Cue-induced cocaine craving enhances psychosocial stress and vice versa in chronic cocaine users

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Supplementary Material

Supplementary Methods

Methods S1. Recruitment and participant selection.

Cocaine users (CU) and healthy controls (HC) were recruited through psychiatric hospitals, drug prevention, and treatment centers (CU); online media, advertisements in public spaces, local newspapers, and word of mouth (CU and HC). They received monetary compensation for their participation. Data were collected at the Psychiatric Hospital of the University of Zurich.

A total of 69 CU and 54 HC participated in a screening-session. 23 individuals (11 CU, 12 HC) were excluded because of psychiatric disorders (n=3), an estimated cumulative lifetime cocaine consumption of <100g (CU, n=4), regular use of substances (HC, n=9) or other substances than cocaine (CU, n=5) shown by urine or hair tests, insufficient German skills (n=1), and an extreme stress reaction to the blood sampling procedure (n=1). Additionally, 15 individuals (11 CU, 4 HC) did not show up for the stress assessment.

Methods S2. Questionnaires.

The *Attention-Deficit/Hyperactivity-Disorder Self-Rating Scale*[1] (ADHD-SR) was carried out at the screening-session day. The *Mehrfachwahl-Wortschatz-Intelligenztest*[2], a standardized German vocabulary test, estimated premorbid verbal intelligence quotient (IQ) at the screening-session. At the stress-session day, the *Beck Depression Inventory*[3] (BDI) assessing symptoms of depression was conducted.

Methods S3. Procedure.

Participants were examined at two test-days – a screening-session and a stress-session – separated by approximately one month. The screening-session with the psychopathological and neuropsychological assessment (as published before [4]) began either at 9.00am or 12.00pm and lasted around 5h. The stress-session day began at 12.30pm as the afternoon was suggested as advantageous to investigate neuroendocrine reactivity[5,6] and lasted around 5-6h. Individuals were asked to only have a light meal before. Upon arrival at the laboratory, participants drank 200ml of juice concentrate high in glucose to standardize the blood glucose level as its' availability was suggested to be a necessary prerequisite for the responsiveness of the HPA axis[7–9]. Subsequently, a resting period during which individuals filled out questionnaires began.

Blood samples were taken by a study nurse through an i.v. catheter that was placed into the individuals' forearm vein. Participants filled out further questionnaires between the first and the second blood sample. A neuropsychological test battery was completed after each stress challenge. Individuals could eat an apple or a pear in the break before the second stress challenge but were otherwise asked to abstain from food, cigarettes, and drinks other than water during the entire test session.

Methods S4. Statistical analysis.

Handling of missing data in noradrenaline

If missing data occurred between acquired samples, we estimated the missing values by calculating the mean of the framing noradrenaline samples. If missing data occurred for the first sample, the average difference of the respective group between the first and the second sample was added to the second value, and if missing data occurred for the second sample, the average difference of the respective group in the respective condition was added to the third value of the individual. One individual had missing data at eight time-points (1.0%) and was therefore not included in the analysis of TSST/Cocaine-Cue-Video stress markers.

Correlations

Spearman rank correlations were performed to assess associations between cocaine hair concentrations and acute stress and craving responses as represented by AUC_G in the TSST and Cocaine-Cue-Video. The significance level for correlation analyses was set at $p<.01$ to avoid alpha-error accumulation.

Linear components

We chose a reactivity_1 (T_1–T_2) and reactivity_2 slope (T_2–T_3) for cortisol to represent the expected increase in cortisol levels in response to the TSST and, as descriptive data suggested, a subsequent plateau where cortisol levels remained steady until 20 minutes after the TSST, as well as a

recovery slope (T_3–T_5). Regarding ACTH, we selected a reactivity slope (T_1–T_2) to model the expected increase in ACTH levels until right after the TSST, and a recovery_1 (T_2–T_3), recovery_2 (T_3–T_4) and recovery_3 slope (T_4–T_5) to model the immediate steep decrease in ACTH levels that flattens from 20 to 40 minutes, followed by a slight increase until 65 minutes later. Noradrenaline had a reactivity slope (T_1–T_2) to depict the expected increase in noradrenaline levels during the TSST, and a recovery_1 (T_2–T_3) and recovery_2 slope (T_3–T_5) to model the immediate decrease in noradrenaline levels after the TSST and a subsequent plateau until the end of the test session. All time slopes for the neuroendocrine response were adjusted for time and represent 10min increments. For subjective stress and craving, we chose a TSST_preparation/Neutral-Video slope (T_1–T_2) to display the response to the TSST preparation phase/Neutral-Video, a reactivity slope (T_2–T_3) to show the reaction to the TSST test phase/Cocaine-Video, and a recovery slope (T_3–T_4).

