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Psychological traits and the cortisol awakening response: Results from the Netherlands Study of Depression and Anxiety

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Summary
Background: Hypothalamus–Pituitary–Adrenal (HPA) axis dysregulation is often seen in major depression, and is thought to represent a trait vulnerability – rather than merely an illness marker – for depressive disorder and possibly anxiety disorder. Vulnerability traits associated with stress-related disorders might reflect increased sensitivity for the development of psychopathology through an association with HPA axis activity. Few studies have examined the association between psychological trait factors and the cortisol awakening response, with inconsistent results. The present study examined the relationship between multiple psychological trait factors and the cortisol awakening curve, including both the dynamic of the CAR and overall cortisol awakening levels, in a sample of persons without psychopathology, hypothesizing that persons scoring high on vulnerability traits demonstrate an elevated cortisol awakening curve.
Methods: From 2981 participants of the Netherlands Study of Depression and Anxiety (NESDA), baseline data from 381 controls (aged 18–65) without previous, current and parental depression and anxiety disorders were analyzed. Psychological measures included the Big Five personality traits (neuroticism, extraversion, openness to experience, conscientiousness, and agreeableness) measured using the NEO-FFI, anxiety sensitivity assessed by the Anxiety Sensitivity Index, cognitive reactivity to sadness (hopelessness, acceptance/coping, aggression, control/perfec-

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tionism, risk aversion, and rumination) as measured by the LEIDS-R questionnaire, and mastery, assessed using the Pearlin and Schooler Mastery scale. Salivary cortisol levels were measured at awakening, and 30, 45, and 60 min afterwards.

Results: In adjusted analyses, high scores of hopelessness reactivity (β = .13, p = .02) were consistently associated with a higher cortisol awakening response. In addition, although inconsistent across analyses, persons scoring higher on extraversion, control/perfectionism reactivity, and mastery tended to show a slightly flatter CAR. No significant associations were found for neuroticism, openness to experience, agreeableness, conscientiousness, anxiety sensitivity, and acceptance/coping, aggression, or risk aversion reactivity.

Conclusion: Of various psychological traits, only hopelessness reactivity, a trait that has been associated with depression and suicidality, is consistently associated with HPA axis dysregulation. Hopelessness reactivity may represent a predisposing vulnerability for the development of a depressive or anxiety disorder, possibly in part mediated by HPA axis activity.

1. Introduction

Depressive illness has been associated with a dysregulation of the Hypothalamus—Pituitary—Adrenal (HPA) axis (Pariante and Lightman, 2008). Although not always consistent, the preponderance of evidence indicates that cortisol hypersecretion is associated with major depression (Holsboer, 2001; Pariante and Lightman, 2008), and possibly anxiety disorder (Mantella et al., 2008; Vreeburg et al., 2010a). Of various HPA axis activity indicators, the most consistent association with depressive disorder in depressed outpatients has been observed for the cortisol awakening response (CAR; Bhagwagar et al., 2005; Cowen, 2010). The CAR reflects the natural response of the HPA axis to awakening, and is not strongly associated with cortisol sampled later in the day (Schmit-Reinwald et al., 1999; Edwards et al., 2001), suggesting that it may represent a discrete aspect of HPA axis function.

Our findings of a higher cortisol awakening curve both among current and remitted depressive and anxiety disorder (Vreeburg et al., 2009a, 2010a), and the presence of cortisol hypersecretion in asymptomatic individuals at familial risk of depression (Mannie et al., 2007; Vreeburg et al., 2010b), suggest that HPA axis dysregulation represents a trait vulnerability — rather than merely an illness marker — for mood disorder and possibly anxiety disorder. If this is true, the CAR might also be related to psychological vulnerability markers of depression in never depressed individuals. To exclude effects of current and previous psychopathology, it is essential to examine the link between psychological traits and the cortisol awakening curve in persons who never experienced a depressive or anxiety disorder. The goal of the present study is to examine the association between multiple personality characteristics and the cortisol awakening curve in a sample free of depressive and anxiety disorders.

