Data Supplement to: Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving, and early age at onset. *Br J Psychiatry* (doi: 10.1192/bjp.bp.112.118091)

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Method DS1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 until January 2012. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. In total 804 prospective participants underwent a standardized telephone interview, whereof 240 subjects were considered to be eligible for the study at the University Hospital of Psychiatry in Zurich. All subjects were aged between 18 and 60 years and had sufficient German language skills. Forty-six participants had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use), or lack of cocaine use. Furthermore, the data of four participants (3 controls, 1 cocaine user) could not be analyzed because of technical problems during the test session and 24 participants were excluded due to matching reasons (age, verbal IQ, and smoking) between groups (15 controls, 9 cocaine users). Hair samples were provided by 163 subjects, as hair analysis was not possible due to an insufficient amount of hair for two controls and one cocaine user.

Method DS2: Urine and hair toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To characterize drug use over the last six months objectively, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was

performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

Method DS3 Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. Two cocaine users were missing either SWM or PAL parameters due to technical problems. These values were excluded from the domain computation. If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains: attention, working memory, declarative memory, and executive function according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention: To assess attentional capacity, we focused primarily on sustained attention by including the two RVP parameters discrimination performance A' and total of hits.[1] In order to diversify this domain we added the RAVLT test parameter trial 1, a supraspan measure with a large attentional component.[2]

Working Memory: The SWM parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory.[3] The LNST measured the verbal working memory by summing up the number of correct responses.[4] The third parameter was the number of correctly located patterns after the first presentation, a PAL parameter measuring primarily a visual working memory component.[5]

Declarative memory: The RAVLT was administered to assess the verbal declarative memory performance.[6] Performance was measured by the parameters learning performance (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (p(A)).[6] To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials.[5]

Executive Functions: Executive functions are commonly separated into the three components shifting, updating, and inhibition.[7] Since inhibition in CU is currently investigated in another study from our laboratory[8], we focused on shifting (IED) and updating tasks (SWM strategy, RAVLT recall consistency). The IED assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility.[9] The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies[3], and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions[10-12] and related with measures of executive functions.[13]

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Table DS1 Pattern and amount of drug use

	Stimulant-naïve controls (n=68)	Recreational cocaine users (n=68)	Dependent cocaine users (n=30)
Alcohol			
Grams per week[a]	116.8 (122.6)	167.8 (117.5)	188.5 (260.6)
Years of use	13.2 (9.3)	11.2 (5.1)	13.5 (9.5)
Nicotine			
Cigarettes per day[a]	9.3 (9.5)	11.7 (8.8)	15.7 (13.5)
Years of use	9.2 (9.2)	9.6 (6.4)	14.2 (9.3)
Cocaine			
Times per week[a]	-	1.1 (1.0)	2.9 (2.6)
Grams per week[a]	-	1.1 (1.4)	7.9 (15.8)
Years of use	-	6.5 (4.0)	9.4 (6.5)
Maximum dose (grams/day)	-	3.5 (2.5)	9.4 (8.4)
Cumulative dose (grams)	-	519.7 (751.2)	5500.9 (9635.2)
Last consumption (days)[b]	-	27.5 (37.6)	21.0 (33.6)
Hair analysis Cocaine pg/mg[c]	-	2739 (4628)	22164 (32609)
Hair analysis Benzoylecgonine pg/mg[c]	-	546 (919)	5048 (7711)
Hair analysis Cocaethylene pg/mg[c]	-	276 (316.)	2006 (3656)
Hair analysis Norcocaine pg/mg[c]	-	62 (101)	586 (758)
Hair analysis $Cocaine_{total}$ pg/mg[c,e]	-	3347 (5580)	27798 (40226)
Urine toxicology (neg/pos)[d]	68 / 0	57 / 10	18 / 12
Cannabis			
Grams per week[a]	0.5 (1.0)	0.9 (2.1)	1.2 (3.7)
Years of use	4.7 (6.5)	7.7 (6.0)	10.5 (9.9)
Cumulative dose (grams)	358.3 (846.2)	1042.8 (1780.0)	3550.3 (5959.0)
Last consumption (days)[b]	36.2 (50.1); n=33	22.1 (32.3); n=44	25.7 (32.8); n=20
Urine toxicology (neg/pos)[d]	58 / 10	55 / 12	20 / 10
Amphetamine			
Grams per week[a]	0.0 (0.0)	0.1 (0.2)	0.0 (0.2)
Years of use	0.0 (0.1)	1.6 (3.0)	1.5 (3.2)
Cumulative dose (grams)	0.2 (1.4)	21.2 (56.8)	22.3 (62.8)
Last consumption (days)[b]	121.6 (0.0), n=1	61.8 (51.3); n=25	78.4 (75.4); n=6
Hair analysis Amphetamine pg/mg[c]	1 (7)	76 (257)	60 (169)

