THE IMPACT OF ADVERSE CHILDHOOD EVENTS ON TEMPORAL SUMMATION OF SECOND PAIN

A Thesis

by

DOKYOUNG SOPHIA YOU

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

MASTER OF SCIENCE

August 2012

Major Subject: Psychology

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ABSTRACT

The Impact of Adverse Childhood Events on Temporal Summation of Second Pain.

(August 2012)

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Adverse childhood events have been identified as a risk factor for developing chronic pain conditions in adulthood. However, previous studies have inconsistently supported the link between adverse childhood events and hypersensitivity to laboratory-induced pain. Therefore, this study intended to investigate the effects of adverse childhood events on temporal summation of second pain (TSSP). A group of 38 healthy and pain-free college students participated in laboratory pain tests after being screened for childhood trauma history. Half of participants (47.5% female) were positive for childhood trauma and the other half (63.2% female) reported no adverse childhood event. The laboratory pain tests measured TSSP using 10 thermal pulses per trial over four consecutive trials. The trauma group showed a tendency of greater sensitization within TSSP trials and lack of habituation over repeated TSSP trials. In sum, adverse childhood events predisposed adults to enhanced TSSP, which is potentially linked to an increased likelihood to develop chronic pain problems.

NOMENCLATURE

ACE	Adverse Childhood Experience
AUC	Area Under the Curve
BNST	Bed Nucleus of the Stria Terminalis
CES-D	Center for Epidemiological Studies Depression Scale
ETISR-SR	Early Trauma Inventory Self Report-Short Form
FPQ	Fear of Pain Questionnaire
HR	Heart Rate
HRV	Heart Rate Variability
IES-R	Impact of Life Event Scale
NA	Negative Affect
NMDA	*N*-methyl-d-aspartic Acid
P	Physiological Measurement
PA	Positive Affect
PANAS	Positive and Negative Affect Schedule
PCL-C	PTSD Symptom Checklist – Civilian
PILL	Pennebaker Inventory of Limbic Languidness
PSS	Perceived Stress Scale
Q	Questionnaire
QST	Quantitative Sensory Test
SACC	Subgenual Anterior Cingulate Cortex
SAM	Self Assessment Manikin

SC	Subscale
SCL	Skin Conductance Level
SR	Self-report
LE ratio	Ratio of the Late to the Early TSSP pain
TSC-40	Trauma Symptom Checklist
TSSP	Temporal Summation of Second Pain
TTP	Time to Peak Pain Intensity

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1. INTRODUCTION

Adverse childhood events are frequently reported by adult patients with various chronic pain problems.[55, 75, 102] Such chronic pain problems include fibromyalgia,[5, 10, 123, 133] chronic pelvic pain,[66, 67, 135] musculoskeletal pain,[71, 73, 74, 134] abdominal pain,[134] and irritable bowel syndrome.[100, 135, 136] Treatment for these pain problems is often unsatisfactory and challenging to both patients and physicians because the exact pathogenesis is unknown. One factor that appears to contribute to the development of chronic pain disorders is adverse childhood events. Individuals who report childhood abuse are 1.4 to 4.4 times more likely to have chronic pain problems than those who do not.[43, 44, 59] Additionally, the prevalence of childhood sexual abuse in chronic pain patients is about 39% in female patients and 7% in male patients.[143] A meta-analysis indicates that the effect of childhood traumatic experience on chronic pain in adulthood is modest but significant across a wide variety of samples.[30] This implies that adverse childhood events may affect chronic pain in adults. Despite these associations, relatively little research has investigated whether adverse childhood events contribute to the development of chronic pain problems and have an impact on specific pain processes that may be involved in the induction and/or maintenance of chronic pain states.

Chronic pain is characterized by persistent hyperalgesia and allodynia. Hyperalgesia is defined as an enhanced pain response to a noxious stimuli and allodynia is defined as pain sensation produced by innocuous stimuli.[142] Laboratory pain testing reveals that allodynia lasts shorter and affects smaller area than hyperalgesia.[65] Both

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This thesis follows the style of *Clinical Journal of Pain*.

hyperalgesia and allodynia are enhanced sensitization states, indicating increased responsiveness in the peripheral nociceptors and central pain pathway.[83] Hyperalgesia manifests as a decreased in pain thresholds, an increased in response to supra-threshold stimuli, and as an expansion of receptive fields. In an acute injury, hypersensitivity provides a protective function for organisms.[54] Because of this hypersensitivity, patients tend to guard the injured area. However, persistent hyperalgesia no longer provides a protective function after a wound is healed, and at this point the pain becomes maladaptive and impairs function.

In persistent hyperalgesia, enhanced responsiveness of central nervous system is a pivotal process.[69, 142] It is reported that secondary hyperalgesia and wind-up are linked to a central sensitization process.[72, 76] Secondary hyperalgesia manifests as enhanced pain in the areas adjacent to the damaged tissue and it is caused by heterosynaptic facilitation.[76, 127] The capsaicin test provides a laboratory model that can be used to assess secondary hyperalgesia. After 20-40 min of capsaicin application, the region surrounding the primary capsaicin application develops enhanced sensitivity to painful (e.g. pin-prick, secondary hyperalgesia) as well as a non-painful stimulation (e.g. light touch, secondary allodynia).[76] Secondary hyperalgesia is characterized by enhanced sensitivity to mechanical but not heat stimulation, and it is believed to be mediated by high threshold A-fiber mechanoreceptors. In contrast, secondary allodynia is mediated by low threshold A-fiber mechanoreceptors such as tactile receptors (e.g. Aβ-fiber).[2, 127]

In order to induce and maintain central sensitization, N-methyl-d-aspartic acid (NMDA) receptor activation is a critical process.[142] Woolf and Thompson have

summarized these two steps as follows.[142] The important first step in the induction of central sensitization is cumulative depolarization of NMDA nociceptors. Synaptic efficacy is enhanced when the voltage-dependent Mg^{2+} block of the NMDA receptor is removed by the summation of the slow potentials. Through the ion channel, inward current flow is increased and depolarization is amplified. For maintaining the state central sensitization, a tonic activation of NMDA receptors or mechanisms mediating the prolonged effects of NMDA receptor activation are critical. At this phase, phosphorylation of the NMDA receptors occurs in dorsal horn neurons, and it may lead to transcriptional changes.

Wind-up, a form of homosynaptic facilitation, indicates increases in pain from repetitive peripheral stimulation of C-fiber nociceptors.[72, 76] In addition, wind-up is thought to contribute to the induction and/or maintenance of chronic pain states.[19, 142] The progressive increases in pain perception that occur during wind-up reflect a summation process via activation of NMDA receptors in the spinal cord.[19, 37, 92, 126, 132, 142] Exposure to repetitive thermal or mechanical stimuli presented at the frequency of at least .33 Hz has been shown to induce wind-up or temporal summation of second pain (TSSP).[82, 86, 104, 118, 132] It is worth noting that wind-up and TSSP are not identical although they often used interchangeably. TSSP reflects wind-up phenomenon occurring primarily within the spinal dorsal horn neurons,[142] but also summation processes occurring in supra-spinal neurons.[120, 130] Second pain is mediated by C-fibers, unmyelinated slow conducting fibers while first pain is mediated by Aδ-fibers, myelinated fast conducting fibers (Fig. 1).[79] In order to induce TSSP in human

laboratory tests, the glabrous skin on the palm of the hand or on the plantar surface of the foot are often used because Type II A-fibers are scarce in glabrous skin in contrast to hairy skin.[129]

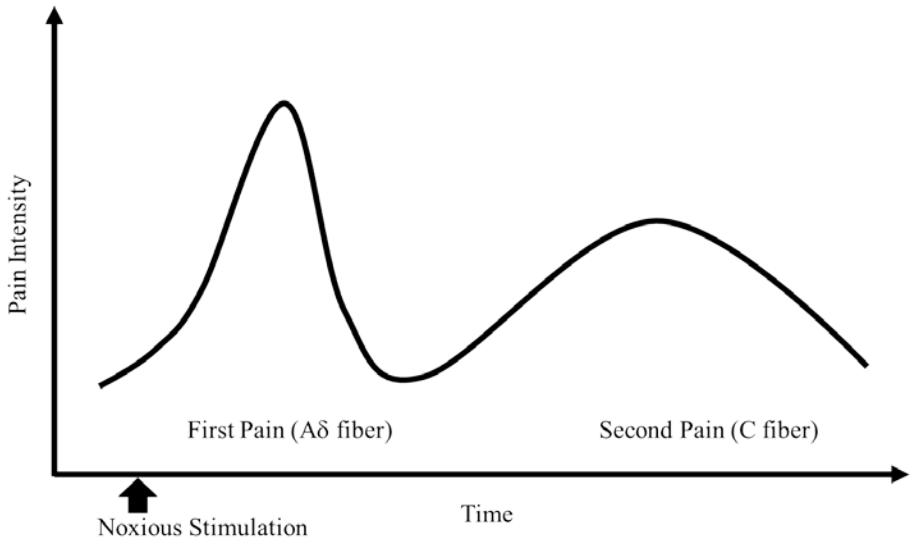

Fig. 1 Depiction of the differences in conduction velocity between first and second pain

In an effort to investigate the role of childhood adversities in adulthood chronic pain, several studies have examined the link between adverse life events and laboratory pain. Earlier studies have reported a lower threshold for pressure pain in women with history of abuse[105] while others have observed no difference in pain threshold for rectal distension between women with and without sexual abuse.[141] Unfortunately, these two studies include women with adult or childhood trauma.

The results of more recent experiments exclusive for childhood trauma are also not consistent. For example, our laboratory has found that individuals reporting a history of

childhood trauma exhibit larger areas of secondary hyperalgesia using a capsaicin-pain model among otherwise healthy women.[26] Since capsaicin temporarily induces neurogenic inflammatory pain and central sensitization,[58, 121] this study suggests that healthy women reporting childhood trauma have heightened central sensitization, which may increase their vulnerability to neurogenic inflammatory pain problems. Arthritis, inflammatory bowel disease, chronic bronchitis, migraine, and interstitial cystitis are examples of neurogenic inflammatory disorders.[28] In fact, the positive link between these inflammatory neurogenic pain conditions and childhood trauma has been reported in several clinical studies. [15,3, 44, 45, 85, 110, 125] Additionally, adverse childhood events are associated with lower basal ischemic pain tolerance, indicating heightened sensitivity to supra-threshold stimulation.[28] However, the effect of childhood trauma on hypersensitivity is reduced under stressful condition (stress-induced hypoalgesia).[28]

Contrary to findings obtained using the capsaicin test, other laboratories have failed to observe hyperalgesia among people with adverse childhood events in pain threshold tests.[27, 39] It is also reported that there is no difference in reported pain intensity using constant heat[27] However, some have observed an opposite relationship. Another study shows that healthy college women with childhood trauma are more resilient to central sensitization process in TSSP testing.[39] In this study, women with reported childhood trauma show significantly lower wind-up pain intensity and unpleasantness as well as greater wind-down of pain intensity and unpleasantness. However, one of the limitations of this study is that the researchers tested TSSP on the forearm. As mentioned previously, hairy skin contains both Aδ as well as C fiber nociceptors.[18] Therefore, the results may

not represent wind-up pain or TSSP. Yet, it is possible that childhood adversities are rather linked to hypoalgesia for healthy population. Additionally, they did not calibrate TSSP temperature and used the two relatively high temperatures (i.e. 49ºC and 52ºC) to all subjects. Therefore, induced pain intensities may vary among subjects.

Although laboratory studies provide mixed findings that contrast with clinical observations, recent animal research has yielded results that support the hypothesis that previous exposure to uncontrollable stressors early in life induces a long lasting sensitization of pain processing. For example, rat pups distressed by maternal separation demonstrate increased number of pain behaviors and stress-induced hyperalgesia in adulthood.[23, 87] Additionally, neonatal stress induced by limited bedding is linked to persistent hyperalgesia and muscle nociceptor sensitization in adult rats.[47] Other studies have shown that exposure to uncontrollable sound stress causes a persistent and generalized enhancement of pain in rats. This sensitization effect is mediated by stress-induced epinephrine and corticosterone which produces in a switch in peripheral nociceptor function.[107]

The purpose of this study is to examine the impact of adverse childhood events on TSSP. Four TSSP tests will be performed on healthy and pain-free adults after screening for history of childhood traumatic events. It is hypothesized that individuals with reported childhood trauma will show increased levels of hyperalgesia indicated by the following: a) increased pain in TSSP (greater wind-up) and reduced wind-down within TSSP trials, b) increased sensitization and decreased habituation and/or adaptation over repeated TSSP trials, and c) slower wind-up decay within and between TSSP trials.

2. METHODS AND MATERIALS

All procedures were approved by IRB at Texas A&M University, and informed consent was obtained from all participants. As participants received course credits for their participation, they were informed that they could withdraw from the study at any time without forfeiting the credit. Subjects were identified only by number, not name or initials.

2.1. Participants

A total of 2,414 undergraduate students in the subject pool were screened for a history of childhood trauma using the Early Trauma Inventory Self Report-Short Form (ETISR-SF).[13] The ETISR-SF is a valid screening tool for general (family dysfunction), physical, emotional, and sexual trauma with 27 items. Potential subjects who endorsed no childhood trauma (n = 207) or whose trauma score was at least 10 (n = 205), which is the reported mean for a trauma group,[13] were invited via email. Inclusion criteria were healthy and pain-free men and women and aged at least 18 years old. Exclusion criteria were current use of psychoactive drugs, history of vasovagal syncope, and chronic illness such as any cardiovascular disease, diabetes, Raynaud's disease, and neurological disorders. Participants were instructed not to use NSAID, allergy medication, tobacco, alcohol, or any recreational drugs three days prior to the experiment. Oral contraceptives and vitamin supplements were allowed to continue.

Among the 40 subjects (21 for the trauma group) who came in for laboratory pain testing, one subject in the trauma group did not complete the experiment due to low pain sensitivity. In this case, it was impossible to induce moderate pain with pre-determined

temperature range (45 to 51°C) used in this experiment. Another subject in the trauma group was excluded from analysis because the subject reported to have pain on the day of the experiment. Therefore, the data of 19 subjects for each no trauma and trauma group were used for the final analysis.

Table 1. Comparison of demographic profiles between groups with and without adverse childhood events

		No Trauma		Trauma	
		N	(%)	*N*	(%)
Participants (%Female)		19	(63.2)	19	(47.4)
Mean age (SD)		18.8	(0.8)	18.7	(0.6)
Ethnicity	Caucasian	14	(73.7)	14	(73.7)
	Latin American	3	(15.8)	0	(0.0)
	African American	0	(0.0)	2	(10.5)
	Asian	2	(10.5)	3	(15.8)
Parental Degree	High School Diploma	0	(0.0)	1	(5.3)
	Associate Degree	3	(42.9)	4	(21.1)
	Bachelor Degree	10	(52.6)	3	(15.8)
	Master and above	5	(26.3)	11	(57.9)
	Other	1	(5.0)	0	(0.0)
Parental Income	16,000 – 49,999	2	(10.5)	4	(21.1)
	50,000 – 74,999	2	(10.5)	4	(21.1)
	75,000 – 99,999	2	(10.5)	2	(10.5)
	100,000 and greater	8	(42.1)	5	(26.3)
	Don’t know	4	(21.1)	4	(21.1)
	No response	1	(5.3)	0	(0.0)
Parental Employment	Full-Time	18	(94.7)	17	(89.5)
	Part-Time	1	(5.3)	0	(0.0)
	Unemployed	0	(0.0)	2	(10.5)

Of the total 38 participants, 73.7% were Caucasian, 13.2% Asian, 7.9% Latin American, and 5.3% African American. The mean of age was 18.7 years ($SD = 0.7$) and 55.3% were female. Most participants (92.1%) were right-handed. Table 1 shows the

comparison of demographic profiles between the groups with and without childhood trauma. There was no significant between- group difference in demographic data, tested with one-way ANOVA (all *p*s = *n.s.*).

2.2. Apparatus and Physiological Recording

Participants were tested in a sound-proof room. Heart rate (HR) sensors were attached to the chest and the trunk. HR was measured using silver-silver chloride electrodes (Grass model F-E11D). Skin conductance level (SCL) sensors were applied to the middle part of the index and the middle fingers of the non-dominant hand. The sensors were silver-silver chloride reusable electrodes (11mm diameter, Grass model F-E9M) filled with saline electrode gel (EC60, grass technology). Skin conductance was measured by an adaptor (Grass Model SCA1), which interfaced with amplifiers (Grass Model LP122).

All physiological data were recorded via a Grass Model 7E polygraph (Grass Instruments, Quincy, MA), which was located outside the sound-proof room. Physical signals were collected and filtered with Grass Instrument Model 7P1E/7DAG low level DC pre-amplifier for HR and 7P1G/7DAG for SCL. All data were obtained by the LabView version 8.0 software (National Instruments, Austin, TX) and a National Instruments Data Acquisition Board (NI 9205 module). The sampling frequency was 100 Hz.

2.3. Self-Report Data

A series of questionnaires (Appendix A) were administered by the LabView program to assess psychological conditions and general health status prior to pain testing. Following psychological and physical health related measures were included.

2.3.1. Psychological conditions

The Positive and Negative Affect Schedule (PANAS) is a validated measure to evaluate two dimensions of current mood such as positive and negative affective states and traits.[137] Participants rate the 10-mood items for each dimension. A 5-point scale, ranging from very slightly (1) to extremely (5), is used. The possible total scores are between 10 and 50 for each positive and negative affect. A higher positive affect score indicates more positive affect, and a higher negative affect score indicates more negative affect. The scale was administered to measure affect at the moment of the experiment.

The Center for Epidemiological Studies Depression Scale (CES-D) is widely used to assess depressive symptomatology during the past week.[95] The CES-D consists of 20 items, scored on a 4-point Likert Scale (0: rarely or none of the time to 3: most or all of the time). The total scores range from 0 to 60 with higher scores indicating more severe depressive symptoms. The cutoff score of 16 has been suggested to screen mild depression.[95]

The 10-item Perceived Stress Scale (PSS) is a valid and reliable instrument, commonly used to measure the perception of stress.[21] The PSS uses a 5-point Likert scale (0: Never to 4: Very often). The total scores range from 0 to 40 with higher scores indicating higher perceived stress during the last month.

