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Cortisol rapidly increases baroreflex sensitivity of heart rate control, but does not affect cardiac modulation of startle

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ABSTRACT

Cortisol, the final product of human HPA axis activation, rapidly modulates the cortical processing of afferent signals originating from the cardiovascular system. While peripheral effects have been excluded, it remains unclear whether this effect is mediated by cortical or subcortical (e.g. brainstem) CNS mechanisms. Cardiac modulation of startle (CMS) has been proposed as a method to reflect cardio-afferent signals at subcortical (potentially brainstem-) level. Using a single blind, randomized controlled design, the cortisol group (n = 16 volunteers) received 1 mg cortisol intravenously, while the control group (n = 16) received a placebo substance. The CMS procedure involved the assessment of eye blink responses to acoustic startle stimuli elicited at six different latencies to ECG-recorded R-waves (R + 0, 100, 200, 300, 400 and 500 ms). CMS was assessed at four measurement points: baseline, -16 min, +0 min, and +16 min relative to substance application. Baroreflex sensitivity (BRS) of heart rate (HR) control was measured non-invasively based on spontaneous beat-to-beat HR and systolic blood pressure changes. In the cortisol group, salivary cortisol concentration increased after IV cortisol administration, indicating effective distribution of the substance throughout the body. Furthermore, BRS increased in the cortisol group after cortisol infusion. There was no effect of cortisol on the CMS effect, however. These results suggest that low doses of cortisol do not affect baro-afferent signals, but central or efferent components of the arterial baroreflex circuit presumably via rapid, non-genomic mechanisms.

1. Introduction

Visceral-afferent neural traffic plays an important role in the experience of emotions [1], in emotion regulation [2,3], and in somatic symptom generation [4]. While it has been demonstrated that stress affects interoception via activation of the autonomic nervous system, e.g. by increasing cardiovascular activity thereby enhancing neural traffic originating from the cardiovascular system [5–7], little is known about the effects of stress-related activation of the hypothalamic-pituitary-adrenocortical (HPA) axis on interoception [8].

A recent study demonstrated that interoceptive accuracy (IAc), which refers to the correspondence between actual and perceived visceral-afferent signals (i.e. heartbeats) [9], is affected by cortisol, the final product of human HPA axis activation: individuals responding to a social stressor with increased cortisol levels (i.e. responders) showed higher IAc than non-responders [10]. Nevertheless, until now the mechanisms underlying this effect remain unclear. For example, it is unknown if this effect is mediated by a genomic or a non-genomic mechanism.

One possible explanation for this finding involves a fast-acting, non-genomic mechanism, as cortisol can rapidly increase the cortical processing of visceral-afferent signals from the cardiovascular system, as indicated by heartbeat-evoked potentials (HEPs) [11]. HEPs are considered psychophysiological indicators of the cortical processing of cardio-afferent signals [12–14] and correlate with IAc [15]. The effect of cortisol on HEPs could either be explained by (1.) increased cardiovascular activation, (2.) altered relaying of cardio-afferent signals in subcortical (e.g., brainstem), or (3.) in cortical structures. As the rapid

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Table 1
Parameters of the autonomic nervous system during the four cardiovascular measurement sessions (baseline, pre-, during- and post-intervention). Each session lasted 5 min. A significant response to cortisol infusion could be observed for BRS and salivary cortisol.

		baseline		pre-intervention		during-intervention		post-intervention	
		M	SD	M	SD	M	SD	M	SD
group: cortisol (n = 16)*									
Sex	m/f	6/10							
Age	years	25.8	3.1						
BMI	kg/m^2	22.7	2.8						
Heart rate[a]	bpm	73.7	9.1	68.8	8.5	68.4	6.8	68.0	6.8
LF HRV	ln ms^2	6.8	0.2	7.0	0.2	7.1	0.1	7.2	0.2
HF HRV	ln ms^2	6.1	0.3	6.1	0.3	6.1	0.2	6.3	0.2
Systolic BP[a]	mmHg	121.9	16.5	124.7	17.0	127.1	15.8	129.9	14.6
Diastolic BP[a]	mmHg	59.1	9.6	62.7	9.7	62.3	7.2	63.6	8.0
HF BPV	mmHg^2	10.3	2.2	9.0	1.4	7.8	0.8	9.8	2.2
LF BPV	mmHg^2	5.4	1.3	4.2	0.8	3.8	0.6	4.8	1.1
BRS[b]	ms/mmHg	8.4	4.5	8.7	3.8	10.0	3.1	10.4	3.9
Salivary Cortisol [b]	nmol/l	5.2	3.1	6.9	6.7	11.1	8.9	9.5	9.9
group: placebo (n = 16)*									
Sex	m/f	6/10							
Age	years	26.1	4.9						
BMI	kg/m^2	22.4	2.4						
Heart rate[a]	bpm	71.1	10.1	68.6	9.7	68.4	9.8	67.3	9.1
LF HRV	ln ms^2	6.7	0.2	6.9	0.2	7.0	0.2	7.0	0.2
HF HRV	ln ms^2	6.0	0.3	6.0	0.3	6.0	0.3	6.1	0.3
Systolic BP[a]	mmHg	126.4	16.7	130.3	15.0	138.5	17.5	132.4	17.0
Diastolic BP[a]	mmHg	57.2	9.5	62.4	9.1	64.0	10.7	63.3	11.9
LF BPV	mmHg^2	7.0	1.3	6.8	1.0	9.3	1.7	7.5	1.4
HF BPV	mmHg^2	4.6	0.8	4.1	0.6	5.2	0.8	5.1	1.0
BRS[b]	ms/mmHg	10.2	5.0	10.1	4.9	9.7	4.7	9.8	4.1
Salivary Cortisol [b]	nmol/l	4.5	2.5	4.5	3.0	3.4	1.9	4.0	2.6

BMI = body mass index, BP = blood pressure; HRV = heart rate variability; BPV = blood pressure variability; BRS = baroreflex-sensitivity.

