Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset

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**Background**
Dependent cocaine users consistently display cognitive deficits but cognitive performance of recreational cocaine users has rarely been investigated.

**Aims**
To examine whether cognitive performance is impaired in relatively pure recreational and dependent cocaine users.

**Method**
The cognitive performance of recreational (n = 68) and dependent cocaine users (n = 30) was compared with the performance of stimulant-naive controls (n = 68) employing an extensive neuropsychological test battery. Moreover, the impact of attention-deficit hyperactivity disorder (ADHD) symptoms, craving and age at onset was analysed.

**Results**
Dependent cocaine users display broad cognitive impairments in the domains of attention, working memory, declarative memory and executive functions. The performance of recreational cocaine users in all four domains was intermediate between that of controls and dependent users and they displayed significant deficits foremost in the domains of attention and working memory. In addition, ADHD symptoms, craving and age at onset were important modulators of cognitive function in cocaine users.

**Conclusions**
Cognitive deficits occur at a recreational and non-dependent level of cocaine use. Cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairment.

**Declaration of interest**
None.

With an annual number of around four million users, cocaine is currently the second most frequently used illicit drug in Europe.1 Given its addictive potential and negative health consequences,2,4 the use of cocaine is regarded as a major public health issue.2,4 For more than two decades, research has tried to examine the long-term impact of cocaine by focusing on dependent cocaine users. Evidence has accumulated that addictive cocaine use leads to neuroadaptive changes and dopaminergic alterations, mainly exerted in the frontostriatal network.5–9 Imaging studies in chronic cocaine users have repeatedly reported reductions in grey matter density in the dorsolateral prefrontal cortex, the anterior cingulate cortex and the orbitofrontal cortex,10–14 areas critically involved in several cognitive functions.15 Accordingly, cognitive deficits in chronic cocaine users have been linked to structural and functional alterations primarily in the prefrontal cortex.5,6,9,16 The recent literature is characterised by a consensus that cocaine dependence is associated with significant neuropsychological impairment, although the aetiology and the severity of these impairments are a matter of ongoing debate.5,16–18 Existing studies with dependent users indicate persisting cognitive impairments including deficits predominantly in the domains of attention, working and declarative memory, and, less consistently, in the ill-defined concept of executive functions.5,10,16–21 However, given that these previous studies differed in their inclusion and exclusion criteria regarding comorbid psychiatric diseases, polytoxic drug-use history, abstinence time and verification of self-reported drug intake, the specific impact of chronic cocaine use on cognitive processes has been difficult to determine.

Whereas most of these studies focused on the chronic misuse of cocaine, relatively little is known about the substantial number of recreational but non-dependent cocaine users (recreational users).1 Moreover, in comparison with studies with dependent cocaine users, the investigation of recreational users has several advantages, as they (a) are not (or not yet) addicted, (b) are less burdened by psychiatric comorbidities,22 (c) usually unmedicated with psychotrophic drugs, and (d) mostly display less polytoxic drug use. It is only recently that research has started to systematically investigate the possible cognitive effects of recreational cocaine use.23 Preliminary data from small samples of recreational users indicate that small and infrequent doses of cocaine affect different cognitive components such as attention, memory or components of executive functions.23–29 However, these studies lacked a unique definition of recreational cocaine use (recreational cocaine use was either defined by cocaine use below a certain level or by not matching dependency criteria according to DSM–IV30), mostly relied on simple self-reported drug use without objective verification, or tested only very small and predominantly male samples with mainly polytoxic drug use patterns. As a consequence, after more than two decades of research and despite concern about public health effects, there is still no clarification on the relationship between the extent of cocaine use and the characteristics of cognitive impairments.

