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Hypothalamic-pituitary-adrenal axis feedback sensitivity in different states of back pain

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ABSTRACT

Pain normally signals a threat to bodily integrity and causes emotional distress. Acute pain serves a protective function, yet, when pain turns chronic, the protective function is lost. A chain of psychophysiological alterations including changes in the stress regulation system, apparent in dysfunctional activity and responsivity of the hypothalamic-pituitary-adrenal (HPA) axis, might be an important factor in this context. Moreover, maladaptive responses may be complicated by affective comorbid symptoms such as anxiety and depression, and alter nociceptive processing. However, the relationship among pain chronicity, stress regulation, and contributing components of comorbid symptomatology as well as somatosensory profiles has rarely been examined. In the present study, we obtained diurnal cortisol profiles at baseline and feedback regulation (following a dexamethasone suppression test (DST)) in subacute (SABP) and chronic (CBP) back pain patients and healthy control individuals (HC). We also assessed anxiety, depression and chronic stress levels and used quantitative sensory testing (QST) to detect sensory abnormalities. We found a hyper-suppression of cortisol following DST and thus enhanced negative stress feedback sensitivity in SABP compared to both CBP and HC. In SABP, DST-related cortisol levels were negatively associated with pain intensity, mediated by cold pain thresholds and anxiety. These data support a stress model of pain chronicity and suggest that stress responses might be indicators of individual vulnerability in the transition period of subacute pain.

1. Introduction

The transition from acute to chronic pain has been associated with a number of peripheral and central physiological, psychological and psychosocial predictors, among them prominently also stress experience and stress reactivity (e.g., Flor, 2017; Vachon-Presseau, 2018). The activation of the hypothalamic-pituitary-adrenal (HPA) axis plays an important mediating role in the relationship between stress and pain (e.g., McEwen and Kalia, 2010). In acute pain, higher baseline cortisol levels are associated with lower pain reports (Al'Absi et al., 2002). Larger cortisol responses to a noxious stimulus have been related to higher acute pain tolerance (Edwards et al., 2003) as well as lower pain unpleasantness ratings (Vachon-Presseau et al., 2013). Moreover, exposure to acute non-noxious stress also leads to higher pain thresholds and tolerance as well as lower pain ratings, a phenomenon known as stress-induced analgesia or hypoalgesia, which has been found in both animal and human studies (Butler and Finn, 2009), and has been viewed as an adaptive mechanism enabling escape from danger. This hypoalgesia also applies to states of fear, which have been associated with predictable threat, whereas anxiety, which is related to uncontrollable and unpredictable stress, has been associated with hyperalgesia (Rhudy and Meagher, 2000). If hypo- or hyperalgesia ensues is also related to the severity of the stress response with higher stress magnitudes related to hyperalgesia and a lower stress response to hypoalgesia (Geva and Defrin, 2018).

However, the evidence from the literature is equivocal. There are several negative findings with respect to the action of cortisol on pain sensitivity in healthy individuals (e.g. Wingenfeld et al., 2015; Lautenbacher et al., 1999). In studies of chronic pain, elevated stress levels were found to be associated with several chronic pain syndromes (Vachon-Presseau, 2018), also highlighting an important role of HPA axis dysfunction (Griep et al., 1998). Both reduced cortisol stress responses and lower baseline levels have been observed, yet, also elevated levels of cortisol were reported (for a review see Vachon-Presseau, 2018) or abnormal variations in the diurnal cortisol profile and heightened feedback sensitivity of the HPA axis (Wingenfeld et al., 2007). Moreover, there are also some studies that reported no significantly different cortisol profiles in patients compared to healthy individuals (e.g., Sudhaus et al., 2007; Wingenfeld et al., 2008).

Despite these controversial findings, a majority of the studies lead to

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the assumption that the HPA axis, as a self-regulating negative feedback system, may be hyperactive in early stages of the pain chronicity process and may turn into an exhausted state of hypoactivity after pain persistence. This is underlined by findings in musculoskeletal pain conditions indicating that hypocortisolism may mediate the effect of stress on pain chronicity (McBeth et al., 2007), while early in the chronicity process, hypercortisolim may be present (Riva et al., 2012). In addition, reduced cortisol release in stress situations has been found to be associated with a higher risk for chronic musculoskeletal pain (Paananen et al., 2015). HPA axis function may thus be an important mediator in the development of chronic pain, yet, the nature of the association of HPA functioning with pain, including the direction (hyper- or hypoexpression) of cortisol secretion, is still unclear. It is important to differentiate between alterations in cortisol profiles as a baseline characteristic of various pain groups and the association between cortisol and the processing of painful and nonpainful stimulation (Nilsen et al., 2007).

