Accepted Manuscript

Title: Opposite Effects of Stress on Pain Modulation Depend on the Magnitude of Individual Stress Response

Author: Nirit Geva, Ruth Defrin

PII: S1526-5900(17)30799-X
DOI: https://doi.org/10.1016/j.jpain.2017.11.011
Reference: YJPAI 3493

To appear in: The Journal of Pain

Received date: 1-7-2017
Revised date: 17-10-2017
Accepted date: 14-11-2017


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Opposite effects of stress on pain modulation depend on the magnitude of individual stress response

Nirit Geva¹ and Ruth Defrin¹*

¹Department of Physical Therapy and Sagol school of Neuroscience, Sackler Faculty of Medicine, Tel-Aviv University, Israel

*Corresponding author:
Ruth Defrin
Dept. Physical Therapy
Sackler Faculty of Medicine
Tel-Aviv University, Israel
Tel-Aviv, 69978
Tel: +972-3-6405431
Fax: +972-3-6409223
Email: rutidef@post.tau.ac.il

Disclosures:
The authors declare no conflicts of interests. This work is part of the PhD thesis of Nirit Geva, Sackler Faculty of Medicine, Tel Aviv University. No funding was received for this research.
Highlights

- Acute stress induced opposite effects; decreased CPM and increased pain adaptation
- Decreased CPM occurred only among high stress-responders
- Increased pain adaptation occurred only among low stress-responders
- Individual stress responsiveness determines how acute stress affects pain modulation

Abstract

The effect of acute stress on pain threshold and intolerance threshold are reported as producing either hypoalgesia or hyperalgesia. Yet, the contribution of individual stress reactivity in this respect has not been established. The aim was to test two pain modulation paradigms under acute stress manipulation, here for the first time, in order to study whether stress differentially affects pain modulation, and whether the effect is related to individual stress response. Participants were 31 healthy subjects. Conditioned pain modulation (CPM) and pain adaptation were measured before and after inducing an acute stress response using the Montreal Imaging Stress Task (MIST). Subjects' stress response was evaluated with salivary cortisol, autonomic function and perceived stress and anxiety. The MIST induced a validated stress response. On a group level, stress induced reduction in CPM magnitude and increase in pain adaptation compared to baseline. These responses correlated with stress reactivity. When the group was subdivided according to stress reactivity, only high stress-responders exhibited reduced CPM whereas only low stress-responders exhibited increased pain adaptation. The results suggest that acute stress may induce opposite effects on pain modulation, depending on individual stress reactivity magnitude, with an advantage to low stress-responders.

Perspectives

This study evaluated the effect of acute stress on pain modulation. Pain modulation under stress is affected by individual stress responsiveness; decreased conditioned-pain-
modulation occurs in high stress-responders whereas increased pain adaptation occurs in low stress-responders. Identification of high-stress responders may promote better pain management.

**Keywords:** acute stress, pain modulation, stress-reactivity, cortisol

**Introduction**

Anecdotes on the ability of individuals to perform under stressful conditions, despite injuries causing excruciating pain, suggest that acute stress may induce analgesia or hypoalgesia. Animal models of acute stress, such as inescapable foot shock or exposure to predators indeed show that acute stress can produce stress-induced analgesia/hypoalgesia (SIA) [e.g., 6,76]. Similarly, acute stress manipulations applied to human subjects, such as public speaking and erythematic tasks produce SIA, manifested as an increase in pain threshold [20,78] and intolerance levels [24,78] and reduced pain ratings [20,78]. However, similar stress manipulations were also reported to produce the opposite effect, namely of stress-induced hyperalgesia (SIH). SIH was observed both in animals [37,38] and human subjects, manifested in decreased pain and intolerance [7,8,15,61] thresholds and increased pain ratings [45].

These contradictory results are not easy to explain, especially as both SIA and SIH were reported in different studies using the same stress manipulation [e.g. 13,29]. One factor that may underlie the contradictory results is the variability in individuals' stress response. Stress is regarded as a *cognitive perception* of uncontrollability and unpredictability that is expressed in a physiological and behavioral responses [39]. The focus on appraisal stem from the understanding of the significant influence of cognitive factors (e.g. thoughts, attitudes and beliefs) on the individual’s response to stressors along with the demonstration that both appetitive and aversive stimuli can cause comparable physiological stress responses even
though individuals are motivated to obtain or avoid them, respectively [37,49,69]. Individual differences can thus determine if, and to what extent a particular stimulus (stressor) is perceived as positive or negative. Stress perception may in turn, influence individual pain responses under stressful conditions and can possibly underlie the inconsistent effects of stress on pain threshold and tolerance reported in the literature. However, since perceived stress was seldom evaluated in these studies, whether or not the effect of acute stress on pain depends on individual stress responsiveness is an open question.

In a recent study, individual differences in brain responses to pain were evaluated by administering noxious stimuli to subjects during functional imaging. The noxious stimuli-evoked cortisol release inversely correlated with pain unpleasantness ratings and activation in several brain structures [70]. Although the authors did not apply a stress manipulation in this study, the findings suggest that individual stress responsiveness can contribute to individual variability in pain perception and pain-related brain activity.