To date, analyses of regular cocaine users categorised by groups of differing consumption patterns have been lacking. Our aim, therefore, was to investigate a large sample of recreational users, dependent users and matched stimulant-naive healthy controls with a comprehensive neuropsychological test battery to examine whether cognitive performance is impaired in relatively pure recreational and dependent cocaine users. Any differences in cognitive performance would have implications notably with regard to risk markers, prevention and treatment.
implications.\textsuperscript{5,12,20} We expect to find considerable cognitive deficits in dependent users and similar, but less pronounced, cognitive impairments in recreational users, as we recently reported deficits in early information processing and blue–yellow colour vision in recreational users suggesting alterations of catecholamine neurotransmission.\textsuperscript{31,32} Although psychiatric comorbidities such as attention-deficit hyperactivity disorder (ADHD) and depression are frequently found in dependent cocaine users,\textsuperscript{33,34} their impact has scarcely been investigated so far. Thus, we conducted a comprehensive psychiatric diagnostic interview and additionally assessed symptoms of ADHD and depression with self-report questionnaires. Finally, by performing urine and hair toxicology analyses, we were uniquely able to objectively characterise not only recent drug use but also drug use over the past 6 months.

Method

Participants

A total of 68 recreational cocaine users, 30 dependent users and 68 cocaine-naïve controls were included in the study (recruitment and selection details in online data supplement Method DS1). The three groups did not differ significantly in age, gender, smoking habits and verbal IQ. Exclusion criteria for all participants were acute or previous neurological disorders or head injury, any clinically significant medical diseases and use of prescription drugs affecting the central nervous system. Additional exclusion criteria for the control group were all acute or previous Axis I DSM-IV psychiatric disorders\textsuperscript{40} including ADHD and any form of addiction, except nicotine, or regular illegal drug use (lifetime use >15 occasions) with the exception of occasional cannabis use. Specific exclusion criteria for the cocaine user groups were use of opioids, a polytoxic drug use pattern according to DSM-IV and acute or previous Axis I DSM-IV adult psychiatric disorders with the exception of cocaine, cannabis and alcohol misuse, history of affective disorders (acute major depression was excluded) or ADHD. None of the cocaine users was help-seeking in our department. Inclusion criteria for the two user groups were cocaine as the primary drug, cocaine use of >0.5 g per month, and an abstinence duration of <6 months. Cocaine dependence was diagnosed according to the DSM-IV criteria,\textsuperscript{50} with only dependent cocaine users fulfilling these criteria. Participants were asked to abstain from illegal substances for at least 72 h and not to consume alcohol for 24 h before the testing session. Adherence with these instructions was controlled by urine and 6-month hair toxicologies (online Method DS2). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and were compensated for their participation.

Procedure

The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study (ZuCo\textsuperscript{\textregistered}St).\textsuperscript{32} Trained psychologists conducted a Structured Clinical Interview (SCID-I)\textsuperscript{33} according to DSM-IV procedures. Drug use was assessed by means of a structured and standardised Interview for Psychotropic Drug Consumption.\textsuperscript{36} For the estimation of verbal intellectual performance, the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) was applied.\textsuperscript{37} The brief version of the Cocaine Craving Questionnaire (CCQ) was used to capture current cocaine craving.\textsuperscript{38} Smoking habits were assessed by the Fagerstrom Test of Nicotine Dependence.\textsuperscript{39} The Beck Depression Inventory (BDI)\textsuperscript{40} measured the current severity of depression and the ADHD Self-Rating scale (ADHD-SR)\textsuperscript{41} focused on the diagnosis of ADHD in adulthood according to DSM-IV criteria. Subsequently, participants underwent a comprehensive neuropsychological test battery as described below. Participants were allowed to take a break at any time and smoking was permitted during the breaks.

