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Temperament and response to the Trier Social Stress Test

A. R. Tyrka^{1,2}, L. M. Wier¹, G. M. Anderson³, C. W. Wilkinson^{4,5}, L. H. Price^{1,2}, and L. L. Carpenter^{1,2}

¹Mood Disorders Research Program and Laboratory for Clinical Neuroscience, Butler Hospital, Providence, RI

²Department of Psychiatry and Human Behavior, Brown Medical School, Providence, RI

³Child Study Center, Yale University School of Medicine, New Haven, CT

⁴Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Providence, RI

⁵Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Abstract

Objective—The personality characteristics behavioural inhibition and neuroticism have been associated with mood and anxiety disorders and, in some studies, hypothalamic–pituitary–adrenal (HPA) axis hyperactivity. We recently reported that low levels of Novelty Seeking were associated with elevated plasma cortisol responses to the dexamethasone/corticotropin-releasing hormone (Dex/CRH) test in healthy adults with no psychiatric disorder. The present study tested the association between temperament and HPA axis function in the same group of subjects using a standardized psychosocial neuroendocrine stress test.

Method—Subjects completed diagnostic interviews, questionnaires, and the Trier Social Stress Test (TSST).

Results—Novelty Seeking was inversely associated with plasma cortisol concentrations at baseline and throughout the TSST, but was not related to adrenocorticotrophic hormone (ACTH) levels.

Conclusion—Results of this study extend our previous finding in the Dex/CRH test to a psychosocial stress test. Future investigations are needed to replicate these findings and further elucidate how temperament and personality are linked to HPA function.

Keywords

Cortisol; adrenocorticotrophic hormone; stress; temperament; personality; inhibition

Introduction

Exposure to stressors and the subjective experience of 'stress' frequently precede the development of mood and anxiety disorders (1–5). Differences in temperament and personality influence how individuals experience potentially challenging or noxious stimuli (6, 7). Cognitive and psychological appraisal of stressors can then influence the intensity of the neuroendocrine stress response, which is largely mediated by activity of corticotropin-releasing hormone (CRH) and the rest of the hypothalamic–pituitary–adrenal (HPA) axis. CRH and HPA axis activity, together with associated autonomic tone, may in turn help shape temperament and personality (8). CRH and HPA axis dysfunction have also been implicated in the pathogenesis of mood and anxiety disorders (9).

Behavioural inhibition is the trait that has been most strongly linked to HPA axis hyperactivity, as it has been extensively studied in human children and adults and has apparent analogues in rodents and non-human primates. Humans and animals with this trait exhibit a stable behavioural tendency to avoid or withdraw from novel situations (10, 11). Humans with high levels of behavioural inhibition are at increased risk for developing anxiety disorders and major depression (10). Behavioural inhibition has been associated with increases in salivary and plasma glucocorticoids in humans (12–17), non-human primates (18–20), and rodents (21–25). Elevated cerebrospinal fluid (CSF) concentrations of CRH have also been shown in non-human primates with behavioural inhibition (11, 19). Behavioural inhibition in humans has been linked to genetic markers at the CRH locus in two studies (26, 27).

A number of studies have measured cortisol concentrations in association with other personality traits, and a few have also assayed adrenocorticotrophic hormone (ACTH) (23–25). Results have been mixed, probably due to variability in trait measures and stress conditions. For example, extroversion or externalizing behaviours are associated with low basal salivary cortisol concentrations in some studies, but others find increases in cortisol concentrations (24, 28, 29). There is some evidence in children that the link between extroversion and cortisol may be mediated by peer rejection, and controlling for this factor may unmask a negative effect of extroversion on cortisol level (29). Neuroticism, a trait that has been closely linked to the development of major depression, has been studied in adults with no history of Axis I psychiatric disorder and found to be associated with an increased salivary cortisol response to awakening (30) and an increased plasma cortisol response to the dexamethasone (Dex)/CRH test (31). However, another study found decreased cortisol responses to the Dex/CRH test in subjects with high neuroticism, many of whom also had a history of psychiatric disorder and a history of childhood adversity (32). There is mounting evidence that early life stress and trauma may be linked to hypocortisolemia and a dampened cortisol response to stress (33–35). A recent report documented an inverse relationship between neuroticism and cortisol response to the Trier Social Stress Test (TSST) in women, but not men (28); this study did not assess childhood history of adversity or maltreatment.

