Supplementary Material

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Cognitive impairment in cocaine users is drug-induced but partially reversible:
evidence from a longitudinal study

Methods S1. Recruitment and selection.

The recruitment focused on the greater area of Zurich and lasted from January 2010 (start recruitment) until March 2013 (finish of the follow-up). Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-and-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were tested in the cross-sectional study. Six participants were not re-invited to participate in the follow-up study (refusal study participation, psychiatric disorders or first-grade family member with schizophrenia). The remaining 234 participants (138 cocaine users, 96 controls) were contacted and invited for a follow-up test session twelve months after baseline testing. One-hundred-and-two participants (59 cocaine users, 43 controls) were not available for the follow-up study due to different reasons (not answering, losing interest, time reasons, death). One-hundred-and-thirty-two participants (56%; 79 cocaine users, 53 controls) agreed to be re-tested and participated in the follow-up. Twenty-seven of these subjects (22 cocaine users, 5 controls) had to be excluded from the final analyses due to hair analyses revealing illegal drug use not allowed by our exclusion criteria (e.g., opioids or excessive MDMA intake) or due to starting use of psychotropic medication (e.g., antipsychotics or antidepressants).

Methods S2. Construction of cognitive domain scores.

Thirteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group (n=48) at t1. 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 functions according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, the four z-scored domains were equally integrated into a broad global cognitive index (GCI). Apart from the non-consideration of two CANTAB Intra/Extradimensional Set Shifting Task (IED) parameters, we used exactly the same approach as in the previously published cross-sectional study (Vonmoos *et al*, 2013).

Attention
To assess attention, we primarily focused on sustained attention by including the two RVP parameters discrimination performance A' and total of hits (Jones *et al*, 1992). In order to diversify this domain, we further added the RAVLT parameter trial 1, a supraspan measure with a strong attentional component (Lezak *et al*, 2004).

Working memory
The SWM parameter total errors tested the capability to retain spatial information and to manipulate remembered items in the working memory (Morris *et al*, 1988). The LNST score measured verbal working memory by summing up the number of correct responses (Wechsler, 1997). The PAL first trial memory score measured visual working memory by counting the number of correctly located patterns after the first presentation (Sahakian *et al*, 1988).

Declarative memory
Three RAVLT parameters were included to assess the verbal declarative memory performance: ∑trials 1-5, delayed recall trial 7, and adjusted recognition performance p(A). Furthermore, the two PAL parameters (adjusted total of errors and adjusted total of trials) were used to capture visual declarative memory (Sahakian *et al*, 1988).

Executive functions
Because we excluded the CANTAB IED from the longitudinal analysis due to an evident ceiling effect at baseline (Vonmoos *et al*, 2013), the executive functions were measured by only two parameters. First, the SWM strategy score assessed the applied heuristic strategies (Morris *et al*, 1988), a typical feature of the executive functions. Second, the RAVLT recall consistency score is a parameter typically impaired in patients with prefrontal lesions (Benedict *et al*, 2005; Jokeit *et al*, 1997) and related with measures of executive functions (Beebe *et al*, 2000).

Table S1. Demographic data and pattern of drug use for the cocaine user group with a *stable* use pattern.