Moreover, a number of factors can influence the association between cortisol expression and chronic pain. For example, comorbid depression (Ataoglu et al., 2003), and anxiety (Rhudy and Meagher, 2000) or chronic stress (Geva and Defrin, 2018) alter HPA axis function. The association of chronic pain and cortisol might be mediated by affective disorders (e.g. Wingenfeld et al., 2010). Thus, depression or anxiety may not only be a covariate, but can also act as a mediating factor.

Based on previous work on acute and chronic pain, we suggest that stress serves as a predisposing and modulating factor in pain chronicity. However, further experimental studies are needed to better characterize the stress response in this pain chronicity process and to elucidate risk and protective mechanisms as well as factors related to comorbid disorders. We hypothesized that patients with chronic back pain (CBP), subacute back pain patients (SABP) and healthy controls (HC) differ in their baseline cortisol profiles as well as feedback HPA axis responsivity. In the present study, we thus investigated diurnal and dexamethasone suppression test (DST) cortisol profiles in CBP, SABP, and HC to characterize HPA axis activity in different states of pain chronicity. Moreover, we assumed that psychological variables such as comorbid anxiety and depression should co-determine the cortisol and HPA axis related changes in the three groups. We also assumed that stress symptoms as well as additional pain variables like the degree of pain and somatosensory processing are important in this context. Therefore, we additionally assessed anxiety, depression, chronic stress, pain intensity, and sensory pain profiles of the patients. The natural course of back pain is a topic of controversy, yet, a mean conversion rate from acute to chronic of a minimum of 20% can be assumed. While some studies reported that only 5–10% go on to develop chronic pain (Shekelle et al., 1995), more recent studies described conversion rates of up to 75% (Costa et al., 2009). Our findings could therefore also be discussed in the context of risk and resilience for chronic back pain and might be useful for follow-up studies on the course of subacute back pain.

2. Methods

2.1. Participants

We investigated subacute back pain patients (SABP, N = 17; mean age = 45.17; 9 females), chronic back pain patients (CBP, N = 22; mean age = 44; 12 females) and healthy controls (HC, N = 30; mean age = 41.01; 16 females), matched for education (see Table 1 for sample description). The participants were recruited through flyers and newspaper announcements, online forums and in cooperation with general practitioners. All participants underwent the Structured Clinical Interview for DSM-IV (SCID-I; Wittchen et al., 1997), performed by a trained clinician, and were tested for both axis I and axis II mental disorders with special emphasis on the exclusion of current and past drug abuse.

The pain patients all complained of upper or lower or both upper and lower back pain. Criteria for subacute pain were pain lasting for 7–12 weeks or having several short pain episodes that did not exceed 3 months (based on Dionne et al., 2008; Chanda et al., 2011). Chronic back pain was defined by a minimum pain frequency of 3 times/week, lasting for more than 6 months. Chronic pain patients were thus characterized by longer-lasting pain, and we excluded patients whose pain was based on neurological problems. As treatment recommendations for chronic pain patients indicate pharmacotherapy, we did not exclude patients with psychotropic medication (which included medication for blood pressure regulation (N = 2), for pain treatment (ibuprofen, aspirin; N = 8) and for treatment of depressive symptoms (trimipramin, N = 1) in the present study), but used medication as a covariate in our analyses. Four of the chronic patients had a comorbid depressive disorder.

Exclusion criteria for all three samples were: age less than 18 or over 70 years, neurological complications, psychotic episodes, current drug abuse, left-handedness, major illness, pregnancy, a pacemaker or metal parts in the body.

The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University. The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Salivary cortisol sampling

Saliva samples were collected at the participants' home on 2 consecutive days using Salivette tubes (Sarstedt, Nümbrecht, Germany), immediately after awakening and 15, 30, 45, and 60 min later (cortisol awakening response; 6–8 am) as well as at 11am, 1 pm, 3 pm, and 6 pm (daytime profile). On the first day, cortisol levels were assessed without any pharmacological challenge (baseline day), on the second day, samples were obtained following the administration of 0.5 mg dexamethasone at 11 pm on the day after the baseline profile had been obtained (low dose DST/dexamethasone challenge; feedback day). We used a diary during the sampling period, where the participants entered information on sleep duration, food intake, and daytime activities. Moreover, self-reports were employed to verify sampling times. The sampling was performed at home and the participants were instructed to refrain from smoking, drinking (including caffeine intake), or eating 10 min and brushing their teeth 5 min before each sampling and to not perform sport activities on the sampling days.