Several psychological traits are closely linked to depression and anxiety, such as the Big Five personality factors neuroticism and extraversion (Costa Jr. and McCrae, 1995; Furukawa et al., 1998; Bienvenu et al., 2001; Spinhoven et al., 2009). Other psychological traits that are related to depression and anxiety include depression-related cognitions such as hopelessness and rumination, anxiety sensitivity and mastery (Kennedy et al., 1998; Kuehner and Weber, 1999; American Psychiatric Association, 2000; De Graaf et al., 2002).

Few studies examined the association of these psychological traits with HPA axis function in persons free of current psychopathology, of which only a small number focused on the cortisol awakening response, with mixed results. For example, for neuroticism, both positive (Portella et al., 2005), negative (Hauner et al., 2008) and absent (Chan et al., 2007) associations were found. High scores of introversion were associated with lower cortisol awakening responses (Hauner et al., 2008), whereas traits associated with introversion, such as high harm avoidance and low novelty seeking, showed higher cortisol awakening levels (Rademaker et al., 2009). In a study of personality traits and morning cortisol among older persons, no associations were found for neuroticism, mastery and self-esteem (Gerritsen et al., 2009). Other traits, such as conscientiousness, openness, and agreeableness have not been investigated yet.

Taken together, these results are indicative, but far from conclusive, of an association between psychological vulnerability traits and morning cortisol levels. Overall, both the number of studies and the sample sizes are limited (highest n = 230, but the majority is well below this), resulting in low power to detect correlations. Furthermore, most studies focused only on one trait, thereby missing out on the contribution of multiple traits to HPA axis functioning.

In the present study we investigated the association between the cortisol awakening curve, including both the dynamic of the CAR and overall cortisol awakening levels, and multiple psychological trait factors related to depression and anxiety disorders (the Big Five personality traits, cognitive reactivity to sadness, anxiety sensitivity, and mastery) in a large sample of participants free of current and past psychopathology. We hypothesize that persons scoring high on vulnerability traits demonstrate an elevated cortisol awakening curve.

2. Methods

2.1. Sample

Study participants come from the Netherlands Study of Depression and Anxiety (NESDA), a large cohort study conducted among 2981 adults (18—65 years). The study examines the long-term course and consequences of depressive and anxiety disorders. Respondents were recruited from the community, general practice, and secondary mental health care, and included persons with psychopathology as well as

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controls without a psychiatric diagnosis. General exclusion criteria were: a primary diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder and not being fluent in Dutch. A detailed description of the NESDA study design, its rationales, methods, and recruitment strategy can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

To obtain an indication of the association between psychological traits and the cortisol awakening curve unbiased by potential psychopathology effects, the present study only included controls from the NESDA cohort. Controls were defined as having no prior lifetime history of depressive disorder (major depressive disorder (MDD) or dysthymia) or anxiety disorder (panic disorder, generalized anxiety disorder, or social phobia) as assessed by the DSM-IV Composite Interview Diagnostic Instrument (CIDI; WHO version 2.1) (n = 676), and no diagnosed parental history of depression or anxiety (n = 140). These criteria fitted 536 NESDA respondents. In addition, we excluded 11 pregnant or breastfeeding women, 29 participants on systemic, dermal or respiratory corticosteroids, and seven daily antidepressant users, leaving an initial sample of 489 respondents. Of these, 400 persons (81.8%) returned at least two saliva morning cortisol samples, 382 of whom returned all four morning measurements. Responders on saliva collection were older than non-responders (47.7 years versus 40.0 years, $p < .001$), were less often smokers (22.0% versus 41.6%, $p < .001$), and scored lower on the psychological traits extraversion (41.4 versus 43.6, $p < .001$), acceptance/coping reactivity (0.82 versus 1.45, $p = .02$), and anxiety sensitivity (22.3 versus 24.6, $p = .02$), but did not differ in terms of the other psychological trait measures, sex, physical activity level, and the presence of cardiovascular disease ($p > .10$).