MDMA			
Tablets per week[a]	-	0.1 (0.3)	0.4 (1.8)
Years of use	0.3 (1.7)	2.5 (3.8)	3.1 (5.2)
Cumulative dose (tablets)	0.9 (2.9)	35.9 (90.5)	157.4 (393.5)
Last consumption (days)[b]	-	75.1 (84.8); n=20	82.1 (45.4); n=9
Hair analysis MDMA pg/mg[c]	3 (16)	545 (1598)	255 (653)
GHB			
Cumulative dose (pipettes)	0.0 (0.0)	1.8 (9.5)	1.3 (2.9)
Hallucinogens			
Cumulative dose (times)	0.9 (2.2)	6.0 (14.6)	6.9 (11.8)

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.

[a] Average use during the last 6 months.

[b] Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.

[c] Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg.[47] Hair samples were voluntary and are deficient for 3 controls and 1 RCU.

[d] Cut-off values for cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml. [49] Urine toxicology test was deficient for 1 RCU.

[e] $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs.[48]

Table DS2 Neurocognitive global and domain z-scores and scores of neuropsychological tests

Measure	n[a]	Stimulant-naïve controls	Recreational cocaine users	Dependent cocaine users	F	df, df_{err}	p	p, Sidak post-hoc			Cohen's d		
								Controls vs. RCU	Controls vs. DCU	RCU vs. DCU	Controls vs. RCU	Controls vs. DCU	RCU vs DCU
Global Cognitive Index	68/68/30	-0.02 (0.06)	-0.35 (0.06)	-0.67 (0.09)	19.345	2, 161	**<.001**	**<.001**	**<.001**	**.01**	0.53	1.04	0.52
Neurocognitive domain scores													
Attention	68/68/30	-0.03 (0.10)	-0.41 (0.10)	-0.68 (0.15)	7.579	2, 161	**<.001**	**.02**	**.001**	.38	0.44	0.74	0.30
Working memory	68/68/30	-0.03 (0.08)	-0.36 (0.08)	-0.81 (0.12)	16.312	2, 161	**<.001**	**.007**	**<.001**	**.005**	0.43	1.00	0.58
Declarative memory	68/68/30	-0.02 (0.09)	-0.4 (0.09)	-0.67 (0.15)	8.333	2, 161	**<.001**	**.01**	**<.001**	.34	0.43	0.73	0.30
Executive functions	68/68/30	-0.02 (0.06)	-0.22 (0.06)	-0.5 (0.09)	11.388	2, 161	**<.001**	**.03**	**<.001**	**.02**	0.39	0.92	0.54
Neuropsychological test scores													
Attention													
RVP Discrimination performance A'	67/68/30	0.917 (0.0)	0.899 (0.0)	0.885 (0.0)	6.254	2, 160	**.002**	**.04**	**.004**	.43	0.42	0.72	0.31
RVP Total hits	67/68/30	18.3 (0.5)	16.5 (0.5)	15.3 (0.8)	5.561	2, 160	**.005**	**.05**	**.008**	.53	0.40	0.67	0.27
RAVLT Supraspan trial 1	68/68/30	8.9 (0.2)	8.4 (0.2)	8.0 (0.4)	2.407	2, 161	.09	.31	.13	.81	0.25	0.41	0.17
Working memory													
LNST Score	68/68/30	15.6 (0.3)	14.5 (0.3)	13.2 (0.5)	8.320	2, 161	**<.001**	.07	**<.001**	.07	0.34	0.78	0.44
SWM Total errors	68/67/30	20.1 (1.9)	23.3 (1.9)	34.5 (2.9)	8.727	2, 160	**<.001**	.53	**<.001**	**.005**	0.19	0.84	0.65
PAL First trial memory score	68/67/30	15.6 (0.4)	14.1 (0.4)	13.4 (0.6)	6.575	2, 160	**.002**	**.02**	**.005**	.67	0.43	0.64	0.21
Declarative memory													
RAVLT Learning performance (∑ trials 1-5)	68/68/30	62.0 (0.9)	58.0 (0.9)	54.9 (1.4)	9.612	2, 161	**<.001**	**.009**	**<.001**	.22	0.45	0.80	0.35
RAVLT Adjusted recognition performance p(A)	68/68/30	0.873 (0.0)	0.858 (0.0)	0.823 (0.0)	2.076	2, 161	.13	.83	.12	.39	0.13	0.44	0.31
RAVLT Delayed recall trial 7	68/68/30	13.1 (0.3)	11.9 (0.3)	11.4 (0.5)	6.046	2, 161	**.003**	**.02**	**.009**	.75	0.44	0.63	0.19
PAL Total errors adjusted	68/67/30	10.6 (1.4)	15.1 (1.4)	16.9 (2.2)	3.852	2, 160	**.02**	.08	.05	.88	0.35	0.49	0.14
PAL Total trials adjusted	68/67/30	8.5 (0.3)	9.5 (0.3)	10.1 (0.5)	4.231	2, 160	**.02**	.09	**.03**	.72	0.34	0.53	0.19
Executive functions													
IED Total errors adjusted	68/68/30	30.3 (4.1)	31.3 (4.1)	32.3 (6.3)	.039	2, 161	.96	1.00	.99	1.00	0.03	0.06	0.03
IED Total trials adjusted	68/68/30	104.1 (7.2)	107.3 (7.3)	108.5 (11.2)	.075	2, 161	.93	.98	.98	1.00	0.05	0.07	0.02
SWM Strategy score	68/67/30	32.7 (0.6)	33.4 (0.6)	34.9 (0.9)	1.887	2, 160	.15	.84	.15	.43	0.12	0.42	0.30
RAVLT Recall consistency in %	68/68/30	92.3 (1.1)	88.1 (1.1)	83.3 (1.6)	11.004	2, 161	**<.001**	**.02**	**<.001**	**.05**	0.43	0.92	0.49