	Baseline (t1)	1-year follow-up (t2)[h]
Age, y	27.0 (5.6)	
Sex (f/m)	8/11	
Verbal IQ (MWT-B)[a]	104.5 (9.1)	
Education, y	10.3 (1.6)	
ADHD-SR score (0-22)	14.4 (10.2)	
ADHD DSM IV (y/n)[b]	4/15	
Weeks between t1 and t2	64.8 (16.3)	
BDI score (0-63)	8.1 (6.2)	
BDI depression (y/n)[d]	2/17	
Cocaine		
Times per week[e]	0.6 (0.6)	0.3 (0.2)
Grams per week[e]	0.7 (0.6)	0.2 (0.3)
Years of use	5.4 (5.0)	6.3 (5.6)
Max. dose (grams/day)[k]	3 (3.1)	1.7 (1.5)
Cumulative dose (grams)[k]	394 (563)	18 (25.4)
Last consumption (days)	42.2 (49.7)	58.2 (116.6)
Cocaine craving (0-70)[f]	18.4 (7.7)	15.1 (7.7)
Hair analysis, ng/mg		
$Cocaine_{total}$	3.2 (9.9)	3.2 (9.4)
Cocaine	2.5 (7.6)	2.6 (7.9)
Benzoylecgonine	0.6 (1.9)	0.5 (1.2)
Cocaethylene	0.3 (0.8)	0.7 (2.1)
Benzoylecgonine	0.1 (0.3)	0.1 (0.3)
Urine toxicology (n/p)[g]	18/1	16/3
Alcohol[k]		
Grams per week[e]	132.3 (86.4)	146.7 (95.1)
Years of use	9.9 (5.0)	11.1 (5.5)
Nicotine[k]		
Smoking (y/n)[c]	14/5	15/4
Cigarettes per day[e]	12.2 (8.3)	12.7 (8.9)
Years of use	9.2 (6.3)	9.5 (6.7)
Cannabis[k]		
Grams per week[e]	1.2 (2.6)	0.9 (1.6)
Years of use	7.8 (5.9)	8.4 (6.2)
Cumulative dose (grams)	1932.7 (4309.1)	55.0 (94.7)
Last consumption (days)[i]	28.7 (41.1);n=15	18.7 (33.1);n=13
Urine toxicology (n/p)[g]	16/3	15/4
Amphetamine[k]		
Grams per week[e]	0.0 (0.1)	0.0 (0.1)
Years of use	1.4 (3.0)	1.9 (3.5)
Cumulative dose (grams)	2.8 (5.8)	1.9 (6)
Last consumption (days)[i]	61.8 (59.6);n=7	65.9 (23.2);n=3
Hair analysis ng/mg	0.0 (0.0)	0.0 (0.0)
MDMA[k]		
Tablets per week[e]	0.0 (0.0)	0.1 (0.1)
Years of use	2.1 (3.8)	2.6 (4.3)
Cumulative dose (tablets)	14.6 (39.9)	4.3 (7.1)
Last consumption (days)[i]	56.4 (43.4);n=6	69.7 (36.4);n=8
Hair analysis ng/mg	0.2 (0.5)	0.2 (0.4)
GHB[k]		
Cumulative dose (pipettes)	4.5 (17.8)	1.2 (5.2)
Hallucinogens[k]		
Cumulative dose (times)	6.3 (14.3)	0.4 (0.8)
Methlyphenidate[k]		
Cumulative dose (tablets)	41.3 (144.6)	1.5 (4.6)
Hair analysis ng/mg	0.0 (0.0)	0.0 (0.0)

Means and standard deviations.
[a] Verbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (Lehrl, 1999).
[b] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria)(Roesler *et al*, 2004).
[c] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton *et al*, 1991).
[d] BDI, Beck Depression Inventory (cut-off ≥18)(Hautzinger *et al*, 1994).
[e] Average use during the last 6 months.
[f] Craving for cocaine was assessed by the Brief-CCQ (Sussner *et al*, 2006).
[g] Cut-off values for cocaine = 150 ng/ml and for tetrahydrocannabinol = 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[h] Parameters at follow-up refer to the 1-year period between t1 and t2.
[i] Last consumption is averaged only for persons who used the drug in the last 6 months.
[k] Use frequency, duration of use, and cumulative doses are averaged within the total group.

Table S2. Correlations between self reported cocaine use parameters and the hair toxicology parameter $cocaine_{total}$.

	Cocaine Users (n=38)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)
Cocaine self-report at baseline	$Cocaine_{total}$ [a]	$Cocaine_{total}$	$Cocaine_{total}$
Times per week	.18	*.48	-.16
Grams per week	-.04	.12	-.18
Years of use	*.38	.39	.35
Max. dose (grams/day)	*.39	-.06	**.67
Cumulative dose lifetime (grams)	**.48	.22	**.62
Cocaine self-report at 1-year follow-up	$Cocaine_{total}$ [a]	$Cocaine_{total}$	$Cocaine_{total}$
Times per week	.14	-.05	.03
Grams per week	.08	-.04	.16
Years of use	.07	.12	.28
Max. dose (grams/day)	.29	.40	.06
Cumulative dose in the last year (grams)	.02	-.06	-.01

Pearson's product-moment correlations in cocaine users (n=38). Significant correlations are marked: *p<.05; **p<.01.
Cocaine parameters at 1-year follow-up refer to the period between t1 and t2.
[a] $Cocaine_{total}$ = Cocaine + Benzoylecgonine + Norcocaine.