Dexamethasone can also affect pain scores (Szucs et al., 2016). We therefore decided to use the low dose DST, which represents a valid measure of HPA axis responsivity (e.g., Isidori et al., 2003; de Kloet et al., 2006).

For the analyses, we used the absolute cortisol levels for each sampling point as well as summary indicators of cortisol with the area under the curve to the ground (AUCg) and to the increase (AUCi) (according to Pruessner et al., 2003) based on the following formulas:

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i)}{2}$$

$$AUC_I = AUC_G - m_1 \cdot \sum_{i=1}^{n-1} t_i$$

For the cortisol data of 2 healthy participants, we observed some small inconsistencies in the labeling and sampling diary, however, we decided to not exclude these two data sets since clear cut-offs are lacking, and their inclusion did not change the results.

Saliva samples were stored at −20 °C until analysis. Measurement of free cortisol levels was performed at the Institute of Biopsychology, Technische Universitaet Dresden, Dresden, Germany, using a commercially available immunoassay (IBL, Hamburg, Germany), and a quality

Table 1
Characteristics of the study populations.

	Chronic back pain patients (CBP)	Subacute back pain patients (SABP)	Controls (HC)	Group significances
Number	22	17	30	
Age, years; mean (SD)	44 (13.23)	45.17 (14.89)	41.01 (16.21)	
Sex female; number	12	9	16	
QST parameters				
Heat pain threshold (°C)	41.04 (3.47)	42.36 (3.15)	39.68 (3.27)	n.s.
Cold pain threshold (°C)	16.33 (8.67)	14.3 (7.92)	17.38 (8.03)	n.s.
Pressure pain threshold	3.75 (1.2)	4.58(2.02)	3.34 (1.41)	n.s.
Wind-up stimulus intensity	284.44 (82.79)	304 (103.2)	290.13 (88.51)	n.s.
MPI – pain intensity; mean (SD)	2.75 (1.5)	2.78 (1.89)	1.03 (2.24)	$p = 0.023$
Pain duration, years (with only short episodes (< 3 months) for SABP); mean (SD)	8.69 (6.62)[a]	1.67 (1.96)[a]	–	
Depression; sum (SD)	9 (3.23)	9.43 (3.79)	5.31 (1.05)	$p = 0.012$
Anxiety; sum (SD)	5.8 (4.21)	5.68 (3.92)	4.25 (2.31)	n.s.
Chronic Stress; mean (SD)	2.42 (1.19)	1.95 (0.9)	1.92 (0.89)	n.s.
Cortisol status; mean (SD)				
Cortisol awakening AUCg	351.27 (135.48)	371.65 (99.62)	396.05 (113.07)	n.s.
Cortisol daytime AUCg	76 (36.49)	81.2 (37.05)	94.3 (40.15)	n.s.
Cortisol awakening AUCi	209.11 (130.8)	235.81 (83.76)	265.37 (125.91)	n.s.
Cortisol daytime AUCi	35.13 (25.89)	34.76 (33.13)	49.92 (38.95)	n.s.
DST cortisol awakening AUCg	59.01 (34.45)	20.63 (9.48)	51.9 (37.8)	$p < 0.001$
DST cortisol daytime AUCg	42.25 (20.89)	32.74 (14.02)	35.23 (20.82)	n.s.
DST cortisol awakening AUCi	36.09 (26.47)	12.23 (8.36)	36.46 (30.28)	$p = 0.001$
DST cortisol daytime AUCi	30.1 (16.16)	27.73 (10.77)	23.92 (15.28)	n.s.
Cortisol awakening nmol/l	35 (15.75)	36.83 (11.43)	38.38 (14.8)	n.s.
Cortisol daytime nmol/l	9.09 (5.99)	9.76 (6.1)	11.03 (5.8)	n.s.
DST cortisol awakening nmol/l	5.78 (4.08)	2.03 (1.34)	5 (3.87)	$p = 0.027$
DST cortisol daytime nmol/l	4.53 (2.6)	3.6 (2.02)	3.9 (2.99)	n.s.

AUCg = area under the curve to the ground; AUCi = area under the curve to the increase; DST = dexamethasone suppression test.

[a] For the chronic back pain patients, the range of pain duration was 1.25–23,25 years; for the subacute back pain patients, the range of pain duration was 0.083–6.332 years. For those, who reported pain lasting longer than 7–12 weeks, pain occurs only at short episodes that did not exceed 3 months (range 1day/year – 33 days/year).

checked kit was performed. Intra- and interassay variabilities were below 10%.