Coding schemes for endocrinological measures, subjective stress, and craving.

	Cortisol				
	-20min (T_1)	0min (T_2)	+20min (T_3)	+40min (T_4)	+65min (T_5)
Reactivity_1	0	2.0	2.0	2.0	2.0
Reactivity_2	0	0	2.0	2.0	2.0
Recovery	0	0	0	2.0	4.5

	ACTH				
	-20min (T_1)	0min (T_2)	+20min (T_3)	+40min (T_4)	+65min (T_5)
Reactivity	0	2.0	2.0	2.0	2.0
Recovery_1	0	0	2.0	2.0	2.0
Recovery_2	0	0	0	2.0	2.0
Recovery_3	0	0	0	0	2.5

	Noradrenaline				
	-20min (T_1)	0min (T_2)	+20min (T_3)	+40min (T_4)	+65min (T_5)
Reactivity	0	2.0	2.0	2.0	2.0
Recovery_1	0	0	2.0	2.0	2.0
Recovery_2	0	0	0	2.0	4.5

	Subjective stress			
	-20min (T_1)	-10min (T_2)	0min (T_3)	+65min (T_4)
TSST_preparation	0	1	1	1
Reactivity	0	0	1	1
Recovery	0	0	0	1

	Craving			
	-20min (T_1)	-10min (T_2)	0min (T_3)	+65min (T_4)
Neutral-Video	0	1	1	1
Cocaine-Video	0	0	1	1
Recovery	0	0	0	1

Random-slopes for time components were included if Bayesian Information Criterion (BIC) indicated better model fit.

Covariates

Possible effects of sex, age, BMI, verbal IQ, smoker, cannabis, MDMA, and alcohol consumption were investigated by adding them manually one at a time to the described models. For each covariate, two models were considered. First, a covariate was entered as a fixed-effect. Second, interactions between a covariate and time components were added as fixed-effects. In both models robustness of our results was examined. Predictors that correlated with each other were never included in the same model to avoid multicollinearity.

Area-under-the curve

Area-under-the-curve with respect to ground (AUC_G) for variable time between measurements was calculated for all outcome measures according to Pruessner et al.[10].

The covariate included for analyses of covariance (ANCOVAs) were the baseline (T_0) levels of the respective dependent variable. In the analysis of noradrenaline AUC_G for the Cocaine-Cue-Video cannabis grams/week was also included. These covariates were chosen as analyses for the respective TSST and Cocaine-Cue-Video trajectories indicated better model fit according to Bayesian Information Criterion (BIC) for the model additionally containing baseline levels of the respective dependent variable and for the Cocaine-Cue-Video noradrenaline AUC_G cannabis grams/week.

Supplementary Tables

Table S1
Additional demographic as well as MDMA and amphetamines use related data.