Neuropsychological assessment

The test battery comprises four tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB):\textsuperscript{42} rapid visual processing (RVP), spatial working memory (SWM), intra/extra-dimensional set shifting (IED), paired associates learning (PAL); a German version of the Rey Auditory Verbal Learning Test (RAVLT),\textsuperscript{43} and the Letter Number Sequencing Task (LNST).\textsuperscript{44} With regard to data reduction and specific analyses, 15 predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. These parameters were reduced to the four cognitive domains commonly used in cocaine research:\textsuperscript{16–18,21} attention, working memory, declarative memory and executive function according to theoretical \textit{a priori} considerations (a detailed description can be found in online Method DS3). Furthermore, these four z-scored domains were equally integrated into a global cognitive index (GCI).

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0 for Windows. Frequency data were analysed by means of Pearson's chi-squared test and quantitative data by analyses of variance (ANOVA). Based on significant main effects, Sidak post \textit{hoc} comparisons were performed. To control for demographic inequalities, the variables age and verbal IQ were introduced as covariates in analyses of covariance (ANCOVA) with linear group contrasts. Correlation analyses (Pearson's product-moment) to relate drug-use parameters to cognitive performance were conducted across a combined user group. Cumulated cocaine use and weekly use in grams were ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal distribution (Shapiro–Wilk \textit{W}<0.001). The effect of depression, ADHD, cocaine craving, recent cocaine use (positive urine test) and age at onset on cognitive performance was examined by correlation analyses and ANCOVA subgroup comparisons additionally corrected for severity of cocaine use. The effect of craving status was investigated because previous studies reported that craving for food and nicotine has an impact on cognitive functioning.\textsuperscript{45,46} Multiple logistic regressions were used to estimate odds ratios associated with the use of cocaine and cognitive performance. The odds ratios were left unadjusted because the values decisive for the group assignment were already adjusted for age and verbal IQ.

Results

Demographic characteristics and drug use

The groups did not differ regarding age, gender distribution, smoking status and verbal IQ but dependent users had fewer years of education than the controls and recreational users (Table 1). As expected, dependent users displayed higher BD and ADHD-SR sum scores than controls and recreational users, whereas recreational users showed higher scores than controls.

Dependent cocaine users had more than eightfold higher concentrations of cocaine and metabolites compared with recreational users in their hair samples (Table 2). Nonetheless, recreational users were regular users with a mean weekly consumption of about 1 g of cocaine but without fulfilling the
DSM-IV criteria for dependence (41 recreational users met the criteria for cocaine abuse). The main route of administration was intranasal; only three dependent users were primarily inhaling the drug (2 free-base, 1 coca paste). In the urine samples, 10 recreational users and 12 dependent users tested positive for cocaine. However, we decided not to exclude them but to investigate the acute and post-acute effects of the drug. Online Table DS1, a more detailed version of Table 2 that also includes details of the patterns and amount of other drug and alcohol use by the three groups, shows that the hair samples revealed a clear domination of cocaine compared with other illegal drug use.

### Neurocognitive measures

The ANCOVA for the GCI showed a significant group effect including a clear linear trend \( (P<0.001) \), and significant pair-wise comparisons between all three groups (Fig. 1, Table 3 and online Fig. DS1), indicating global cognitive impairment in both cocaine user groups. Likewise, all four domains \( (P<0.001) \) and 12 of 15 test parameters \( (P<0.05–0.00001) \), except the two IED parameters and the SVM strategy score displayed significant linear trends, suggesting robust dose–response relationships (Table 3 and online Table DS2 for a more detailed analysis including all parameters). In all domains, recreational and dependent users differed significantly from controls. Additionally, the domains working memory and executive functions showed significant group differences between recreational and dependent users. The single test parameters within the attention, working memory and declarative memory domains (detailed RAVLT analysis, online Fig. DS2) showed similar results. However, the effect in the executive function domain was mainly driven by a strong effect regarding RAVLT recall consistency and, to a lesser degree, by the SVM strategy score, whereas the two IED parameters did not show any substantial group differences (detailed IED analysis, online Fig. DS3).

