Universität Zürich[UZH]

Psychiatrische Universitätsklinik Zürich

The endocannabiniod system and drug addiction: basal ~~and stress-related~~ endocannabinoid plasma levels in chronic cocaine users ~~and prescription opioid users~~

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BRAIN & BEHAVIOR RESEARCH FOUNDATION
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No conflict of interests to declare!

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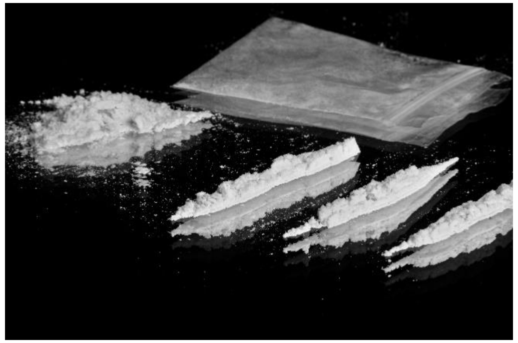
IMPORTANCE

COCAINE

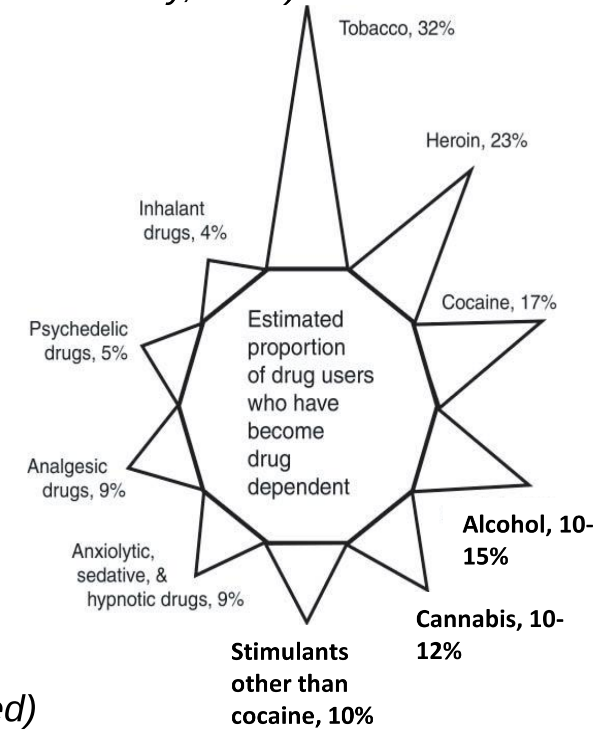


- Highly addictive:
  - 5% - 6% of cocaine user develop dependence within first year
  - 15% -21% lifetime risk for dependence

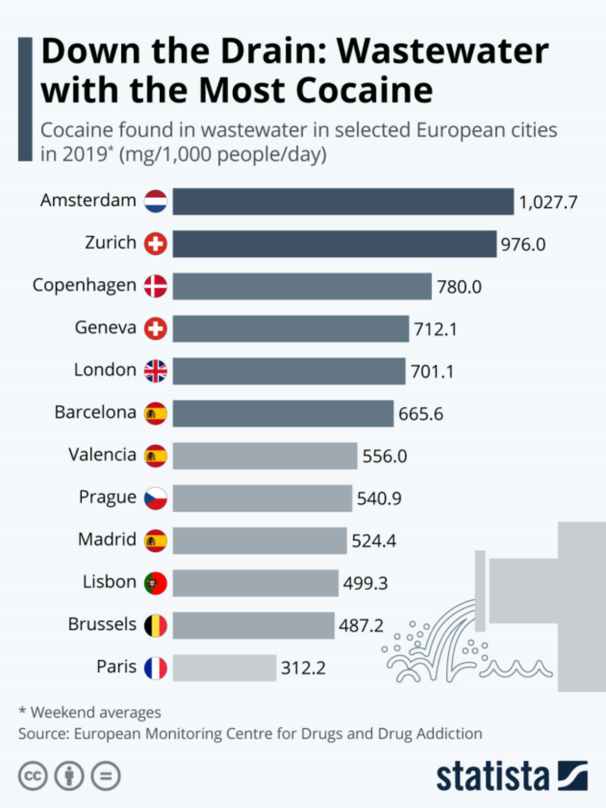
  (Degenhardt & Hall, 2012; Lopez-Quintero et al., 2011; Wagner & Anthony, 2002)

- High relapse rates
  - 40% - 60% relapse during or after treatment

  (McLellan et al., 2000; Simpson et al., 1999)



(Anthony 2002, updated)



COCAINE EFFECTS

- Non-selective monoamine transporter inhibitor (DAT) → increase of neurotransmitter

(Iversen et al., 2013; 2014; Kreek et al, 2002)

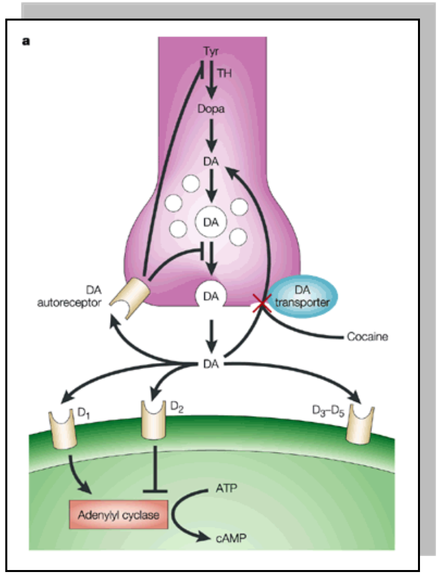
- Intense stimulation of the mesolimbic DA reward system → long-term synaptic plasticity → **altered reward behavior**

(Kalivas & O'Brien, 2008; Thomas et al, 2008)

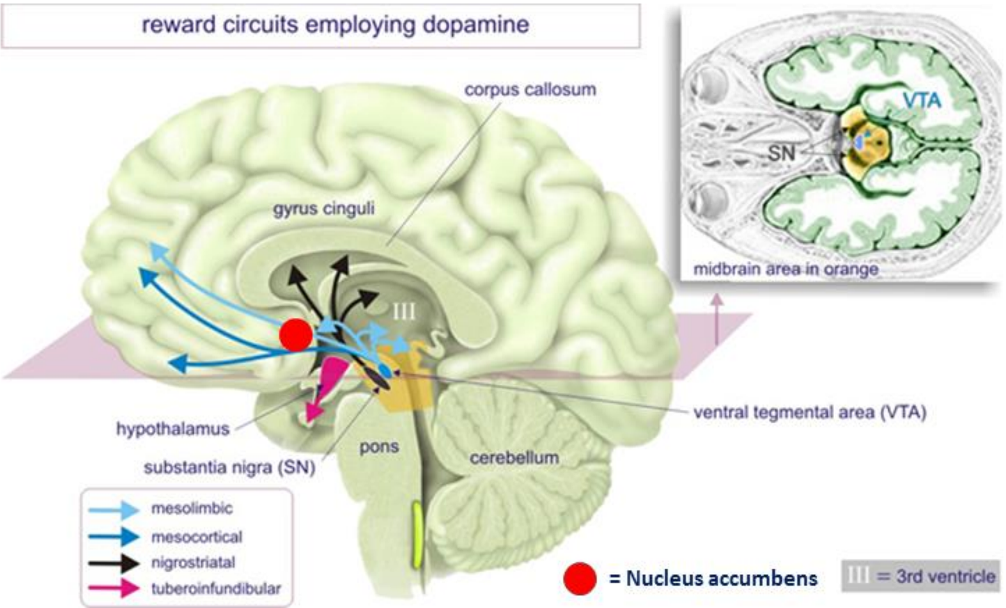
- Acute and chronic cocaine administration increases physiological stress load → **dysfunctional stress response**

(Koob & Kreek, 2007; Sinha, 2008; Wemm & Sinha, 2019)

→ Impaired **reward** and **stress resgulation**



(Kreek et al. 2002)



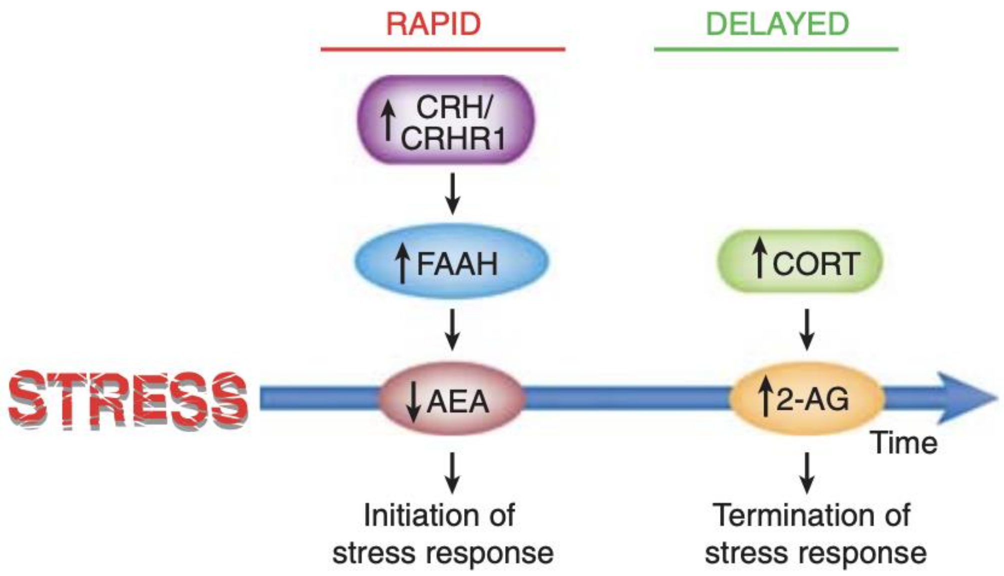
ENDOCANNABINOID SYSTEM

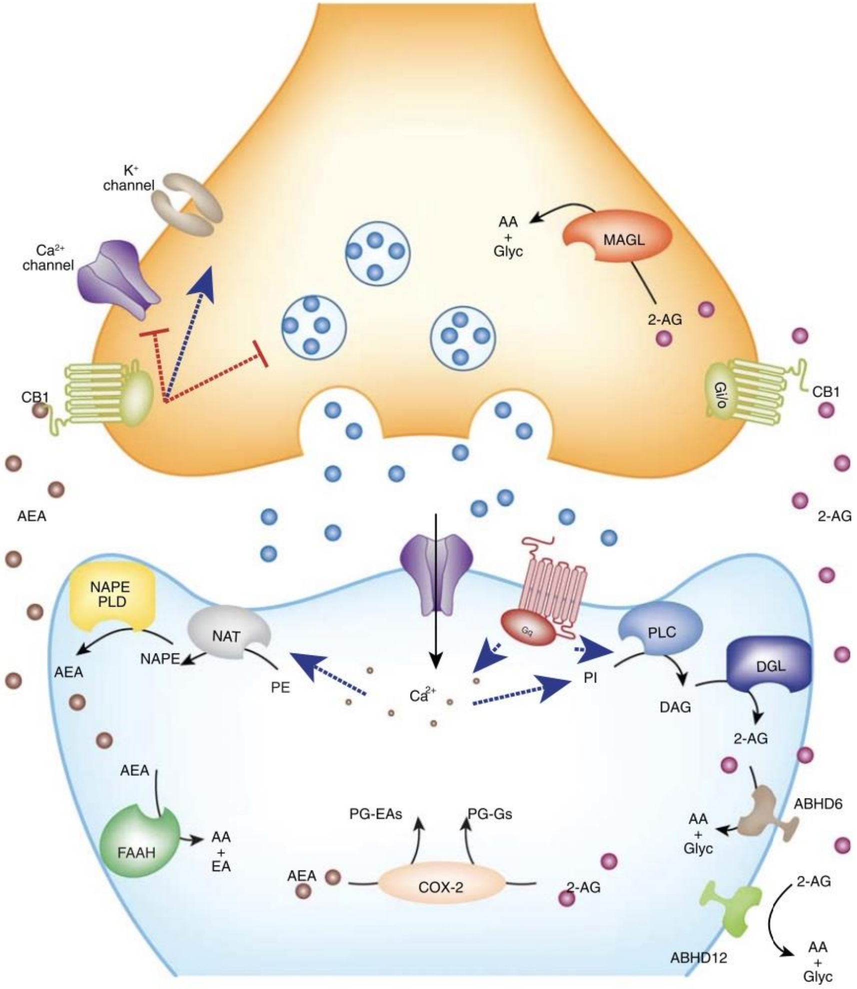
→ Associated with **reward & drug-seeking response**

(Moreira et al., 2015 , Parsons & Hurd, 2015; Spanagel, 2020, Schreyer et al., 2022)

→ Crucial regulator of **stress response**

(Moreira et al., 2015; Morena et al., 2016; de Roon-Cassini et al., 2020)





(Morena et al., 2016)