In data cleaning we assigned missing values to 18 cortisol values (out of 1580) that were higher than two standard deviations from the mean, and to 19 samples collected outside of a 5 min margin around the time protocol. This procedure left 337 respondents with all four saliva samples, 34 with three samples, and 10 persons with two samples (n = 381) that formed the study sample for the present analyses.

2.2. Measurements

2.2.1. Cortisol

A minimally intrusive way to measure basal cortisol levels is through saliva sampling, reflecting the active unbound form of cortisol (Kirschbaum and Hellhammer, 1989). As described in more detail elsewhere (Vreeburg et al., 2009a), respondents were instructed to collect saliva samples at home on a regular (preferably working) day shortly after the interview. Instructions concerning saliva sampling prohibited eating, smoking, drinking tea or coffee or brushing teeth within 15 min before sampling. Furthermore, no dental work 24 h prior to sampling was allowed. The median time between the interview and saliva sampling was 9.0 days. Saliva samples were obtained using Salivettes (Sarstedt, Germany) at four time points; at awakening (T1) and 30 min (T2), 45 min (T3), and 60 min (T4) afterwards, determining the cortisol awakening curve. After return by mail, samples were stored at −80 °C. Cortisol analyses were performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switserland), as described by van Aken et al. (2003). The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%.

Cortisol awakening curve. In addition to conducting Linear Mixed Model analyses (see Section 2.4), using all four saliva samples that determine the cortisol awakening curve we calculated the area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg), using Pruessner's formulas (Pruessner et al., 2003). The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of the dynamic of the CAR, more related to the sensitivity of the system, emphasizing changes over time after awakening (Pruessner et al., 2003). For AUC analyses all four morning samples had to be available (n = 337). Mixed model analyses included all persons with at least two valid morning cortisol values (n = 381), since the analyses can adequately interpolate for missings (Gueorguieva and Krystal, 2004). LMM analysis was used as a confirmation of the results of the regression analyses; only associations with p-values below .10 in both regression and LMM analyses were considered relevant, thereby decreasing the chance of irrelevant chance findings.

2.2.2. Psychological traits

Personality. Personality was operationalized using the NEO-FFI personality questionnaire, a 60-item questionnaire measuring five personality domains: neuroticism, extraversion, openness to experience, conscientiousness and agreeableness. Items (e.g. 'I often feel inferior to others') are answered on a 5-point Likert scale, ranging from 'strongly disagree' to 'strongly agree' (Costa Jr. and McCrae, 1995). Each domain constitutes of 12 items, with scores ranging from 12 to 60 per domain. Internal consistency values range from .74 to .89 (Costa and McCrae, 1992).

Cognitive reactivity to sadness. The revised Leiden index of depression sensitivity (LEIDS-R questionnaire) assessed the extent in which dysfunctional cognitions are triggered during normal mood variations. The measure consists of 34 items (e.g. 'when in a sad mood, I become more bothered by perfectionism') that are answered on a 5-point Likert scale, ranging from 'not at all' to 'very strongly', and divided into six reactivity subscales: hopelessness, acceptance/coping, aggression, control/perfectionism, risk aversion and rumination, with adequate internal consistency (Van der Does, 2002; Van der Does and Williams, 2003). Hopelessness reactivity and acceptance/coping reactivity both constitute of 5 items, with a maximum score of 20, whereas the other scales are based on 6 items with maximum scores of 24 per subscale.

Anxiety cognitions. The Anxiety Sensitivity Index (ASI; Reiss et al., 1986) was used to assess the degree to which subjects fear the potential negative consequences of anxiety related symptoms and sensations (e.g. 'it scares me when I am unable to keep my mind on a task'). The questionnaire comprises 16 items, which are answered on a 5-point Likert scale (0 = 'hardly' to 4 = 'very much'). By summation of all ASI responses, a total score of anxiety sensitivity was calculated, ranging from 0 to 64, with a high internal consistency (Vujanovic et al., 2007).

