

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

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The authors have no conflicts of interest to declare.

Cocaine

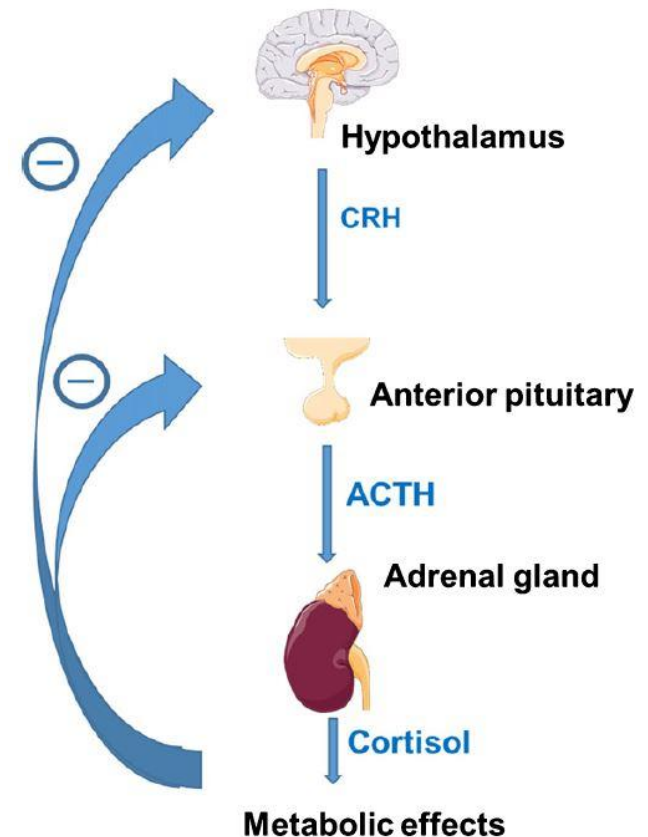
- High risk for dependency (Degenhardt & Hall, 2012; Nutt et al., 2007)
 - 5 – 7% of cocaine users develop addiction during the first year of use (Lopez-Quintero et al., 2011; Wagner & Anthony, 2002)
 - 16 – 21% develop cocaine dependence during lifetime (Degenhardt & Hall, 2012; Lopez-Quintero et al., 2011)
- High relapse rates (McLellan et al., 2000; Simpson et al., 1999)
- Severe negative consequences for personal health and social relationships (Degenhardt & Hall, 2012; Nutt et al., 2007; Volkow et al., 2011)

Mean last-year prevalence

- Europe: 2,2% of the population aged 15 – 34 \approx 2,2 million (EMCDDA, 2022)
- Zürich: 10.8% of young adults at age 20 (9.4% with positive hair test, i.e., use in the last 3 months) (Quednow et al., 2022; Steinhoff et al., in press)

Cocaine, Stress and Craving

- Psychological and physical stress are risk factors for the development, maintenance, and relapse in cocaine use disorder (Koob et al., 2014; Lemieux & al'Absi, 2016; Sinha, 2001)
- Acute use: activation of reward and stress systems (Sinha, 2008; Wemm & Sinha, 2019)
 - Hypothalamic-pituitary-adrenal axis (HPA) (Baumann et al., 1995; Mello & Mendelson, 1997; Mendelson et al., 1992)
 - Animal studies: activation of HPA axis enhances the sensitivity for cocaine reward
 - Increased likelihood to develop dependency (Goeders, 2002)
- Chronic use: adaptations in reward and stress systems (Sinha, 2011; Wemm & Sinha, 2019)
 - Chronic state of stress → cocaine use to reduce stress (Wand, 2008)
- Regular cocaine users showed significantly lower gene expression of the glucocorticoid receptor (NR3C1) (Schote et al., 2019)



Cocaine, Stress and Craving

- Craving is also associated with a greater relapse vulnerability in cocaine users (Brady & Sinha, 2005; Sinha, 2001, 2008)
 - Confrontation with experimental stress- and drug-related cues: HPA axis response, craving, subjective stress (Sinha et al., 1999, 2000, 2003; Waldrop et al., 2010)
 - Altered HPA axis responses, subjective stress, and craving in response to experimental stress- and drug-related cues were predictive of later relapse (Back et al., 2010; Sinha et al., 2006)
- Although stress and craving seem to trigger cocaine use, how they interact remains largely unknown

Aim and hypotheses

- Investigate acute psychosocial stress and cocaine-cue reactivity and their interaction in chronic cocaine users

Hypotheses

1. Psychosocial stress and the cocaine-cue increase craving in cocaine users.
2. Psychosocial stress evokes HPA-axis responses, with a more blunted response in cocaine users.
3. The cocaine-cue paradigm elicits HPA-axis responses only in cocaine users.
4. Psychosocial stress and cocaine-cue reactivity intensify each other.

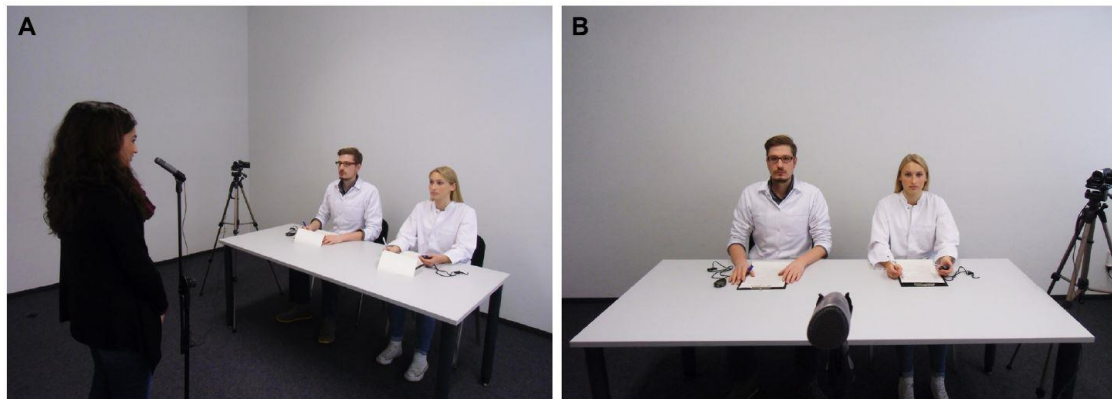
Methods

Sample

- $n = 38$ stimulant-naïve healthy controls
- $n = 47$ chronic cocaine users

Trier Social Stress Test (TSST; Kirschbaum et al., 1993)

- Preparation phase (10 minutes)
- Free speech (5 minutes)
- Mental arithmetic (5 minutes)



Frisch et al., 2015

Methods

Cocaine-Cue-Video (Engeli et al., 2020)

