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Stress and thermoregulation: Different sympathetic responses and different effects on experimental pain

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ABSTRACT

Stress and thermoregulation both activate the sympathetic nervous system (SNS) but might differently affect pain. Studies investigating possible interactions in patients are problematic because of the high prevalence of SNS disturbances in patients. We therefore analyzed the influence of these different sympathetic challenges on experimentally-induced pain in healthy subjects. SNS was activated in two different ways: by mental stress (Stroop task, mental arithmetic task), and by thermoregulatory stimulation using a water-perfused thermal suit (7 °C, 32 °C, or 50 °C). Attentional effects of the mental stress tasks were controlled by using easy control tasks.

Both, stress and thermoregulatory stimuli, robustly activated SNS parameters. However, the patterns of activation were different. While stress co-activated heart rate, blood pressure, peripheral vasoconstriction and sweating, thermal stimulation either increased blood pressure (cold) or heart rate and sweating (warm). Only stress was able to induce a significant reduction of pain. The control tasks neither activated the SNS nor altered pain perception.

Our results suggest that (1) different patterns of sympathetic activation can be recorded after stress and thermoregulatory challenges and (2) that only stress is able to interfere with sensation of experimental pain. Whether SNS activation is causally responsible for analgesia needs to be further investigated.

1. Introduction

Pain is not a pure sensory phenomenon as the awareness of pain and the reaction to pain comprises motor, behavioural and in particular sympathetic nervous system (SNS) responses (Manning, 2004). The reverse connection, whether sympathetic challenges affect pain, is far less clear. The most important SNS challenges in daily life are stress and thermoregulation. While chronic stress is undoubtedly associated with chronic pain (Martinez-Lavin et al., 2002; Okifuji and Turk, 2002; Nilsen et al., 2007), the effects of short term SNS stimuli or thermoregulation on pain and nociception are still to be exactly determined. Animal studies suggest that stress induces analgesia (Weiss et al., 1986). Most human studies examining such interactions have utilized samples of patients with chronic pain, such as neck pain (Westgaard, 1999; Holte and Westgaard, 2002), headache (Bansevicius and Sjaastad, 1996; Bansevicius et al., 1999; Leistad et al., 2006), or fibromyalgia (Bansevicius et al., 2001). The results were inconsistent (Martinez-Lavin et al., 2002; Okifuji and Turk, 2002). This is not surprising since in patients with chronic pain (Rubin et al., 1985; Baron and Janig, 1998; Mosek et al., 1999) disturbances of the recruitment pattern of SNS functions are frequently prevalent (van Denderen et al., 1992; Martínez-Lavin et al., 1997; Cohen et al., 2000, 2001; Torpy et al., 2000). Therefore, chronic pain patients may be not ideally suited to investigate whether SNS stimuli are associated with amplification or suppression of pain perception.

Studies in healthy subjects exposed to experimental pain seem more appropriate to address this issue. Capsaicin-induced pain in skin and muscle was investigated before. Effectively startling subjects activates the SNS and suppresses capsaicin-evoked pain (Drummond et al., 2001), while different experiments have shown that thermoregulatory SNS activation has no effect in this pain model (Baron et al., 1999; Wasner et al., 2000, 2002).

In the current investigation, which was conducted to dissect similarities and differences of the two modes of sympathetic activation, we applied both stimuli in the same experimental setting in order to compare them directly. Stress-induced SNS activation was achieved by the Colour-Word Interference Test (CWT) (Stroop, 1935) and mental arithmetic (Bonelli, 1982; Hoshikawa and Yamamoto, 1997; Seraganian et al., 1997; Nazzaro et al., 2005; Boutcher and Boutcher, 2006). For thermoregulatory-induced SNS

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activation, a thermal suit was used, perfused either with warm or cold water (Wasner et al., 2000; Baron et al., 2002). Not only the way of SNS-activation but also the way of experimental nociceptive stimulation might be critical. Acute painful stimulation induces stress-related SNS activation and could interfere with possible pain modifying task effects. Capsaicin-induced pain is short but intense. Consecutively, SNS activation might be high and mask the modulation of pain by additional SNS stimuli (Geber et al., 2007). Therefore, we used the tonic electrical current C-fiber stimulation which induces less activation of the SNS (Koppert et al., 2003). This pain model provides reproducible results and its validity has been demonstrated in experimental (Geber et al., 2007) and interventional studies (Koppert et al., 2005).

The results of our experimental approach show that SNS recruitment pattern is quite different between stress and thermoregulation, and they support stress-related but not thermoregulatory-related pain modulation in healthy subjects.

