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Cortisol rapidly affects amplitudes of heartbeat-evoked brain potentials—Implications for the contribution of stress to an altered perception of physical sensations?

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Summary Little is known about the impact of stress and stress hormones on the processing of visceral-afferent signals. Clinical data suggest that cortisol may lower the threshold for interoceptive stimuli, while a pharmacological administration of cortisol decreases the sensitivity for physical symptoms. To clarify the role of cortisol for the processing of interoceptive signals, we investigated 16 healthy men on two occasions, once during the infusion of 4 mg of cortisol and once during the infusion of a placebo substance. Heartbeat-evoked potentials (HEP; derived from resting EEG and ECG, during open and closed eyes), which are psychophysiological indicators for the cortical processing of cardioceptive signals, were measured over 6-min periods once before, and four times after the infusion (1—7, 11—17, 21—27 and 31—37 min). We found that HEP amplitudes were higher during open than during closed eyes between 1 and 17 min after cortisol infusion. There was no effect of cortisol on heart rate. We conclude that cortisol may rapidly modulate the cortical processing of cardioceptive neural signals. These results may have relevance for the effects of stress on the development and maintenance of psychosomatic symptoms.

1. Introduction

Interoception, the perception of bodily processes, plays an important role in the subjective experience of emotions (Wiens, 2005), in consciousness (Damasio, 2003), and in somatic symptom generation (Eley et al., 2004). Stress affects interoception in that activation of the autonomic

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nervous system, as one of two major physiological stress systems (Chrousos and Gold, 1992), mobilizes the cardiovascular system and may therefore enhance cardioceptive neural traffic (Eichler and Katkin, 1994; Schandry et al., 1993; Schulz et al., 2011, 2013). Little is known, however, about the impact of HPA stress axis activation (the second physiological stress system) on the processing of visceral-afferent signals.

While clinical data suggest that cortisol may lower the sensory threshold for the detection of interoceptive stimuli (Rief et al., 1998), exogenous administration of cortisol has been shown to decrease pain sensitivity (Michaux et al., 2012), and metyrapone-induced acute hypocortisolism to increase pain sensitivity (Kuehl et al., 2010b). One possible explanation for these contradictory findings could be the difference between acute and chronic exposure to stress and stress hormones, resulting in hyposensitivity to physical symptoms in acute stress and hypersensitivity under chronic stress conditions (Pruessner et al., 1999; Rief and Barsky, 2005). Nevertheless, the role of cortisol for the processing of non-pain related physical symptoms remains unclear.

Glucocorticoids, such as cortisol, may affect cells in the entire body by binding on mineralocorticoid and glucocorticoid receptors, and by slowly inducing changes in gene transcription (de Kloet et al., 1998). This may be observed earliest after 20—30 min and can last for several hours (Groner et al., 1983). Furthermore, glucocorticoids may also elicit rapid (i.e. within minutes), non-genomic effects on the cell, and it has been proposed that the mineralocorticoid membrane receptor is responsible for these effects (de Kloet et al., 2008; Groeneweg et al., 2011). Recent findings on cortisol rapidly affecting thalamic activity suggest an impact of glucocorticoids on the processing of sensory information due to non-genomic mechanisms (Strelzyk et al., 2012), which may also play a role for the perception of physical symptoms (Cameron, 2001).

Heartbeat-evoked brain potentials (HEPs) represent electrocortical potentials, which are related to the perception of cardiac signals, such as heartbeats. HEPs can be measured 250—600 ms after a cardiac R-wave and have their largest amplitude over the right hemisphere (Leopold and Schandry, 2001; Pollatos and Schandry, 2004; Schandry et al., 1986). HEP amplitudes have been demonstrated to reflect an individuals' performance in heartbeat detection tasks (Katkin et al., 1991; Pollatos and Schandry, 2004; Schandry and Montoya, 1996), motivation to perform in those tasks (Weitkunat and Schandry, 1990) and attentional focus on heartbeats (Montoya et al., 1993; Schandry et al., 1986; Schandry and Weitkunat, 1990). As summarized by Shao et al. (2011, p. 1843), HEPs can also been found independently from an individuals' conscious heartbeat perception, since ''afferent signals from the body continuously reach the brain, and consciously or unconsciously, the brain is continuously monitoring interoceptive information''. Taken together, HEP amplitudes are interpreted as psychophysiological indicator for cortical processing of cardioceptive signals, independently from a conscious process of body perception.