Means and standard errors. ANCOVA (all groups, corrected for age and verbal IQ). Significant *P* are shown in bold.
GCI and cognitive domain scores are z-transformed values.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, only one pairwise Sidak post-hoc comparison above turned from a significant group difference into a statistical trend (RAVLT recall consistency; cocaine rec vs. cocaine dep $p_{post\text{-}hoc}$=.08).
[a] Sample size control group/RCU/DCU. In each of the tasks RVP, PAL, and SWM one subject is missing due to a technical failure.

Table DS3 Intercorrelation cocaine use parameters in cocaine users

	1)	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	13)
1) Cumulative dose (grams) log	1	*.24	*.22	***.57	.02	***.62	-.09	***.34	***.37	*.21*	***.39	***.36	***.81
2) Times per week		1	***.70	-.09	.09	.17	.15	.18	.14	*.23	.16	.18	**.32
3) Grams per week log			1	-.13	.04	.13	.13	.04	-.04	.18	-.01	.03	.19
4) Years of use				1	-.03	.06	-.10	***.42	***.37	***.37	***.39	***.42	***.56
5) Age of onset					1	.07	-.17	.16	.20	.05	.17	.17	.09
6) Maximum dose (grams/day)						1	-.09	.14	*.23	-.08	*.22	.16	***.72
7) CCQ sum score (0-70)							1	.03	-.01	-.03	.01	.02	-.12
8) Hair analysis Cocaine pg/mg								1	***.91	***.70	***.86	***1.00	***.59
9) Hair analysis Benzoylecgonine pg/mg									1	***.55	***.95	***.94	***.61
10) Hair analysis Cocaethylene pg/mg										1	***.62	***.68	***.33
11) Hair analysis Norcocaine pg/mg											1	***.89	***.60
12) Hair analysis $Cocaine_{total}$ pg/mg												1	***.61
13) Severity of cocaine use Index[a]													1

Analyses only for cocaine users (n=98; Hair samples were voluntary and are deficient for 1 recreational cocaine user).
Pearson's product-moment correlation. Significant correlations (two-tailed) are marked: *p<.05; **p<.01; ***p<.001.
[a] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

Table DS4 Correlations between cognitive test scores and cocaine use parameters in cocaine users