* A priori group differences: sex: x2 = 0; age: T [30] = 0.17; p = .86; BMI: T [30] = −0.40; p = .69; HR: T [30] = −0.757; p = .45; LF HRV: T [30] = −0.29; p = .77; HF HRV: T[30] = −0.20; p = .85; SPB: T[30] = 0.76; p = .45; DPB: T [30]= −0.54; p = .59; LF BPV: T [30] = −1.29; p = .21; HF BPV: T [30] = −0.51; p = .61; BRS: T [30] = 1.08; p = .29; Cortisol: T[30] = −0.68; p = .51.

[a] Main effect 'time of measurement', significant difference baseline vs. during-intervention.

[b] Significant interaction 'drug infusion' × 'time of measurement', significant differences between subsequent times of measurement in the CORT group only in bold

effect of cortisol on the cortical processing of cardio-afferent signals (3.) has already been established without affecting cardiovascular activation (1.) [11], the aim of the current study was to clarify if cortisol rapidly affects the transmission of cardio-afferent signals at brainstem level (2.).

Brainstem centers that relay visceral-afferent neural signals include the nucleus tractus solitarius (NTS), and the rostral (RVLM) and caudal ventrolateral medulla (CVLM) [16]. The NTS also projects onto the parabrachial nucleus and the locus coeruleus, from where hypothalamic and thalamic nuclei are reached [17]. At cortical level, visceral-afferent signals are processed by the anterior cingulate cortex (ACC), the frontal cortex, the somatosensory cortex and the right insula [17–19]. Glucocorticoids promote constriction of peripheral blood vessels [20] and increase metabolism in cardiac muscle cells [21], which can both affect the neural feedback from cardiovascular interoceptors (e.g., arterial baroreceptors). Cortisol could also affect brainstem mechanisms that process afferent cardiac signals, such as the RVLM [22,23], and cortical structures, such as the ACC and the insular cortex [24–27]. While the effect of cortisol on cortical structures can be observed in vivo using neuroimaging techniques, the effect on brainstem structures requires an indirect approach, such as based on psychophysiological indicators.

The cardiac modulation of startle (CMS) was established as a methodology to assess afferent neural traffic originating from the cardiovascular system, since it relies on intact baro-afferent signal transmission [28]. In this CMS paradigm, increased baro-afferent feedback during the early cardiac cycle phase attenuates responsiveness to acoustic startle stimuli compared to the late cardiac cycle phase [28–33]. Furthermore, CMS also reflects changes in baro-afferent signal transmission induced by an acute autonomic stress response [32]. The precise neural substrate of the CMS is yet unclear, although the arterial baroreflex [16] and the primary acoustic startle circuit [34] are likely to be involved [28].

The arterial baroreflex contributes to the homeostatic control of arterial blood pressure [16]. The reflex circuit responsible for this effect is located in the brainstem (NTS, nucleus ambiguus [NA], RVLM, CVLM), and continuously controls the length of heart periods in response to blood pressure changes. Information of blood pressure changes are transmitted over arterial baroreceptors and baro-afferent nerve fibers (N. glossopharyngeus). Baroreflex sensitivity (BRS) of heart rate control is an indicator for the integrity of this mechanism [35] and has been shown to be associated with the CMS [28]. In summary, both BRS and CMS reflect the processing of baro-afferent signals at subcortical (mainly brainstem) level, whereas the BRS also includes efferent output.

To clarify whether cortisol rapidly affects the sub-cortical relaying of baro-afferent neural signals, we conducted a between-subjects experiment, including the assessment of CMS and cardiovascular indicators (including BRS), which took place before the cannulation of a cubital vein, and before and after the infusion of 1 mg of cortisol (n = 16) or a placebo substance (n = 16). We expected (I) an attenuation of startle responses during the early as compared to the late cardiac cycle phase, as previously observed. Furthermore, given that visceral-afferent signal transmission is reflected by the amplitude of CMS and HEPs [13,28], as well as by BRS, and cortisol may rapidly increase HEP amplitudes [11], we expected (II) an increase of CMS and BRS after cortisol infusion.

2. Methods

2.1. Participants

Thirty-two healthy undergraduate students (20 females) participated in the experimental sessions and received a compensation of 20 Euros. The sample size was twice as large as in a previous study addressing rapid cortisol effects on HEPs in a within-subjects design ($n = 16$) [11], as the current study comprised a between-subjects design. Physical health status was assessed prior to the experiment with a customized interview administered by a psychologist (A.S.) and a physician (S.R.). Exclusion criteria were: hearing problems (impairments, tinnitus), regular use of contact lenses, any acute or chronic physical or mental health complaint, current medication, critical life events over a time period of six months before participation, or major examinations two weeks prior to or after the experiment. All participants provided written informed consent and were made aware of their right to discontinue participation in the study at any time. Study procedures were approved by the Ethics Committee of the State Board of Physicians of Rhineland-Palatinate (Germany). Participants were randomly assigned either to a cortisol administration (CORT) group ($n = 16$) or a placebo administration (PLAC) group ($n = 16$), which did not differ in sex, age, or BMI (see Table 1).