The aim of the current study was to investigate rapid, non-genomic effects of cortisol on HEP amplitudes. Since previous observations about cortisol effects on pain perception were based on oral administration of cortisol and over longer time periods (Michaux et al., 2012), it is difficult to attribute the effects to either genomic or non-genomic mechanisms of cortisol. We, therefore, used a different strategy and assessed the effects of intravenous cortisol infusion on HEPs in a within-subject, double blind, placebo-controlled trial. To control for possible effects of cortisol on cardiovascular activity we also monitored heart rate (HR) during all sessions. As open or closed eyes have a large impact on resting EEG (i.e. the increase of alpha band power in closed eyes), we tested all participants in conditions with open and closed eyes. Based on previous studies showing a reduction in pain sensitivity after cortisol administration and an increase in pain sensitivity as a consequence of metyrapone-induced hypocortisolism (Kuehl et al., 2010b; Michaux et al., 2012), we expected cortisol to affect cortical processing of cardioceptive stimuli in that HEPs would be decreased after cortisol infusion.

2. Method

2.1. Participants

Sixteen right-handed, healthy men (mean age = 23.8 years; SD = 2.1 years) took part in the study and received monetary compensation for participation (€ 50,—). Medical status was carefully screened prior to the experiment by using a customized interview performed by a physician (H.S.) and a psychologist (F.S.), as this is required for any bio-behavioral research at the University of Trier. Exclusion criteria were any acute or chronic physical or mental health complaints, smoking, current medication, critical life events in 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 a community-based Ethics Committee (Landesärztekammer Rheinland-Pfalz).

2.2. Experimental procedure

Participants attended two laboratory sessions, one week apart, and at exactly the same time of day (between 13:00 h and 17:00 h), in a within-subject design. They received cortisol and placebo in a randomized and counterbalanced order, to control for sequence effects. All participants arrived 1 h prior to the experimental session, and a flexible intravenous infusion line was inserted into one of the radial veins, which remained there until the end of the experiment. The 1 h waiting period before the start of the experiment was intended to reduce potential carry-over stress effects related to the initial pain induced by placing the intravenous infusion line. It was repeatedly demonstrated that HEPs can be derived from simultaneous resting EEG/ECG assessment for several minutes without the instruction to focus on heartbeats (Montoya et al., 1993; Schandry et al., 1986; Shao et al., 2011). Since this study was designed to investigate rapid pharmacological effects of cortisol on HEPs, an exact timing of the psychophysiological measurement session was mandatory. Based on our own previous research on rapid cortisol effects on thalamus perfusion (Strelzyk et al., 2012) we divided the experiment into five

EEG/ECG measurement epochs (pre-infusion; post-infusion 1—4), each of 6 min length, and each interrupted by a 4 min break. During the breaks, participants were asked to perform a non-challenging word discrimination task to keep them engaged in the experiment and to prevent them from falling asleep. The task required participants to determine whether prerecorded, audibly presented nouns had either one or two syllables (examples translated into English: e.g., two syllables: "topic"; one syllable: "plan"). The presented words had no relationship to body parts or awareness. The EEG measurements were separated into six sessions of 1 min length, during which participants were instructed either to keep their eyes open (O) or closed (C) in an intra- and inter-individually balanced order that alternated between and within the individual EEG measurement blocks (O-C-C-O-O-C or C-O-O-C-C-O). Participants were asked to relax and neither to speak nor to move during the EEG measurements.

2.3. Substance infusion

Oral administration of cortisol is followed by passage through the stomach. Since there is variability in gastric transit, the onset of cortisol activity cannot be timed appropriately. Therefore, in this study we administered cortisol (4 mg of hydrocortisone) or physiological saline solution (placebo) intravenously from outside the laboratory room in a double-blind fashion during the first break. As summarized by Schilling et al. (2013), a dose of 4 mg of cortisol corresponds to the cortisol secretion after a moderate psychosocial stressor (Kirschbaum et al., 1993; Nater et al., 2007). Infusions were controlled by a CPU-operated modular Fluid-Management System (B. Braun Melsungen Co., Melsungen, Germany) located in an adjacent room. As there were no visual or auditory infusion-related cues, participants were not able to detect infusion onset or offset (Kuehl et al., 2010a; Richter et al., 2011; Strelzyk et al., 2012).