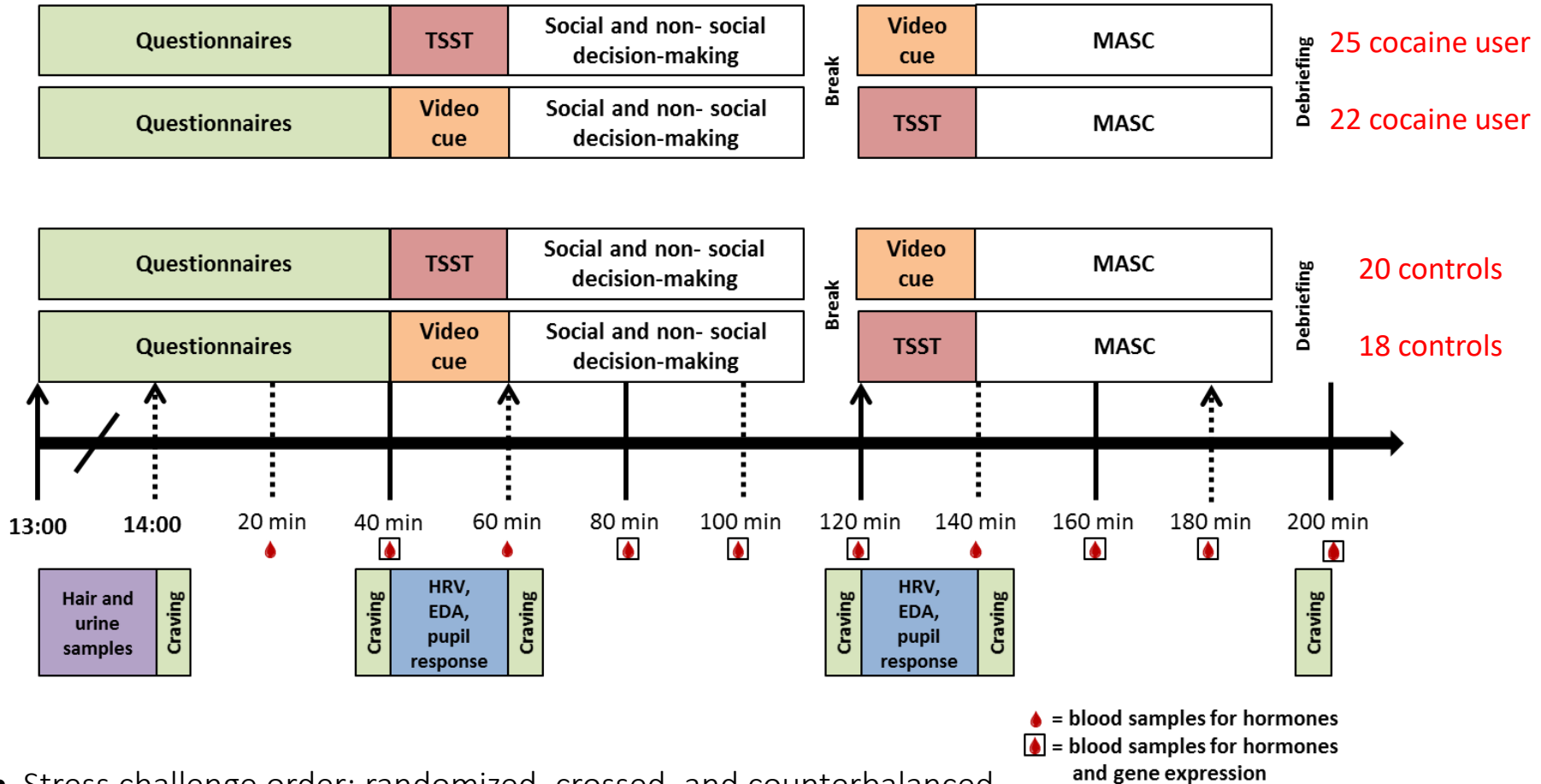
- Neutral chess video (10 minutes)
- Cocaine cue video (10 minutes)
 - Preparation and consumption scene



Statistics

- Discontinuous growth models were used to decompose the neuroendocrine, and subjective stress/craving responses over the course of the TSST into 3 or 4 linear components (e.g., for cortisol. reactivity_1 (T1–T2) and reactivity_2 slope (T2–T3), recovery slope (T3–T5)).

Method – Procedure and Study Design



- Stress challenge order: randomized, crossed, and counterbalanced
- Plasma sampling: ACTH, cortisol, noradrenaline

Results

Demographic and clinical data

Table 1
Demographic, clinical and substance use related data.

	Controls (n = 38)	Cocaine Users (n = 47)	Test Statistic	df	p
<i>Demographics</i>					
Sex (m/f) (n)	24/14	31/16	$\chi^2 = 0.1^1$	1	0.788
Age	29.5 (7.1)	31.8 (7.7)	$t = -1.4^2$	83	0.153
BMI	23.1 (3.2)	24.9 (3.8)	$t = -2.3^2$	83	0.021
Verbal IQ	103 (9.2)	95.5 (6.1)	$t = 4.1^3$	61.37	<0.001
Years of school education	10.5 (1.5)	9.6 (1.0)	$t = 3.4^3$	62.61	0.001
<i>Clinical</i>					
ADHD-SR sum score	10.1 (9.6)	14.7 (10.3)	$t = -2.1^2$	83	0.036
ADHD, y/n ⁵	5/33	12/35	$\chi^2 = 2.0^1$	1	0.156
BDI sum score ⁶	1.0 (0.0 – 22.0)	7.0 (0.0 – 31.0)	$U = 498^4$		<0.001

Note. Significant p-values are shown in bold. Counts or means and standard deviation of means in parenthesis. Abbreviations: ADHD-SR: ADHD self-rating scale; BDI: Beck Depression Inventory. ¹ χ^2 test for frequency data. ² Independent t-test. ³ Welch's t-test. ⁴ Mann-Whitney U test. ⁵ According to DSM-IV criteria as assessed by ADHD-SR. ⁶ Median (range) is reported. ⁷ Individuals were considered smokers if they smoked ≥ 7 cigarettes/week^{61,62}. ⁸ Only for smokers. ⁹ Average use during the current consumption period. ¹⁰ Cocaine_{total} (= cocaine + benzoylecgonine + norcocaine) as a more robust parameter⁵¹.

Results

Substance use

Table 1 continued

Demographic, clinical and substance use related data.