Correlation analyses within the total group of cocaine users \( (n=98) \) revealed that the GCI and the domains working memory, declarative memory and executive functions were all inversely correlated.
associated with cumulative cocaine dose, duration of cocaine use, cocaine metabolites benzoylecgonine and norcocaine in the hair, and a composite index reflecting the severity of cocaine use (Table 4; intercorrelation of use parameters, online Table DS3). Interestingly, the domain attention was only strongly correlated with the cumulative cocaine dose. The relatively high correlations in the domain executive functions were again driven by both the RAVLT and SWM parameters, whereas no associations were found for the two IED measures (single test correlation analysis, online Table DS4).

### ADHD, age at onset, craving, depression and acute drug effects

Our analysis of ADHD and craving subgroups, by further splitting user groups according to predefined criteria41 (yes/no fulfilling DSM-IV criteria on ADHD-SR) or median split (low/high, CCQ ≤16) suggested an impact of these variables on cognitive performance (Fig. 2). The ANCOVAs showed significant group effects for ADHD (F(4,158) = 9.56, P < 0.001) and craving subgroups (F(4,158) = 9.35, P < 0.001). The presence of craving additionally decreased cognitive performance only in recreational users (d = 0.26) (Fig. 2b), an ADHD diagnosis had a detrimental effect on cognitive functioning in both recreational (d = 0.30) and dependent users (d = 0.33) (Fig. 2a). Notably, recreational and dependent users without ADHD still significantly differed from controls. A combined analysis of ADHD and craving status in an integrated group of cocaine users confirmed this assumption by revealing a significant main effect for group (F(4,158) = 7.66, P < 0.001), whereby the controls differed significantly from all the cocaine user groups (Fig. 2c).

Age at onset of cocaine use played a crucial role (F(2,160) = 10.92, P < 0.001), as users starting cocaine use before the age 19 years performed significantly worse than users with a later age at onset (d = 0.66). Both users groups differed substantially from the control group (d_{＜18} = 1.10, d_{＞18} = 0.43) (Fig. 3).

Splitting the user groups and controls according to a predefined depression criterion40 (low/mild–strong, BDI ≥11) showed a significant group effect (F(5,157) = 7.41, P < 0.001) reflecting a weak additive impact of depressive symptoms on cognitive performance only in recreational users (d = 0.28). Also, cocaine users without depression differed significantly from controls without depression (online Fig. DS4).

To test the influence of recent cocaine use, cocaine users were divided into users with positive (n = 22, range 217–24 888ng/ml, mean 3873ng/ml, s.d. = 6 461ng/ml) and users with negative urine samples (n = 75) and compared with controls (n = 68). Results revealed significant group effects for the GCI (F(2,160) = 14.76, P < 0.001). Pair-wise Sidak comparisons yielded still significant and relatively strong differences between controls and both user groups (d_{pos} = 0.63, d_{neg} = 0.84), and users with positive urine samples showed slightly but non-significantly lower GCI scores than users with negative urine samples (d = 0.22). Similar patterns were found for all four domains (online Fig. DS5).

Multiple regression analyses conducted only in cocaine users confirmed that cumulative dose and duration of cocaine use were the best predictors of cognitive performance in contrast to psychopathological symptoms (online Table DS5).

### Risk threshold for cognitive impairments

As the use of cocaine proved to be an important determinant for cognitive performance, odds ratios (ORs) were calculated to assess the risk of impairment when using cocaine. If a progressive clinical criterion of −1 standard deviation was applied to define a cognitive decline, the use of cocaine indicated significant relative risks for deficits in attention (OR = 3.52, 95% CI 1.60–7.72, P < 0.01), working memory (OR = 3.08, 95% CI 1.47–6.49, P < 0.01), declarative memory (OR = 2.40, 95% CI 1.11–5.19, P < 0.05) and

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**Fig. 1** Mean z-scores and standard errors for the global cognitive index (GCI) and the four cognitive domains (values corrected for age and verbal IQ).