2.4. EEG measurement and data pre-processing

EEG was recorded continuously by 32 Ag—AgCl pin-type active electrodes (BrainAmp: Brain Products, Munich, Germany). The electrodes — FP(1, 2), F(3, z, 4), FC(7, 2, 4, 8), T(7, 1, 2, 8), C(3, z, 4), CP(5, 1, 2, 6), P(7, 3, z, 4, 8), O(1, z, 2), A(1, 2) — were mounted according to the 10—20 system, and referenced to FCz. Impedances of the EEG electrodes were below 10 kΩ. The highpass-filter was set to 0.0159 Hz (24 dB/octave rolloff), and the lowpass-filter was set to 250 Hz. The signals were digitized at 1000 Hz and stored for offline analysis. The EEG was re-referenced to mathematically linked mastoids, then re-filtered (band pass: 0.1—35 Hz; 24 dB/octave) to minimize drifts and noise that were present in some data channels, and re-sampled to 250 Hz. Continuous EEG recordings were visually inspected. Epochs with non-stereotyped artifacts (e.g., electrode cable movements, swallowing, etc.) were excluded from further analysis. As described in earlier studies on heartbeat-evoked potentials (Pollatos et al., 2005; Pollatos and Schandry, 2004), eye blink correction was conducted using the Gratton—Coles algorithm (Gratton et al., 1983). All steps of EEG analysis were performed with Brain Vision Analyzer 2.0 (BrainProducts, Munich, Germany).

2.5. Calculation of heartbeat-evoked potentials

R-waves were automatically detected and manually confirmed in offline ECG signals. EEG data were segmented relatively to the detected R-waves in epochs ranging from 200 ms before the R-wave to 1000 ms after the R-wave. Segments of R-wave-triggered EEG were averaged according to whether they were recorded during open or closed eyes, separated for each EEG measurement session. Since the duration of periods with open and closed eyes was kept constant (1 min per period, 3 min per condition in each session), the total number of heartbeats in this period varies with the participants' actual heart rate (M = 197 [SD = 22] heartbeats per condition, range: 154—268). Up to 450 ms after the R-wave, the HEP amplitude and the electro-cardiac field partially overlap (Dirlich et al., 1997; Schandry et al., 1986). We, therefore, calculated mean voltage in the time interval of 455—595 ms after the R-wave, during which the electro-cardiac field is considered minimal (Gray et al., 2007). Grand averages were calculated over all electrodes to be included in the statistical model.

2.6. Cardiovascular data

Electrodes for ECG measurement (ECG Tyco Healthcare H34SG Ag/AgCl electrodes of 45 mm diameter) were placed according to a standard lead II configuration. The ECG signal was high-pass filtered (0.05 Hz) and stored on an external disk (1 kHz). ECG data were analyzed with WinCPRS 1.160 software (Absolute Aliens Oy, Turku, Finland). Interbeat intervals were calculated from the ECG and manually corrected, with a normal cycle RR-interval time series as output signal, of which mean heart rate data was derived.

2.7. Salivary cortisol

Cortisol levels were monitored using three saliva samples (Salivette cotton swab, Sarstedt, Nümbrecht, Germany) per session, to check if the pharmacological manipulation was successful. Participants provided their first sample upon arrival (baseline), the second before the first EEG measurement (pre-infusion), and the third after the last EEG measurement (post-infusion). 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%) (see Dressendorfer et al., 1992). Cortisol levels were determined twice, and their average was used in further statistical analysis, which represents the standard procedure at the Biochemical Laboratory of the University of Trier.

2.8. Statistical analysis

HEP and HR data were analyzed via a 2 × 5 × 2 repeated-measurement ANOVA with the factors 'substance' (cortisol, placebo), 'time of measurement' (pre-infusion, post-infusion 1—4), and 'eyes' (open, closed). Cortisol data were analyzed via a 2 × 3 repeated-measurement ANOVA with the factors

'substance' (cortisol, placebo) and 'time of measurement' (baseline, pre-infusion, post-infusion). Critical α-level was set to .05. For any effect with repeated measurement and more than two conditions, Greenhouse–Geisser corrected *p*-values are reported. For post hoc analyses, Bonferroni-corrected *T*-tests for dependent samples were calculated. All statistics were conducted with SPSS 19.0 (SPSS, Inc.).