So far, stress effects on pain perception were evaluated mainly with pain threshold/tolerance, static measurements that are considered highly variable both between and within-subjects [51,67]. Because pain perception is dynamic, and influenced by inhibitory and excitatory mechanisms, it is valuable to study stress effects also using ‘dynamic measurements’ that evaluate traits of central pain modulation [1,31,76]. One such measurement is conditioned pain modulation (CPM), that evaluate the phenomenon of diffuse noxious inhibitory control (DNIC) [71,77] namely of pain inhibition by another, heterotrophic painful stimulus [42,43]. Recently, CPM was reported to decrease following acute stress manipulation [28,54] however other measurements of pain modulation such as pain adaptation were never tested under stress. Using two different pain modulation paradigms, the aim was to study the effect of acute stress on pain modulation and the role of individual stress responsiveness in this respect.
Methods

1. Subjects

Participants were 31 healthy male subjects (mean age 34±11 years, range 24-65). We included only adult men in order to minimize the confounding effect of sex on the responses to the pain and stress manipulations [21]. The subjects were recruited by advertisements posted around the university campus. Exclusion criteria were: acute or chronic pain, present or previous pathology in the hands (testing site), bruises or any other skin lesions on the hands, diseases causing potential neural damage (e.g. diabetes), systemic and mental illnesses (e.g. anxiety disorders, depression, bipolar disorder) and communication disabilities. Informed consent was obtained from all the subjects. The experiment was approved by the Helsinki committee of Sheba Medical Center and institutional review board of Tel-Aviv University.

2. Equipment

2.1. Recording and processing of physiological signals

The physiological signals were recorded, sampled, and stored using a personal computer with the PMD-100 system (Medasense Biometrics Ltd., Ramat Gan, Israel) through a finger probe. A 1-lead electro-cardiogram (ECG) signal was sampled with a frequency of 500 Hz, and a reflectance-mode Photo-plethysmogram (PPG) signal from the right-hand index finger was sampled with the same frequency. Skin conductance (measured in micro-Siemens, µS) was measured using 2 electrodes positioned on the volar pads of the distal phalanx in the middle and ring fingers of the right hand and was sampled with a frequency of 31.25 Hz. The recorded signals were synchronized and processed off-line using Matlab R2010 scientific software (The Mathworks, Inc., MA, USA).

2.2. Thermal stimulators

Heat stimuli were delivered using two Peltier-based computerized thermal stimulators (TSA II, Medoc Ltd., Ramat-Ishay, Israel), with 3 x 3 cm contact probes. According to the
principles of the Peltier element, a passage of current through the Peltier element produces temperature changes at rates determined by an active feedback system. As soon as the target temperature is attained, probe temperature actively reverts to a preset adaptation temperature by passage of an inverse current. The adaptation (baseline) temperature was set to 35°C. The probes were attached to the testing site by means of a Velcro band.

3. The Montreal Imaging Stress Task (MIST)

The MIST was used to induce acute mental stress. The MIST was chosen as it is a reliable and validated tool for inducing stress perception and physiological responses [16]. In addition, the MIST can be used in an fMRI environment [16,58] and thus has potential in future studies assessing brain function under stress. The principal component of the MIST is a computer program that displays a mental arithmetic task, a rotary dial for submission of a response, a text field that provides feedback on the submitted response (“correct,” “incorrect” or “timeout”), and 2 default performance indicators, one for the individual subject’s performance and one for average performance of all subjects. The program runs for 8 minutes during which the tasks appear one by one. Each task is time-limited; the elapsed time is displayed by a progress bar moving from left to right on the computer screen, with the exact time allowed for each task depending on the subject’s previous performance. The program continuously records the subject’s average response time and the number of correct responses and adjusts the time limit continuously to enforce a range of about 20% to 45% correct answers. Before the task, the investigator informs the subject that the average performance is about 80%–90% correct answers and that his individual performance should be close or equal to the average performance of all subjects if the subject’s data are to be used in the study. Finally, the subject is told that the investigator is following his performance but cannot help or talk with him and that the director of research is following the performance on a second monitor in the control room. After the end of the
session, the investigator informs the subject about a poor performance and asks him to try again to do his best. After completion of the second session, the subject receives again a negative feedback about his performance.

4. Measurements of the stress response

4.1. Perceived stress

Perceived stress was evaluated using a visual analogue scale (VAS). The VAS consisted of a 10 cm line with two anchor points at its extremes, set as 0=no stress and 10=most intense stress imaginable [28].

4.2. State anxiety

Anxiety was evaluated with the short form of the State-Trait Anxiety Inventory (STAI) [65]. This questionnaire contains 10 items and subjects are asked to rate the degree to which they experienced each symptom of anxiety at that moment, on a 4-point Likert-type scale (1= not at all, to 4 =very much so). This measure of state anxiety has been used extensively in previous research and has consistently demonstrated good psychometric properties, especially under conditions of stress [48].