The Personality Assessment Inventory – Borderline feature (PAI-BOR) is one of the clinical scales in the PAI,[84] which has good psychometric properties. The PAI-BOR assesses personality pathology associated with borderline personality disorder. The scale consists of 24 items, with four 6-item subscales (affective instability, identify disturbance, negative relationship, and self-harm/impulsivity) rated on a 4-point scale (0: false to 3: very true). PAI subscale raw scores are translated to T scores with a mean of 50 and a standard deviation of 10.

The Adverse Childhood Experiences (ACE) is a 10-item questionnaire, developed to study the link between childhood maltreatment and adult health and well-being by a collaborative research team (i.e. the Division of Adult and Community Health at the Centers for Disease Control and Prevention and Kaiser Permanente's Department of Preventive Medicine in San Diego).[4] This is one of the widely used instruments to study the impact of adverse childhood event on general health. The measure assesses three major stressful or traumatic childhood events such as family dysfunction, child abuse, and child neglect prior to age 18. Each item is rated on dichotomous response, coded yes (1) or no (0).

The PTSD symptom checklist – civilian (PCL-C) is a 17-item self-report measure, which consists of the 17 DSM-IV symptoms of PTSD[138] and has acceptable psychometric property.[101] The PCL-C can be used to screen for PTSD symptoms, diagnose PTSD, and evaluate response to a treatment. The items are scored on a 5-point scale (1: not at all to 5: Extremely). The total scores (range 17 - 85) indicate PTSD symptom severity with higher scores representing more severe symptoms. The measure

is comprised of three symptom clusters: re-experiencing (item 1-5), avoidance (item 5-12), and hyper-arousal (item 13-17). PTSD diagnostic criteria are met when at least one of experiencing, three avoidance, and two hyper-arousal symptoms are endorsed. A cutoff score of 44 has been proposed to identify individuals with PTSD.[101]

The Impact of Life Event Scale –Revised (IES-R) is a 22-item self-report measure, assessing level of distress from one specific traumatic life event during the past 7 days.[139, 140] This measure is a reliable and useful tool to screen or assess the symptom severity of traumatic distress.[7, 25] Fourteen items corresponds to the 17 DSM-IV symptoms of PTSD. Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely). The total IES-R scores range from 0 to 88. There are three subscales such as intrusion (8 items), avoidance (8 items), and hyperarousal (6 items) symptoms. The items for each subscale are randomly placed. The cutoff score of 33 has been shown optimal diagnostic accuracy against the PCL-C.[25]

The Trauma Symptom Checklist-40 (TSC-40) is a valid 40-item instrument assessing common symptoms after traumatic experiences with a 4-point rating scale ranging from never (0) to often (3).[14, 38] The total score ranges from 0 to 120 with higher scores indicating more trauma related symptoms for the past 2 months. The TSC-40 has 6 subscales such as anxiety, depression, dissociation, sexual abuse trauma index, sexual problems, and sleep disturbances. This measure is an acceptable measure to evaluate common psychological symptoms of sexual abuse survivors.[145] Yet, the TSC-40 is developed for research purpose only and a clinical cutoff score is not available.[14]

The Fear of Pain Questionnaire-III is a 30-item self-report to assess fear and anxiety about pain. [81] Each item has been selected based on principal component analysis. Items are rated on a 5-point Likert scale (1: not at all to 5: extreme). It contains three 10 item subscales: severe pain, minor pain, and medical pain. Total score ranges from 30 to 150 and higher score indicates greater fear about various painful experiences. This measure has reported to have a good predictive validity about pain-relevant behavior of avoidance.[81]

2.3.2. Physical conditions

The Pennebaker Inventory of Limbic Languidness (PILL) [88] assesses common physical symptoms with 54 items, rated on a 5-point scale (A: have never or almost never experienced the symptom to E: more than once every week). The total score was calculated using binary technique, which was to sum the number of items scored C, D, or E on the scale. Therefore, the possible total scores range from 0 to 54 with higher number indicating frequent experience of physical symptoms. The last additional three items, which are not included in the total score, ask a) the number of visits to health care center or private physician for illness during a semester, b) the number of sick days, and c) the number of days of restricted activity due to illness.

2.4. Pain Testing and Numerical Pain Ratings

Three quantitative sensory tests (QST) were performed. First, two threshold tests were performed to measure a thermal pain threshold. Second, sensitivity tests were performed to identify a peak temperature to induce moderate pain. Lastly, four temporal

summation of second pain (TSSP) tests were conducted using the peak temperature identified during sensitivity testing.

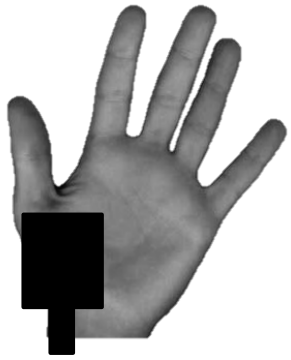

Fig. 2 Application of a thermode on the thenar eminence

2.4.1. Thermal pain threshold testing

Thermal pain threshold was measured using the Medoc Advance Thermal Stimulator (Medoc Ltd. Ramat Yishai, Israel). Participants were informed about threshold testing and asked to place the thenar eminence of non-dominant hand on the $3\times3cm^2$ thermode (Fig. 2). A warm thermode (baseline temperature of 35 °C) was used to equilibrate subjects and the temperature was increased at a rate of 0.5 °C/s until subjects reported their first painful sensation by clicking a mouse. A cut-off temperature of 51 °C was used in threshold testing. None of the subjects failed to detect a threshold within the temperature limit.

2.4.2. Thermal pain sensitivity testing

All subjects went through thermal pain sensitivity testing.[113, 114] The purpose of this sensitivity test was to find a temperature that could induce moderate pain with four heat pulses to individualize the peak temperature for TSSP testing. The moderate pain range was defined between 35 and 55 out of 100.[113, 114, 116] The standardized numerical pain scale[112, 114, 116, 117] is described further in the section 2.5.

Individuals received four thermal phasic stimuli at 0.33 Hz using a 2.7×2.7cm^2 Contact Heat Evoked Potential thermode (Medoc Ltd, Ramat Yishai, Israel) on the thenar eminence of the non-dominant hand. The palm was chosen for this experiment because primate glabrous skin does not have Type II mechano-heat A fiber.[83, 128] Thus, first pain sensation is not evoked in humans when heat stimuli are applied to this area.[15, 129] The basal temperature was always 38 °C and the initial peak temperature was 47 °C. The rise time from the base to the peak temperature was 0.5 s, the plateau time was 0.5 s, and the descent time to the baseline temperature was 0.5 s. Thus, subjects were exposed to a thermal stimulus for a total of 1.5 s and the baseline temperature for 1.5 s. These phasic thermal pulses at least 0.33 Hz are known to induce temporal summation of second pain.[90, 91, 113, 114, 118] The subjects were instructed to rate their late sensations after each peak temperature on a 0 - 100 scale. If the pain rating after the last heat pulse was not 45 ± 10, sensitivity tests were repeated with adjusted temperature by ± 0.5 until pain rating of 45 ± 10 was achieved. If moderate pain was not evoked with a peak temperature between 45 and 51 °C, TSSP testing was not conducted and the experiment was ended.

2.4.3. TSSP testing

After the sensitivity test, four TSSP tests were performed using the calibrated peak temperature (Fig. 3). The interval between TSSP tests was at least 3 min. For each TSSP test, 10 heat pulses were applied to the thenar eminence of the non-dominant hand.[115] The subjects were instructed to rate their second pain after each peak temperature as they did during the sensitivity tests. They were also asked to rate their after-sensations or "wind-up decay" at 15 s and 30 s after the last pulse.

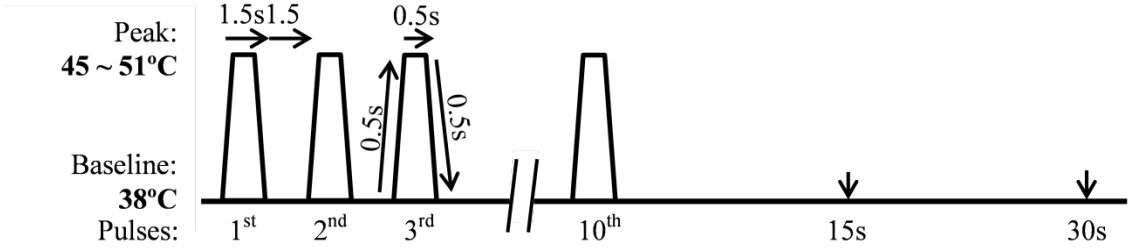

Fig. 3 Design of repetitive thermal pulses used for TSSP experiment. The two arrows indicate after-sensations measured at 15 s and 30 s after the last thermal pulse.

2.5. Numerical Pain Ratings

A computerized visual analog scale (Medoc, Ramat Yishai, Israel) was used to measure intensity of painful sensation. The scale ranges from 0 (no pain) to 100 (the most intense pain imaginable) in increment of 1 with verbal descriptors at intervals of 10: 10 = warm sensation, 20 = a barely painful sensation, 30 = very weak pain, 40 = weak pain, 50 = moderate pain, 60 = slightly strong pain, 70 = strong pain, 80 = very strong pain, and 90 = nearly intolerable pain. This 0-100 scale was reported to be advantageous

for reporting intensity of pain during series of repetitive stimuli and to differentiate perceived TSSP intensities between people with and without chronic pain problems.[112, 114, 116, 117]

2.6. Measures for Psychophysical Response to Pain

In addition to the perceived pain intensity, changes of perceived unpleasantness were measured using the Self Assessment Manikin (SAM) -valence. Perceived level of arousal and sympathetic responses were assessed by the SAM-arousal and SCL. Cardiac responses to painful stimuli were measured by HR. Lastly, sympathovagal responses to noxious stimuli were measured by Heart Rate Variability (HRV).

2.6.1. Emotional response to pain testing

To measure subjective emotional reaction to pain testing, the SAM was administered at pre- and post-pain tests.[12] The SAM measures valence, arousal, and dominance using a pictogram scale. The level of valence ranges from happy (1) to unhappy (9), arousal ranges from calm (1) to excite (9), and dominance ranges from weak (1) to strong (9). This measure provides a valid and reliable measure to assess emotional responses to stimulation.[12]

2.6.2. Physical response to pain testing

Physiological reactions to pain were measure by SCL, HR, and HRV for 3 min before and after each pain test. In addition, the physiological data were collected during pain testing. For the analysis of physiological response to the actual TSSP, the data were broken down into two parts; during the TSSP testing (the first 30 s) and after-sensations

(the second 30 s). The average SCL (μS) and HR (beat/min) were compared between the two groups. The HRV was calculated with the standard deviation of R-R intervals (ms).

Phase	Pre				Pain Tests																Post	
	Baseline				Test1						Test 2		Test 3								Exit Q	
	1			2			T1-1		T1-2			T2		T3-1		T3-2		T3-3		T3-4		
Measures	P	SR	P	S	Instruction for Threshold Test	P	P	P	P	S P	Instruction for Sensitivity test		Instruction for TSSP test	P	P	S P	P	S P	P	S P	P	S P	SR
Time (min)	3	30	3			3	1	3	1	3		5		3	1.5	3	1.5	3	1.5	3	1.5	3	5

Fig. 4 Timeline of the experiment, Test 1 = threshold testing, Test 2 = sensitivity testing, Test 3 = TSSP Testing, T1-1 = 1st threshold test, T1-2 = 2nd threshold test, T3-1 = 1st TSSP test, T3-2 = 2nd TSSP test, T3-3 = 3rd TSSP test, T3-4 = 4th TSSP test, Exit Q = exit questionnaires, P = physiological measurement (i.e. SCL, HR, & HRV), SR = self-reports, S= the SAM-valence, arousal, and dominance.

2.7. Procedures

Fig. 4 illustrates the experimental procedures. After the informed consent was obtained, the first baseline physiological data was collected for 3 min. Next, the subjects completed the self-reports that were listed in the section 2.3. The subjects were allowed to change their answers until they clicked ‘next.’ The subjects were informed that they could skip any questions if they did not want to answer. At the end of each self-report, however, a pop-up message would show up on a computer screen, verifying ‘missing item found, do you want to continue?’ If they pressed to ‘continue’, the computer screen showed the next psychological questionnaires. If no, subjects could answer the missed

item(s). After the self-reports, the second baseline physiological data sample was collected and the first SAM was administered.

Before the first QST, the subjects were trained to make pain threshold ratings. Then, they were asked to remain still and relaxed for 3 min to collect the third physiological data sample. At this time, their physical state might be influenced by their level of anticipatory anxiety because subjects were made to expect the impending thermal pain threshold testing. Before the sensitivity testing, the subjects were trained to use the computerized visual analog scale and asked to rate their late warmth or painful sensation after each peak. They were instructed that sensation intensity might increase, decrease or stay the same with stimulus repetition. They were also informed that they should remove their hand from the thermode before they would experience intolerable pain or reach 100 on the computerized visual analog scale.

Before the TSSP phase of testing, the subjects were informed about the nature of the thermal stimuli and trained in how to rat their sensations. However, the subjects were not informed about the number of the TSSP tests. If the subject was asked about how many TSSPs would occur during the experiments, the experimenters replied that they were ‘not allowed to disclose.’ Once the last TSSP test was completed, the subjects were informed about its completion and asked to remain still for the last physiological data collection. Lastly, the subjects completed a short exit questionnaire asking whether they had any thought about the experiment’s purpose or hypothesis in order to assess for potential expectancy effects. Majority (89.5%) did not know the hypothesis. Four subjects (2 subjects for each group) described a guess that was close to the hypothesis,

e.g., to investigate a link between pain and traumatic experience in childhood. As a final step, the experimenters provided a written and verbal debriefing to the subjects. This experiment took about 1.5 to 2 hrs.

2.8. Data Analysis

All variables were examined for missing values, outliers, normality of distribution, and homogeneity of variance. Next, one-way ANOVAs were conducted for intergroup comparison. In addition, repeated-measures ANOVAs were performed for intergroup comparisons of psychophysiological changes over time in response to the QSTs. The Greenhouse-Geisser correction was applied to the degrees of freedom where ε s were noted for violation of sphericity.[122] All statistical tests were 2-tailed tests conducted at $p < .050$, unless otherwise indicated.

2.8.1. Handling missing value and outliers

Missing values were replaced with the group mean. There were no missing values in the self-reports and the QSTs. Missing values in the physiological data due to technical difficulties were replaced with the group mean. For one person in the no-trauma group, entire physiological data was not recorded. For another person in the no-trauma group, physiological data during and after TSSP4 were not recorded. Therefore, these two cases were replaced with the group mean. However, R-R intervals at post-threshold were neither replaced nor analyzed because these data at this time point were not collected due to a programing error.

The extreme outliers, of which values were more than 3 interquartile range in each group, were replaced with the group means. There was no outlier in the psychological

measures. Most of the QST variables did not have outliers, however a few TSSP indices[1] had maximum of one outlier in each group.

In physiological data, there were few outliers. For SCL, one outlier in the trauma group was replaced with the group mean at baseline1. For HR, one outlier in the no-trauma group was replaced at baseline2 and post-threshold testing. All the other SCL and HR variables did not have outliers. For HRV, there was at least one outlier in the no-trauma group from pre-threshold to the final physiological measure; of the no-trauma group, there were two outliers at pre-TSSP3 and pre-TSSP4, and three outliers during TSSP2 and TSSP3. These outliers were replaced with the group mean. In contrast, there was no outlier in HRV among people with childhood trauma.

2.8.2. Test of normality

Shapiro-Wilk's normality tests were performed to check normality after outliers were replaced with the group mean. The assumption of normality was not violated for most psychological, physiological and QST data (all *p*s >.050). However, even when normality could not be assumed for some measures, robustness was expected in this sample because of equal samples in groups, no outliers, two-tailed tests, and greater than 20 degrees of freedom for error.[122]

2.8.3. Test for homoscedasticity

Levene's tests indicated equal variance for most physiological and QST variables (all *p*s > .050). Although the variance of all psychological variables were unequal (all *p*s

[1] In the 1st TSSP, maximum pain rating and wind-up ratio with average pain ratings; In the 2nd TSSP, wind-up ratio with AUC and with average pain ratings; In the 3rd TSSP, wind-up ratio with AUC and with average pain ratings, and the pain ratio of the late to the early phase of the TSSP. More detailed TSSP index can be found in the section 2.8.5.

< .050) except the PANAS-NA, ANOVA was robust to heteroscedasticity because firstly, sample sizes were greater than 5, and secondly, all F_{max} (the ratio of max group variance to min group variance) was ≤ 10,[122] except for variables of the PCL, the TSC, the IES, and the ACE. For these four measures of trauma history and symptoms, ANOVA were not robust to heteroscedasticity. Thus, additional nonparametric Mann-Whitney U tests were conducted to confirm the results of ANOVA. No statistical analysis was attempted to compare the means or the medians of the ACE because no variance existed in the no-trauma group, of which values were all zero.

2.8.4. ANOVA with bootstrap resampling method

One-way ANOVAs were used to compare the mean differences between the no-trauma and the trauma groups. In addition, a bootstrap resampling method was used to test the replicability and generalizability of the result. A sample size of 2,000 is needed for reliable hypothesis testing.[17] A minimum sample size of 14 from original data is reported to be satisfactory in the two-class problems.[17] SPSS version 18 was used for all the analyses.

2.8.5. TSSP pain indices for analysis

Twelve pain indices listed below were computed to compare different aspects of pain perception during each TSSP testing. In addition to the nine TSSP indices used in other papers, exploratory analyses were conducted with slope, average pain ratings, and the pain ratio of the late to the early phase of TSSP. Simple linear slopes were added to compare degrees of sensitization to a thermal pulse, and average scores were added to AUC because this simple calculation could be easily used in practice. Additionally, pain

ratios of the late to the early phase of TSSP were computed to compare whether the two groups would differ in persistent sensitization in the later phase in compared with the earlier phase of TSSP.

The following TSSP indices were used in analyses;

i) pain ratings at the 1st, the 5th, and the 10th pulse,[93, 111, 115, 119]

ii) average pain ratings for the 10 thermal stimuli,[36, 39]

iii) maximum pain intensity,[39, 77, 117, 118]

iv) wind-up difference score: maximum pain ratings minus pain ratings at the first thermal pulse,[1, 34, 39, 98, 117, 118]

v) time to peak pain intensity: the number of pulses required to a peak pain,[51]

vi) slope: wind-up difference score divided by time to peak pain intensity

vii) area under the curve (AUC),[34, 51, 77] indicating total pain ratings summed across all 10 stimuli

viii) absolute wind-up: AUC minus 10 times the initial response,[34]

ix) wind-up ratio or relative wind-up calculated by two methods

   a. AUC divided by the first response[64, 99] and

   b. mean pain ratings for the 10 thermal pulses divided by the initial pain rating,

x) the early TSSP pain calculated by two methods

   a. AUC from the 1st pulse to the 5th pulse[52, 53] and

   b. average pain ratings from the 1st pulse to the 5th pulse

xi) the late TSSP pain calculated by two methods

a. AUC from the 6th pulse to the 10th pulse[52, 53] and

b. average pain ratings from the 6th pulse to the 10th pulse

xii) ratio of the late to the early TSSP pain (the LE ratio) calculated by two methods

a. AUC

b. Average pain ratings

Except for the LE ratio, the two ratio scales were transformed by adding 10 to each rating in order to avoid zero denominators and over-inflation of the ratio scales.

