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ORIGINAL ARTICLE

Fear of pain and cortisol reactivity predict the strength of stress-induced hypoalgesia

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Abstract

Background: Acute stress can have an effect on pain sensitivity, yet the direction of the effect – whether it is hypoalgesic or hyperalgesic – is mixed across studies. Moreover, which part of the stress response influences pain sensitivity is still unclear. In the current experimental study, we aim to examine the effect of acute stress on heat pain thresholds and pain tolerance levels in healthy participants, while taking into account individual differences in stress responses.

Methods: Forty-two healthy participants were randomly assigned to either a well-validated stress paradigm: the Maastricht Acute Stress Task (MAST; combining physical and psychological stressors) or to a nonstressful version of the task. Heat pain thresholds and tolerance levels were assessed at three times: prior to the MAST, immediately after the MAST during the presumed sympatho-adrenal medullary (SAM) response, and 15 min after MAST to cover the presumed hypothalamus–pituitary–adrenal (HPA) axis response. Stress responses were assessed both subjectively and physiologically.

Results: We observed that the acute stress induction led to increased heat pain thresholds, an effect that was present only in participants showing a cortisol response following stress induction and only in the presumed HPA axis time window. The strength of this hypoalgesic effect was further predicted by the change in cortisol and by fear of pain levels.

Conclusions: Our findings indicate that the HPA axis – and not the autonomic – stress response specifically underlies this stress-induced hypoalgesic effect, having important implications for clinical states with HPA axis dysfunctions.

Significance: This experimental study shows that an acute stress induction – that combines physical and psychological stressors – increases heat pain thresholds, but not tolerance in healthy participants. Furthermore, the magnitude of this stress-induced hypoalgesic effect is predicted by cortisol reactivity and fear of pain, revealing specific involvement of the HPA axis stress system and interactions with pain-related psychosocial aspects.

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1. Introduction

There are multiple interactions between stress and pain. Experimental stress manipulations often use pain to evoke (dis)stress (e.g. cold pressor task (CPT); Lovallo, 1975), while pain perception can also be affected by stress. Some studies report that acute stress decreases pain sensitivity (hypoalgesia; Aghajani et al., 2012; al'Absi and Petersen, 2003; Butler and Finn, 2009; Flor and Grusser, 1999). For instance, participants reported less pain during the CPT when preceded by psychosocial stress (al'Absi and Petersen, 2003), which can be adaptive in a fight or flight situation (Butler and Finn, 2009). Other studies showed that acute stress increases pain sensitivity (hyperalgesia; Caceres and Burns, 1997; Crettaz et al., 2013; Olango and Finn, 2014; Rivat et al., 2007). For example, psychosocial stress made participants more sensitive to pain (Crettaz et al., 2013), which can be adaptive by increasing attention to pain and motivating behaviour to promote healing. Others have found no effects of acute stress on pain sensitivity (Geva et al., 2014). These opposing results might arise from inter-individual differences in type and strength of stress responses (Reinhardt et al., 2013), and lack of proper control groups or conditions.

The stress response is characterized by two major temporal physiological responses, preparing the body to respond adaptively when confronted with a threat. The fast response is driven by the autonomic sympatho-adrenal medullary (SAM) system, causing release of catecholamines (e.g. (nor)adrenalin), increasing heart rate, blood pressure and respiration. The slower response is triggered by hypothalamus–pituitary–adrenal (HPA) axis activation, ultimately causing release of glucocorticoids (cortisol in humans; De Kloet et al., 2005; Ulrich-Lai and Herman, 2009). Changes in pain sensitivity have been linked to both SAM (al'Absi and Petersen, 2003) and HPA axis responses (Vachon-Presseau et al., 2013a). As there is considerable variation in stress responses across individuals (i.e. especially the degree of HPA axis activation), sex and type of manipulation (e.g. psychosocial or physical) (Dickerson and Kemeny, 2004; Ulrich-Lai and Herman, 2009), assessing these responses separately and in their appropriate time window is crucially important for reliably interpreting the influence of stress on pain.

Besides demographics and genetics, there are psychosocial factors contributing to individual differences in stress and pain responses (Dickerson and Kemeny, 2004; Fillingim, 2005; Nielsen et al., 2009). For example, trait anxiety (Tang and Gibson, 2005), fear of pain (Hirsh et al., 2008) and pain catastrophizing (France et al., 2002) have been related to pain sensitivity, while negative affect and trait anxiety have been related to the strength of stress responses (Chida and Hamer, 2008). Taking these factors into account is essential.

Here, we aim to examine effects of acute stress on heat pain thresholds and tolerance levels in healthy participants, while taking into account individual differences in stress responses, and including psychosocial factors and a no stress control group. More specifically, acute stress is induced using a well-validated paradigm that reliably induces SAM and HPA axis stress responses using a combination of physical and psychological stressors: the Maastricht Acute Stress Task (MAST; Smeets et al., 2012). Stress responses are monitored using subjective and physiological measures (i.e. pulse and blood pressure to assess SAM; cortisol to assess HPA axis). To separate SAM and HPA axis influences, pain sensitivity is assessed three times: at baseline, directly after MAST offset (presumably during the SAM response) and 15 min after the MAST (presumably during the HPA axis response; based on Joëls and Baram, 2009; Smeets et al., 2012; Ulrich-Lai and Herman, 2009). We expect to see SAM and HPA axis responses post-MAST in these separate time windows. Hypoalgesic effects would be reflected in increased pain thresholds and/or tolerance levels, while hyperalgesic effects would result in decreases. If the SAM component is driving the effect, we would expect changes in pain sensitivity specifically in the presumed SAM window that correlate with blood pressure. If the HPA axis is driving the effect, we expect changes in the presumed HPA axis window that correlate with cortisol. Irrespective of stress system, we expect effects to be related to pain-related psychosocial factors.

2. Methods and materials

2.1 Participants

Forty-two healthy volunteers participated in this study and were randomly assigned to the experimental or control group. Sample size calculation was performed using G*Power 3 (based on a repeated-measures ANOVA having within- and between-subjects factors, two groups, three measurements, expected effect size of 0.25, desired power 0.90 and alpha of 0.05, advising a minimum of 18 participants per group; Faul et al., 2007). Participants were

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screened for eligibility using the Qualtrics platform for online data collection (Qualtrics, Provo, USA; http://www.qualtrics.com). Inclusion criteria were as follows: right-handedness, having a healthy body-mass index (BMI between 18 and 30), use of oral contraceptives for women (to reduce variability in cortisol levels related to menstrual cycle phase; Kudielka et al., 2009). Exclusion criteria were as follows: history of chronic pain or pain condition requiring treatment in the past six months; psychopathological, neurological or endocrine health issues; regular drug use and heavy smoking (>15 cigarettes a day). Three participants were excluded from the sample: two from the control group because of a cortisol response (see section 2.6.2.), and one from the stress group because of a lack of differentiation between pain threshold and pain tolerance temperature (i.e. the participant reached plateau levels of 51 °C for both pain threshold and tolerance). The final sample consisted of 20 participants in the stress group (eight men, 12 women, mean age 22.9 years, range: 20–29 years) and 19 in the control group (seven men, 12 women; mean age 23.5 years, range 18–29 years; Table 1). Participants were recruited through advertisements and were given a small monetary reward or research credits for participation. The study was approved by the ethics committee of the Faculty of Psychology and Neuroscience (ECP), Maastricht University.