Sidak post hoc tests: *P < 0.05, **P < 0.01, ***P < 0.001.
Table 3 Neurocognitive global and domain scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>Stimulant-naive controls</th>
<th>Recreational users</th>
<th>Dependent users</th>
<th>Controls</th>
<th>Recreational v. Controls</th>
<th>Dependent users v. Controls</th>
<th>Recreational users v. Dependent users</th>
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<tbody>
<tr>
<td>Mean (s.e.)</td>
<td>0.3 (0.06)</td>
<td>0.3 (0.06)</td>
<td>0.4 (0.06)</td>
<td>0.5 (0.06)</td>
<td>0.4 (0.06)</td>
<td>0.1 (0.06)</td>
<td>0.1 (0.06)</td>
</tr>
</tbody>
</table>

Significant Sidak post hoc test was applied. *P < 0.05, **P < 0.01, ***P < 0.001

Fig. 2 Mean global cognitive index (GCI) scores and standard errors in groups stratified for cocaine use and confounding variables (values corrected for age, verbal IQ and cocaine usage). Significant Sidak post hoc test v. control group: *P < 0.05, **P < 0.01, ***P < 0.001. Cohen’s d v. control group. (a) Attention-deficit hyperactivity disorder (ADHD), DSM-IV criteria based on ADHD-Self Report (ADHD-SR). (b) Cocaine Craving Questionnaire (CCQ), craving for cocaine status based on median split <16. (c) Combined user group (n = 98) stratified for ADHD DSM-IV criteria based on ADHD-SR and CCQ, craving for cocaine status based on median split <16. RCU, recreational cocaine users; DCU, dependent cocaine users.

Cognitive deficits in cocaine users

In summary, cocaine users were 3.8 times more likely to manifest global cognitive deficits (GCI) than controls (OR = 3.80, 95% CI 1.81–7.97, P < 0.001). If a conservative clinical criterion of −2 standard deviations was applied, 15% (n = 8) of the recreational users and 30% (n = 9) of the dependent users revealed strong global cognitive impairment.

Figure 4 illustrates a clearly increasing risk of cognitive impairment with increasing cumulative doses of cocaine. Although this analysis emphasised the long-term impact of cocaine use on all four cognitive domains, declarative memory is the latest, whereas working memory is generally the earliest.
and most affected domain. Interestingly, a lifetime consumption of more than 1 kg cocaine seemed to strongly enhance the risk for cognitive impairment (Fig. 4a), whereas a lifetime consumption of more than 100 g was associated with an approximately 50% risk for mild cognitive impairment (Fig. 4b).

## Discussion

### Main findings

The aim of the present study was to examine whether cognitive performance is impaired in non-dependent recreational cocaine users and dependent cocaine users. In contrast to previous studies, hair toxicologies and comprehensive psychiatric diagnostics allowed the investigation of relatively pure cocaine users with little psychiatric comorbidity. Moreover, this is the largest published sample of neuropsychologically examined cocaine users to date (n = 98) and the first study directly comparing the cognitive performance of stimulant-naive controls with both recreational and dependent users. The major finding of the present study is that intensive recreational users showed small but significant cognitive dysfunction, with dysfunction deteriorating further in dependent users. Recreational users displayed the strongest effects in the attention domain, whereas in dependent users working memory was most affected. Correlation and regression analyses revealed negative associations between cognitive performance and cocaine metabolites in the hair, cumulative cocaine dose and duration of cocaine use, suggesting that cognitive impairments might be partially cocaine-induced.

The influence of ADHD and cocaine craving on the cognitive functioning of cocaine users had not systematically been investigated before. We found that symptoms of ADHD and depression as well as craving for cocaine are important modulators of cognitive function in cocaine users, whereas recent cocaine use seemed to be less important. However, cognitive dysfunction is still present in cocaine users without the presence of craving, depression or ADHD symptoms. Finally, we demonstrated that the risk for cognitive impairment increases with early age at onset and ascending cumulative cocaine doses, in particular if estimated lifetime doses of 500 g to 1 kg cocaine are exceeded (Fig. 4).