ENDOCANNABINOID SYSTEM & COCAINE

cocaine

→ Associated with **reward** & **drug-seeking response**

(Moreira et al., 2015 , Parsons & Hurd, 2015; Spanagel, 2020, Schreyer et al., 2022)

→ Crucial regulator of **stress response**

(Moreira et al., 2015; Morena et al., 2016; de Roon-Cassini et al., 2020)

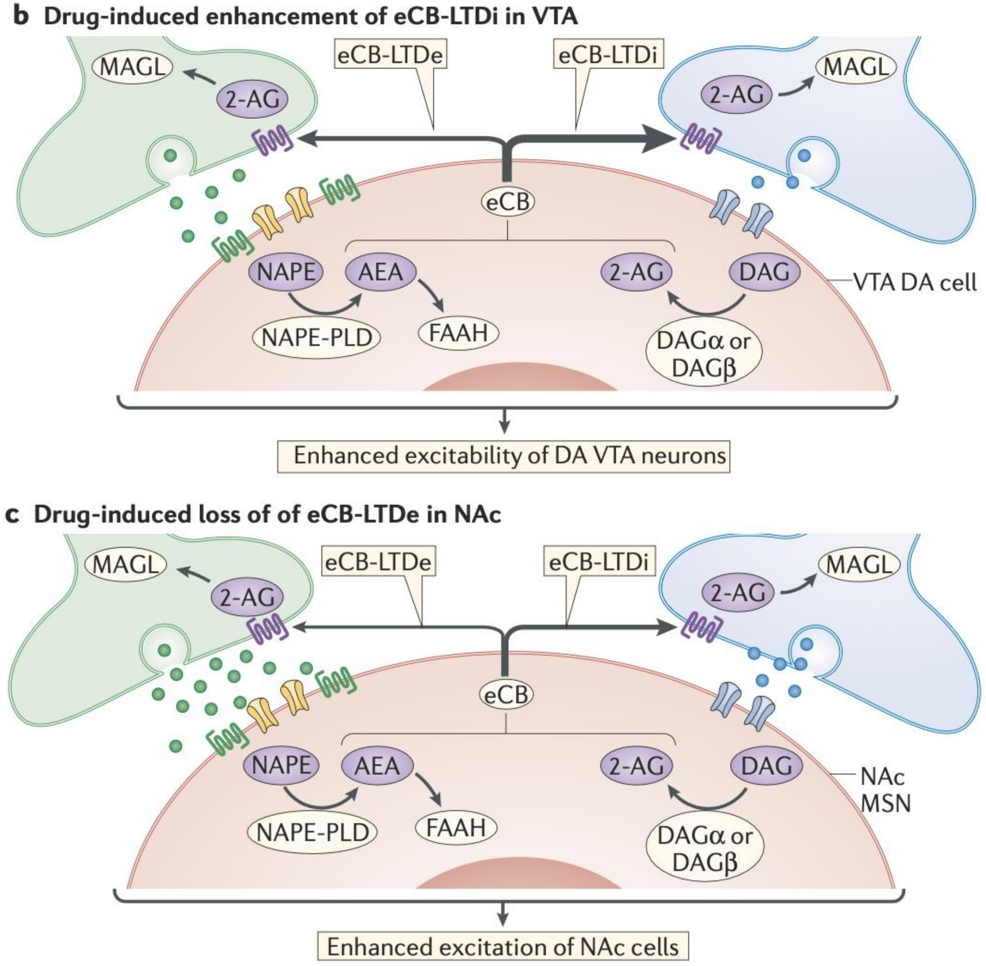
Acute cocaine adminstration:

→ VTA: 2-AG ↑

→ VTA: eCB-LTD ↑

→ NAc: eCB-LTD ↓

(Bystrowska et al., 2014; 2019; Fourgeaud et al., 2004; Wang et al., 2015;)



(Parsons & Hurd, 2015)

ENDOCANNABINOID SYSTEM & COCAINE

→ Associated with **reward & drug-seeking response**

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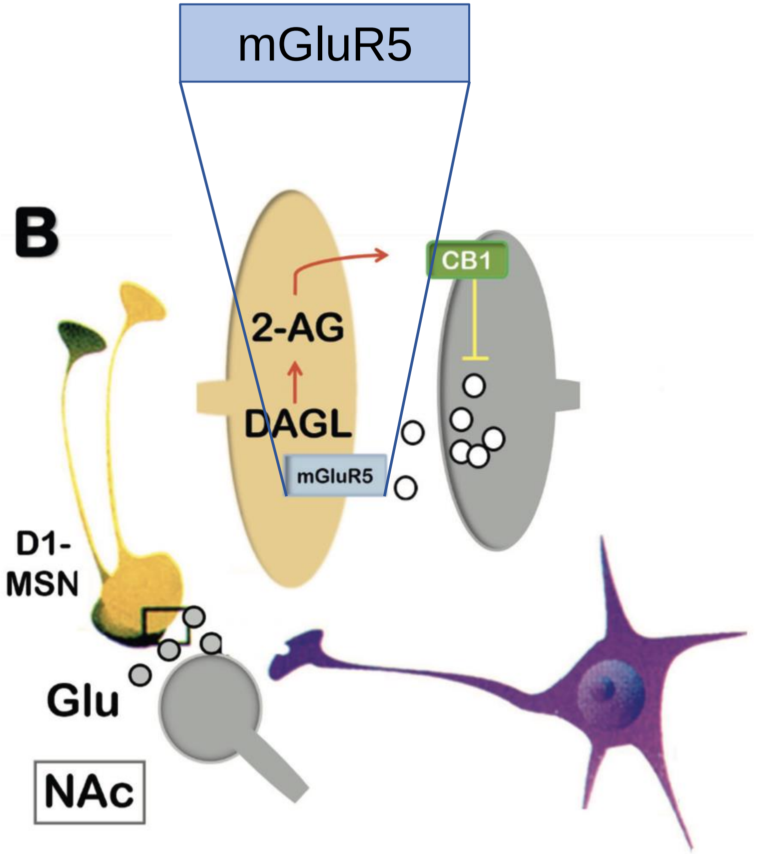


→ Endocannabinoid LTD in NAc D1 neurons mediates reward-seeking behavior

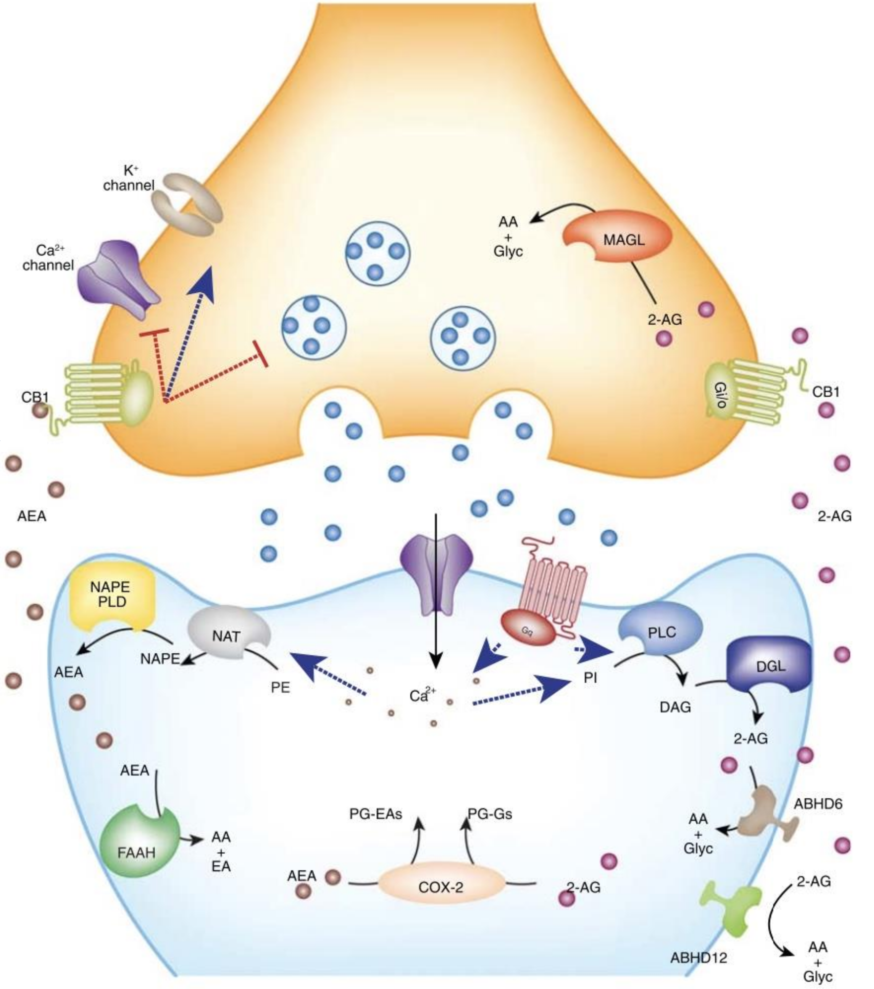
(Bilbao et al., 2020)

(Spanagel, 2020)

ENDOCANNABINOID SYSTEM & COCAINE

HUMAN FINDINGS

- Abstinent cocaine users 2-AG plasma ↓
  (Pavon et al., 2013)
- Chronic cocaine users: CORT ↑ OEA and PEA in hair ↓
  (Voegel, Kroll et al., 2022)
- No differences of mGluR5 density between cocaine users and controls
  (Hulka et al., 2014)



(Morena et al., 2016)

NOVELTY

Animal models indicate a crucial role of the ECS in CUD!

→ ***2-AG-modulated reward response and stress regulation***
→ ***mGluR5/2-AG interaction in reward-seeking behaviour***

→ *Translational human studies are missing*

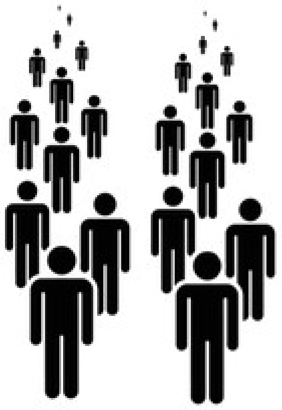
Aim:

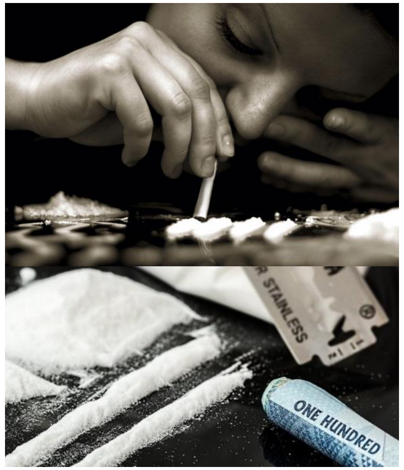
To investigate **basal endocannabinoid plasma levels** as well as **an eCB/mGluR5 interaction** in chronic cocaine users compared to healthy controls to identify a specific eCB profile of cocaine addiction in humans.

The Zurich Cocaine Cognition Study (ZuCo^{2}St)

Endocannabinoid plasma

Stimulant-naïve healthy control group
n = 92





Endocannabinoid plasma

Chronic cocaine user
n = 103
Recreational cocaine users: RCU n=69
Dependent cocaine users: DCU n=34

6 months later follow-up

Stimulant-naïve healthy control group
n = 43

6 months later follow-up

Chronic cocaine user
n= 33
Increaser n=16
Decreaser n= 17

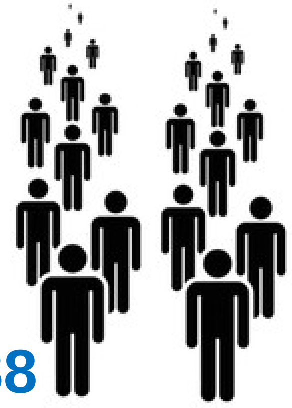
The Zurich Cocaine Cognition Study (ZuCo²St)

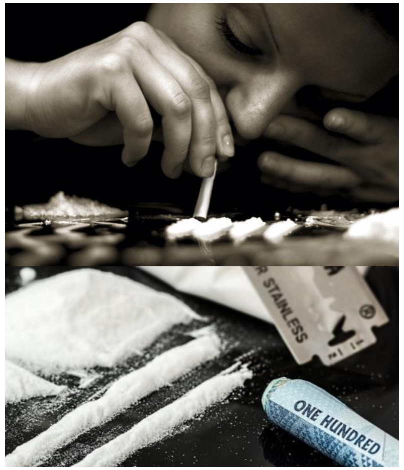
Endocannabinoid plasma

Stimulant-naïve healthy control group
n = 92

PET data using ^{11}C-ABP688

Stimulant-naïve healthy control group
n = 16 (m)





Endocannabinoid plasma

Chronic cocaine user
n = 103
recreational cocaine users: RCU n=69
dependent cocaine users: DCU n=34

PET data using ^{11}C-ABP688

Chronic cocaine user
n = 18 (m)
recreational cocaine users: RCU n=11
dependent cocaine users: DCU n=7