2.2. Experimental intervention

Participants attended the laboratory sessions between 13:00 h and 17:00 h. We employed a constant background sodium-chloride (NaCl 0.9%, B. Braun Melsungen Co., Melsungen, Germany) infusion (120 ml/h) that was reduced for the cortisol (Hydrocortison 100, Rotexmedica, Trittau, Germany) and placebo (NaCl 0.9%) target infusions to keep flow constant at any time. Infusions were controlled by a CPU-operated modular Fluid-Management System (B. Braun Melsungen Co., Melsungen, Germany) located in an adjacent room. Because of absence of visual or auditory infusion-related cues, participants were not able to detect infusion onset or offset. During Session 3 of each group (see below), 1 mg of cortisol or placebo was infused over the 5 min duration in a single-blind design. Thus, every participant received either a cortisol or a placebo infusion. As a previous study demonstrated an effect of 1 mg of cortisol on the modulation of acoustically-evoked startle responses [36], the same was used in the current study to investigate the effect on the CMS. It corresponds to the endogenous secretion, which is to be expected in response to a mild stressor [37]. All participants received the same dose of 1 mg, as we tested a homogenous group of healthy students, within a normal BMI range, and no differences in BMI between groups.

2.3. Procedure

Participants were asked to relax, to neither speak nor move, to avoid longer periods of eye closure, and to listen carefully to all acoustic stimuli. The experimental procedure consisted of four identical sessions each containing a five-minute cardiovascular measurement session, the collection of a saliva sample, which took approx. one minute, and a seven-minutes startle session in a fixed order (total length per session: 13 min). During each cardiovascular measurement, a finger-blood pressure cuff was attached to assess beat-to-beat systolic and diastolic blood pressure non-invasively. The blood pressure cuff was detached afterwards to avoid any somatosensory feedback of cardiac activity during the startle presentations. Six startle probes preceded the first startle session without any relationship to the participants' heartbeats, which served as habituation trials and were not analyzed further. The startle sessions consisted of 60 startle probes with a jittering inter-stimulus-interval of 8 to 12 s, identical to an earlier applied protocol [32], in which startle stimuli were presented with six different latencies after a detected R-wave (0 ms, 100 ms, 200 ms, 300 ms, 400 ms, and 500 ms).

After Session 1 ('baseline'), a cubital vein of the left arm was cannulated (18 G venflon, vasofix-safety, B. Braun Melsungen Co., Melsungen, Germany), followed by a 30-min resting period. The completion of the resting period was followed by three sessions (Session 2: 'pre-intervention', 3:'during-intervention', 4:'post-intervention'), each interrupted by a three-minute break. During the cardiovascular measurement of Session 3, 1 mg cortisol or placebo infusion was administered. The 'during-intervention' startle session, therefore, started approx. one minute after completion of the infusion,[1] while the 'pre-intervention' startle session took place 16 min earlier and the 'post-intervention' startle session 16 min later, relative to this time point (see Fig. 1). The total length of the experimental procedure, including screening and instructions, was 100 min on average.

2.4. Recording parameters

Physiological data were collected using a Biopac MP150 amplifier system (Biopac Systems, Inc.) at 16-bit resolution and 1 kHz sampling rate. EMG-responses to acoustic white noise startle probes (105 dB, 50 ms duration, instantaneous rise time, binaural stimulation; Sennheiser headphone, Wedemark, Germany) were assessed with two electrodes (Kendall Arbo H124SG; diameter: 24 mm) placed below the left eye with a distance of 1.5 cm to assess activity of the M. orbicularis oculi. Hardware band-pass filter settings were 10 to 500 Hz, followed by a 28 Hz software high-pass filter [38]. The raw signal was rectified and integrated online with a time constant of 10 ms [39]. Electrodes for ECG-measurement (Kendall Arbo H34SG; diameter: 45 mm) were placed according to an Einthoven lead II configuration. The ECG signal was high-pass filtered (0.5 Hz). R-waves were identified online by a Hellige ECG detection device (Hellige, Freiburg, Germany). Accuracy of R-wave detection in sinus rhythm was higher than 99.8%, with a latency below 3 ms. Non-invasive continuous blood pressure was recorded during the cardiovascular measurement sessions at the middle finger of the right hand with a Finometer device (Finapres Medical Systems, Amsterdam, Netherlands), but this recording device was detached during all startle sessions. For each participant, the absolute Finometer-collected blood pressure values were adjusted by an additional Riva-Rocci-based measurement during the baseline session.

2.5. Cardiovascular data

Interbeat-intervals were calculated from the ECG and manually corrected, with a normal cycle RR-interval time series as output signal, from which mean heart rate (HR) data was derived. Continuous signals of adjusted blood pressure waves were manually corrected for calculation of mean systolic (SBP) and diastolic blood pressure (DBP) throughout each session. Spectral analyses of RR interval and SBP series were carried out using Fast Fourier Transformation (FFT). The RR-interval and SBP time series were linearly interpolated and resampled with a sampling rate of 5 Hz, the resampled data was tapered using a Hanning window and the windowed data zero padded to the next power of 2. The high frequency bands (HF) of heart rate variability (HRV) and blood pressure variability (BPV) were defined as 0.15 to 0.4 Hz, the low frequency band (LF) as 0.04 to 0.14 Hz. LN-transformed values of HRV power bands were calculated to correct for skewed distributions [40].