2. Subjects and methods

2.1. Subjects

For stress-induced SNS activation, we examined 15 young healthy volunteers (9 men; median age 24 years; range 22–29 years); ten subjects completed both mental stress tasks, additional five only the CWT (see below). For thermoregulatory-induced SNS activation a second group of 10 male volunteers was tested (median age 31 years; range 22–35 years). None of them had a history of autonomic diseases (e.g. diabetes mellitus) or was on medication with potential influences on the SNS. Moreover, there was no evidence of arterial hypertension in any subject. All participants abstained from smoking and drinking coffee on the day of investigation. Informed consent was obtained from all subjects and the study adhered to the tenets of the Declaration of Helsinki. Our study was approved by the Rhineland-Palatinate ethics committee.

2.2. Experimental

Volunteers rested in a supine position for at least 30 min prior to the investigation. All investigations were performed in a temperature (24 °C) and humidity (50% relative humidity) controlled lab. At the end of the acclimatisation period, skin temperature was measured at the finger tips using an infrared thermometer and was found to be above 30 °C in all subjects.

2.3. Pain stimulation

Electrical painful stimulation was applied at the right frontal lower leg in the middle between ankle and knee. A stainless steel needle (25 gauge) was inserted intracutaneously at a length of 0.5 cm. A surface electrode (0.5 × 0.5 cm) was attached directly above and served as anode (Kramer et al., 2003). For electrical stimulation we used a constant current stimulator (Digitimer, Model DS 7a, UK). In the mental stress tasks, electrical current was increased in steps of 5 mA every 5 min up to 30 mA, or until subjects reported constant pain of between 4 and 5 of 10 on an eleven step rating scale for 5 min. Frequency (1 Hz), duration (0.5 ms) of impulses and current after adjustment were kept constant for the whole experimental period. During the experiment, pain rating was assessed every minute on a 10 cm visual analog scale with left anchor "no pain" to right anchor "most intense pain imaginable", and every two minutes when a task was performed.

In order to investigate the effect of stress-induced SNS activation on pain, ratings were assessed directly before and after each task. To assess thermoregulatory-induced SNS effects on pain perception, rating was obtained every 5 min throughout the electrical stimulation (see below).

2.4. Stress-induced SNS activation

In our study, the Colour-Word Interference Test (CWT) was automatically paced. Colour words written in different colours (interferent condition) were presented on a PC screen every 1.2 s (50 pictures per minute) and the subjects had to indicate the colour of the presented word (instead of its meaning). The percentage of correct responses was recorded using a keyboard. Under the same condition, subjects were presented a congruent version of CWT (i.e. colours were identical to the presented words) to control for the effects of general task-specific attentional shifts.

In the mental arithmetic task, subjects had to perform multiple-choice (four possible solutions) mathematical subtraction problems (e.g. 5023–78), which were visually presented. Subjects were instructed to respond verbally as quickly as possible. Similar to CWT, we additionally presented simple calculations (e.g. 7–3) to control for general attentional effects.

The stress tasks were presented in a randomised balanced order. The duration of each task was exactly two minutes. Between the tasks was a rest period of at least three minutes.

2.5. Thermoregulatory-induced SNS activation

Thermoregulatory-induced SNS activation is a tonic process. Subjects lay in a thermal suit with a variable temperature of the perfusing water. All experiments were performed three times (neutral, cold, warm), each on a separate day. The temperature of the water circulating in the suit was 32 °C during a 30 min baseline period. Temperature was kept at 32 °C for another 40 min (neutral condition), or was cooled to a temperature of 7 °C within 10 min (body cooling) (Baron et al., 1999). For the warming session, temperature was increased to 50 °C within 10 min (body heating) (Wasner et al., 2000). Target temperature was kept constant for 30 min. Thereafter, pain stimulation – as described above – commenced. Current was increased up to 20 mA within 15 min and then kept constant for another 20 min. Pain was rated every 5 min.

2.6. Sympathetic activation parameters

Cardio–vascular parameters (blood pressure and heart rate) were registered with a Finometer® and processed with a dedicated software package (Finapres Medical Systems BV, Amsterdam, The Netherlands).

Sweating was measured using quantitative hygrometry. In brief, sweat capsules were affixed to palms (for emotional sweating) or on hairy skin to volar forearm (for thermoregulatory sweating) and constantly streamed by dry nitrogen. Humidity was measured downstream by capacitance hygrometry. Curves were integrated for quantification; the area under the curve (AUC) for baseline was defined as zero. The respective period was computed and compared to the AUC of baseline and in a second step to the AUC of the control condition (Birklein et al., 1997).