Table S3. Cognitive test scores at the baseline (t1) and the 1-year follow-up (t2).

	Baseline (t1)							1-year follow-up (t2)						
	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2
Attention														
RVP Discrimination perf. A'	0.92 (0.04)	0.90 (0.04)	0.90 (0.04)	1.92	2,83	.15	.04	0.93 (0.04)	0.91 (0.04)	0.92 (0.04)	2.00	2,83	.14	.05
RVP Total hits	18.35 (4.21)	16.26 (4.62)	16.79 (4.38)	1.95	2,83	.15	.04	19.98 (4.19)	17.79 (4.77)	18.63 (3.85)	2.02	2,83	.14	.05
RAVLT Supraspan trial 1[b]	9.38 (2.47)	8.47 (2.2)	8.26 (2.18)	1.99	2,82	.14	.05	9.66 (2.43)	8.68 (2.08)	9.37 (2.87)	1.06	2,82	.35	.03
Working memory														
LNST Score	15.54 (2.92)	14.00 (3.48)	14.00 (2.56)	2.84	2,83	.06	.06	15.69 (3.10)	13.74 (3.11)	14.32 (2.94)	3.27	2,83	**.04**	.07
SWM Total errors	20.31 (16.38)	27.11 (19.75)	26.95 (19.77)	1.49	2,83	.23	.03	13.52 (14.14)	25.53 (15.99)*	20.84 (15.64)	4.94	2,83	**.009**	.11
PAL First trial memory score	15.48 (3.87)	13.84 (4.26)	13.58 (2.43)	2.45	2,83	.09	.06	16.42 (3.08)	13.95 (3.63)*	15.63 (3.70)	3.71	2,83	**.03**	.08
Declarative memory														
RAVLT Learning perf. (∑trials 1-5)[b]	63.38 (6.53)	57.37 (9.66)*	57.84 (10.30)*	5.19	2,82	**.008**	.11	64.40 (6.64)	58.26 (10.55)*	62 (10.00)	3.63	2,82	**.03**	.08
RAVLT Adjusted recognition p(A)[b]	0.87 (0.11)	0.84 (0.19)	0.85 (0.14)	.54	2,82	.59	.01	0.87 (0.11)	0.84 (0.16)	0.86 (0.18)	.31	2,82	.73	.01
RAVLT Delayed recall trial 7[b]	13.19 (2.00)	12.00 (3.04)	11.89 (2.92)	2.66	2,82	.08	.06	13.66 (1.77)	12.05 (3.66)	13.42 (2.39)	3.00	2,82	.06	.07
PAL Total errors adjusted	11.96 (13.76)	19.32 (15.73)	15.00 (12.11)	1.95	2,83	.15	.04	6.96 (6.69)	18.47 (16.17)**	11.74 (17.59)	6.17	2,83	**.003**	.13
PAL Total trials adjusted	8.71 (3.44)	10.74 (4.01)	9.63 (3.29)	2.31	2,83	.11	.05	7.88 (2.20)	10.37 (4.09)**	8.47 (3.61)	4.62	2,83	**.01**	.10
Executive functions														
SWM Strategy score	32.27 (6.13)	33.53 (6.28)	33.00 (5.45)	.32	2,83	.72	.01	29.54 (6.03)	31.47 (6.81)	32.89 (4.41)	2.40	2,83	.10	.05
RAVLT Recall consistency (%)	93.05 (5.75)	87.54 (9.84)*	87.70 (8.61)*	5.52	2,82	**.006**	.12	93.43 (6.34)	88.76 (10.97)	91.61 (6.06)	2.61	2,82	.08	.06

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001).
[b] In the RAVLT task, the value for one control subject is missing due to a technical failure.