4.3. Autonomic variables

The sympathetic–adrenal–medullary (SAM) system responds to stress by secreting noradrenaline thereby increasing sympathetic tone, resulting in changes in heart rate, blood pressure, respiration, skin conductance, etc. [7,16]. The sympathetic response was thus investigated by recording the change in heart rate (HR), heart rate variability (HRV), Galvanic Skin Response (GSR) and number of skin conduction fluctuations (NCSF) using the PMD-100 system. HR, HRV, GSR and NSCF were recorded continuously at a rate of 500 Hz during the experiment and the values were extracted off-line for relevant time points as described below.

4.4 Salivary cortisol
The hypothalamic–pituitary–adrenal HPA axis is strongly activated by psychosocial stress and secretes the stress hormone cortisol [19]. Saliva samples of cortisol were collected with Salivettes (Sarstedt, Rommels-dorft, Germany). Participants were asked to place a salivette (cotton roll) in their mouths, chew on it for a minute until it became saturated, and place it in storage container. The samples were then stored at -20°C until assayed. Cortisol levels were assayed using a commercial ELISA kit (Assay Design, MI, USA). Measurements were performed in duplicate, according to the kit’s instructions with the reagents provided. Cortisol levels were calculated using MatLab-7, according to standard parametric calibration curves based on the data from the kit [44].

5. Quantitative Sensory testing (QST)

5.1. Stimulus-response functions

Stimulus-response functions were created for each subject in order to extract the stimulation intensities necessary to test conditioned pain modulation and pain adaptation. Subjects received a series of thermal stimuli and were asked to rate their pain following each stimulus on the visual analog scale (VAS). The VAS consisted of a plastic ruler with an inner slider. Moving the slider exposes a horizontal red bar (the visual side) to the subject, while the side facing the experimenter displays an analogue scale with values between 0 and 10. The end points were set as 0="no pain sensation" and 10= "the most intense pain sensation imaginable". The stimulus intensities, presented in an ascending manner, rose from a baseline temperature of 35°C (rate of rise 2°C/sec), to a destination temperature ranging between 38°C to the intensity eliciting 7 on the VAS, at which it remained for 1 sec and then returned to baseline. An inter-stimulus interval of 45 seconds was maintained to avoid any changes in skin sensitivity and to allow for adequate VAS scoring. Individual stimulus-response functions were obtained for each subject. The
temperatures eliciting a value of 3-4 and 5-6 in the VAS were extracted from the functions to be used for subsequent testing [28].

5.2. Conditioned pain modulation (CPM)

CPM is an experimental paradigm of the pain inhibiting pain phenomenon reflecting the function of the diffuse noxious inhibitory control (DNIC) loop mediated in part, by the brain stem subnucleus reticularis dorsalis (SRD) [31,77]. CPM was measured by applying a noxious stimulus to one forearm (the "test stimulus"-TS) and evaluating its perceived intensity alone, and in the presence of another noxious stimulus applied to the other forearm ("conditioning stimulus"-CS). The two stimuli were administered with two thermal stimulators. The TS consisted of noxious heat at an intensity equivalent to 5-6 on the VAS, applied to the volar aspect of the forearm for a duration of 10 seconds. The CS was noxious heat at an intensity equivalent to 5-6 on the VAS, applied to the volar aspect of the contralateral forearm for 25 seconds (note that noxious heat stimuli of the same intensity, modality and areal extent were used for the TS and CS in order to minimize any confounding effect of attention towards either of the stimuli). The second application of the TS occurred 15 seconds after the application of the CS. The magnitude of CPM was calculated by subtracting the VAS rating of the TS in the presence of the CS from the VAS rating of the TS alone [28].

5.3. Pain adaptation

Pain adaptation refers to a phenomenon in which perceived pain gradually decreases in response to a constant, mildly noxious stimulus of fixed intensity. Although the underlying mechanisms of pain adaptation have not been fully elucidated, it refers to segmental inhibition of neurons from which the nociceptive input has emerged [3,11,56] and therefore was measured as an index of pain inhibition. To test for pain adaptation, subjects were administered a noxious heat stimulus at an intensity equivalent to 3-4 on the
VAS (individually adjusted), for duration of 50 seconds. This initial stimulation intensity was chosen based on a previous study in which pain adaptation did not occur when stimulation intensity exceeded a rating of 5 on the VAS [75]. The subjects were asked to rate the amount of perceived pain (using VAS) every 10 seconds (at times 0, 10, 20, 30, 40, and 50 seconds). The subjects were not informed of the time elapsed from the beginning of stimulation. The magnitude of pain adaptation was calculated by subtracting the first VAS rating from the last [75].

6. Procedure

6.1. Preliminary study of reliability and reproducibility of the pain measurements

Since CPM and pain adaptation were measured twice; prior to and immediately after the application of the stress manipulation, it was important to ascertain that any changes occurring in these measurements are indeed due to the manipulation. Therefore, the reliability and reproducibility of the CPM and pain adaptation was evaluated in a preliminary study. Thirteen healthy men (mean age 26.3 ±2.7 years) underwent two measurements of CPM and pain adaptation in exactly the same protocol used in the present study (section 5.2 and 5.3 above), with 30-45 minutes separation between the tests (an interval used in the main study). These men were not included in the main study.