	Attention			Working memory			Declarative memory					Executive functions			
	RVP A'	RVP Hits	RAVLT Trial 1	LNST Score	SWM Error[d]	PAL First trial[d]	RAVLT ∑ Trials 1-5	RAVLT p(A)	RAVLT Trial 7	PAL Errors adj.[d]	PAL Trials adj.[d]	IED Errors adj.	IED Trials adj.	SWM Strat.[d]	RAVLT Recall cons.
Cumulative dose (grams) log[a]	*-.23	*-.22	***-.38	**-.30	***.33	*-.26	***-.43	**-.31	***-.34	**.29	**.29			*.24	***-.39
Cumulative dose (grams) log, adj.	**-.27	**-.26	***-.35	**-.27	**.27	*-.22	***-.39	**-.31	***-.35	*.25	*.22				***-.37
Times per week[a]							*-.20		-.17						*-.25
Grams per week log[a]															
Years of use[a]			*-.25	*-.21	**.32	*-.22	***-.33	*-.23	-.20	.17	.20			***.35	**-.31
Years of use, adj. age[b]			-.19		*.23		*-.25	*-.25	*-.20					*.24	**-.30
Maximum dose (grams/day)[a]	*-.21	*-.21		*-.20			*-.24	*-.23	*-.22	.18					-.18
CCQ sum score (0-70)[a]															
Hair analysis Cocaine pg/mg[a,c]			-.18		.19		*-.24		-.19					.19	
Hair analysis Benzoylecgonine			*-.24	*-.23	*.23		**-.31		*-.24	.19	*.22			*.22	
Hair analysis Cocaethylene pg/mg[a,c]					**.27									**.27	
Hair analysis Norcocaine pg/mg[a,c]			**-.27	*-.22	**.29		**-.31		*-.23	.17	*.20			*.21	
Hair analysis $Cocaine_{total}$ pg/mg[a,,c,e]			-.19		*.21		*-.26		*-.20					.20	
Severity of cocaine use Index[a,f]			**-.31	**-.26	*.26		**-.44	*-.25	**-.32	.20	*.21			*.25	**-.38

Analyses only for cocaine users (n=98). Correlations with a p-level below 10% are shown, while significant correlations are marked as follows: *p<.05; **p<.01; ***p<.001.
[a] Pearson's product-moment correlation. [b] Partial Correlation corrected for age.
[c] Hair samples were voluntary and are deficient for 1 recreational cocaine user.
[d] Two cocaine users were missing either SWM or PAL parameters due to technical problems.
[e] $Cocaine_{total}$ = Cocaine + Benzoylecgonine + Norcocaine.
[f] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

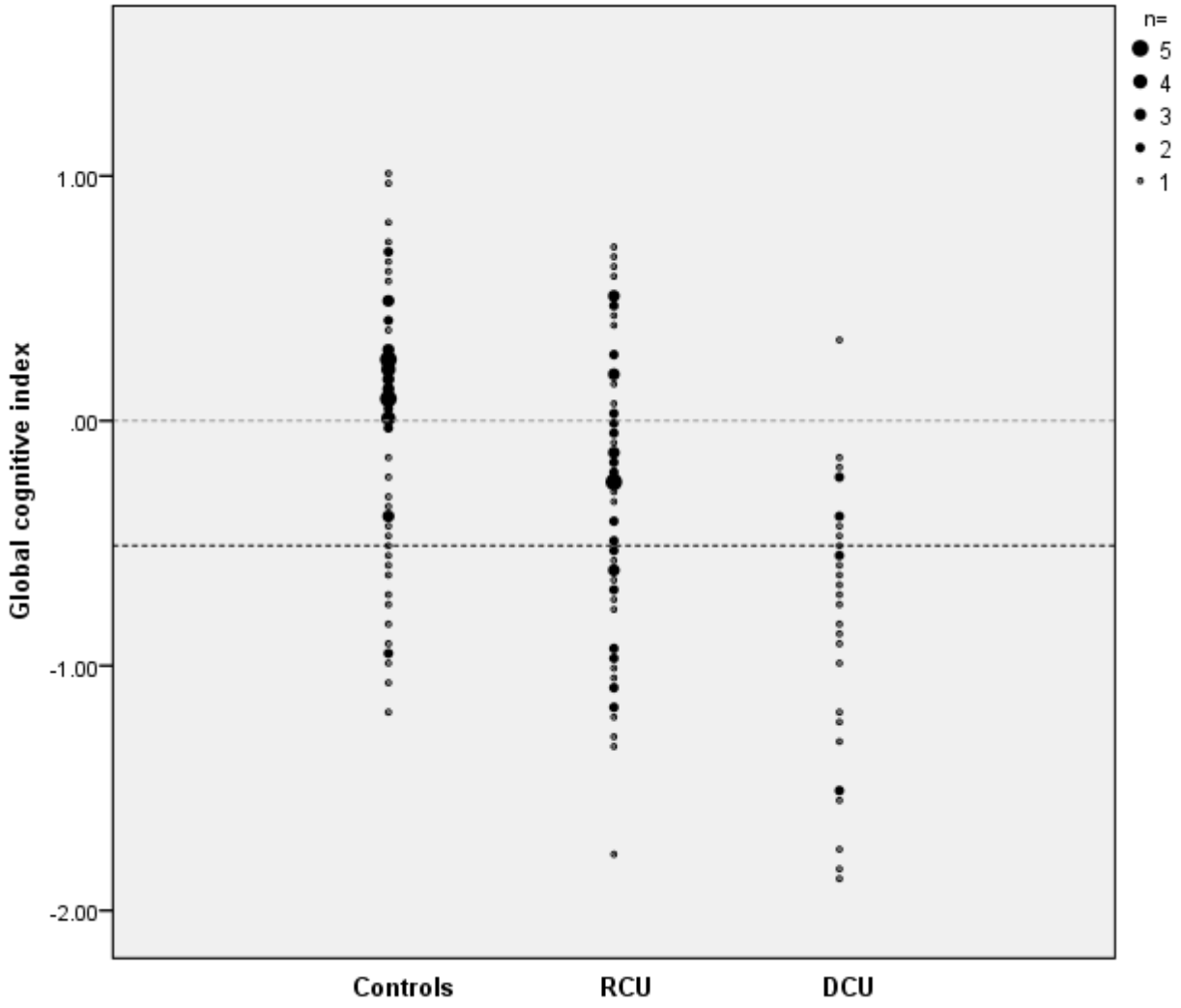
Table DS5 Predictors of the global cognitive index in cocaine users