	Controls (n = 38)	Cocaine Users (n = 47)	Test Statistic	df	p
<i>Cocaine</i>					
Lifetime experience, y/n	5/33	47/0			
Times/week ⁹		2.4 (2.2)			
Grams/week ⁹		4.0 (6.7)			
Years of use		12.1 (7.4)			
Abstinence (days)		26.3 (46.3)			
Cumulative lifetime dose (grams)		1 750 (2 145)			
Cocaine _{total} , pg/mg in hair ¹⁰		24 703 (59 913)			
Cocaine, pg/mg in hair		18 438 (44 527)			
Benzoyllecgonine, pg/mg in hair		5 799 (15 046)			
Norcocaine, pg/mg in hair		467 (882)			
Cocaethylene, pg/mg in hair		512 (861)			
Urine toxicology (neg/pos)	38/0	26/21	$\chi^2 = 22.5^1$	1	<0.001

Note. Significant p-values are shown in bold. Counts or means and standard deviation of means in parenthesis. Abbreviations: ADHD-SR: ADHD self-rating scale; BDI: Beck Depression Inventory. ¹ χ^2 test for frequency data. ² Independent t-test. ³ Welch's t-test. ⁴ Mann-Whitney U test. ⁵ According to DSM-IV criteria as assessed by ADHD-SR. ⁶ Median (range) is reported. ⁷ Individuals were considered smokers if they smoked ≥ 7 cigarettes/week^{61,62}. ⁸ Only for smokers. ⁹ Average use during the current consumption period. ¹⁰ Cocaine_{total} (= cocaine + benzoyllecgonine + norcocaine) as a more robust parameter⁵¹.

Results

Substance use

Table 1 continued

Demographic, clinical and substance use related data.

Kexel et al., 2022

	Controls (n = 38)	Cocaine Users (n = 47)	Test Statistic	df	p
<i>Nicotine</i>					
Smoker/Non-Smoker (n) ⁷	29/9	37/10	$\chi^2 = 0.1^1$	1	0.791
Cigarettes/week ^{6, 8, 9}	70.0 (7.0 – 158)	90.0 (33.3 – 280)	$U = 339^4$		0.010
Years of use ⁸	12.2 (6.4)	15.6 (7.3)	$t = -2.0^2$	64	0.053
<i>Alcohol</i>					
Times/week ^{6, 9}	2.1 (0.0 – 8.5)	2.0 (0.0 – 11.0)	$U = 889^4$		0.972
Grams/week ^{6, 9}	45.8 (0.4 – 248)	100 (0.0 – 672)	$U = 646^4$		0.029
Years of use	14.4 (6.9)	16.6 (7.3)	$t = -1.4^2$	83	0.155
<i>Cannabis</i>					
Lifetime experience, y/n	31/7	43/4	$\chi^2 = 1.8^1$	1	0.176
Times/week ^{6, 9}	0.0 (0.0 – 2.0)	0.1 (0.0 – 6.0)	$U = 657^4$		0.028
Grams/week ^{6, 9}	0.0 (0.0 – 0.6)	0.0 (0.0 – 12.6)	$U = 663^4$		0.032
Years of use	6.2 (6.0)	11.5 (9.7)	$t = -3.1^3$	78.27	0.003
Abstinence (days) ⁶	163 (2.0 – 8807)	51.0 (1.0 – 10753)	$U = 565^4$		0.266
Cumulative lifetime dose (grams) ⁶	3.5 (0.0 – 1972)	426.3 (0.0 – 25719)	$U = 472^4$		<0.001
THC, pg/mg in hair ⁶	0.1 (0.0 – 320)	2.0 (0.0 – 540)	$U = 687^4$		0.057
CBN, pg/mg in hair ⁶	0.0 (0.0 – 47.0)	0.0 (0.0 – 170)	$U = 621^4$		0.003
CBD, pg/mg in hair ⁶	0.0 (0.0 – 26.0)	0.6 (0.0 – 75.0)	$U = 636^4$		0.018
Urine toxicology (neg/pos)	36/2	41/6	$\chi^2 = 1.8^1$		0.239

Note. Significant p-values are shown in bold. Counts or means and standard deviation of means in parenthesis. Abbreviations: ADHD-SR: ADHD self-rating scale; BDI: Beck Depression Inventory. ¹ χ^2 test for frequency data. ² Independent t-test. ³ Welch's t-test. ⁴ Mann-Whitney U test. ⁵ According to DSM-IV criteria as assessed by ADHD-SR. ⁶ Median (range) is reported. ⁷ Individuals were considered smokers if they smoked ≥ 7 cigarettes/week^{61,62}. ⁸ Only for smokers. ⁹ Average use during the current consumption period. ¹⁰ Cocaine_{total} (= cocaine + benzoylecgonine + norcocaine) as a more robust parameter⁵¹.

Results

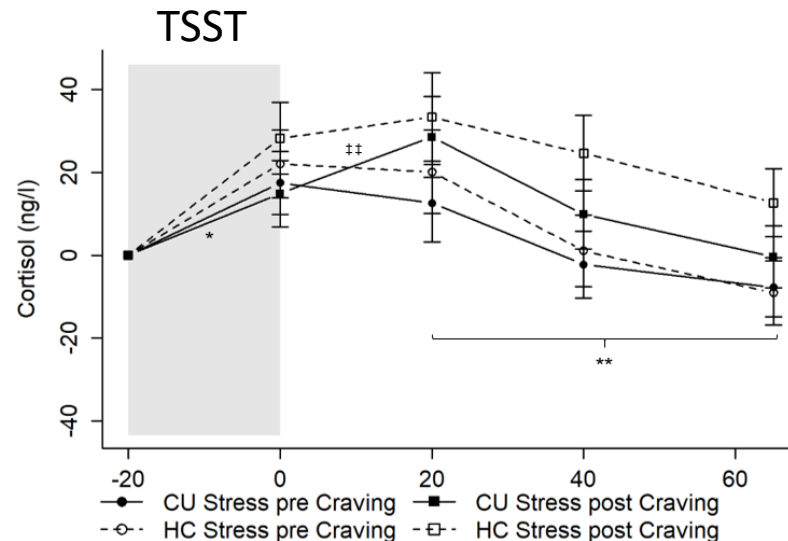
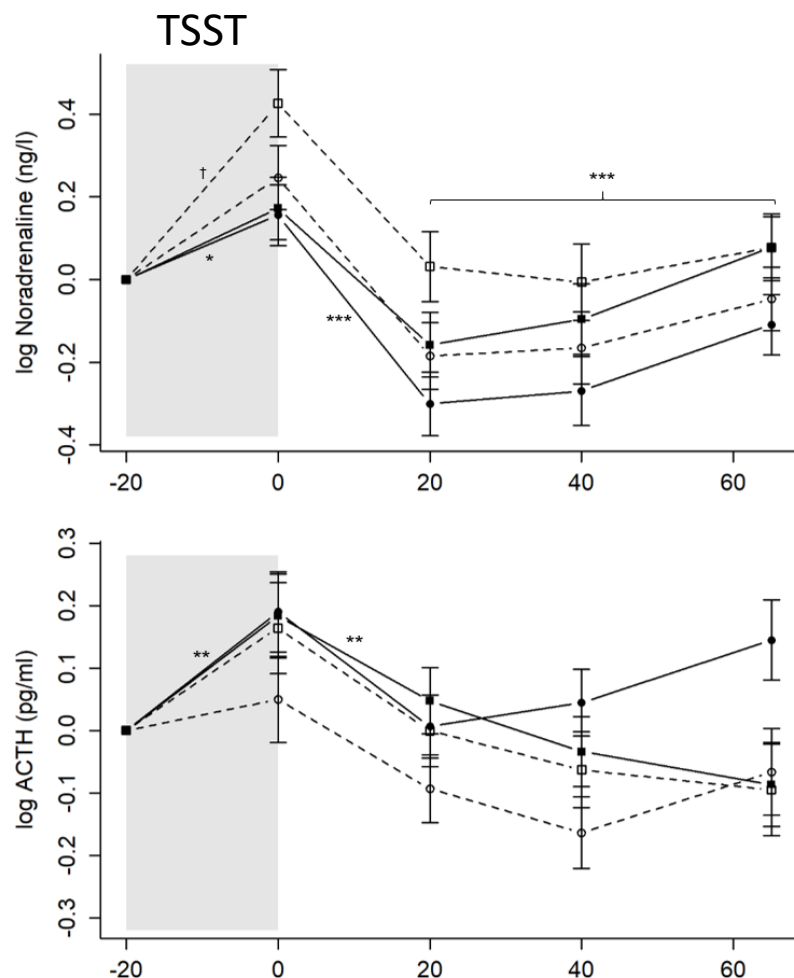
Baseline neuroendocrine levels and subjective stress in the beginning of the test-day (t -20). Means and standard deviations in parenthesis.