Mastery. Locus of control was assessed by the 5-item mastery scale (Pearlin and Schooler, 1978), with good

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construct validity (Pearlin et al., 1981). The items (e.g. 'I have little control about the things that happen to me') are answered on a 5-point Likert scale, ranging from 'strongly disagree' to 'strongly agree', resulting in scores from 5 (low mastery) to 25 (high mastery).

All used subscales had high internal consistencies, with Crohnbach's alpha ranging from .78 for openness to experience to .98 for anxiety sensitivity.

2.3. Covariates

As associations have been described between salivary cortisol variables and sociodemographics (sex, age), sampling factors (awakening time, work status, season), and cardiovascular disease (Vreeburg et al., 2009b), these determinants were considered as standard covariates. Additional adjustments were made for sleep duration, smoking, and physical activity to check whether results were independent of these possible explanatory factors. Participants reported their time of awakening and working status on the sampling day. Date information of the sampling day was used to determine the season, which was categorized in months with less (October through February) or more (March through September) daylight. Cardiovascular disease (including coronary disease, angina, heart failure and myocardial infarction) was ascertained using an algorithm based on self-report data and the use of cardiovascular medication. Average sleep duration in the last 4 weeks was assessed using the Insomnia Rating Scale (Levine et al., 2005), and was dichotomized as more or less than 6 h per night. Smoking status was indicated as current versus no smoker. Physical activity was assessed using the International Physical Activity Questionnaire (Craig et al., 2003) and is indicated as the total number of Metabolic Energy Turnover (MET)-minutes a week. A MET-minute is

Table 1 Sample characteristics (n = 381).

	Mean (SD)	Range
Age	47.7 (11.8)	19–65
% Female	60.1	
Physical activity (in 1000 MET-min/week)	3.8 (3.0)	0–16.5
% Smoking	22.0	
% Cardiovascular disease	5.8	
Sampling factors		
Time of awakening	07:17 h (01:07 h)	
% Working on day of sampling	65.9	
% Sampling during light month	52.8	
% >6 h of sleep	81.6	
Psychological factors		
Personality traits		
Neuroticism	26.6 (7.5)	12–48
Extraversion	41.3 (6.5)	23–57
Openness to experience	36.9 (5.2)	18–50
Agreeableness	45.5 (4.8)	31–58
Conscientiousness	45.4 (5.3)	28–59
Cognitive reactivity to sadness[a]		
Hopelessness reactivity	1.6 (2.3)	0–15
Acceptance/coping reactivity	0.8 (1.5)	0–10
Aggression reactivity	2.5 (2.8)	0–17
Control/perfectionism reactivity	3.3 (3.1)	0–16
Risk aversion reactivity	4.4 (3.8)	0–15
Rumination reactivity	4.7 (4.0)	0–18
Anxiety sensitivity[a]	7.4 (5.4)	0–33
Mastery[a]	20.8 (3.4)	10–25
Cortisol indicators		
Morning cortisol (nmol/l)		
T1, at awakening	16.9 (7.5)	2.7–62.6
T2, +30 min	19.6 (7.6)	2.0–50.6
T3, +45 min	18.2 (8.6)	1.4–71.7
T4, +60 min	16.1 (8.4)	1.6–85.5
AUCg (nmol/l/h)	18.1 (6.2)	2.0–42.1
AUCi (nmol/l/h)	1.3 (6.4)	−26.5 to 23.9

Abbreviations: SD, standard deviation; MET, metabolic energy turnover; AUCg, area under the morning curve with respect to the ground (= $(((T_1 + T_2)/2) \times 0.5) + (((T_2 + T_3)/2) \times 0.25) + (((T_3 + T_4)/2) \times 0.25)$); AUCi, area under the morning curve with respect to the increase (= $(((T_1 + T_2)/2) \times 0.5) + (((T_2 + T_3)/2) \times 0.25) + (((T_3 + T_4)/2) \times 0.25)) - (T_1 \times (0.5 + 0.25 + 0.25))$ (Pruessner et al., 2003).

[a] n = 371 due to missings.

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defined as the Metabolic Equivalent of the number of calories consumed by a person (of 60 kg) per minute in an activity relative to the basal metabolic rate (http://www.ipaq.ki.se), expressed per 1000 MET-minutes.