Baroreflex sensitivity (BRS) of heart rate control is quantified in 'ms/mmHg' units as changes in heart period (ms) in response to a blood pressure change of 1 mmHg [41]. The BRS value should be, therefore, associated with the strength of afferent neural traffic from arterial

[1] As the experiment consisted of four identical blocks, the third startle session is consistently labeled 'during-intervention', although it actually took place directly after the infusion was completed.

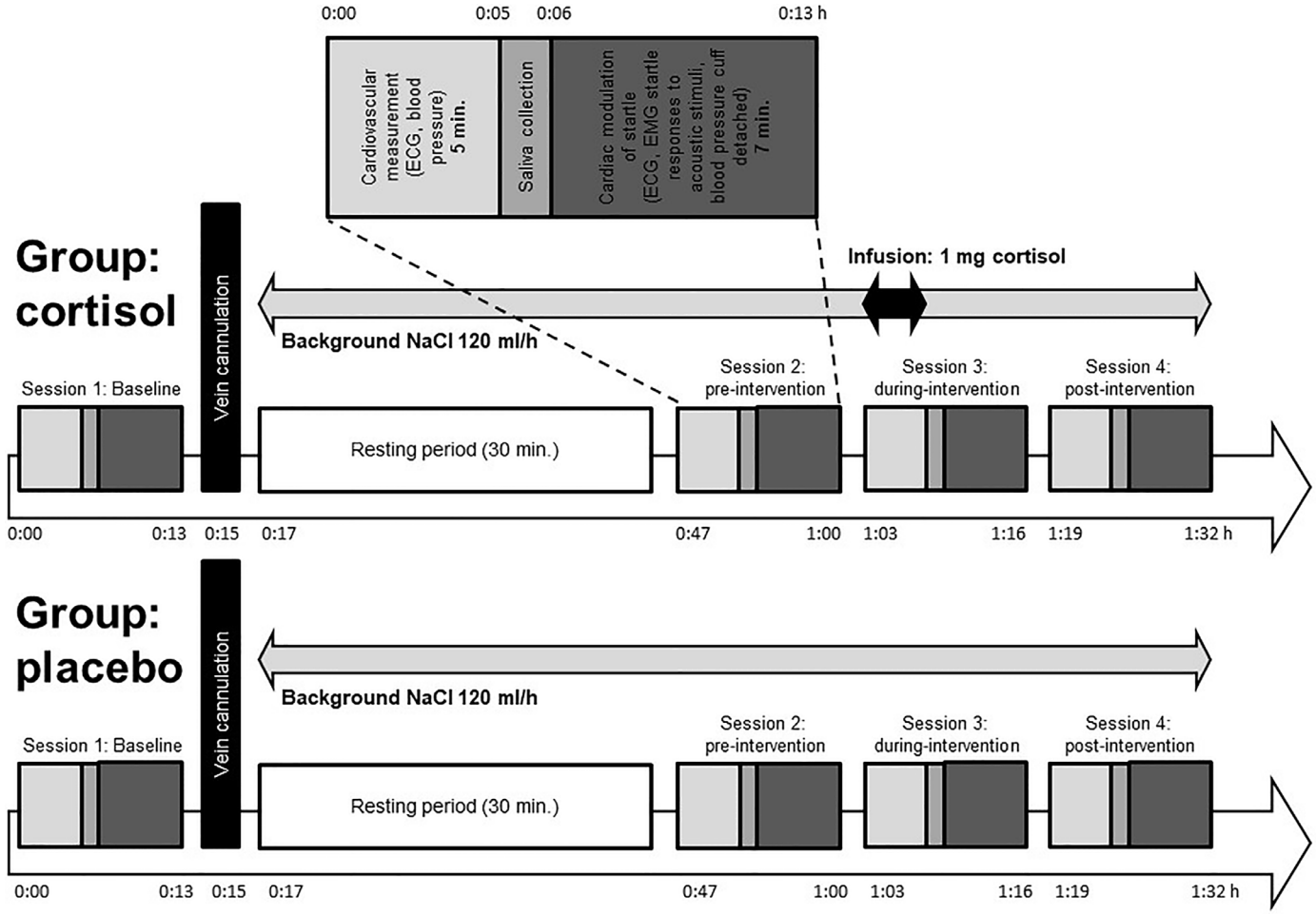

Fig. 1. Experimental protocol was identical for both groups, except for the infusion of 1 mg of cortisol during the cardiovascular measurement of session 3 ('during-intervention'). A resting period of 30 min. was included to overcome potential stress effects of vein cannulation. Due to the background NaCl infusion and the control of the infusion device from an adjacent room, participants were not aware of onset and offset of the cortisol administration. Please note that the third startle session is labeled 'during-intervention' to be consistent throughout the manuscript, although it actually took place directly after the cortisol administration was completed.

baroreceptors [28]. BRS can be estimated from spontaneous beat-to-beat HR and SBP changes. It is calculated by transfer function analysis (gain, transfer magnitude). We determined the transfer functions (coherence and transfer magnitude) in the LF band. BRS was calculated by integrating the transfer magnitude (modulus function) over frequency points with coherence values higher than 0.5 [41].