	Controls	Cocaine Users	Comparison
Noradrenaline (ng/l; log)	6.01 (0.54)	6.21 (0.46)	NS
ACTH (pg/ml; log)	3.88 (0.59)	3.54 (0.51)	p < 0.01, d = 0.63
Cortisol (ng/ml)	93.77 (28.34)	93.51 (37.12)	NS
Subjective stress	2.01 (1.96)	2.25 (2.18)	NS

- CU and HC did not differ in baseline plasma cortisol and noradrenaline and subjective stress ratings (ps >0.086).
- However, CU had lower baseline ACTH levels than HC.

Kexel et al., 2022

Results – TSST

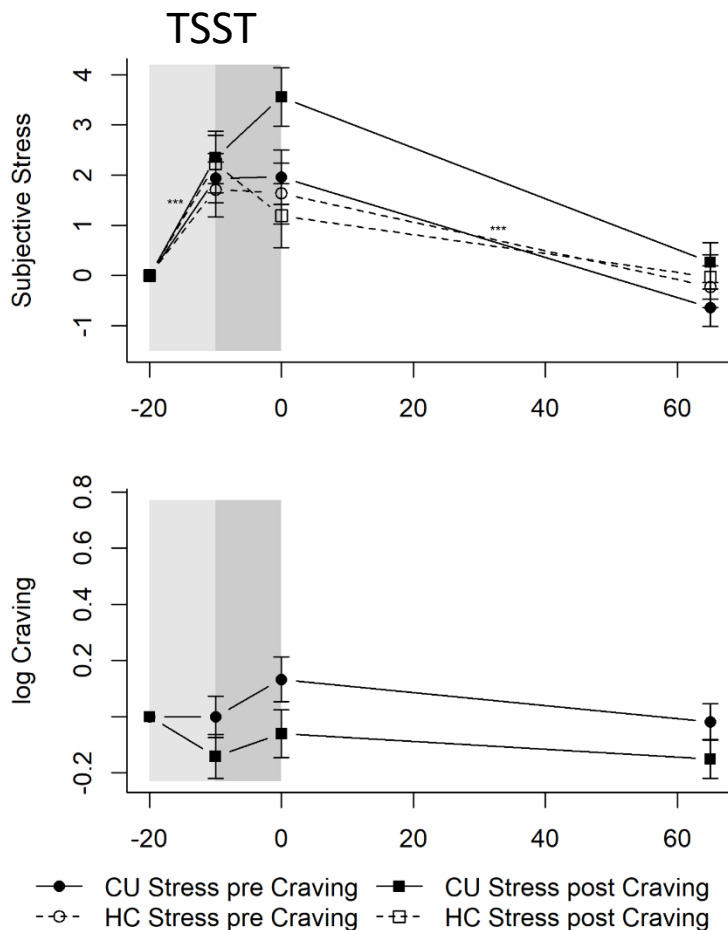


- The cortisol response in cocaine users was enhanced by previous craving

CU Stress pre Craving slope: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
 CU Stress pre Craving vs. HC Stress post Craving: † $p < 0.05$
 CU Stress pre Craving vs. CU Stress post Craving: ‡ $p < 0.01$

Kexel et al., 2022

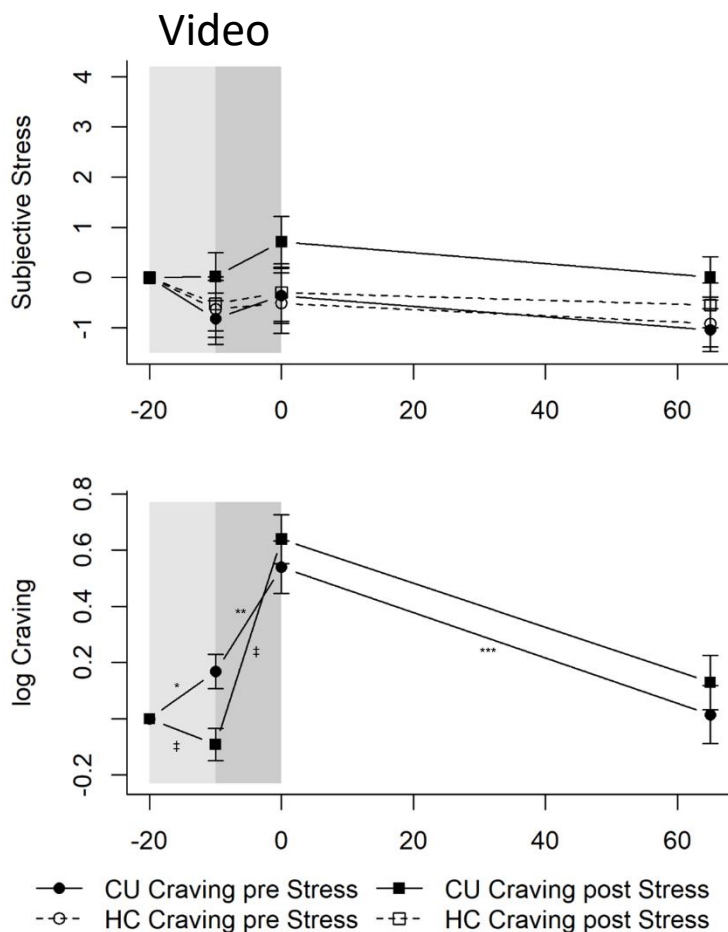
Results – TSST



- Cocaine users and controls showed a similar subjective stress response to the TSST.
- The TSST did not induce craving in cocaine users.