2.3. Psychometric assessment

For the assessment of pain characteristics in SABP, CBP and HC, we used a structured interview and the West Haven-Yale Multidimensional Pain Inventory (MPI; German version; Flor et al., 1990). The MPI is a measure of several important dimensions of the chronic pain experience (Part I: pain intensity, pain-related interference, spouse support, perceived life control, affective distress; Part II: patients' perceptions of spouses' or significant others' responses to pain behaviors with the scales punishing, solicitous, distracting; Part III: frequency of engagement in everyday activities (household activities, leisure activities, activities outside the home)), with 52 items on a 0–6 rating scale. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS; Herrmann et al., 1995), and chronic stress was measured using a short version of the Trier Inventory of Chronic Stress (TICS; Schulz et al., 2004). The HADS consist of 14 items (7 items are computed as total score of depression, and 7 items are computed as total score for anxiety), with possible answers ranging from 0-3. A sum of 0–7 is treated as normal, 8–10 as borderline case, and 11–21 as abnormal case. The TICS measures chronic stress with a mean sore of six scales (work overload, worries, social stress, lack of social recognition, work discontent, and intrusive memories). The answers are recorded on a 0–4 rating scale, with a total number of 30 items.

To test our hypotheses, we used the mean score of the pain intensity scale from the MPI and of the TICS for chronic stress as well as the sum score of the anxiety and depression scales from the HADS. The data of 2 HC had to be excluded due to reports of pain.

2.4. Quantitative sensory testing

For the assessment of thermal cold and hot pain thresholds, mechanical pain sensitivity including thresholds for blunt pressure, and temporal pain summation to repetitive pinprick stimuli (wind-up like pain) we used a QST protocol according to the standardized battery of the German Research Network on Neuropathic Pain (DFNS; Rolke et al., 2006). The QST was developed to assess sensory changes in neuropathic pain, however, sensory abnormalities also occur in musculoskeletal pain disorders, including chronic back pain (e.g., Nijs et al., 2010).

For thermal stimulus application, we used a TSA 2001II (MEDOC, Israel) with a thermode contact area of 9.0 cm^2. All thresholds were obtained with ramped stimuli, with a baseline temperature of 32 °C (centre of neutral range) and cut-off temperatures of 0 and 50 °C. We calculated the mean threshold temperature of three consecutive measurements.

For the wind-up ratio, pinprick stimuli (256 mN Pinprick) were used and wind-up was defined as the temporal summation of suprathreshold painful stimuli, with the wind-up ratio calculated by the mean pain rating of five series of repetitive stimuli divided by the mean pain rating of the five single stimuli (Rolke et al., 2006). For the pressure stimuli, we used a pressure gauge device (FDN100, Wagner Instruments, USA) with a probe area of lcm^2 (probe diameter 1.1 cm; forces up to 10 kg/cm^2 or ~1000 kPa over the left forearm).

2.5. Data processing and statistical evaluation

Cortisol data were analyzed with pain status (HC, SABP, CBP) x cortisol awakening profile (time points 1–5) and x cortisol daytime profile (time points 6–9) repeated-measures analyses of variance (ANOVAs), for both the baseline and the feedback (DST) day (using mean levels and AUCg and AUCi). Day was not used as additional factor, as we did not expect a significant group x day interaction a

priori, but group differences for both the baseline and feedback profile.

We further investigated the association between the cortisol profiles and pain, and affective symptomatology, chronic stress-related subjective and QST measures depending on the status of pain chronicity (i.e. depending on differences between HC, SABP and CBP). For this, a mediation analyses (with PROCESS (written by Andrew F. Hayes, http://www.afhayes.com) under the Statistical Package for Social Sciences (SPSS) for Windows) was used for each of the samples, involving cortisol levels (mean values for baseline and feedback day) as predictors and pain intensity (mean values of the MPI pain intensity scale) as outcome, and anxiety and depression scores from the HADS, the TICS total score and the QST measures as mediators. We followed an ordinary least squares path analytic framework to estimate the moderation effects with bootstrap confidence intervals. For all statistical analyses, α was set to 0.05 (two-tailed), and the Greenhouse-Geisser adjustment was applied in the case of violation of the assumption of homogeneity of variances, and adjusted degrees of freedom were reported. Paired t-tests with Bonferroni adjustment were performed in the case of significant main effects or interactions.

The data were analyzed with the SPSS version 25.0 for Windows.