METHODS

	Stimulant-naïve controls n=92	Recreational cocaine users n=69	Dependent cocaine users n=34	Value	*df1, df2*	*p*
Female/male	26/66	18/51	9/25	χ^2= 0.1	2	0.949
Age	30.6 (9.1)	28.7 (7.6)	34.0 (10.6)†	F = 4.1	2, 192	**0.018**
Years of education	10.8 (1.8)	10.4 (1.7)	9.5 (1.2)°†	F = 7.9	2, 192	**<0.001**
Verbal IQ	108.0 (12.1)	103.1 (9.7)°	100.9 (11.4)°	F = 6.6	2, 192	**0.002**
BDI sum score	4.2 (4.2)	7.7 (6.6)°	11.5 (8.2)°†	F = 20.4	2, 192	**<0.001**
ADHD-SR	7.5 (4.9)	12.9 (9.1)°	16.9 (8.4)°†	F = 24.1	2, 192	**<0.001**
Smoking (y/n)	66/26	57/12	27/7	χ^2= 2.8	2	0.251
Cigarettes/ week[a]	84.1 (61.7)	107.9 (55.9)	135.0 (95.7)°	F = 5.8	2, 147	**0.004**
Alcohol grams/week	107.1 (115.6)	170.7 (114.8)	226.2 (322.0)°	F = 6.9	2, 192	**0.001**

Demographic data with significant *p*-values shown in bold and significant post-hoc tests (Bonferroni) marked with:
[o] Compared to control group
[†] Compared to RCU
[a] Within smokers

METHODS

Cocaine use variables

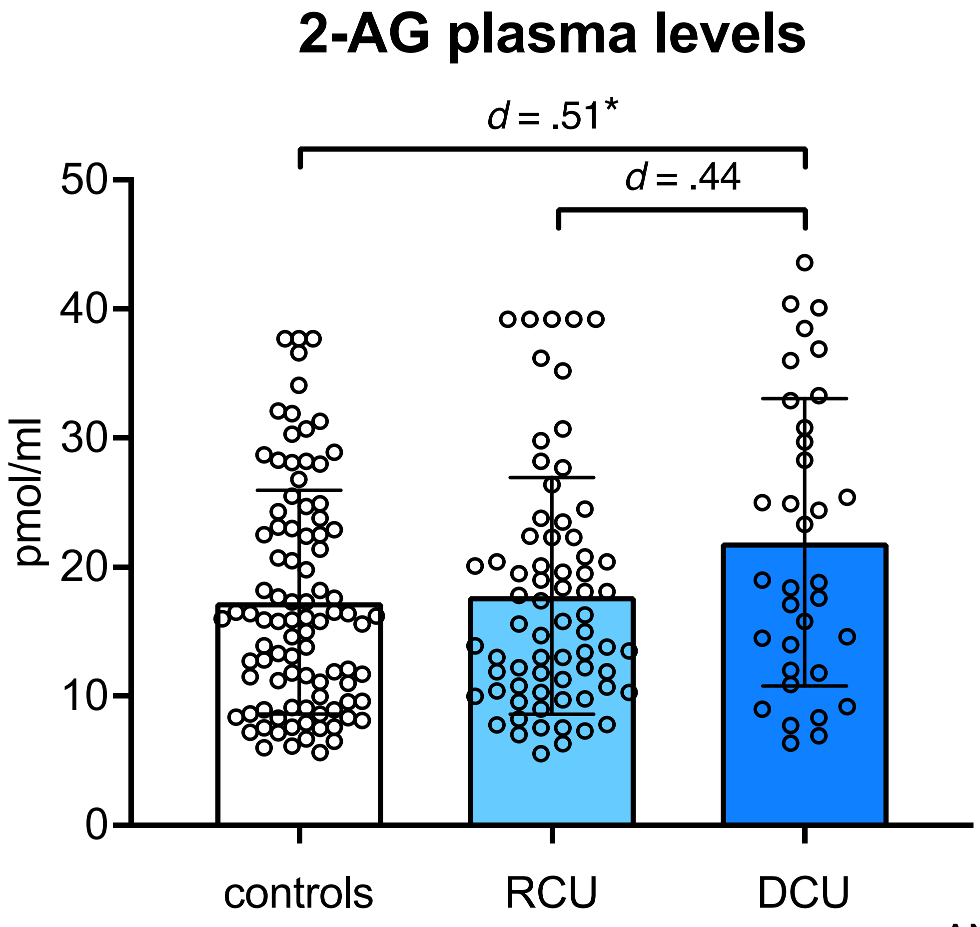
COCAINE	Controls	RCU	DCU	Value	*df1, df2*	*p*
Cocaine craving	-	19.1 (9.2)	20.5 (11.4)	F = 0.4	1, 101	0.518
Grams/week	-	1.1 (1.4)	5.5 (6.9)	F = 25.7	1, 101	**<0.001**
Cocaine abstinence in h	-	643.4 (881.0)	535.1 (814.6)	F = 0.4	1, 101	0.549
Years of use[b]	-	6 (0.8 - 17)	9 (1 - 30)	F = 8.7	1, 101	**0.004**
Hair concentration pg/mg	-	3’070 (6685.8)	18’685.7 (21’478.2)	F = 30.7	1, 101	**<0.001**
Urine sample positive (y/n)	-	9/59	13/21	χ^2= 8.4	1	**0.004**

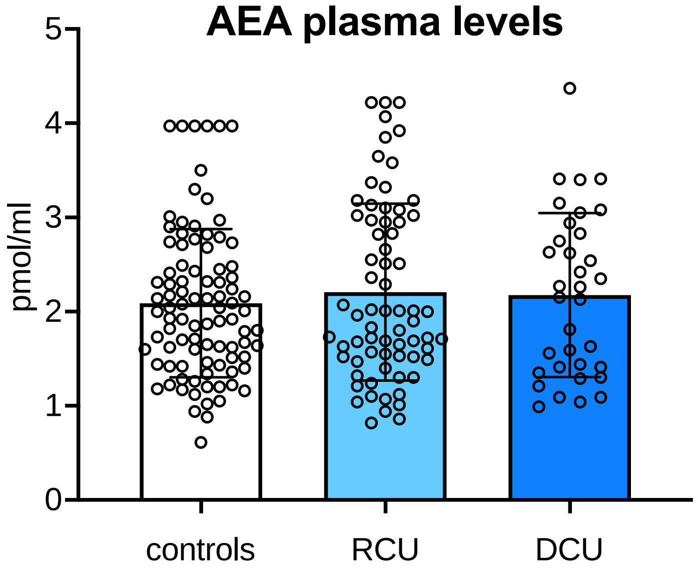
Group differences within the chronic cocaine user group: mean & SD; significant *p*-values are shown in bold.

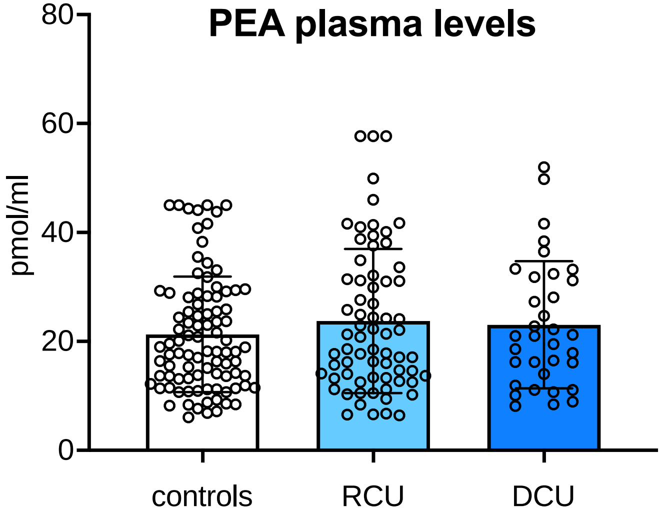
[b] Median (range)