CU Stress pre Craving slope: *** $p < 0.001$.

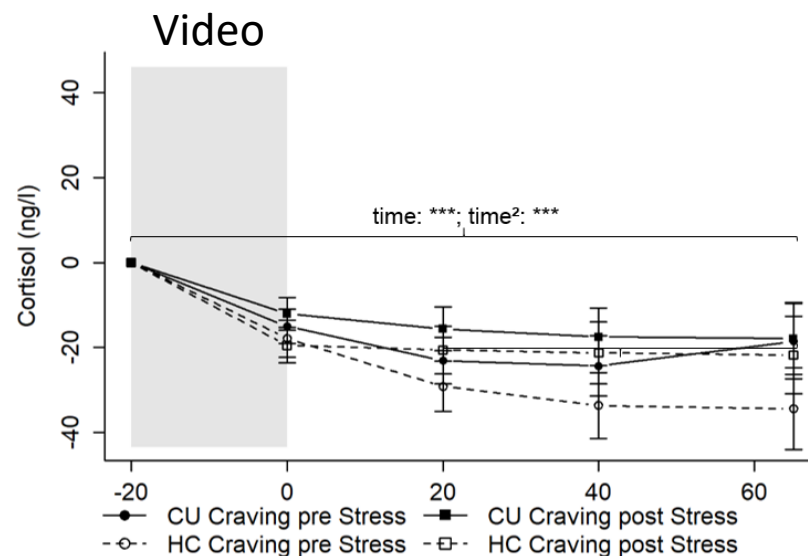
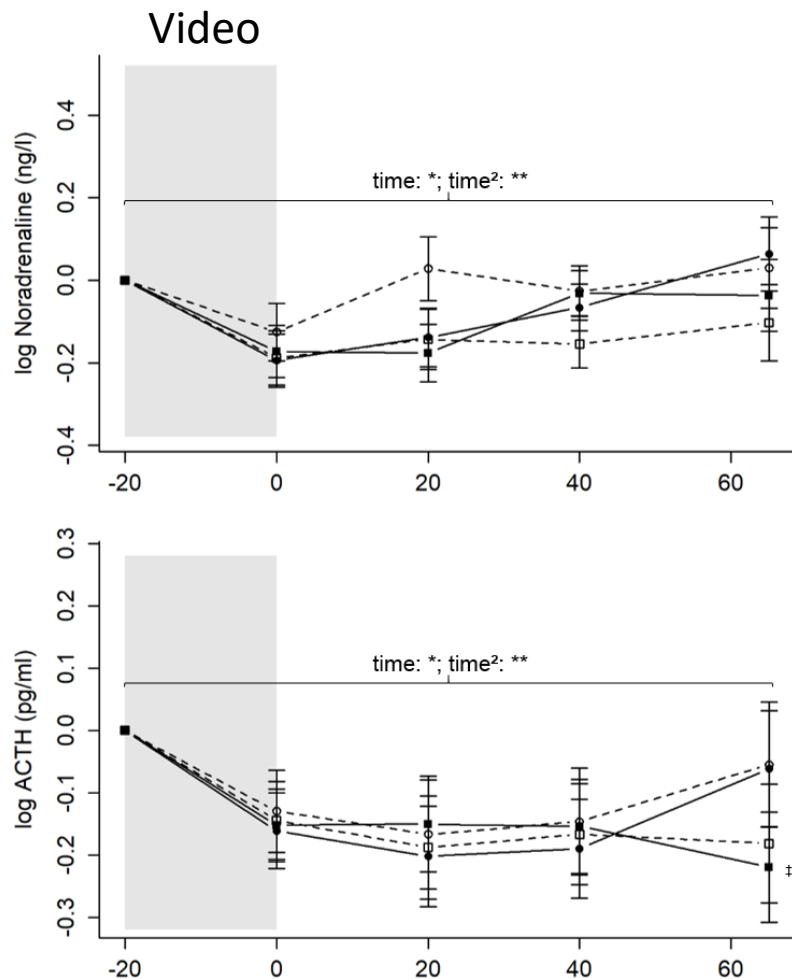
Results – Cocaine-Cue-Video



- Craving in cocaine users was intensified by a preceding confrontation with the psychosocial stressor.
- The Cocaine-Cue-Video did not induce a subjective stress response.

CU Craving pre Stress slope: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
 CU Craving pre Stress vs. CU Craving post Stress: † $p < 0.05$.

Results – Cocaine-Cue-Video



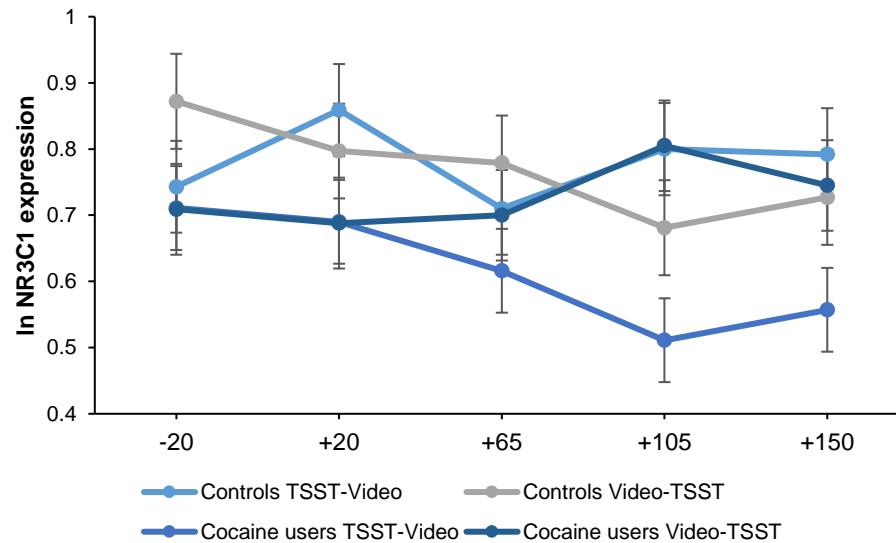
- Cocaine users experienced craving but no physiological stress response to the Cocaine-Cue-Video