As both early-life stress and a history of psychiatric illness have been associated with HPA axis dysfunction (9), we have studied adults with no history of Axis I psychiatric disorder

and assessed for a history of childhood maltreatment. We used the Tridimensional Personality Questionnaire [TPQ; (36)] subscales Novelty Seeking and Harm Avoidance to assess traits related to behavioural inhibition and neuroticism. Low Novelty Seeking and high Harm Avoidance reflect introversion and inhibition, and Harm Avoidance additionally contains the elements of anxiety and negative affect which are related to neuroticism. We hypothesized that low levels of Novelty Seeking and high Harm Avoidance would predict elevated cortisol reactivity. In a recent study, we found that low Novelty Seeking was associated with greater cortisol responses to a neurobiological challenge, the Dex/ CRH test (37). However, Harm Avoidance was not associated with cortisol responses in this sample.

Aims of the study

The present study was designed to test the hypothesis that low levels of Novelty Seeking and high levels of Harm Avoidance would be predictive of increased cortisol and ACTH responses to a psychosocial stress test in the same healthy sample. In addition, the relationship of the TPQ construct Reward Dependence with ACTH and cortisol responses was investigated in an exploratory fashion.

Material and methods

Subjects

Participants were 17 females and 14 males, aged 18–50 years. Most participants were Caucasian ($n = 24$) and a few were Black ($n = 2$), Asian ($n = 1$), or did not identify their race ($n = 4$). Complete physical and neurological exams were conducted and subjects were excluded if they had one or more of the following conditions: acute or unstable medical illness, endocrine disease, or ongoing treatment with drugs which might influence HPA axis function, including psychotropics, beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids. Oral contraceptives were allowed. All subjects gave voluntary written informed consent to participate in this study, which was approved by the Butler Hospital Institutional Review Board.

Interviews and measures of personality and psychiatric symptomatology

Current and lifetime history of Axis I psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (38). Subjects were selected for the present investigation if they did not meet criteria for a current or past Axis I psychiatric disorder.

Temperament was assessed with the TPQ (36), which has three scales: Novelty Seeking, Harm Avoidance, and Reward Dependence. The Novelty Seeking scale includes the dimensions Exploratory Excitability vs. Stoic Rigidity, Impulsiveness vs. Reflection, Extravagance vs. Reserve, and Disorderliness vs. Regimentation. High levels of Novelty Seeking are correlated with extraversion (39) and low levels are indicative of a more introverted personality style. The Harm Avoidance scale contains the subscales Anticipatory Worry and Pessimism, Fear of Uncertainty, Shyness with Strangers, and Fatigability and Asthenia. Harm Avoidance is positively correlated with measures of neuroticism (39, 40). Reward Dependence is composed of four subscales: Sentimentality, Persistence, Attachment, and Dependence.

In addition, the following self-report questionnaires which have been demonstrated to have good psychometric properties were used: the Inventory for Depressive Symptomatology – Self Report [IDS-SR; (41)], the State-Trait Anxiety Inventory [STAI; (42)], the Childhood Trauma Questionnaire [CTQ; (43)], and the Perceived Stress Scale [PSS; (44)].

Trier Social Stress Test

On a separate day, subjects completed the TSST as follows. Upon arrival for the test, subjects were queried about whether they had experienced any somatic symptoms, stressors or changes in usual habits over the preceding week, and if they reported any significant aberrations the visit was rescheduled. A topical anesthetic cream [EMLA® (lidocaine 2.5% and prilocaine 2.5%)] was applied to the subject's forearm between 12:30 and 12:45 hours. At 13:00 hours, an indwelling intravenous (IV) catheter was inserted in the subject's forearm by a research nurse with extensive experience with IV catheter placement. In every case, the catheter was placed on the first attempt, and none of the subjects reported more than minimal discomfort associated with the catheter placement. A wireless cardiac monitor was placed on the subject's wrist and chest. At 13:50 hours, the subject was taken to another room containing a microphone, a video camera, and a panel of three adult 'judges' wearing laboratory coats. The subject was told they would give a speech in a simulated job interview, and was then brought back to the first room and asked to prepare the 5-min speech. At 14:00 hours, the subject gave the speech followed by a 5-min mental arithmetic task in front of the panel of judges. Blood was obtained at 15-min intervals from 13:45 hours to 15:15 hours for ACTH and cortisol assay. Subjective mood states were assessed at 13:15, 14:15, and 15:00 hours using visual analog scales (VAS; scored 0 to 100), including 'Anxious,' 'Depressed,' 'Fearful,' 'Irritable,' 'Nervous,' and 'Sad.' Two subjects did not complete the VAS and two additional subjects were missing one of the time points for the VAS Anxious. At 15:50 hours, the IV catheter was removed and the subject was discharged home.