3. Results

3.1. Cortisol responses at baseline and feedback day

3.1.1. Mean cortisol levels

For the baseline day, we did not observe any significant effects (for the individual values see Table 1). For the feedback day, we found a significant main effect of pain status (HC, SABP, CBP) on the awakening cortisol response following DST ($F(2,43) = 4.367$, $p = 0.027$; see Fig. 1). Awakening cortisol responses were significantly reduced in SABP compared to both HC (block time points 1-5: $t(45) = 3.563$, $p = 0.001$; for the single time points during the awakening course see Fig. 1), and CBP (block time points 1-5: $t(38) = 4.594$, $p < 0.001$; for the single time points during the awakening course see Fig. 1). Although the ANOVA did not result in significant effects of the factor group for the daytime profile of the feedback day, in Fig. 1 and Table 1, we have also presented all the significant differences for each of the single time points following the DST (for an overview on the distribution of the cortisol data in each group see **Supplemental** Fig. 1).

3.1.2. Area under the curve

For the baseline day, we did not observe any significant group effects, neither for the awakening nor the daytime profile. For the feedback day, we observed a significant effect of group for the awakening AUC (AUCg: $F(2,63) = 9.087$, $p < 0.001$ (see Fig. 1); AUCi: $F(2,63) = 7.313$, $p = 0.001$), but not for the daytime AUC. For the awakening AUC, SABP showed significantly lower AUCs compared both HC (AUCg: $t(45) = 3.515$, $p = 0.001$; AUCi: $t(45) = 3.582$, $p = 0.001$) and CBP (AUCg: $t(38) = 4.729$, $p < 0.001$; AUCi: $t(38) = 3.947$, $p < 0.001$) (see Table 1).

3.2. Association of the feedback-related cortisol profile with pain intensity and cold pain thresholds

We observed a significant negative correlation of cortisol levels following DST (feedback day) and pain intensity ($r = -0.301$; $p = 0.033$), mediated by cold pain thresholds ($p = 0.04$) and anxiety ($p = 0.045$) only in SABP ; (see Fig. 2). DST cortisol levels and cold pain thresholds ($r = -0.298$, $p = 0.036$) and anxiety ($r = -0.152$, $p = 0.043$) were significantly negatively related.

We did not find any significant effects for depression or chronic stress and also no significant difference between the groups for the QST measures.

4. Discussion

The aim of the present study was to elucidate the relationship among different states of back pain, stress regulation, and contributing factors of anxiety, depression, and alterations in somatosensory and nociceptive processing. For SABP compared to both HC and CBP, we found reduced cortisol levels following DST. Moreover, in the SABP, cortisol levels were significantly correlated with pain intensity, and this correlation was mediated by cold pain thresholds and anxiety. These