	Model 1: Cumulative dose			Model 2: Years of use			Model 3: Weekly use		
	B	SE	β	B	SE	β	B	SE	β
Constant	.26	.33		-.10	.38		.53	.34	
Age	-.01	.01	-.16	.01	.02	.10	-.02	.01	**-.28
Depression	.00	.01	.04	.00	.01	.03	.00	.01	.02
ADHD	.00	.01	-.05	-.01	.01	-.11	-.01	.01	-.17
Craving for cocaine	-.01	.01	-.20	-.01	.01	-.15	-.01	.01	-.21
Urine sample (neg/pos)	.11	.14	.08	.08	.15	.05	.19	.14	.13
Cocaine cumulative dose (grams)	.00	.00	*-.29						
MDMA cumulative dose (tablets)	.00	.00	-.16						
Amphetamine cumulative dose (grams)	.00	.00	-.05						
Cannabis cumulative dose (grams)	.00	.00	-.08						
Cocaine years of use				-.04	.02	*-.29			
MDMA years of use				.00	.01	-.03			
Amphetamine years of use				.03	.02	.16			
Cannabis years of use				.00	.01	.05			
Alcohol years of use				.00	.02	-.01			
Nicotine years of use				-.02	.01	-.21			
Cocaine grams per week							.00	.01	-.02
MDMA tablets per week							-.15	.06	**-.25
Amphetamines grams per week							.11	.31	.03
Cannabis grams per week							-.01	.02	-.02
Alcohol grams per week							.00	.00	**.28
Cigarettes per week							.00	.00	*-.22
R^2			.22			.19			.29
F			**2.80			1.83			**3.20
p			.006			.06			.001

Multiple regression, only cocaine users (n= 98), *p<.05; **p<.01. Models included clinical variables linked to cognitive functioning (depression, ADHD, cocaine craving, and cocaine urine status) but included either cumulative, current, or duration of drug use parameters.
B, Unstandardized regression coefficient; SE, Unstandardized standard error; β, Standardized Beta.