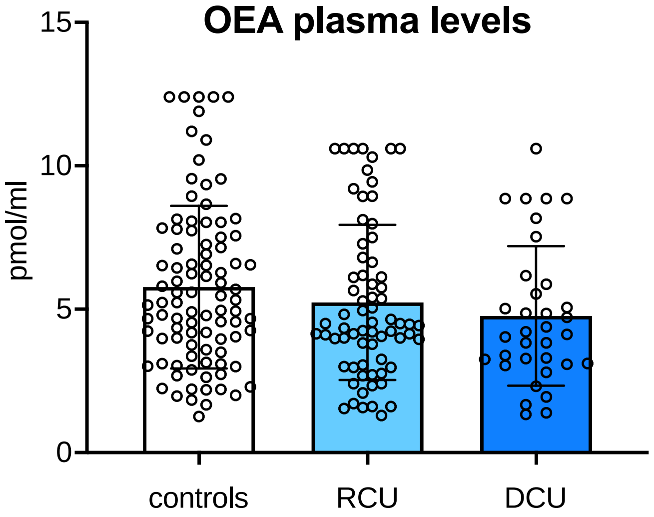
RESULTS

1. Elevated 2-AG in dependent cocaine users (DCU)





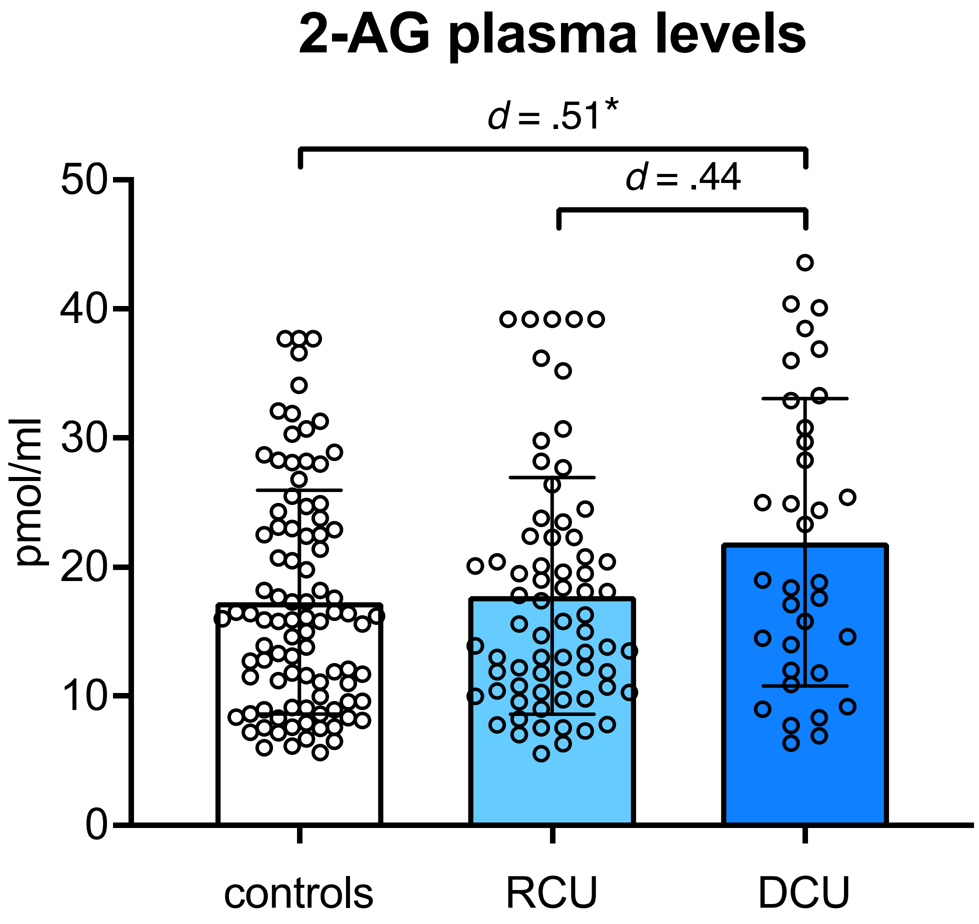


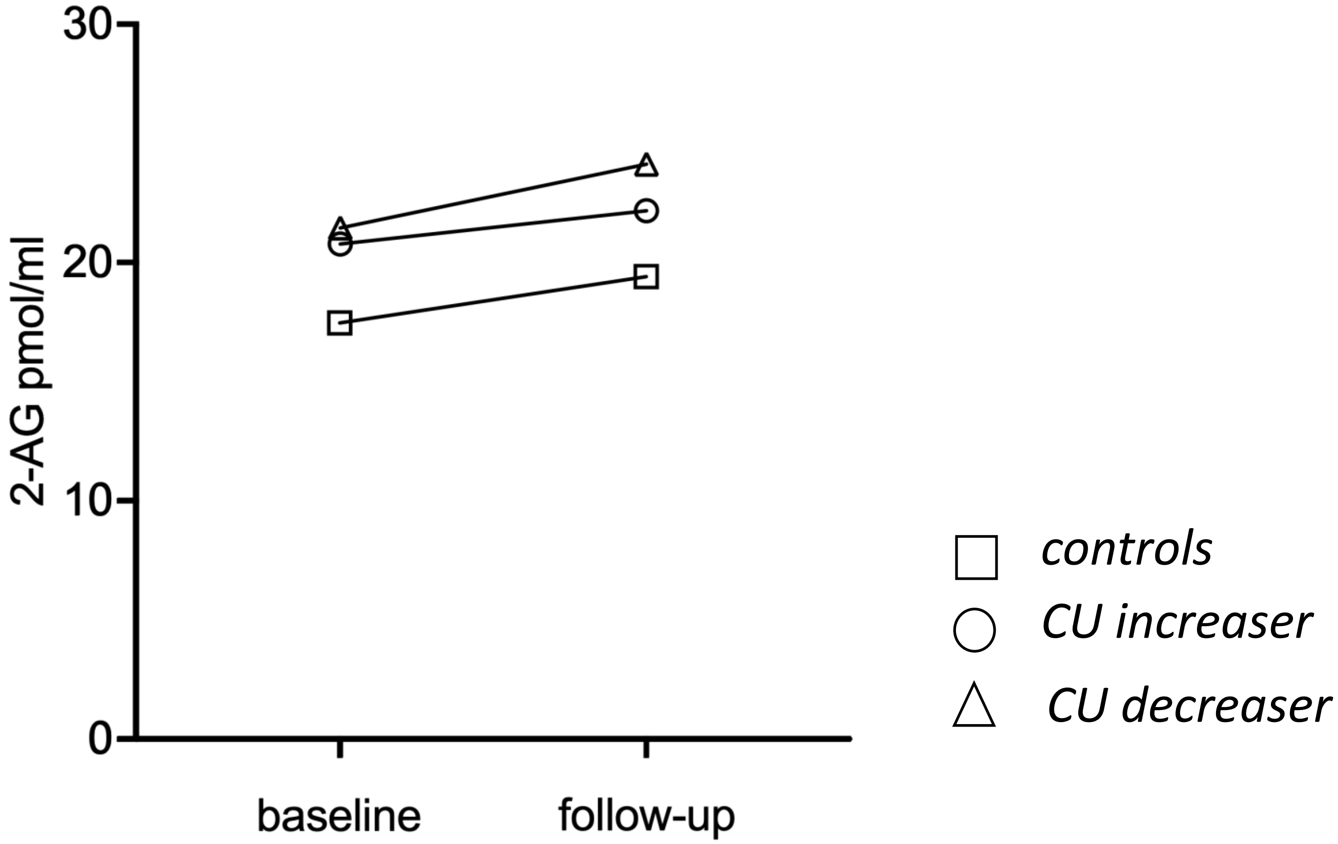


ANCOVAs controlled for sex, age, and acute cannabis effects (plasma THC & CBD levels)

p<0.05*, *p*<0.01**, *p*<0.001***

1. Elevated 2-AG in dependent cocaine users (DCU)

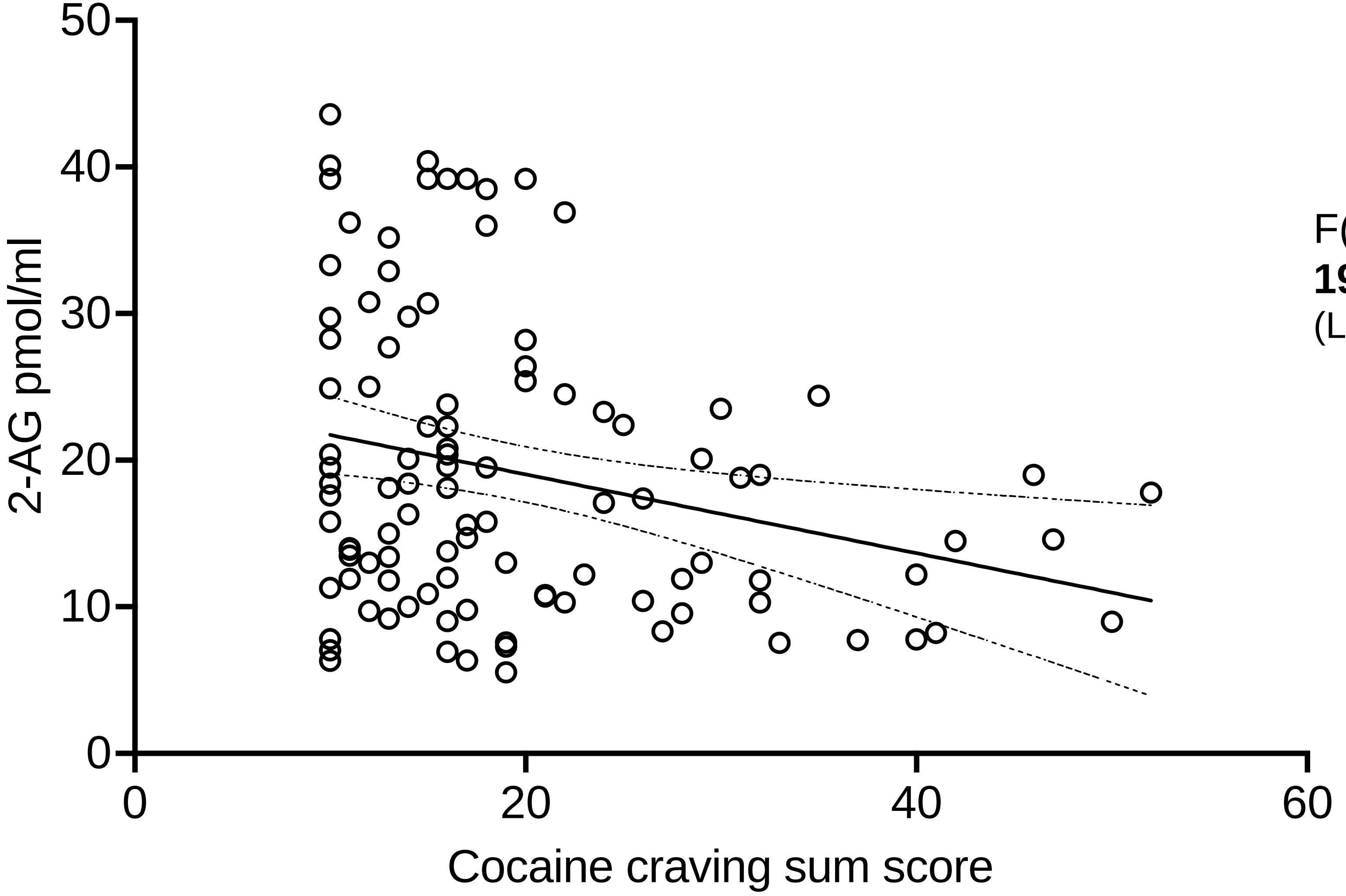




$p<0.05$*, $p<0.01$**, $p<0.001$***

rmANCOVAs controlled for sex, age

2. Lower 2-AG is associated with cocaine craving

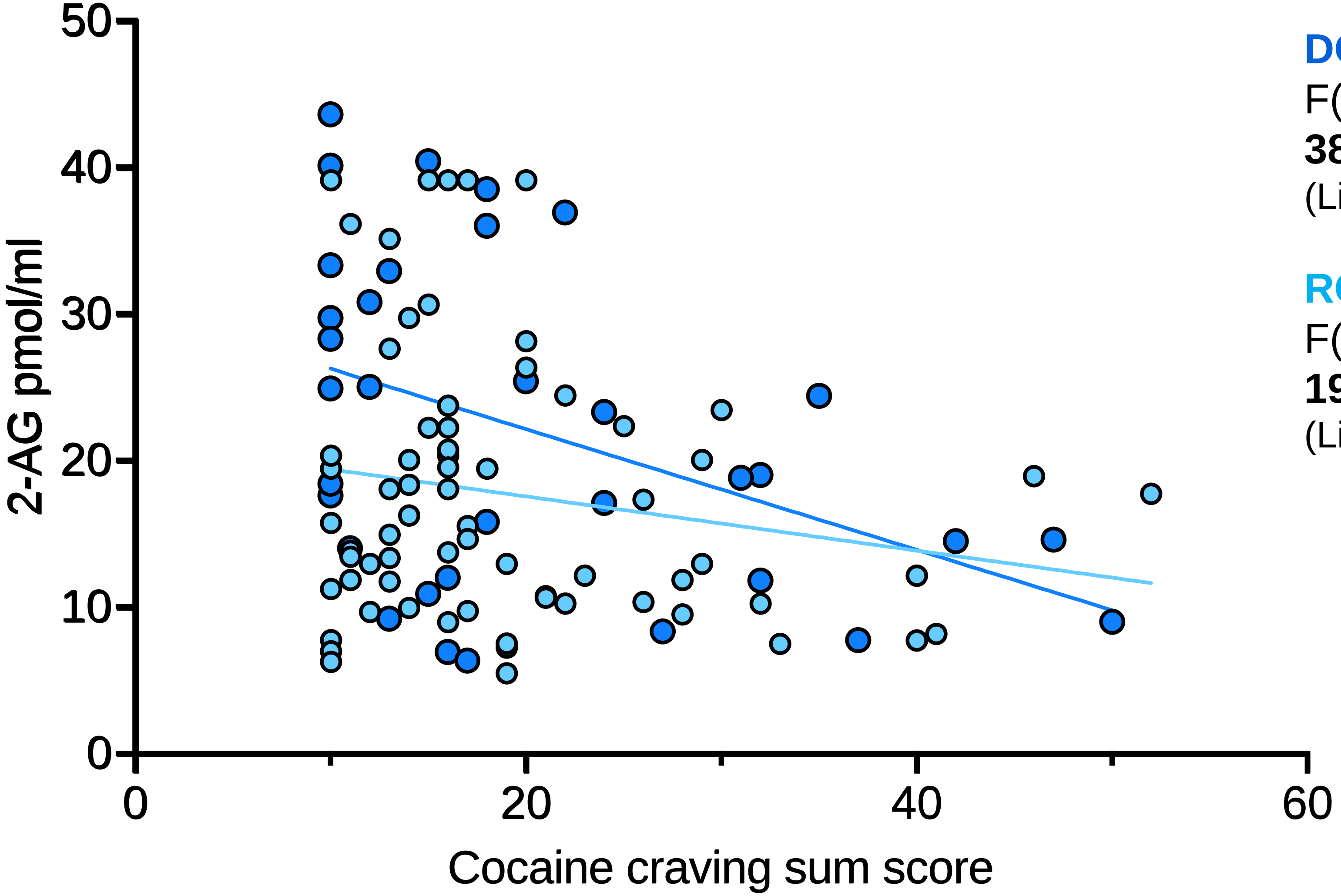


F(5,97)=4.67, *p*<.001, R^2=.19

19% explained variance

(Linear regression model controlling for covariates)

2. Lower 2-AG is associated with cocaine craving



DCU

F(5,28)=3.42, *p*=.015, R^2=.38

38% explained variance

(Linear regression model controlling for covariates)

RCU

F(5,63)=2.96, *p*=.019, R^2=.19

19% explained variance

(Linear regression model controlling for covariates)

3. Elevated 2-AG is associated with higher mGluR5 density in chronic cocaine users

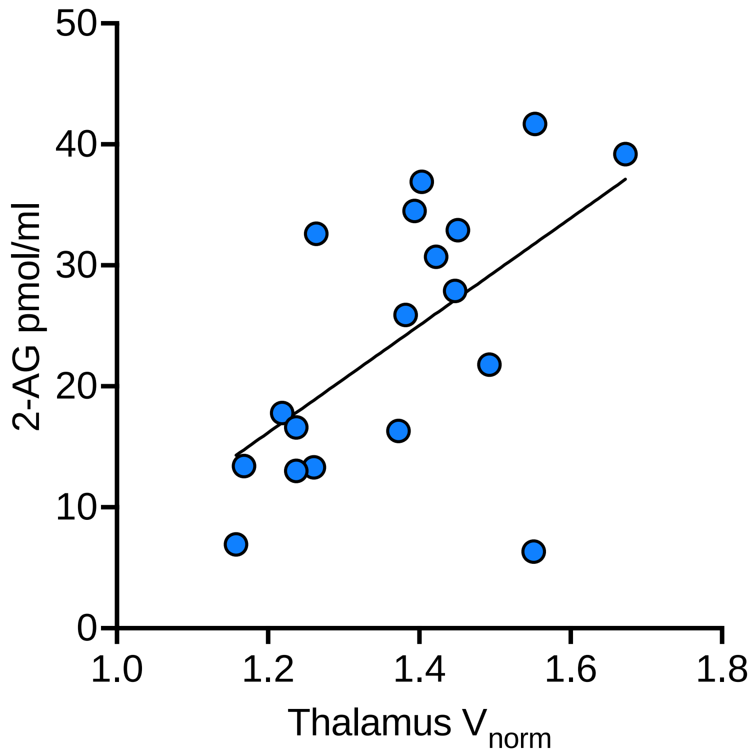
Spearman’s rho correlation coefficent

CU (n=18)	2-AG
PFC	0.44
Amygdala	**0.51**
Insula	**0.52**
ACC	**0.48**
MCC	**0.48**
Thalamus	**0.59**
Caudate	**0.56**
Putamen	0.42
Hyppocampal region	**0.47**

HC (n=16)	2-AG
PFC	-0.28
Amygdala	-0.34
Insula	-0.26
ACC	-0.28
MCC	-0.14
Thalamus	-0.31
Caudate	-0.33
Putamen	-0.27
Hyppocampal region	-0.30

p<0.05 in bold

3. Elevated 2-AG is associated with higher mGluR5 density in chronic cocaine users



Binary Logistic Regression Models

DV:
GROUP (controls [0] – CU [1])

	B	SE *B*	*Wald*	*p*	*OR*	*95% CI for OR*
Constant	19.64	11.24				
2-AG	-1.41	0.67	4.44	**0.035**	0.24	0.07; 0.91
Thalamus	-14.98	8.18	3.35	0.067	< .001	0.00; 2.90
Thalamus x 2-AG	1.09	0.51	4.61	**0.032**	2.96	1.10; 7.98
Age	-0.04	0.05	0.57	0.452	0.96	0.86; 1.07
Smoking	1.22	1.51	0.65	0.420	3.38	0.18; 64.75

Conclusion

1. Elevated 2-AG basal plasma levels in ***DCU*** might indicate a **higher response to the reinforcing effects** of cocaine.
2. Stable 2-AG levels → potential biomarker for vulnerability to develop CUD?
3. Cocaine **craving is associated with lower (phasic) 2-AG levels** supporting our recent findings of dysfunctional stress response.
4. Findings support results of recent animal models suggesting an **interaction between 2-AG & mGluR5** related to drug-reward and drug-seeking behavior.