2.6. Startle eye blink data

A customized *C++* based semi-automated PC program was used to analyze EMG responses offline. The algorithm identified response peaks in the rectified and integrated signal in the time interval of 20 to 150 ms after the startle probe onset. The baseline period was defined by a 50 ms interval prior to acoustic stimulation. All response data were manually inspected. Signals with electrical and physiological artifacts, such as coinciding blinks or excessive noise from other facial muscular activity, were rejected from analysis and defined as missing. If responses were not visible in the typical response latency range of a particular subject, response amplitude was set to zero. Zero response data were included in the averaging procedure, with startle response magnitude as the final output measure [42]. Averaging was done per participant and according to the six latency conditions. To reveal possible effects of cortisol on the overall startle response magnitude, raw values were used.

2.7. Salivary cortisol

Cortisol levels were monitored using four saliva samples (Salivette cotton swab, Sarstedt, Nümbrecht, Germany) to check if the pharmacological manipulation was successful. Participants provided their saliva sample prior to each of the four CMS measurement sessions (baseline; pre-intervention; during intervention; post-intervention). They were instructed to put the cotton swab into their mouth and chew on it for approx. 1 min. Samples were stored in a freezer at −20 °C before analysis. Salivary cortisol was analyzed by a time-resolved immunoassay with fluorescence detection (intra-assay coefficient of variation: 4.0–6.7%; inter-assay coefficient of variation: 7.1–9.0%) [43] in the Biochemical Laboratory at the University of Trier. Cortisol levels were determined twice, and their average was used in further statistical analysis.

2.8. Statistical analysis

A-priori group differences in demographic variables and during the baseline period in autonomic variables were analyzed with *T*-tests for independent samples between the 'cortisol' (CORT) and the 'placebo' (PLAC) group. To inspect the impact of the cortisol infusion on cardiovascular parameters and salivary cortisol we conducted mixed-design 4 × 2 ANOVAs (for HR, LF HRV, HF HRV, SBP, DBP, LF BPV, HF BPV, BRS, salivary cortisol) with the within-subjects factor 'time of measurement' (baseline; pre-intervention; during-intervention; post-

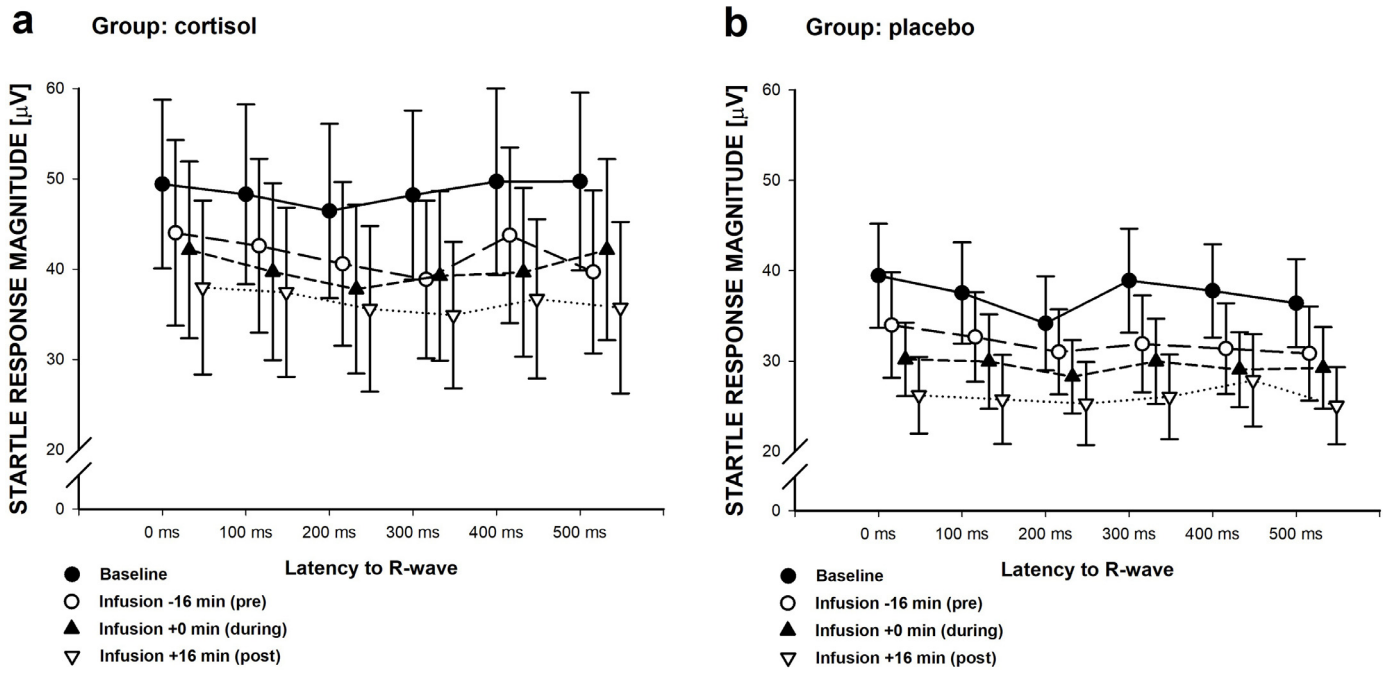

Fig. 2. Startle response magnitudes during the four CMS sessions in the cortisol (a) and the placebo (b) group. Error bars represent SEM. Startle magnitudes were lower from one session to the next (habituation effect) and were significantly lower 200 ms after the R-wave than at other time points within the cardiac cycle (CMS effect), aggregated over both groups. The CMS was not affected by cortisol infusion. No differences in startle magnitudes between both groups emerged.