6.2. The main study

Each subject was invited to a single testing session that lasted approximately 2 hours. The subjects were instructed to avoid intense physical exercise 24 hours prior to the testing day and to refrain from food and caffeine 1 hour before testing. Since cortisol levels normally fluctuate throughout the day, all subjects were tested beginning at 1 PM. Testing took place in a quiet room. Temperature in the room was maintained at 22°C. The subject sat in a comfortable armchair. After signing an informed consent the subject was trained in
the psychophysical and endocrine measurements. After a short break, the subject was connected to the monitor sensors that remained active thereafter for the entire experiment.

Figure 1 describes the experimental protocol. There were 4 main epochs from which data were obtained, as follows: A) **REST.** The subject was asked to rest quietly for 10 minutes (from which time baseline autonomic variables were extracted) immediately after which the first saliva sample was taken and the first perceived stress and state anxiety scores were obtained. B) **BASELINE (Pre-stress pain measurements).** Following the 10 minutes rest, the subject underwent the measurements of stimulus-response function, CPM and pain adaptation. The former always preceded the two latter tests that were done in random order. Upon completion of these pain measurements, the second saliva sample was taken and the second perceived stress and state anxiety scores were obtained in order to evaluate whether pain testing induced a stress effect. C) **STRESS (Induction of stress and during-stress pain measurements).** About 5 minutes after the completion of the cognitive evaluation, the subjects were explained how to operate the software of the MIST and received the preparatory explanations for the stress manipulation after which the software was run for 8 minutes. At the end of the task the subjects received a negative feedback about their performance and were asked to perform the task again for additional 8 minutes after which they received again a negative feedback about their performance. Immediately upon completion of the two MIST tasks, the third saliva sample was taken and the third perceived stress and state anxiety scores were obtained in order to evaluate whether the manipulation induced stress. Immediately afterwards, all the sensory testing as in epoch B were performed in the same order. Note that a stimulus-response function was obtained again in order to adjust the stimulation intensities to the same VAS values used in the baseline measurements in order to avoid bias. D) **RECOVERY.** Upon completion of the pain measurements the subjects received an explanation of the true purpose of the MIST.
and were assured that their performance was satisfactory. They were informed that the experiment is over and were asked to relax and rest. Approximately 20 minutes after the reassurance the forth saliva sample was taken and the forth perceived stress and state anxiety scores were obtained in order to evaluate whether stress response had subsided.

7. Data analysis

Data were analyzed using IBM SPSS statistic software version 21. Continuous variables were described as means ± standard deviation (SD) and categorical variables as counts and %. Sample size was calculated based on CPM as it usually have greater variability than pain adaptation. For a sample of 28 individuals, if α=0.05 statistical power is 92.6%, if α=0.01 statistical power is 88.1%. All data underwent Kolmogorov-Smirnov analysis for normality of distribution. Test-retest reliability reproducibility was evaluated by calculating the difference and correlation between test 1 and 2 (using paired t-tests and interclass correlation, respectively) and by calculating standard error of measurement (SEM= SD x √1-ICC). Parametric and non-parametric analyses of variance with corrected post hoc tests were used to evaluate the effect of condition (rest, baseline, stress, recovery) on perceived stress, perceived anxiety, HR, HRV, GSR, NSCF, cortisol, and the sensory tests (CPM and pain adaptation). The magnitude of change in the sensory indices following the stress manipulation was calculated by subtracting the level measured during stress from that measured at baseline. These test were also used to compare the two subgroups. The correlations between changes in the sensory indices (delta values) and the stress indices were calculated using Pearson's correlation coefficients. p<0.05 was considered significant.

Results

1. Test - retest reliability and reproducibility

There were no significant differences between test 1 and test 2 in CPM (-1.87±1.9 and -2.12±1.8, p=0.32) and in pain adaptation (-1.48±2.1 and -1.83±1.4, p=0.21). Reliability of
CPM and pain adaptation as assessed with ICC was fair to good; ICC=0.51 and 0.59 respectively. SEMs were 1.05 and 0.96 VAS units, for CPM and pain adaptation, respectively. These results suggested satisfactory levels of reliability and reproducibility as also obtained in other studies [25,32].

2. Validation of the stress response

Table 1 presents values of stress indices under the 4 conditions of the study; rest, baseline, stress (post-MIST), and recovery, as well as the results of the ANOVAs and post-hoc comparisons. A significant main effect of condition was found for all the stress indices including perceived stress, anxiety, HR, HRV, GSR, NSCF and cortisol (Table 1). Post-hoc comparisons revealed that perceived stress, anxiety and cortisol levels increased from the rest to the stress condition but not from baseline pain measurements to the stress condition, and then decreased in recovery. The levels of HR and GSR increased from rest to the baseline pain measurements condition, and then further increased at the stress condition while HRV and NSCF increased only at the stress condition (Table 1). These changes are indicative of a specific and a significant stress response induced by the manipulation but not by the pain measurements.