Table S4. Test-retest effect adjusted and ADHD corrected cognitive change scores between baseline (t1) and one-year follow-up (t2).

Change scores (Δ_{t2-t1})	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)
Global Cognitive Index	-0.09 (0.10)	0.15 (0.10)
Neurocognitive domains		
Attention	-0.02 (0.15)	0.16 (0.15)
Working memory	-0.22 (0.10)	0.10 (0.10)
Declarative memory	-0.14 (0.18)	0.23 (0.18)
Executive functions	0.02 (0.17)	0.11 (0.17)
Attention		
RVP Discrimination perf. A'	0.00 (0.01)	0.00 (0.01)
RVP Total hits	-0.10 (0.78)	0.22 (0.78)
RAVLT Supraspan trial 1	-0.10 (0.55)	0.86 (0.55)
Working memory		
LNST Score	-0.40 (0.64)	0.16 (0.64)
SWM Total errors	5.14 (2.99)	0.76 (2.99)
PAL First trial memory score	-0.83 (0.82)	1.12 (0.82)
Declarative memory		
RAVLT Learning perf. (∑trials 1-5)	-0.24 (1.79)	3.25 (1.79)
RAVLT Adjusted recognition p(A)	0.01 (0.04)	0.02 (0.04)
RAVLT Delayed recall trial 7	-0.44 (0.53)	1.08 (0.53)
PAL Total errors adjusted	4.25 (2.64)	1.65 (2.64)
PAL Total trials adjusted	0.49 (0.66)	-0.35 (0.66)
Executive functions		
SWM Strategy score	0.66 (0.96)	2.64 (0.96)
RAVLT Recall consistency in %	0.73 (1.58)	3.64 (1.58)

Mean change scores and standard errors (values corrected for ADHD). Change scores are adjusted for the test-retest effect.

Table S5. Correlations between cognitive change scores and cocaine use parameters during the interval period.

Change scores (Δ_{t2-t1})	Cocaine use during the interval period (between baseline and 1-year follow-up)	
	Cumulative dose (grams)	Hair analysis $Cocaine_{total}$ ng/mg
Attention		
RVP Discrimination perf. A'	*.36	
RVP Total hits	*.34	
RAVLT Supraspan trial 1		
Declarative memory		
RAVLT Learning perf. (∑trials 1-5)	.31	
RAVLT Adjusted recognition p(A)		*-.39
RAVLT Delayed recall trial 7	**.44	-.28
PAL Total errors adjusted		
PAL Total trials adjusted		