intervention), and the between-subject factor 'drug' (CORT group; PLAC group). CMS was analyzed using a mixed-design 4 × 6 × 2-ANOVA with the within-subject factors 'time of measurement' (baseline, pre-intervention, during-intervention, post-intervention) and the latency between R-wave and stimulus presentation ('cardiac cycle phase': 0; 100; 200; 300; 400; 500 ms), the between-subjects factor 'drug infusion' (CORT group; PLAC group), and the dependent variable startle response magnitude. Critical alpha-level was set to 0.05 in all analyses. All *p*-values of within-subjects factors with more than two conditions are reported after Greenhouse-Geisser correction. *Post-hoc* analyses of simple main effects within the ANOVA-models were performed using *a-posteriori* planned contrasts comparing only subsequent levels against each other.

3. Results

3.1. A-priori group differences

Groups did not differ in age, sex, or BMI, or any baseline physiological data (HR, LF HRV, HF HRV, SBP, DBP, LF BPV, HF BPV, BRS, salivary cortisol; see Table 1).

3.2. Cardiovascular indices

3.2.1. Heart rate

There was a main effect for 'time of measurement' (F[3,90] = 14.20; $p < .001$; $\eta^2 = 0.28$). *A-posteriori* contrasts revealed that mean HR significantly decreased from the 'baseline' (72.4 [SEM = 1.7] bpm) to the 'pre-intervention' (68.7 [1.6] bpm; $p < .001$), and from the 'during-' (68.4 [1.5] bpm) to the 'post-intervention' session (67.6 [1.4] bpm; $p < .05$; see Table 1).

3.2.2. Systolic blood pressure

The main effect for 'time of measurement' was significant (F[3,90] = 4.50; $p = .009$; $\eta^2 = 0.13$). *A-posteriori* contrasts indicated that SBP increased from the 'pre-intervention' (127.5 [2.8] mmHg) to the 'during-intervention' (132.8 [2.9] mmHg) session ($p < .01$; see Table 1), but remains unchanged between the 'baseline' and the 'pre-intervention', as well as between the 'during-' and the 'post-intervention' sessions (all *ps* > 0.05).

3.2.3. Diastolic blood pressure

There was a significant main effect for 'time of measurement' (F[3,90] = 10.88; $p < .001$; $\eta^2 = 0.27$). *A-posteriori* contrasts showed that mean DBP increased from the 'baseline' session (58.1 [1.7] mmHg) to the 'pre-intervention' session (68.7 [1.6] mmHg; $p < .001$) and remains constant thereafter (all *ps* > 0.05).

3.2.4. Heart rate variability

Neither a main effect of 'time of measurement', nor an interaction effect of 'time of measurement' × 'drug' was significant for LF or HF power.

3.2.4. Blood pressure variability

Neither a main nor an interaction effect was significant for LF or HF power.

3.2.6. Baroreflex sensitivity

We found a significant interaction 'time of measurement' × 'drug' (F[3,90] = 3.14; $p = .033$; $\eta^2 = 0.10$). Our *a-posteriori* contrasts showed that in the CORT group, BRS values increased between the 'pre-' and the 'during-intervention' sessions ($p < .05$; see Table 1), and remained constant thereafter (although BRS descriptively even more increased; $p > .05$), suggesting a BRS-increasing effect of the cortisol-infusion. In the PLAC group, there were no differences in BRS values across all sessions. The main effects 'time of measurement' (F[3,90] = 1.18; $p = .35$) and 'drug infusion' (F[1,30] < 1) were not significant.

3.3. Salivary cortisol

We observed a significant interaction of 'time of measurement' × 'drug' (F[3,90] =8.59; $p = .004$; $\eta^2 = 0.22$). *A-posteriori* contrasts revealed that in the CORT group salivary cortisol levels

increased from the 'pre-' to the 'during-intervention' session ($p < .001$) and decreased between the 'during-' to the 'post-intervention' session ($ps < 0.05$; see Table 1). There were no differences in salivary cortisol levels between the sessions in the PLAC group.