Lastly, wind-down (the peak pain rating minus the final rating)[39] and after-sensations (wind-up decay)[93, 118] were compared between the two group. Higher score in wind-down index indicates greater decrease. The wind-down index of zero indicates no wind-down within a TSSP trial. Higher intensity of after-sensations indicates slower TSSP recovery. All of these indices were analyzed within and between TSSPs in order to compare between-group difference of TSSP changes during and over repeated trials.

3. RESULTS

3.1. Comparison of Psychophysical Characteristics at Baseline

3.1.1. Psychological characteristics

Table 2 shows the means of the self-report data for participants with and without adverse childhood events. Overall, the trauma group reported relatively poor mental health at baseline. All of the psychological symptom scores were significantly higher in the trauma group except the PANAS-PA, the PANAS-NA, and the FPQ. For depression symptoms, only 5.3% (n = 1) screened positive for at least mild depression in the no-trauma group by using the CES-D cutoff score of 16. In contrast, 52.6% (n = 10) screened positive for at least mild depression in the trauma group.

While all participants were healthy subjects, the trauma group reported worse physical health than the no-trauma group as evidenced by the trauma group's higher PILL scores, a measure of common physical symptoms and sensations. Firstly, the average number of days for doctor's office visits during a semester was 0.2 (SD = 0.4, mode = 0, range: 0-1) for the no-trauma group and 0.4 (SD = 0.6, mode = 0, range: 0-2) for the trauma group. Both groups, on average, reported less than one visit to a doctor's office per semester. Thus, this confirms that the participants were generally healthy. Secondly, the average number of sick days for a semester was 1.9 (SD = 2.7, mode = 0, range: 0-10) for the no-trauma group and 4.6 (SD = 8.0, mode = 0, range: 0-30) for the trauma group. Lastly, the average number of days with limited activity due to illness was 1.8 (SD = 4.0, mode = 0, range: 0-14) for the no-trauma group and 2.1 (SD = 7.2, mode = 0, range: 0-30) for the trauma group.

Table 2. Comparison of the self-reports between no-trauma and trauma groups

	No Trauma (n = 19)			Trauma (n = 19)				
Self-reports	*M*	*SD*	95% CIs	*M*	*SD*	95% CIs	*F*	*p*
PANAS-PA	30.1	7.7	26.6-33.4	30.8	7.1	27.7-33.9	0.09	*n.s.*
PANAS-NA	12.3	2.4	11.3-13.4	13.9	3.1	12.6-15.3	3.28	.078
CES-D	8.8	5.2	6.7-11.3	18.6	11.4	13.7-23.7	11.51	.002
PSS	12.8	4.3	10.8-14.6	20.5	7.8	17.3-24.2	14.22	.001
PAI-BOR	13.9	5.7	11.4-16.5	25.7	8.8	22.1-29.7	23.84	< .001
PAI_{SC1}	2.3	1.9	1.5-3.3	6.7	3.2	5.4-8.2	26.76	< .001
PAI_{SC2}	5.2	2.4	4.1-6.3	7.1	3.0	5.7-8.4	4.63	.038
PAI_{SC3}	4.1	2.6	2.9-5.3	7.7	2.7	6.6-8.9	17.82	< .001
PAI_{SC4}	2.4	1.8	1.6-3.2	4.2	3.3	2.8-5.7	4.61	.039
FPQ	84.3	20.5	75.2-93.5	75.4	22.3	65.9-85.5	1.64	*n.s.*
FPQ_{SC1}	35.7	7.8	32.3-39.1	32.7	8.2	29.1-36.3	1.33	*n.s.*
FPQ_{SC2}	20.9	6.7	18.1-23.9	18.4	6.2	15.8-21.2	1.47	*n.s.*
FPQ_{SC3}	27.6	10.0	22.9-32.2	24.3	10.3	20.0-29.1	1.05	*n.s.*
PILL	11.2	7.4	8.4-14.8	17.4	10.9	12.5-22.2	4.16	.049

Note:95% CI (Confidence Intervals) based on 2000 stratified bootstrap samples *t*-test; *n.s.* = not significant at $p > .100$; PANAS = Positive and Negative Affect Scale; PA = Positive Affect; NA = Negative Affect; CES-D = Center for Epidemiologic Studies for Depression; PSS = Perceived Stress Scale; PAI-BOR = Personality Assessment Inventory Borderline clinical scale; PAI_{SC1} = Subscale1 (affect instability); PAI_{SC2} = subscale2 (identity problem); PAI_{SC3} = subscale3 (negative relationship); PAI_{SC4} = subscale4 (self-Harm/impulsivity); FPQ = Fear of Pain Questionnaire; FPQ_{SC1} = subscale 1 (severe pain); FPQ_{SC2} = subscale 2 (minor pain); FPQ_{SC3} = subscale 3 (medical pain); PILL = Pennebaker Inventory of Limbic Languidness.

A series of one-way ANOVAs conducted on the three instruments measuring symptoms of trauma (i.e. the PCL, the IES, and the TSC) revealed higher traumatic symptoms in participants reporting a history of childhood trauma (Table 3). Overall, the results of Mann-Whitney U tests were consistent with those of the ANOVAs; the average ranks of the three trauma assessment measures were higher in the trauma group

than the no-trauma group (Table 3). Except the TSC subscale 1 measuring anxiety symptoms, the totals as well as the subscale scores of the PCL, the IES, and the TSC were, on average, significantly higher in the trauma group when tested both with ANOVA and Mann-Whitney U tests. In screening for PTSD with the cutoff scores, none of the participants screened positive for PTSD in the no-trauma group. Of the subjects in the trauma group, eight (42.1%) and nine (47.4%) people screened positive for PTSD using the PCL and the IES respectively.

3.1.2. Physiological characteristics

At baseline1, physiological characteristics were not significantly different between the no-trauma and the trauma groups (all *p*s > .100, Fig. 5); the means of SCL, HR, and HRV were, respectively, 3.8 (*SD* = 2.4), 80.8 (*SD* = 10.5), and 60.5 (*SD* = 25.9) for the no-trauma group and 3.4 (*SD* = 2.1), 76.7 (*SD* = 15.8), and 61.7 (*SD* = 26.9), for the trauma group. After completing self-reports at baseline2, none of the measures were significantly different between the two groups. Repeated measures ANOVAs indicated that HR and HRV were not significantly changed from baseline1 ($p > .100$) whereas SCL was significantly increased ($p < .001$). In addition, there was a marginally significant time by group interaction (F (1, 36) = 3.06, $p = .089$). Average SCL increased by 3.2 in the no-trauma group. In contrast, only 1.6 increased in the trauma group.

Table 3. Comparison of the trauma related self-reports between no trauma and trauma

	No trauma (n = 19)			Trauma (n = 19)							
Self-reports	*M*	*Q1*	*Q3*	*M*	*Q1*	*Q3*	*F*	*p*	*U**	*Z**	*p**
PCL	21.4	19.0	24.0	38.7	28.0	50.0	26.60	< .001	37.50	-4.18	< .001
PCL_{SC1}	6.1	5.0	7.0	12.2	7.0	17	19.18	< .001	63.50	-3.47	< .001
PCL_{SC2}	8.2	7.0	9.0	15.5	11.0	21	34.31	< .001	35.00	-4.29	< .001
PCL_{SC3}	7.2	6.0	8.0	10.9	8.0	14	14.97	.002	54.00	-3.73	< .001
IES	4.7	0.0	12.0	32.9	16.0	49.0	34.81	< .001	29.50	-4.46	< .001
IES_{SC1}	1.6	0.0	2.0	12.8	7.0	18.0	35.63	< .001	36.00	-4.33	< .001
IES_{SC2}	2.5	0.0	5.0	12.0	7.0	14.0	27.65	< .001	49.00	-3.97	< .001
IES_{SC3}	.7	0.0	2.0	8.2	3.0	13.0	36.26	< .001	22.00	-4.76	< .001
TSC	11.9	7.0	16.0	32.3	10.0	53.0	17.02	< .001	70.00	-3.23	.001
TSC_{SC1}	2.9	1.0	4.0	6.3	2.0	12.0	6.59	.015	131.00	-1.46	.154
TSC_{SC2}	2.2	1.0	3.0	6.5	1.0	11.0	11.04	.002	94.50	-2.54	.011
TSC_{SC3}	2.4	1.0	3.0	6.5	2.0	11.0	12.66	.001	85.50	-2.80	.005
TSC_{SC4}	1.1	0.0	1.0	4.9	1.0	9.0	18.72	< .001	70.50	-3.28	.001
TSC_{SC5}	0.5	0.0	1.0	3.7	1.0	5.0	19.13	< .001	63.00	-3.64	< .001
TSC_{SC6}	4.2	2.0	6.0	8.0	4.0	11.0	9.88	.003	86.00	-2.77	.005
ACE	0.0	-	-	3.5	2.0	5.0	-	-	-	-	
ETISR	0.0	-	-	12.7	10.0	14.0	-	-	-	-	

Q1 = 25th interquartile range; Q3 = 75th interquartile range; PCL = PT*SD* Checklist; PCL_{SC1} = subscale 1 (re-experience); PCL_{SC2} = subscale 2 (avoidance); PCL_{SC3} = subscale 3 (hyper-arousal symptoms); IES = Impact of Life Event Scale; IES_{SC1} = subscale 1 (intrusion); IES_{SC2} = subscale 2 (avoidance); IES_{SC3} = subscale 3 (hyper-arousal symptoms); TSC: Trauma Symptom Checklist; TSC_{SC1} = subscale1 (anxiety); TSC_{SC2} = subscale 2 (depression), TSC_{SC3} = subscale 3 (dissociation); TSC_{SC4} = subscale 4 (sexual abuse trauma index); TSC_{SC5} = subscale 5 (sexual problems), TSC_{SC6} = subscale 6 (sleep disturbances); ACE = Adverse Childhood Event; ETISR = Early Trauma Inventory Self Report; * Mann Whitney U tests were carried out on mean ranks; all exact significances.

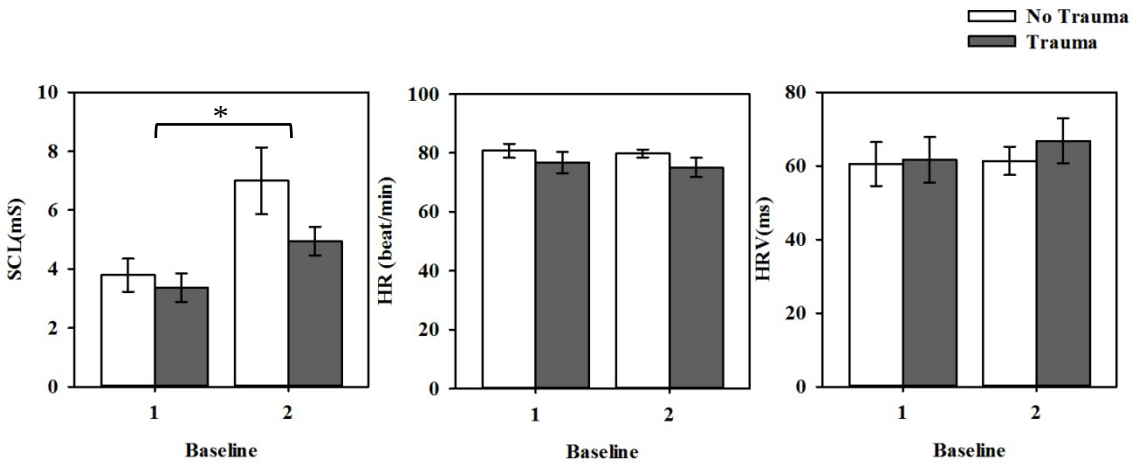

Fig. 5 Comparison of average SCLs, HRs, and HRVs between the groups with and without trauma at baseline1 and baseline2; Error bars = SEM, * = $p < .001$.

3.2. Comparison of Psychophysical Responses to the QST

The effects of thermal stimulations on emotion and psychophysiological reactions were analyzed firstly with the SAM self-reports and secondly with SCL, HR, and HRV before and after each of the QST. Fig. 6 shows changes of the SAM-valence and arousal over repeated TSSP trials. Using a one-way ANOVA, the between-group difference was significant for the SAM-valence, but not for the SAM-arousal and dominance. Next, average psychophysical responses to the QSTs were compared between the two groups during the tests of thermal pain threshold, pain sensitivity, and TSSP. Again, there were no between-group differences in psychophysiological responses during the QST using one-way ANOVAs (all *p*s > .100).

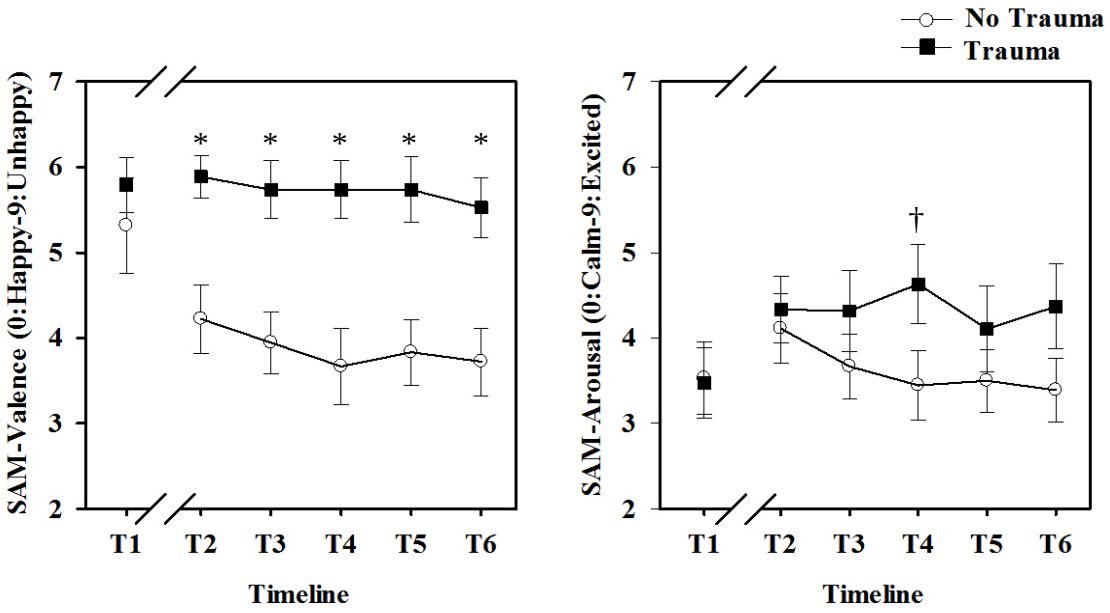

Fig. 6 Comparison of the SAM-valence and arousal between the no-trauma and trauma groups at each time point. T1 = baseline2; T2 = post-threshold test/pre-TSSP1; T3 =post-TSSP1/pre-TSSP2, T4 = post-TSSP2/pre-TSSP3; T5 = post-TSSP3/pre-TSSP4, T6 = post-TSSP4, Error bars = SEM, * = $p \leq .002$; † = $p < .100$.

3.2.1. Psychological response to pain

One-way ANOVA indicated that there was no significant between-group difference in the SAM-valence at baseline. However, the valence ratings of the trauma group were significantly higher than those of the no-trauma group after threshold testing (Fig. 6). A repeated measures ANOVA showed a significant main effect of group (F (1, 36) = 15.25, $p < .001$) and a marginally significant main effect of trial (F (2, 70) = 2.95, $p = .060$; $W_{\text{Mauchly}} = .03$, χ^2 (14) = 118.71, $p < .001$, $\varepsilon = .39$). From post-threshold to post-TSSP4, the average score of the SAM-valence was 3.9 (SD = 1.5) for the no-trauma group and 5.7 (SD = 1.5) for the trauma group. Even after the QSTs were completed, the trauma group continuously reported significantly higher levels of unpleasantness than the no-

trauma group (F (1, 36) = 11.80, p =.002). This may indicate that the trauma group showed a lack of habituation to unpleasant sensory experiences.

Based on the results of a one-way ANOVA, the mean perceived levels of the SAM-arousal were not different between the groups from baseline until pre-TSSP3 (Fig. 6). At pre-TSSP3, the trauma group (M = 4.6, SD = 2.0) showed a trend toward, on average, higher in the perceived level of arousal than the no-trauma group (M = 3.4, SD = 1.8; F (1, 36) = 3.74, p = .061). Then, this difference no longer existed after TSSP3 (p > .100). A repeated measures ANOVA indicated that the main effect of trials (F (3, 100) = 2.00, p > .100) and group×time interactions (F (3, 100) = 1.76, p > .100; W_{Mauchly} = .15, χ^2 (14) = 65.67, p < .001, ε = .56) were not significant. Additionally, there was no significant main effect of group (F (1, 36) = 1.36, p > .100).

For the SAM-dominance, a one-way ANOVA showed no significant difference at any time point between the two groups. At baseline, the average rating of the SAM-dominance was 5.9 (SD = 1.4) for the no-trauma group and 5.8 (SD = 1.5) for the trauma group. From post-threshold to post-TSSP4, the average rating of dominance was 5.9 (SD = 1.3) for the no-trauma group and 6.0 (SD = 1.6) for the trauma group. A repeated measures ANOVA indicated no significant main effect of trial or group by trial interaction (all ps > .100).

3.2.2. Psychophysical response to pain

A one-way ANOVA indicated that the trauma and no-trauma groups did not differ from each other on SCL at any time point (all ps > .100, Fig 6). Using a repeated measures ANOVA, there was no significant time by group interaction when comparing

all SCLs at five time points such as baseline2 and pre- and post-QSTs. However, there was a significant main effect of time (F (2, 76) = 12.54, p < .001, W_{Mauchly} = .18, χ^2 (9) = 59.18, p < .001, ε = .53, Fig. 6). The average level of SCL was increased as the QST were repeated, and this trend was best fit with a liner function (F (1, 36) = 31.83, p < .001). Bonferroni pairwise comparisons indicated that the average SCL at pre- and post-threshold was not significantly different from baseline2 (p > .100). However, the average SCL at pre-TSSP1 and all the others after pre-TSSP1 were significantly different from baseline2 (all ps ≤ .023). Additional Pearson correlation tests indicated that SCL and the SAM-arousal were not related at each time point (all ps > .100).