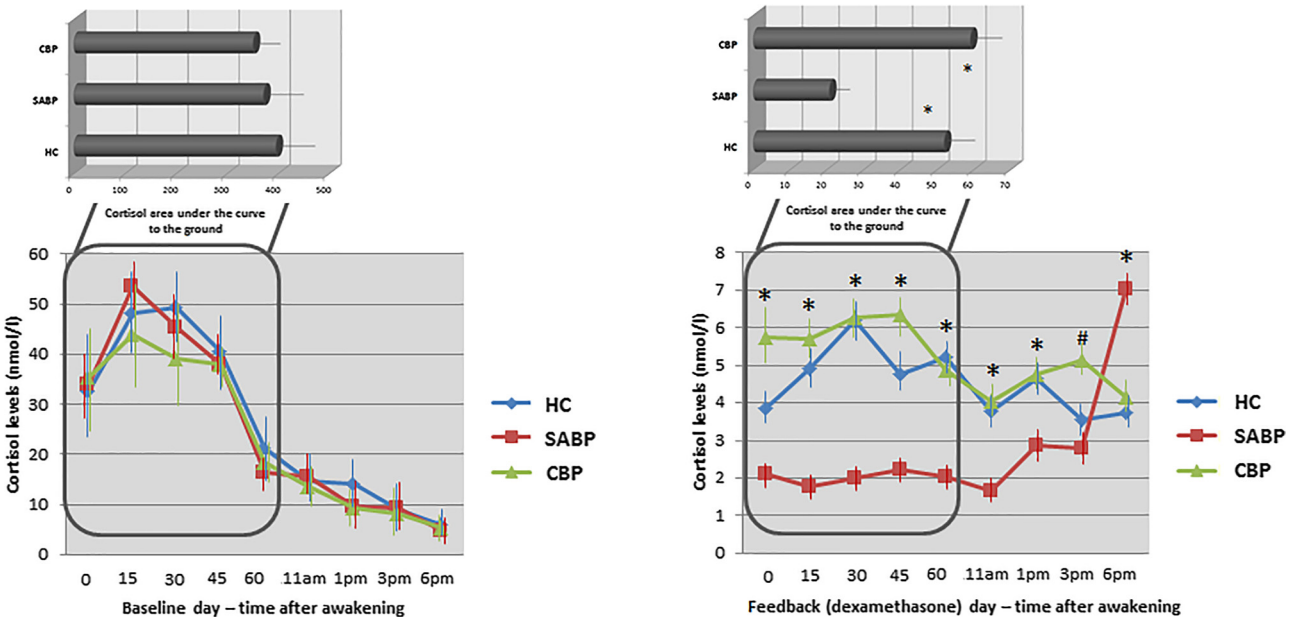

Fig. 1. Salivary cortisol levels (0 = directly after awakening, 15 min, 30 min, 45 min and 60 min after awakening, at 11am, 1 pm, 3 pm and 6 pm; and area under the curve to the ground for the awakening response (0, 15, 30, 45, 60) and daytime response (11am, 1 pm, 3 pm and 6 pm)) at baseline (left) and under the feedback condition, i.e. following the dexamethasone suppression test (right), in healthy controls (HC), patients with subacute (SABP) and chronic back pain (CBP). *significant differences between HC and SABP and between CBP and SABP, $p < 0.05$; #significant differences between CBP and SABP, $p < 0.05$; depicted are mean values and standard errors of the mean.