Peripheral vasoconstriction was determined by measuring skin blood flow at the fingertips of the index finger, employing the single point mode of a Laser Doppler Imager (LDI, Moor Instruments Limited, London, UK) as previously described (Eicke et al., 2004). In order to avoid movement artefacts, the forearm was fixed in a splint. Sampling frequency of the LDI was 20 Hz, time constant was set to 0.1 s, and distance to skin was 50 cm. Laser signals were further processed using dedicated software (moorLDI SPM 3.01; Moor Instruments, London, UK) and expressed as flux values (FV).

As all parameters of sympathetic activation underlie physiological fluctuations, the period of task performance (120 s) was preceded by a baseline period (30 s) before each task. Mean values were computed for both periods. For thermoregulation, we calculated mean values during thermoregulatory stimulation (warm, cold, neutral) and during a baseline period (30 min, 32 °C).

2.7. Statistical analysis

2.7.1. Stress-induced SNS activation

For analysis of pain ratings and activation of SNS parameters by the emotional stress tasks, we defined a 2×2-ANOVA design with repeated measurement on the factors "stress" (stressful vs non-stressful) and "time" (parameters during baseline vs during task). Concerning CWT, "stressful" refers to the interferent version, "non-stressful" to the congruent task. For mental arithmetic, "stressful" refers to the difficult mental arithmetic task, "non-stressful" to the easy mental arithmetic task.

Since we found a significant interaction "stress × time" on pain in the primary analysis, the effect of SNS-activation on pain reduction was estimated using an ANCOVA with SNS activation parameters (heart rate, vasoconstriction, blood pressure, emotional sweating) as covariates in a subsequent analysis of pooled data for stressful CWT and mental arithmetic.

2.7.2. Thermoregulatory SNS activation

For pain ratings and thermoregulatory-induced SNS activation, we applied a 3×2-ANOVA design on the factors "thermoregulatory state" (cold, neutral, warm) and "time" (baseline vs stimulation).

In both models, the dependent variables were heart rate (in beats per minute, bpm), systolic and diastolic blood pressure (both in mmHg), the area under the curve (AUC in V*s) for emotional/thermoregulatory sweating, and skin blood flow (in flux values, FV).

Greenhouse-Geisser Epsilon was used to correct possible lacks of sphericity. Bonferroni-Correction was applied to adjust for multiple comparisons. Statistical significance was considered for $p < 0.05$. All statistical procedures were calculated using SPSS 13.0 for Windows.

3. Results

3.1. Stress-induced SNS activation

3.1.1. Pain ratings

Pain was reduced after performance of CWT as compared to baseline, indicated by the significant effect of "time" ($F_{1/14} = 20.29$, $p < 0.001$), which was pronounced during interferent CWT (interaction "stress x time": $F_{1/14} = 5.09$, $p < 0.05$). In detail, pain was reduced by 0.84 cm VAS during interferent CWT (from

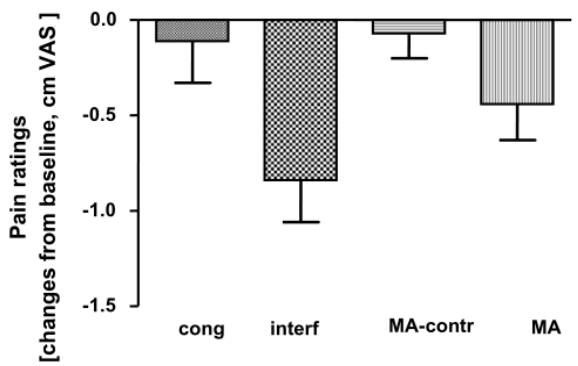

Fig. 1. Mean and SEM reduction of subjective pain ratings after performance of emotional stress tasks are presented. cong/interf: congruent/interferent version of CWT; MA-contr/MA: "non-stressful" control task for mental arithmetic/"Stressful" mental arithmetic task.