3. Perceived pain intensity

Extrcated from the stimulus-response functions done in the baseline and stress conditions, the temperatures eliciting a value of 3-4 on the VAS were similar for these two conditions (45.0±3 and 45.2±2, respectively, p=0.36). The temperatures eliciting a value 5-6 on the VAS were also similar (46.52±2.5 and 46.7±2.8, respectively, p=0.27). Thus, the stimulation intensities used in the CPM and pain habituation paradigms were similar for both the baseline and the stress conditions.

4. Conditioned pain modulation (CPM)
Fig. 2 presents the CPM procedure at the baseline and the stress conditions. There was a significant effect of time \([F(1,25)=40.68, p<0.0001]\) and a borderline effect of condition \([F(1,25)=3.7, p=0.064]\) on the VAS ratings of perceived pain. The interaction condition*time was significant \([F(1,25)=11.1, p<0.01]\), suggesting that the magnitude of CPM was not uniform in the two conditions. At baseline condition, perceived pain of the test stimulus decreased from 5.36±0.6 to 2.98±1.7 VAS units \((p<0.0001)\), in the presence of the conditioning stimulus. At the stress condition, perceived pain of the test stimulus decreased from 5.24±0.5 to 3.95±1.9 \((p<0.001)\) in the presence of the conditioning stimulus. Thus, CPM magnitude significantly declined from the baseline to the stress condition \((2.38±1.4 \text{ vs. } 1.29±1.3 \text{ VAS units}, \text{ respectively, } p<0.01)\) (Figure 3, left bars).

The decline in CPM magnitude from baseline to the stress condition correlated with the magnitude of the subjects' stress response as indicated by the level of perceived stress in the stress condition \((r=-0.45, p<0.05)\) and the change in perceived stress from rest to stress \((r=-0.62, p<0.05)\). Namely, the greater the perceived stress and its increase following the stress manipulation, the greater was the decline in CPM.

5. Pain adaptation

Fig. 4 presents the pain adaptation procedure at baseline and stress conditions. There was a significant effect of time \([F(5,85)=12.9, p<0.0001]\) but not of condition \([F(1,85)=1.86, p=0.19]\) on the VAS ratings of perceived pain. The interaction condition*time was significant \([F(5,85)=3.58, p<0.01]\), suggesting that the magnitude of pain adaptation was not uniform in the two conditions. At baseline condition, perceived pain decreased from 4.25±1.7 to 2.75±2.3 VAS units \((p<0.01)\), from the start to the end of the stimulus. At the stress condition, perceived pain decreased from 4.56±1.6 to 1.89±2.4 \((p<0.001)\) from the start to the end of the stimulus. Thus, pain adaptation magnitude
significantly increased from baseline to the stress condition (1.5±2.5 vs. 2.67±2.9 VAS units, respectively, p<0.01) (Figure 3, right bars).

The increase in pain adaptation from baseline to the stress condition correlated with the magnitude of the subjects' stress response as indicated by the level of perceived stress (r=0.52, p<0.05), perceived anxiety (r=0.43, p<0.05), and cortisol level (r=0.6, p<0.05) in the stress condition and the change in perceived stress from rest to stress condition (r=0.39, p=0.055). Namely, the higher the perceived stress, anxiety and cortisol level during stress, the smaller the increase in pain adaptation.

6. High vs. low stress responders

Due to the significant correlation between stress responsiveness and pain modulation capacity at a group level, and in order to test further the role of individual stress responsiveness on pain modulation, the subjects were subdivided into two subgroups; high- and low stress responders. The division was determined according to the change in perceived stress due the stress manipulation (delta between perceived stress at rest and perceived stress following the stress manipulation). Thus, high and low stress-responders had delta perceived stress values above and below group mean. We chose perceived stress as the dividing factor for two reasons; first, perceived stress is the manifestation of the definition of stress as a cognitive perception [39] and second, physiological responses such as cortisol and autonomic variables are not necessarily specific and pathognomonic to negative stress [37,49,69]. The mean change in perceived stress of the high (n=13) and low (n=18) stress-responders was 3.75±1.1 and 0.3±0.7, VAS units, respectively (p<0.0001). The two groups also differed in the magnitude of perceived stress during the stress condition (5.52±2.1 vs. 3.33±3.5 in high vs. low stress-responders, p<0.05). Cortisol levels were not significantly different between the groups but high stress-responders exhibited increased autonomic function, manifested in a
significantly higher HR (90.65±14 vs. 75.2±11, p<0.05) and NSCF (2.38±0.5 vs. 1.65±0.5, p<0.05) compared to low stress-responders.

Figure 5 presents the opposite trends of the stress-induced changes occurring in CPM and pain adaptation among high and low stress-responders. With regard to CPM, a significant interaction was found between the magnitude of the stress response and the magnitude of the change in pain ratings at baseline vs. the stress conditions (F(1,25)=18.69, p<0.0001). The magnitude of CPM among low stress-responders did not significantly change from baseline to the stress condition (-2.1±1.4 and -1.64±1.7 VAS units, respectively, p=0.07). In contrast, the magnitude of CPM among high stress-responders significant declined from baseline to the stress condition by -1.43±1.8 VAS units (from -2.53±1.5 to -1.06±1.9, respectively, p<0.01). The difference between the subgroups in the magnitude of CPM during stress was significant (p<0.05) (Fig. 5).

