiveness to immediate rewards, which could manifest as less delay discounting, or rather, selection of larger, distant rewards.

4.4 Limitations

The shift in reduced delay discounting in the pain group was based on post hoc mean comparisons using a paired samples *t*-test. The *t*-test was used as a follow-up to a significant main effect of time observed when using a mixed ANOVA, rather than a time by group interaction. While a significant interaction was not observed when using a mixed ANOVA, a recent study from our lab also observed a reduction in delay discounting for individuals experiencing a laboratory cold pressor pain stimulus, relative to a control group.[86]

Although a shift in delay discounting rate in the pain group was observed in the current study, the use of a between-within group design may have also been a limitation that may have prevented a more robust effect from being observed. Considering the brief interval between the first and second administration of the DDQ, the participants may have recalled their response style from the first DDQ and tried to mimic it for the second DDQ. However, a within-subject design with a stressor manipulation has been successfully used in previous delay discounting work during one session.[82] Moreover,

the current study observed a significant effect of time for the DDQ, suggesting that there were changes in responses between the two administrations.

Additionally, the current study induced a lower level of pain intensity, unpleasantness, and arousal relative to other heat + capsaicin studies.[76,100,101] The lower ratings may have contributed to the small effect size observed. A future study may want to replicate the current study's design, but incorporate standardization of pain levels by adjusting heating temperatures until a certain pain rating is attained.[76]

4.5 Conclusion

In conclusion, the current study found that tonic laboratory pain led to a reduction of delay discounting for future rewards. Although physiological arousal induced by the pain stimulus was minimal, pain that increased subjective stress ratings produced reductions in impulsive decision-making on a monetary intertemporal choice task.

REFERENCES

1. Rangel, A. & Hare, T. Neural computations associated with goal-directed choice. *Curr. Opin. Neurobiol.* **20,** 262–270 (2010).
2. Wiech, K. & Tracey, I. Pain, decisions, and actions: a motivational perspective. *Front. Neurosci.* **7,** 46 (2013).
3. Fields, H. A motivation-decision model of pain: the role of opioids. *Proc. 11th world Congr. pain* (2006).
4. Moriarty, O., McGuire, B. E. & Finn, D. P. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog. Neurobiol.* **93,** 385–404 (2011).
5. Furl, B., Rassu, F. & Meagher, M. W. Pain and decision style affects performance on emotional decision-making. in *Society for Neuroscience* (2014).
6. Apkarian, a V., Bushnell, M. C., Treede, R.-D. & Zubieta, J.-K. Human brain mechanisms of pain perception and regulation in health and disease. *Eur. J. Pain* **9,** 463–84 (2005).
7. Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A. & Bechara, A. Executive function and decision-making in women with fibromyalgia. *Arch. Clin. Neuropsychol.* **24,** 113–22 (2009).
8. Walteros, C. *et al.* Altered associative learning and emotional decision making in fibromyalgia. *J. Psychosom. Res.* **70,** 294–301 (2011).
9. Hess, L. E., Haimovici, A., Muñoz, M. A. & Montoya, P. Beyond pain: modeling decision-making deficits in chronic pain. *Front. Behav. Neurosci.* **8,** 263 (2014).

10. Berger, S. E. *et al.* Risky monetary behavior in chronic back pain is associated with altered modular connectivity of the nucleus accumbens. *BMC Res. Notes* **7,** 739 (2014).

11. Apkarian, A. V. *et al.* Chronic pain patients are impaired on an emotional decision-making task. *Pain* **108,** 129–36 (2004).

12. Elvemo, N., Nilsen, K. B., Landrø, N. I. & Christian, P. Patients with chronic pain lack somatic markers during decision-making. *J. Pain Res.* **7,** 425–437 (2014).

13. Reynolds, B., Ortengren, A., Richards, J. B. & de Wit, H. Dimensions of impulsive behavior: Personality and behavioral measures. *Pers. Individ. Dif.* **40,** 305–315 (2006).

14. Evenden, J. L. Varieties of impulsivity. *Psychopharmacology (Berl).* **146,** 348–361 (1999).

15. Green, L., Myerson, J. & Mcfadden, E. Rate of temporal discounting decreases with amount of reward. *Mem. Cognit.* **25,** 715–723 (1997).

16. van den Bos, W. & McClure, S. M. Towards a general model of temporal discounting. *J. Exp. Anal. Behav.* **99,** 58–73 (2013).

17. Eccleston, C. & Crombez, G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol. Bull.* **125,** 356–66 (1999).

18. Solberg Nes, L., Carlson, C. R., Crofford, L. J., de Leeuw, R. & Segerstrom, S. C. Self-regulatory deficits in fibromyalgia and temporomandibular disorders. *Pain* **151,** 37–44 (2010).

19. Solberg Nes, L., Roach, A. R. & Segerstrom, S. C. Executive functions, self-

regulation, and chronic pain: a review. *Ann. Behav. Med.* **37,** 173–83 (2009).

20. Hamilton, N. a., Karoly, P. & Kitzman, H. Self-Regulation and Chronic Pain:The Role of Emotion. *Cognit. Ther. Res.* **28,** 559–576 (2004).

21. Berns, G. S., Laibson, D. & Loewenstein, G. Intertemporal choice--toward an integrative framework. *Trends Cogn. Sci.* **11,** 482–8 (2007).

22. Loewenstein, G., Rick, S. & Cohen, J. D. Neuroeconomics. *Annu. Rev. Psychol.* **59,** 647–72 (2008).

23. Ainslie, G. W. Impulse control in pigeons. *J. Exp. Anal. Behav.* **21,** 485–9 (1974).

24. Ainslie, G. Specious Reward: A Behavioral Theory of Impulsiveness and Impulse Control. *Psychol. Bull.* **82,** 463–496 (1975).