In comparing HR data collected at five points (baseline 2 as well as pre- and post QSTs), one-way ANOVA indicated no significant difference between the groups (all ps > .100). The results of a repeated measures ANOVA also indicated that there were no significant main effects of group nor time×group interaction (all ps > .100). However, there was a significant main effect of time (F (3, 101) = 7.33, p < .001; W_{Mauchly} = .43, χ^2 (9) = 29.09, p < .001, ε = .70, Fig 6). The trend of heart rate changes over repeated QSTs was best fit with a quadratic equation (F (1, 36) = 24.10, p < .001); average HRs were increased over time from baseline2 until pre-TSSP1, and then decreased to the end of the experiment. While Bonferroni pairwise comparisons indicated that all of the HRs at pre- and post-QST were not significantly different from baseline2, final HR was, on average, significantly lower than all the other time points.

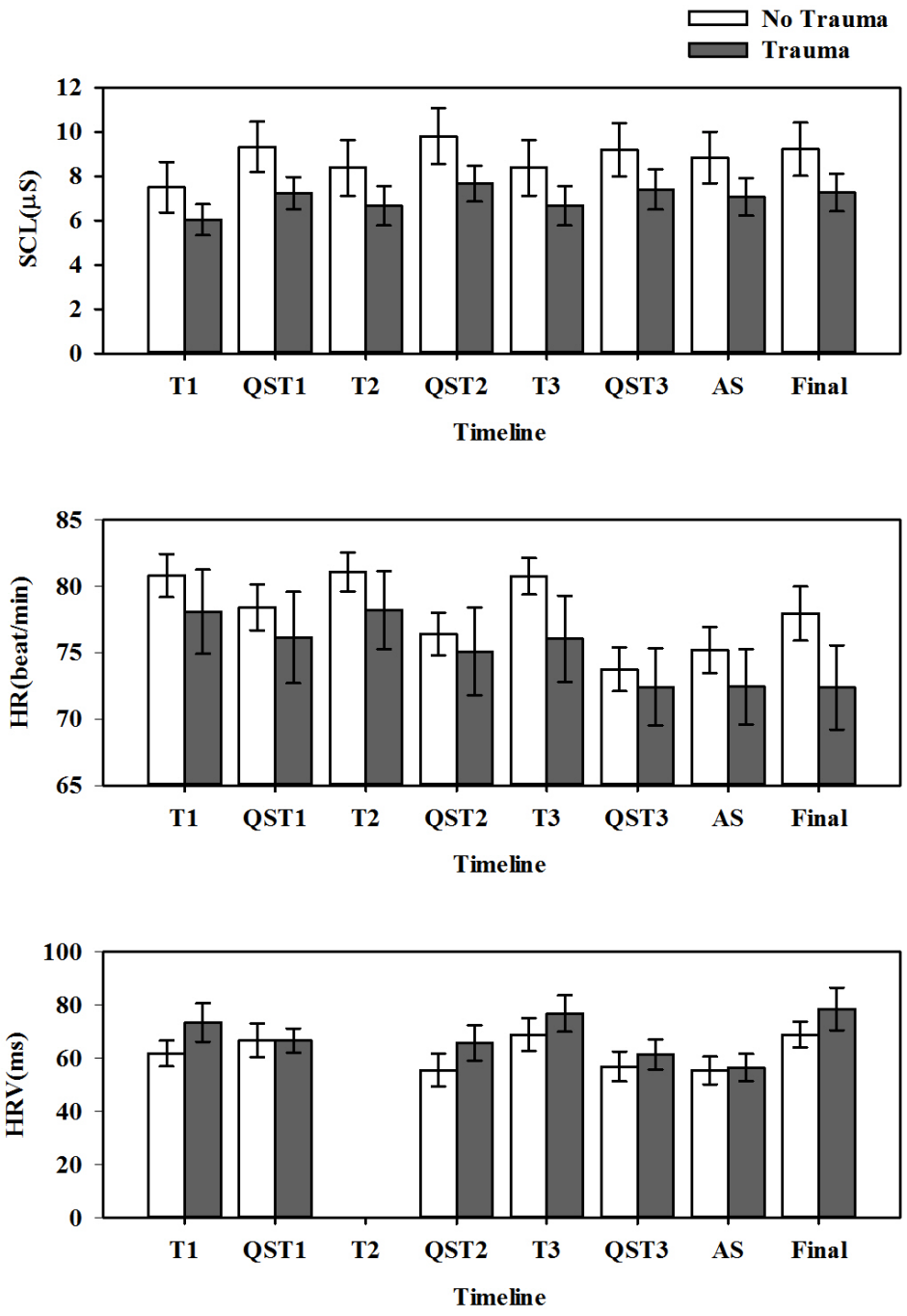

Fig. 7 Between-group comparisons of the average SCLs, HRs, and HRVs at pre- and post-QSTs, T1 = pre-threshold; QST1=threshold testing, T2 = post-threshold/pre-sensitivity testing; QST2 = sensitivity testing; T3 = post-sensitivity testing/pre-TSSP testing; QST3 = TSSP testing; AS = after-sensation; Final = post-TSSP testing, Error bars = SEM

In comparing HRVs at the four different time points (baseline2, pre-thresholds, pre-TSSP, and post-TSSP), the results of one-way ANOVA showed no significant between-group difference. A repeated measures ANOVA also indicated no significant main effect of group nor group×time interaction. While there was a significant main effect of time (F (2, 89) = 3.63, p = .022; W_{Mauchly} = .70, χ^2 (5) = 12.18, p = .033, ε = .83), the Bonferroni pairwise comparison revealed no significant difference among different time points.

A series of repeated measures ANOVAs was conducted to examine the between-group changes in average SCL, HR, and HRV before and during each QST. The main effect of group was not significant across these measures (all ps > .100). Yet, a consistent pattern was observed over repeated QST trials. During each QST, repeated measures ANOVA showed significant increase in SCL and decrease in HR from the physiological states prior to each QST (all ps ≤ .016). While no significant change occurred in average HRV during threshold testing (p > .100), HRV was significantly decreased during TSSP testing and after-sensation compared to HRV at pre- and at post-TSSP testing (all ps < .001).

In contrast to the other QSTs, there was a significant group×time interaction in repeated HR measures before TSSP, during TSSP, after-sensations, and after TSSP (F (2, 75) = 3.21, p = .044; W_{Mauchly} = .35, χ^2 (5) = 36.23, p < .001, ε = .70). Bonferroni Pairwise comparison indicated that HR at pre-TSSP (M = 80.7, SD = 6.0) was significantly different from HRs during TSSP (M = 73.7, SD = 7.2, p < .001) and after-sensations (M = 75.2, SD = 7.6, p = .002). However, HR at post-TSSP (M = 78.0, SD = 8.9) was not significantly different from pre-TSSP (p > .100) for the no-trauma group,

indicating HR recovery at post-TSSP. Of the trauma group, HR at pre-TSSP (*M* = 76.0, *SD* = 14.2, *p* =.019) was significantly different from all other HRs such as during TSSP (*M* = 72.4, *SD* = 12.7), after-sensation (*M* = 72.4, *SD* = 12.4), and post-TSSP (72.4, *SD* = 13.8), indicating no HR recovery.

In order to evaluate the true recovery function of HR, the final HR was compared with HR at baseline2 using paired sample *t*-tests. For the no-trauma group, average HR after the last TSSP testing (95% bootstrap confidence intervals (CIs): 73.9-81.8) was not significantly different from baseline2 (*M* = 78.7, *SD* = 7.9, 95% bootstrap CIs: 74.9-82.1; *t* (18) = 0.36, *p* > .100). A paired sample *t*-test with bootstrap sampling also found no difference between them (*p* > .100). However, the final HR sample from the trauma group (95% bootstrap CIs: 66.2-78.6) was lower than at baseline2 but this difference failed to reach significance (*M* = 75.1, *SD* = 14.0, 95% bootstrap CIs: 69.0-81.4; *t* (18) = 1.92, *p* = .071). A paired sample *t*-test with bootstrap sampling consistently showed the marginally significant difference between them (*p* = .076).

3.3. Comparison of Pain Perception

3.3.1. Thermal pain threshold

Using one-way ANOVAs, no significant differences were found for the first (*F* (1, 36) = 1.71, *p* >.100) and the second pain threshold (*F* (1, 36) = 1.46, *p* >.100) between the no-trauma and the trauma groups. The results of independent sample *t*-tests with bootstrap sampling were consistently insignificant (*p* > .100). For the first pain threshold, the mean temperature was 44.5ºC (*SD* = 2.9, 95% bootstrap CIs: 43.2-45.8ºC) for the no-trauma group and 45.6ºC (*SD* = 2.3, 95% bootstrap CIs: 44.6-46.7ºC) for the trauma

group. On the second test, the mean threshold temperature was 45.4ºC (*SD* = 2.4, 95% bootstrap CIs: 44.7-46.5ºC) for the no-trauma group and 46.4ºC (*SD* = 2.5, 95% bootstrap CIs: 45.3-47.6ºC) for the trauma group. A paired sample *t*-test indicated that the second threshold (*M* = 45.9, *SD* = 2.5) was significantly different from the first threshold (*M* = 45.1, *SD* = 2.7; *t* (37) = -3.90, $p < .001$), indicating that both groups showed increased in threshold in the second test.

3.3.2. Sensitivity testing

The peak temperature identified to induce moderate pain during the sensitivity test was not different between the no-trauma (*M* = 47.9, *SD* = 2.4, 95% bootstrap CIs: 46.9-48.9) and trauma (*M* = 48.4, *SD* = 1.7, 95% bootstrap CIs: 47.6-49.1; *F* (1, 36) = .68, $p > .100$) groups. This between-group difference was also insignificant with *t*-test with bootstrap sampling ($p > .100$). This indicated that calibrated temperatures did not contribute to differences in TSSP between the groups. The relationship between threshold and temperature identified in the sensitivity test was strong (Pearson *r*s = .63-.67, all *p*s < .001).[103] Using the bootstrap sampling method, Pearson's r ranges from .43 to .53 ($p \leq .007$), which indicate a moderate relationship between thermal threshold and TSSP temperature.

On average, there were 4.1 trials (*SD* = 2.2) of sensitivity tests. The average number of sensitivity tests was 3.7 (*SD* = 2.2) for the no-trauma group and 4.3 (*SD* = 2.1) for the trauma group. The number of sensitivity test was not significantly different between the two groups (*F* (1, 36) = .80, $p > .100$).

3.3.3. TSSP testing

As shown in Fig. 8, the trauma group tended to exhibit enhancement of TSSP compared with the no-trauma group both within and across the four TSSP trials. A series of statistical analyses conducted on several indicators of the wind-up process confirmed this impression. Before presenting the detailed analyses below, a brief summary of the findings is as follows. During TSSP1 testing, the trauma group showed a greater wind-up difference, a larger absolute AUC, and a greater wind-up ratio. During the second and the third TSSP tests, the results indicated a trend toward higher average pain intensity and a larger AUC in the trauma group. However, this between-group difference was driven by increases in pain ratings occurring during the later heat pulses in the TSSP testing because the group difference only existed during the late phase of TSSP testing, not the early phase.

In TSSP4, there was no significant between-group difference except for a marginal effect observed for the maximum pain intensity rating. The maximum pain intensity of TSSP4 was marginally higher in the trauma group than in the no-trauma group. Time to peak pain intensity and wind-down were, on average, not significantly different between the two groups within TSSP trials. Repeated measures ANOVAs with between-TSSP indices revealed that the no-trauma group showed a trend toward a decrease in the ratio of the late to the early TSSP pain rating (the EL ratio) in contrast the trauma group showed no significant change over time. This indicated that the no-trauma showed habituation over repetitive TSSP trials. A detailed description of each analysis is presented below.

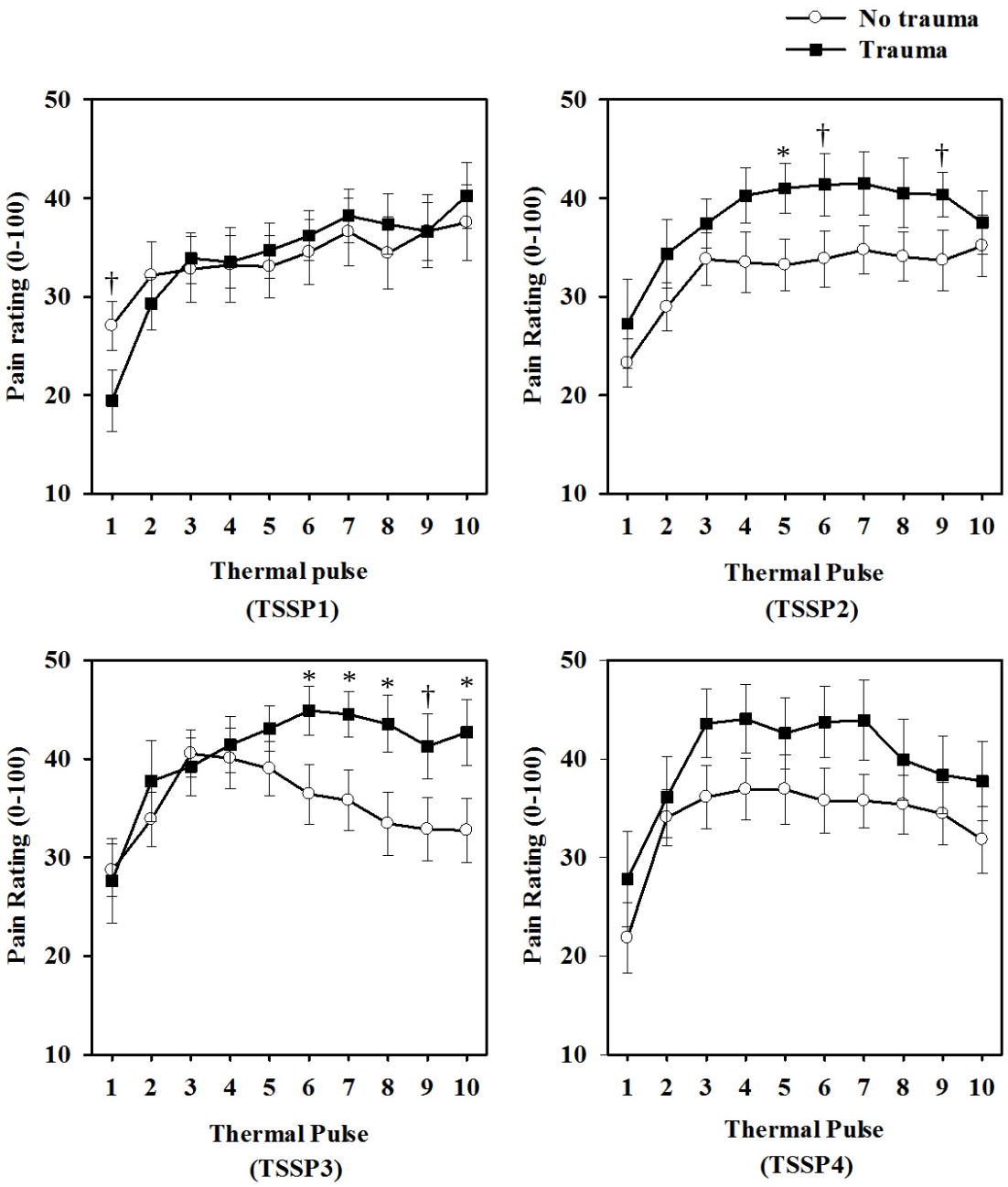

Fig. 8 Comparison of pain ratings between the no-trauma and trauma groups at each thermal pulse using one-way ANOVAs, * = $p < .050$, † = $p < .100$, Error bars = SEM.

Comparison of pain ratings at the 1st, 5th, and the 10th pulses; the mean pain ratings for the first pulse were not different between the no-trauma and trauma groups except for the first TSSP trial. In TSSP1, the result of a one-way ANOVA indicated that the average pain ratings at the first pulse was higher in the no-trauma group (M = 27.1, SD = 10.9, 95% bootstrap CIs: 22.4-31.8) than in the trauma group (M = 19.5, SD =13.6, 95% bootstrap CIs: 13.9-26.1) at p value of .066 (F (1, 36) = 3.60; Fig 7). The average reported pain at the 5th pulse was significantly higher in the trauma group (M = 41.0, SD = 11.1, 95% bootstrap CIs: 36.4-46.0) than in the no-trauma group (M = 33.2, SD = 11.4, 95% bootstrap CIs: 28.7-38.3; F (1, 36) = 4.56, p = .040) only for TSSP2 testing. For pain ratings at the 10th pulse, the trauma group (M = 42.7, SD = 14.5, 95% bootstrap CIs: 36.6-49.2) reported, on average, significantly higher pain than the no-trauma group (M = 32.7, SD = 14.2, 95% bootstrap CIs: 26.5-39.2) in TSSP3 (F (1, 36) = 4.55, p = .040). In the last TSSP test, there was no significant intergroup difference. Using bootstrap sampling, independent sample t-tests failed to show a significant intergroup difference in any of the reported pain ratings at the different time points (all ps > .100).

Comparison of average pain ratings for the 10 thermal stimuli; repeated measures ANOVAs with the 10 pain ratings at TSSP1 indicated that there was no significant main effect of group on TSSP (F (1, 36) = .002, p > .100). Based on the result of independent sample t-tests with bootstrap sampling, the average pain ratings for the 10 thermal pulses was also not different between the groups (p > .100). Additionally, there was no significant interaction between thermal pulse and group (F (4, 131) = 1.59, p > .100; W_{Mauchly} = .003, χ^2 (44) = 193.89, p < .001, ε = .40). Yet, thermal pulse was a significant

main effect (F (4, 131) = 12.20, $p < .001$). Bonferroni-adjusted pairwise comparisons indicated that the average pain at the first thermal pulse was significantly lower than all the other pulses ($p < .004$). Average pain ratings were increased over time as the thermal pulses were repeatedly presented to the palm. This showed the occurrence of the TSSP phenomenon. A linear trend model provided the best fit for both no-trauma (F (1, 18) = 4.28, $p = .053$) and trauma (F (1, 18) = 21.25, $p < .001$) groups.