2.2 Study procedure

An overview of the study is shown in Fig. 1. All testing took place in the morning (8.30 a.m. or 10.30 a.m.). Upon arrival, participants received information about study procedures and signed informed consent. Then, they were asked whether they adhered to the instructions to get up at least 2 h before the test session (i.e. to avoid confounding effects of the cortisol awakening response), and not to eat, drink or smoke in the 2 h before the session. At t_0, baseline measures were taken, including self-reported negative affect (assessed with the negative affect items from the Positive And Negative Affect Schedule; PANAS; Watson et al., 1988), blood pressure, pulse and a first salivary cortisol sample. These measures were repeated several times throughout the test session (Fig. 1). At t_{45}, participants underwent the Maastricht Acute Stress Task (MAST) or a non-stressful control version of the task. Pain thresholds and tolerance measures were performed at three time points during the session (at t_0, directly after the stress induction [t_{55}] and 15 min after the end of the stress induction [t_{70}]; with the time referring to the minutes since participants' arrival).

On the day preceding the session, participants received questionnaires to assess vulnerability to stress, anxiety and pain. Self-reported stress-vulnerability, anxiety, depression, fear of pain, pain catastrophizing and hypervigilance to pain were assessed with the Depression, Anxiety and Stress Scales (DASS-21; Lovibond and Lovibond, 1995), Perceived Stress Scale (PSS; Cohen et al., 1983), State-Trait Anxiety Inventory (Trait part; STAI-Y2; Spielberger et al., 1983); Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983); Fear of Pain Questionnaire (FPQ III; McNeil and Rainwater, 1998), Pain Catastrophizing Scale (PCS; Sullivan

Table 1 Participant characteristics; statistical analyses (right column) showed that none of the scores differed significantly across the groups.

	Stress group	Control group	Statistics of group comparisons
Sample size	$n = 20$	$n = 19$	
Age (years)	Mean = 22.9, SE = 0.5	Mean = 23.5, SE = 0.7	$F_{1,37} = 0.51$; $p = 0.48$
Sex	8 men, 12 women	7 men, 12 women	$\chi^2_{1,\ N\ =\ 39} = 0.04$; $p = 0.84$
BMI (kg/m^2)	Mean = 22.4, SE = 0.4	Mean = 21.9, SE = 0.5	$F_{1,37} = 0.58$; $p = 0.45$
Perceived Stress Scale (PSS; scale from 0 to 40)	Mean = 9.3, SE = 1.3	Mean = 12.8, SE = 1.6	$F_{1,37} = 3.19$; $p = 0.08$
Depression, Anxiety, and Stress Scale	D: mean = 0.7, SE = 0.3	D: mean = 1.1, SE = 0.4	D: $F_{1,37} = 0.70$; $p = 0.41$
(DASS21; scale from 0 to 21 per subscale)	A: mean = 0.5, SE = 0.3	A: mean = 0.8, SE = 0.4	A: $F_{1,37} = 0.59$; $p = 0.48$
	S: mean = 1.8, SE = 0.7	S: mean = 1.8, SE = 0.4	S: $F_{1,37} < 0.01$; $p = 0.99$
Trait Anxiety (STAI-Y2; scale from 20 to 80)	Mean = 32.6, SE = 1.6	Mean = 35.3, SE = 2.3	$F_{1,37} = 0.99$; $p = 0.33$
Pain catastrophizing (PCS; scale from 0 to 52)	Mean = 13.8, SE = 2.5	Mean = 14.2, SE = 2.2	$F_{1,37} = 0.02$; $p = 0.89$
Fear of Pain (FPQ; scale from 30 to 150)	Mean = 71.0, SE = 3.6	Mean = 78.8, SE = 4.6	$F_{1,37} = 1.86$; $p = 0.18$
Pain Hypervigilance (PVAQ; scale from 0 to 80)	Mean = 26.5, SE = 2.8	Mean = 31.8, SE = 3.5	$F_{1,37} = 1.47$; $p = 0.23$
Hospital Anxiety and Depression Scale (HADS;	D: mean = 1.5, SE = 0.5	D: mean = 1.4, SE = 0.3	D: $F_{1,37} = 0.05$; $p = 0.83$
scoring 0–12 per subscale)	A: mean = 2.7, SE = 0.5	A: mean = 3.8, SE = 0.7	A: $F_{1,37} = 1.86$; $p = 0.18$

BMI, body mass index; n.a., not applicable; SE, standard error.

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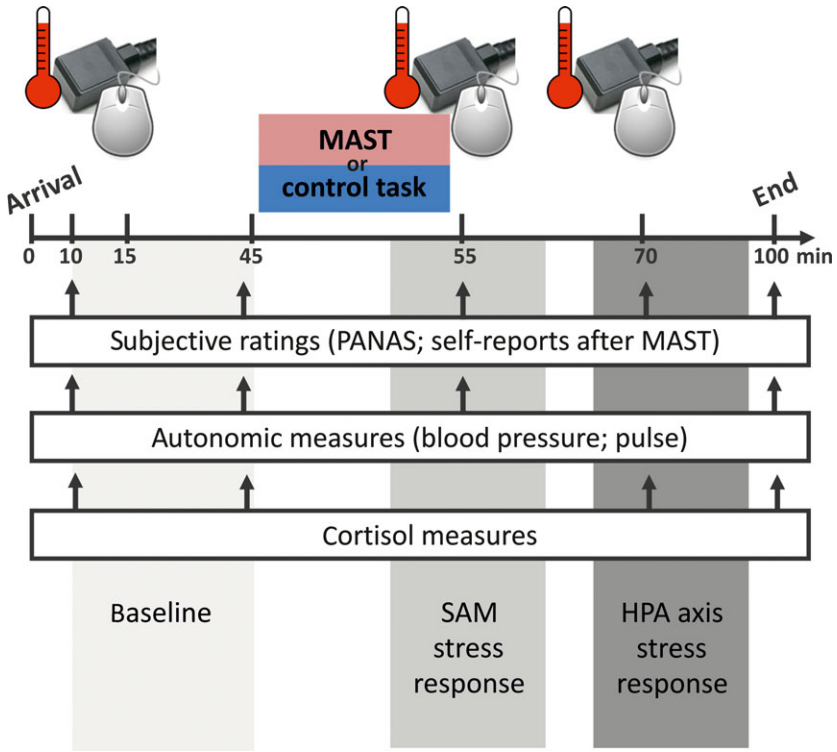