25. Angeletos, G., Laibson, D. I., Repetto, A., Tobacman, J. & Weinberg, S. The Hyperbolic Consumption Model: Calibration, Simulation, and Empirical Evaluation. *J. Econ. Perspect.* **15,** 47–68 (2001).

26. Frederick, S., Loewenstein, G. & O'Donoghue, T. Time discounting and time preference: A critical review. *J. Econ. Lit.* **40,** 351–401 (2002).

27. Kirby, K. N. One-year temporal stability of delay-discount rates. *Psychon. Bull. Rev.* **16,** 457–462 (2009).

28. Odum, A. L. Delay discounting: trait variable? *Behav. Processes* **87,** 1–9 (2011).

29. Lempert, K. M. & Phelps, E. A. The Malleability of Intertemporal Choice. *Trends Cogn. Sci.* **20,** 64–74 (2015).

30. Kim, B. K. & Zauberman, G. Can Victoria's Secret change the future? A subjective time perception account of sexual-cue effects on impatience. *J. Exp.*

Psychol. Gen. **142,** 328–35 (2013).

31. Giordano, L. a. *et al.* Mild opioid deprivation increases the degree that opioid-dependent outpatients discount delayed heroin and money. *Psychopharmacology (Berl).* **163,** 174–182 (2002).

32. Yi, R. & Landes, R. D. Temporal and probability discounting by cigarette smokers following acute smoking abstinence. *Nicotine Tob. Res.* **14,** 547–58 (2012).

33. Mitchell, S. H. Effects of short-term nicotine deprivation on decision-making: delay, uncertainty and effort discounting. *Nicotine Tob. Res.* **6,** 819–28 (2004).

34. Field, M., Santarcangelo, M., Sumnall, H., Goudie, A. & Cole, J. Delay discounting and the behavioural economics of cigarette purchases in smokers: the effects of nicotine deprivation. *Psychopharmacology (Berl).* **186,** 255–63 (2006).

35. Loewenstein, G. Out of control: Visceral influences on behavior. *Organ. Behav. Hum. Decis. Process.* **65,** 272–292 (1996).

36. Metcalfe, J. & Mischel, W. A hot/cool-system analysis of delay of gratification: dynamics of willpower. *Psychol. Rev.* **106,** 3–19 (1999).

37. McClure, S. M., Laibson, D. I., Loewenstein, G. & Cohen, J. D. Separate neural systems value immediate and delayed monetary rewards. *Science (80-.).* **306,** 503–507 (2004).

38. Pais-Vieira, M., Aguiar, P., Lima, D. & Galhardo, V. Inflammatory pain disrupts the orbitofrontal neuronal activity and risk-assessment performance in a rodent decision-making task. *Pain* **153,** 1625–35 (2012).

39. Fu, Y. *et al.* PKA and ERK, but not PKC, in the amygdala contribute to pain-related synaptic plasticity and behavior. *Mol. Pain* **4,** 26 (2008).

40. Mongini, F., Keller, R., Deregibus, A., Barbalonga, E. & Mongini, T. Frontal lobe dysfunction in patients with chronic migraine: a clinical–neuropsychological study. *Psychiatry Res.* **133,** 101–106 (2005).

41. Pais-Vieira, M., Mendes-Pinto, M. M., Lima, D. & Galhardo, V. Cognitive impairment of prefrontal-dependent decision-making in rats after the onset of chronic pain. *Neuroscience* **161,** 671–9 (2009).

42. Ji, G. *et al.* Cognitive impairment in pain through amygdala-driven prefrontal cortical deactivation. *J. Neurosci.* **30,** 5451–64 (2010).

43. Jarcho, J. M., Mayer, E. a, Jiang, Z. K., Feier, N. a & London, E. D. Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction. *Pain* **153,** 744–54 (2012).

44. Wood, P. B. Mesolimbic dopaminergic mechanisms and pain control. *Pain* **120,** 230–234 (2006).

45. Scott, D. J., Heitzeg, M. M., Koeppe, R. A., Stohler, C. S. & Zubieta, J.-K. Variations in the Human Pain Stress Experience Mediated by Ventral and Dorsal Basal Ganglia Dopamine Activity. *J. Neurosci.* **26,** 10789–10795 (2006).

46. Klein, T., Magerl, W., Rolke, R. & Treede, R.-D. Human surrogate models of neuropathic pain. *Pain* **115,** 227–33 (2005).

47. Woolf, C. J. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* **152,** S2-15 (2011).

48. Torebjörk, H., Lundberg, L. & LaMotte, R. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J. Physiol.* **448,** 765 (1992).

49. Lorenz, J. *et al.* A unique representation of heat allodynia in the human brain. *Neuron* **35,** 383–93 (2002).

50. Volkow, N. D., Fowler, J. S., Wang, G. J., Baler, R. & Telang, F. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology* **56,** 3–8 (2009).

51. Dagher, A. & Robbins, T. W. Personality, Addiction, Dopamine: Insights from Parkinson's Disease. *Neuron* **61,** 502–510 (2009).

52. De Wit, H., Enggasser, J. L. & Richards, J. B. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* **27,** 813–825 (2002).

53. Boettiger, C. A. *et al.* Immediate Reward Bias in Humans: Fronto-Parietal Networks and a Role for the Catechol-O-Methyltransferase 158Val/Val Genotype. *J. Neurosci.* **27,** 14383–14391 (2007).