With regard to pain adaptation, a significant interaction was found between the magnitude of the stress response and pain ratings in the baseline vs. the stress conditions (F(5,140)=7.33, p<0.0001). The magnitude of pain adaptation among low stress-responders increased significantly from baseline to the stress condition by 2.07±3 VAS units (from 2.37±2.5 to 4.44±1.6, respectively, p<0.05). In contrast, the magnitude of pain adaptation among high stress-responders remained unchanged from baseline to the stress condition (0.8±2.3 and 0.95±3.2 VAS units, p=0.24). The difference between the subgroups in the magnitude of pain adaptation during stress was significant (p<0.01) (Fig. 5).

Discussion

The results show that on a group level, acute psychosocial stress induced a decline in CPM as well as an increase in pain adaptation, suggesting opposite effects of stress on pain modulation. However, further analysis revealed that the stress effect depended on individual attributes: only “high stress-responders” exhibited a significant decline in CPM whereas only
“low stress-responders” exhibited a significant increase in pain adaptation. These findings are reported here for the first time and are attributed specifically to the stress manipulation considering the SEM values of CPM and pain adaptation in the preliminary study.

Previously we reported a decline in CPM following acute stress manipulation [28] as did Nilsen et al. [54] but the inclusion of another pain modulation test in the present study revealed a more complex effect of acute stress than recognized previously. In two other studies, acute psychological stress did not affect temporal summation of pain [9,13] although a tendency towards increased pain ratings following repeated noxious stimulation under stress [61] may indirectly correspond with the CPM decline herein. To date, we were unable to find studies evaluating pain adaptation under stress.

It is unlikely that the seemingly opposite stress effects stem from methodological factors, since the effects occurred in the same participants, under the same experimental conditions and stress manipulation. Furthermore, the stimulation intensities used for the CPM and pain adaptation tests remained unchanged in the baseline and stress conditions. The opposite stress effects are thus probably mediated by factors related to individual stress response, the pain modulation paradigm used, or both, as discussed below.

The role of individual stress responsiveness

Despite the seemingly opposite effects of stress on pain modulation at the group level, the division of the subjects into high- and low stress responders according to perceived stress revealed a specific trend. CPM decreased only among high stress-responders and pain adaptation increased only among low stress-responders. Because stress is a cognitive perception of uncontrollability and/or unpredictability [39], these results suggest that under stress, the pain modulation response is dictated, at least partly, by individual appraisal of threats. Previous results on the effect of acute stress on pain threshold and tolerance were inconsistent showing either SIA or SIA [e.g. 8,13,20,78]. Based on our results and
considering that perceived stress was seldom evaluated previously, the inconsistency in 
previous studies may stem from individual differences in stress reactivity that were not 
accounted for. In other words, analyzing stress-related pain responses at a group level only 
may be misleading and mask individual variability; strong and weak stress responses that can 
have opposite effects on pain perception.

Resembling our finding are results from animal studies in which a mild stressor 
produced either hyperalgesia or hypoalgesia in rats [35] but hyperalgesia occurred in rats 
deemed as hyper-emotional whereas hypoalgesia occurred in "quiet" rats. Furthermore, 
stress-induced hyperalgesia was abolished following anxiolytic drugs [36] and stress-induced 
hypoalgesia was absent in rats with anxiety-related behaviors [72]. Indeed, increased trait 
stress and anxiety ratings are associated with increased clinical/experimental pain ratings in 
patients [14,18,26,64] and healthy subjects [57,63,66,68]. Moreover, positive correlation 
between stress reactivity and stress-induced hyperalgesia was found among headache patients 
[8] and healthy subjects [7] yet stress reactivity also correlated with SIA under different stress 
manipulations [20,29,78]. Our study demonstrates that under controlled conditions, a strong 
stress reactivity consistently produced diminished pain modulation and vice versa.

The mechanisms underlying the opposite stress effects on pain modulation depending 
on individual stress responsiveness are unclear. However, there is evidence that brain 
structures involved in emotion and stress modulation can induce opposite effect on brain stem 
structures involved in pain modulation. For example, activation of the hypothalamic 
dorsomedial nucleus (DMN) and medial amygdala during stress can recruit the 
rostroventromedulla (RVM) “ON-cells” leading to pain facilitation [34,47,60,73]. On the 
other hand, activation of the hypothalamic paraventricular nucleus (PVN) and the prefrontal 
cortex (PFC) via the basolateral amygdala and Periquaductal grey (PAG), can inhibit the 
RVM "ON-cells" and activate the "OFF-cells", thus inducing an antinociception effect [6,50].
Thus, the hypothalamus and amygdala can induce both pro- and antinociceptive effects. Furthermore, differential PAG connectivity was recently attributed to individual differences in pain-induced salivary cortisol [70] and individual differences in negative affect [12]. Different stress responses correlated with parallel enhancement or reduction of nociceptive responses by particular substances also in animal models [34].