CU Craving pre Stress slope: *p < 0.05; **p < 0.01; ***p < 0.001
 CU Craving pre Stress time2 vs. CU Craving post Stress: ‡p < 0.05

Kexel et al., 2022

Results – NR3C1

NR3C1 expression under psychosocial stress and craving



- Group: $F(1,71) = 4.18, p = .045$
- Time*Group*Order: $F(4,284) = 4.07, p = .003$

Kexel et al., in preparation

Conclusion

- Regular but high-functioning cocaine users displayed neither dysregulated HPA axis responses at baseline nor robust craving symptoms to experimentally-induced psychosocial stress.
- The cocaine-cue paradigm reliably evoked craving but no neuroendocrine stress response.
- Psychosocial stress and craving seem to have mutually augmenting effects on HPA axis reactivity and craving in cocaine users, which possibly contribute to the maintenance of and relapse in chronic cocaine use.
- Preliminary results suggest a similar effect at the NR3C1 expression level, which goes down specifically in cocaine users who were stressed after craving induction.

Many thanks to ...

University of Zurich
Experimental and Clinical
Pharmacopsychology
SSCP-Team

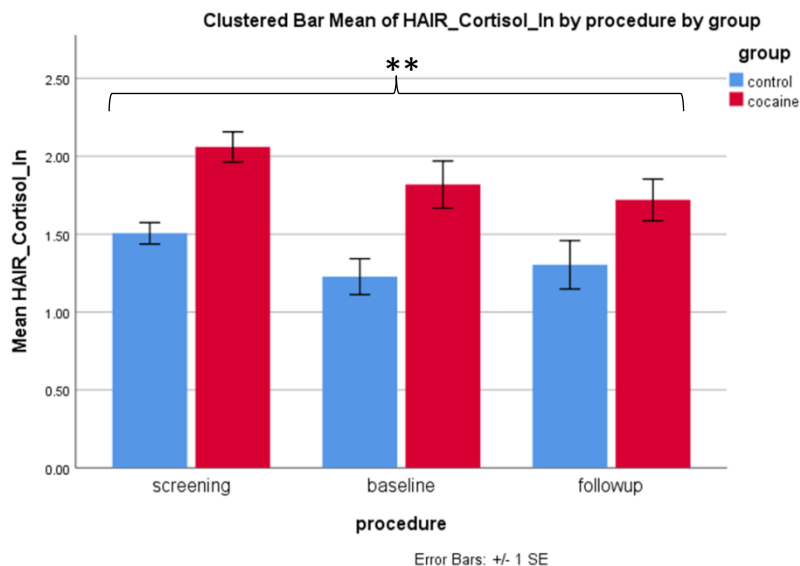
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Chronic stress load in cocaine users

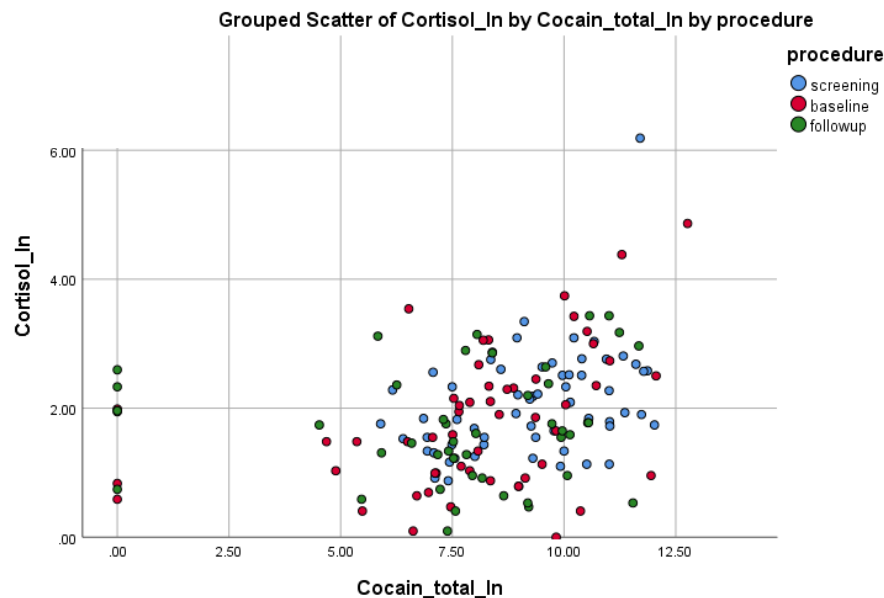


Cocaine users showed robust and stable elevations of hair cortisol across three measurements covering ~9-10 month (~4 months each).