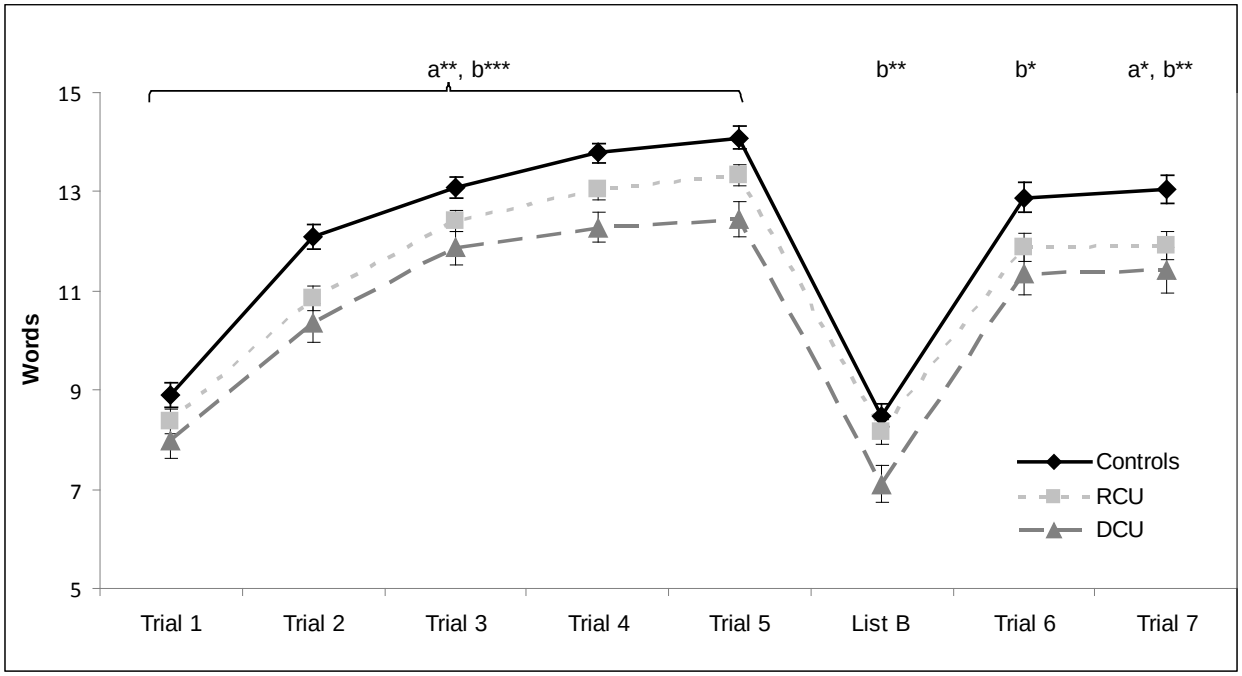
In the first model, cumulative cocaine dose was the only significant predictor for the GCI. In the second model, duration of cocaine use was again the only significant predictor for the GCI. The direction of the standardized beta coefficients reflected that increasing amount and duration of cocaine use was associated with decreased cognitive performance. In the third model, weekly consumption during the last 6 months could not account for a significant cocaine impact but was foremost influenced by age, the use of alcohol, cigarettes, and MDMA.

Figure DS1: GCI score scatterplot



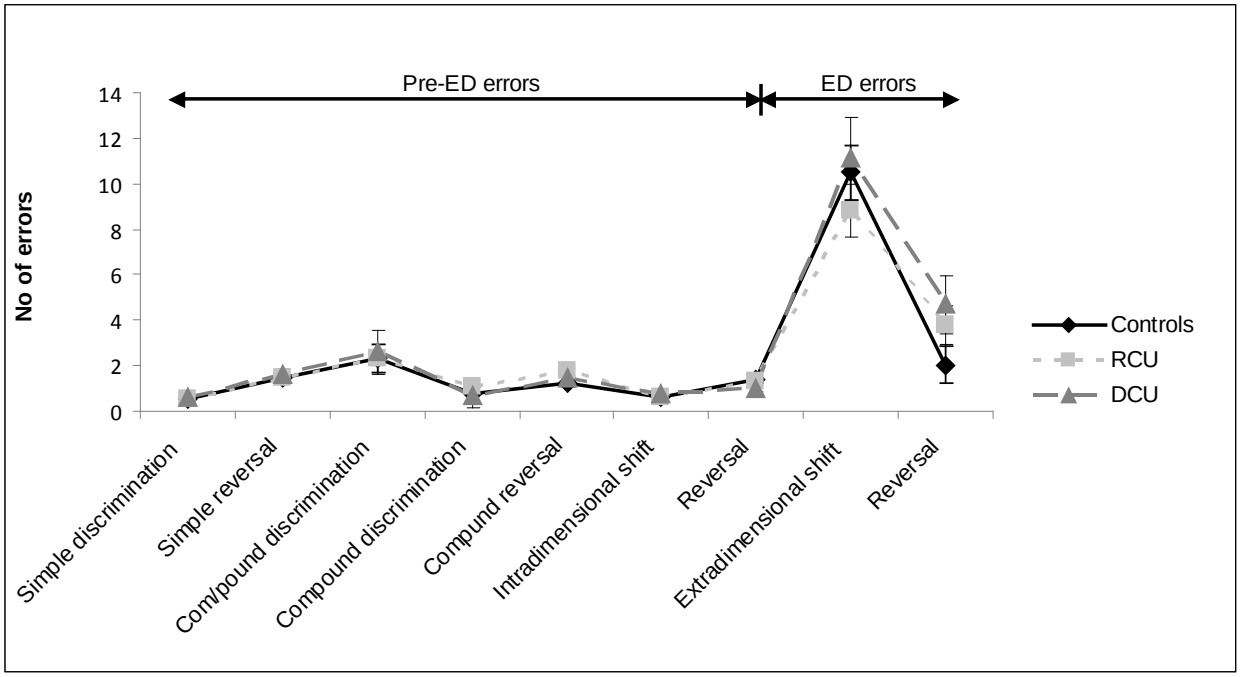
Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). The dotted black line represents the clinical criterion of -1 SD of the control group.