Figure 1 Overview of the study procedure. The study procedure is presented plus the timing of the different measures and the presumed time windows for the two stress responses (SAM stress response in light grey; HPA axis stress response in dark grey). The thermometer with the thermode and response button (top) represents the pain threshold and tolerance measures. Note that for the analyses, baseline measures at t_{10} and t_{45} were averaged ($t_{baseline}$), except for blood pressure (MAP). MAST, Maastricht Acute Stress Task; PANAS, positive and negative affect schedule; SAM, sympatho-adrenal medullary, HPA, hypothalamus–pituitary–adrenal.

et al., 1995); and Pain Vigilance and Awareness Questionnaire (PVAQ; McCracken, 1997). None of the scores differed significantly across groups (Table 1).

2.3 Stress induction

The MAST consists of a 5-min instruction phase and a 10-min acute stress phase in which physical, cognitive and social stressors are included. Physical stress alternated with cognitive stress and included immersion of the left hand into an ice-cold water pressor (4 °C; CPT; 60–90 s per period), while cognitive stress was elicited by a mental arithmetic exercise in which participants had to count backwards in steps of 17 starting at 2043 as quickly and accurately as possible (45–90 s per period). Negative feedback was given during the counting, and participants thought they were videotaped for analysis of facial expressions and hence were instructed to look into a video camera, while the video was displayed on a monitor (i.e. the social stress component). Previous studies have shown that the MAST is an effective stress task (Smeets et al., 2012; Meyer et al., 2013; Quaedflieg et al., 2016; Shilton et al., 2017). The control version included immersion of the left hand into lukewarm water (36 °C), a simple counting task, no video-taping and no monitoring by the experimenter.

2.4 Assessment of the stress responses

A visual analogue scale (VAS) was used to assess subjective stress related to the MAST, asking how stressful participants had felt during the task, how painful it was and how unpleasant it felt (anchored from 'not at all' to 'very'). Negative affect was assessed using the negative items from the PANAS (Fig. 1).

To assess general arousal and SAM axis activity, the systolic and diastolic blood pressure (SP and DP) and pulse were measured using the Omron 705IT (HEM-759-E; Omron Healthcare Europe BV, Hoofddorp, the Netherlands). Mean arterial pressure (MAP) was calculated to obtain one total value representing averaged blood pressure [MAP = DP +

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0.412 (SP − DP)] (Meaney et al., 2000). Cortisol (HPA axis) measures of stress were obtained at four time points during the session using a synthetic Salivette (Sarstedt, Etten-Leur, the Netherlands). Two baseline samples were taken at t_0 and t_{45}, one 15 min after the end of the MAST at t_{70}, and one at the end of the session at t_{100}. Timing was based on the information that the cortisol response peaks 10–20 min after the offset of the MAST (Smeets et al., 2012). After collection, saliva samples were immediately stored at −20 °C. Cortisol levels were determined by a commercially available luminescence immuno assay kit (IBL, Hamburg, Germany).

2.5 Pain thresholds and tolerance assessments

The pain threshold and tolerance levels were assessed using a 3 × 3 cm thermode of the Pathway System advanced thermal stimulator (ATS; Medoc, Advanced Medical Systems). The thermode was