3.4. Startle response magnitude

There was a main effect for 'time of measurement' (F[3,90] = 33.95; $p < .001$; $\eta^2 = 0.53$). *A-posteriori* contrasts showed that the startle magnitude decreased from one measurement occasion to the following and that all differed significantly from each other ('baseline': 43.0 [SEM = 5.5] μV; 'pre-': 36.3 [5.3] μV; 'during-': 34.3 [5.2] μV; 'post-intervention': 30.7 [5.1] μV; all $ps < 0.001$; see Fig. 2), except for the difference between the 'pre-' and 'during-intervention' ($p = .054$). We also found a main effect for 'cardiac cycle phase' (F[5150] = 4.58; $p = .002$; $\eta^2 = 0.13$). *A-posteriori* contrasts revealed that startle magnitude marginally decreased from 'R + 0 ms' (M = 37.6 [5.4] μV) to 'R + 100 ms' (36.4 [5.4] μV; $p = .067$), and significantly decreased from 'R + 100 ms' to '+200 ms' (34.5 [5.1] μV; $p = .029$). Although descriptively increasing from 'R + 200 ms' to all following conditions, the differences between subsequent levels remained insignificant ('+300 ms': 35.6 [5.0] μV; '+ 400 ms': 36.6 [5.3] μV; '+500 ms': 35.7 [5.2] μV), except for a trend towards a decrease between 'R + 400 ms' and 'R + 500 ms' ($p = .076$). Startle response magnitudes did not differ between groups (F[1,30] = 1.01; $p = .32$). None of the interaction effects were significant ('time of measurement' × 'group': F[3,90] < 1; 'cardiac cycle phase' × 'group': F[5150] = 1.06; $p = .38$; 'time of measurement' × 'group': F[15,450] < 1), with the non-significant 3-way interaction 'time of measurement' × 'group' × 'cardiac cycle phase' (F[15,450] < 1) indicating that CMS did not change depending on cortisol infusion.

4. Discussion

The aim of this study was to clarify whether the previously reported effect of cortisol on the cortical representation of afferent signals [11] is unique to the level of the cortex or may already occur at subcortical (i.e. brainstem-) level. To this end, we investigated the effects of a 1 mg infusion of cortisol on CMS and BRS, as indicators for baro-afferent signal transmission at brainstem level [28]. The effectiveness of cortisol administration was confirmed by the increase in salivary cortisol after drug infusion. In support of hypothesis (I.) and corroborating earlier findings on the CMS effect [28–30,32,44], we observed the lowest startle responses when startle stimuli were presented 200 and 300 ms after an R-wave, presumably due to the occurrence of the arterial pulse wave. Nevertheless, there was no effect of cortisol infusion on the CMS. Notwithstanding, the intravenous administration of cortisol lead to an increase in BRS, without affecting parameters of autonomic activation, such as HR, HRV, SBP, DBP, or BPV.

There are two ways of signal transmission for glucocorticoids, such as cortisol. The slow effects result in gene expression, and are therefore called genomic effects [45]. In addition, glucocorticoids can also elicit rapid, non-genomic effects, for instance by binding to the mineralocorticoid membrane receptor [46,47]. The application of glucocorticoids 'in vitro' leads to the transcription of mRNA after a latency of 7.5 min [48], which is followed by protein synthesis that occurs within a time period of minutes to hours [49]. While the earliest genomic effects of glucocorticoids on neurons have been observed approx. 30 min after administration [50,51], typically they occur after 60 min. or later [52,53]. Since previous observations have shown that cortisol can rapidly modulate the cortical representation of afferent cardiac signals between 1 and 17 min after intravenous infusion [11], we focused on effects occurring within a latency of approximately 16 min after cortisol infusion. The last startle session ended 28 min. after onset of cortisol infusion and, therefore, before the possible onset of genomic effects. At later time intervals, genomic and non-genomic effects of cortisol may overlap and be difficult to disentangle in 'in vivo' experiments. A recent study in human participants demonstrated that a bolus of 200 mg of cortisol decreases BRS three hours thereafter [54], corroborating earlier findings in rats [55,56]. There are at least two explanations for the contrasting findings of Adlan et al. [54] and the present study: (1.) the substantially higher dose of cortisol in [54] may reverse the effect into the opposite, as the relationship between cortisol dose and neurophysiological outcome is typically quadratic [37]; (2.) the decreasing effect is due to the genomic mechanisms of cortisol. Nevertheless, due to the time frame (during infusion up to +11 min.), the increase of BRS in the current study could be clearly attributed to a non-genomic mechanism.

One possible conclusion may be that visceral-afferent signal transmission, originating from the cardiovascular system is not affected by non-genomic effects of a low dose of cortisol (1 mg; hypothesis II.), since the CMS pattern did not change after cortisol infusion (+0 min and +16 min). In support of this notion, neither BP nor HR, which can both affect baro-afferent neural traffic, changed after cortisol infusion. Furthermore, HRV and BPV as estimated by normalized power in the LF and HF band, which are considered indicators for relative central sympathetic and parasympathetic tone [40,57], was unaffected by cortisol infusion. This finding implies that a 'physiological' dose of 1 mg of cortisol does not substantially affect vasomotor, cardiodynamic or autonomic regulatory processes via a rapid, non-genomic mechanism. In contrast, we found an increase in BRS during and 11 min after cortisol infusion. Its neural circuit involves brainstem structures, which incorporate sensory structures processing baro-afferent traffic (i.e. NTS), central components including interneurons (i.e. CVLM), as well as structures responsible for baro-efferent neural traffic (i.e. NA, RVLM, dorsolateral funiculus, intermediolateral nucleus, dorsal motor nucleus of the vagus nerve/DMNX) [16]. BRS is a measure that can serve as an indicator of the integrity of this neural circuit [58], but it does not allow for the separation of baro-afferent, central and baro-efferent function. One explanation for the discrepancy between cortisol effects on CMS and BRS may be that the neural relaying of baro-afferent signals is affected by an application of a low dose of cortisol, but not at the afferent branch of the baroreflex circuit (e.g., from effector organ to the NTS), as indicated by the zero effect of cortisol on CMS. We would argue, therefore, that cortisol exerts a non-genomic effect on the central or efferent components [22] of the arterial baroreflex arc and, as a consequence, modulates the translation of baro-afferent traffic into motor output (i.e. heart rate change or vasomotor output), but not the sensory representation of baro-afferent traffic itself. One possible mechanism of cortisol rapidly affecting baro-efferent output may involve glutamatergic neurons, as glucocorticoids can induce a potentiation of glutamate release in the hippocampus [59,60], the dentate gyrus [61] and the (pre-)frontal cortex [62] through a non-genomic mechanism mediated by mineralocorticoid membrane receptors. This mechanism may be translated to glutamatergic neurons in other brain areas, as well [63]. As both central (i.e. CVLM) [64] and efferent components of the baroreflex circuit (e.g., NA) [65] include glutamatergic neurons, they may be involved in mediating the rapid BRS-increasing effect of cortisol.