Figure DS2: RAVLT performance



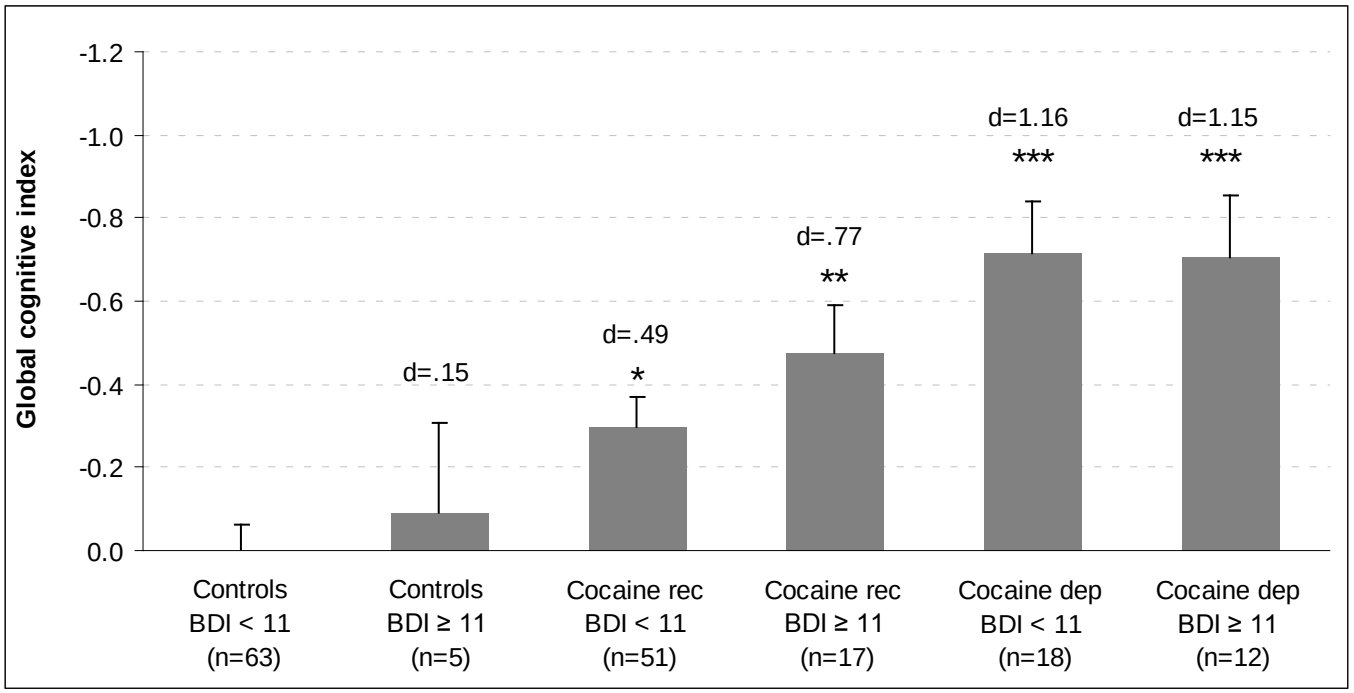
Performance in the first five learning trials, the interference list B, the recall after interference trial 6, and the delayed recall trial 7 in the Ray **Auditory Verbal Learning Test (RAVLT)**. Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). [a] Sidak post hoc tests: Controls vs. Cocaine rec. [b] Sidak post hoc tests: Controls vs. Cocaine dep. *p<.05, **p<.01, ***p<.001.