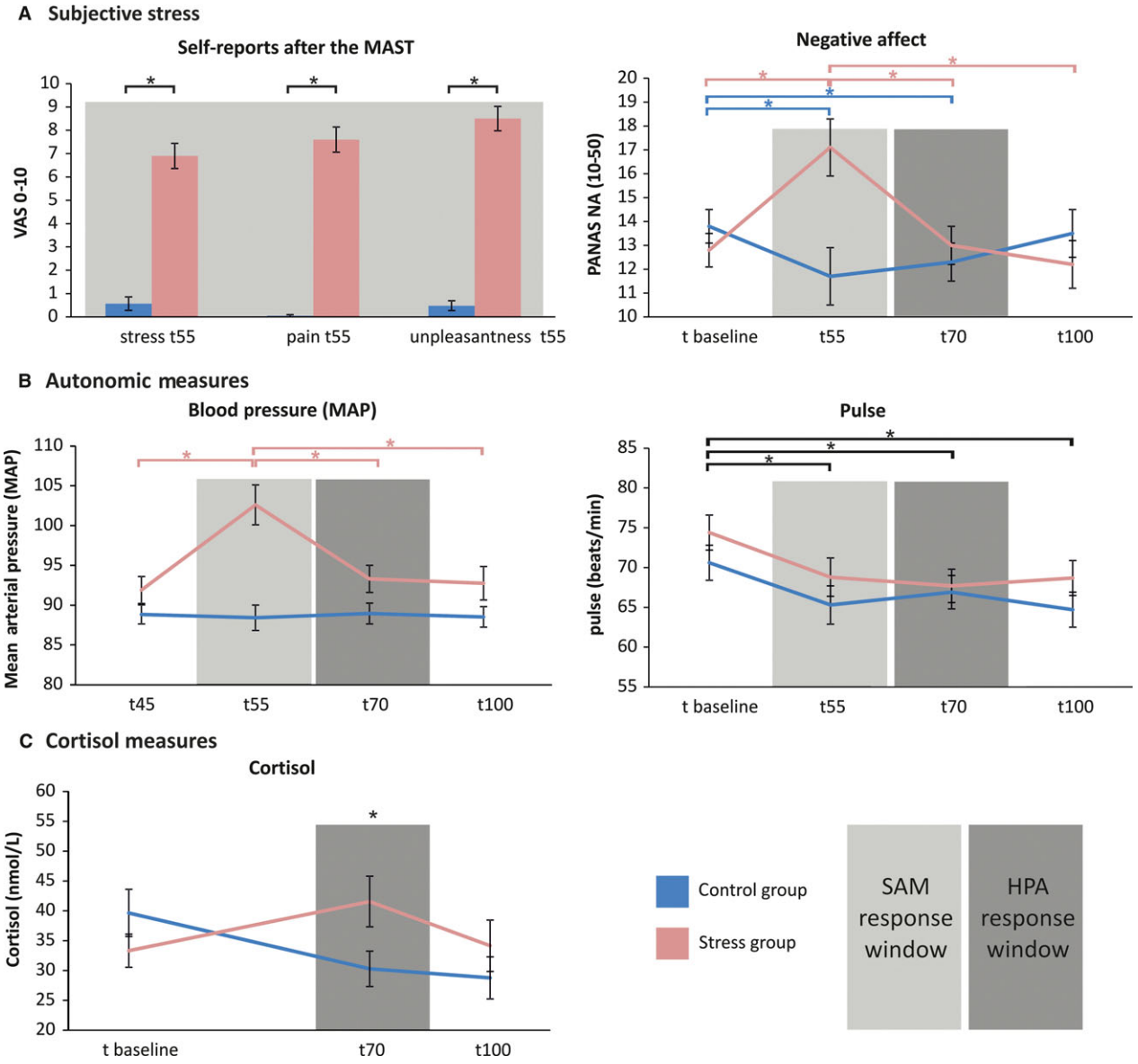

Figure 2 Overview of the manipulation checks. Presented are (A) subjective stress measures, (B) autonomic measures [MAP, mean arterial pressure], and (C) cortisol measures. Significant effects are indicated with an asterisk (*$p < 0.05$) in the figure (black: main effects; in colour: specific group effect). Note that presumed time windows for the sympatho-adrenal medullary (SAM) stress response (t_{55}) and hypothalamus–pituitary–adrenal (HPA) axis stress response (t_{70}) are highlighted by light and dark grey backgrounds, respectively.

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placed on the dorsal surface of the right (dominant) hand. To assess the pain threshold, the thermode would heat up with 2 °C per second from the baseline temperature (31 °C, 32 °C or 33 °C) and participants were instructed to press a response button whenever the sensation started to become uncomfortable and started to become painful. After the assessment, participants were asked to rate the (average) intensity of the stimuli and the fear towards the heat stimuli on a VAS. Then, for pain tolerance, the thermode heated up with 3 °C per second from the baseline temperature (34 °C, 35 °C or 36 °C) and participants were instructed to press a response button whenever the heat was too painful and no longer tolerable. Afterwards, participants rated the intensity and fear for the pain tolerance temperatures.[1] Both assessments were repeated three times with variable baseline temperatures to avoid any participant strategies based on timing aspects (i.e. as ramping rates were constant) and to make the assessment less predictable.[2] The first assessment was discarded to account for unfamiliarity effects. In case participants reached 51 °C, the ATS stopped out of safety precautions (this occurred only for pain tolerance, except for one participant in the stress group who was discarded as 51 °C was reached for all assessments, see section 2.1.).

2.6 Data analysis

2.6.1 Baseline and stress manipulation checks

Questionnaires, demographics and self-reported stress after the MAST were compared across groups using a univariate general linear model (GLM) with group (stress versus control) as between-subjects (BS) factor. Baseline measures (self-reports, autonomic and cortisol measures) taken at t_{10} and t_{45} were averaged ($t_{baseline}$) for all subsequent analyses, except for blood pressure (MAP) as for this measure, there was an interaction effect when comparing t_{10} and t_{45} across groups [$F_{1,37} = 5.42$, $p = 0.03$].[3] For MAP, t_{45} was taken as baseline.

Negative affect (PANAS), blood pressure (MAP) and pulse were investigated using a repeated-measures GLM (rmGLM) with group (stress vs control) as a BS factor and time ($t_{baseline}$, t_{55}, t_{70}, t_{100}) as a within-subjects (WS) factor (note that for MAP, the levels of time were t_{45}, t_{55}, t_{70} and t_{100}).

Cortisol data were log-transformed prior to the analysis, as normality checks showed typical skewness of the data. The cortisol responses were investigated using a rmGLM with group (stress versus control) as a BS factor and time ($t_{baseline}$, t_{70}, t_{100}) as WS factor. For each participant, the area under the curve with respect to increase (AUCi) was calculated as a total value for the cortisol increase in response to the MAST (Pruessner et al., 2003). In addition, stress reactivity defined as the delta increase in cortisol (t_{70}–$t_{baseline}$) was calculated. Both were compared across groups using a univariate GLM.

2.6.2 Effects of stress on pain sensitivity

The effect of the stress manipulation on pain thresholds and tolerance levels was assessed using an rmGLM with group (stress versus control) as BS factor and time ($t_{baseline}$, t_{55}, t_{70}) as WS factor. As we specifically hypothesized an effect of time in the stress group only, an rmGLM was performed per group as well, with time as WS factor.

To further inspect the effect of the SAM and HPA axis stress responses in an exploratory manner, correlations were examined between the effect on pain thresholds and tolerance with the stress response measures and with self-reported vulnerability to stress, anxiety and pain (including all participants from both groups). In case of correlations, linear regression analyses were performed using a Backward entry approach.

In addition, the effect of HPA axis stress response was further examined by defining participants who showed a delta increase in cortisol of 1.5 nmol/L or more at t_{70} compared to $t_{baseline}$ (Miller et al., 2013) as cortisol responders. In the stress group, 12 participants (57%) showed this response (hence termed cortisol responders), while nine did not (cortisol non-responders). For two participants in the control group, not enough saliva was collected for analyses, while two other participants responded with a delta cortisol increase of >1.5 nmol/L (which is thought to reflect a cortisol secretory episode as described above; these latter two were excluded from any further analyses, see section 2.1.). Analyses on pain thresholds and pain tolerance were then repeated using three groups (control, cortisol non-responders and cortisol responders).

Outliers were defined as deviating >3 SD from the (group) mean and were replaced by values of ±2 SD of the (group) mean[4] (Field, 2009). Statistical effects were evaluated using the Greenhouse–Geisser correction when appropriate. Alpha of 0.05 was considered significant and was corrected for multiple comparisons using the Bonferroni if necessary.

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3. Results

3.1 Stress manipulation check

3.1.1 Subjective stress

The stress group reported significantly higher subjective stress values post-MAST in domains of stress, pain and unpleasantness [stress: $F_{1,37} = 148.03$, $p < 0.001$, $\eta_p^2 = 0.80$; pain: $F_{1,37} = 361.73$, $p < 0.001$, $\eta_p^2 = 0.91$; unpleasantness: $F_{1,37} = 443.45$, $p < 0.001$, $\eta_p^2 = 0.92$] (Fig. 2). For negative affect (PANAS), there was a significant group × time interaction [$F_{1.7,66.9} = 16.28$, $p < 0.001$, $\eta_p^2 = 0.29$]. Simple effects per group revealed that in both groups, there was a significant main effect of time on negative affect [stress: $F_{1.4,28.1} = 12.0$, $p = 0.001$, $\eta_p^2 = 0$ .38; control: $F_{2.3,46.4} = 5.77$, $p = 0.004$, $\eta_p^2 = 0.22$]. *Post hoc* comparisons showed that in controls, negative affect was lower at t_{55} and t_{70} compared to $t_{baseline}$ [both p-corr < 0.05]. In the stress group, t_{55} showed higher negative affect compared to $t_{baseline}$, t_{70} and t_{100} [all p-corr < 0.05].