With the 10 pain ratings at TSSP2, a repeated measures ANOVA revealed that the main effect of group on average pain ratings was marginally significant (F (1. 36) = 3.13, $p = .086$). A t-test with bootstrap sampling indicated a significant group difference of the average pain ratings in TSSP2 but again it was a marginal effect ($p = .084$). As being consistent with TSSP1 results, there was no significant thermal pulse × group interaction (F (4, 142) = 0.42, $p >.100$; $W_{\text{Mauchly}} = .003$, χ^2 (44) = 188.96, $p < .001$, $\varepsilon = .44$), but a significant main effect of thermal pulse (F (4, 142) = 7.95, $p < .001$). Bonferroni-adjusted pairwise comparison indicated that the mean pain rating at the first thermal pulse was significantly lower than all the other pulses after the second pulse ($p < .050$). An exploratory trend analysis showed that the TSSP pattern was best fit by a cubic model (F (1, 18) = 4.40, $p = .050$) for the no-trauma group, indicating on general upward trend. In contrast, a quadratic model was the best fit for the trauma group (F (1, 18) = 15.51, $p = .001$), indicating the occurrence of wind-down following the wind-up phenomenon.

For the TSSP3 trial, the result of a repeated measures ANOVA conducted on the 10 thermal pulse pain ratings showed that the main effect of group on average pain ratings

was not significant ($p > .100$). However, an independent sample *t*-test with bootstrap sampling indicated a marginally significant group difference of the mean pain ratings during the TSSP3 testing ($p = .090$). In addition, the results indicated no significant interaction between thermal pulse and group (F (3, 107) = 2.07, $p = .109$; $W_{\text{Mauchly}} = .001$, χ^2 (44) = 246.30, $p < .001$, $\varepsilon = .33$), but a significant main effect of thermal pulse (F (3, 107) = 6.22, $p = .001$). Bonferroni-adjusted pairwise comparisons indicated that the pain rating at the first thermal pulse was significantly lower than all the other pulses from the third pulse to the 7th pulse (all *p*s < .050). The mean pain rating for the 8th pulse was marginally different ($p = .056$), but the rating for the 9th pulse was not significantly different from the rating of the first pulse ($p > .100$). This might reflect the occurrence of wind-down. An exploratory trend analysis revealed that TSSP trend was again best fit with a cubic model for the no-trauma group (F (1, 18) = 13.12, $p = .002$) and a quadratic function for the trauma group (F (1, 18) = 12.30, $p = .003$).

When comparing pain ratings in TSSP4 using a repeated measures ANOVA, a main effect of group on average pain ratings was not significant ($p > .100$). This result was consistent with *t*-test with bootstrap sampling ($p > .100$). The results also indicated no significant thermal pulse × group interaction (F (3, 110) = 0.44, $p > .100$; $W_{\text{Mauchly}} < .001$, χ^2 (44) = 251.27, $p < .001$, $\varepsilon = .34$). Yet, there was a significant main effect of thermal pulse (F (3, 110) = 10.27, $p < .001$). Bonferroni-adjusted pairwise comparisons indicated that average pain ratings at the first thermal pulse was significantly lower than all the other pulses ($p < .050$) until the last pulse ($p > .100$). Therefore, it may indicate the occurrence of wind-down following wind-up. An exploratory trend analysis indicated

that the best fit for TSSP pattern was provided by a cubic model for both the no-trauma (F (1, 18) = 20.59, $p < .001$) and trauma (F (1, 18) = 23.70, $p < .001$) groups.

A repeated measures ANOVA with average pain ratings was conducted between the four TSSP trials. The results indicated no significant main effect of group or time by group interaction (all ps > .100). While there was a marginally significant main effect of time (F (2, 78) = 2.40, p = .093; W_{Mauchly} = .59, χ^2 (5) = 18.41, p = .002, ε = .73), Bonferroni pairwise comparison indicated no significant difference in average pain ratings among trials.

Comparison of maximum pain intensities; with one-way ANOVAs comparing maximum pain ratings in each of the four TSSP trials, the last two TSSP tests showed a trend toward higher pain ratings in the trauma group compared to the no-trauma group (Table 4). Yet, the results of t-tests with bootstrap resampling showed a marginally significant difference between the two groups only in TSSP4. Results of repeated measures ANOVA between TSSP trials revealed no significant main effects or group by trial interaction (all ps > .100).

Comparison of wind-up difference scores; the results of a one-way ANOVA indicated that the wind-up difference was significantly different between the two groups only during the first TSSP trial. A repeated measures ANOVA was conducted to examine wind-up difference between TSSP trials. The result revealed no significant main effects or group by trial interaction (all ps > .100).

Comparison of time to peak pain intensities; a one-way ANOVA showed that there was no significant between-group difference at each TSSP trial. The results of the

repeated measures ANOVA showed that time to peak pain intensity was not significantly different within and between TSSP trials (all *p*s > .100). Across the four TSSP trials, the average number of pulses required to induce peak pain intensity was 5.8 (*SD* = 2.1) collapsing across groups.

Comparison of slopes; a one-way ANOVA indicated that the average slope to the peak pain showed a marginally steeper in the trauma group only for TSSP1 (F (1, 36) = 3.20, p = .082). A *t*-test with bootstrap sampling also indicated a marginal between-group difference only in the TSSP1 slope (p = .079). A repeated measures ANOVA showed that the slope was not significantly different across TSSP trials (all *p*s > .100). The average slope across the four trials was 2.8 (*SD* = 2.1) for the combined group. This slope describes, on average, a 2.8 increase in pain rating with each thermal pulse presentation until peak pain ratings.

Comparison of AUCs; using one-way ANOVA, the between-group analyses of AUC indicated a marginally significant difference for the TSSP2 trial, but not for the other trials. However, independent sample *t*-tests with bootstrap sampling indicated a marginal effect of group, with the trauma group having a larger AUC compared to the no-trauma for both TSSP2 (p = .074) and TSSP3 (p = .093). Repeated measures ANOVA with the AUC showed that there was no significant main effect of group or group by trial interaction (p > .100). However, marginally significant changes occurred in over trials (F (2, 78) = 1.29, p = .070; W_{Mauchly} = .59, χ^2 (5) = 18.5, p = .002, ε = .72). Bonferroni-adjusted pairwise comparison indicated that the AUC of TSSP3 was larger than that of TSSP1, but this was a marginal effect (p = .088).

Comparison of absolute wind-ups; one-way ANOVA showed that average absolute wind-up indices were significant different between the groups only in TSSP1. The results of the repeated measures ANOVA showed that absolute wind-up index was not significantly different between TSSP trials (all *p*s > .100). In addition, there was no significant main effect of group nor group by trial interaction (all *p*s > .100).

Comparison of wind-up ratio; when comparing wind-up ratio with both AUC and mean pain ratings, one-way ANOVAs yielded similar results (Table 4). Wind-up ratio was significantly higher in the trauma group only in TSSP1. Independent *t*-tests with bootstrap sampling showed consistent outcome. A repeated measures ANOVA showed that there was no significant main effects nor time by group interaction. While wind-up ratios were often examined with AUC, average pain rating also produced interpretable and pertinent results. In TSSP1, overall pain magnitude during TSSP was increased by 1.2 times the initial pain intensity for the no-trauma group and 1.7 times for the trauma group.

Comparison of the early and the late TSSP ratings; for between-group comparisons of pain during the early and the late phases of TSSP, a series of one-way ANOVAs using average pain ratings yielded similar results to the analysis with AUC index (Table 4). The early TSSP pain ratings were not significantly different between the no-trauma and trauma groups. For the late TSSP, the trauma group reported, on average, higher pain than the no-trauma group only in TSSP3.

Repeated measures ANOVA with AUC revealed that there was no significant main effect of group or group by trial interaction. However, there was a significant trial effect

in the early TSSP pain ratings (F (2, 83) = 4.35, p = .012; W_{Mauchly} = .67, χ^2 (5) = 14.09, p = .015). Bonferroni-adjusted pairwise comparison indicated that the early phase of AUC in TSSP3 was significantly larger than that of TSSP1 (p = .009). The best fit for the pattern of the early TSSP with AUC was provided by a linear model (F (1, 36) = 6.22, p = .017). The significant main effect of trial was consistent when using average pain ratings during the early TSSP (F (3, 54) = 4.64, p = .006; W_{Mauchly} = .76, χ^2 (5) = 4.58, p > .100). For the late TSSP ratings, there were neither significant main effects nor trial by group interaction over repeated TSSP trials (p > .100).

Comparison of the pain ratio of the late to the early phase of TSSP (the LE ratio); the LE ratio showed a significant difference between the groups in TSSP3. While the no-trauma group experienced, on average, a minimal change during the late TSSP3 (the LE ratio of 1.0), the trauma group experienced an overall increase in pain ratings during the late phase of TSSP3 compared to pain in the early phase (the LE ratio of 1.3). A repeated measures ANOVA with the LE ratio of AUC indicated that there was no significant main effect of group or trial. However, there was a marginally significant group by time interaction (F (2, 78) = 2.92, p = .055). While no significant main effect of trial was found for the trauma group (p > .100), there was a significant main effect of trial for the no-trauma group (F (3, 54) = 2.86, p = .045; W_{Mauchly} = .59, χ^2 (5) = 8.88, p > .100), but Bonferroni pairwise comparison failed to show significant difference between trials. A cubic trend provided the best fit for the no-trauma group (p = .033); the LE ratio was decreased until the last TSSP.

Table 4. Comparison of the pain indices in TSSP between no trauma and trauma groups

	No trauma (n = 19)			Trauma (n = 19)						
	M	*SD*	95% CIs	*M*	*SD*	95% CIs	*F*	η_p^2	*p*	
Mean Pain										
TSSP1	33.8	12.9	28.2-39.9	34.0	10.1	29.6-38.7	0.00		*n.s.*	
TSSP2	32.4	8.4	28.9-36.1	38.2	11.4	33.4-43.2	3.13	0.080	.086	†
TSSP3	35.3	9.6	31.1-39.6	40.6	9.9	36.2-45.0	2.78	0.072	.104	†
TSSP4	33.9	11.3	29.1-38.7	39.8	14.6	33.3-46.0	1.94		*n.s.*	
Max Pain										
TSSP1	43.8	13.4	38.2-50.2	44.5	11.9	39-4-50.1	0.03		*n.s.*	
TSSP2	43.5	11.0	38.8-48.1	48.9	12.5	43.5-54.5	2.01		*n.s.*	
TSSP3	46.4	11.8	41.2-51.4	52.4	9.7	48.2-56-8	2.87	0.074	.099	
TSSP4	42.6	13.2	37.0-48.4	50.6	15.4	43.9-57.4	2.95	0.076	.094	†
WU Difference										
TSSP1	16.8	11.3	11.9-21.8	25.1	12.6	19.6-30.6	4.54	0.040	.040	
TSSP2	20.3	14.0	14.2-26.4	21.7	13.6	15.9-27.6	0.10		*n.s.*	
TSSP3	17.7	13.9	12.2-23.7	24.7	17.0	17.5-32.4	1.93		*n.s.*	
TSSP4	20.9	13.8	15.0-26.6	22.8	15.5	16.5-29.3	0.17		*n.s.*	
TTP										
TSSP1	5.8	3.6	4.2-7.4	6.7	3.0	5.4-8.1	0.77		*n.s.*	
TSSP2	6.3	3.3	4.8-7.6	6.3	3.1	4.9-7.6	0.00		*n.s.*	
TSSP3	4.9	2.7	3.7-6.1	5.8	3.3	4.4-7.2	0.94		*n.s.*	
TSSP4	5.2	2.6	4.1-6.3	5.0	2.5	4.0-6.2	0.07		*n.s.*	
Slope										
TSSP1	2.9	2.3	2.0-4.0	4.3	2.6	3.2-5.5	3.20	0.082	.082	†
TSSP2	3.2	2.2	2.3-4.3	3.4	2.5	2.4-4.5	0.06		*n.s.*	
TSSP3	4.2	3.5	2.7-5.7	3.9	2.9	2.6-5.1	0.10		*n.s.*	
TSSP4	3.7	2.4	2.7-4.9	4.6	2.8	3.4-5.9	0.98		*n.s.*	

95% CI (Confidence Intervals) based on 2000 stratified bootstrap samples, * = $p < .050$, † = $p < .100$ based on independent sample *t*-tests with bootstrap sampling; η_p^2 = partial eta square; WU Difference = max pain rating minus the first pain rating; TTP: Time to peak pain intensity; Slope = WU difference divided by TTP.

Table 4 Continued. Comparison of the pain indices in TSSP between no trauma and trauma groups

	No trauma (n = 19)			Trauma (n = 19)						
	M	*SD*	95% CIs	*M*	*SD*	95% CIs	*F*	η_p^2	*p*	
AUC										
TSSP1	305.7	119.4	254.9-362.8	309.7	90.7	270.7-353.4	0.01		*n.s.*	
TSSP2	294.9	79.9	262.0-330.4	349.2	101.3	306.2-393.9	3.36	0.085	.075	†
TSSP3	322.6	88.9	284.7-361.5	370.8	87.7	332.2-408.7	2.83	0.101	.101	†
TSSP4	312.0	104.1	266.2-357.1	365.0	131.2	308.0-425.3	1.90		*n.s.*	
Absolute WU										
TSSP1	35.1	110.4	-12.8-82.4	115.0	97.7	70.8-157.6	5.57	0.134	.024	*
TSSP2	62.3	130.7	9.7-122.7	76.6	153.6	4.1-138.2	0.10		*n.s.*	
TSSP3	35.8	126.3	-17.6-94.8	94.5	148.0	26.7-159.0	1.73		*n.s.*	
TSSP4	93.6	149.9	30.0-159.2	87.1	141.1	25.5-145.6	0.02		*n.s.*	
WU ratio-AUC										
TSSP1	8.8	2.8	7.6-10.0	12.5	5.0	10.5-14.9	8.07	0.183	.007	*
TSSP2	10.9	9.0	8.2-15.8	11.4	5.0	9.4-13.7	0.05		*n.s.*	
TSSP3	10.0	7.4	7.7-13.9	12.7	6.1	10.1-15.6	1.44		*n.s.*	
TSSP4	13.7	10.4	9.5-18.4	11.7	5.3	9.5-14.1	0.51		*n.s.*	
WU ratio (mean pain)										
TSSP1	1.2	.3	1.1-1.4	1.7	.7	1.5-2.1	8.04	0.183	.007	*
TSSP2	1.5	1.1	1.2-2.1	1.6	.6	1.3-1.8	0.03		*n.s.*	
TSSP3	1.4	.9	1.1-1.8	1.7	.8	1.3-2.1	1.41		*n.s.*	
TSSP4	1.9	1.3	1.3-2.5	1.6	.7	1.3-1.9	0.62		*n.s.*	

95% CI (Confidence Intervals) based on 2000 stratified bootstrap samples, * = $p < .050$, † = $p < .100$ based on independent sample *t*-tests with bootstrap sampling; η_p^2 = partial eta square; AUC = area under the curve; Absolute WU = AUC minus 10 times the initial response; WU ratio = AUC divided by the first response

Table 4 Continued. Comparison of the pain indices in TSSP between no trauma and trauma groups

	No trauma (n = 19)			Trauma (n = 19)						
	M	*SD*	95% CIs	*M*	*SD*	95% CIs	*F*	η_p^2	*p*	
AUC for Early TSSP										
TSSP1	128.2	53.2	105.2-154.2	123.8	40.7	106.5-142.8	0.08		*n.s.*	
TSSP2	124.4	38.6	108.1-142.3	146.2	48.1	126.3-167.0	2.36		*n.s.*	
TSSP3	148.3	39.0	131.4-164.9	153.7	49.9	130.6-174.5	0.14		*n.s.*	
TSSP4	136.4	48.5	114.6-157.8	158.9	60.1	133.3-186.5	1.61		*n.s.*	
AUC for Late TSSP										
TSSP1	177.4	72.3	147.0-212.8	185.9	56.9	161.5-212.6	0.16		*n.s.*	
TSSP2	170.5	52.1	148.0-193.1	203.0	60.0	178.0-229.1	3.18	0.081	.083	†
TSSP3	174.3	59.9	148.7-200.0	217.1	54.1	194.0-241.5	5.33	0.129	.027	*
TSSP4	175.6	60.1	149.0-201.7	206.1	81.2	170.3-242.4	1.73		*n.s.*	
LE Ratio with AUC										
TSSP1	1.5	.4	1.3-1.6	1.5	.3	1.4-1.7	0.44		*n.s.*	
TSSP2	1.4	.5	1.2-1.6	1.4	.3	1.3-1.6	0.01		*n.s.*	
TSSP3	1.2	.4	1.0-1.3	1.6	.9	1.3-2.0	4.10	0.102	.050	†
TSSP4	1.3	.3	1.2-1.4	1.3	.4	1.2-1.5	0.04		*n.s.*	

95% CI (Confidence Intervals) based on 2000 stratified bootstrap samples, * = $p < .050$, † = $p < .100$ based on independent sample *t*-tests with bootstrap sampling; η_p^2 = partial eta square; AUC for Early TSSP = AUC from the 1st pulse to the 5th pulse, AUC for Late TSSP = AUC from the 6th pulse to the 10th pulse; the LE ratio with AUC: the ratio of AUC for Late TSSP to Early TSSP.