### Comparison with findings from other studies

The present results indicate impaired attention in both recreational and dependent users, with moderate to strong effect sizes respectively. As attention involves several subprocesses, it should be emphasised that our domain is primarily based on two RVP parameters measuring sustained attention. Our findings replicated previous reports on sustained attention deficits in dependent cocaine users but extended the current knowledge regarding relatively pure recreational users, as

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### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Global cognitive index</th>
<th>Attention</th>
<th>Working memory</th>
<th>Declarative memory</th>
<th>Executive functions</th>
</tr>
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<tbody>
<tr>
<td>Cumulative dose, g: log&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98</td>
<td>-0.50&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.31&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.39&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.43&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.42&lt;sup&gt;***&lt;/sup&gt;</td>
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<tr>
<td>Cumulative dose, g: log, adjusted for age&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98</td>
<td>-0.47&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.34&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.34&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.39&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.37&lt;sup&gt;***&lt;/sup&gt;</td>
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<tr>
<td>Times per week&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98</td>
<td>-0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grams per week log&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Years of use&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>-0.33&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.33&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.20&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.40&lt;sup&gt;***&lt;/sup&gt;</td>
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<tr>
<td>Years of use, adjusted for age&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98</td>
<td>-0.28&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.25&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.22&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.36&lt;sup&gt;***&lt;/sup&gt;</td>
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<tr>
<td>Maximum dose, g/day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98</td>
<td>-0.26&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.23&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.22&lt;sup&gt;**&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Cocaine Craving Questionnaire sum score (0–70)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hair analysis&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cocaine pg/mg</td>
<td>97</td>
<td>-0.22&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>-0.20</td>
<td>-0.18</td>
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<td>Benzoylecgonine pg/mg</td>
<td>97</td>
<td>-0.29&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.17</td>
<td>-0.24&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.28&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.20&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Cocaethylene pg/mg</td>
<td>97</td>
<td>-0.29&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>Norcocaine pg/mg</td>
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<td>-0.28&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.26&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Cocaine&lt;sub&gt;Total&lt;/sub&gt; pg/mg</td>
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<td>-0.24&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.17</td>
<td>-0.22&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.19</td>
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<tr>
<td>Severity of Cocaine Use Index&lt;sup&gt;d&lt;/sup&gt;</td>
<td>98</td>
<td>-0.40&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.21&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.28&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.37&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.42&lt;sup&gt;***&lt;/sup&gt;</td>
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| a. Pearson’s product-moment correlation. | b. Partial correlation corrected for age. | c. Hair samples were voluntary and data are missing for one recreational user. | d. Severity of Cocaine Index use corresponds to the mean of the z-transformed parameters: cumulative dose, grams per week, years of use, maximum dose and hair analysis.

Comparison of participants with a P-level below 10% are shown, and significant correlations are marked: *P<0.05, **P<0.01, ***P<0.001.
Attentional deficits have previously been indicated only in small samples ($n = 13–18$) of polytoxic recreational users.\textsuperscript{23,24,29}

Regarding working memory, the strong effect sizes found for dependent users confirm previous findings, also mostly drawn from much smaller samples.\textsuperscript{17,18} In addition, in accordance with a recent study investigating a small sample of polydrug recreational users ($n = 17$), we found that recreational cocaine use is associated with subtle visuospatial working memory impairment.\textsuperscript{17} Our results are the first to indicate small to moderate verbal working memory deficits in recreational users.