Hormone assays

Plasma ACTH was assayed in duplicate 200 µl plasma samples using an immunoradiometric assay (45) according to the manufacturer's instructions (Scantibodies Laboratory, Santee, CA, USA). The minimum detectable ACTH concentration was 2 pg/ml, and the intra- and inter-assay coefficients of variation for this series of assays were 4.6% and 5.3%, respectively. Two subjects did not have enough plasma available for ACTH assay. Plasma cortisol concentrations were assayed in duplicate using the GammaCoat cortisol I-125 coated-tube radioimmunoassay (RIA) kit (INCSTAR Corp., Stillwater, MN, USA). The intra-assay and interassay CVs observed for quality assessment samples (3 and 20 µg/dl) were less than 5% and 10% respectively.

Statistical analyses

Analyses were conducted using spss 11.5.0 for Windows, (SPSS Inc., Chicago, IL, USA). All analyses were two-tailed with alpha set to 0.05. For both ACTH and cortisol, summary variables were created as follows. Net area under the hormone curve over time (netAUC) was calculated using the trapezoidal method, and the change in hormone concentration from baseline to peak (Peak Delta) was calculated. Correlations and *t*-tests were used to test for

associations between the hormone measures and age, sex, psychiatric symptoms and scores on the CTQ and PSS. Correlations conducted with the summary ACTH and cortisol measures were used to test for associations between these hormones. Repeated-measures general linear models were used to determine whether there were changes in the hormone, heart rate, and mood variables over time in the TSST. For all general linear models, Mauchley's Test of Sphericity was used and when appropriate, the Huynh-Feldt adjustment was made.

The main hypotheses regarding the relationship between hormone concentrations and temperament were tested using separate repeated-measures general linear models. Cortisol, ACTH, and VAS mood states were the dependent repeated measures, and Novelty Seeking, Harm Avoidance, and Reward Dependence were the predictor variables. Due to a malfunction of the cardiac monitor, heart rate data were only available for 15 subjects, so associations between heart rate and the temperament factors were not tested due to the small N. Effects of mood state on cortisol response were explored by entering relevant VAS scales into the general linear models testing the relationship between temperament and cortisol response.

Because the general linear models described above involve continuous predictor variables in a repeated measures design, it was necessary to dichotomize the predictor variables in order to illustrate their relationships with cortisol over time. Thus, the temperament and mood state variables were dichotomized via median split and the two groups are displayed in the figures.

Results

Sample characteristics

Characteristics of the sample are summarized in Table 1. Scores on the TPQ scales were generally similar to published norms (36, 46). Novelty Seeking was negatively correlated with Harm Avoidance [$r(31) = -0.48$, $P < 0.01$]. ACTH and cortisol concentrations did not vary as a function of sex, age, or symptoms of depression or anxiety in this healthy sample. There were also no significant correlations between the ACTH or cortisol concentrations and the measures of CTQ or PSS. Peak Delta ACTH was significantly correlated with both the Peak Delta and netAUC cortisol values [$r(27) = 0.83$, $P < 0.0001$ and $r(27) = 0.45$, $P < 0.05$, respectively]; netAUC ACTH was also significantly correlated with both Peak Delta and netAUC cortisol [$r(27) = 0.81$, $P < 0.0001$ and $r(27) = 0.40$, $P < 0.05$ respectively].

Neuroendocrine, autonomic, and affective responses to the TSST

Repeated measures general linear models for ACTH and cortisol values indicated significant effects of time for both hormones [$F(6,23) = 7.54$, $P = 0.0001$ and $F(6,25) = 23.83$, $P = 0.0001$ respectively]. For the 15 subjects with heart-rate data, heart rate increased in response to the TSST [$F(5,65) = 18.50$, $P = 0.0001$]. VAS ratings of Anxious, Irritable, and Nervous increased in intensity during the stressor ($P < 0.05$).