	Controls (n = 38)	Cocaine Users (n = 47)	Test Statistic	df	p
Demographics					
Menstrual cycle (n)[1]					
Follicular	4	3	$\chi^2 = 0.19$[2]	1	0.663
Luteal	10	11[3]			
Hormonal contraception y/n[1]	4/10	5/11	$\chi^2 = 0.03$[2]	1	0.873
MDMA					
Lifetime experience, y/n	9/29	42/5	$\chi^2 = 37.77$[2]	1	**<0.001**
Times/week[5]	0.00 (0.00 – 0.08)	0.00 (0.00 – 0.69)	$U = 628.50$[4]		**0.002**
Grams/week[5]	0.00 (0.00 – 0.01)	0.00 (0.00 – 0.17)	$U = 594.50$[4]		**0.001**
Years of use	0.00 (0.00 – 3.55)	4.09 (0.00 – 31.51)	$U = 232.00$[4]		**<0.001**
Abstinence (days)	150.00 (47.00 – 8 512.00)	239.00 (4.00 – 9 130.00)	$U = 185.50$[4]		0.932
Cumulative lifetime dose (grams)	0.00 (0.00 – 0.56)	3.30 (0.00 – 912.50)	$U = 195.00$[4]		**<0.001**
MDMA, pg/mg in hair	0.00 (0.00 – 75.00)	12.00 (0.00 – 55 000.00)	$U = 478.00$[4]		**<0.001**
MDA, pg/mg in hair	0.00 (0.00 – 12.00)	0.00 (0.00 – 3 700.00)	$U = 567.00$[4]		**<0.001**
Amphetamines					
Lifetime experience, y/n	4/34	35/12	$\chi^2 = 34.60$[2]	1	**<0.001**
Times/week[5]	0.00 (0.00 – 0.12)	0.00 (0.00 – 0.24)	$U = 617.50$[4]		**0.001**
Grams/week[5]	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.23)	$U = 584.00$[4]		**<0.001**
Years of use	0.00 (0.00 – 0.71)	2.24 (0.00 – 20.51)	$U = 292.00$[4]		**<0.001**
Abstinence (days)	763.00 (4.00 – 4 099.00)	198.00 (4.00 – 3 139.00)	$U = 69.50$[4]		0.982
Cumulative lifetime dose (grams)	0.00 (0.00 – 0.32)	1.29 (0.00 – 1 304.54)	$U = 276.00$[4]		**<0.001**
Amphetamines, pg/mg in hair	0.00 (0.00 – 25.00)	00.00 (0.00 – 300.00)	$U = 628.00$[4]		**<0.001**

Note. Significant p-values are shown in bold. Counts or median and range in parenthesis. [1] Only for females. [2] χ^2 test for frequency data. [3] One CU had menopause, one CU had not had her period due to hormonal contraception. [4] Mann-Whitney U test. [5] Average use during the current consumption period.

Table S2

Baseline neuroendocrine levels and subjective stress in the beginning of the test-day.

	Controls (n = 38)	Cocaine Users (n = 47)
Noradrenaline (ng/l; log)[1]	6.01 (0.54)	6.21 (0.46)
ACTH (pg/ml; log)[1]	3.88 (0.59)	3.54 (0.51)
Cortisol (ng/ml)[1]	93.77 (28.34)	93.51 (37.12)
Subjective stress	2.01 (1.96)	2.25 (2.18)

Note. Means and standard deviations in parenthesis. [1] Seven individuals had no blood sample (Controls: *n* = 36; Cocaine users: *n* = 42).

Table S3

Results for AUC_G in the analysis of the TSST and the Cocaine-Cue-Video.

	Controls (*n* = 38)		Cocaine Users (*n* = 47)				
TSST	Stress-pre-Craving (*n* = 20)	Stress-post-Craving (*n* = 18)	Stress-pre-Craving (*n* = 25)	Stress-post-Craving (*n* = 22)	Group	Order	Group * Order
Physiological response							
Cortisol AUC_G[1]	9 146.61 (740.72)	7 823.04 (783.27)	8 081.66 (686.07)	7 571.38 (720.01)	$F(1,73)=0.81$, $p=.370$	$F(1,73)=1.52$, $p=.222$	$F(1,73)=0.31$, $p=.579$
ACTH AUC_G[1]	8.20 (0.07)	8.16 (0.07)	8.17 (0.07)	8.25 (0.07)	$F(1,73)=0.19$, $p=.668$	$F(1,73)=0.09$, $p=.772$	$F(1,73)=0.75$, $p=.389$
Noradrenaline AUC_G[1,2]	10.58 (0.09)	10.45 (0.10)	10.47 (0.09)	10.65 (0.09)	$F(1,72)=0.26$, $p=.609$	$F(1,72)=0.09$, $p=.768$	$F(1,72)=2.76$, $p=.101$
Subjective experience							
Stress AUC_G	237.86 (31.83)	170.59 (33.71)	300.12 (28.48)	250.79 (30.33)	$F(1,80)=5.23$, ***p=.025***	$F(1,80)=3.49$, $p=.066$	$F(1,80)=0.83$, $p=.774$
Craving AUC_G	–	–	3.44 (0.46)	2.32 (0.50)	–	$F(1,44)=2.69$, $p=.108$	–