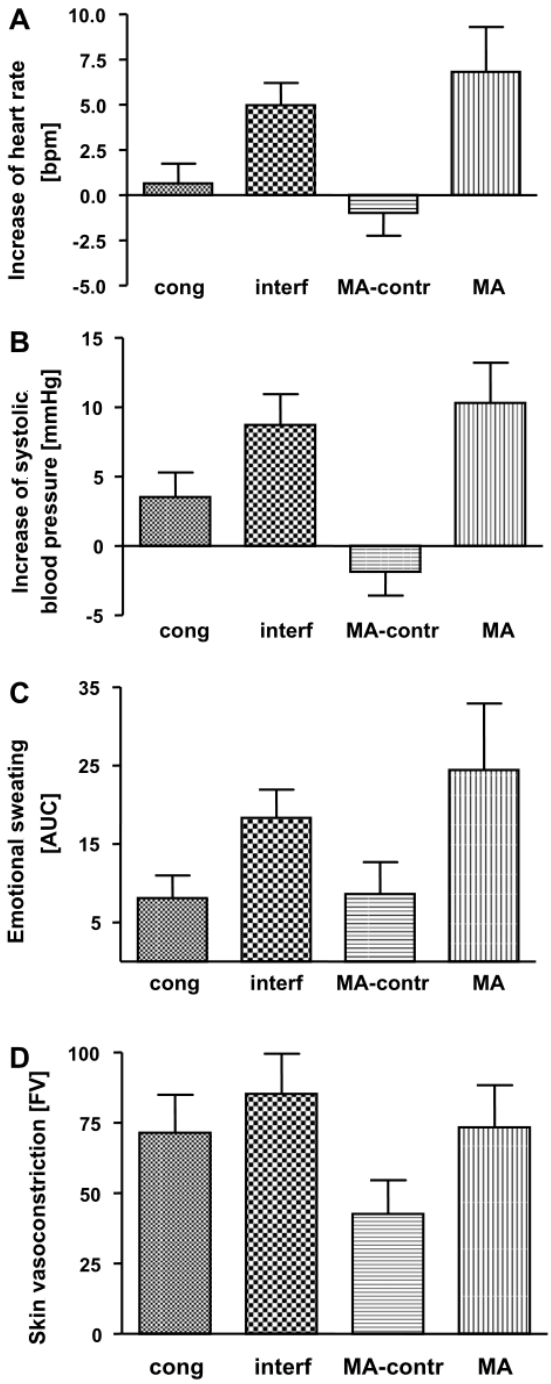

Fig. 2. All data present mean and SEM of sympathetic parameters (differences during task performance and baseline). (A) Increase of heart rate during stress task performance. (B) Increase of systolic blood pressure during stress task performance. (C) Emotional sweating expressed as area under the curve (AUC). (D) Skin vasoconstriction. cong/interf: congruent/interferent version of CWT; MA-contr/MA: "non-stressful" control task for mental arithmetic/"Stressful" mental arithmetic task.

3.89 to 3.05 cm VAS) and by 0.11 cm VAS during congruent CWT (from 3.6 to 3.49 cm VAS). Baseline pain ratings did not differ significantly between both tasks.

The significant effect of "time" on pain ratings during mental arithmetic ($F_{1/9} = 32.8$, $p < 0.001$) displays reduced pain when performing these tasks. The interaction of "stress × time" furthermore indicates a stronger reduction of pain during performance of the stressful mental arithmetic task. In summary, pain was reduced by 0.44 cm VAS during stressful mental arithmetic (from 3.81 to 3.37 cm VAS) and by 0.07 cm VAS during easy mental arithmetic (from 3.25 to 3.18 cm VAS). Baseline pain ratings did not differ for stressful as compared to the easy task. Differences to baseline are presented in Fig. 1.

3.1.2. Sympathetic activation parameters

3.1.2.1. Heart rate. For CWT, ANOVA showed a significant effect of "time" on heart rate ($F_{1/14} = 7.2$, $p < 0.05$). This effect was pronounced in the interaction "stress × time" ($F_{1/14} = 19.42$, $p < 0.001$), indicating that heart rate increased during the interferent CWT (77.7 bpm) as compared to baseline (72.8 bpm), whereas heart rate was not altered during congruent CWT (74.8 bpm) and baseline (74.1 bpm).

For the mental arithmetic task, an effect of "stress" was found ($F_{1/9} = 9.42$, $p < 0.05$), indicating that the stressful mental arithmetic task increased heart rate compared to the easy task (stressful mental arithmetic: 78.8 bpm; easy mental arithmetic: 74.2 bpm). We also observed an effect of the interaction "stress x time" on heart rate ($F_{1/9} = 8.38$, $p < 0.05$). This interaction revealed an increase of heart rate during the difficult arithmetic task (82.2 bpm) as compared to baseline (75.4 bpm), whereas the easy task did not alter heart rate (easy mental arithmetic: 73.7 bpm; baseline: 74.7 bpm). Differences during task performance and baseline are presented in Fig. 2A.