54. Johnson, M. W. & Bickel, W. K. An algorithm for identifying nonsystematic delay-discounting data. *Exp. Clin. Psychopharmacol.* **16,** 264–74 (2008).

55. Richards, J. B., Zhang, L., Mitchell, S. H. & de Wit, H. Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *J. Exp. Anal. Behav.* **71,** 121–43 (1999).

56. Reynolds, B. A review of delay-discounting research with humans: relations to drug use and gambling. *Behav. Pharmacol.* **17,** 651–67 (2006).

57. Fields, S. A., Lange, K., Ramos, A., Thamotharan, S. & Rassu, F. The relationship between stress and delay discounting: a meta-analytic review. *Behav. Pharmacol.* **25,** 434–444 (2014).

58. Lempert, K. M. & Pizzagalli, D. A. Delay discounting and future-directed thinking in anhedonic individuals. *J. Behav. Ther. Exp. Psychiatry* **41,** 258–64 (2010).

59. Johnson, M. W. & Bickel, W. K. Within-subject comparison of real and hypothetical money rewards in delay discounting. *J. Exp. Anal. Behav.* **77,** 129–46 (2002).

60. Madden, G. J., Begotka, A. M., Raiff, B. R. & Kastern, L. L. Delay discounting of real and hypothetical rewards. *Exp. Clin. Psychopharmacol.* **11,** 139–145 (2003).

61. Madden, G. J. *et al.* Delay discounting of potentially real and hypothetical rewards: II. Between- and within-subject comparisons. *Exp. Clin. Psychopharmacol.* **12,** 251–61 (2004).

62. Myerson, J., Green, L. & Warusawitharana, M. Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* **76,** 235–43 (2001).

63. Bencherif, B. *et al.* Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET). *Pain* **99,** 589–98 (2002).

64. Holzer, P. Capsaicin: Cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol. Rev.* **43,** 143–202 (1991).

65. Campbell, C. M. *et al.* Catastrophizing delays the analgesic effect of distraction.

Pain **149,** 202–207 (2010).

66. Anderson, W. S., Sheth, R. N., Bencherif, B., Frost, J. J. & Campbell, J. N. Naloxone increases pain induced by topical capsaicin in healthy human volunteers. *Pain* **99,** 207–16 (2002).

67. Price, D. D., Bush, F. M., Long, S. & Harkins, S. W. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* **56,** 217–226 (1994).

68. Bradley, M. & Lang, P. J. Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *J. Behav. Ther. Exp. Psychiatry* **25,** 49–59 (1994).

69. Lang, P. J., Bradley, M. M. & Cuthbert, B. N. International Affective Picture System (IAPS): Technical Manual and Affective Ratings. *NIMH Cent. Study Emot. Atten.* 39–58 (1997). doi:10.1027/0269-8803/a000147

70. You, D. S. *et al.* Effect of written emotional disclosure on secondary hyperalgesia in women with trauma history. *Psychosom. Med.* **76,** 337–46 (2014).

71. You, D. S., Creech, S. K. & Meagher, M. W. Enhanced Area of Secondary Hyperalgesia in Women with Multiple Stressful Life Events: A Pilot Study. *Pain Med.* pnw049 (2016). doi:10.1093/pm/pnw049

72. Stern, R. M., Ray, W. J. & Quigley, K. S. *Psychophysiological Recording*. (Oxford University Press, Inc., 2000). doi:10.1017/CBO9781107415324.004

73. Tabachnick, B. G. & Fidell, L. S. *Using multivariate statistics*. *Using multivariate statistics* (Allyn & Bacon, Inc., 2006). doi:10.1037/022267

74. Allison, P. D. *Missing data*. *Quantitative applications in the social sciences*

(2002).

75. Field, A. *Discovering Statistics using IBM SPSS Statistics*. (SAGE, 2013). doi:10.1016/B978-012691360-6/50012-4

76. Gandhi, W., Becker, S. & Schweinhardt, P. Pain increases motivational drive to obtain reward, but does not affect associated hedonic responses: A behavioural study in healthy volunteers. *Eur. J. Pain* **17,** 1093–1103 (2013).

77. Walteros, C. *et al.* Altered associative learning and emotional decision making in fibromyalgia. *J. Psychosom. Res.* **70,** 294–301 (2011).

78. Porcelli, A. J. & Delgado, M. R. Acute stress modulates risk taking in financial decision making. *Psychol. Sci.* **20,** 278–83 (2009).

79. Lighthall, N. R., Mather, M. & Gorlick, M. a. Acute stress increases sex differences in risk seeking in the balloon analogue risk task. *PLoS One* **4,** e6002 (2009).

80. Goodin, B. R. *et al.* Salivary cortisol and soluble tumor necrosis factor-α receptor II responses to multiple experimental modalities of acute pain. *Psychophysiology* **49,** 118–27 (2012).

81. Kaltsas, G. A. & Chrousos, G. P. in *Handbook of Psychophysiology* (eds. Cacioppo, J., Tassinary, L. G. & Berntson, G. G.) 303 – 318 (Cambridge University Press, 2007).

82. Kimura, K. *et al.* The biological effects of acute psychosocial stress on delay discounting. *Psychoneuroendocrinology* **38,** 2300–8 (2013).

83. Lempert, K. M., Porcelli, A. J., Delgado, M. R. & Tricomi, E. Individual

differences in delay discounting under acute stress: the role of trait perceived stress. *Front. Psychol.* **3,** 251 (2012).