Cocaine-Cue-Video	Craving-pre-Stress (*n* = 18)	Craving-post-Stress (*n* = 20)	Craving-pre-Stress (*n* = 22)	Craving-post-Stress (*n* = 25)	Group	Order	Group * Order
Physiological response							
Cortisol AUC_G[1]	6 573.67 (531.94)	6 159.38 (503.04)	6 451.15 (488.98)	5 857.68 (465.93)	$F(1,73)=0.18$, $p=.670$	$F(1,73)=1.00$, $p=.322$	$F(1,73)=0.03$, $p=.857$
ACTH AUC_G[1]	8.09 (0.06)	8.04 (0.06)	8.14 (0.06)	8.10 (0.06)	$F(1,73)=0.74$, $p=.392$	$F(1,73)=0.61$, $p=.439$	$F(1,73)=0.02$, $p=.903$
Noradrenaline AUC_G[1,2,3]	10.28 (0.08)	10.43 (0.08)	10.51 (0.08)	10.35 (0.08)	$F(1,71)=0.97$, $p=.329$	$F(1,71)=0.01$, $p=.934$	$F(1,71)=3.71$, $p=.058$
Subjective experience							
Stress AUC_G	126.17 (31.84)	113.48 (30.07)	118.50 (28.65)	201.12 (26.91)	$F(1,80)=1.85$, $p=.178$	$F(1,80)=1.41$, $p=.239$	$F(1,80)=2.63$, $p=.109$
Craving AUC_G	–	–	4.03 (0.38)	4.65 (0.36)	–	$F(1,44)=1.39$, $p=.244$	–

Note. Significant p-values are shown in bold. Means and standard error of the mean in parenthesis. Adjusted for baseline levels. [1] Seven individuals had no blood sample. [2] One individual had a missing in noradrenaline. [3] Values were additionally adjusted for Cannabis grams/week.

Table S4

Non-normalized values for noradrenaline, ACTH, cortisol, subjective stress, and craving during the TSST.

	Controls ($n = 38$)		Cocaine Users ($n = 47$)	
Noradrenaline (ng/l; log)[1]	Stress-pre-Craving ($n = 20$)	Stress-post-Craving ($n = 18$)	Stress-pre-Craving ($n = 25$)	Stress-post-Craving ($n = 22$)
-20min (T_1)	6.12 (0.42)	5.74 (0.74)	6.20 (0.51)	6.22 (0.69)
0min (T_2)	6.37 (0.40)	6.17 (0.69)	6.36 (0.43)	6.39 (0.59)
+20min (T_3)	5.94 (0.44)	5.77 (0.68)	5.90 (0.46)	6.06 (0.58)
+40min (T_4)	5.96 (0.42)	5.74 (0.73)	5.94 (0.39)	6.12 (0.56)
+65min (T_5)	6.08 (0.47)	5.82 (0.63)	6.10 (0.42)	6.30 (0.54)
ACTH (pg/ml; log)[1]				
-20min (T_1)	3.97 (0.54)	3.82 (0.57)	3.50 (0.46)	3.65 (0.45)
0min (T_2)	4.02 (0.69)	3.98 (0.59)	3.69 (0.60)	3.83 (0.50)
+20min (T_3)	3.88 (0.69)	3.82 (0.64)	3.50 (0.56)	3.70 (0.47)
+40min (T_4)	3.81 (0.69)	3.75 (0.63)	3.54 (0.47)	3.62 (0.52)
+65min (T_5)	3.90 (0.61)	3.72 (0.65)	3.64 (0.44)	3.56 (0.50)
Cortisol (ng/ml)[1]				
-20min (T_1)	103.31 (38.07)	64.17 (23.06)	92.68 (36.98)	72.88 (30.24)
0min (T_2)	125.44 (56.17)	92.43 (43.02)	110.15 (63.08)	87.78 (31.23)
+20min (T_3)	123.47 (61.83)	97.57 (55.18)	105.29 (62.19)	101.45 (40.14)
+40min (T_4)	104.40 (51.64)	88.81 (43.24)	90.45 (47.28)	82.76 (30.67)
+65min (T_5)	94.25 (43.24)	76.86 (32.49)	84.96 (39.44)	72.51 (27.76)
Subjective stress				
-20min (T_1)	2.03 (1.83)	1.06 (1.60)	2.75 (2.31)	1.01 (1.99)
-10min (T_2)	3.74 (2.68)	3.28 (2.54)	4.69 (2.70)	3.36 (2.45)
0min (T_3)	3.66 (2.65)	2.25 (2.16)	4.71 (2.83)	4.57 (2.60)
+65min (T_4)	1.80 (1.83)	1.03 (1.98)	2.11 (2.18)	1.27 (1.79)
Craving (log)				
-20min (T_1)	–	–	0.73 (0.79)	0.59 (0.73)
-10min (T_2)	–	–	0.73 (0.88)	0.45 (0.72)
0min (T_3)	–	–	0.86 (0.84)	0.53 (0.85)
+65min (T_4)	–	–	0.71 (0.85)	0.44 (0.78)