3.1.2.2. Blood pressure. Systolic blood pressure significantly increased during CWT (from 126.1 to 132.3 mmHg; $F_{1/14} = 16.41$, $p < 0.001$) and similarly during mental arithmetic (from 133.1 to 137.37 mmHg; $F_{1/9} = 6.12$, $p < 0.05$).

For the mental arithmetic task, this effect was pronounced in the interaction "stress x time" ($F_{1/9} = 13.54$, $p < 0.01$), so that this effect can be attributed to the stressful mental arithmetic task (141.9 mmHg; baseline: 131.5 mmHg) but not to easy mental arithmetic (132.9 mmHg; baseline: 134.7 mmHg). The interaction "stress x time" for CWT marginally failed to reach significance ($F_{1/14} = 3.9$, $p = 0.068$).

Comparable changes were found for diastolic blood pressure (data not shown). See Fig. 2.B. for more details.

3.1.2.3. Emotional sweating. Emotional sweating was affected by the factor "stress" for performance of CWT ($F_{1/14} = 5.72$, $p < 0.05$). A stronger response of emotional sweating was found for interferent CWT (9.2 V∗s) as compared to congruent CWT (4.0 V∗s). Responses to the tasks (13.2 V∗s) were pronounced ($F_{1/14} = 29.39$, $p < 0.001$). A significant interaction "stress × time" ($F_{1/14} = 5.72$, $p < 0.05$) furthermore indicated that the induction of emotional sweating was stronger during interferent (18.3 V∗s) than during congruent CWT (8.1 V∗s).

Similar effects could be observed for mental arithmetic. The effect of "stress" on emotional sweating revealed that difficult mental arithmetic (12.22 V∗s) induced stronger emotional sweating than the easy task (4.3 V∗s) ($F_{1/9} = 8.48$, $p < 0.05$). Emotional sweating increased during mental arithmetic tasks (16.5 V∗s). Moreover, the significant interaction "stress × time" ($F_{1/9} = 8.48$, $p < 0.05$) showed a stronger induction of emotional sweating during difficult mental arithmetic (24.4 V∗s) as compared to the easy task (8.6 V∗s). Details are presented in Fig. 2.C.

3.1.2.4. Skin vasoconstriction. CWT induced significant vasoconstriction, resulting in reduction of skin blood flow from 211.3 FV to 133 FV ($F_{1/14} = 51.60$, $p < 0.001$).

Mental arithmetic induced vasoconstriction, which was pronounced during the difficult (139.3 FV) as compared to the easy

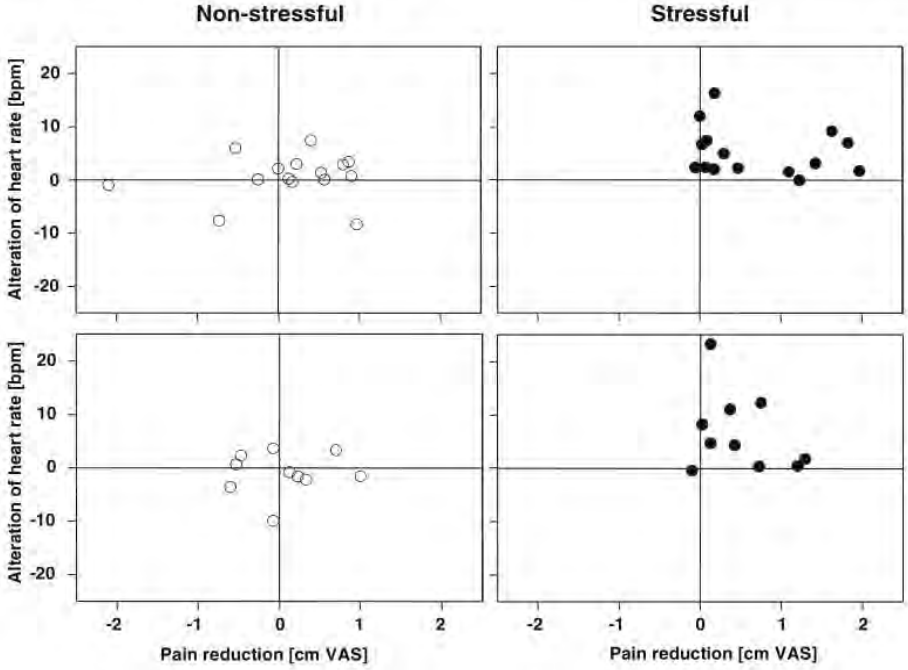

Fig. 3. Graphs represent scatter plots of pain reduction (positive values for reduced pain) and changes of heart rate from baseline during non-stressful (left half, open circles) and stressful tasks (right half, filled circles) for CWT (upper graphs) and mental arithmetic (lower graphs).

task (173.8 FV; $F_{1/9} = 17.56$, $p < 0.01$). However, vasoconstriction was significant as compared to baseline (185.6 FV) for both – stressful and easy task (127.6 FV; $F_{1/9} = 44.2$, $p < 0.001$). Details are presented in Fig. 2D.