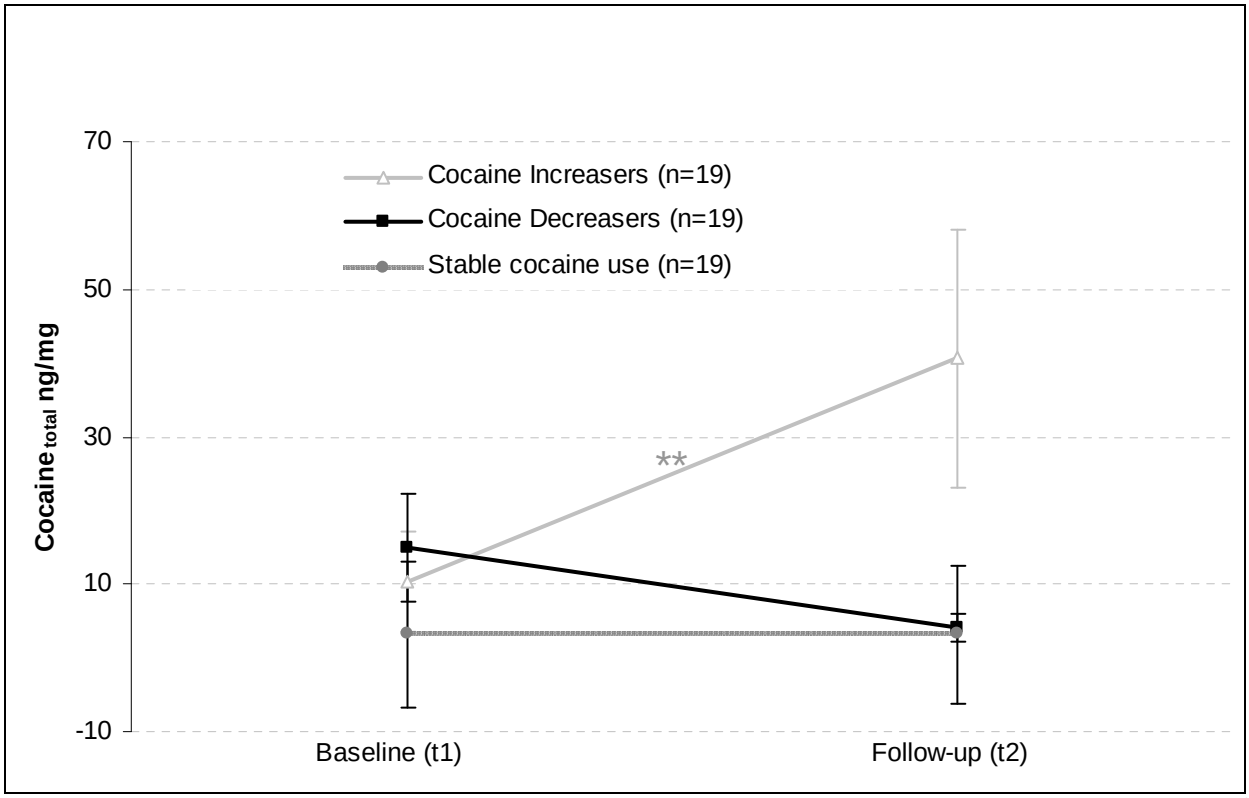
Pearson's product-moment correlations in cocaine users (n=35).
Correlations with a p-level below 10% (2-tailed) are shown, while significant correlations are marked: *p<.05; **p<.01.
Three cocaine users with more than 4 standard deviations difference in cumulative doses or $cocaine_{total}$ were excluded.

Table S6. Demographic data and hair analysis in cocaine user subgroups.

	Controls (n=48)	Cocaine Increasers low, <10 ng/mg (n=11)	Cocaine Increasers high, >10 ng/mg (n=8)	Cocaine Decreasers ongoing use (n=11)	Cocaine Decreasers no more use (n=8)	F	df, df_{err}	p
Global Cognitive Index (Δ_{t2-t1})[d]	0.00 (0.38)	-0.04 (0.48)	-0.15 (0.42)	0.04 (0.51)	0.29 (0.34)	1.3[a]	4,81	.28
Demographic data								
Age, y	30.3 (8.9)	29.5 (8.5)	34.3 (10.4)	33.5 (9.3)	28.5 (6.0)	.80[a]	4,81	.53
Sex (f/m)	16/32	3/8	0/8	3/8	2/6	3.84[b]	4	.43
Verbal IQ (MWT-B)	107.6 (10.0)	104.1 (12.1)	101.3 (5.5)	102.6 (8.5)	105.4 (4.7)	1.28[a]	4,81	.28
Education, y	10.8 (1.8)	10.7 (2.0)	10.0 (1.6)	10.3 (1.8)	9.6 (1.1)	.99[a]	4,81	.42
Smoking (y/n)	37/11	9/2	5/3	8/3	6/2	1.08[b]	4	.90
BDI score (0-63)	3.5 (3.3)	7 (4.5)	7.8 (11.5)	8.5 (7.9)	9.0 (4.6)	3.72[a]	4,81	**.008**
ADHD-SR score (0-22)	7.7 (5.2)	12.5 (9.4)	14.9 (9.8)	13.3 (6.7)	15.1 (7.3)*	4.60[a]	4,81	**.002**
Weeks between t1 and t2	58.2 (10.1)	58.4 (11.0)	60.6 (14.2)	62.4 (13.9)	61.2 (16.4)	.39[a]	4,81	.81
Hair analysis cocaine$_{total}$ ng/mg								
t1	-	2.9 (3.0)	20.3 (44.6)	23.8 (40.7)	2.6 (2.6)	1.37[c]	3,34	.27
t2	-	5.8 (3.4)°°	88.7 (101.6)	7.2 (9.9)°°	0.1 (0.2)°°	6.90[c]	3,34	**<.001**
Δ_{t2-t1}	-	+2.9 (2.4)°	+68.3 (83.8)	-16.6 (34.5)°°°	-2.5 (2. 6)°	6.82 [c]	3,34	**.001**