Note. Means and standard deviations in parenthesis. [1] Seven individuals had no blood sample (Controls: $n = 36$; Cocaine users: $n = 42$).

Table S5

Non-normalized values for noradrenaline, ACTH, cortisol, subjective stress, and craving during the Cocaine-Cue-Video.

	Controls (*n* = 38)		Cocaine Users (*n* = 47)	
Noradrenaline (ng/l; log)[1, 2]	Craving-pre-Stress (*n* = 18)	Craving-post-Stress (*n* = 20)	Craving-pre-Stress (*n* = 22)	Craving-post-Stress (*n* = 25)
-20min (T_1)	5.71 (0.62)	6.08 (0.47)	6.15 (0.49)	6.10 (0.42)
0min (T_2)	5.59 (0.59)	5.89 (0.46)	5.96 (0.57)	5.92 (0.49)
+20min (T_3)	5.74 (0.63)	5.93 (0.44)	6.02 (0.58)	5.92 (0.49)
+40min (T_4)	5.69 (0.67)	5.92 (0.39)	6.09 (0.52)	6.06 (0.42)
+65min (T_5)	5.74 (0.74)	5.98 (0.41)	6.22 (0.69)	6.06 (0.48)
ACTH (pg/ml; log)[1]				
-20min (T_1)	3.87 (0.57)	3.90 (0.61)	3.71 (0.52)	3.64 (0.44)
0min (T_2)	3.74 (0.59)	3.76 (0.73)	3.55 (0.57)	3.49 (0.45)
+20min (T_3)	3.70 (0.64)	3.72 (0.72)	3.51 (0.50)	3.49 (0.45)
+40min (T_4)	3.73 (0.62)	3.74 (0.70)	3.52 (0.49)	3.49 (0.41)
+65min (T_5)	3.82 (0.57)	3.72 (0.74)	3.65 (0.45)	3.42 (0.49)
Cortisol (ng/ml)[1]				
-20min (T_1)	98.55 (46.46)	94.25 (43.24)	91.40 (51.67)	84.96 (39.44)
0min (T_2)	80.67 (38.97)	74.81 (26.52)	76.37 (37.36)	72.87 (32.44)
+20min (T_3)	69.40 (28.00)	73.65 (29.97)	68.36 (32.38)	69.37 (26.57)
+40min (T_4)	64.90 (24.25)	73.01 (34.11)	67.08 (30.44)	67.44 (29.56)
+65min (T_5)	64.17 (23.06)	72.47 (34.93)	72.88 (30.24)	67.09 (31.66)
Subjective stress				
-20min (T_1)	1.97 (2.21)	1.80 (1.83)	2.06 (2.56)	2.11 (2.18)
-10min (T_2)	1.35 (1.46)	1.28 (1.67)	1.24 (2.38)	2.13 (2.49)
0min (T_3)	1.46 (2.00)	1.50 (1.75)	1.69 (2.08)	2.82 (2.71)
+65min (T_4)	1.06 (1.60)	1.25 (1.75)	1.01 (1.99)	2.12 (2.59)
Craving (log)				
-20min (T_1)	–	–	0.58 (0.85)	0.71 (0.85)
-10min (T_2)	–	–	0.74 (0.83)	0.62 (0.82)
0min (T_3)	–	–	1.12 (0.86)	1.35 (0.70)
+65min (T_4)	–	–	0.59 (0.73)	0.84 (0.87)

Note. Means and standard deviations in parenthesis. [1] Seven individuals had no blood sample (Controls: *n* = 36; Cocaine users: *n* = 42). [2] One individual had a missing in noradrenaline.

Table S6

Random effect variances for discontinuous growth models in the analyses of the TSST.