Table 4 Continued. Comparison of the pain indices in TSSP between no trauma and trauma groups

	No trauma (n = 19)			Trauma (n = 19)						
	M	*SD*	95% CIs	*M*	*SD*	95% CIs	*F*	η_p^2	*p*	
Early TSSP										
TSSP1	31.7	12.6	26.2-37.7	30.2	10.1	25.9-34.9	0.16		*n.s.*	
TSSP2	30.5	9.0	26.7-34.7	36.1	12.1	31.1-41.4	2.55		*n.s.*	
TSSP3	36.4	9.5	32.3-40.5	37.8	12.1	32.3-42.9	0.16		*n.s.*	
TSSP4	33.2	12.0	27.9-38.6	38.8	15.2	32.4-45.9	1.63		*n.s.*	
Late TSSP										
TSSP1	35.9	14.7	29.6-43.0	37.7	11.8	32.8-43.2	0.17		*n.s.*	
TSSP2	34.3	11.0	29.4-39.0	40.3	12.2	35.2-45.4	2.52		*n.s.*	
TSSP3	34.2	12.1	29.0-39.5	43.4	11.4	38.6-48.5	5.75	0.138	.022	*
TSSP4	34.6	12.2	29.1-40.0	40.7	16.4	33.6-48.0	1.70		*n.s.*	
LE Ratio										
TSSP1	1.2	.4	1.0-1.3	1.2	.3	1.2-1.4	0.88		*n.s.*	
TSSP2	1.2	.4	1.0-1.4	1.2	.3	1.0-1.3	0.01		*n.s.*	
TSSP3	1.0	.4	.8-1.1	1.3	.7	1.1-1.7	4.19	0.104	.048	†
TSSP4	1.1	.3	1.0-1.2	1.1	.4	.9-1.2	0.02		*n.s.*	
Wind-down										
TSSP1	6.3	10.0	2.4-11.1	4.3	8.5	1.2-8.2	0.47		*n.s.*	
TSSP2	8.4	10.2	4.1-13.2	11.4	11.1	6.7-16.5	0.78		*n.s.*	
TSSP3	13.7	12.3	8.6-19.5	9.7	13.4	4.5-16.0	0.92		*n.s.*	
TSSP4	10.8	10.8	6.3-16.1	12.9	15.4	6.6-20.2	0.22		*n.s.*	

95% CI (Confidence Intervals) based on 2000 stratified bootstrap samples, * = $p < .050$, † = $p < .100$ based on independent sample *t*-tests with bootstrap sampling; η_p^2 = partial eta square; Early TSSP = Average Pain rating from the first pulse to the 5th pulse; Late TSSP = Average pain rating from the 6th pulse to the 10th pulse, the LE ratio = the ratio of the late TSSP to the early TSSP; Wind-down = the Peak pain rating minus the final rating

3.3.4. Wind-down

One-way ANOVAs showed no significant difference in wind-down between the two groups ($p > .100$, Table 4). Of the four TSSPs, the average magnitude of wind-down was 9.8 ($SD = 1.9$) for the no-trauma group and 9.6 ($SD = 1.9$) for the trauma group. Repeated measures ANOVA indicated that there was no significant main effect of group or group by trial interaction (all ps > .100). However, there was a significant main effect of time (F (3, 108) = 1.2, $p = .010$; $W_{\text{Mauchly}} = .79$, χ^2 (5) = 8.1, $p > .100$). The average magnitude of wind-down in TSSP3 and TSSP4 were significantly higher than those in TSSP1 ($p = .026$). This indicated that more wind-down occurred in TSSP3 and TSSP4.

3.3.5. After-sensations

Only in TSSP3, the results of one-way ANOVA showed that the trauma group ($M = 19.9$, $SD = 13.4$) reported significantly higher pain than the no-trauma group ($M = 11.7$, $SD = 9.0$; F (1, 37) = 4.92, $p = .033$, Fig. 9) at the first after-sensation. Since the pain magnitude at the last pulse could influence after-sensations, another one-way ANOVA was conducted with the pain rating at the 10th pulse entered as a covariate. The results of ANCOVA showed that the first after-sensation of the trauma group was still marginally different from that of the no-trauma group (F (1, 37) = 3.42, $p = .073$) in TSSP3. All other results were insignificant using the repeated measures ANOVA with first and second after-sensations between TSSP trials (all ps > .100).

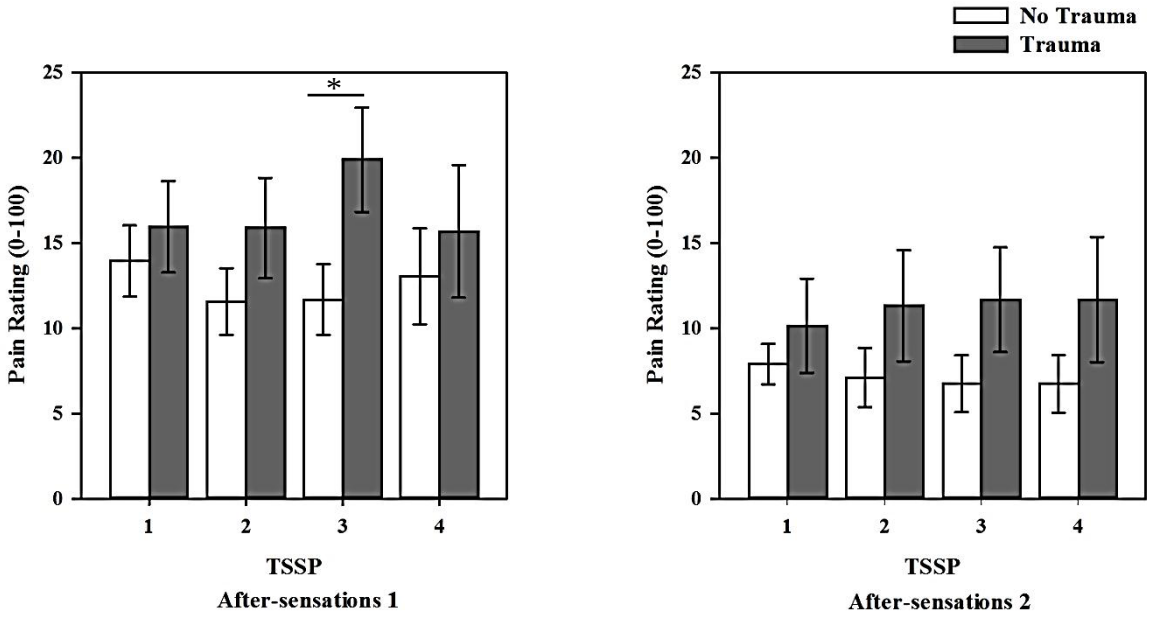

Fig. 9 Comparison of the after-sensations between no-trauma and trauma groups. After-sensations were measures 15 s (after-sensation 1) and 30 s (after-sensation 2) after the last thermal pulse in each TSSP. * = $p < .050$, Error bars = SEM.

4. SUMMARY AND CONCLUSION

4.1. Major Study Findings

The three hypotheses are partially supported. The first hypothesis of greater TSSP in trauma group was supported by the several TSSP indices, but predicted between-group differences of wind-down were not significant. The second hypothesis was also partially supported; habituation and/or adaptation did not occur over repeated TSSP trials in the trauma group whereas the no-trauma group showed a decrease in the LE ratio over TSSP trials. However, the pattern of sensitization over repeated trials was not significantly different between the two groups. Lastly, slower wind-up decay was observed in the trauma group during TSSP3. However there was no significant changes in the magnitude of wind-up decay over repeated TSSP trials.

Overall, the results suggest that individuals reporting a history of adverse childhood events report a hyperalgesic response to TSSP testing and prolonged wind-up decay after TSSP testing. When significant between-group differences were observed on TSSP indices, the trauma group constantly reported greater pain intensity compared to the no-trauma group. This pattern of results is consistent with our previous finding that trauma history is associated with enhancement of capsaicin-induced secondary hyperalgesia, another measure of central sensitization.[26] Moreover, this pattern of results is consistent with the differences between healthy control and patients with chronic pain problems.[116] However, no significant between-group differences were found for peak temperature to induce moderate pain in TSSP, for the number of pulses required to peak pain, or for thermal threshold in this otherwise healthy sample. Other studies have also failed to

observe differences between healthy control and chronic pain on one of these measures. For example, the number of pulses to induce moderate pain in TSSP testing does not differ between healthy control and patients with fibromyalgia.[111] Yet, researchers have observed that patients with chronic pain often require a less intense peak temperature to induce the same magnitude of TSSP.[24, 111] and have lower thermal threshold.[70, 109] Perhaps leftward shifting in these pain domains is not affected by adverse childhood events, and occurs only in chronic pain state. Evidently, most previous studies have observed no effect of childhood adversities on pain threshold. It is also suggested that a static index such as a threshold testing can measure only the final effect of central neuroplastic changes that contribute to pathological pain states.[61]

Lack of habituation between-TSSP trials might be another difference between the trauma and no-trauma groups. We observed a decrease in the LE ratio between-TSSP trials in the no-trauma group, whereas the trauma group failed to show habituation over the repeated trials of TSSP. Although the underlying mechanisms of habituation to painful stimuli are still under investigation, habituation deficits appear to be related to impaired anti-nociceptive system at the cortical level and low activity in central serotonergic pathways.[9, 22, 29] A recent fMRI study suggests that the subgenual anterior cingulate cortex (SACC) may play a critical role in mediating habituation to repetitive painful stimuli.[9, 29] The SACC is involved in mediating the arousal accompanying reward-based emotion/motivation and autonomic control.[29] Thus, the SACC seems to play a role in the interaction effect between emotional state and arousal on pain modulation. It is also suggested that a reduced ascending serotonergic control

contributes to cortical dysfunction, which is linked to the loss of habituation.[22] Prior research has shown reduced habituation to repetitive painful stimuli in patients with fibromyalgia,[108] and patients with migraine.[22, 131] Thus, the lack of habituation over trials in the trauma group may reflect a dysfunction of anti-nociceptive system and ascending serotonergic pathways.

In fact, it is unclear whether the decreases in pain intensity observed across TSSP trials results from peripheral sensory adaptation or central habituation process. It was reported that habituation on a fixed location occurred in a greater magnitude (70% reduction) and ten times faster than a variable stimulus location (40% reduction).[48] While peripheral adaptation of Aδ and C fiber may contribute to reduced nociceptive inputs to the spinal cord, central habituation is still likely to contribute to a reduction of TSSP. Moreover, several pieces of evidence support that supra-spinal antinociceptive systems are involved in habituation to repetitive thermal stimulation.[6, 9] In human studies, reduced pain over repeated trials has been reported in not only thermal wind-up tests[35, 36] but also during repeated laser pulse[62] and heat threshold tests.[9, 108] Notably, it is suggested that lack of habituation may be a risk factor for the transition from acute to chronic pain or it may simply contribute to the persistence of chronic pain states.[41, 89] Thus, lack of habituation over repetitive TSSP trials in the trauma group may potentially reveal the vulnerability of the trauma group to chronic pain problems.

4.2. Difference between Tonic and Phasic Noxious Stimulation

The effect of childhood trauma on TSSP was smaller than its effect on the area of secondary hyperalgesia in the capsaicin test. In order to compare the effect size between

these two pain modalities, Cohen's d [†] was calculated from the reported F test results of the area of secondary hyperalgesia.[26, 124] The effect size of childhood trauma on the area of secondary hyperalgesia was large (d = .91).[20] In contrast, the effect size of trauma on any of the TSSP indices was small to medium (Table 4).[20] There are several possible explanations for this large difference. First of all, the prior study selected subjects whose childhood trauma scores were 2 standard deviations above the mean. In contrast, the current study used a cutoff score of 10, which is the reported mean for trauma group.[13] In fact, a high trauma score in the 95th percentile or above was 13 based on the current screening data.

Second, capsaicin induces longer lasting tonic pain, which may exhibit qualitatively different pain perception than the brief phasic pain such as TSSP. It is reported that tonic pain induces more intense pain and more aversive affective states than phasic pain.[16] Consequently, capsaicin method may be more efficient to discriminate altered central sensitization between healthy subjects with and without childhood trauma.

Additionally, different degrees of anxiety might explain the discrepancy, which is linked to an anxiety-induced hyperalgesia phenomenon. It is reported that anxiety is provoked when an organism either anticipates or experiences sustained fear in response to a threat.[31] Although fear and anxiety are often thought to be similar states, they differ in several ways. Where fear is an adaptive response to a short-term threat that begins rapidly and resolves quickly once the threat is removed (phasic fear), anxiety is a more

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[†] $d = \sqrt{F\left(\frac{n_t + n_c}{n_t n_c}\right)\left(\frac{n_t + n_c}{n_t + n_c - 2}\right)}$

F = F statistic, *n* = number of subjects, *t* = treatment (or compared group), *c* = control group

prolonged response elicited by less predictable and uncertain threats, as well as by prolonged anticipation of potential threats. Therefore, anxiety is a considered to be a long-lasting state of apprehension (sustained fear). Animal studies suggest that phasic fear is mediated by the amygdala, which signals the hypothalamus and brainstem to produce fear behaviors. Although sustained fear is also mediated by the amygdala, it leads to the release of a stress hormone, corticotropin-releasing factor, which then acts on receptors in the bed nucleus of the stria terminalis (BNST), a part of the so called 'extended amygdala.'[97] Thus, depending on the nature of the threat stimulus, the amygdala and BNST send outputs to the same hypothalamic and brainstem nuclei to produce either phasic or sustained fear, respectively. Animal and human research using phasic fear paradigms induce decreased pain sensitivity or hypoalgesia, whereas sustained fear paradigms induce increased pain or hyperalgesia. This leads us to speculate that pain tests that induce phasic or sustained fear states may yield divergent patterns of results. By extension the hyperalgesic effects of trauma history on pain sensitivity may be better detected by tonic pain tests in which the pain stimulus itself induced sustained rather than phasic fear paradigms. Thus, the sustained fear state induced by tonic capsaicin pain is more likely to induce anxiety and reveal hyperalgesia in individuals with past trauma, whereas the phasic fear state induced by TSSP is more likely to induce a stress-induced hyperalgesia. Consequently, effect of childhood traumatic experience on the secondary hyperalgesia in capsaicin pain method as expected is large.[97] Moreover, people with PTSD are reported to have heightened

sustained fear without elevated phasic fear in conjunction with the anxiety-induced hyperalgesia phenomenon.[31]

Lastly, the previous studies with capsaicin-evoked pain model include only women subjects. Women often report more distress after trauma,[42] and women reporting childhood trauma also report more chronic pain problems.[40, 106] Moreover, women generally suffer from more inflammation-mediated autoimmune disorders,[78] and neuropathic pain than men.[11] Given capsaicin-evoked pain simulates neurogenic inflammatory pain processing, using only female subjects with adverse childhood events potentially yields more robust outcome in capsaicin-induced secondary hyperalgesia.

4.3. Psychophysical Reactivity to Repeated TSSP Trials

We did not observe any baseline differences between the trauma and no-trauma groups on a state measure of unpleasantness despite evidence of increased state negative affect on the CES-D and trauma measures. The QSTs using thermal stimulation did not induce more unpleasantness. Previous studies suggest that contact heat pain induces less unpleasantness than other pain methods (i.e. ischemic exercise and cold-pressure pain), and therefore, contact heat may be more suitable to examine the sensory dimension of pain perception.[96] However, the current findings suggest that the trauma group showed failure to habituate over the repeated QSTs. After the first QST, the trauma group maintained the initially elevated unpleasantness throughout the experiment while the no-trauma group reported linearly reducing unpleasantness after they experienced the first QST. It is suggested that affect regulation and affect intensity may be important in managing chronic pain because it is associated with inability to mobilize affective

resources following negative sensory experience.[113] Consequently, affect dysregulation is linked to slower recovery from or difficult adjustment to chronic pain.[50, 144] Thus, the results of the current study may indicate that the trauma group has difficulty regulating affective dimension of pain (e.g. pain unpleasantness), which may contribute to their failure to habituate to the pain over the repeated TSSP trials.

Based on the PAI subscale 1, the trauma group reported more affect instability than the no-trauma group, indicating that the trauma group had reduced ability to regulate emotion prior to the QST. However, it is worth mentioning that affect instability did not reach a critical point. The average scores of the PAI subscale 1 in the trauma group was 6.7, which is a T score of about 56 and this is only slightly elevated from the population mean. In order to raise a clinical concern, the raw score should be above 11, which is T score of 70 and 2 standard deviations above the population mean. Additionally, HRV scores of the trauma group at baseline and during the QSTs were not significant different from those of the no-trauma group. Thus, there may be no between-group difference in adaptability to stress as HRV often reflects adaptability to psychophysical stressors.[32, 56, 80, 94] In sum, the trauma group has a reduced ability to regulate their emotion than the no-trauma group. Even though the level of affect instability in the trauma group is within a subclinical range, individuals with adverse childhood events seem to have difficulty in regulating negative affective response to TSSP testing.

In general, the current study showed that painful stimulation resulted in an increase in SCLs and a decrease in HRs. Obviously, increased SCL confirms the sympathetic arousal response to laboratory pain stimulation.[57, 97] There are three explanations for

decelerated HR during a stress. First, HR deceleration may be associated with attention and orienting reflex.[46] It is reported that highly unpleasant stimuli induce an increase in SCL and a decrease in HR. Additionally, people pay attention to the unpleasant stimuli for an extended time.[68] Therefore, decelerated HR during TSSP may indicate that the subjects pay attention and orient to the unpleasant sensory stimuli in TSSP testing.

Another explanation is that decelerated HR during an acute stressor is a healthy response. It is reported that deceleration of HR to trauma-related stimuli reflects resilience because deceleration of HR indicates ability to reduce attention to the aversive stimuli and consequently down-regulate or block negative emotion in compared to people with low resilience.[33] Given that the trauma subjects are also all healthy and pain-free young college adults, their ability to regulate emotion might not be critically diminished. Therefore, the trauma group showed the same pattern of suppressed HR as the no-trauma group.

Alternatively, diminished physiological reactivity during acute stressors has been associated with the dissociative symptoms of PTSD, which is a response of physical numbness, a maladaptive coping strategy, and a risk factor for development of PTSD.[49, 63] It is reported that those who have dissociative symptoms of PTSD report increased level of perceived arousal during or immediately after disclosure of their traumatic experience, but show markedly suppressed physiological responses.[49] Therefore, the inverted intergroup pattern between perceived arousal and physiological responses may be explained by dissociative symptoms of PTSD. Evidently, dissociation scores on the TSC subscale 3 were significantly elevated in the trauma group. Yet, Griffin, Resick,

and Mechanic claim that suppression of autonomic responses linked to dissociation symptoms of PTSD may be rather trauma-specific, and may not generalize to other stressful experience. Thus, further research is needed to determine whether decelerated HR in response to noxious sensory and affective experience is indicative of suppressed autonomic response, which is linked to dissociative symptoms of PTSD.

Differential ability to recover heart rate after TSSP was another important finding. When TSSP was completed, the no-trauma group showed a trend of returning their suppressed HR back to their baseline. However, the trauma group showed a continuously depressed HR response even after they were informed about completion of the experiment. This delayed recovery may indicate persistent arousal driven by sustained anxiety.[60] A prior study showed that after an acoustic startle task, a delayed recovery of physiological function was only observed in HR among other physiological indices such as SCL and eyeblink electromyography, and delayed recovery of HR was significantly related to PTSD severity.[60] Another study reported that delayed blood pressure recovery was observed in veterans with PTSD after an anger recall task, which was not directly related to their traumatic events.[8] Therefore, delayed HR recovery after the final TSSP in the trauma group may indicate vulnerability to develop psychological and physical stress-related conditions. In fact, the results of current study showed that most of the psychological health indicators were worse in the trauma group. In addition, the trauma group reported more physical symptoms than the no-trauma group even though the trauma group participants otherwise claimed to be healthy and pain-free individuals.