84. Haushofer, J. *et al.* No effects of psychosocial stress on intertemporal choice. *PLoS One* **8,** e78597 (2013).

85. McRae, A. L. *et al.* Strees reactivity: Biological and subjective responses to the cold pressor and Trier Social stressors. *Hum. Psychopharmacol.* **21,** 377–385 (2006).

86. Rassu, F. S. *et al.* Acute pain decreases impulsive decision-making in individuals with high perceived stress. *J. Pain* **17,** S2 (2016).

87. Borsook, D. *et al.* Reward-aversion circuitry in analgesia and pain: Implications for psychiatric disorders. *Eur. J. Pain* **11,** 7–7 (2007).

88. Becerra, L. & Borsook, D. Signal valence in the nucleus accumbens to pain onset and offset. *Eur. J. Pain* **12,** 866–869 (2008).

89. Leknes, S. & Tracey, I. A common neurobiology for pain and pleasure. *Nat. Rev. Neurosci.* **9,** 314–20 (2008).

90. Marbach, J. J. & Lund, P. Depression, anhedonia and anxiety in temporomandibular joint and other facial pain syndromes. *Pain* **11,** 73–84 (1981).

91. Marbach, J. J., Richlin, D. M. & Lipton, J. A. Illness behavior, depression and anhedonia in myofascial face and back pain patients. *Psychother. Psychosom.* **39,** 47–54 (1983).

92. Elvemo, N. a., Landrø, N. I., Borchgrevink, P. C. & Håberg, a. K. Reward responsiveness in patients with chronic pain. *Eur. J. Pain* n/a-n/a (2015).

doi:10.1002/ejp.687

93. Berghorst, L. H., Bogdan, R., Frank, M. J. & Pizzagalli, D. a. Acute stress selectively reduces reward sensitivity. *Front. Hum. Neurosci.* **7,** 133 (2013).

94. Bogdan, R. & Pizzagalli, D. a. Acute stress reduces reward responsiveness: implications for depression. *Biol. Psychiatry* **60,** 1147–54 (2006).

95. Low, L. a & Fitzgerald, M. Acute pain and a motivational pathway in adult rats: influence of early life pain experience. *PLoS One* **7,** e34316 (2012).

96. Kumar, P. *et al.* Differential effects of acute stress on anticipatory and consummatory phases of reward processing. *Neuroscience* **266,** 1–12 (2014).

97. Porcelli, A. J., Lewis, A. H. & Delgado, M. R. Acute stress influences neural circuits of reward processing. *Front. Neurosci.* **6,** 157 (2012).

98. Basar, K. *et al.* Nucleus accumbens and impulsivity. *Prog. Neurobiol.* **92,** 533–57 (2010).

99. Kim, S. & Lee, D. Prefrontal cortex and impulsive decision making. *Biol. Psychiatry* **69,** 1140–6 (2011).

100. Campbell, C. M. *et al.* Self-reported sleep duration associated with distraction analgesia, hyperemia, and secondary hyperalgesia in the heat- capsaicin nociceptive model. *Eur. J. Pain* **15,** 561–567 (2011).

101. Becker, S., Gandhi, W., Kwan, S., Ahmed, A. & Schweinhardt, P. Doubling Your Payoff : Winning Pain Relief Engages Endogenous Pain Inhibition. *eneuro* **2,** 1–11 (2015).

APPENDIX

Phase	Baseline							Pain or Control Manipulation				End	
Tasks	Informed Consent	SAM Training	Self-Report Measures	VAS Training	Attach Electrodes	Physiological Recording	DDQ1	Manipulation Assignment: Heat + a) Pain (Capsaicin) OR b) Control (Vehicle)	Pain or Control Stimulation Pain Ratings Physiological Recording	DDQ2	Pain Ratings	Self-Report Measures	Debriefing
Time (min)	10	5	10	5	10	10	10	5	15	10	5	20	2

Figure 1 | Timeline of the experiment.

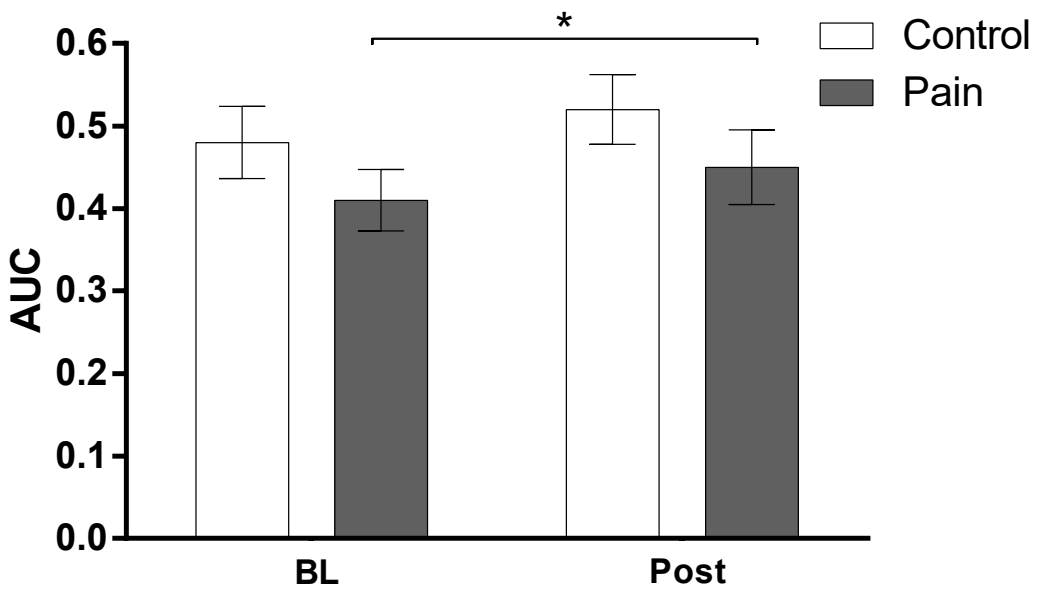

Figure 2 | Comparison of DDQ values between the control and pain groups at baseline and after group manipulations. Paired samples *t*-test revealed a significant increase in DDQ values from baseline to after stimulation in the pain group. Mean ± SEM. * = $p < .05$.