The ECS system might be a promising pharmaco-therapeutic target for novel treatments of cocaine use disorder to prevent drug relapse and improve cocaine abstinence.

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Next steps:

Experimental and Clinical Pharmacopsychology
Psychiatric University Hospital Zurich, University of Zurich
Prof. Dr. Boris Quednow

→ Mechanistic understanding of eCB system in drug addiction

1. Differences in **tonic** eCB signaling in chronic cocaine users vs controls (hair concentration) (Voegel, Kroll, et al., *PNEC*, 2022) ☑
2. Alterations of basal eCB levels in chronic cocaine ☑
3. Stress response (TSST & craving) of the ECS in chronic cocaine users ☐

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THANKS

Elevated endocannabinoids in cocaine use disorder and their interaction with cocaine craving and metabotropic glutamate receptor 5 density

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→ Associated with **reward & drug-seeking response**

(Moreira et al., 2015 , Parsons & Hurd, 2015; Spanagel, 2020, Schreyer et al., 2022)

→ Crucial regulator of **stress response**

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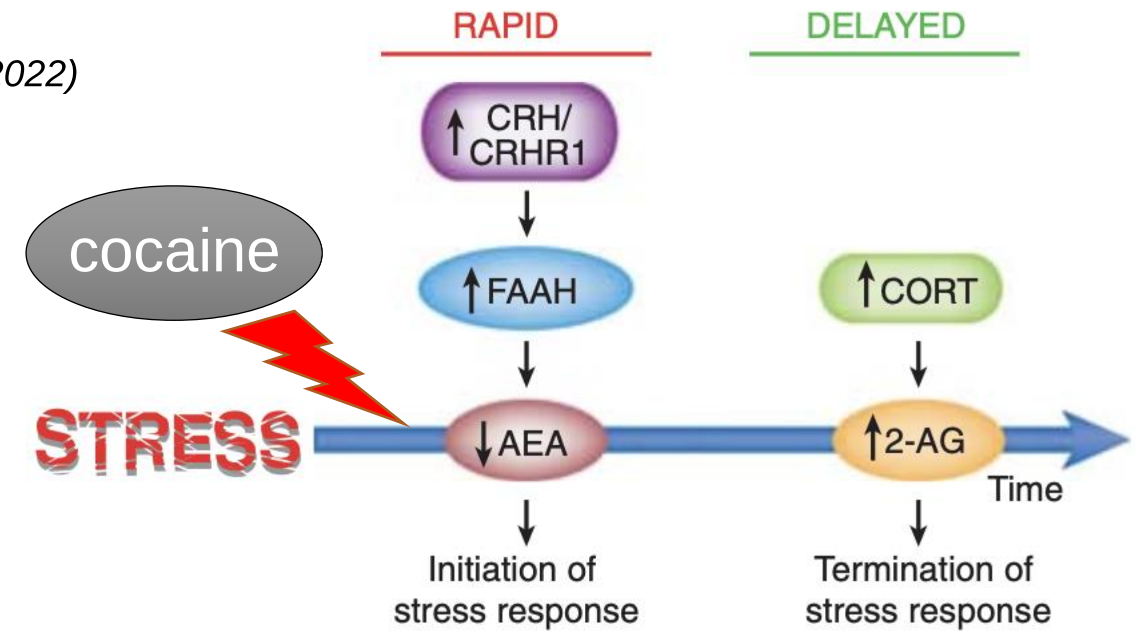
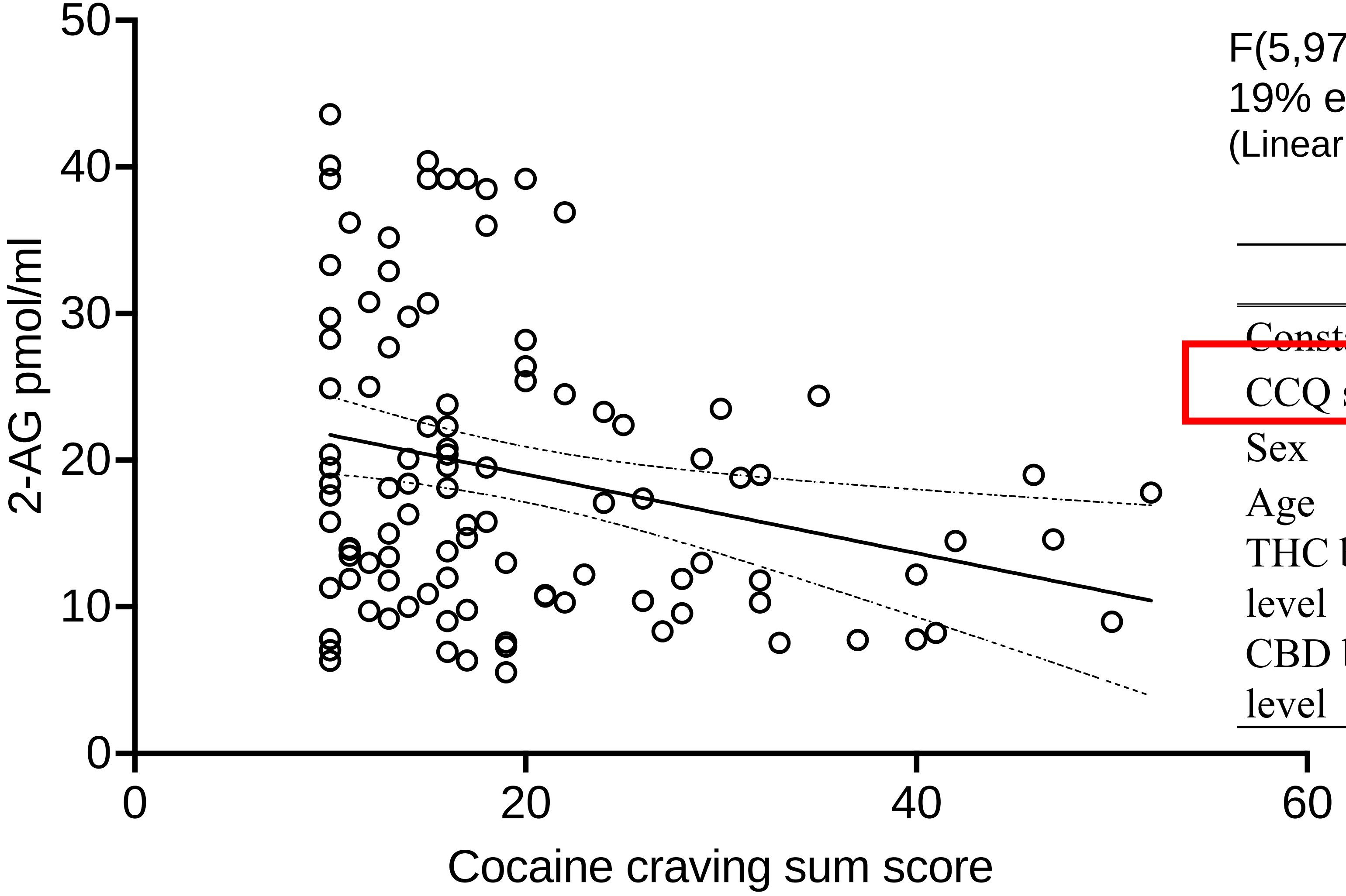
- Chronic cocaine users: CORT ↑ OEA and PEA in hair ↓
  (Voegel, Kroll et al., 2022)
- Abstinent cocaine users 2-AG plasma ↓
  (Pavon et al., 2013)



(Morena et al., 2016)

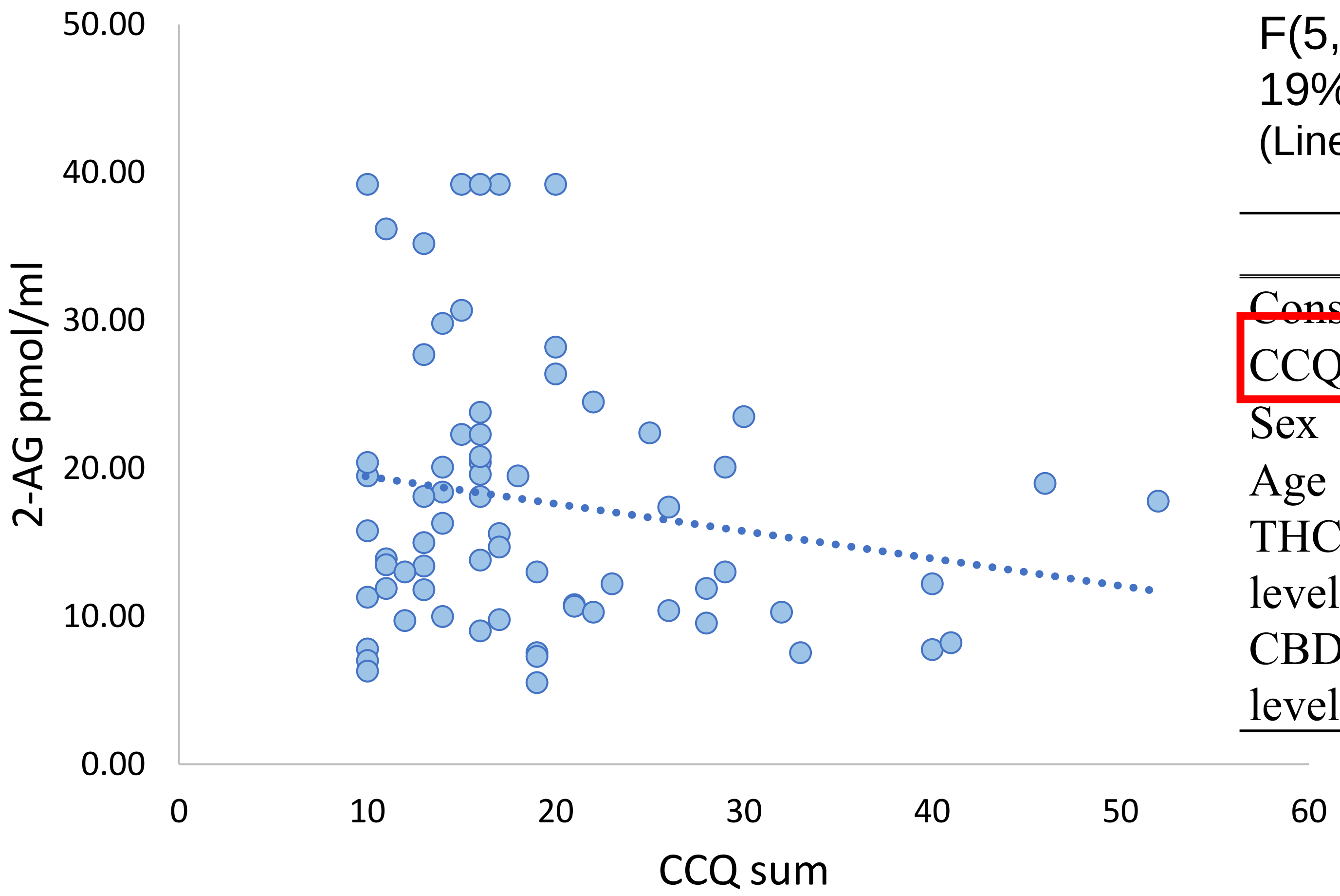
2. Elevated 2-AG is associated with lower cocaine craving