3. Results

3.1. Heartbeat-evoked potential (HEP) amplitudes

We found a significant main effect for the factor 'eyes' on the HEP amplitudes ($F[1,15] = 9.35$; $p = .008$; $\eta^2 = .38$], indicating a larger HEP amplitude during open ($M = .19$ [SEM = .06] μV) than during closed eyes (.07 [.07] μV). However, this effect was superseded by a significant 3-way interaction 'substance' $\times$ 'time of measurement' $\times$ 'eyes' ($F[4,60] = 3.12$; $p = .036$; $\eta^2 = .17$). Post hoc analyses showed that the difference between HEP amplitudes in open and closed eyes could only be found in post-infusion sessions 1 (open: .24 [.08]; closed: −.02 [.13] μV) and 2 (open: .22 [.11]; closed: −.07 [.12] μV; all *p*s $< .05$) after the infusion of cortisol (see Fig. 1a), but not in any session after the placebo infusion (see Fig. 1b). Full HEP amplitudes averaged over sessions post-infusion 1 and 2, separated for substances 'placebo' and 'cortisol' are illustrated in Fig. 2. Neither the main effect for the factor 'substance' ($F[1,15] = 2.52$; $p = .13$), nor any of the remaining effects were significant.

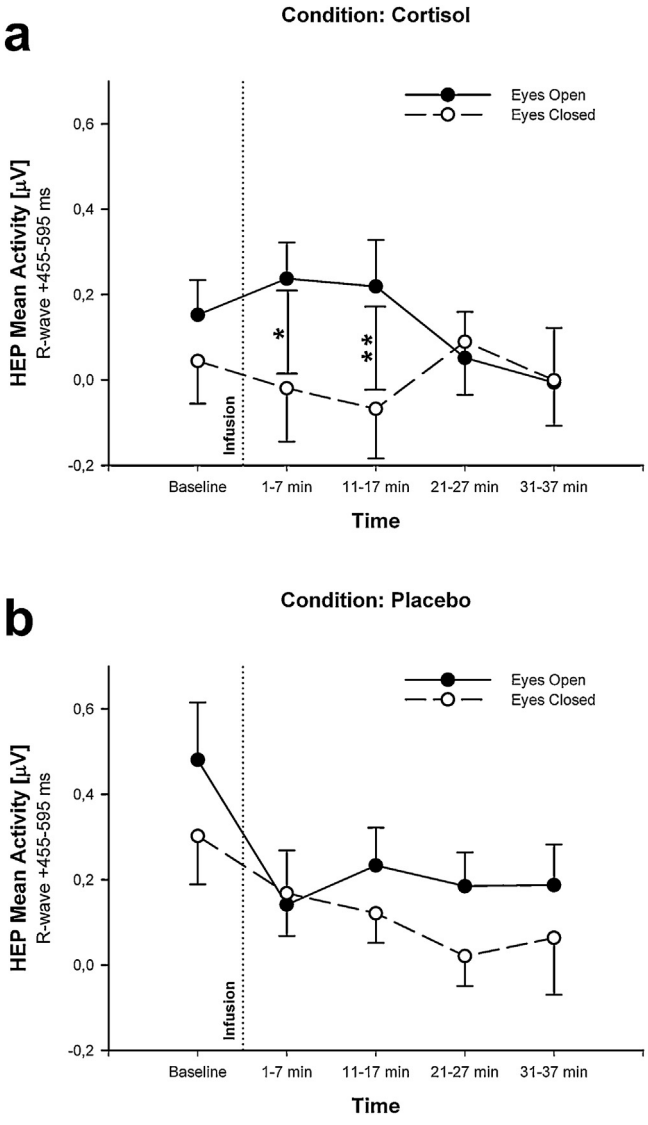

Figure 1 Amplitudes of heartbeat-evoked potentials (HEPs) between 455 and 595 ms after an R-wave. 1–17 min after the infusion of cortisol larger HEP amplitudes were observed in a condition with open compared to a condition with closed eyes (a). After the infusion of a placebo substance HEP amplitudes in conditions with open and closed eyes did not differ from each other (b).