Neuroendocrine responses				Subjective ratings		
	Random effect variances	Estimate			Random effect variances	Estimate
Noradrenaline (ng/l; log)	Participant ID			Subjective stress	Participant ID	
	Intercept	0.16			Intercept	1.46
	Reactivity	0.01			Residual	2.95
	Residual	0.03				
				Craving (log)	Participant ID	
ACTH (pg/ml; log)	Participant ID				Intercept	0.28
	Intercept	0.04			Residual	0.11
	Residual	0.04				
Cortisol (ng/ml)	Participant ID					
	Intercept	500.64				
	Reactivity_1	248.88				
	Reactivity_2	92.28				
	Recovery	30.57				
	Residual	106.99				

Table S7

Random effect variances for growth models and discontinuous growth models in the analyses of the Cocaine-Cue-Video.

Neuroendocrine responses				Subjective ratings		
	Random effect variances	Estimate			Random effect variances	Estimate
Noradrenaline (ng/l; log)	Participant ID			Subjective stress	Participant ID	
	Intercept	0.08			Intercept	1.44
	Residual	0.05			Residual	2.33
ACTH (pg/ml; log)	Participant ID			Craving (log)	Participant ID	
	Intercept	0.03			Intercept	0.28
	Residual	0.04			Neutral-Video	0.04
					Cocaine-Video	0.21
Cortisol (ng/ml)	Participant ID				Recovery	0.31
	Intercept	1435.08			Residual	0.05
	Time	49.78				
	Time^2	0.32				
	Residual	56.66				

Table S8

The effect of sex on cortisol in the analysis of the TSST.

Cortisol (ng/ml)	
Fixed effects	Coefficient (SE)
Intercept	94.77 (5.91)***
Reactivity_1	12.75 (4.03)**
Reactivity_2	-2.42 (2.84)
Recovery	-6.00 (1.48)***
CU Stress post Craving	-15.86 (7.78)*
CU Stress post Craving * Reactivity_1	-2.36 (5.34)
CU Stress post Craving * Reactivity_2	8.97 (3.75)*
CU Stress post Craving * Recovery	-1.49 (1.96)
HC Stress pre Craving	8.27 (7.83)
HC Stress pre Craving * Reactivity_1	1.42 (5.41)
HC Stress pre Craving * Reactivity_2	1.15 (3.80)
HC Stress pre Craving * Recovery	-1.61 (1.98)
HC Stress post Craving	-22.09 (8.10)**
HC Stress post Craving * Reactivity_1	5.42 (5.56)
HC Stress post Craving * Reactivity_2	6.16 (3.91)
HC Stress post Craving * Recovery	-0.20 (2.04)
Baseline Cortisol	0.50 (0.07)***
Female	-10.93 (6.08)
Female * Reactivity_1	-9.82 (4.09)*
Female * Reactivity_2	-2.64 (2.87)
Female * Recovery	3.85 (1.50)*

Random effect variances	Estimate
Participant ID	
Intercept	481.11
Reactivity_1	226.94
Reactivity_2	90.69
Recovery	27.20
Residual	106.99

Note. Male CU that underwent the TSST in the beginning of the test session were defined as the reference group. Baseline cortisol levels were grand-mean centered. CU = Cocaine users; HC = Heavy controls. Time components indicate slopes per 10 minutes increments. *p<0.05; **p<0.01; ***p<0.001.

Table S9

Discontinuous growth model for craving in the analysis of the TSST for light and heavy cocaine users[1] only.

Craving (log)	
Fixed effects	Coefficient (SE)
Intercept	0.39 (0.20)
TSST_preparation	0.05 (0.13)
Reactivity	0.21 (0.13)
Recovery	-0.33 (0.13)*
Light CU Stress post Craving	0.00 (0.28)
Light CU Stress post Craving * TSST_preparation	-0.16 (0.18)
Light CU Stress post Craving * Reactivity	-0.18 (0.18)
Light CU Stress post Craving * Recovery	0.15 (0.18)
Heavy CU Stress pre Craving	0.72 (0.30)*
Heavy CU Stress pre Craving * TSST_preparation	-0.10 (0.19)
Heavy CU Stress pre Craving * Reactivity	-0.18 (0.19)
Heavy CU Stress pre Craving * Recovery	0.37 (0.19)†
Heavy CU Stress post Craving	0.75 (0.36)*
Heavy CU Stress post Craving * TSST_preparation	-0.24 (0.24)
Heavy CU Stress post Craving * Reactivity	-0.01 (0.24)
Heavy CU Stress post Craving * Recovery	0.46 (0.24)†
Random effect variances	Estimate
Participant ID	
Intercept	0.63
Residual	0.32