$F(5,97)=4.67$, $p<.001$, $R^2=.19$
19% explained variance
(Linear regression model controlling for covariates)

	B	SE *B*	*β*	t-value	*p*
Constant	8.16	5.34		1.53	0.130
CCQ sum	-0.22	0.10	-0.22	-2.31	**0.023**
Sex	3.98	2.13	0.18	1.87	0.064
Age	0.28	0.11	0.25	2.62	**0.010**
THC blood level	0.11	0.10	0.10	1.07	0.286
CBD blood level	-6.64	3.10	-0.21	-2.14	**0.035**

2. Elevated 2-AG is associated with lower cocaine craving



RCU

F(5,63)=2.96, *p*=.019, R^2=.19

19% explained variance

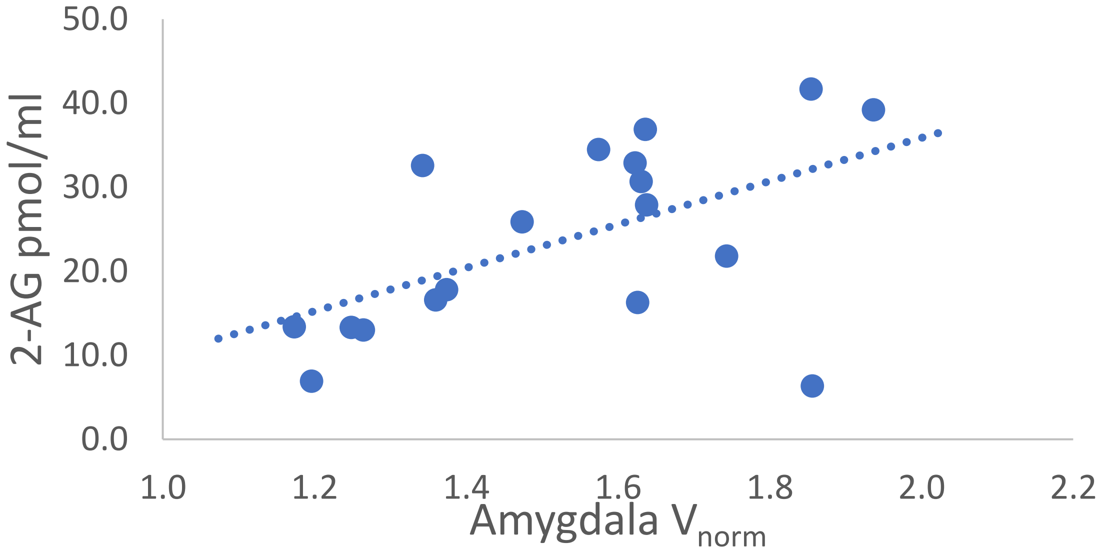
(Linear regression model controlling for covariates)

	B	SE *B*	*β*	t-value	*p*
Constant	4.59	6.75		0.68	0.499
CCQ sum	-0.13	0.12	-0.24	-1.05	0.297
Sex	6.85	2.43	0.33	2.81	**0.007**
Age	0.11	0.14	0.10	0.81	0.420
THC blood level	0.15	0.11	0.16	1.41	0.163
CBD blood level	-8.51	39.67	-0.03	-0.22	0.831

Binary Logistic Regression Models

DV:
GROUP (controls – CU)
IV:
- mGluR5 density
- 2-AG
- **mGluR5 x 2-AG**
- Age (control variable)
- Smoking (y/n) (control variable)

	B	SE *B*	*Wald*	*p*	*OR*	*95% CI for OR*
Constant	7.95	6.67				
2-AG	-0.87	0.44	3.96	**0.047**	0.42	0.18; 0.99
Amygdala	-5.96	4.17	2.04	0.153	.003	0.00; 9.19
Amygdala x 2-AG	0.62	0.30	4.34	**0.037**	1.85	1.04; 3.30
Age	-0.04	0.05	0.59	0.442	0.96	0.87; 1.07
Smoking	1.98	1.59	1.57	0.211	7.28	0.31; 162.58

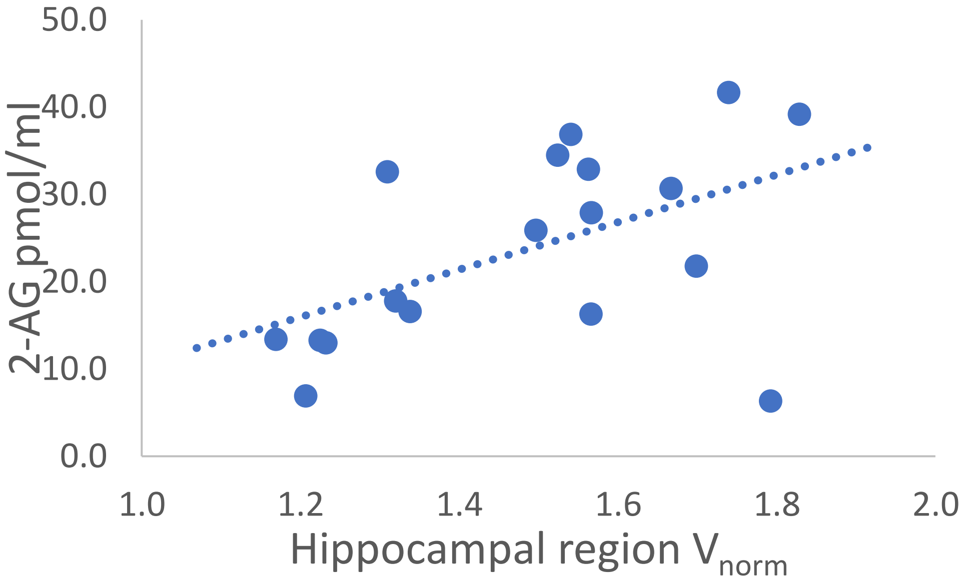


RESULTS

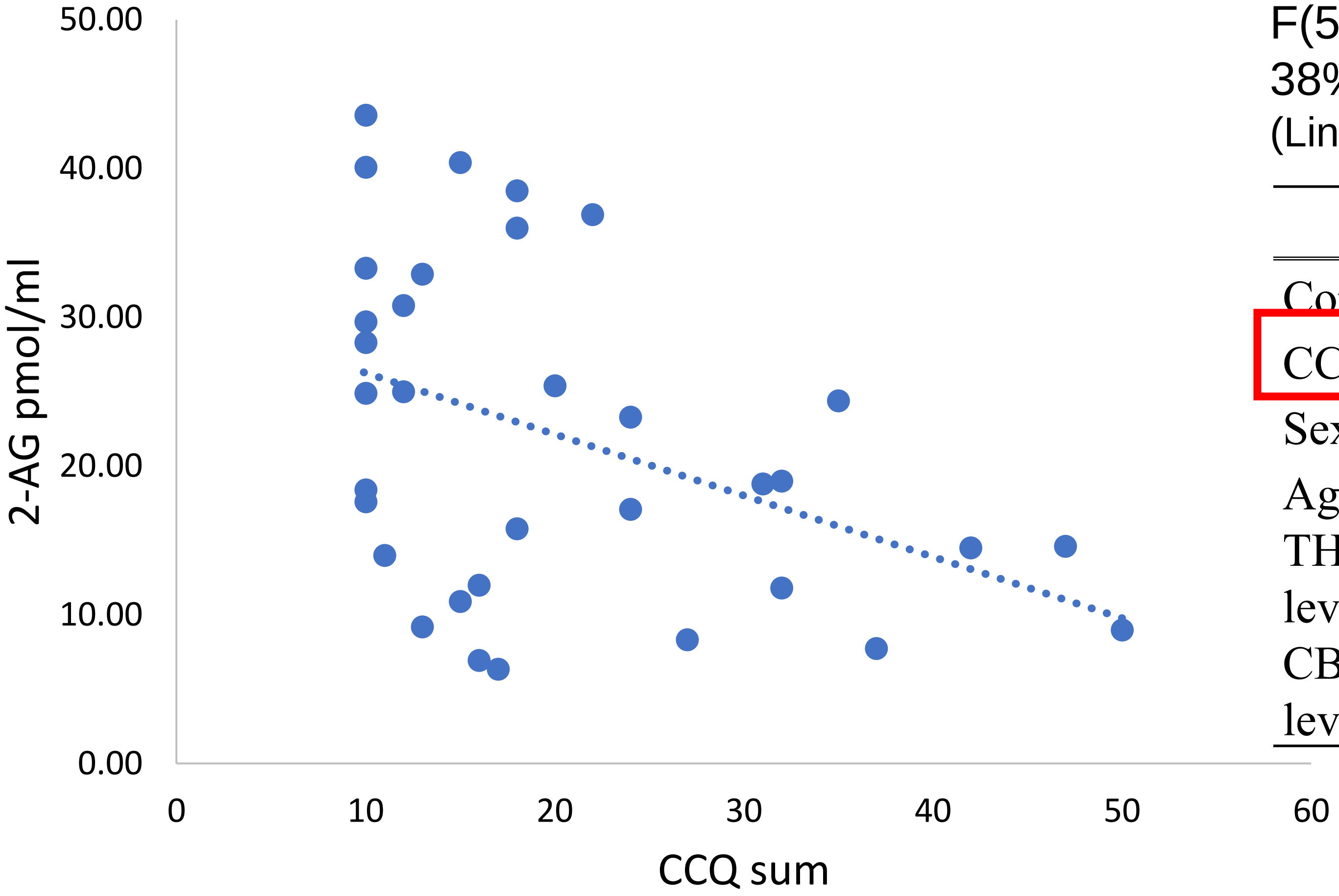
Binary Logistic Regression Models

DV:
GROUP (controls – CU)
IV:
- mGluR5 density
- 2-AG
- **mGluR5 x 2-AG**
- Age (control variable)
- Smoking (y/n) (control variable)

	B	SE *B*	*Wald*	*p*	*OR*	*95% CI for OR*
Constant	10.63	7.35				
2-AG	-1.05	0.51	4.19	**0.041**	0.35	0.13; 0.96
Hippocampal	-8.11	4.92	2.72	0.099	< 001	0.00; 4.63
Hippocampal x 2-AG	0.77	0.37	4.39	**0.036**	2.15	1.05; 4.40
Age	-0.04	0.05	0.63	0.428	0.96	0.86; 1.07
Smoking	1.98	1.79	1.22	0.269	7.21	0.22; 240.31



2. Elevated 2-AG is associated with lower cocaine craving



DCU
F(5,28)=3.42, *p*=.015, R^2=.38
38% explained variance
(Linear regression model controlling for covariates)

	B	SE *B*	*β*	t-value	*p*
Constant	22.54	9.12		2.47	0.020
CCQ sum	-0.41	0.16	-0.42	-2.60	**0.015**
Sex	-2.02	3.97	-0.08	-0.51	0.615
Age	0.37	0.17	0.35	2.17	**0.039**
THC blood level	0.04	0.25	0.03	0.16	0.875
CBD blood level	-7.64	4.02	-0.37	-1.90	0.068

Logistic Regression Models

DV:
GROUP (controls – CU)
IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age (control variable)
- Smoking (y/n) (control variable)

Classification Table[a,b]

Observed			Predicted Group_LMM .00	Predicted Group_LMM 1.00	Percentage Correct
Step 0	Group_LMM	.00	0	16	.0
		1.00	0	18	100.0
	Overall Percentage				52.9

a. Constant is included in the model.
b. The cut value is .500

Classification Table[a]

Observed			Predicted Group_LMM .00	Predicted Group_LMM 1.00	Percentage Correct
Step 1	Group_LMM	.00	10	6	62.5
		1.00	4	14	77.8
	Overall Percentage				70.6

a. The cut value is .500

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	8.018	8	.432

Logistic Regression Models

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Amygdala_L_R_cer_corrected	-5.396	3.818	1.997	1	.158	.005	.000	8.061
	b2AG_winsGroups	-.733	.354	4.288	1	.038	.480	.240	.962
	Amygdala_L_R_cer_corrected by b2AG_winsGroups	.503	.236	4.536	1	.033	1.653	1.041	2.626
	CRF_Alter	-.017	.051	.108	1	.743	.983	.890	1.087
	Nikotinkonsum_1129_Nichtraucher	-1.392	1.336	1.086	1	.297	.249	.018	3.406
	Constant	10.211	5.740	3.164	1	.075	27206.469		

a. Variable(s) entered on step 1: Amygdala_L_R_cer_corrected, b2AG_winsGroups, Amygdala_L_R_cer_corrected * b2AG_winsGroups , CRF_Alter, Nikotinkonsum_1129_Nichtraucher.

Logistic Regression Models

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Amygdala_L_R_cer_corrected	-6.733	3.674	3.358	1	.067	.001	.000	1.598
	b2AG_winsGroups	-.652	.318	4.222	1	.040	.521	.280	.970
	Amygdala_L_R_cer_corrected by b2AG_winsGroups	.447	.212	4.426	1	.035	1.563	1.031	2.370
	Constant	9.900	5.551	3.181	1	.074	19936.297		

a. Variable(s) entered on step 1: Amygdala_L_R_cer_corrected, b2AG_winsGroups, Amygdala_L_R_cer_corrected * b2AG_winsGroups .