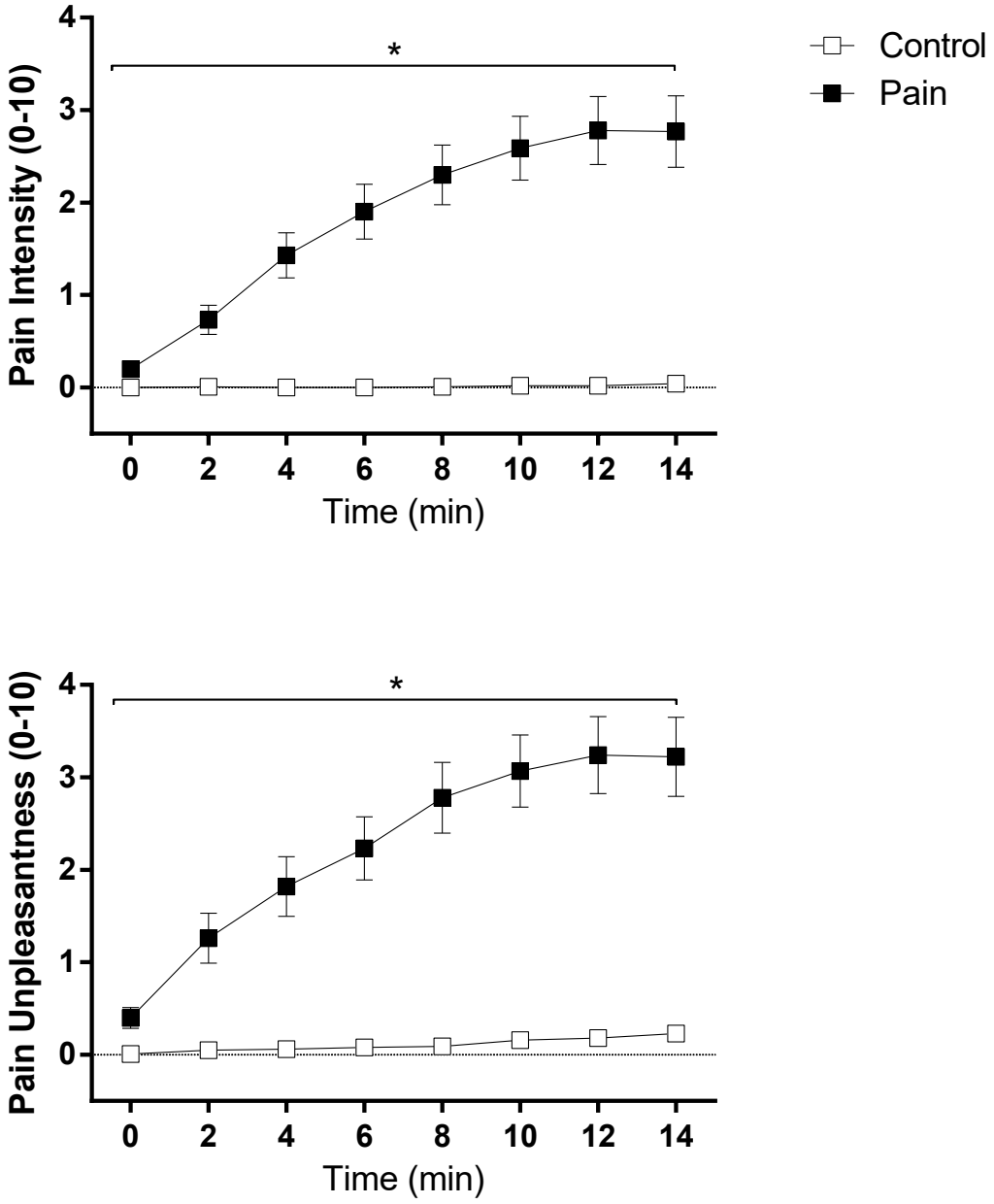

Figure 3 | Comparison of pain ratings between the control and pain groups during the stimulation period. Mean ± SEM. * = $p < .05$.