2.4. Statistical analyses

AUCg and AUCi showed normal distributions, allowing regression analyses with non-transformed values. For Linear Mixed Model (LMM) analyses, the four morning cortisol values were slightly positively skewed and therefore log-transformed. All results presented in Table 1 show untransformed values. To analyze the relationship between the psychological trait variables and cortisol measures, linear regression analysis was performed. Each of the psychological measures was entered in two separate analyses with the cortisol measures AUCi and AUCg as outcomes and which included all standard covariates. In addition, for each psychological factor random coefficient analysis of the four log-transformed morning samples was performed using LMM analyses, using values of all four data points, accommodating for incomplete cases, and taking into account the correlation between repeated data. Psychological trait, time point (1, 2, 3, 4) and all standard covariates were entered as fixed factors, subjects were treated as a random effect and a random intercept was estimated. To examine whether the course of cortisol level after awakening was different for different levels of psychological measures, we added a trait by time interaction term. All analyses were conducted using SPSS version 16.0. A confidence level of 95% ($p = .05$) was chosen, and p-values below .10 were considered a trend.

3. Results

Sample characteristics are shown in Table 1. The mean age was 47.7 years and 60.1% was female. Means and standard deviations of the psychological measures are comparable to (Hoekstra et al., 1996) or slightly lower than those found in the general population (Struzik et al., 2004; Williams et al., 2008). High ($r > .60$) and significant ($p < .01$) correlations among psychological measures were found between the cognitive reactivity subscales hopelessness and risk aversion ($r = .63$), rumination and risk aversion ($r = .76$), and rumination and hopelessness ($r = .64$).

3.1. Cortisol awakening curve

Table 2 shows results of regression analyses for AUCg and AUCi and Linear Mixed Models (LMM) analyses for the four morning samples. With respect to the cortisol awakening curve, two elements can be distinguished. First, a direct effect on overall morning cortisol values was indicated by a larger AUCg and/or a significant (direct) effect for a factor in LMM analyses. Second, a difference in the course over time (or the shape of the CAR) can be found, reflected by a difference in AUCi and/or a significant interaction between factor by time in the LMM analyses. Traits for which $p < .10$ in both AUC and LMM analyses were considered relevant.

A consistent effect on the cortisol awakening curve was only found for hopelessness reactivity, indicated by a significant association with the AUCi ($\beta = .13$, $p = .02$, $R^2 = .014$, R^2 total model = .021) as well as a significant interaction with time in LMM analyses ($F(3,1043.11) = 3.85$, $p = .01$). After awakening, persons with higher scores of hopelessness reac-

Table 2 Results of linear regression analyses, associating psychological factors with the cortisol awakening curve.

	AUCg ($n = 337$)		AUCi ($n = 337$)		Linear mixed models ($n = 381$)			
					Direct effect		Time interaction	
	β[a] (SE)	p	β[a] (SE)	p	F	p	F	p
Personality								
Neuroticism	.08 (.05)	.12	.07 (.05)	.21	0.98	.32	0.47	.71
Extraversion	−.01 (.05)	.83	−.09 (.05)	.10	0.02	.90	1.29	.28
Openness to experience	−.04 (.07)	.44	−.07 (.07)	.23	0.05	.82	0.08	.97
Agreeableness	.00 (.07)	.96	.04 (.08)	.48	0.56	.46	1.41	.24
Conscientiousness	−.02 (.06)	.76	−.09 (.07)	.12	0.05	.82	1.55	.20
Cognitive reactivity to sadness								
Hopelessness reactivity	.05 (.16)	.33	.13 (.16)	.02	0.95	.33	3.85	.01
Acceptance/coping reactivity	−.04 (.23)	.43	−.01 (.24)	.91	2.46	.12	1.49	.22
Aggression reactivity	.00 (.14)	.94	.06 (.14)	.29	0.00	.98	0.99	.40
Control/perfectionism reactivity	−.04 (.11)	.45	−.07 (.12)	.21	0.96	.33	4.27	.005
Risk aversion reactivity	−.03 (.09)	.60	.03 (.10)	.44	0.09	.77	0.98	.40
Rumination reactivity	.07 (.09)	.22	.04 (.09)	.47	2.73	.10	1.23	.30
Anxiety sensitivity	.04 (.06)	.43	.05 (.07)	.36	0.32	.57	0.58	.63
Mastery	.01 (.10)	.85	−.10 (.10)	.06	1.33	.25	1.18	.32