3.1.2 Autonomic measures

For mean arterial pressure (MAP), there was a significant group × time interaction [$F_{2.3,86.2} = 20.46$, $p < 0.001$, $\eta_p^2 = 0.36$]. Simple effects per group revealed that only in the stress group, there was an effect of time [stress: $F_{1.9,35.4} = 30.74$, $p < 0.001$, $\eta_p^2 = 0.62$; control: $F_{2.6,46.9} = 0.13$, $p = 0.92$, $\eta_p^2 = 0.007$] (Fig. 2). *Post hoc* comparisons in the stress group showed that MAP was significantly higher at t_{55} compared to t_{45}, t_{70} and t_{100} [all p-corr < 0.05].

For pulse, there was a main effect of time [$F_{2.6,105.4} = 13.52$, $p < 0.001$, $\eta_p^2 = 0.25$], but no group effect [$F_{1,40} = 1.10$, $p = 0.30$, $\eta_p^2 = 0.03$] nor an interaction effect [$F_{2.6,105.4} = 1.02$, $p = 0.38$, $\eta_p^2 = 0.03$]. *Post hoc* comparisons showed that pulse was significantly higher at $t_{baseline}$ compared to t_{55}, t_{70} and t_{100} [all p-corr < 0.05].

3.1.3 Cortisol measures

For cortisol, a significant group × time interaction effect was observed [$F_{1.8,66.0} = 3.54$, $p = 0.04$, $\eta_p^2 = 0.09$]. Simple effects per time point showed that the groups only differed at t_{70} [$F_{1,38} = 4.27$, $p = 0.046$, $\eta_p^2 = 0.10$], and not at $t_{baseline}$ or t_{100} [$t_{baseline}$: $F_{1,38} = 0.52$, $p = 0.48$, $\eta_p^2 = 0.01$; t_{100}: $F_{1,36} = 0.59$, $p = 0.45$, $\eta_p^2 = 0.02$]. For the delta increase in cortisol, a group effect was found [$F_{1,38} = 6.02$, $p = 0.02$, $\eta_p^2 = 0.14$], with the stress group showing a larger cortisol increase compared to the control group. Also the area under the curve with respect to increase (AUCi) showed a group effect [$F_{1,36} = 8.51$, $p = 0.006$, $\eta_p^2 = 0.19$], with the stress group showing a larger AUCi compared to the control group.

3.2 Effects of stress manipulation on pain thresholds and tolerance

For pain thresholds, there was a main effect of time [$F_{1.5,55.6} = 6.67$, $p = 0.005$, $\eta_p^2 = 0.15$], but no group difference [$F_{1,37} = 0.54$, $p = 0.47$, $\eta_p^2 = 0.01$] and no significant group × time interaction effect [$F_{1.5,55.6} = 1.16$, $p = 0.31$, $\eta_p^2 = 0.03$]. Planned comparisons per group, however, showed that only the stress group contributed to this effect [stress: $F_{1.5,28.9} = 6.55$, $p = 0.008$, $\eta_p^2 = 0.26$; control: $F_{1.5,26.8} = 2.12$, $p = 0.15$, $\eta_p^2 = 0.11$] (Fig. 3). *Post hoc* comparisons in the stress group showed that pain thresholds at t_{70} were significantly higher compared to both $t_{baseline}$ and t_{55} [both p-corr < 0.05].

For pain tolerance, there were no significant effects [time: $F_{1.7,63.0} = 0.47$, $p = 0.60$, $\eta_p^2 = 0.01$; group: $F_{1,37} = 0.02$, $p = 0.89$, $\eta_p^2 = 0.001$; interaction: $F_{1.7,63.0} = 1.20$, $p = 0.30$, $\eta_p^2 = 0.03$]. Also planned comparisons per group did not reveal any time effects in either group [stress: $F_{1.5,26.2} = 0.50$, $p = 0.56$, $\eta_p^2 = 0.03$; control: $F_{1.8,34.2} = 1.30$, $p = 0.28$, $\eta_p^2 = 0.06$].

3.3 SAM-specific influences on pain sensitivity

To further assess the relation between SAM reactivity and pain thresholds, correlation analyses were performed between the pain thresholds effect in the SAM time window (t_{55}–$t_{baseline}$) and changes in blood pressure (t_{55}–t_{45}), changes in PANAS (t_{55}–$t_{baseline}$), self-reported stress and vulnerability to anxiety, pain and stress. A significant correlation between the pain threshold difference t_{55}–$t_{baseline}$ and trait anxiety was found (STAI-Y2: $r = -0.37$, $p = 0.02$), and correlations approaching significance with fear of pain and state anxiety (FPQ: $r = -0.30$, $p = 0.07$; HADS-A: $r = -0.28$, $p = 0.09$). The effect did not correlate with any of the stress measures (subjective, autonomic, cortisol), nor with any of the other questionnaires [all p's > 0.1]. A linear regression model was fitted on the pain threshold effect (pain threshold difference t_{70}–$t_{baseline}$) using trait and state anxiety (STAI-Y2 and HADS-A, respectively), fear of pain (FPQ) and sex as predictors. Using the backward

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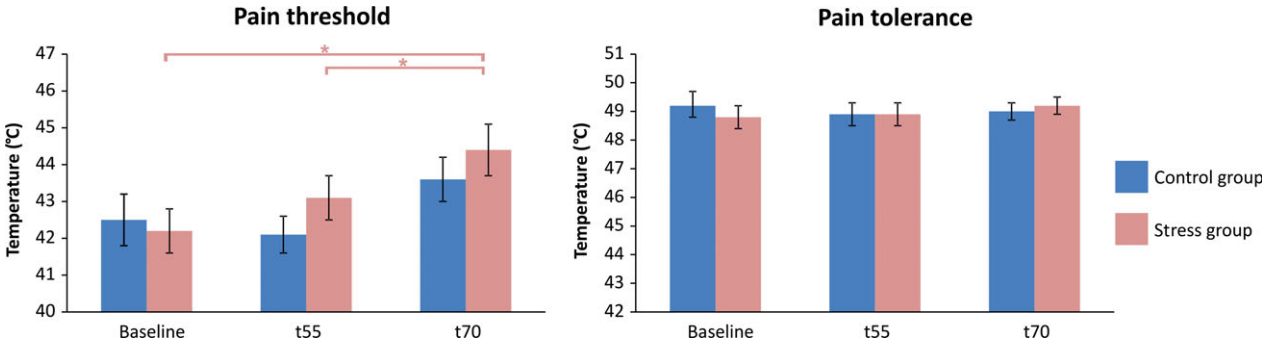

Figure 3 Pain threshold and pain tolerance levels, per group. Presented are pain threshold and pain tolerance levels per group and per time point. Note that the main effect of time on pain thresholds was only significant in the stress group. Presented are estimated marginal means and standard errors (SE).

method for entry of variables, a final model was created with sex and trait anxiety as significant predictors [overall model: $R^2 = 0.17$, $F_{2,36} = 3.64$, $p = 0.04$; sex: $b = -0.31$, $t_{34} = 2.13$, $p = 0.06$; STAI-Y2: $b = -0.36$, $t_{34} = -2.09$, $p = 0.03$].