Logistic Regression Models

MODEL 1

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age
- Smoking (y/n)

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	10	6	62.5
		1.00	4	14	77.8
	Overall Percentage				70.6

a. The cut value is .500

MODEL 2

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age x 2-AG
- Smoking (y/n) x mGluR5

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	9	7	56.3
		1.00	3	15	83.3
	Overall Percentage				70.6

a. The cut value is .500

MODEL 3

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age
- Smoking (y/n)
- Age x 2-AG
- Smoking (y/n) x mGluR5

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	10	6	62.5
		1.00	2	16	88.9
	Overall Percentage				76.5

a. The cut value is .500

RESULTS

Logistic Regression Models

MODEL 1

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	9.084	5	.106
	Block	9.084	5	.106
	Model	9.084	5	.106

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	37.932[a]	.234	.313

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

MODEL 2

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	10.405	5	.065
	Block	10.405	5	.065
	Model	10.405	5	.065

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	36.612[a]	.264	.352

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

MODEL 3

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	14.922	7	.037
	Block	14.922	7	.037
	Model	14.922	7	.037

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	32.094[a]	.355	.474

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Logistic Regression Models

MODEL 1

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Amygdala_L_R_cer_corrected	-5.396	3.818	1.997	1	.158	.005	.000	8.061
	b2AG_winsGroups	-.733	.354	4.288	1	.038	.480	.240	.962
	Amygdala_L_R_cer_corrected by b2AG_winsGroups	.503	.236	4.536	1	.033	1.653	1.041	2.626
	CRF_Alter	-.017	.051	.108	1	.743	.983	.890	1.087
	Nikotinkonsum_1129_Nichtraucher	-1.392	1.336	1.086	1	.297	.249	.018	3.406
	Constant	10.211	5.740	3.164	1	.075	27206.469		

a. Variable(s) entered on step 1: Amygdala_L_R_cer_corrected, b2AG_winsGroups, Amygdala_L_R_cer_corrected * b2AG_winsGroups , CRF_Alter, Nikotinkonsum_1129_Nichtraucher.

Logistic Regression Models

MODEL 2

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Step 1[a]	Amygdala_L_R_cer_corrected	-4.710	4.260	1.223	1	.269	.009	.000	38.041
	b2AG_winsGroups	-.741	.377	3.863	1	.049	.477	.228	.998
	Amygdala_L_R_cer_corrected by b2AG_winsGroups	.581	.268	4.714	1	.030	1.788	1.058	3.021
	CRF_Alter by b2AG_winsGroups	-.003	.003	.998	1	.318	.997	.991	1.003
	Amygdala_L_R_cer_corrected by Nikotinkonsum_1129_Nichtraucher	-.964	.806	1.432	1	.231	.381	.079	1.850
	Constant	8.630	5.984	2.080	1	.149	5596.981		

a. Variable(s) entered on step 1: Amygdala_L_R_cer_corrected, b2AG_winsGroups, Amygdala_L_R_cer_corrected * b2AG_winsGroups , CRF_Alter * b2AG_winsGroups , Amygdala_L_R_cer_corrected * Nikotinkonsum_1129_Nichtraucher .

Logistic Regression Models

MODEL 3

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Amygdala_L_R_cer_corrected	12.434	14.135	.774	1	.379	251142.458	.000	2.700E+17
	b2AG_winsGroups	-.725	.430	2.845	1	.092	.484	.209	1.125
	Amygdala_L_R_cer_corrected by b2AG_winsGroups	.749	.370	4.099	1	.043	2.114	1.024	4.364
	Nikotinkonsum_1129_Nichtraucher	29.025	20.819	1.944	1	.163	4.031E+12	.000	2.120E+30
	CRF_Alter	.106	.129	.681	1	.409	1.112	.864	1.430
	CRF_Alter by b2AG_winsGroups	-.011	.008	1.998	1	.157	.989	.975	1.004
	Amygdala_L_R_cer_corrected by Nikotinkonsum_1129_Nichtraucher	-18.221	12.523	2.117	1	.146	.000	.000	557.682
	Constant	-23.623	22.265	1.126	1	.289	.000		

a. Variable(s) entered on step 1: Amygdala_L_R_cer_corrected, b2AG_winsGroups, Amygdala_L_R_cer_corrected * b2AG_winsGroups , Nikotinkonsum_1129_Nichtraucher, CRF_Alter, CRF_Alter * b2AG_winsGroups , Amygdala_L_R_cer_corrected * Nikotinkonsum_1129_Nichtraucher .

RESULTS

WHICH Model?

MODEL 1

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age
- Smoking (y/n)

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	10	6	62.5
		1.00	4	14	77.8
	Overall Percentage				70.6

a. The cut value is .500

MODEL 2

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age x 2-AG
- Smoking (y/n) x mGluR5

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	9	7	56.3
		1.00	3	15	83.3
	Overall Percentage				70.6

a. The cut value is .500

MODEL 3

DV:

GROUP (controls – CU)

IV:

- mGluR5 density (Amygdala)
- 2-AG
- **mGluR5 x 2-AG**
- Age
- Smoking (y/n)
- Age x 2-AG
- Smoking (y/n) x mGluR5

Classification Table[a]

			Predicted		
			Group_LMM		Percentage Correct
Observed			.00	1.00	
Step 1	Group_LMM	.00	10	6	62.5
		1.00	2	16	88.9
	Overall Percentage				76.5

a. The cut value is .500

ENDOCANNABINOID SYSTEM & COCAINE

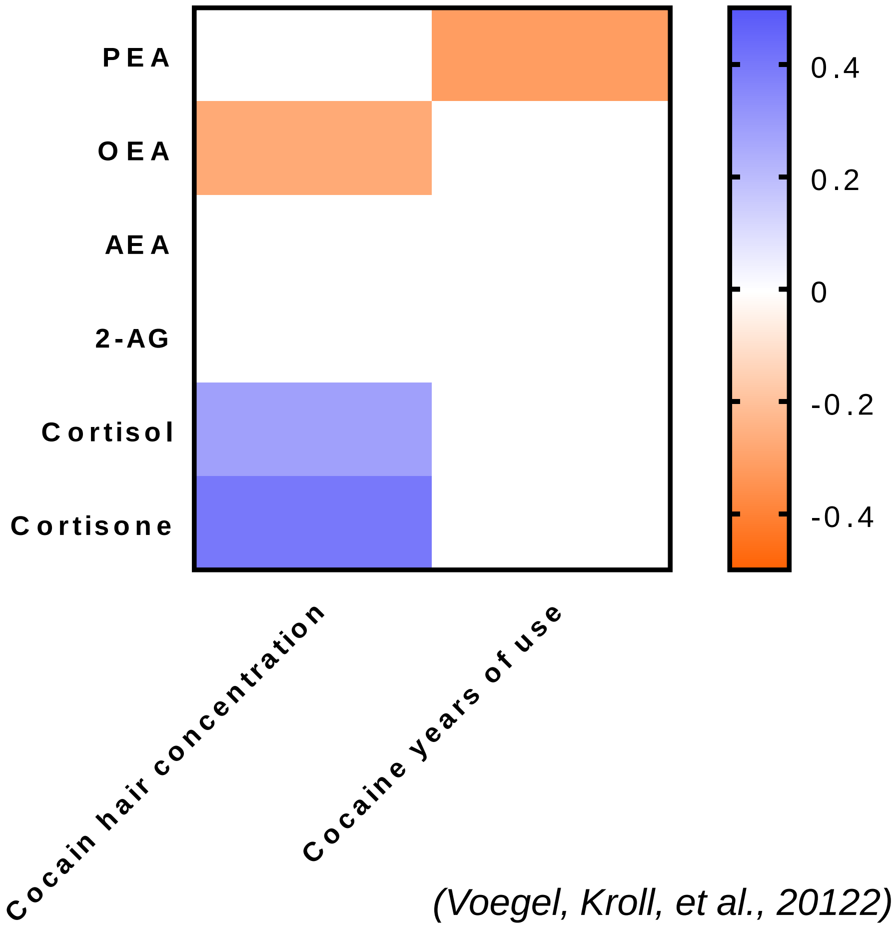
→ Associated with **reward & drug-seeking response**

(Moreira et al., 2015 , Parsons & Hurd, 2015; Spanagel, 2020, Schreyer et al., 2022)

→ Crucial regulator of **stress response**

(Moreira et al., 2015; Morena et al., 2016; de Roon-Cassini et al., 2020)

- Abstinent cocaine users 2-AG plasma ↓
  (Pavon et al., 2013)
- Chronic cocaine users: CORT ↑ OEA and PEA in hair ↓
  (Voegel, Kroll et al., 2022)



(Voegel, Kroll, et al., 20122)

In- & Exclusion criteria

Inclusion criteria for the **chronic cocaine users**:

- cocaine use of at least 1 g per month
- cocaine as primary used illegal substance
- current abstinence duration <6 months.

Exclusion criteria for the **user groups**:

- past or current use of opioids
- polytoxic substance use pattern
- axis-I DSM-IV adult psychiatric disorder with the exception of cocaine, cannabis, tobacco, and alcohol use disorder as well as history of affective disorders and attention deficit hyperactivity disorder (ADHD)

Exclusion criteria for the **control group**:

- acute or history of any axis-I DSM-IV psychiatric disorder.

→ All subjects were asked to abstain from **illegal substances for a minimum of 72 h** and not to consume **alcohol for a minimum 24 h** before the test session.

Drug use

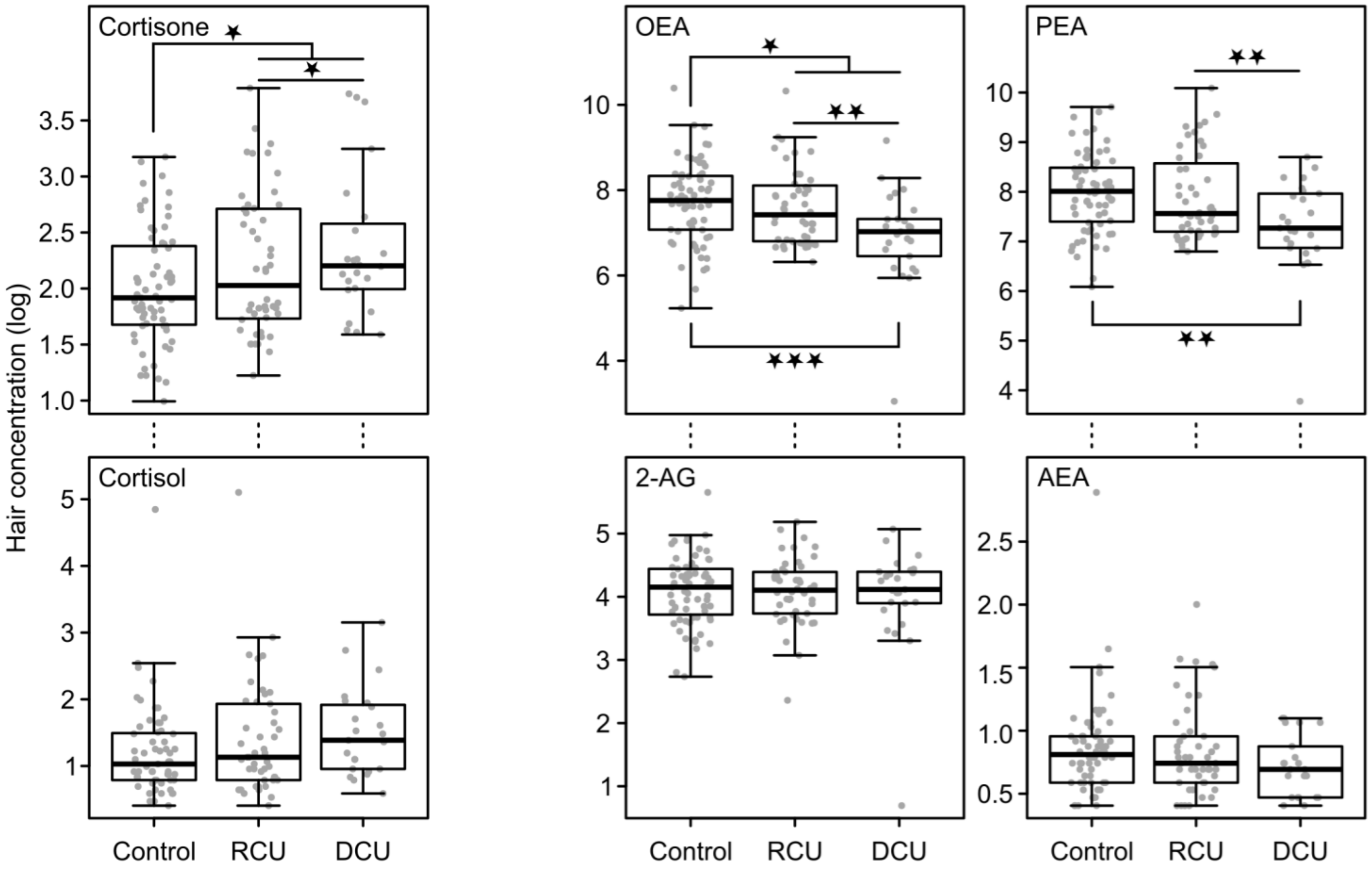
	Controls	RCU	DCU	Value	*df1, df2*	*p*
Cannabis y/n	40/52	46/23°	22/12°	χ^2= 10.0	2	**0.007**
Grams/week[a]	1.2 (1.9)	1.4 (2.4)	2.5 (5.4)	F = 1.3	2, 105	0.286
Plasma THC	0.8 (3.5)	2.9 (10.0)	2.9 (8.4)	F = 2.0	2, 192	0.139
Plasma CBD	0.0	0.0	0.17 (0.5)°†	F = 7.7	2, 192	**<0.001**
Urine sample positive (y/n)	12/79	14/54	11/23°	χ^2= 6.0	2	**0.050**
MDMA y/n	1/91	22/47°	10/24°	χ^2= 31.2	2	**<0.001**
Pills/week[b]	-	0.3 (0.4)	1.2 (3.1)	F = 2.1	1, 30	0.157
Hair concentration pg/mg	-	436.2 (1'371.2)	225.1 (617.4)	F = 0.7	1, 99	0.396