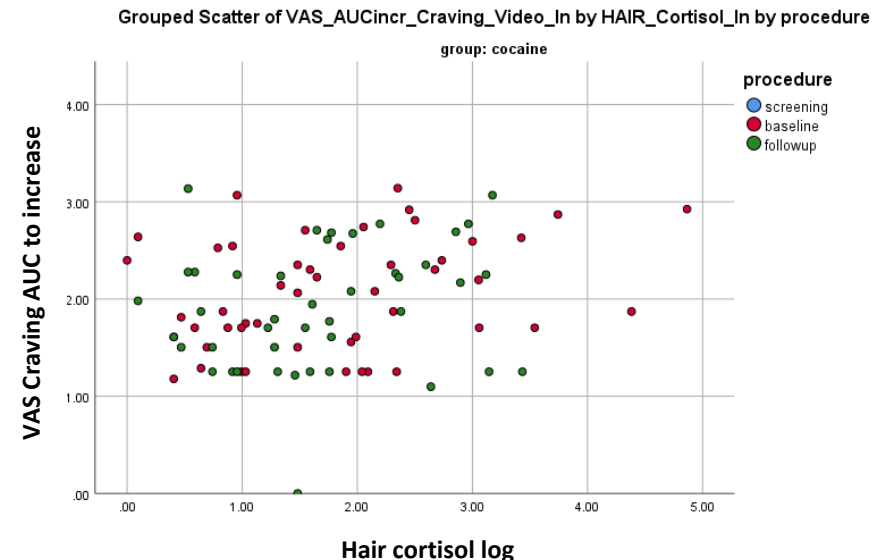
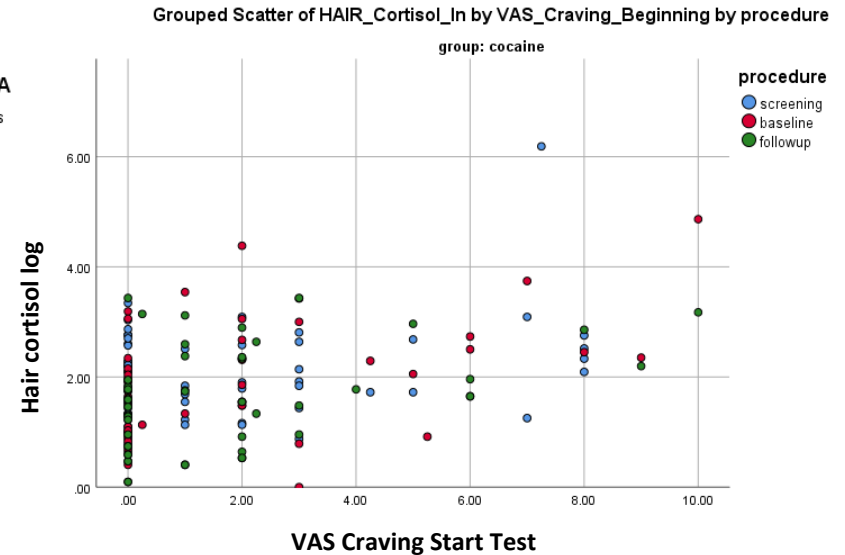
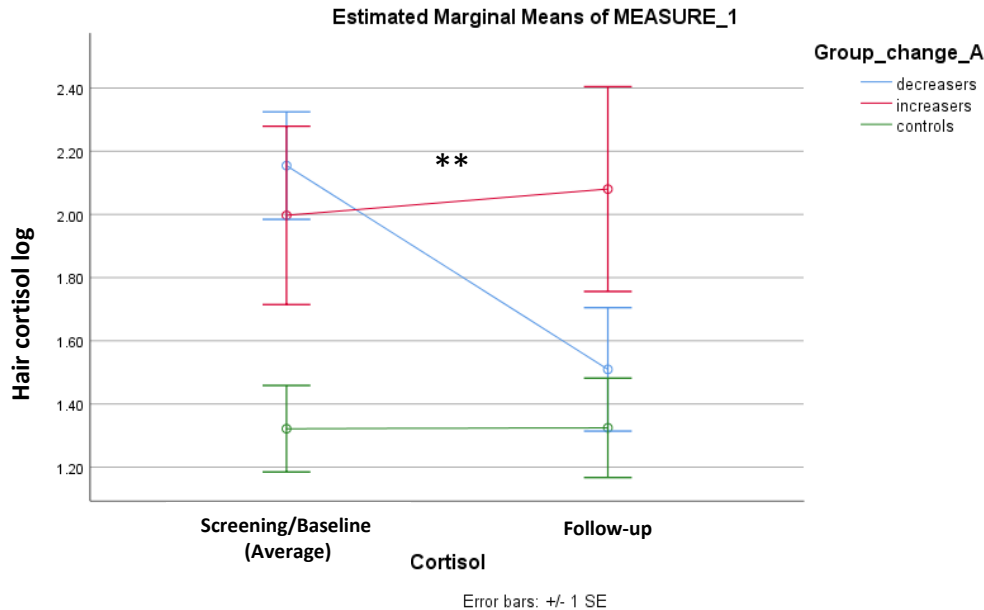
Age was a significant covariate but **not** sex, alcohol, smoking, and critical life events in the last 2 years.

Cocaine and cortisol hair concentrations were strongly correlated (Spearman's $r=0.38$, $p<.0001$), indicating that more severe cocaine use is going along with more cortisol release.

Cortisol hair concentrations were not correlated with critical life events in the last 2 years (Holmes Rahe Scale: $r=0.05$) or early life stress (Childhood Trauma Q.: $r=0.10$).



Changes of hair cortisol with changed cocaine use

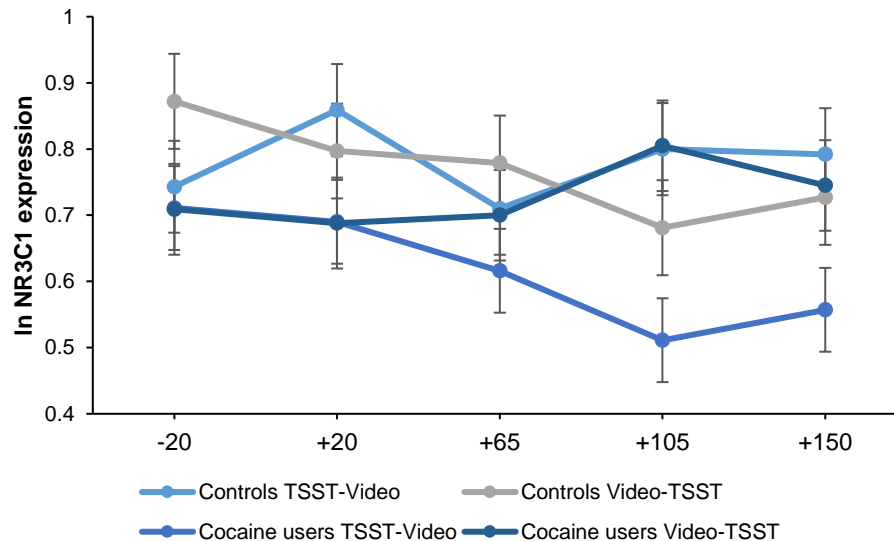


Changes in cocaine consumption during the 4-months interval also changes hair cortisol levels.

Cortisol hair concentrations were strongly correlated with VAS craving (but not with VAS stress) at the beginning of the tests (Spearman's $r=0.32$, $p<.0001$), but also with the craving response to drug cue exposure (Spearman's $r=0.26$, $p<.01$).

Results – NR3C1

NR3C1 expression under psychosocial stress and craving



- Repeated measures ANOVA with the within-subjects factor 'time' (T₁ to T₅) and the between-subjects factors 'group' (controls – cocaine users) and 'order' (TSST-Video – Video-TSST)
- Covariates: sex, age, BMI

Results – NR3C1

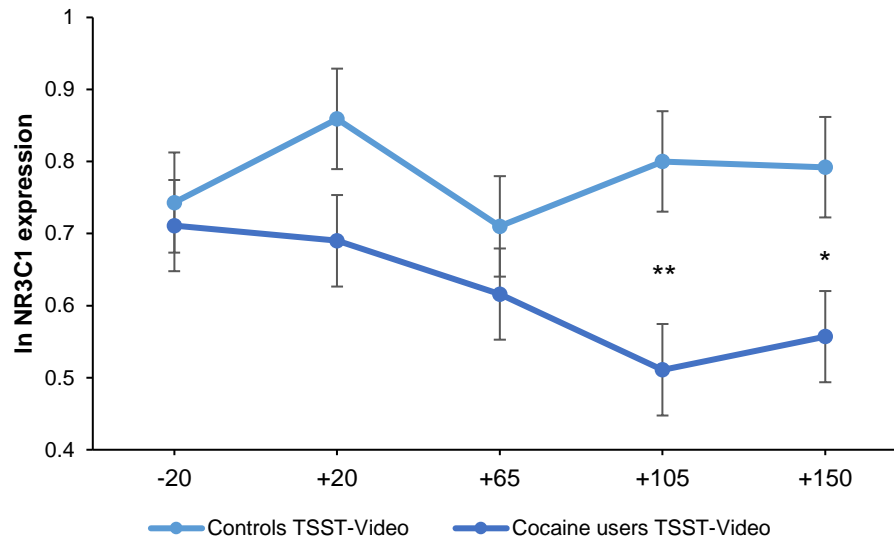
NR3C1 expression under psychosocial stress and craving