Abbreviations: AUCg, area under the morning curve with respect to the ground; AUCi, area under the morning curve with respect to the increase. Analyses are adjusted for sociodemographics (sex, age), sampling factors (awakening time, work status, season), and cardiovascular disease.

[a] Standardized regression coefficient with standard error.

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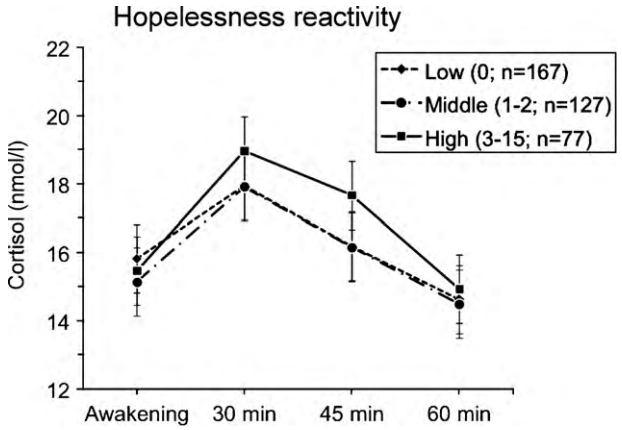

Figure 1 Mean salivary cortisol levels of the cortisol awakening response for subjects with low, middle, and high scores of hopelessness reactivity. All results are adjusted for sex, age, awakening time, work status, season, and cardiovascular disease.

tivity showed a higher CAR. To facilitate the interpretation of this association, a figure was created, after dividing the variable into three levels of severity, as shown in Fig. 1. Due to the skewed distribution of hopelessness reactivity scores, division was based on the best possible group sizes.

Although LMM analyses also revealed a significant interaction with time for control/perfectionism reactivity ($F(3,1041.74) = 4.27$, $p = .005$), the association with AUCi was not significant ($\beta = -.07$, $p = .21$, $R^2 = .002$). Persons scoring higher on control/perfectionism reactivity showed a slightly flatter CAR. A trend was found for an association between extraversion and the AUCi ($\beta = -.09$, $p = .10$, $R^2 = .006$), which was not confirmed in LMM analyses ($F(3,1067.66) = 1.29$, $p = .28$). A trend for a direct effect in LMM analyses was found for rumination reactivity ($F(1,362.73) = 2.73$, $p = .10$), however, the association with the AUCg was not significant, nor a trend ($\beta = .07$, $p = .22$, $R^2 = .001$). Lastly, a trend was found for an association between the AUCi and mastery ($\beta = -.10$, $p = .06$, $R^2 = .007$), but no association was found in LMM analyses ($F(3,1042.41) = 1.18$, $p = .32$).

No significant results or trends were found for neuroticism, openness to experience, agreeableness, conscientiousness, acceptance/coping reactivity, aggression reactivity, risk aversion reactivity, and anxiety sensitivity. When additionally adjusting for sleep duration, smoking and physical activity results remained similar.

4. Discussion

-This study examined the associations between multiple psychological traits and the cortisol awakening curve, including both the dynamic of the CAR and overall cortisol awakening levels, in a large cohort of respondents free of current and past psychiatric disorders. We found that, as hypothesized, high scores of hopelessness reactivity were significantly associated with a higher cortisol awakening response. In contrast to our hypotheses, none of the other investigated traits was consistently associated with the cortisol awakening curve.