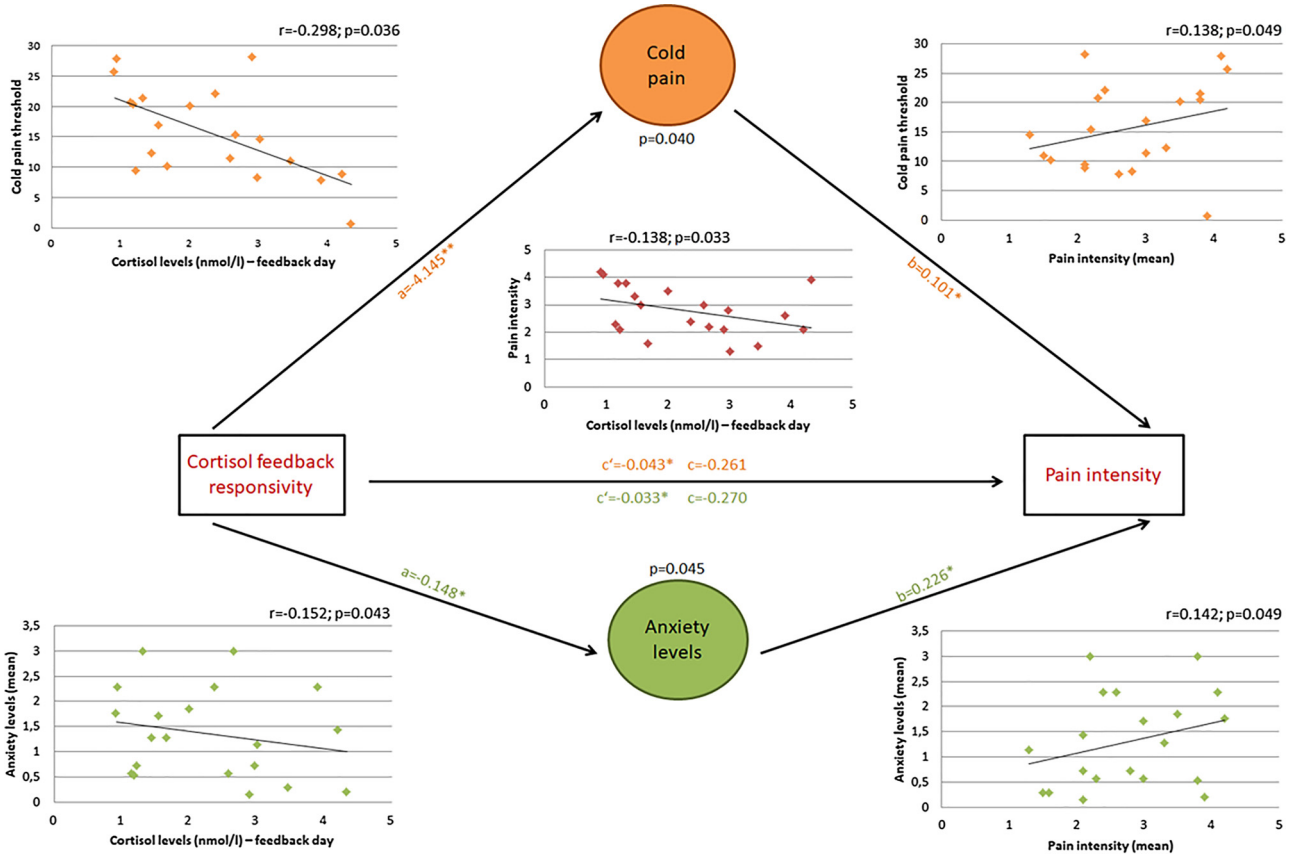

Fig. 2. This schematic diagram depicts associations between the following factors: salivary cortisol responses under the feedback condition (following the dexamethasone suppression test) and pain intensity, mediated by cold pain thresholds and anxiety levels in the group of subacute back pain patients. Path values between the involved factors are included next to the arrows, a positive correlation between two factors is additionally highlighted with scatterplots. *significant at $p < 0.05$; **significant at $p < 0.01$.

data point to cortisol as a psychobiological marker that could be involved in pain coping at the subacute stage and be a critical factor for pain chronicity.

In the context of the transition to chronic pain, a number of psychological factors might play a role, and in addition to depression, anxiety, fear of pain or pain coping strategies, (chronic) stress may also be critical (e.g., Vlaeyen and Linton, 2000). A potential link between these psychological and physiological factors is the functioning of the HPA axis (Hawk and Baum, 2013). The expression of cortisol is a significant marker of HPA axis functioning and the stress regulation system. Cortisol levels are usually expressed in a diurnal profile, with higher levels in the morning and lower levels in the evening, and with an increase in the magnitude in response to acute stress. The regulation of cortisol in the course of negetaive feedback is an important factor for the maintenance of these basal cortisol profiles (Aschbacher et al., 2012).

An increased expression of cortisol has been reported similarly for acute stress (Kudielka et al., 2004) and acute pain (Muller et al., 2006). In contrast, reduced cortisol levels have been found in both chronic stress and chronic pain syndromes including chronic back pain (Griep et al., 1998). According to the three-phasic-model of chronic stress, stress-associated pain disorders might be related to an increased concentration of glucocorticoids in the early phase of pain chronicity, followed by stronger pituitary feedback, and, in consequence, a state of hypocortisolism (Fries et al., 2005). This hypocortisolism is suggested to directly relate to symptoms of pain, fatigue and increased stress sensitivity (Fries et al., 2005). This type of hypocortisolism has also been reported in previous studies, such as in the study by Griep et al., (1998), who found hypocortisolemia in patients with low back pain compared to controls. For HPA feedback responsivity, however, only a tendency for disruption was observed in the back pain patients. In the presents study, we did not find any significant differences, neither in basal nor feedback cortisol levels in the CBP compared to controls, and also not for baseline levels, including the awakening profile, for all three groups. This awakening response is viewed as a measure of the capacity of the HPA axis to respond, also as a preparatory response, to anticipated stress, and was undisturbed in our CBP compared to HC and SABP. As mentioned in the Introduction, the evidence on cortisol profile changes in (chronic) pain from the literature is equivocal, and also our data suggest potential CBP subgroups, which need to be studied in future research.

Feedback sensitivity, however, was altered in SABP compared to both CBP and HC. Reduced cortisol levels following DST in SABP may represent a coping mechanism at the level of the stress system that could, in the following SABP period co-determine the course of resolution of pain or transition to pain chronicity. A hyperactive HPA axis feedback sensitivity, represented by lower cortisol levels following DST, has also been found in some of the previous chronic pain studies, yet, mainly in fibromyalgia patients (e.g. Ataoglu et al., 2003; Griep et al., 1993). Moreover, previous studies have indicated that cortisol feedback levels, examined via DST, and thus stress-related HPA axis functioning (Edwards et al., 2003), were stronger predictors of the pain chronicity process than baseline cortisol levels (McBeth et al., 2007). In this context, the investigation of subgroups of subacute patients where the pain continues or resolves could provide further important information.

Interestingly, cortisol DST levels were significantly negatively associated with pain intensity in SABP, i.e., at the subacute stage, individuals with lower cortisol levels after the DST experience more pain. So far, studies have reported an association of enhanced cortisol increase upon awakening with greater pain intensity and unpleasantness

ratings to acute pain (e.g., Mayes et al., 2009). Individuals with higher levels of pain are suggested to be in particular vulnerable for developing chronic pain. At the subacute stage, feedback-related cortisol expression might be a critical marker for pain chronicity. This association needs to be tested in a longitudinal study, where the cortisol DST levels of those who become chronic and those whose pain resolves can be compared.