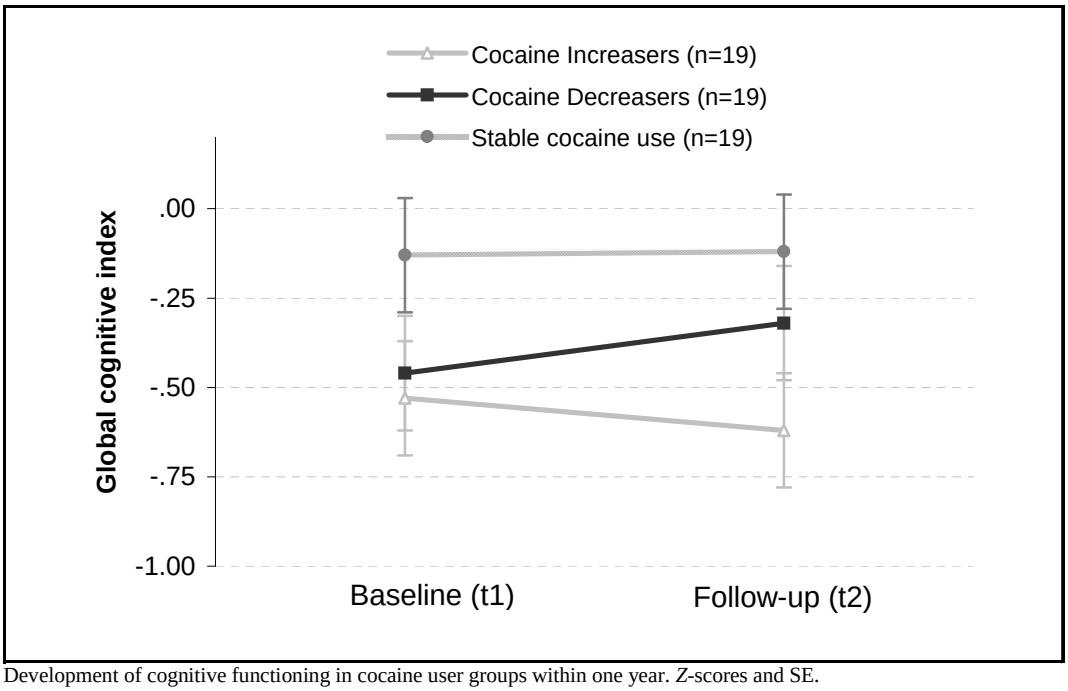
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group:*p<.05).
[b] χ^2 test (all groups) for frequency data.
[c] ANOVA (only cocaine user groups, with significant Sidak post-hoc test vs. subgroup cocaine increaser high: °p<.05; °°p<.01; °°°p<.001).
[d] GCI change scores are adjusted for the test-retest effect.

Figure S1. Hair concentration cocaine$_{total}$ in three cocaine user groups at baseline (t1) and one-year follow-up (t2).



Hair concentration cocaine$_{total}$ (ng/mg) in cocaine user groups. Means and standard deviation. A mixed design analysis (ANOVA) showed a significant group*test interaction effect ($F_{2,54}$=5.70, p<.10). **indicates a significant pairwise Sidak pre-post comparison (p<.10).