RESULTS

FDR corrected p-values	
CU (n=18)	**2-AG**
Thalamus	0.062
Caudate	0.062
Insula	0.062
Amygdala	0.062
MCC	0.062
ACC	0.062
Hippocampal region	0.062
PFC	0.075
Putamen	0.083

p-values	
CU (n=18)	**2-AG**
Thalamus	0.011
Caudate	0.016
Insula	0.027
Amygdala	0.033
MCC	0.043
ACC	0.046
Hippocampal region	0.048
PFC	0.067
Putamen	0.083

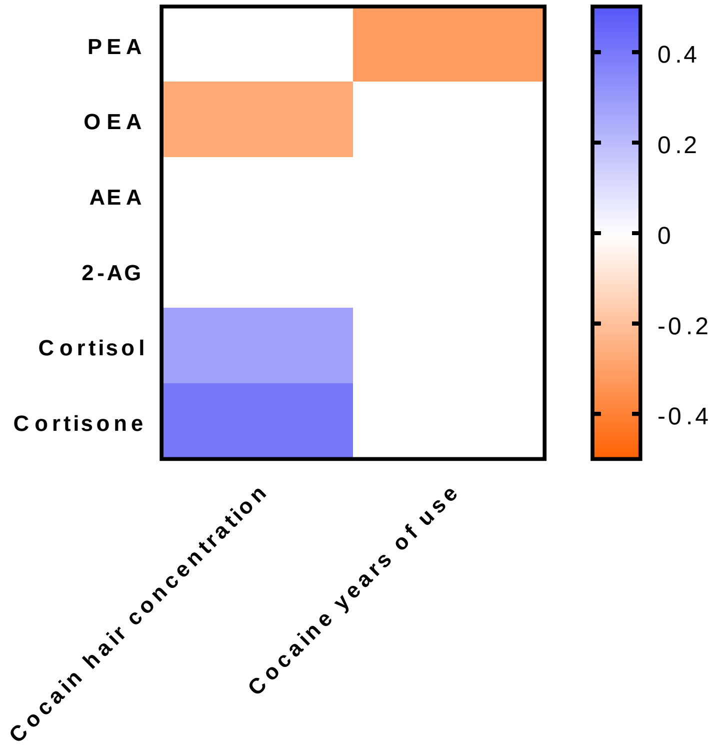
Stress marker concentrations: Group contrast



p<0.05*, p<0.01**, p<0.001***

Effect of cocaine on stress marker concentrations

Psychiatrische Universitätsklinik Zürich



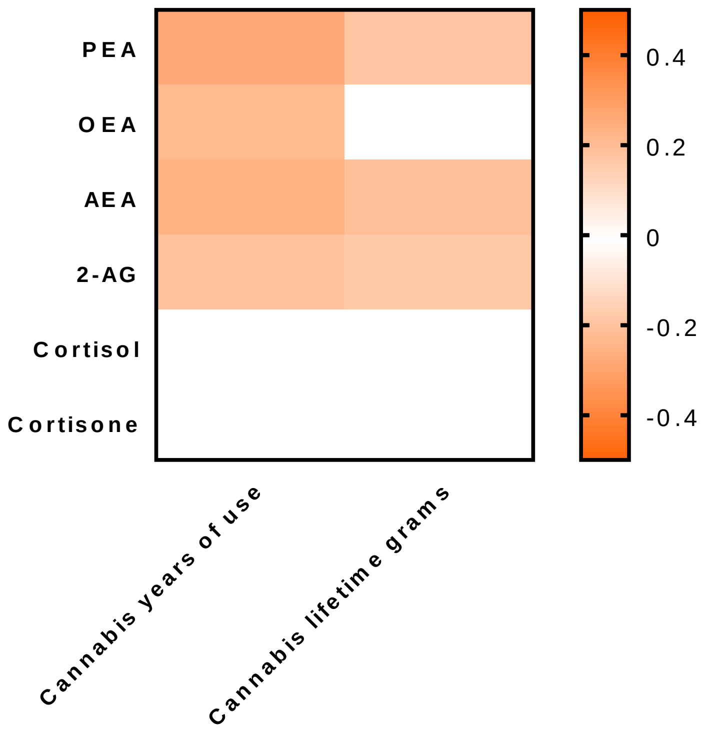
Heat matrix of regression coefficients with significant standardized β-values

→ Dysfunctional HPA stress response in cocaine users

→ Reduced eCB signaling

Psychiatrische Universitätsklinik Zürich

Effects of cannabis consumption on stress markers



→ Repeated cannabis use might down-regulate the eCB signaling system

ENDOCANNABINOID SYSTEM

→ Crucial regulator of **stress response**

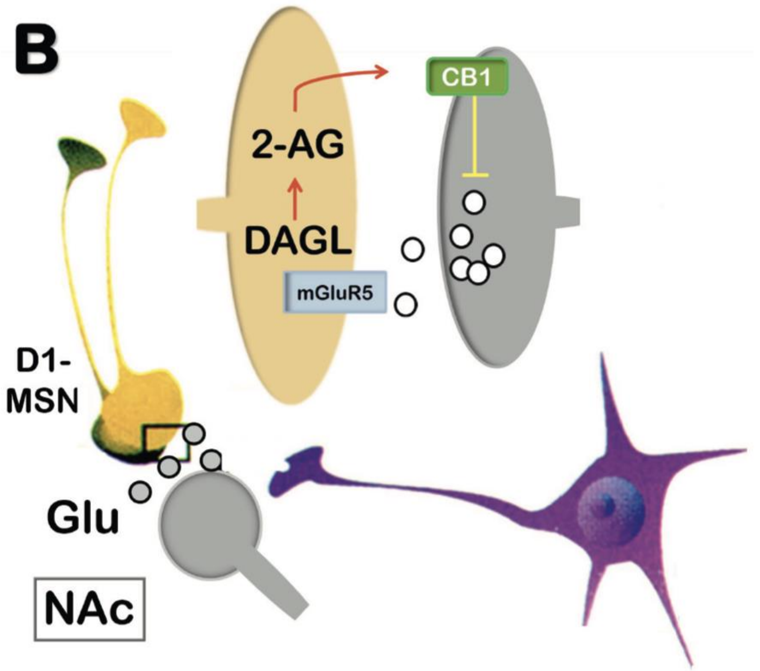
(Moreira et al., 2015; Morena et al., 2016; de Roon-Cassini et al., 2020)

→ Associated with **reward & drug seeking response**

(Bilbao et al., 2020; Moreira et al., 2015; Parsons & Hurd, 2015; Spanagel, 2020)

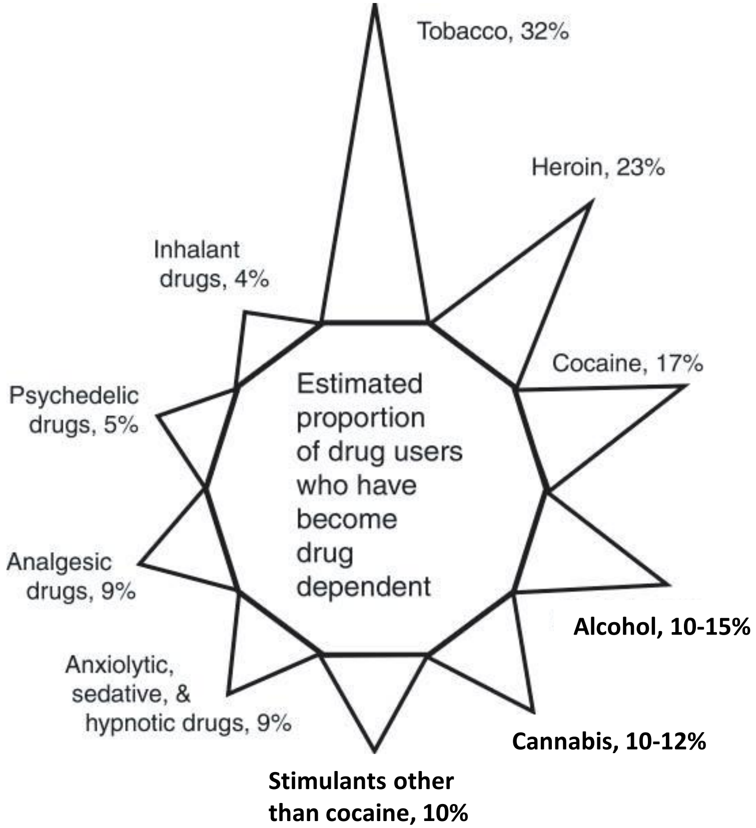
- Acute cocaine adminstration → 2-AG stimulation in the VTA facilitats DA release in the Nac → cocaine reinforcement
  (Wang et al., 2015)
- Single cocaine administration abolishes eCB-LTD in Nac & inhibited cue-induced natural reward response
  (Fourgeaud et al., 2004; Bilbao et al., 2020)
- Elevated 2-AG levels in the NAc during cocaine-induced reinstatement but also in the hippocampus, no differences in striatum
- 2-AG reduced in 14d repeated cocaine use in striatum, hippocampus, FC, and no differences in NAc

  (Bystrowska et al., 2014; 2019)

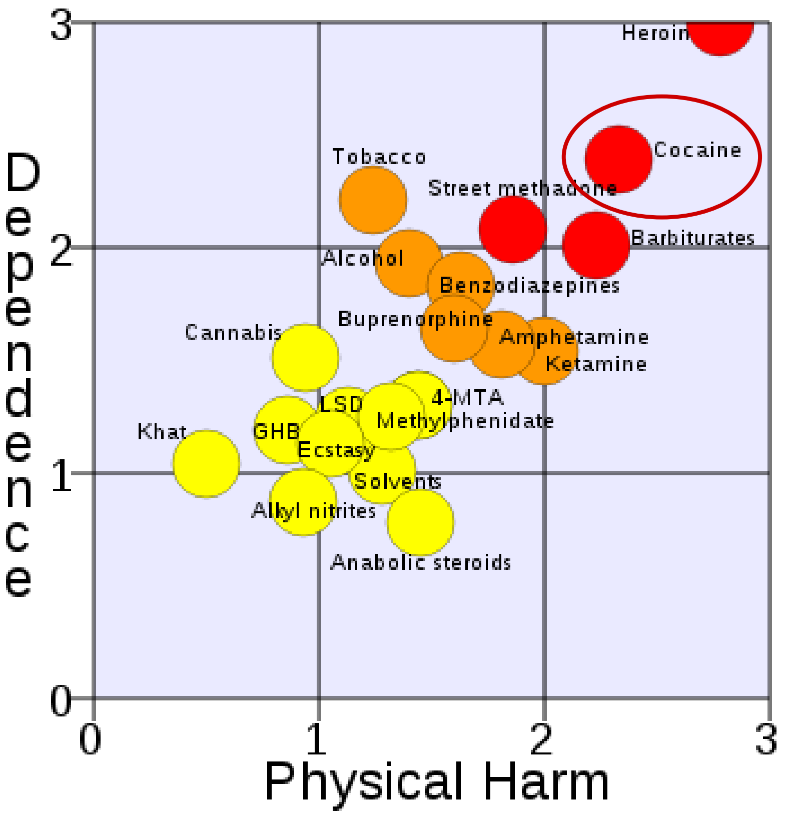


(Spanagel, 2020)

Addictive potential of cocaine



Estimated probability for addiction in specific substance user group
Anthony 2002, updated



Expert estimations (Delphi study) regarding the risk of drug consumption
Nutt et al. 2007