Temperament and neuroendocrine responses to the TSST

Novelty Seeking was not associated with ACTH concentrations in the TSST (Fig. 1). In contrast, there was a main effect of Novelty Seeking on cortisol levels [$F(1,29) = 8.87, P < 0.01$], with lower levels of Novelty Seeking predicting higher cortisol values overall in the TSST (Fig. 1). There was no interaction of Novelty Seeking with cortisol over time. Harm Avoidance was not significantly associated with either ACTH or cortisol in the general linear models. Reward Dependence was also not associated with hormonal responses to the TSST.

Temperament and affective responses to the TSST

The only VAS scale demonstrating a significant relationship with the personality measures was Anxious. In the repeated measures general linear model predicting Anxious with the variable Novelty Seeking, there was an effect of Anxious over time [$F(2,50) = 6.94, P < 0.005$], and an interaction of Novelty Seeking with Anxious over time [$F(2,50) = 3.26, P < 0.05$]. Figure 2 depicts this relationship with a dichotomized version of the Anxious VAS. Novelty Seeking appeared to be inversely related to Anxious ratings at baseline and immediately following the stressor, but *post hoc* correlations did not reach significance ($r = -0.33, P = 0.08$; $r = -0.30, P = 0.13$; and $r = 0.09, P = 0.63$ for the three Anxious ratings in the test respectively).

Mood state vs. novelty seeking trait effect

Two exploratory analyses were conducted in order to determine whether changes in mood state during the TSST could account for the relationship between Novelty Seeking and cortisol concentrations to the test. First, because Anxious was the only mood state that changed during the TSST and was also significantly related to Novelty Seeking, the possible mediating effects of this variable were tested. Area under the curve for Anxious over time in the TSST was calculated using the trapezoidal method. This variable was then entered into the repeated measures model with Novelty Seeking as a predictor of cortisol over time in the TSST. Anxious AUC was not predictive of cortisol in this model, and after controlling for this variable, the main effect of Novelty Seeking on cortisol values persisted [$F(1,24) = 7.49, P = 0.01$]. Next, we considered whether the other mood states that changed in response to the TSST might have contributed to this effect. We created a composite variable of the VAS scales Anxious, Nervous, and Irritable by taking the mean of these scales. In a general linear model, this variable did increase in response to the TSST [$F(2,24) = 6.12, P < 0.01$], but was not related to Novelty Seeking. Next, we computed the AUC for this variable, and called this 'Anxious Distress.' When entered into the model with Novelty Seeking predicting cortisol concentration, Anxious Distress was a significant positive predictor of cortisol concentration [$F(1,24) = 9.09, P < 0.01$]. Figure 3 shows the relationship between Anxious Distress (dichotomized) and cortisol values over time. After controlling for the effects of Anxious Distress, Novelty Seeking remained a robust predictor of cortisol concentration [$F(1,24) = 9.97, P < 0.005$].

Discussion

The results of this study are largely consistent with our previous findings of low levels of Novelty Seeking in association with increased cortisol responses to the Dex/CRH test in this sample (37). The present investigation extends the association to a standardized psychosocial stress test. Because the sample was carefully assessed for psychiatric history and those with a present or past disorder were excluded, these findings cannot be explained by HPA axis dysfunction secondary to a psychiatric disorder. Other potential confounds, such as symptoms of anxiety and depression and reports of stress and childhood maltreatment, also did not account for the findings.

Interestingly, the effect of Novelty Seeking was constant from baseline through the TSST (i.e. there was a main effect of Novelty Seeking but no interaction with time). This was also the case with the composite VAS variable, Anxious Distress. This suggests that Novelty Seeking and Anxious Distress may be associated with basal HPA axis function without causing an exaggerated cortisol response to the stressor *per se*. However, as the baseline measure was taken just prior to the start of the test, it is possible that the elevated cortisol in relation to low Novelty Seeking and to high Anxious Distress simply reflects anticipatory anxiety. Similarly, although the IV catheters were inserted by a very experienced nurse after application of a topical anesthetic, it is possible that pain or anxiety related to the catheter placement influenced cortisol or VAS ratings. It is important to note, however, that the findings for low Novelty Seeking are not accounted for by the relationship with Anxiety or by the effect of Anxious Distress on cortisol reactivity. Indeed, the models examining the unique contribution of these variables in the prediction of cortisol concentration indicated that the influence of the trait Novelty Seeking remained after accounting for the significant effect of mood state.