Furthermore, our study confirmed previous findings of broad deficits in verbal\textsuperscript{16,20,21} and visual learning and memory\textsuperscript{46,17,26} in dependent users. The only other report that studied recreational users described similar verbal memory deficits for recreational and dependent users. These inconsistencies are typical for the heterogeneous concept of executive functions reflecting varying task requirements and difficulty levels between studies.\textsuperscript{17} Nevertheless, the existing literature reported executive deficits in dependent users on complex but only scarcely on simple tasks.\textsuperscript{17} As 71% of the participants in the user groups achieved the highest IED stage, a ceiling effect can be assumed. Furthermore, we found strong correlations between the executive domain and several cocaine-use parameters confirming similar relationships that were found in earlier studies on dependent\textsuperscript{19} and recreational users.\textsuperscript{26}

Sustained attention and working memory processes are both associated with increased activity in prefrontal, parietal and cingulate brain regions.\textsuperscript{17} Accordingly, the LSNT involves the lateral prefrontal cortex,\textsuperscript{51} SWM performance is associated with the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex,\textsuperscript{23,53} and the PAL depends on frontal and medial temporal lobe function.\textsuperscript{54} In-depth analysis of the RAVLT revealed that cocaine users primarily display learning and retrieval deficits, whereas recognition was less affected – a pattern specifically reported for prefrontal cortex lesions.\textsuperscript{55} Likewise, prefrontal cortex lesions have been related to impairments in recall consistency.\textsuperscript{56,57}

Finally, glucose metabolism in the dorsolateral prefrontal cortex significantly predicted visual and verbal memory performance in participants who were cocaine addicted and in controls.\textsuperscript{16} Together with previous findings that dependent cocaine users display decreased grey matter volume and glucose metabolism in the orbitofrontal cortex and dorsolateral prefrontal cortex,\textsuperscript{30–14,68–61} the neuropsychological profile therefore suggests that similar but less pronounced alterations in the prefrontal cortex might be present in recreational users.

We investigated potential cofactors frequently associated with cocaine use or commonly addressed as confounding factors for cognition such as ADHD and depressive symptoms.\textsuperscript{23,62} Moreover, craving for food\textsuperscript{45} and nicotine\textsuperscript{46} has been shown to have an impact on cognitive functioning but the specific impact of cocaine craving has not been investigated to date. Here, high craving and depression scores or an ADHD diagnosis further decreased the cognitive performance within the group of recreational users. Additionally, dependent users with clinically relevant ADHD symptoms displayed stronger cognitive deficits ($d = 1.37$) than dependent users without ADHD ($d = 1.04$), whereas neither craving nor depression symptoms had an additional effect in this group. Importantly, cocaine users without clinically relevant ADHD or depression scores and also with low craving scores still displayed significant cognitive deficits, whereas a combination of an ADHD diagnosis and high craving lead to the strongest impairments, similar to our results on early information processing.\textsuperscript{12} Regarding the impact of depression, our findings confirm a previous result reporting no additional effect of dysphoria on cognitive performance in a sample of predominantly dependent cocaine users\textsuperscript{18} but our data additionally indicate a small impact of depression at a recreational level of use.

Attention-deficit hyperactivity disorder is characterised by problems in attentional performance and inhibitory control and patients with ADHD on average perform worse than healthy controls on tests of attention and executive function.\textsuperscript{63} Nevertheless, the influence of ADHD symptoms on the cognition of cocaine users, in which ADHD is highly prevalent, had not been investigated previously. The exact pathogenesis underlying ADHD...
is still unknown, but as abnormalities within catecholamine systems and the prefrontal cortex seem to play a major role in ADHD and cocaine use, it can be assumed that similar pathologies might lead to a mutual aggravation of detrimental effects on cognitive performance.

In contrast to a previous finding, showing that cocaine users with a positive urine toxicology have slightly improved cognitive performance, users with positive cocaine urine tests displayed slightly worse cognitive scores in the present study. As urine toxicologies were performed by immunoassays, which are only presumptively and potentially biased by external factors, positive urine tests do not necessarily prove a violation of the requested 3-day cocaine retention period.