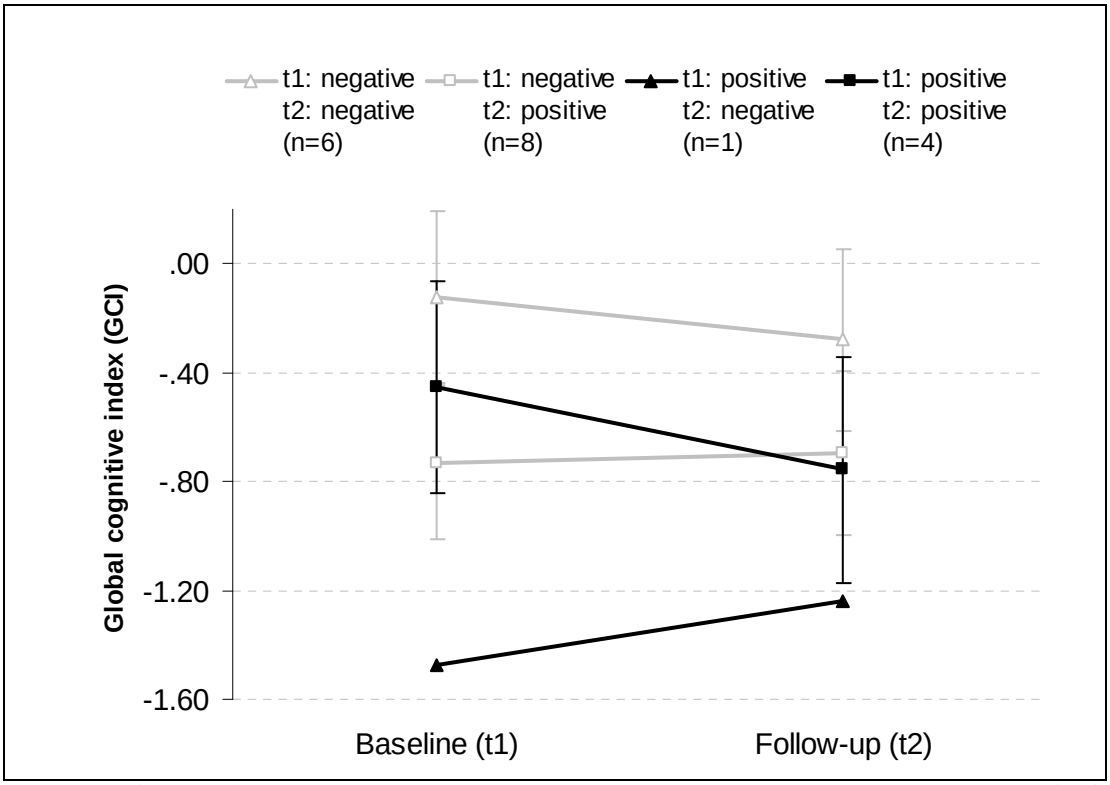
Figure S2. Development of cognitive functioning in all three cocaine user groups within one year.



Development of cognitive functioning in cocaine user groups within one year. Z-scores and SE.
Z-score transformation was based on control group mean and standard deviation at baseline. Values at follow-up were adjusted for the test-retest effect.
A mixed design analysis (corrected for ADHD) showed a non-significant group*time interaction effect ($F_{2,53}$=1.22, p=.30).
Pairwise Sidak pre-post comparisons were non-significant for *increasers* (p=.41), *decreasers* (p=.18), and *stable* cocaine users (p=.89).

As presented in Figure S1 (or more detailed in Table 1 and Table S1), the user group with *stable* cocaine use consists mainly of subjects with a comparatively low level of current cocaine use, whereas the *increaser* and *decreaser* groups consist of subjects with a substantially stronger former and/or current drug use. Consequently, GCI scores of the *stable* cocaine users are on a higher level than the GCI scores of the two other user groups.

Figure S3. Impact of cocaine urine toxicology status on global cognitive performance in cocaine *increasers* at baseline (t1) and 1-year follow-up (t2).



Development of cognitive functioning in cocaine user groups within one year. Z-scores and standard errors in groups stratified for urine toxicology (negative/positive) at baseline and follow-up in cocaine *increasers* (*n*=19).
Z-score transformation was based on control group mean and standard deviation at baseline. Values at follow-up were adjusted for the test-retest effect.
A mixed design analysis (corrected for ADHD) showed a non-significant group*time interaction effect ($F_{3,14}$=0.75, *p*=.54).
All pairwise Sidak pre-post comparisons were non-significant.

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