4.4. Limitations and Future Studies

One of the limitations of the current study is a small sample size, which result in the low power. While replication study with a large sample is needed to confirm the link, this study has tested reproducibility of the experiments with a bootstrapping resampling method. Another limitation is a possible dissimilarity between laboratory-induced TSSP and pathophysiologically-induced wind-up phenomena. This study has examined the link between adverse childhood events and TSSP in healthy individuals in order to study the effect of adverse childhood events on chronic pain problems. While the current findings may not generalize to clinical pain processes, both TSSP and wind-up phenomena are dependent on facilitation mediated by the NMDA receptor activation within the spinal cord dorsal horn neurons, which suggests that similar neural mechanisms are involved. Another limitation of this study is the range of pain induced in the experiment. This study used calibrated thermal stimuli to elicit moderate pain. Therefore, the results of current study may not apply to severe or intolerable pain conditions. Despite the restricted range of pain used in this study, the current study has adopted a TSSP method,[116] which has been shown to distinguish differential TSSP response patterns between subjects with and without chronic pain. Therefore, by comparison of the two TSSP patterns between healthy people with adverse childhood events and patients with chronic pain problems, it is possible to evaluate whether adults with adverse childhood events are the at-risk for enhanced sensitization of pain as indicated by abnormal TSSP processes, and therefore potentially vulnerable to development chronic pain problems.

One of the strengths of this study is that it used a valid screening instrument for assessing adverse childhood events. Moreover, the screening instrument were administered twice (at home and in the laboratory) to confirm their memory of adverse childhood events. An additional strength is that this study used healthy and pain-free subjects to examine pre-existing vulnerability of developing chronic pain problems. Therefore, this method enabled us to avoid the impact of chronic pain on central sensitization, but rather focus on the contribution of adverse childhood events to enhance central sensitization. Lastly, all different characteristics of TSSP were examined. It seems that different TSSP indices reflect different underlying processes.

Additional study is warranted to further characterize different aspects of TSSP and to delineate TSSP indicators and mechanisms. Future research is also required to examine whether the two pain tests that induce sensitization of pain such as secondary hyperalgesia and TSSP will show the same pattern in individuals with childhood trauma or whether there will be a subgroup that shows hyperalgesia to only on one test. It will be also useful to further investigate whether protective factors moderate the effects of adverse childhood events on TSSP. The potential protective effects of habituation to repetitive trials warrant further investigation.

4.5. Conclusions

The results of current study suggest the potential vulnerability of adults with childhood trauma to central sensitization, a process that contributes to the induction and maintenance of chronic pain. The trauma groups showed a tendency to develop greater sensitization within TSSP trials and no occurrence of habituation over repeated TSSP

trials. Lastly, slower wind-up decay was observed in the trauma group within a TSSP trial. These results reveal that adverse childhood events predispose adults to enhanced TSSP, which is potentially linked to an increased likelihood to develop chronic pain problems.

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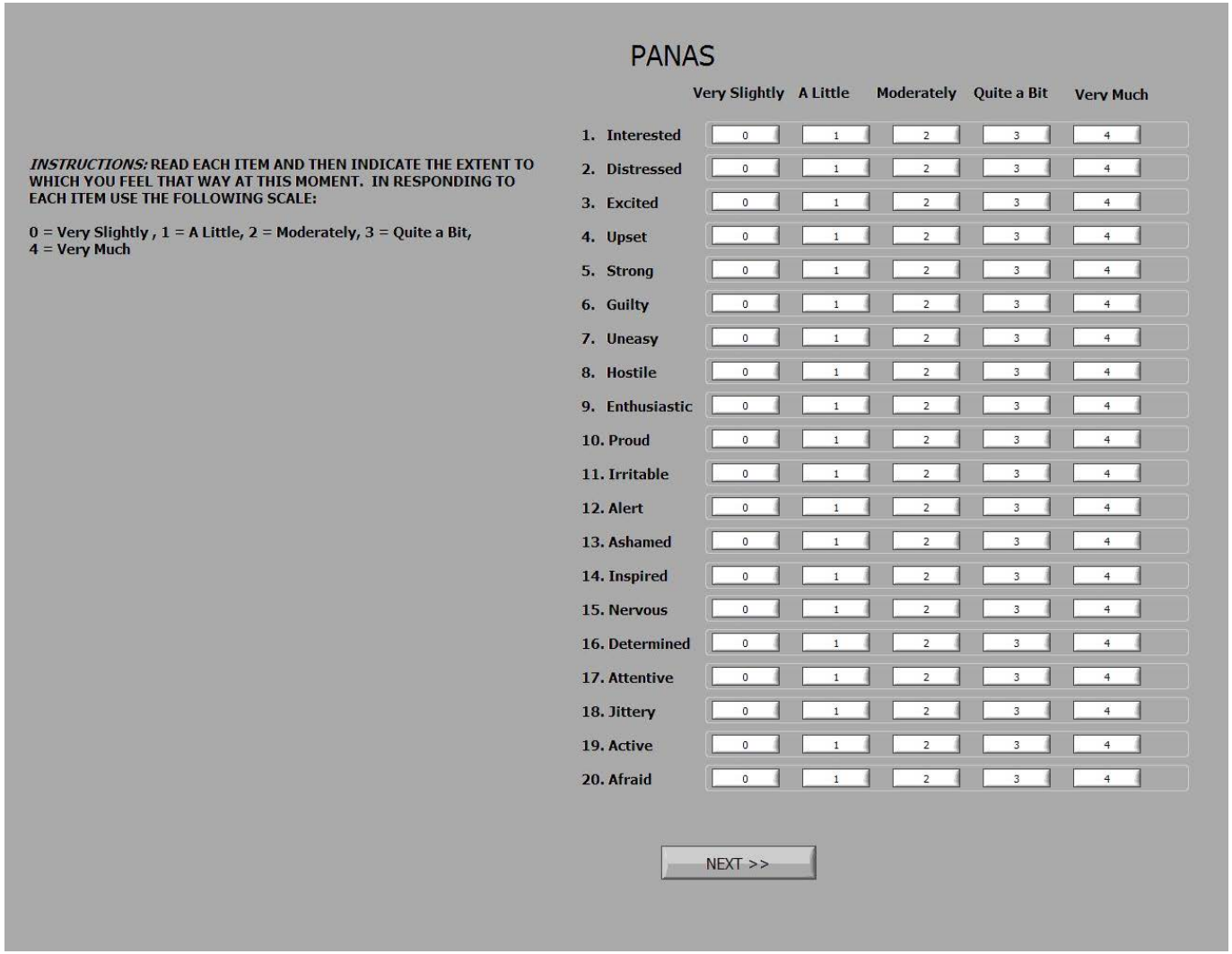
APPENDIX A. SELF REPORTS



PANAS

INSTRUCTIONS: **READ EACH ITEM AND THEN INDICATE THE EXTENT TO WHICH YOU FEEL THAT WAY AT THIS MOMENT. IN RESPONDING TO EACH ITEM USE THE FOLLOWING SCALE:**

0 = Very Slightly , 1 = A Little, 2 = Moderately, 3 = Quite a Bit, 4 = Very Much

	Very Slightly	A Little	Moderately	Quite a Bit	Very Much
1. Interested	0	1	2	3	4
2. Distressed	0	1	2	3	4
3. Excited	0	1	2	3	4
4. Upset	0	1	2	3	4
5. Strong	0	1	2	3	4
6. Guilty	0	1	2	3	4
7. Uneasy	0	1	2	3	4
8. Hostile	0	1	2	3	4
9. Enthusiastic	0	1	2	3	4
10. Proud	0	1	2	3	4
11. Irritable	0	1	2	3	4
12. Alert	0	1	2	3	4
13. Ashamed	0	1	2	3	4
14. Inspired	0	1	2	3	4
15. Nervous	0	1	2	3	4
16. Determined	0	1	2	3	4
17. Attentive	0	1	2	3	4
18. Jittery	0	1	2	3	4
19. Active	0	1	2	3	4
20. Afraid	0	1	2	3	4

NEXT >>

CES-D

INSTRUCTIONS: Select the number for each statement which best describes how often you felt this way DURING THE PAST WEEK

	Rarely or none of the time (Less than 1 Day)	Some or a Little of the Time (1-2 Days)	Occasionally or a Moderate Amount of Time (3-4 Days)	Most or All of the Time (5-7 Days)
I was bothered by things that usually don't bother me	0	1	2	3
I did not feel like eating; my appetite was poor	0	1	2	3
I felt that I could not shake off the blues even with the help from my friends	0	1	2	3
I felt that I was just as good as other people	0	1	2	3
I had trouble keeping my mind on what I was doing	0	1	2	3
I felt depressed	0	1	2	3
I felt that everything I did was an effort	0	1	2	3
I felt hopeful about the future	0	1	2	3
I thought my life had been a failure	0	1	2	3
I felt fearful	0	1	2	3
My sleep was restless	0	1	2	3
I was happy	0	1	2	3
I talked less than usual	0	1	2	3
I felt lonely	0	1	2	3
People were unfriendly	0	1	2	3
I enjoyed life	0	1	2	3
I had crying spells	0	1	2	3
I felt sad	0	1	2	3
I felt that people disliked me	0	1	2	3
I could not get "going"	0	1	2	3

NEXT >>

PSS

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often

	Never	Almost Never	Sometimes	Fairly Often	Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

NEXT >>

PAI-BOR

Give your own opinion about yourself. Be sure to answer every statement. Please ask the research assistant any questions that you may have.

If the statement is FALSE, NOT TRUE AT ALL, check F.
If the statement is SLIGHTLY TRUE, check the ST.
If the statement is MAINLY TRUE, check the MT.
If the statement is VERY TRUE, check the VT.

	F	ST	MT	VT
1.	My mood can shift quite suddenly			
2.	My attitude about myself changes a lot			
3.	My relationships have been stormy			
4.	My moods get quite intense			
5.	Sometimes I feel terribly empty inside			
6.	I want to let certain people I know how much they have hurt me			
7.	My mood is very steady			
8.	I worry a lot about other people leaving me			
9.	People once close to me have let me down			
10.	I have little control over my anger			
11.	I often wonder what I should do with my life			
12.	I rarely feel very lonely			
13.	I sometimes do things so impulsively that I get into trouble			
14.	I've always been a pretty happy person			
15.	I can't handle separation from someone close to me very well			
16.	I've made some real mistakes in the people I've picked as friends			
17.	When I'm upset, I typically do something to hurt myself			
18.	I've had times when I was so mad I couldn't do enough to express my anger			
19.	I don't get bored very easily			
20.	Once someone is my friend, we stay friends			
21.	I'm too impulsive for my own good			
22.	I spend money too easily			
23.	I'm a reckless person			
24.	I'm careful about how I spend my money			

NEXT >>

FPQ

The items listed below describe painful experiences. Please look at each item and think about how **FEARFUL** you are of experiencing the **PAIN** associated with each item. If you have never experienced the **PAIN** of a particular item, please answer on the basis of how **FEARFUL** you expect you would be if you had such an experience. Use the answers below to rate your **FEAR OF PAIN** in relation to each event.

1 = Not at all, 2 = A Little, 3 = A Fair Amount, 4 = Very Much, 5 = Extreme

1. being in an automobile accident
2. biting your tongue while eating
3. breaking your arm
4. cutting your tongue licking an envelope
5. having a heavy object hit you in the head
6. breaking your leg
7. hitting a sensitive bone in your elbow - your "funny bone"
8. having a blood sample drawn with a hypodermic needle
9. having someone slam a heavy car door on your hand
10. falling down a flight of concrete stairs
11. receiving an injection in your arm
12. burning your fingers with a match
13. breaking your neck
14. receiving an injection in your hip/buttocks
15. having a deep splinter in the sole of your foot probed an removed with tweezers

16. having an eye doctor remove a foreign particle stuck in your eye
17. receiving an injection in your mouth
18. being burned on your face by a lit cigarette
19. getting a paper-cut on your finger
20. receiving stitches in your lip
21. having a foot doctor remove a wart from your foot with a sharp instrument
22. cutting yourself while shaving with a sharp razor
23. gulping a hot drink before it has cooled
24. getting strong soap in both your eyes while bathing or showering
25. having a terminal illness that causes you daily pain
26. having a tooth pulled
27. vomiting repeatedly because of food poisoning
28. having sand or dust blow into your eyes
29. having one of your teeth drilled
30. having a muscle cramp

NEXT >>

PILL

Several common symptoms or bodily sensations are listed below. Most people have experienced most of them at one time or another. We are currently interested in finding out how prevalent each symptom is among various groups of people. On the page below, write how frequently you experience each symptom. For all items, use the following scale:

A	B	C	D	E
Have never or almost never experienced the symptom	Less than 3 or 4 times per year	Every month or so	Every week or so	More than once every week

A	B	C	D	E	1. Eyes water	A	B	C	D	E	28. Swollen joints
A	B	C	D	E	2. Itchy eyes or skin	A	B	C	D	E	29. Stiff or sore muscles
A	B	C	D	E	3. Ringing in ears	A	B	C	D	E	30. Back pains
A	B	C	D	E	4. Temporary deafness or hard of hearing	A	B	C	D	E	31. Sensitive or tender skin
A	B	C	D	E	5. Lump in throat	A	B	C	D	E	32. Face flushes
A	B	C	D	E	6. Choking sensations	A	B	C	D	E	33. Tightness in chest
A	B	C	D	E	7. Sneezing spells	A	B	C	D	E	34. Skin breaks out in rash
A	B	C	D	E	8. Running nose	A	B	C	D	E	35. Acne or pimples on face
A	B	C	D	E	9. Congested nose	A	B	C	D	E	36. Acne/pimples other than face
A	B	C	D	E	10. Bleeding nose	A	B	C	D	E	37. Boils
A	B	C	D	E	11. Asthma or wheezing	A	B	C	D	E	38. Sweat even in cold weather
A	B	C	D	E	12. Coughing	A	B	C	D	E	39. Strong reactions to insect bites
A	B	C	D	E	13. Out of breath	A	B	C	D	E	40. Headaches
A	B	C	D	E	14. Swollen ankles	A	B	C	D	E	41. Feeling pressure in head
A	B	C	D	E	15. Chest pains	A	B	C	D	E	42. Hot flashes
A	B	C	D	E	16. Racing heart	A	B	C	D	E	43. Chills
A	B	C	D	E	17. Cold hands or feet even in hot weather	A	B	C	D	E	44. Dizziness
A	B	C	D	E	18. Leg cramps	A	B	C	D	E	45. Feel faint
A	B	C	D	E	19. Insomnia or difficulty sleeping	A	B	C	D	E	46. Numbness or tingling in any part of body
A	B	C	D	E	20. Toothaches	A	B	C	D	E	47. Twitching of eyelid
A	B	C	D	E	21. Upset stomach	A	B	C	D	E	48. Twitching other than eyelid
A	B	C	D	E	22. Indigestion	A	B	C	D	E	49. Hands tremble or shake
A	B	C	D	E	23. Heartburn or gas	A	B	C	D	E	50. Stiff joints
A	B	C	D	E	24. Abdominal pain	A	B	C	D	E	51. Sore muscles
A	B	C	D	E	25. Diarrhea	A	B	C	D	E	52. Sore throat
A	B	C	D	E	26. Constipation	A	B	C	D	E	53. Sunburn
A	B	C	D	E	27. Hemorrhoids	A	B	C	D	E	54. Nausea

Since the beginning of the semester, how many:

- ☐ Visits have you made to the student health center or private physician for illness
- ☐ Days have you been sick
- ☐ Days you activity has been restricted due to illness

NEXT >>

PCL-C

NEXT >>

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1) Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?	1	2	3	4	5
2) Repeated, disturbing dreams of a stressful experience from the past?	1	2	3	4	5
3) Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?	1	2	3	4	5
4) Feeling very upset when something reminded you of a stressful experience from the past?	1	2	3	4	5
5) Having physical reactions (e.g., heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?	1	2	3	4	5
6) Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?	1	2	3	4	5
7) Avoid activities or situations because they remind you of a stressful experience from the past?	1	2	3	4	5
8) Trouble remembering important parts of a stressful experience from the past?	1	2	3	4	5
9) Loss of interest in things that you used to enjoy?	1	2	3	4	5
10) Feeling distant or cut off from other people?	1	2	3	4	5
11) Feeling emotionally numb or being unable to have loving feelings for those close to you?	1	2	3	4	5
12) Feeling as if your future will somehow be cut short?	1	2	3	4	5
13) Trouble falling or staying asleep?	1	2	3	4	5
14) Feeling irritable or having angry outbursts?	1	2	3	4	5
15) Having difficulty concentrating?	1	2	3	4	5
16) Being "super alert" or watchful on guard?	1	2	3	4	5
17) Feeling jumpy or easily startled?	1	2	3	4	5