3.4 HPA axis-specific influences on pain sensitivity

To further assess the relation between HPA axis and pain thresholds, correlation analyses were performed between the pain thresholds effect in the HPA axis time window (t_{70}–$t_{baseline}$) and delta increase in cortisol, changes in blood pressure (t_{70}–t_{45}), changes in PANAS (t_{70}–$t_{baseline}$), self-reported stress and vulnerability to anxiety, pain and stress. The pain threshold difference t_{70}–$t_{baseline}$ correlated significantly with delta cortisol ($r = 0.34$; $p = 0.03$) and anxiety (DASS-A, $r = -0.37$; $p = 0.02$) and correlations with trait anxiety (STAI-Y2; $r = -0.28$; $p = 0.07$), fear of pain (FPQ; $r = -0.30$; $p = 0.06$) and HADS anxiety ($r = -0.29$; $p = 0.07$) approached significance. The effect did not correlate with any of the other stress measures (subjective or autonomic), nor with any of the other questionnaires [all p's > 0.1]. A linear regression model was fitted on the pain threshold effect (pain threshold difference t_{70}–$t_{baseline}$) using delta increase in cortisol, fear of pain (FPQ), state and trait anxiety (HADS-A, DASS-A, STAI-Y2) and sex as predictors. Using the backward method for entry of variables, a final model was created with delta cortisol and fear of pain as significant predictors [overall model: $R^2 = 0.48$, $F_{2,33} = 4.97$, $p = 0.01$; delta cortisol: $b = 0.33$, $t_{34} = 2.13$, $p = 0.04$; FPQ: $b = -0.32$, $t_{34} = -2.09$, $p = 0.04$] (Fig. 4).

In addition, cortisol responders were contrasted to cortisol non-responders and controls.[5] For the pain thresholds, there was a main effect of time [$F_{1.5,50.9} = 5.83$, $p = 0.01$, $\eta_p^2 = 0.15$], but no group difference [$F_{2,34} = 0.79$, $p = 0.46$, $\eta_p^2 = 0.04$] and no group × time interaction effect [$F_{3.0,50.9} = 1.08$, $p = 0.37$, $\eta_p^2 = 0.06$]. Planned time comparisons per group, however, showed that only cortisol responders contributed to the time effect [cortisol responders: $F_{1.5,14.8} = 5.4$, $p = 0.03$, $\eta_p^2 = 0.35$; cortisol nonresponders: $F_{1.4,10.8} = 1.39$, $p = 0.28$, $\eta_p^2 = 0.15$; control: $F_{1.4,24.0} = 1.71$, $p = 0.21$, $\eta_p^2 = 0.09$] (Fig. 5). *Post hoc* comparisons in cortisol responders showed that pain thresholds at t_{70} were significantly higher compared to both $t_{baseline}$ and t_{55} [both p's-corr < 0.05]. Adding sex as a covariate did not change the outcome of this analysis. For pain tolerance, there was no main effect of time [$F_{1.8,61.1} = 0.51$, $p = 0.59$, $\eta_p^2 = 0.02$], nor a group difference [$F_{2,34} = 1.42$, $p = 0.27$, $\eta_p^2 = 0.08$], nor an interaction effect [$F_{3.6,61.1} = 1.57$, $p = 0.20$, $\eta_p^2 = 0.08$]. Planned comparisons confirmed the absence in all groups [cortisol responders: $F_{1.6,16.0} = 1.18$, $p = 0.32$, $\eta_p^2 = 0.11$; cortisol nonresponders: $F_{1.8,14.3} = 0.59$, $p = 0.55$, $\eta_p^2 = 0.07$; control: $F_{1.6,26.4} = 1.84$, $p = 0.18$, $\eta_p^2 = 0.10$].

4. Discussion

The present study aimed to investigate the effect of an acute stress induction on heat pain thresholds and tolerance levels. Our main finding was that heat pain thresholds increased in the group that underwent the acute stress manipulation, and not in the control group. No effects on pain tolerance were found. More specifically, we found that the effect on pain thresholds was only present in cortisol responders (i.e. participants showing a cortisol response) and not in cortisol non-responders. Furthermore, the amount of change in pain threshold could be predicted by both the strength of the cortisol response

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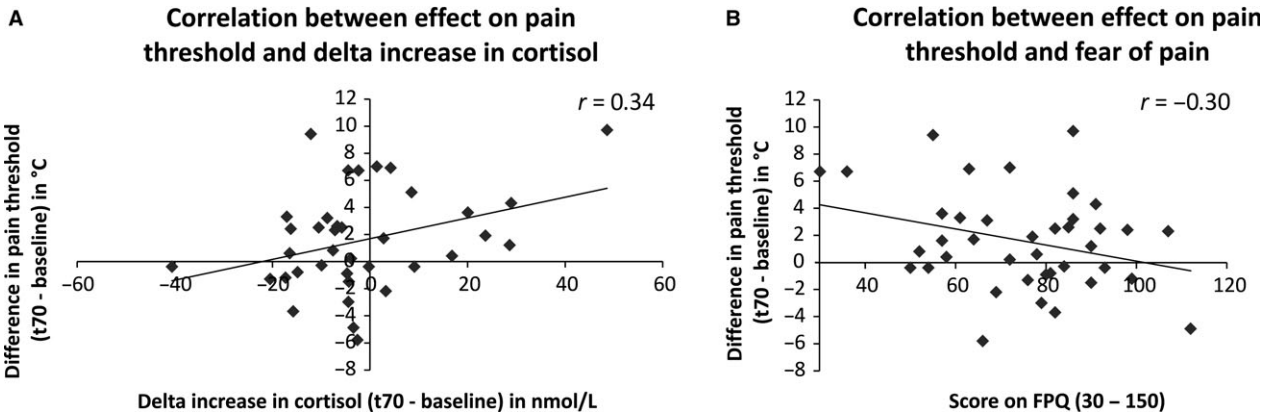

Figure 4 Correlations with the effect of stress on pain thresholds. Presented are correlations between the pain threshold difference t_{70}–$t_{baseline}$ and delta cortisol (A), fear of pain (B). Note that relevant statistics on outliers and influential cases has been checked.