3.2. Cardiovascular data

3.2.1. Heart rate (HR)

HR was significantly higher during open ($M = 65.9$ [SEM = 1.8] bpm) than during closed eyes (64.5 [1.6] bpm; $F[1,15] = 6.62$; $p = .021$; $\eta^2 = .31$). Furthermore, a significant 'time of measurement' $\times$ 'eyes' interaction ($F[4,60] = 4.46$; $p = .013$; $\eta^2 = .23$) indicated that this difference between HR in open and closed eyes increased with time during the experiment (sessions 2, open: 66.0 [1.9], closed: 64.0 [1.8] bpm; session 3, open: 66.9 [2.0], closed: 64.1 [1.7] bpm; session 4, open: 65.5 [1.8], closed: 63.6 [1.5] bpm; all *p*s $< .05$), without any interaction with 'substance' (see Fig. 3a and b).

3.3. Salivary cortisol

We observed a significant interaction of 'substance' $\times$ 'time of measurement' ($F[2,30] = 11.56$; $p = .0003$; $\eta^2 = .43$). Post hoc analyses revealed an increase of salivary cortisol at the post-infusion measurement ($M = 8.3$ [SEM = 1.2] nmol/l) compared to both earlier measurements (baseline: 5.7 [.8]; $p = .064$; pre-infusion: 5.3 [.8]; $p = .008$) after the cortisol infusion only, whereas there was no difference between the measurements after the placebo infusion (baseline: 6.9 [1.5]; pre-infusion: 5.9 [1.4]; post-infusion: 3.9 [.6]). No other effects were observed.

4. Discussion

The aim of the current study was to investigate rapid effects of cortisol on electrocortical processing of cardioceptive signals. We observed a change of heartbeat-evoked brain potentials (HEPs) after the venous infusion of 4 mg of cortisol compared to placebo, dependent on the instruction to participants to either open or close their eyes. Furthermore, we found that HEP amplitudes were higher during open than during closed eyes. Nevertheless, a higher order interaction indicated that this difference could only be observed in a timeframe of 1–17 min after the cortisol infusion. There were no differences in HEP amplitudes between the period before cortisol infusion, later than 20 min after cortisol infusion, or across all time points in placebo infusion. In contrast to what would be expected based on previous reports on the effects of cortisol on pain perception, there

was no general attenuation effect of cortisol vs. placebo infusion on HEP amplitudes. Higher salivary cortisol concentrations after the infusion of cortisol confirmed the success of the pharmacological manipulation. Heart rate (HR) was generally higher during open than during closed eyes, and this difference increased with time during the experiment. However, HR did not change in relation to whether placebo or cortisol was administered. We thus conclude that the observed modulation effect of cortisol on HEPs was not due to altered cardiac activation.

The amplitude of HEPs is a psychophysiological indicator of cortical processing of cardioceptive signals, such as the perception of heartbeats (Pollatos and Schandry, 2004; Schandry et al., 1986). In previous studies, HEPs were measured during the task and participants asked to silently count heartbeats (Leopold and Schandry, 2001; Pollatos and Schandry, 2004; Schandry and Montoya, 1996). Nevertheless, it was also demonstrated that HEPs could be found without that instruction (Fukushima et al., 2011; Gray et al., 2007; Schandry et al., 1986; Shao et al., 2011; Yuan et al., 2007). The HEP amplitude was repeatedly shown to reflect attentional resources allocated to heartbeats (Montoya et al., 1993; Schandry et al., 1986; Schandry and Weitkunat, 1990). In the current study participants were instructed to relax during the HEP assessments. Thus, in the present study, HEPs may reflect a participants' tendency to shift attention to cardiac sensations, which can certainly be affected by the intensity of cardiac activation (e.g., inotropy) itself. Since HR was not affected by cortisol infusion, we conclude that the effect of cortisol on HEPs reflects an altered afferent or central processing of cardioceptive signals.