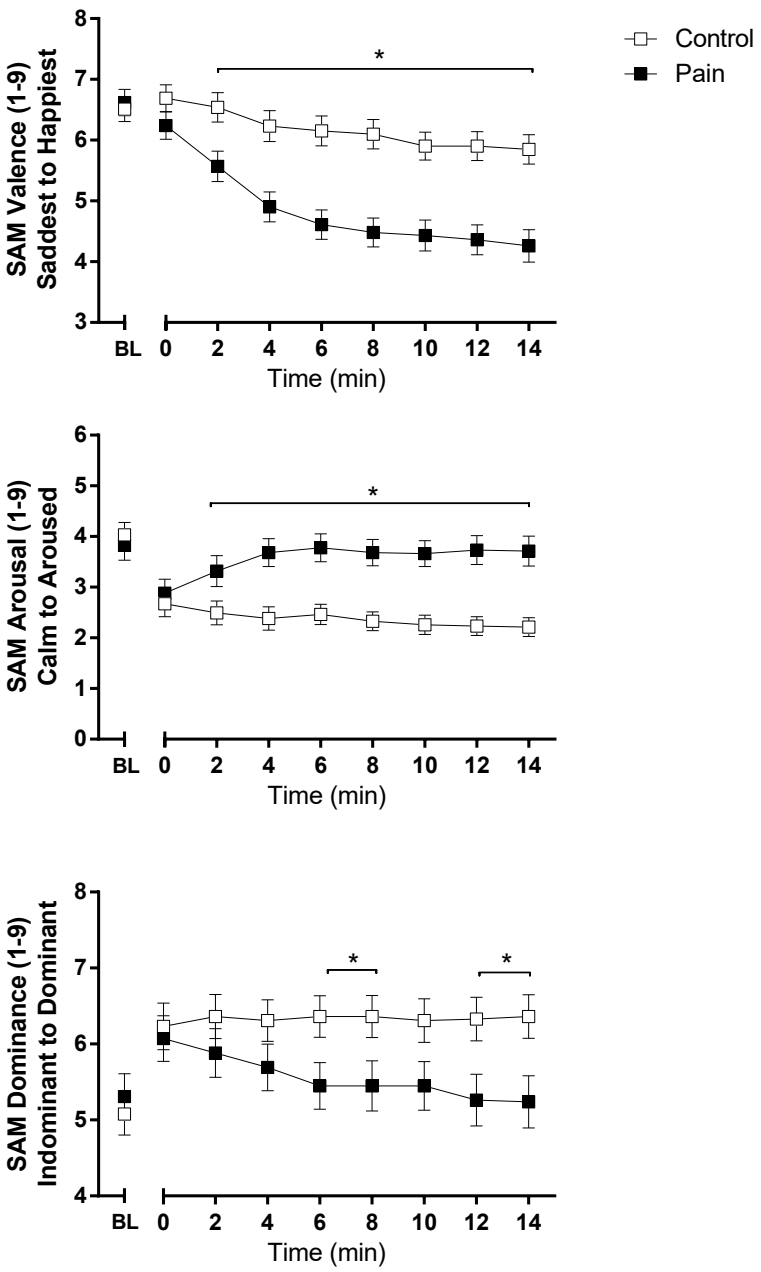

Figure 4 | Comparison of SAM ratings between the control and pain groups during the stimulation period. Mean ± SEM. * = $p < .05$.

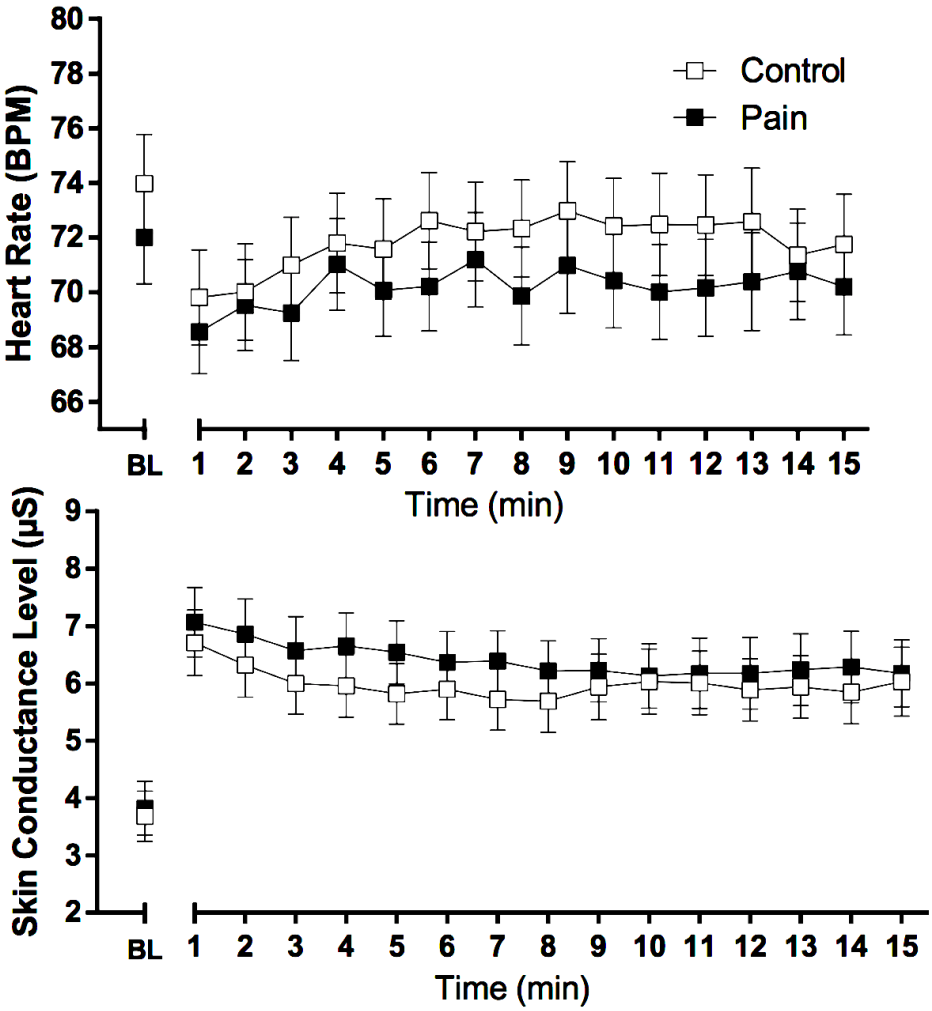

Figure 5 | Comparison of physiological activity between the control and pain groups during the stimulation period. Mean ± SEM. * = $p < .05$.