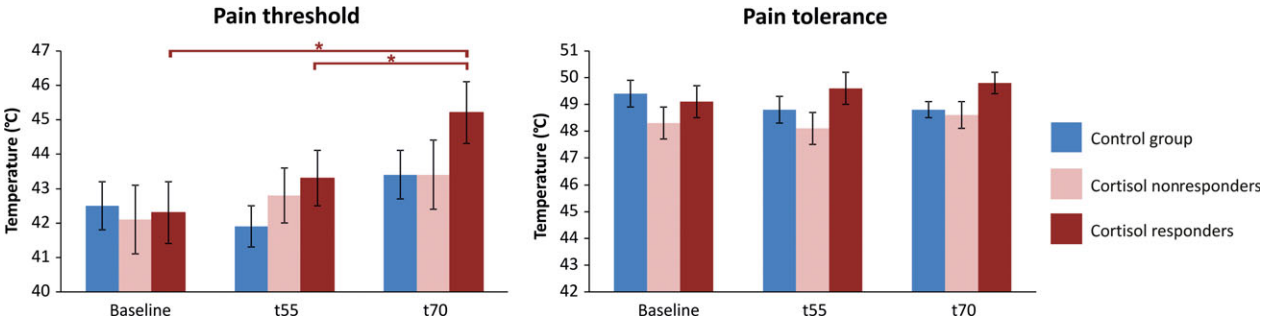

Figure 5 Hypothalamus–pituitary–adrenal axis effects on pain threshold and pain tolerance levels. Presented are pain threshold and pain tolerance levels per cortisol responder group and per time point. Presented are estimated marginal means and standard errors (SE). Note that the main effect of time on pain thresholds was only significant in the cortisol responders, and not in both other groups.

(higher cortisol increase was associated with higher pain threshold increase) and by fear of pain (lower fear of pain was associated with higher pain threshold increase). Taken together, we observed a hypoalgesic effect of acute stress, predicted by the cortisol response and fear of pain.

Our aim was to separate effects associated with the fast autonomic (sympatho-adrenal medullary or SAM) stress system from those associated with the slower hypothalamus-pituitary-adrenal (HPA) axis stress system. Although no absolute separation of multi-faceted stress responses is possible, our data support the relative separation of stress responses into two time windows, which is in accordance with the suggested different time scales of the three major stress mediators (Joëls and Baram, 2009). Specifically, self-reported and autonomic stress responses predominated the first time window, while the cortisol stress response predominated the second time window (when the autonomic system had already normalized). Our findings reveal specific involvement of the HPA axis stress system, and no effects related to the SAM stress system. First, the effects on pain thresholds were observed only within the presumed HPA axis time window, 15 min after stressor offset; when blood pressure and self-reported stress were already normalized. We should note here that this effect was revealed by planned comparisons per group and subsequent Bonferroni-corrected post hoc comparisons, while the interaction effect failed to reach significance. No increases in pain thresholds were observed on a group level in the presumed SAM time window, directly after stressor offset, indicating the specificity of our findings instead of reflecting a general effect of a painful manipulation or emotional distress. Correlation and regression analyses, nevertheless, showed that trait anxiety and sex predicted increases in pain thresholds in this time window: lower trait anxiety and being male was associated with more stress-induced hypoalgesia. Second, the effect on pain thresholds was only present in participants who responded to acute stress

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with a cortisol response – the output of HPA axis activation (revealed by planned comparisons). Third, the magnitude of the pain thresholds effect in the presumed HPA axis time window was predicted by cortisol increase – the greater the change in cortisol, the greater the change in pain thresholds. Increase in blood pressure or subjective stress did not correlate with the pain threshold effect, nor did any of the self-reported measures concerning the stress manipulation – not in the SAM nor in the HPA axis time window.

The observed chief role for the HPA axis in this study is in line with previous studies (McLean et al., 2005; Vachon-Presseau et al., 2013a; Sudhaus et al., 2015; Sveinsdottir et al., 2016). For instance, Vachon-Presseau et al. (2013a) found that participants showing a greater cortisol response reported less pain unpleasantness and showed reduced activation in several brain regions during the painful stimulus. These regions, including the nucleus accumbens, mid-cingulate cortex and posterior insula, are involved in cognitive modulation of pain and interact with the descending inhibitory pain pathway, mediating stress-induced hypoalgesia (Butler and Finn, 2009). However, other studies reported contrasting data (al'Absi and Petersen, 2003; Yilmaz et al., 2010; Muhtz et al., 2013; Fischer et al., 2016). al'Absi and Petersen (2003) showed that blood pressure but not cortisol was predictive of the stress effect on pain ratings. It should be noted here that their design was quite different from ours. They used the CPT as a pain stimulus where pain ratings were recorded every 15 s during a 90-s immersion in combination with social stress. Moreover, their pain induction procedure also resulted in cortisol increases, making it difficult to separate effects of the pain and stress induction. In addition, the outcome measures differ in an important manner. Our outcome measure was the *temperature* at which heat stimuli start to become painful, while al'Absi and Petersen (2003) recorded pain *ratings* during a sustained pain induction. As blood pressure and self-reported stress both peak directly after stressor offset, it is conceivable that they affect the concurrent self-reported intensity. Although we observed increases in pain thresholds directly after the MAST, these were not significant. Also, we did not find any correlations between blood pressure increase and pain thresholds, nor with self-reported pain intensity. Future studies employing different ways of inducing and quantifying pain that allow explicit comparisons will have to shed more light on this.

It is well-known that fears and cognitions towards pain are important modifiers of the pain experience, generally amplifying pain intensity (Tang and Gibson, 2005; George et al., 2006; Hirsh et al., 2008). Also, pain-related fear plays a major role in chronic pain (Vlaeyen et al., 1995; de Jong et al., 2011; Zale et al., 2013) and is a main predictor of pain-related disability (Crombez et al., 1999). Interestingly, our data showed that in healthy participants, higher levels of fear of pain and trait anxiety were associated with weaker or absent stress-induced hypoalgesia, suggesting a disadvantage. Note that fear of pain and trait anxiety levels did not correlate with pain sensitivity at baseline. Our findings further highlight the importance of interactions between anxiety and pain-related fears, pain sensitivity and the stress response. It has been suggested before that acute stress might facilitate the acquisition of pain-related fear and that stress during extinction could hamper the efficacy of extinction of pain-related fear (Elsenbruch and Wolf, 2015). Additional studies are needed to further disentangle these interactions, investigate this effect in a clinical sample, and the implications for chronic pain and its treatment.