Over activation of the DMN and amygdala during intense distress, e.g. in patients with posttraumatic stress disorder (PTSD) [23,40] who also exhibit abolished CPM [17] may thus underlie the pronociceptive response observed among high stress-responders herein. Specifically, CPM is associated with excitation of OFF-cells and inhibition of ON-cells [10,33], and therefore maladaptive or over activation of the DMV-amygdala-RVM link among high stress-responders may underlie their diminished CPM. The finding that CPM was detected only among those chronic pain patients with high optimism and low negative affect [14] and that more efficient CPM among healthy subjects is associated with reduced stress levels and positive affect [4,27,30,53] support this possibility. Thus, strong or maladaptive responses to stress may hamper pain modulation among patients and healthy subjects.

In contrast, more adaptive emotion regulation to stress via activation of the PFC and the PVN/PAG-RVM link, that is also involved in pain adaptation [3,74], may underlie the stress induced increase in pain adaptation among low-stress-responders. The positive correlation between pain adaptation and parasympathetic function among healthy subjects [52] corroborates this idea. In patients, the reduction of clinical pain following stress-relieving treatment that also improved the HPA-axis [5,15] and the decreased pain sensitivity among patients with BPD [2] and PTSD [18] with increased individual dissociation levels support the notion that certain aspects of emotional control can reinforce pain modulation and vice versa. Thus, although the potential for both pro- and antinociceptive responses exist,
individual emotional responses to stress being maladaptive or adaptive may determine the
direction of these effects.

**Effects related to the pain modulation paradigm**

In the present study, CPM did not correlate with pain adaptation, as also reported
elsewhere [80] suggesting that CPM and pain adaptation evaluate different aspects of
endogenous pain inhibition. CPM reflects "extra-segmental" inhibition wherein pain is
inhibited by a painful stimulus applied to a heterotrophic or extra-segmental body region
[42,77]. Pain adaptation reflects "intra-segmental" inhibition, wherein a single painful
stimulus applied to a fixed location is inhibited over time [11,62]. In addition, somewhat
different brain structures are implicated in CPM vs. pain adaptation [3,79] and pain
adaptation may also have peripheral components, such as primary afferents fatigue [56]
lacking in CPM. Consequently, the differential effect of stress on CPM vs. pain adaptation
within subjects (diminished CPM yet unchanged pain adaptation among high stress-
responders and vice versa among low stress-responders) may also be related to the structure
and function of the each of these pain modulation pathways.

**The evolutionary perspective**

Decreased CPM along with increased pain adaptation under acute stress may serve a
survival need. CPM is tested with moderately strong painful stimuli [31,55,77], whereas pain
adaptation, with mildly painful stimuli [41,59,75] as herein. Pain elicited in two body regions
at strong intensity (CPM) may signify a greater threat than pain elicited in a single body
region at lesser intensity (pain adaptation). Thus, while the former condition produces
pronociception under stress in order to constantly and unequivocally alarm the organism to
promote protective behavior, the latter condition produces antinociceptive reaction in order to
maintain function. The increase in salience of potentially harmful stimuli and disregard of
less harmful/alarming stimuli benefit the organism by optimizing its survival under stressful
conditions [22]. The results suggest that the magnitude of individual stress responsiveness may dictate the extent of these survival processes, whether pronociceptive (reduced CPM) or antinociceptive (increased pain adaptation).

Limitations and Summary

Although the study provides new insights on the stress-pain interactions some reservations should be considered. First, the manipulation induced psychosocial stress that may differ from other types of stress. Additional studies are needed to allow for generalization of the results. Second, CPM was measured with two noxious contact heat stimuli. Although this paradigm was found reliable herein and by others [25,32], testing of additional CPM paradigms is recommended. Third, as all subjects were adult men, the results cannot be generalized to the entire population. In conclusion, this study demonstrates that acute psychosocial stress may induce opposite effects on pain modulation depending on individual stress reactivity; high stress-reactivity induces pronociception and low stress-reactivity produces antinociception. The findings may have several implications. First, it is important to study stress effects not only on a group level but also considering individual differences in stress reactivity. With respect to pain management, since reduced CPM is associated with chronic pain [46,55], high stress-responders may be at higher risk for developing chronic pain. Therefore, identification of high vs. low stress-responders and closer monitoring of the former may enable individually tailored treatment with improved efficacy. In addition, interventions for stress management may improve pain modulation and reduce the risk of pain chronicity.

Acknowledgement

The authors wish to thank Drs. Orna Zagoory-Sharon and Ruth Feldman for their support in salivary cortisol analysis. The authors wish to thank Jens Pruessner for the MIST.
 References


17. Defrin R, Lahav Y, Solomon Z. Dysfunctional pain modulation in torture


26. Geisser ME, Roth RS, Theisen ME, Robinson ME, Riley III JL. Negative


36. Jørum E. Noradrenergic mechanisms in mediation of stress-induced


45. Levine FM, Krass SM, Padawar WJ. Failure hurts: the effects of stress due to


56. Peng YB, Ringkamp M, Meyer RA, Campbell JN. Fatigue and paradoxical


73. Wagner KM, Roeder Z, DesRochers K, Buhler AV, Heinricher MM, Cleary
DR. The dorsomedial hypothalamus mediates stress-induced hyperalgesia and is the source of the pronociceptive peptide cholecystokinin in the rostral ventromedial medulla. Neurosci 238:29-38, 2013.