	Control (n = 38)				Pain (n = 42)							
	M	*SD*	95% CIs		*M*	*SD*	95% CIs		*F*	partial η²	*p*	Significance
Pain Intensity												
0 min	0.00	0.01	0.00	0.01	0.20	0.38	0.08	0.32	10.02	0.11	0.002	*
2 min	0.01	0.05	0.00	0.03	0.73	1.04	0.41	1.05	18.12	0.19	< 0.0001	*
4 min	0.00	0.02	0.00	0.01	1.43	1.58	0.94	1.93	30.97	0.28	< 0.0001	*
6 min	0.00	0.01	0.00	0.01	1.90	1.94	1.30	2.51	36.57	0.32	< 0.0001	*
8 min	0.01	0.02	0.00	0.01	2.30	2.09	1.65	2.95	45.77	0.37	< 0.0001	*
10 min	0.02	0.06	0.00	0.04	2.59	2.24	1.89	3.29	49.81	0.39	< 0.0001	*
12 min	0.02	0.05	0.01	0.04	2.78	2.38	2.03	3.52	50.80	0.39	< 0.0001	*
14 min	0.04	0.11	0.01	0.08	2.77	2.52	1.98	3.55	44.34	0.36	< 0.0001	*
Pain Unpleasantness												
0 min	0.01	0.05	0.00	0.03	0.40	0.73	0.17	0.62	10.66	0.12	0.002	*
2 min	0.05	0.22	-0.02	0.13	1.26	1.75	0.72	1.81	17.86	0.19	< 0.0001	*
4 min	0.06	0.24	-0.02	0.13	1.82	2.10	1.16	2.47	26.38	0.25	< 0.0001	*
6 min	0.08	0.27	-0.02	0.17	2.23	2.22	1.53	2.92	35.05	0.31	< 0.0001	*
8 min	0.09	0.29	0.00	0.19	2.78	2.48	2.01	3.56	44.27	0.36	< 0.0001	*
10 min	0.16	0.41	0.03	0.30	3.07	2.55	2.28	3.87	48.21	0.38	< 0.0001	*
12 min	0.18	0.44	0.04	0.33	3.24	2.69	2.40	4.08	47.95	0.38	< 0.0001	*
14 min	0.23	0.56	0.05	0.42	3.22	2.79	2.36	4.09	42.20	0.35	< 0.0001	*

Table 1 | Comparison of pain ratings between the control and pain groups.

The pain group experienced significantly greater pain intensity and unpleasantness than the control group during each minute of the stimulation period. * = $p < .05$

	Control (n = 39)				Pain (n = 41)							
	M	*SD*	95% CIs		*M*	*SD*	95% CIs		*F*	partial η²	*p*	Significance
SAM Valence												
Baseline	6.51	1.28	6.10	6.93	6.62	1.40	6.18	7.05	0.13	0.00	0.72	
0 min	6.69	1.38	6.25	7.14	6.24	1.45	5.79	6.69	2.09	0.03	0.15	
2 min	6.54	1.50	6.05	7.03	5.57	1.60	5.07	6.07	7.86	0.09	0.01	*
4 min	6.23	1.60	5.71	6.75	4.90	1.59	4.41	5.40	14.01	0.15	< 0.0001	*
6 min	6.15	1.55	5.65	6.66	4.61	1.56	4.12	5.10	19.68	0.20	< 0.0001	*
8 min	6.10	1.52	5.61	6.59	4.48	1.52	4.00	4.95	23.21	0.23	< 0.0001	*
10 min	5.90	1.45	5.43	6.37	4.43	1.63	3.92	4.94	18.35	0.19	< 0.0001	*
12 min	5.90	1.50	5.41	6.38	4.36	1.58	3.87	4.85	20.24	0.20	< 0.0001	*
14 min	5.85	1.51	5.36	6.34	4.26	1.70	3.73	4.79	19.54	0.20	< 0.0001	*
SAM Arousal												
Baseline	4.03	1.56	3.52	4.53	3.83	1.92	3.23	4.43	0.24	0.00	0.63	
0 min	2.67	1.61	2.14	3.19	2.88	1.79	2.31	3.44	0.31	0.00	0.58	
2 min	2.49	1.47	2.01	2.96	3.32	1.97	2.70	3.94	4.54	0.06	0.04	*
4 min	2.38	1.44	1.92	2.85	3.68	1.78	3.12	4.25	12.75	0.14	< 0.01	*
6 min	2.46	1.25	2.06	2.87	3.78	1.78	3.22	4.34	14.53	0.16	< 0.0001	*
8 min	2.33	1.18	1.95	2.71	3.68	1.68	3.15	4.21	17.15	0.18	< 0.0001	*
10 min	2.26	1.19	1.87	2.64	3.66	1.65	3.14	4.18	18.84	0.20	< 0.0001	*
12 min	2.23	1.18	1.85	2.61	3.73	1.83	3.15	4.31	18.79	0.19	< 0.0001	*
14 min	2.21	1.17	1.82	2.59	3.71	1.91	3.10	4.31	17.69	0.19	< 0.0001	*
SAM Dominance												
Baseline	5.08	1.74	4.51	5.64	5.31	1.93	4.71	5.91	0.32	0.00	0.57	
0 min	6.23	1.93	5.61	6.86	6.07	1.93	5.47	6.67	0.14	0.00	0.71	
2 min	6.36	1.83	5.77	6.95	5.88	2.05	5.24	6.52	1.22	0.02	0.27	
4 min	6.31	1.72	5.75	6.86	5.69	1.97	5.08	6.30	2.24	0.03	0.14	
6 min	6.36	1.72	5.80	6.92	5.45	1.98	4.84	6.07	4.80	0.06	0.03	*
8 min	6.36	1.74	5.80	6.92	5.45	2.12	4.79	6.11	4.39	0.05	0.04	*
10 min	6.31	1.81	5.72	6.89	5.45	2.06	4.81	6.10	3.91	0.05	0.05	
12 min	6.33	1.81	5.75	6.92	5.26	2.19	4.58	5.94	5.72	0.07	0.02	*
14 min	6.36	1.81	5.77	6.95	5.24	2.20	4.55	5.92	6.22	0.07	0.02	*