That the association between Novelty Seeking and cortisol in the present study is not explained by the psychological response to the test is consistent with our previous finding of an inverse relationship between Novelty Seeking and cortisol response to the Dex/CRH test in this sample. Psychological factors were expected to be less influential in the former study, which involved a neurobiological challenge rather than a psychosocial stressor, and indeed, there were no changes in mood state during the Dex/CRH test. Thus, the association between Novelty Seeking and cortisol in both the TSST and Dex/CRH test appears to involve a direct neurobiological effect in addition to any psychologically mediated influences on HPA axis stress reactivity. Exogenous CRH activity may be involved in this association, given that in addition to effects on pituitary-adrenal function, CRH has been linked to behavioural inhibition. For example, central administration of CRH in rodents and monkeys causes neophobia and diminished exploratory and social behaviour, and increases physiological reactivity to novel stimuli (for reviews see Refs (47, 48)).

Surprisingly, the findings for cortisol were not consistent with those for ACTH: there was no relationship between Novelty Seeking and ACTH concentrations in this study. This pattern suggests the possibility of adrenocortical hypertrophy or enhanced adrenocortical sensitivity in subjects with low levels of Novelty Seeking. A similar pattern has been reported in major depression, in which increases in plasma cortisol levels are not proportional to changes in

plasma ACTH concentrations (49, 50). This issue will require further examination in a larger study.

Similar to our findings with the Dex/CRH test, Harm Avoidance was not related to plasma cortisol levels in the TSST. This is surprising, given that Harm Avoidance is theoretically and empirically related to both neuroticism and inhibition, and may be due to the limited power in the present study. Further work in this area will be necessary to replicate these findings and further elucidate the relationship of personality with HPA axis reactivity and affective responses to stress.

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Significant outcomes

- Inhibited temperament and excessive cortisol reactivity have each been linked to anxiety disorders and major depression. In this study of healthy adults, low levels of Novelty Seeking were associated with increased cortisol concentrations to a standardized psychosocial stress test suggesting that such individuals may be at increased risk for developing a mood or anxiety disorder.
- Negative mood states also increased during this test and were predictive of elevated cortisol concentrations, but Novelty Seeking remained a negative predictor of cortisol concentration even after controlling for mood state. This suggests that temperament may have links to neuroendocrine stress reactivity that go beyond simple changes in affect state.

Limitations

- This study is limited by a modest sample size.
- The sample was restricted to subjects with no Axis I psychiatric disorder in order to rule out potential illness-related confounds, and consequently, the results may not generalize to clinical populations.
- Findings of this study are restricted to the laboratory stressor and measure of temperament employed. Assessments of diurnal rhythm of cortisol and ACTH as well as other types of stress exposures or different measures of personality traits may have yielded additional findings.

Fig. 1.

Adrenocorticotrophic hormone (ACTH) (top) and cortisol (bottom) concentrations in the TSST in subjects with low and high levels of Novelty Seeking (NS). NS was not a significant predictor of ACTH concentrations. There was a significant main effect of NS on cortisol concentrations [$F(1,29) = 8.87, P < 0.01$].

Fig. 2.

VAS ratings of Anxious in the TSST in subjects with low and high levels of Novelty Seeking (NS). There was a significant interaction of NS with anxious over time [$F(2,50) = 3.26, P < 0.05$], but *post hoc* correlations did not reach significance ($r = -0.33, P = 0.08$; $r = -0.30, P = 0.13$; and $r = 0.09, P = 0.63$ for the three time-points respectively).

Fig. 3. Cortisol concentrations in subjects with high and low levels of Anxious Distress (AD) during the TSST. There was a significant main effect of AD on cortisol concentrations [$F(1, 24) = 9.09, P < 0.01$].

Table 1

Study Sample Characteristics (N = 31; 14 males, 17 females)

	Mean	SD
Age (years)	25.9	8.5
Childhood Trauma Questionnaire (CTQ) Total	7.1	2.2
Perceived Stress Scale (PSS) Total	25.1	9.4
State-Trait Anxiety Inventory-State	29.4	6.3
State-Trait Anxiety Inventory-Trait	31.7	7.4
Inventory for Depressive Symptomatology-Self Report (IDS-SR)	8.3	4.7
Novelty Seeking	17.2	4.8
Harm Avoidance	12.4	6.6
Reward Dependence	15.1	4.0