**Figure 1:** The experimental protocol. SNS= Sympathetic nervous system indices (heart rate, heart rate variability, Galvanic skin response and number of skin conductance fluctuations). Sensory testing= quantitative evaluation of conditioned pain modulation and pain adaptation. MIST= Montreal Imaging Stress Task.

**Figure 2:** In the CPM procedure, pain intensity of the test stimulus was decreased in the presence of the conditioning stimulus in both the baseline (**$p<0.0001$**) and stress (**$p<0.001$**) conditions. The magnitude of reduction in pain intensity (delta between ratings) was greater in the baseline compared to the stress condition (**$p<0.01$**) indicating weaker CPM during stress. Values denote mean VAS scores ± SE.

**Figure 3:** The magnitude of CPM declined (**$p<0.01$**) whereas the magnitude of pain adaptation increased (**$p<0.01$**) from baseline to the stress condition indicating opposite effects of stress on pain modulation. Bars denote mean delta VAS values ± SE.

**Figure 4:** In the pain adaptation procedure, pain intensity decreased over time in both the baseline (**$p<0.01$**) and stress (**$p<0.001$**) conditions. The reduction in pain intensity was greater during stress compared to baseline condition (**$p<0.05$**) indicating greater pain adaptation during stress. Values denote mean VAS scores ± SE.

**Figure 5:** Among high stress-responders, CPM significantly declined from baseline to the stress condition (**$p<0.05$**) but pain adaptation did not change significantly. In contrast, among low stress-responders, pain adaptation significantly increased from baseline to the stress condition (**$p<0.05$**) but CPM did not change significantly. Bars denote mean delta VAS values ± SE.
Table 1: Stress indices obtained in the 4 epochs of the study

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Baseline</th>
<th>Stress</th>
<th>Recovery</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stress (0-10)</td>
<td>1.34(1.8)</td>
<td>1.22(1.8)</td>
<td>4.28(3.3) <strong>c</strong></td>
<td>0.78(1.5) <strong>d</strong></td>
<td>28.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>State anxiety (10-40)</td>
<td>13.32(4.0)</td>
<td>13.58(4.1)</td>
<td>19.35(6.7) <strong>c</strong></td>
<td>13.4(3.8) <strong>d</strong></td>
<td>10.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>69.86(12.4)*a</td>
<td>72.78(12.0)*b</td>
<td>80.36(13.9)*c</td>
<td>71.16(12.9)*d</td>
<td>11.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HRV (Hz)</td>
<td>33.14(8.7)</td>
<td>30.79(8.1)*b</td>
<td>27.01(7.1)*c</td>
<td>29.51(6.9)</td>
<td>3.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GSR (mho)</td>
<td>4.48(3.3)**a</td>
<td>8.1(5.4)*b</td>
<td>10.71(5.1)*c</td>
<td>10.13(6.3)*c</td>
<td>10.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NSCF (nps)</td>
<td>1.24(0.5)</td>
<td>1.28(0.5)**b</td>
<td>1.92(0.6)*c</td>
<td>1.37(0.5)*d</td>
<td>7.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortisol (pg/ml)</td>
<td>494.7(251)</td>
<td>529.47(321)</td>
<td>899.06(818)*c</td>
<td>458.38(260)*d</td>
<td>3.79</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean (±SD). HR=hear rate, HRV=heart rate variability, GSR=galvanic skin response, NSCF= number of skin conductance fluctuations, bpm=beats per minute, mho=1 simens, npm=number per second, pg/ml=picogram/milliliter. F- and P-values are of the analyses of variance. Paired comparisons: a=between rest and baseline measurements, b=between baseline and stress measurements, c=between rest and stress measurements, d=between stress and recovery measurements, e=between rest and recovery measurements. The asterisks are for the paired comparisons: *p<0.05,  **p<0.01,  ***p<0.001, ****p<0.0001.
Figure 1

![Diagram showing cortisol, SNS, and anxiety levels at different time points: Rest, Baseline testing, Break, MIST, Stress testing, and Recovery.](image)

Figure 2

![Graph showing perceived pain (VAS) over time with Baseline and Stress conditions, with significance markers for differences.](image)
Figure 3

![Graph showing perceived pain (VAS) versus time with bars for Baseline and Stress conditions.]

- CPM
- Pain adaptation

Magnitude (absolute VAS values)

Figure 4

![Graph showing perceived pain (VAS) over time with lines for Baseline and Stress conditions.]

- Baseline
- Stress

Perceived pain (VAS)

Time (seconds)
Figure 5

- High stress-responders
- Low stress-responders

Magnitude (absolute VAS values)

CPM

Pain adaptation