Note. [1]Cocaine users were categorized as light users if cocaine hair concentrations were <5000pg/mg and categorized as heavy users if cocaine hair concentrations were ≥5000pg/mg. Light users that underwent the TSST in the beginning of the test session were defined as the reference group. Light CU = Light cocaine users; Heavy CU = Heavy cocaine users. Time components indicate slopes per 10 minutes increments. Light CU Stress pre Craving: $n = 13$; Light CU Stress post Craving: $n = 16$; Heavy CU Stress pre Craving: $n = 12$; Heavy CU Stress post Craving: $n = 6$. †$p<0.06$; *$p<0.05$.

Table S10

Growth models for noradrenaline, ACTH, and cortisol in the analysis of the Cocaine-Cue-Video for light and heavy cocaine users[1] only.

Noradrenaline (ng/l; log)		ACTH (pg/ml; log)		Cortisol (ng/ml)	
Fixed effects	Coefficient (SE)	Fixed effects	Coefficient (SE)	Fixed effects	Coefficient (SE)
Intercept	6.14 (0.14)***	Intercept	3.83 (0.12)***	Intercept	95.68 (11.98)***
Time	-0.22 (0.07)**	Time	-0.21 (0.06)***	Time	-19.07 (4.76)***
Time^2	0.06 (0.02)***	Time^2	0.05 (0.01)**	Time^2	3.59 (1.01)***
Light CU Craving post Stress	-0.05 (0.21)	Light CU Craving post Stress	-0.20 (0.19)	Light CU Craving post Stress	-15.08 (18.06)
Light CU Craving post Stress * Time	0.05 (0.11)	Light CU Craving post Stress * Time	0.16 (0.09)	Light CU Craving post Stress * Time	9.12 (7.17)
Light CU Craving post Stress * Time^2	-0.02 (0.03)	Light CU Craving post Stress * Time^2	-0.04 (0.00)*	Light CU Craving post Stress * Time^2	-1.44 (1.52)
Heavy CU Craving pre Stress	-0.02 (0.25)	Heavy CU Craving pre Stress	-0.39 (0.23)	Heavy CU Craving pre Stress	-14.26 (21.87)
Heavy CU Craving pre Stress * Time	0.20 (0.13)	Heavy CU Craving pre Stress * Time	0.03 (0.11)	Heavy CU Craving pre Stress * Time	2.03 (8.68)
Heavy CU Craving pre Stress * Time^2	-0.04 (0.03)	Heavy CU Craving pre Stress * Time^2	-0.00 (0.03)	Heavy CU Craving pre Stress * Time^2	-0.44 (1.84)
Heavy CU Craving post Stress	-0.09 (0.21)	Heavy CU Craving post Stress	-0.22 (0.19)	Heavy CU Craving post Stress	-7.96 (18.06)
Heavy CU Craving post Stress * Time	0.14 (0.11)	Heavy CU Craving post Stress * Time	0.07 (0.09)	Heavy CU Craving post Stress * Time	6.49 (7.17)
Heavy CU Craving post Stress * Time^2	-0.03 (0.03)	Heavy CU Craving post Stress * Time^2	-0.03 (0.02)	Heavy CU Craving post Stress * Time^2	-2.16 (1.52)

Random effect variances	Estimate	Random effect variances	Estimate	Random effect variances	Estimate
Participant ID		Participant ID		Participant ID	
Intercept	0.45	Intercept	0.41	Intercept	42.98
Residual	0.24	Residual	0.20	Time	15.26
				Time^2	3.09
				Residual	7.27