3.1.3. Sympathetic responses and pain reduction

Subsequent Analysis of covariance (ANCOVA) for the stressful tasks revealed that only the acceleration of heart rate negatively co-varied with alteration of pain (2nd order effect, $F_{1/24} = 4.7$, $p < 0.05$) in a way that acceleration of heart rate negatively co-varied with pain reduction. Fig. 3 shows pain reduction and changes of heart rate during stressful and non-stressful tasks.

3.2. Thermoregulatory-induced SNS activation

3.2.1. Pain ratings

The mean pain rating across the whole experiment for all subjects and conditions was 3.6 cm VAS. We found a significant effect of "time" ($F_{1/9} = 110.00$, $p < 0.001$), but neither for "thermoregulatory state" nor for the interaction "thermoregulatory state × time". For details see Fig. 4.

3.2.2. Sympathetic activation parameters

3.2.2.1. Heart rate. Thermoregulatory stimulation significantly influenced heart rate ($F_{2/18} = 11.64$, $p < 0.001$): Heart rate increased during warm stimulation (75.4 bpm; baseline: 68.4 bpm) whereas no effect was found for neutral (68.3 bpm; baseline: 70.4 bpm) or cold (65.4; baseline 69.2 bpm) stimulation. Details are presented in Fig. 5A.

3.2.2.2. Blood pressure. Systolic blood pressure significantly increased during stimulation from 123.1 to 126.2 mmHg ($F_{1/9} = 5.23$, $p < 0.05$), especially during cold temperature from 121.8 to 135.7 mmHg ($F_{2/18} = 21.32$, $p < 0.001$). In contrast, warm stimulation decreased blood pressure (from 124.2 to 118.1 mmHg). Neutral stimulation did not alter blood pressure (from 123.3 to 124.7 mmHg). Comparable results were obtained for diastolic blood pressure (data not shown). For details see Fig. 5B.

3.2.2.3. Skin vasoconstriction. Significant differences in skin blood flow were found between thermoregulatory states ($F_{2/18} = 8.354$, $p < 0.05$). As expected, cold stimulation induced vasoconstriction whereas warm stimulation induced vasodilation compared to the neutral condition. Details are presented in Fig. 5C.

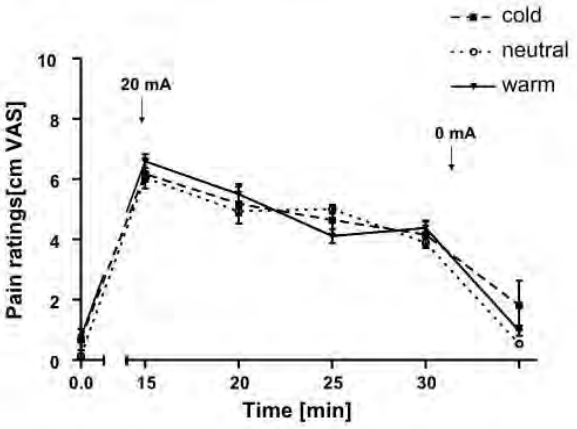

Fig. 4. Mean and SEM of pain ratings during electrical stimulation in neutral, cold, and warm thermoregulatory situation. Cold: water temperature 7 °C; neutral: water temperature 32 °C, warm: water temperature 50 °C.