- Time: $F(4,284) = 0.20, p = .937$
- Time*Group: $F(4,284) = 0.17, p = .953$
- Time*Order: $F(4,284) = 0.78, p = .537$
- Time*Group*Order: $F(4,284) = 4.07, p = .003$

- Group: $F(1,71) = 4.18, p = .045$
- Order: $F(1,71) = 1.07, p = .304$
- Group*Order: $F(1,71) = 1.57, p = .214$

Results – NR3C1

NR3C1 expression under psychosocial stress and craving

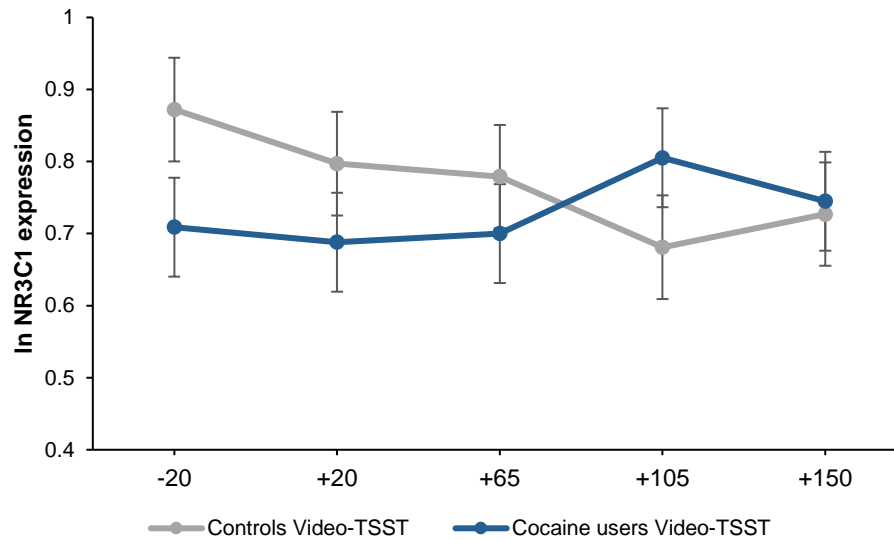


TSST-Video

- T2: Controls > Cocaine users, $p = .061$
- T4: Controls > Cocaine users, $p = .004$
- T5: Controls > Cocaine users, $p = .026$

Results – NR3C1

NR3C1 expression under psychosocial stress and craving

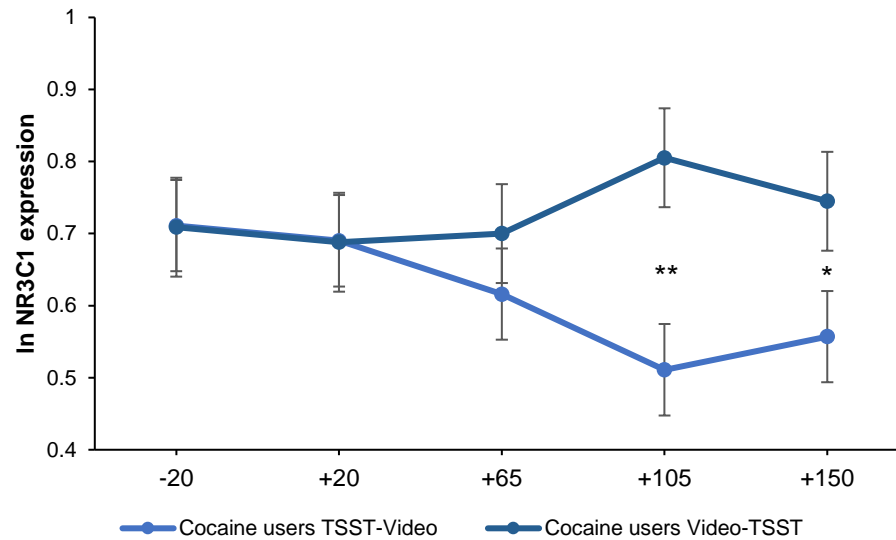


Video-TSST

- No differences between controls and cocaine users for the order Video-TSST.

Results – NR3C1

NR3C1 expression under psychosocial stress and craving

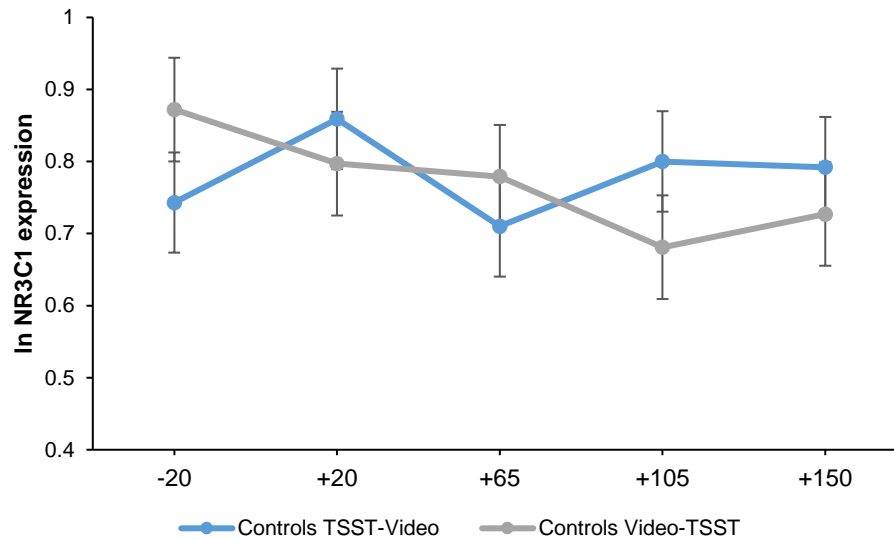


Cocaine users

- T4: TSST-Video < Video-TSST, $p = .001$
- T5: TSST-Video < Video-TSST, $p = .042$
- TSST-Video: T1 > T4, $p = .076$

Results – NR3C1

NR3C1 expression under psychosocial stress and craving



Controls

- No differences between TSST-Video and Video-TSST for controls.