IES-R

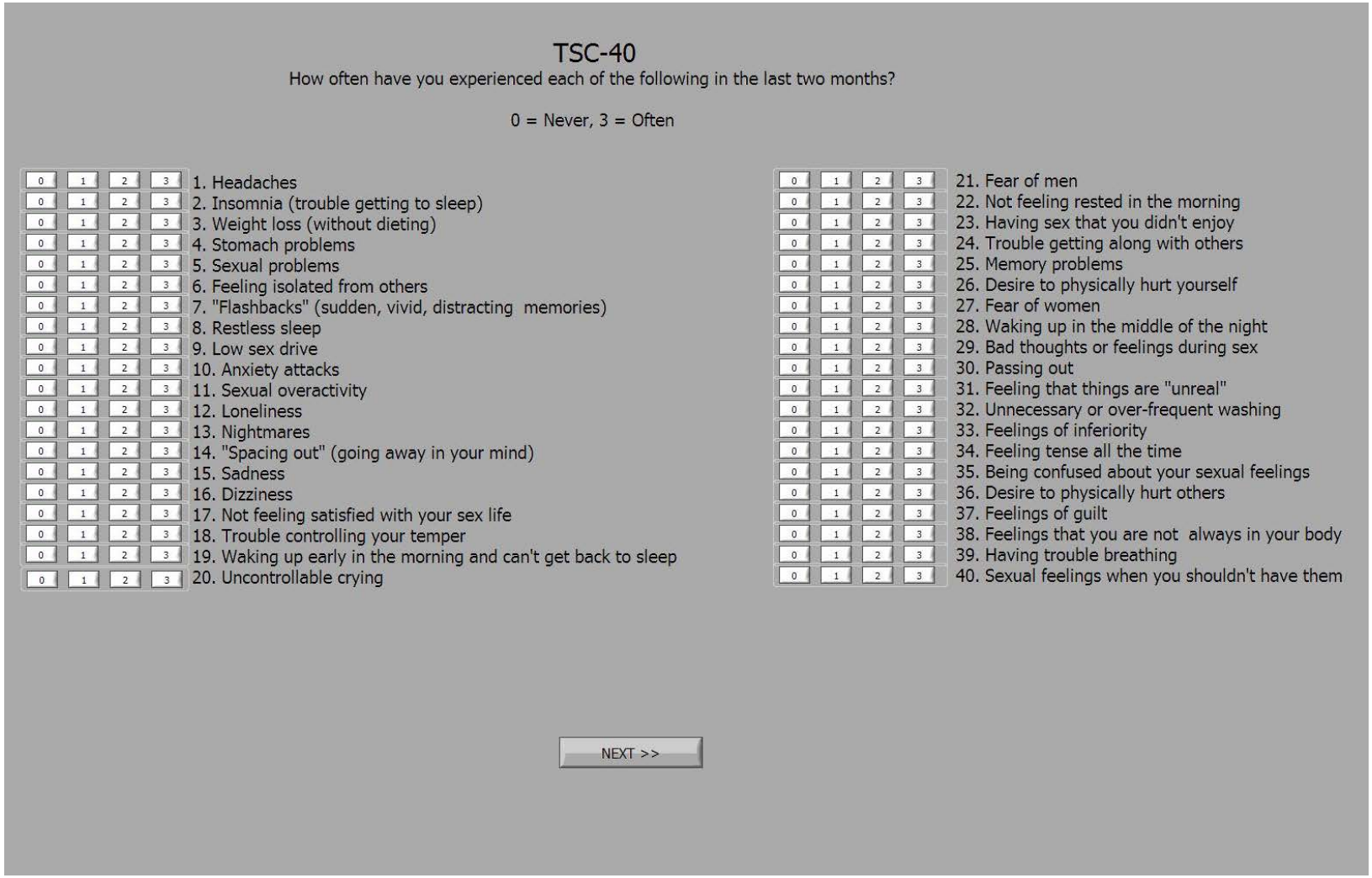
NEXT >>

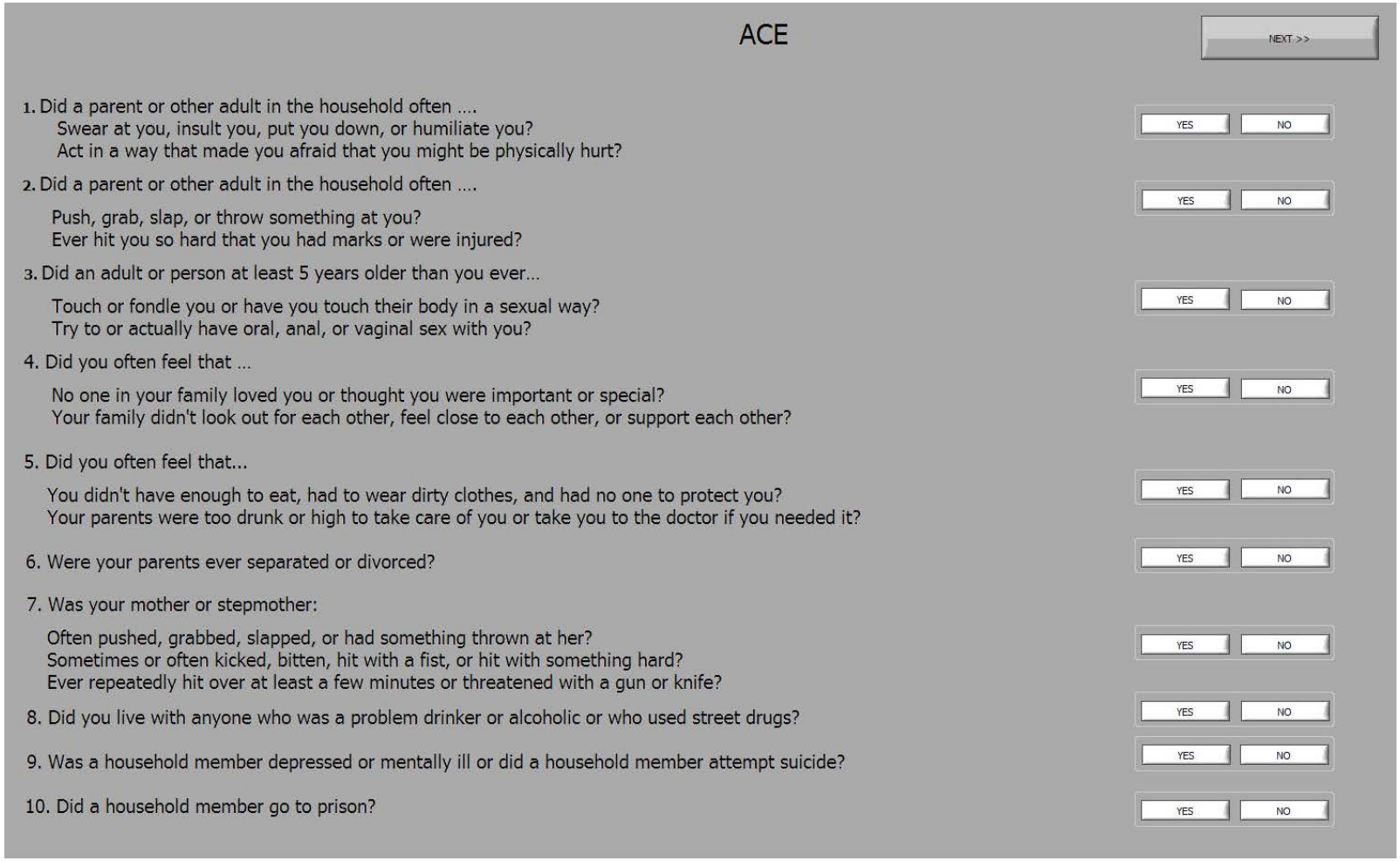
Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to ,

[ ]

how much were you distressed or bothered by these difficulties?

	Not at all	A little bit	Moderately	Quite a bit	Very Much
1. Any remainder brought back feelings about it	0	1	2	3	4
2. I had trouble staying asleep	0	1	2	3	4
3. Other things kept making me think about it	0	1	2	3	4
4. I felt irritable and angry	0	1	2	3	4
5. I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
6. I thought about it when I didn't mean to	0	1	2	3	4
7. I felt as if it hadn't happened or wasn't real	0	1	2	3	4
8. I stayed away from reminders about it	0	1	2	3	4
9. Pictures about it popped into my mind	0	1	2	3	4
10. I was jumpy and easily startled	0	1	2	3	4
11. I tried not to think about it	0	1	2	3	4
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them	0	1	2	3	4
13. My feelings about it were kind of numb	0	1	2	3	4
14. I found myself acting or feeling as though I was back at that time	0	1	2	3	4
15. I had trouble falling asleep	0	1	2	3	4
16. I had waves of strong feelings about it	0	1	2	3	4
17. I tried to remove it from my memory	0	1	2	3	4
18. I had trouble concentrating	0	1	2	3	4
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	2	3	4
20. I had dreams about it	0	1	2	3	4
21. I felt watchful or on-guard	0	1	2	3	4
22. I tried not to talk about it	0	1	2	3	4


TSC-40
How often have you experienced each of the following in the last two months?
0 = Never, 3 = Often
0 1 2 3 1. Headaches
0 1 2 3 2. Insomnia (trouble getting to sleep)
0 1 2 3 3. Weight loss (without dieting)
0 1 2 3 4. Stomach problems
0 1 2 3 5. Sexual problems
0 1 2 3 6. Feeling isolated from others
0 1 2 3 7. "Flashbacks" (sudden, vivid, distracting memories)
0 1 2 3 8. Restless sleep
0 1 2 3 9. Low sex drive
0 1 2 3 10. Anxiety attacks
0 1 2 3 11. Sexual overactivity
0 1 2 3 12. Loneliness
0 1 2 3 13. Nightmares
0 1 2 3 14. "Spacing out" (going away in your mind)
0 1 2 3 15. Sadness
0 1 2 3 16. Dizziness
0 1 2 3 17. Not feeling satisfied with your sex life
0 1 2 3 18. Trouble controlling your temper
0 1 2 3 19. Waking up early in the morning and can't get back to sleep
0 1 2 3 20. Uncontrollable crying
0 1 2 3 21. Fear of men
0 1 2 3 22. Not feeling rested in the morning
0 1 2 3 23. Having sex that you didn't enjoy
0 1 2 3 24. Trouble getting along with others
0 1 2 3 25. Memory problems
0 1 2 3 26. Desire to physically hurt yourself
0 1 2 3 27. Fear of women
0 1 2 3 28. Waking up in the middle of the night
0 1 2 3 29. Bad thoughts or feelings during sex
0 1 2 3 30. Passing out
0 1 2 3 31. Feeling that things are "unreal"
0 1 2 3 32. Unnecessary or over-frequent washing
0 1 2 3 33. Feelings of inferiority
0 1 2 3 34. Feeling tense all the time
0 1 2 3 35. Being confused about your sexual feelings
0 1 2 3 36. Desire to physically hurt others
0 1 2 3 37. Feelings of guilt
0 1 2 3 38. Feelings that you are not always in your body
0 1 2 3 39. Having trouble breathing
0 1 2 3 40. Sexual feelings when you shouldn't have them
NEXT >>


ACE
NEXT >>
1. Did a parent or other adult in the household often ....
Swear at you, insult you, put you down, or humiliate you?
Act in a way that made you afraid that you might be physically hurt?
YES
NO
2. Did a parent or other adult in the household often ....
Push, grab, slap, or throw something at you?
Ever hit you so hard that you had marks or were injured?
YES
NO
3. Did an adult or person at least 5 years older than you ever...
Touch or fondle you or have you touch their body in a sexual way?
Try to or actually have oral, anal, or vaginal sex with you?
YES
NO
4. Did you often feel that ...
No one in your family loved you or thought you were important or special?
Your family didn't look out for each other, feel close to each other, or support each other?
YES
NO
5. Did you often feel that...
You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you?
Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?
YES
NO
6. Were your parents ever separated or divorced?
YES
NO
7. Was your mother or stepmother:
Often pushed, grabbed, slapped, or had something thrown at her?
Sometimes or often kicked, bitten, hit with a fist, or hit with something hard?
Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?
YES
NO
8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?
YES
NO
9. Was a household member depressed or mentally ill or did a household member attempt suicide?
YES
NO
10. Did a household member go to prison?
YES
NO

ETISR-SF

NEXT >>

1. General Traumas. Before the age of 18

1. Were you ever exposed to a life-threatening natural disaster?	YES	NO
2. Were you involved in a serious accident?	YES	NO
3. Did you ever suffer a serious personal injury or illness?	YES	NO
4. Did you ever experience the death or serious illness of a parent or a primary caretaker?	YES	NO
5. Did you experience the divorce or separation of your parents?	YES	NO
6. Did you experience the death or serious injury of a sibling?	YES	NO
7. Did you ever experience the death or serious injury of a friend?	YES	NO
8. Did you ever witness violence towards others, including family members?	YES	NO
9. Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown"?	YES	NO
10. Did your parents or primary caretaker have a problem with alcoholism or drug abuse?	YES	NO
11. Did you ever see someone murdered?	YES	NO

2. Physical Punishment. Before the age of 18

1. Were you ever slapped in the face with an open hand?	YES	NO
2. Were you ever burned with hot water, a cigarette or something else?	YES	NO
3. Were you ever punched or kicked?	YES	NO
4. Were you ever hit with an object that was thrown at you?	YES	NO
5. Were you ever pushed or shoved?	YES	NO

3. If you responded "YES" for any of the above events, answer the following for the one that has had the greatest impact on your life. In answering consider how you felt at the time of the event.

1. Did you experience emotions of intense fear, horror or helplessness?	YES	NO
2. Did you feel out-of-your-body or as if you were in a dream?	YES	NO

ETISR-SF Contd...

NEXT >>

4. Emotional Abuse. Before the age of 18

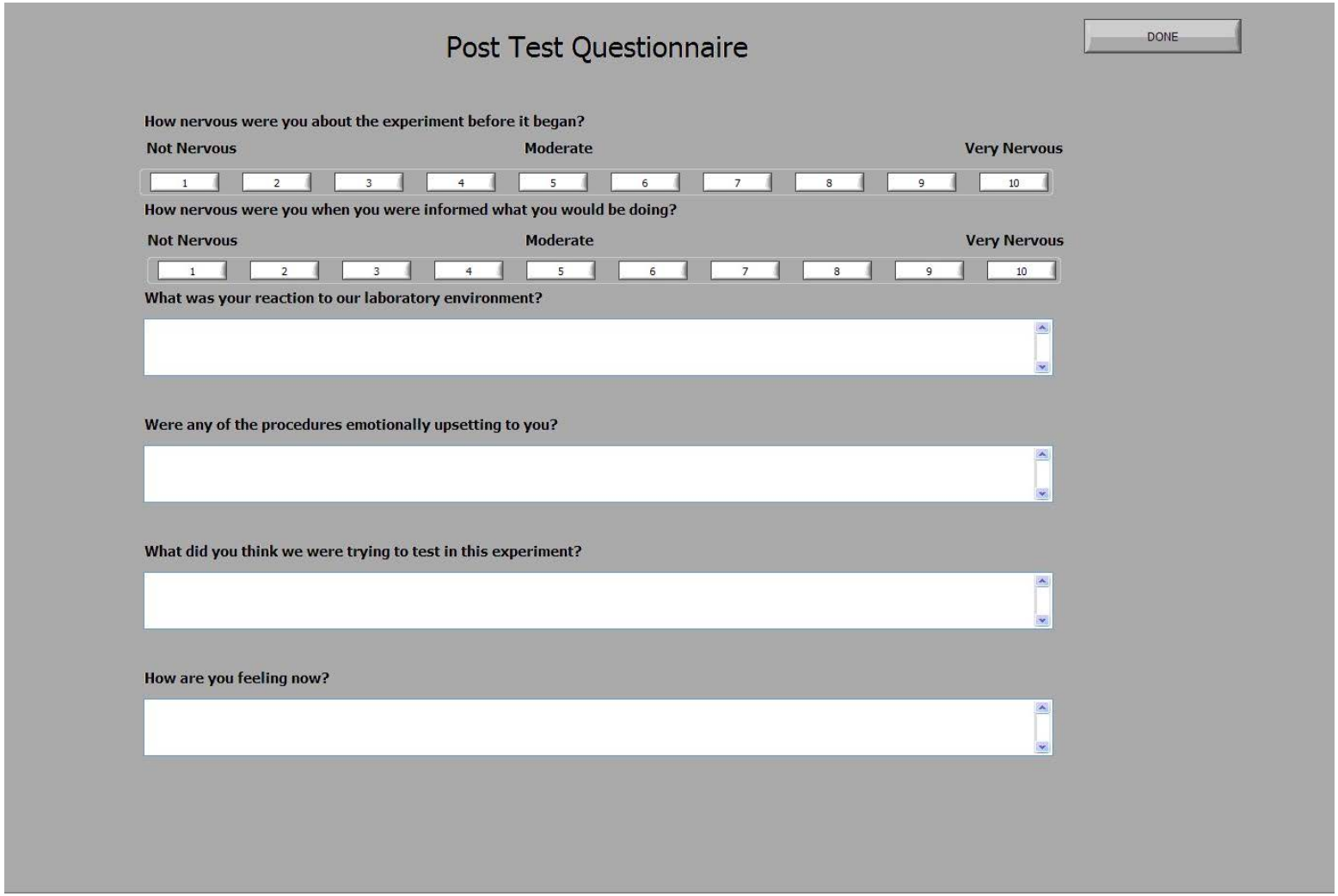
1. Were you often put down or ridiculed?	YES	NO
2. Were you often ignored or made to feel that you didn't count?	YES	NO
3. Were you often told you were no good?	YES	NO
4. Most of the time were you treated in a cold, uncaring way or made to feel like you were not loved?	YES	NO
5. Did your parents or caretakers often fail to understand you or your needs?	YES	NO

5. Sexual Events. Before the age of 18

1. Were you ever touched in an intimate or private part of your body (e.g. breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable?	YES	NO
2. Did you ever experience someone rubbing their genitals against you?.....	YES	NO
3. Were you ever forced or coerced to touch another person in an intimate or private part of their body?	YES	NO
4. Did anyone ever have genital sex with you against your will?	YES	NO
5. Were you ever forced or coerced to perform oral sex on someone against your will?	YES	NO
6. Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way?	YES	NO

6. If you responded "YES" for any of the above events, answer the following for the one that has had the greatest impact on your life. In answering consider how you felt at the time of the event.

1. Did you experience emotions of intense fear, horror or helplessness?.....	YES	NO
2. Did you feel out-of-your-body or as if you were in a dream?.....	YES	NO


Post Test Questionnaire
DONE
How nervous were you about the experiment before it began?
Not Nervous
Moderate
Very Nervous
1 2 3 4 5 6 7 8 9 10
How nervous were you when you were informed what you would be doing?
Not Nervous
Moderate
Very Nervous
1 2 3 4 5 6 7 8 9 10
What was your reaction to our laboratory environment?
Were any of the procedures emotionally upsetting to you?
What did you think we were trying to test in this experiment?
How are you feeling now?

VITA

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B.A., Psychology, Case Western Reserve University, 2007

Honors and Awards

2012, May First place winner for poster presentation and Glasscock Research award at the 2012 Annual Student Research Week at Texas A&M University

2011, Oct Second place winner for first year student poster presentation. Dept. of Psychology, Texas A&M University

Presentations

Poster Presentation

You, D. S., Furl, B. A., & Meagher, M. W. (2011, November). Relationship between affect regulation and wind-up pain. Poster Presentation at the Annual Meeting of Society for Neuroscience. Washington D.C. Also presented at the for first year student poster presentation. Dept. of Psychology, Texas A&M University. College Station, TX.

Oral Presentations

You, D. S., & Meagher, M. W. (2012, March). Impact of childhood adverse event on temporal summation of second pain. Oral Presentation at the Annual Student Research Week at Texas A&M University, College Station, TX.