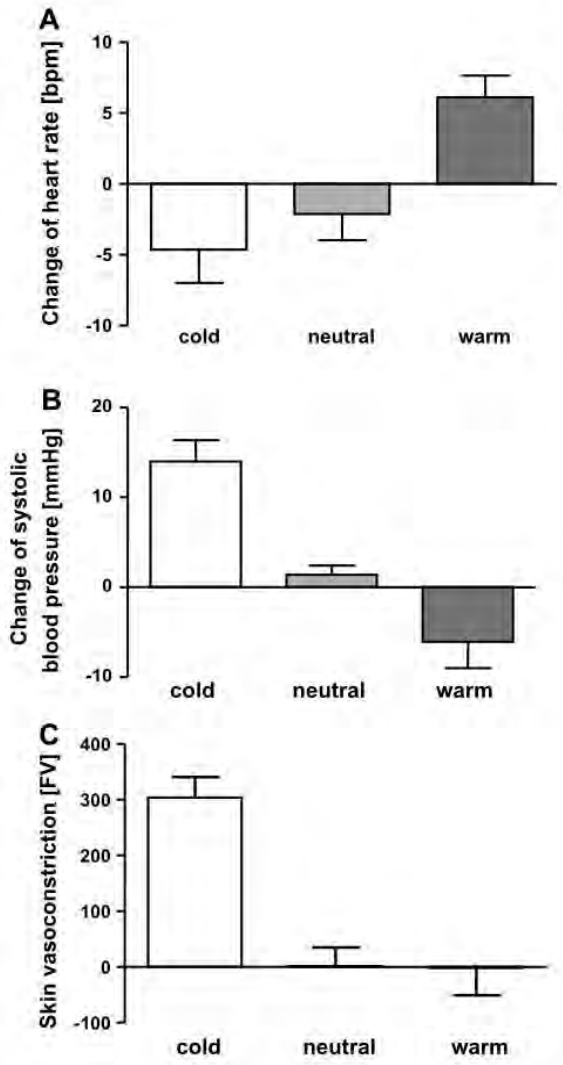

Fig. 5. All data present mean and SEM of sympathetic parameters (differences between thermoregulatory stimulation and baseline). A. Heart rate. B. Systolic blood pressure. C. Skin vasoconstriction. cold: water temperature 7 °C; neutral: water temperature 32 °C, warm: water temperature 50 °C.

3.2.2.4. Thermoregulatory sweating. Induction of thermoregulatory sweating was exclusively present during warm stimulation (541 V∗s; neutral and cold: 0 V∗s). This is underlined by the significant interaction "thermoregulatory state × time" ($F_{2/18} = 13.08$, $p < 0.001$). Neutral or cold stimulation had no effect on sweating.

4. Discussion

The results presented herein suggest that the SNS is activated by both, thermoregulatory and stressful tasks. However, thermoregulatory and emotional stressors profoundly differ in the activation pattern of the SNS (Critchley, 2005; Shibasaki et al., 2006). Our results furthermore suggest that stress and thermoregulation also differ concerning pain modulation: Only stress tasks interfered with ongoing experimental pain. Interestingly, the increase of heart rate is the only SNS activation read-out, which was associated with analgesia during stress. Our findings in healthy subjects conflict with patient studies showing that thermoregulatory chal-

lenges also modulate spontaneous and evoked pain (Baron et al., 2002). This might be explained by the various disturbances of the SNS and the afferent nervous system which are present in patients with chronic pain (Cohen et al., 2001; Cortelli and Pierangeli, 2003), differentially affecting pain perception and generation (Seminowicz and Davis, 2007; Tracey and Mantyh, 2007).

The association of SNS activation during stress tasks and analgesia in our study might be either

(a) causal, if SNS and analgesia are controlled by the same neuronal structures, most likely in the brain, or
(b) indirectly, mediated e.g. via baroreflex-induced changes in pain processing (Angrilli et al., 1997), or
(c) coincident, as a side-effect of any mechanism involved in stress-induced analgesia.

The fact that the cold thermoregulatory challenge increases blood pressure, which in turn activates baroreceptors as indicated by the decrease of heart rate, but which is not accompanied by pain reduction, almost completely excludes mechanism (b). Only the possibility that phasic (during stress tasks) and tonic (during cold stimulation) baroreceptor activation might have different impacts on pain (Edwards et al., 2008) might offer the alternative explanation.