4.1. Hopelessness reactivity

One previous study examined the link between morning cortisol levels and hopelessness/helplessness, and did not find a significant association (Kaspers and Scholz, 2004). However, their analyses were performed in a small group of chronically stressed nurses ($n = 25$), which were not screened for psychopathology. Furthermore, we measured hopelessness *reactivity* to sad mood, which may be a more sensitive measure than hopelessness, particularly in a healthy sample. Our finding of a higher cortisol awakening response in persons with higher scores of hopelessness might provide a link between the hopelessness theory of depression and physiological correlates. The hopelessness theory of depression (Abramson et al., 1989) states that individuals with the tendency to attribute negative events to stable and global causes, and who possess a negative attributional style, will more likely become hopeless and, as a result thereof, become depressed, than those without these negative inferential styles. Joiner et al. (2005) showed that hopelessness produced an increase in depressive symptoms partly as a function of generating interpersonal stress. As we found hopelessness to be associated with increased levels of morning cortisol, our result suggests that this process might be accompanied by an increased cortisol awakening response.

The cortisol increase after awakening is suggested to have an adaptive function, as it is affected by the anticipation of upcoming demands (Schlotz et al., 2004). Individuals who tend to anticipate on upcoming situations with ineffective cognitions or coping styles, e.g. more hopelessness, might exhibit higher morning cortisol levels, as is suggested by our findings.

The association between hopelessness reactivity and the cortisol awakening response could also be accounted for by genetic factors. Hopelessness is for 30% genetically determined (Jang et al., 2004), and the cortisol awakening curve for 32–48% (Wust et al., 2000a; Kupper et al., 2005). The same genes might underlie hopelessness as well as the cortisol awakening curve, e.g. 5-HTTLPR, as it is associated with both hopelessness (Gonda et al., 2009) and the CAR (Wust et al., 2009). We excluded persons with diagnosed parental depressive or anxiety disorders. Nevertheless, the sample still included persons with self-reported parental psychopathology. Common environmental factors could also have played a role. Exposure to family stress during childhood might have increased cortisol levels, as well as levels of hopelessness reactivity, possibly through ineffective coping styles (Shek and Lee, 2005; Ellenbogen and Hodgins, 2009; Taylor et al., 2010).

4.2. Other psychological traits

Control/perfectionism reactivity and mastery, for which we found a trend towards a flatter morning cortisol response, have not been previously examined in relation to morning cortisol levels, but were found to be associated with higher and lower cortisol responses to stress (Pruessner et al., 1999; Wirtz et al., 2007).

For rumination and neuroticism, two strong predictors of the development of depression and anxiety disorders (Kuehner and Weber, 1999; De Graaf et al., 2002), we observed a trend

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and no association with a higher cortisol awakening curve, respectively. Rumination has previously been associated with a decreased CAR (Kuehner et al., 2007). However, the CAR measurement in that study was based on only two cortisol samples, in a small sample of students ($n = 42$), with limited covariates taken into account. Regarding the cortisol awakening curve and neuroticism, results are divergent, as both higher (Portella et al., 2005), lower (Hauner et al., 2008) and absent (Chan et al., 2007) associations have been found. These inconsistencies might result from differences in the presence of current or past psychiatric disorders, i.e. the possibility that potential effects of neuroticism might actually be accounted for by psychopathology. Furthermore, these analyses were unadjusted for possible parental history of psychopathology.

Whereas we found a nonsignificant trend towards a lower CAR for extraversion, *intro*version has previously been associated with a lower CAR (Hauner et al., 2008). We found no association for risk aversion reactivity, but the comparable trait harm avoidance has been associated with a lower CAR (Rademaker et al., 2009). For both traits, inconsistencies may be due to differences in construct operationalization, as well as differences in sample size, sample characteristics, and the fact that only a limited number of covariates were taken into account in other studies.

Other investigated traits, such as openness to experience, agreeableness, conscientiousness and anxiety cognitions, for which we found no significant associations, have not been studied previously in relation to the cortisol awakening curve.