We also found that anxiety mediates the association between cortisol and pain intensity in SABP. Anxiety may thus increase the negative association between cortisol suppression after the DST and pain intensity. This is in line with findings from Cacciaglia et al. (2017), who reported stronger cortisol suppression following DST in traumatized compared to control individuals. Moreover, prior traumatization has been associated with higher pain levels in chronic pain patients (e.g., Tesarz et al., 2015). It might thus be an important environmental factor in determining pain chronicity, mediated by the HPA axis response. In addition to anxiety, previous studies also reported on a role of further psychological variables such as depression or catastrophizing in chronic pain and pain processing (e.g., Hosoi et al., 2010). In the present study, we therefore also assessed depression and chronic stress, yet, did not find significant associations with cortisol feedback and pain intensity in SABP. In the subacute stage of the pain experience, anxiety might thus be prominent, and could determine the subsequent behavioral response pattern to either deal with pain or become involved in a negative pain-anxiety circle.

Our data also suggest that the HPA axis regulation system interacts with the somatosensory system, which we assessed with QST. QST measures have been shown to be useful in a mechanistic classification of pain patients and in the prediction of treatment responses (e.g., Boivie, 2003). We observed that the association between cortisol levels following DST and pain intensity was mediated by cold pain thresholds in SABP. This indicates that during the subacute state of pain, there might be an interaction of HPA axis feedback sensitivity and quality of pain, with lower levels of cortisol also being significantly related to higher pain thresholds for cold pain and thus less sensitivity to cold pain. This association was not present at the chronic stage, and might thus represent a factor important for managing the subacute process rather than being a consequence of chronic pain. Contrary to our hypotheses, we only observed significant effects for cold, but not heat pain thresholds or windup. This specific association might be related to a higher variability in the cold pain than the heat pain or windup values. However, such a higher variance was found in all three groups and one should then have seen similar associations between pain intensity, cold pain thresholds and cortisol across groups, which was not the case. Although cold pain thresholds have been identified as the least reliable indicator among the QST measures in chronic low back pain patients (Vuilleumier et al., 2015), several studies have reported changes in cold pain thresholds regarding (chronic) musculoskeletal, non-mechanical pain profiles (O'Sullivan et al., 2014), and as critical marker of chronic (neck) pain development (Shahidi and Maluf, 2017). Together with lower cortisol responsivity to stress, cold pain thresholds were associated with musculoskeletal pain development early in life (Paananen et al., 2015). Moreover, a previous study found DST cortisol recovery being associated with cold pressor pain tolerance, but not with pain thresholds (Godfrey et al., 2014). However, these effects were observed in a healthy sample and under a different experimental procedure, namely the cold pressor test, while in the present study, QST was used. Future studies are therefore needed to substantiate the role of cold pain thresholds for pain chronicity.

The present data need to be considered in the light of several limitations. First, for the QST measures, we did not assess mechanical or pin-prick thresholds, which might have permitted more specific conclusions about involved somatosensory mechanisms. Second, we examined the SABP sample in a cross-sectional study, and thus interpretations and conclusions with respect to pain chronicity still need to be treated with caution. Third, the number of the SABP group was too low to investigate possible subgroup-specific effects – this would be an important aspect for future studies. Fourth, as the variance in the subacute back pain group was not extremely high, it is not clear if there are subgroups with resistance or susceptibility to develop CBP. However, we do not yet know the specific time point during the subacute period when the individual response pattern indicates CBP, and this change could also occur rather sharply, since there is no clear indication so far that this is a linear process. Our data show that persons in the subacute stage of back pain show stress-related processes that differ from those at the chronic stage (and compared to healthy individuals). These processes might be compensatory and / or reflect some coping attempts of the individuals at the subchronic stage (and compared to healthy individuals). Although we cannot yet predict the course, we believe that the different patterns could still add significantly to the literature. Last, there is also some evidence that dexamethasone significantly reduces pain scores, described, for example, in patients 6 h after surgery receiving a single dose of intravenous dexamethasone 0.1 mg kg^{-1} preoperatively (Szucs et al., 2016). However, this is a different context and pain dimension, and thus not directly comparable to the data of present study, and the DST has already been used in several studies of (chronic) pain (e.g., Wingenfeld et al., 2007; McBeth et al., 2007).

In sum, our data show that the stress regulation system differs in subacute and chronic states of back pain, and could thus be one important factor in the transition period of after the subacute stage, where the course into risk or resilience will be set. The DST might be a useful marker in this context, and levels of pain intensity, anxiety and somatosensory profiles might help to identify and classify further pain subgroups. Longitudinal studies are needed to determine causality and in the psychophysiological mechanisms of chronic pain development.

Conflicts of interests

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.10.026.

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