Previous studies allow for two competing hypotheses regarding the impact of cortisol on central processing of interoceptive signals: (1) based on clinical data, cortisol may lower the sensory threshold for the detection of interoceptive stimuli (Rief et al., 1998) or (2) based on experimental pharmacology, cortisol may decrease sensitivity for symptom perception (Kuehl et al., 2010b; Michaux et al., 2012). The current results do not support either hypothesis, as there was no two-way interaction between 'substance' and 'time of measurement'. Nevertheless, HEP amplitudes were modulated directly after cortisol infusion depending on whether participants had to open or close their eyes. Open eyes result in a higher perceptual load compared to closed eyes (Perfect et al., 2011; Vredeveldt et al., 2011). Higher perceptual load affects attentional processes (Lavie, 2005) and eventually increases wakefulness and vigilance (e.g., the sensitivity for warning signals) (Neelon et al., 2011). These processes can be interpreted as factors of the 'alerting' component of attention (Posner and Petersen, 1990). This assumption is also supported by electroencephalographic studies that showed larger power in the alpha-band during

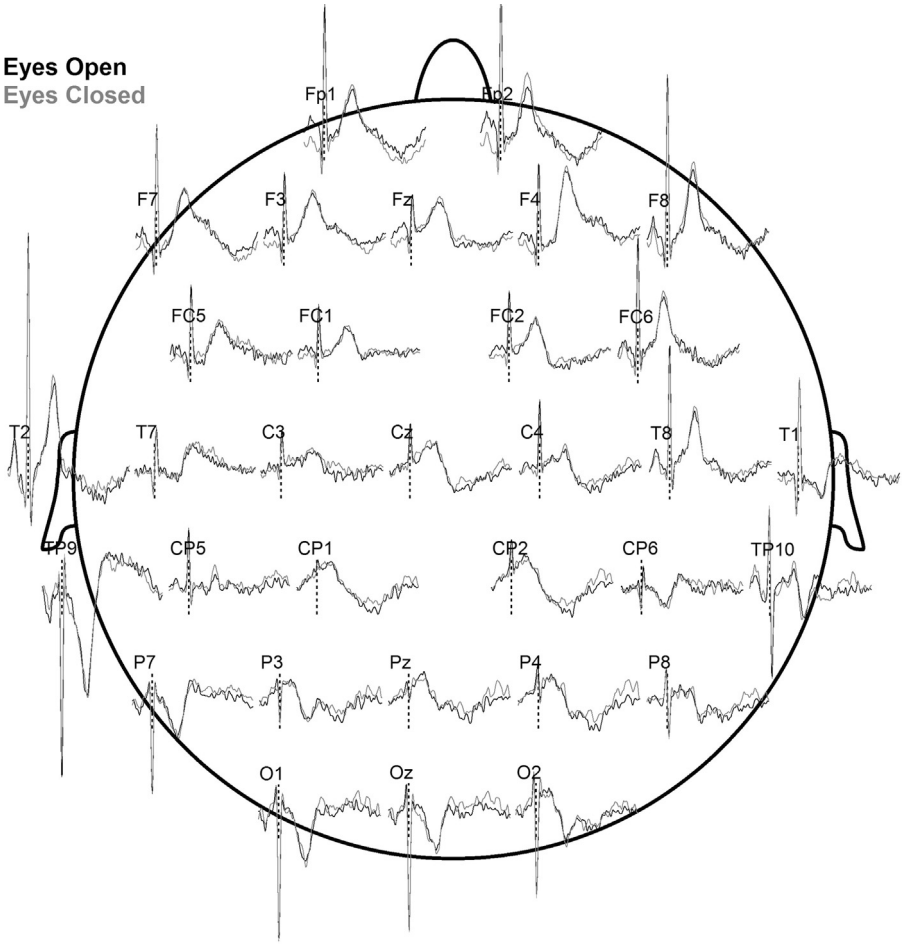

Figure 2 Grand averages of HEP amplitudes over post-infusion sessions 1 and 2, which took place 1—7 and 11—17 min after cortisol infusion. HEP amplitudes were separately displayed to whether participants had open or closed eyes.