4.3. Salivary cortisol measures

Morning cortisol levels in our study were lower than those found in previous studies (Wust et al., 2000b), which could be reflective of differences in cortisol assays used, or of non-compliance (Kudielka et al., 2003). Although it was not possible to electronically monitor compliance, evidence suggests high concordance between self-reported and objectively measured awakening times in morning cortisol collection (DeSantis et al., 2010).

The explained variances of cortisol levels by psychological traits were small. However, as the HPA axis reacts to various internal and external stimuli, it may not be very likely that psychological traits explain a much larger amount of variance in cortisol values. In addition, the CAR has shown to be determined in part by genetic factors (Wust et al., 2000a; Kupper et al., 2005).

The clinical relevance of the cortisol awakening curve remains to be determined. However, recent evidence suggests that a higher CAR is associated with an increased risk of the development of MDD in young adults (Adam et al., 2010). Furthermore, higher morning cortisol levels are associated with unfavorable somatic health (Eller et al., 2005; Dekker et al., 2008).

Our study is unique in several ways. Firstly, we examined the association between psychological traits and the cortisol awakening curve in a large enough sample to detect small effects while allowing to adjust for relevant covariates. Secondly, the inclusion of multiple psychological traits provides a broad overview of possibly relevant factors. Lastly, our sample comprised of persons without previous and current depressive and anxiety disorders, ruling out possible state effects of psychopathology.

Nevertheless, some limitations need to be taken into account. First, our study has a cross-sectional nature, which prevents us from drawing conclusions regarding causality. Second, since we performed multiple tests and found few significant results, we cannot completely rule out that our results represent chance findings. Nevertheless, we proved consistency by confirming our findings with LMM analyses, and only traits that showed an association for both AUCg/AUCi regression and LMM analyses were regarded relevant. Third, cortisol sampling took place on only one day. It has been examined that multiple days of sampling are superior to obtain reliable salivary cortisol measures, since AUCi measured on a single day is determined by situational factors (Hellhammer et al., 2007). Unfortunately, a design of multiple days of cortisol sampling was not possible in our large-scale study. This limitation regarding the reliability of individual measures might possibly be partly compensated by our large sample size. Fourth, no information was gathered on the perception of current stress on the sampling day, so state effects could not be accounted for. However, when additionally adjusting our analyses for two measures of the amount of recent stress experienced (Daily Hassles scores and Inventory of Depressive Symptoms), assessed at the day of the interview, our results remained similar. Fifth, as mentioned before, non-compliance could have affected our results. This could have resulted in measurement error and may have contributed to the finding that part of the respondents (32.5%) did not show an increase in cortisol within the first hour after awakening. Indeed, electronic monitoring has shown a flattened CAR in non-compliant persons (Kudielka et al., 2003). Conversely, it was also found that, when closely monitoring awakening, still at least 15% of all persons did not respond with a cortisol rise (Dockray et al., 2008). As a check, we repeated our analyses in only those persons showing a rise of cortisol in the morning, and found very similar results for hopelessness reactivity ($\beta = .13$, SE = .14, $p = .06$). Furthermore, the wide age range of our sample can be considered another limitation. We cannot exclude the option that associations between psychological measures and the CAR may be stronger among, e.g. younger samples. Lastly, it should be noticed that, since we excluded persons with previous, present and parental depressive and anxiety disorders, our results may only generalize to the healthiest portion of the general population.

In conclusion, we found that, of multiple vulnerability traits, only hopelessness reactivity is associated with HPA axis dysregulation. In persons who never experienced a depressive or anxiety disorder, the cortisol awakening response was higher in persons with a personality characteristic that is a confirmed risk factor for depression and suicidality: hopelessness reactivity. Our finding suggests that the predisposing vulnerability of hopelessness reactivity for the development of a depressive disorder might in part be accompanied by HPA axis activity. This confirms the hypothesis that HPA axis dysregulation represents a trait vulnerability rather than a state marker.

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The funders of this study (as mentioned in the acknowledgements) had no further role in the study design; in the collection, analysis, and interpretation of data; in the writing

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of the report; and in decision to submit the paper for publication.

Conflict of interest

None declared.

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