Sympathetic activation by stress was associated with an increased cerebral blood flow in different subcortical and cortical areas (Critchley et al., 2000). Particularly, the anterior cingulate cortex and the amygdalae are involved in generating efferent activation of sympathetic responses, while the insula and the orbitofrontal cortex also subserve perception of autonomic arousal states (Critchley, 2005). These assumptions have been supported by lesion studies. For example, patients with lesions affecting the dorsal anterior cingulate regions showed blunted sympathetic responses to emotional stress (mental arithmetic task) even though cognition was unaffected (Cohen et al., 1999; Swick and Turken, 2002; Critchley, 2005; Fellows and Farah, 2005). This pattern of cortical activation during emotional stressful situations probably reflects a "top-down" control over midbrain and brainstem sympathetic centres including hypothalamus, periaqueductal gray, rostral ventral medulla and intermedio-lateral or intermedio-medial cell columns in the spinal cord, which finally mediates the autonomic responses (Saper, 2002; Critchley, 2005). Interestingly, these cortical areas involved in stress-induced sympathetic activation have also been described to be critical for pain perception and control of pain (Tracey and Mantyh, 2007). If future imaging studies indeed show that cortical activation, which is essential for SNS activation, could directly affect activity in pain modulating regions of the brain, the causal association (mechanism (a)) between SNS activation and analgesia would be supported. Unfortunately, such studies are presently lacking. If existent, such connections cannot be linear. Then, e.g. heart rate increase and analgesia should covary in a positive way – not inversely like in our study. Either these central interactions are more complex, or peripheral reflex counter reactions significantly modulate the SNS response.

In contrast to stress, the role of the cortex in thermoregulatory SNS activation is less defined. Thermoregulatory challenges reflect a "bottom-up" (starting in the periphery)-activation of sympathetic centres in midbrain and brainstem (Benarroch, 2007). Warm-sensitive (WS) neurons of the medial preoptic/anterior hypothalamic region are activated by an increase of core temperature. Inhibition of these neurons via input from dermal cold receptors is likely mediated by temperature-insensitive preoptic hypothalamic neurons. Activation of these WS neurons leads to compensatory heat loss via different yet unspecified pathways. The nucleus raphe pallidus is considered to be involved in mediating skin vasodilation and sweating by descending projections. Moreover, WS neurons tonically inhibit cold-responsive neurons in the dorsomedial nucleus of the hypothalamus, periaquaeductal gray and nucleus raphe (Nagashima et al., 2000; Benarroch, 2007; Romanovsky, 2007). The involvement of the hypothalamus and the lack of a critical involvement of the cerebral cortex have been affirmed in animal studies utilizing decerebrate cats, rabbits, and dogs (Chambers et al., 1974). Human functional imaging studies supported that changes of temperature mainly activate sympathetic centres in midbrain and brainstem (McAllen et al., 2006). Cortical regions (e.g. insula, anterior cingulate) are activated only to a much smaller extent than by stress (Egan et al., 2005). According to the arguments discussed above (mechanism (a)), it is therefore not astonishing that thermoregulatory challenges have no impact on pain. But however, thermoregulatory stimuli definitely activate the SNS, thus supporting mechanism (c), the co-incident but unspecific in-parallel recruitment of stress-related antinociception and SNS activation.

Weighing all arguments and based on the present results, we currently support mechanism (c) – unless undisclosed evidence for mechanism (a) will be presented in forthcoming imaging studies, which are highly recommended. Emotional and thermoregulatory sympathetic challenges both recruit regions in limbic cortex, midbrain and brainstem, and activate sympathetic peripheral effectors. Yet, it still remains undetermined, if activation of sympathetic outflow is necessary for pain suppression at all.

Another mechanism of pain suppression by stress tasks, which is unrelated to SNS activation, might be due to attentional shift from the painful stimulus towards the current stress task (Levine et al., 1982; Villemure and Bushnell, 2002). Using easy control versions of each task, we sought to control for attention as a confounding factor (Zysset et al., 2001). However, the more stressful tasks require more attention than easy control conditions, and especially than passive thermoregulatory challenges. It has been demonstrated that the capacity of human attention is limited (Saults and Cowan, 2007), which, however, is more relevant for stimuli within the same sensory modality than between different modalities as in our study (Duncan et al., 1997). Nevertheless, we cannot firmly exclude that attentional shifts away from the painful stimulus contributed to analgesia.

The last critical point is that pain itself is a strong stressor and thus activator of the SNS (Terkelsen et al., 2005; Leone et al., 2006; Sarzi-Puttini et al., 2006). However, this point should not critically interfere with our results because SNS activation during the stress tasks was robust and the extent of SNS activation was comparable to relaxed conditions (Fechir et al., 2008). This indicates a successful adjustment to the painful stimulus by the subjects in our experimental procedure.

In summary, our study shows that stress and thermoregulation robustly but differently activate the sympathetic nervous system, and that only stress-related SNS activation is associated with suppression of experimental pain whereas thermoregulatory stimulation is not. Although there are some arguments that stress-induced SNS activation and analgesia might be causally connected, based on the present findings it remains undetermined, if recruitment of SNS is necessary for analgesia at all. This question needs to be addressed in future studies – finally to develop new therapeutic approaches for pain control and prevention.

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