Table 2 | Comparison of SAM ratings between the control and pain groups.

The pain group reported significantly lower valence and greater arousal than the control group within the first two minutes of the stimulation period. The pain group also experienced less dominance, or less control, than the control group, beginning at minute 6. SAM = self-assessment manikin; * = $p < .05$

	Control (n = 29)				Pain (n = 30)							
	M	*SD*	95% CIs		*M*	*SD*	95% CIs		*F*	partial η²	*p*	Significance
HR Means												
Baseline	73.98	9.73	70.35	77.61	72.01	9.34	68.52	75.50	0.64	0.01	0.43	
1 min	69.82	9.36	66.26	73.38	68.55	8.39	65.42	71.68	0.04	0.00	0.84	
2 min	70.02	9.47	66.42	73.62	69.53	9.16	66.11	72.95	0.61	0.01	0.44	
3 min	71.00	9.45	67.40	74.59	69.25	9.54	65.69	72.81	0.02	0.00	0.90	
4 min	71.81	9.85	68.06	75.56	71.02	9.16	67.61	74.44	0.33	0.01	0.57	
5 min	71.58	9.88	67.82	75.33	70.08	9.22	66.63	73.52	0.01	0.00	0.94	
6 min	72.62	9.52	69.00	76.24	70.22	8.94	66.88	73.56	0.39	0.01	0.54	
7 min	72.23	9.77	68.52	75.95	71.20	9.44	67.68	74.73	0.15	0.00	0.70	
8 min	72.34	9.54	68.71	75.97	69.87	9.77	66.23	73.52	0.35	0.01	0.56	
9 min	72.99	9.70	69.31	76.68	70.99	9.62	67.39	74.58	0.07	0.00	0.80	
10 min	72.43	9.44	68.84	76.02	70.43	9.47	66.90	73.97	0.09	0.00	0.77	
11 min	72.49	10.08	68.66	76.33	70.02	9.54	66.45	73.58	0.33	0.01	0.57	
12 min	72.46	9.90	68.69	76.22	70.17	9.74	66.53	73.81	0.20	0.00	0.66	
13 min	72.59	10.58	68.57	76.61	70.39	9.79	66.74	74.05	0.10	0.00	0.75	
14 min	71.36	9.11	67.90	74.83	70.78	9.70	67.16	74.41	0.37	0.01	0.55	
15 min	71.75	9.90	67.92	75.59	70.20	9.68	66.59	73.81	0.00	0.00	0.97	
SCL Means												
Baseline	3.68	2.38	2.79	4.57	3.82	2.57	2.86	4.78	0.05	0.00	0.82	
1 min	6.71	3.08	5.56	7.86	7.07	3.33	5.82	8.31	0.14	0.00	0.71	
2 min	6.32	3.04	5.19	7.46	6.86	3.36	5.60	8.11	0.47	0.01	0.50	
3 min	6.00	2.89	4.92	7.07	6.57	3.27	5.35	7.79	0.66	0.01	0.42	
4 min	5.96	2.93	4.86	7.05	6.66	3.15	5.49	7.84	1.17	0.02	0.28	
5 min	5.82	2.86	4.75	6.89	6.54	3.01	5.41	7.66	1.35	0.02	0.25	
6 min	5.90	2.87	4.83	6.97	6.37	2.95	5.27	7.47	0.49	0.01	0.49	
7 min	5.72	2.87	4.64	6.79	6.39	2.88	5.31	7.46	1.29	0.02	0.26	
8 min	5.69	2.94	4.59	6.79	6.22	2.89	5.14	7.30	0.69	0.01	0.41	
9 min	5.94	3.10	4.78	7.10	6.23	3.01	5.11	7.35	0.09	0.00	0.77	
10 min	6.03	3.06	4.89	7.17	6.13	3.09	4.97	7.28	0.00	0.00	0.95	
11 min	6.01	3.00	4.89	7.13	6.18	3.39	4.92	7.45	0.01	0.00	0.95	
12 min	5.89	2.95	4.79	6.99	6.18	3.45	4.90	7.47	0.07	0.00	0.79	
13 min	5.94	2.93	4.84	7.03	6.24	3.42	4.96	7.52	0.08	0.00	0.78	
14 min	5.85	2.99	4.74	6.97	6.29	3.45	5.00	7.58	0.25	0.00	0.62	
15 min	6.03	3.25	4.79	7.26	6.18	3.23	4.98	7.39	0.00	0.00	0.99	

Table 3 | Comparison of physiological responses between the control and pain groups. After adjustment for baseline physiological covariates, comparisons of autonomic activity between the two groups during the stimulation period lacked clear distinction for heart rate and skin conductance level means. HR = heart rate; SCL = skin conductance level; * = $p < .05$