In our previous study we showed that cortisol exerts a rapid effect on heartbeat-evoked potentials (HEPs) [11], which are considered psychophysiological indicators of cortical processing of cardiac interoceptive signals [13,14]. HEPs and CMS represent different psychophysiological approaches to assess afferent neural signals originating from the cardiovascular system. HEPs are electrocortical potentials, which are generated in the ACC, the right insula, the prefrontal cortex and the somatosensory cortex [66]. These brain regions are substantially involved in the cortical processing of interoceptive signals [18,67]. The detailed neural substrate of the CMS remains unclear, but the involvement of the arterial baroreflex circuit (e.g., NTS) [16] and the primary acoustic startle circuit (cochlear root neurons, nucleus reticularis pontis caudalis) [34] appears likely [28]. As CMS effects can be observed in a time frame of less than 100 ms after the arterial pulse

wave reaches the arterial baroreceptors [32,68], an involvement of cortical structures is implausible. Nevertheless, both CMS and HEPs are substantially reduced in individuals with degeneration of afferent autonomic nerves due to a long history of diabetes [13,28], suggesting that intact afferent signal transmission from the cardiovascular system is required for both indicators.

In an earlier study of our group, we found that exposure to the socially-evaluated cold pressor stress test (SECPT), lead to an earlier onset of the CMS effect, but no increase in its amplitude [32]. The SECPT has repeatedly been shown to reliably induce activation of the autonomic nervous system [7,32,69] and the HPA axis, as indicated by an increase of salivary cortisol [70–72]. In the present study, the administration of 1 mg of cortisol did not rapidly affect the CMS and, therefore, baro-afferent signal transmission. We would argue, therefore, that low cortisol doses do not play a role in the previously observed effects of the SECPT on the CMS, which may thus be attributed predominantly to autonomic stress responses. Notwithstanding, it needs to be emphasized that these interpretations are limited to the dose of 1 mg and may not be generalized to (non-genomic) cortisol effects in general.

The experimental substance used in the current study consisted of 1 mg of intravenously administered cortisol. As summarized by Schilling and colleagues [37], this dose corresponds to cortisol secretion after a mild stressor [73,74], and is, therefore, considered a 'physiological' dose, since the daily production of endogenous cortisol is about 15–30 mg [75,76]. One may argue that this dosage may have been too low to affect CNS processing of sensory signals. Nevertheless, in a number of previous studies we could show that doses between 1 and 4 mg of cortisol can modulate signal processing at the level of the brainstem [36], the limbic system [77] and the cortex, as indicated by explicit memory performance [37]. All these effects were due to a rapid, presumably non-genomic mechanism. Furthermore, the increase in salivary cortisol concentrations after intravenous administration confirms the distribution of the drug in body tissue.

4.1. Limitations

Since we investigated non-genomic effects of cortisol on baro-afferent signal transmission, further studies should aim to replicate these findings and extend the time protocol to also include genomic effects of cortisol. As the cortisol dosage in this study was based on earlier investigations on modulatory effects on startle [36], it is not identical with the dosage as applied in the study on cortisol effect on HEPs [11]. Furthermore, the sample in the HEP study consisted of men only, while in the current study men and women were investigated. To increase comparability across both methods we suggest that follow-up studies should investigate cortisol effects on both HEPs and CMS to assess the central representation of visceral-afferent signals in the same sample using the same cortisol dose. The present sample size is in line with a previous study addressing rapid cortisol effects [11], however doubled in size due to the between-subjects design. Nevertheless, a power calculation may have strengthened the interpretation of null findings. With respect to the literature on CNS effects of cortisol [37], however, the amount of cortisol as administered in both studies (1 mg, 4 mg) can be considered a low dosage and thus comparable, which is also confirmed by similar increases in salivary cortisol (this study/1 mg: baseline: 5.2; post: 9.5 nmol/l; HEP study/4 mg: baseline: 5.7; post: 8.3 nmol/l). Finally, it needs to be acknowledged that it is yet unclear to which extent changes in the CMS is indicative of altered perception of bodily states, which implies the awareness of bodily sensations.

5. Conclusion

The effect of cortisol on BRS, but not CMS, suggests that central and efferent components of the arterial baroreflex are rapidly affected by cortisol, whereas afferent components are unaffected. The previously published effect of cortisol on the cortical processing of cardio-afferent signals is, therefore, due to cortical mechanisms rather than peripheral activation or mediation by brainstem structures.

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