Our study showed a hypoalgesic effect of stress on pain sensitivity, by showing increased heat pain thresholds after an acute stress induction. Such an effect can be considered adaptive – the minimum intensity that is perceived as painful is higher, enabling organisms to focus on either fight or flight. No effect was found on heat pain tolerance, indicating this stress-induced hypoalgesic effect is specific for thresholds. It should be noted that we cannot fully exclude the possibility that effects on pain thresholds and pain tolerance were due to differential baseline temperatures across the procedures. However, we verified that within each procedure, the baseline temperature did not affect the outcome, making it unlikely that baseline temperatures could explain our effects. Differential modulation of thresholds versus tolerance was also revealed by a recent meta-analysis, showing that heat pain thresholds, but not tolerance, were subject to age-related changes (Lautenbacher et al., 2017). Our finding that the pain threshold effect is underlain by the HPA axis, and that the strength is correlated with HPA axis reactivity, has important implications, as there are numerous studies showing HPA axis dysfunctions in chronic pain. It has been shown that people with chronic low back pain have higher basal levels of cortisol (Vachon-Presseau et al., 2013b), higher cortisol awakening responses (CAR; Sveinsdottir et al., 2016), and that stressful events are

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linked to pain exacerbations (Lampe et al., 1998). In contrast, other studies have found lower baseline cortisol levels in these patients (Muhtz et al., 2013) and normal cortisol reactivity to stressors (Vachon-Presseau et al., 2013a). Despite mixed results, it has been suggested that a dysfunctional stress system is an important etiological risk factor for chronic pain (Woda et al., 2016). Indeed, our findings suggest that individuals with no or low HPA axis reactivity and/or high levels of fear of pain are less likely to benefit from this adaptive response to acute stress. In clinical practice, it might be of added value to assess – in addition to psychosocial factors – patients' stress reactivity, and to take stress (reactivity) into account when designing therapeutic strategies.

There are several considerations worth discussing. One major consideration is the potential effect of habituation. Repeated exposure to the heat probe could have caused habituation of the skin and hence increased pain thresholds. We indeed found that every third trial in a row was higher compared to the second trial (i.e. the first of the three trials was discarded, the second and third were averaged to obtain the threshold and tolerance levels). However, this effect was similar across groups and time points[6] and absent for pain tolerance, making it an unlikely explanation for the observed effects. Furthermore, components of our stress induction (i.e. CPT) were experienced as unpleasant and slightly painful. However, the CPT and heat pain levels were not assessed on the same location, nor at the same time. In addition, subjective pain ratings of the stress induction were not associated with the pain threshold effect, while cortisol increases were. Regardless, it is impossible to fully separate the effects of stress and the effects of pain. It would be interesting, furthermore, to assess heat pain levels during the CPT (i.e. as in conditioned pain modulation) to investigate the effect of acute stress on endogenous hypoalgesia. Also, we should note that all sessions took place in the morning, in which cortisol levels are known to fluctuate. It is unlikely, however, that cortisol awakening responses (CAR) influenced our findings, as the CAR lasts 30–45 min following awakening (Pruessner et al., 1997; Wilhelm et al., 2007) and our participants reported adherence to our instructions to be awake for at least 2 h prior to the experiment. Also, baseline cortisol levels were similar to levels at the end of the experiment, making it unlikely that morning cortisol fluctuations biased our results. Lastly, the effects – although robust in the sense that they point in the same direction from several perspectives, using different analyses – were relatively subtle. Our planned comparisons confirmed the hypothesis of differential effects across groups showing medium to large effect sizes, but interaction effects did not reach significance, most likely due to power issues. The small effects might be partly due to the fact that we choose to include only women that are on oral contraceptives, which are known to blunt the cortisol response (Kudielka et al., 2009). Note that this could have also posed a selection bias. Future studies could consider including women in the luteal phase of their menstrual cycle. Lastly, future research may opt for larger samples, which would provide a unique opportunity to investigate the impact of sex on stress-induced changes in pain experience.

In conclusion, we show that a powerful acute stress induction – that included noxious, cognitive and social stressors – induced increased heat pain thresholds in healthy participants. The results highlight the importance of taking into account interactions between pain-related fears, pain sensitivity and stress responses. Finally, our findings suggest that the HPA axis – and not the autonomic – stress response specifically underlies this stress-induced hypoalgesic effect, having important implications for clinical states with HPA axis dysfunctions.

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Author contributions

I.T., A.K., C.Q., E.B., T.S., J.J. performed conception and design, interpretation of data, revising the article and final approval of the version to be published. I.T. performed acquisition of data, analysis of data and drafting the article.

Notes

[1]Overall, self-reports were in the expected ranges: at $t_{baseline}$ intensity of the heat pain threshold temperature was scored on average 3.5 (SE .4), and the heat pain tolerance temperature as 6.8 (SE .5). Fear related to the heat-stimulus was scored on average 1.1 (SE .3) for heat pain thresholds and 4.1 (SE .6) for pain tolerance temperatures.

[2]Note that there was no main effect of baseline temperature on subsequent pain threshold or pain tolerance, nor did it interact with Group [all $p's > .1$].

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[3]At t_{10}, the groups differed [$F_{1,37} = 6.86$, $p = 0.01$] with the stress group showing higher MAP compared to control group. At t_{45}, this difference was no longer present [$F_{1,37} = 1.61$, $p = 0.21$]. No other interaction effects were found, and hence, baselines were averaged. [PANAS: $F_{1,37} = 3.12$, $p = 0.09$; pulse [$F_{1,37} < 0.01$, $p = 0.99$; cortisol [$F_{1,34} = 0.69$, $p = 0.41$]

[4]One delta increase in cortisol value was replaced with +2 SD from the mean.

[5]The three groups did not differ in cortisol at baseline and did not differ in any of the baseline characteristics [all p's > 0.05], except for a borderline significant effect of sex [$\chi^2_{1,\ N\ =\ 37} = 5.89$, $p = 0.05$]. There was no effect of Group (cortisol responders, cortisol nonresponders) on Subjective stress [stress – $F_{1,18} = 0.25$, $p = 0.62$; pain – $F_{1,18} = 2.39$, $p = 0.14$; unpleasantness: $F_{1,18} = .58$, $p = 0.46$], difference in negative affect [PANAS: $F_{1,18} = 0.09$, $p = 0.77$], difference in MAP [$F_{1,18} = 0.90$, $p = 0.35$] or difference in pulse [$F_{1,18} = 0.11$, $p = 0.75$].

[6]Analyses showed that for pain thresholds there was only an effect of Trial (trial 2, trial 3): values were higher in the third trial compared to second trial [Trial: $F_{1,37} = 10.62$, $p = 0.002$]. The trial effect did not interact with group or time [Trial × Group: $F_{1,37} = 0.96$, $p = 0.33$; Trial × Time: $F_{1.8,66.8} = 1.46$, $p = 0.24$; Trial × Time × Group: $F_{1.8,66.8} = 2.21$, $p = 0.12$].

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