Figure DS3: IED performance



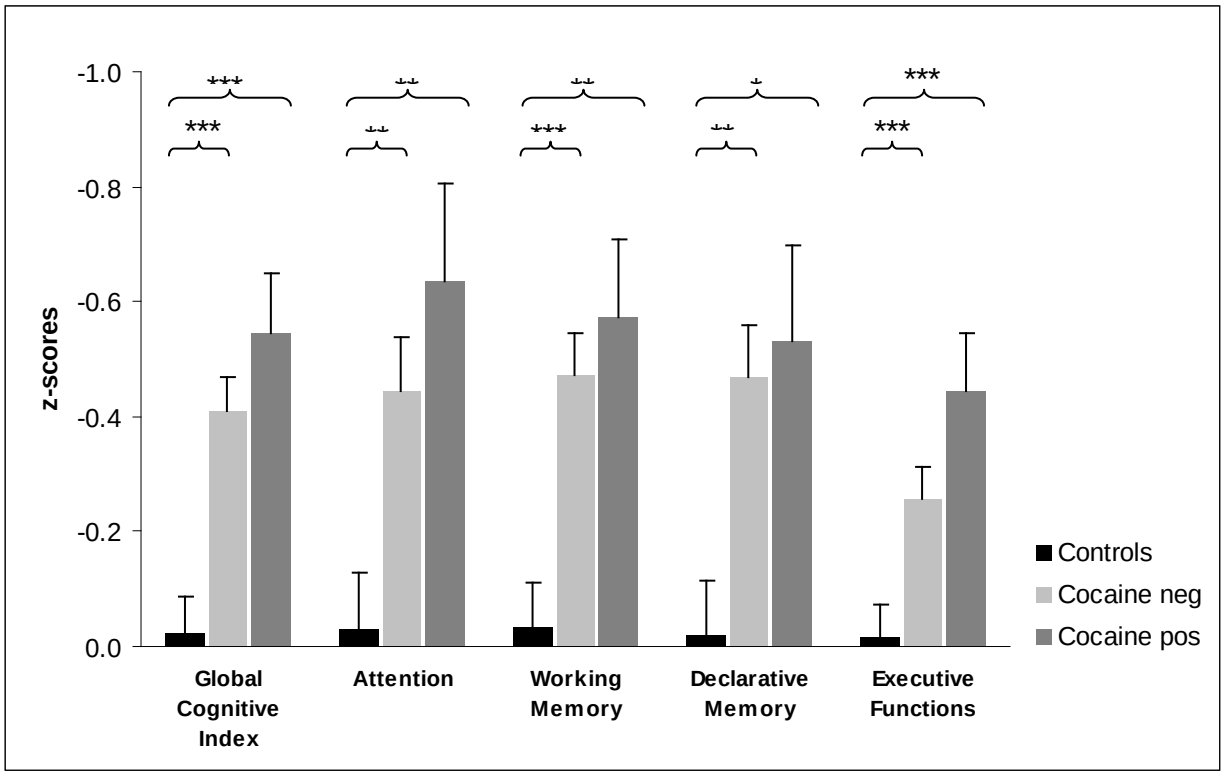
Error rates across the nine stages of the Intra/Extradimensional Attentional Set Shifting task (IED). Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). No significant pairwise Sidak post hoc tests.

Figure DS4: Impact depression status



Mean GCI scores and standard errors in groups stratified for cocaine use and BDI score. Values are corrected for age, verbal IQ, and cocaine gram/week. Group sizes (n) are shown. Significant Sidak post-hoc test vs. reference control group low depression (on the very left): *p<.05; **p<.01; ***p<.001. Cohen's d vs. control group low depression (on the very left).

Figure DS5: Impact current cocaine effects tested by urine status



Mean z-scores and standard errors for the global cognitive index and the four cognitive domains (values corrected for age and verbal IQ) in groups with controls (n=68), negative (n=75), and positive (n=22) urine samples. Data for 1 hair sample (recreational cocaine user) was missing. Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.