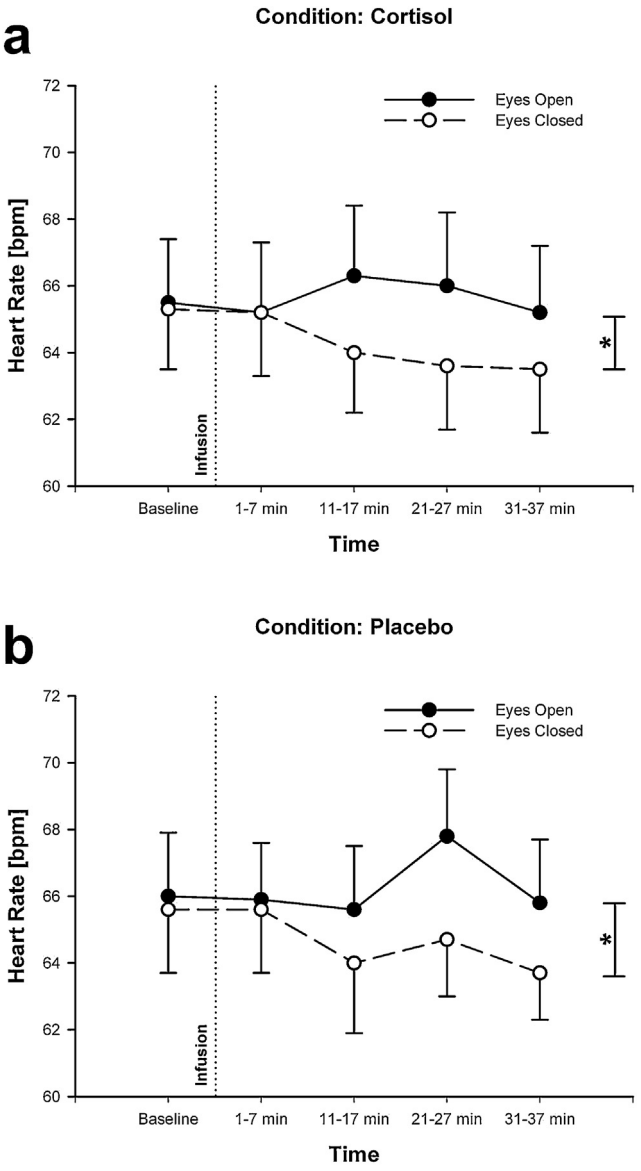

Figure 3 Mean heart (HR) rate during cortisol (a) and placebo infusion (b). HR was generally higher in open than in closed eyes, independent from substance infusion. This effect was based on significant differences during the last three measurement occasions.

closed compared to open eyes (Niedermeyer and Lopes da Silva, 1993), which is associated with a state of relaxation. The 'alerting' component of attention is associated with central noradrenergic structures (Fan et al., 2005; Posner and Petersen, 1990), which also play a role for the control of the autonomic nervous system. This assumption is in concordance with our finding on lower HR under closed eyes conditions compared with open eyes. Our data suggest that after cortisol infusion cardioceptive signals have a higher cortical impact during an increased perceptual load of the visual system, potentially associated with an increased activation of the 'alerting' component of attention. Taken together, cortisol may amplify visceral-afferent signal transmission during increased alertness (open eyes) and favor their function of signaling and warning, compared to a state of decreased alertness (closed eyes).

Visceral-afferent neural signals from the cardiovascular system, which represent the neural basis for heartbeat perception, are relayed in the nucleus tractus solitarius (NTS) (Jänig, 2006). The NTS projects onto the parabrachial nucleus and the locus coeruleus, from where hypothalamic and thalamic nuclei, as well as cortical structures, the anterior cingulate cortex (ACC), the frontal cortex, the somatosensory cortex and the insular cortex are reached (Cameron, 2001; Critchley et al., 2004; Pollatos et al., 2007). Pollatos et al. (2005) demonstrated that the principal components underlying the HEP signal originate from exactly those four cortical areas. Cortisol was found to be associated with activity in the ACC and the right insula during stress (Wang et al., 2005), whereas cortisol infusion rapidly decreases blood perfusion in the thalamus (Strelzyk et al., 2012). As the thalamus also plays a key role in the 'alerting' component of attention (Fan et al., 2005), it may play an important role in the here reported effects. Nevertheless, this should be addressed by follow-up studies as the current study was not designed to identify the brain structures or cognitive processes that are associated with cortisol-induced HEP-changes.