Note. [1]Cocaine users were categorized as light users if cocaine hair concentrations were <5000pg/mg and categorized as heavy users if cocaine hair concentrations were ≥5000pg/mg. Light users that underwent the TSST in the beginning of the test session were defined as the reference group. Light CU = Light cocaine users; Heavy CU = Heavy cocaine users. Time components indicate slopes per 10 minutes increments. Noradrenaline: Light CU Craving pre Stress: $n = 14$; Light CU Craving post Stress: $n = 11$; Heavy CU Craving pre Stress: $n = 6$; Heavy CU Craving post Stress: $n = 10$. ACTH and cortisol: Light CU Craving pre Stress: $n = 14$; Light CU Craving post Stress: $n = 11$; Heavy CU Craving pre Stress: $n = 6$; Heavy CU Craving post Stress: $n = 11$. *p<0.05; **p<0.01; ***p<0.001.
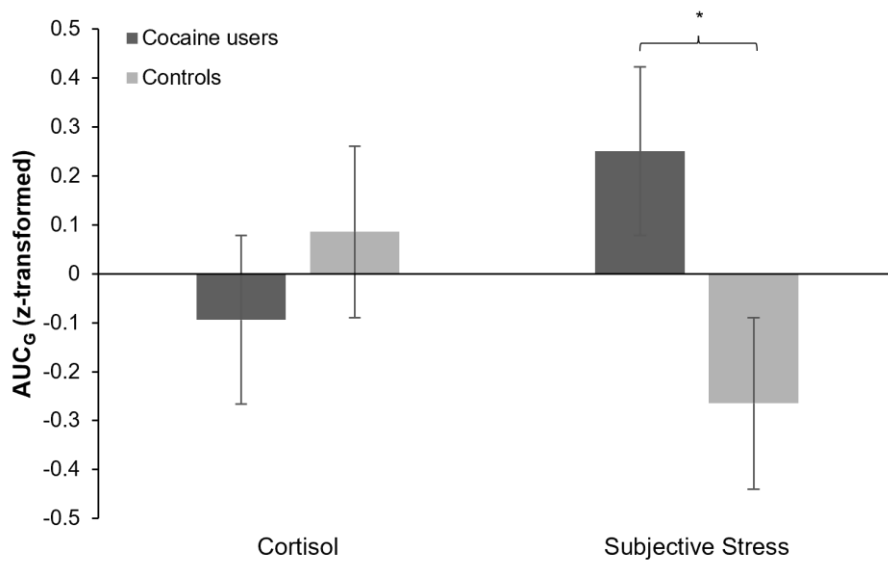
Supplementary Figures

Figure S1. Mean z-transformed levels of AUC_G and standard errors for the cortisol and subjective stress response in healthy controls ($n = 36$) and cocaine users ($n = 42$). Sidak-corrected post-hoc tests: *p=0.05.
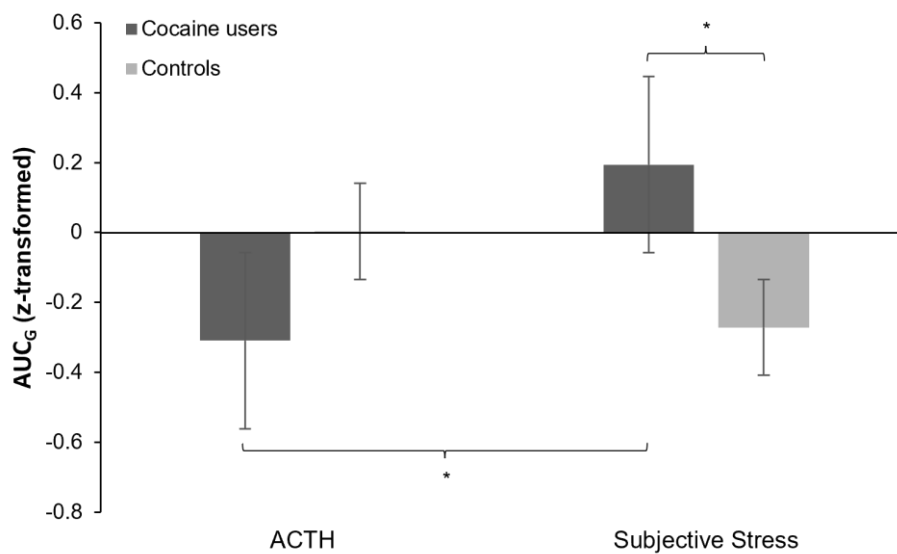

Figure S2. Mean z-transformed levels of AUC_G and standard errors for the ACTH and subjective stress response in healthy controls ($n = 36$) and cocaine users ($n = 42$). Sidak-corrected post-hoc tests: *p=0.05.

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