We applied a dose of 4 mg of cortisol intravenously. The daily production of cortisol in humans is about 25—30 mg. According to Schilling et al. (2013), a dose of 4 mg of cortisol corresponds to the cortisol secretion after a moderate psychosocial stressor (Kirschbaum et al., 1993; Nater et al., 2007). As mentioned previously, there are two ways for glucocorticoids to act on effector cells: a genomic mechanism, whose effects can be earliest found about 20—30 min after infusion (Groner et al., 1983), and a non-genomic mechanism, whose effects are instantaneous. In the current study the modulatory effects on HEPs occurred in a timeframe of 1—17 min after cortisol infusion and could not be found later than 20 min after infusion. These effects can, therefore, be clearly attributed to a rapid, presumably non-genomic mechanism of cortisol. This result is well in line with earlier findings indicating that cortisol exerts rapid effects on thalamic perfusion within a period of ca. 15 min after infusion (Strelzyk et al., 2012).

Our findings may also have implications for the role of stress in the generation of psychosomatic symptoms. Individuals who are exposed to early life or chronic stress often suffer from a dysregulation of HPA axis activity, such as a hypercortisolism (Gold et al., 1988; Tafet and Bernardini, 2003). As demonstrated in the current study, an increase in cortisol may modulate the cortical impact of afferent signals originating from the cardiovascular system depending on whether individuals are in a state of activity or relaxation. Patients with panic disorder or somatoform disorders are thought to have an altered ability in perceiving their heartbeats (Ehlers et al., 1995; Pollatos et al., 2011), and are prone to be in a chronic state of activation (Hammad et al., 2001). We would argue that this modulation of cardioceptive accuracy may be associated with cortisol-induced modulation of cardioceptive signals on a cortical level, which could be due to early life or chronic stress exposure, and which feeds into a vicious circle of increased attentional focus on physical symptoms, increased anxiety and higher levels of cortisol. This effect may represent a possible psychoneuroendocrine mechanism underlying psychological

feed-forward models of somatosensory amplification (Barsky et al., 1988). Interestingly, the rapid effects of interoceptive signal modulation by cortisol reported here may interact with classical conditioning enhancement found after cortisol infusion (Kuehl et al., 2010a). Both processes would support the generation of psychosomatic symptoms.

5. Limitations

In previous studies the assessment of HEPs was performed during rest (Schandry et al., 1986; Shao et al., 2011; Yuan et al., 2007), or during a heartbeat tracking task (Leopold and Schandry, 2001; Montoya et al., 1993; Pollatos et al., 2005; Pollatos and Schandry, 2004; Schandry and Montoya, 1996; Schandry and Weitkunat, 1990; Terhaar et al., 2012). Since pharmacological studies require an exact time frame, resting EEG and ECG were assessed without implementing a heartbeat tracking task. However, even though HEPs passively assessed during a resting condition may still represent the processing of afferent signals from the cardiovascular system (Shao et al., 2011), it is unclear to what degree our results may also have implications for an active process of body perception.

The current study aimed at investigating rapid effects of a single dose of 4 mg of cortisol on HEPs, without participants experiencing concomitant stress. This involved a computer-controlled infusion protocol, which ensured that participants were not only unaware (double-blind design) about the substance (placebo or cortisol) that they received, but also about the timing, onset, and end of the infusions (covert infusion protocol). The reported effects may be limited to the dosage of cortisol applied in the current study. Thus, general conclusions about effects of cortisol on HEPs should be drawn with caution. Furthermore, the effect of cortisol on HEPs may be different when individuals experience acute or chronic stress with full awareness. Since the modulatory function of cortisol on the perception of physical symptoms may vary between acute and chronic stress exposure (Pruessner et al., 1999; Rief and Barsky, 2005), future studies should focus on the question whether psychophysiological indicators of interoception, such as HEPs, may also be altered in patients with panic disorder or somatoform disorders, and if there is any relationship with endogenous cortisol levels.

6. Conclusion

The current results suggest that cortisol modulates the cortical processing of cardioceptive neural signals dependent on whether individuals are in a state of high vs. low alertness (open or closed eyes). This effect can be attributed to a rapid, presumably non-genomic mechanism. The main contribution of this study is to demonstrate that stress hormones (i.e. cortisol) may affect brain—body interaction. The exact neuro-anatomic and neuro-pharmacological mechanisms underlying the reported effects still need to be evaluated in the future, as well as possible implications for chronic stress-related conditions and psychosomatic symptoms.

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Conflict of interest

All authors declare that they have no potential conflicts of interest.

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