**Study limitations and future research**

The study has some limitations. First, cocaine dependency was diagnosed according to DSM-IV criteria. These criteria depend on introspection and self-report but do not consider features such as duration and amount of cumulative doses. Thus, some participants in the recreational users group might be misclassified as non-dependent. Second, although this is one of the first investigations employing hair analysis in a neurocognitive study of cocaine users, we can only rely on self-reports for all illegal drug use prior to 3–6 months (depending on hair length). This is, however, an inevitable constraint of all studies with illegal drug users. Third, a cross-sectional design cannot determine whether the cognitive deficits found in the cocaine users were pre-existent traits (vulnerability or resilience), drug-induced consequences or both. Hence, to answer this question we need to await the findings of the second part of the ZuCo2St longitudinal study in 2013. Finally, cocaine users participating voluntarily in a study session lasting several hours require a certain level of motivation and cognitive functionality; we assume that the cocaine users in our sample are therefore not the most impaired individuals, and probably even perform relatively well. Thus, the cognitive impairments shown here might partially be underestimated for both recreational and dependent users.

In conclusion, our results confirmed that dependent cocaine use is associated with broad cognitive impairments in the domains attention, working memory, declarative memory and parts of executive functions. In all four domains, recreational users' performance was intermediate between that of controls and dependent users, and they displayed significant deficits, predominantly in the domains attention and working memory. This is in line with our previous work indicating catecholamine dysfunction at a recreational level of use. Furthermore, all cognitive domains displayed correlations with the long-term intake parameters duration and amount of cocaine use and specifically early age at onset was linked to considerable cognitive dysfunction. The neuropsychological profile suggests prefrontal cortex dysfunction as the common denominator of these cognitive impairments, which is in line with previous findings showing alterations to the frontostriatal dopamine system in addicted cocaine users. Additionally, cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairments. Altogether these results indicate gradual impairments in both recreational and dependent cocaine users, and clinically relevant cognitive deficits seem to arise with long-term cocaine use, as best reflected by cumulative cocaine dose.

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**References**


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²Center of Forensic Hairanalytics, Institute of Forensic Medicine, University of Zurich, Switzerland
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⁴Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, USA

Method DS1: Recruitment and selection
Method DS2: Urine and hair toxicologies
Method DS3: Construction of cognitive domain scores

Table DS1: Pattern and amount of drug use
Table DS2: Neurocognitive global and domain z-scores and scores of neuropsychological tests
Table DS3: Intercorrelation cocaine use parameters in cocaine users
Table DS4: Correlations between cognitive test scores and cocaine use parameters in cocaine users
Table DS5: Predictors of the global cognitive index in cocaine users

Figure DS1: GCI score scatterplot
Figure DS2: RAVLT performance
Figure DS3: IED performance
Figure DS4: Impact of depression status
Figure DS5: Impact of current cocaine effects tested by urine status
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 Prominance 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. In order to diversify this domain we added the RAVLT test parameter trial 1, a supraspan measure with a large attentional component.

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

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

**Executive Functions:** Executive functions are commonly separated into the three components shifting, updating, and inhibition. Since inhibition in CU is currently investigated in another study from our laboratory, 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. 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, and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions and related with measures of executive functions.

Additional references

<table>
<thead>
<tr>
<th></th>
<th>Stimulant-naive controls (n=68)</th>
<th>Recreational cocaine users (n=68)</th>
<th>Dependent cocaine users (n=30)</th>
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<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
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</tr>
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<td>Grams per week ā</td>
<td>116.8 (122.6)</td>
<td>167.8 (117.5)</td>
<td>188.5 (260.6)</td>
</tr>
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<td>Years of use</td>
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<td>11.2 (5.1)</td>
<td>13.5 (9.5)</td>
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<td></td>
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<td>11.7 (8.8)</td>
<td>15.7 (13.5)</td>
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<td>9.6 (6.4)</td>
<td>14.2 (9.3)</td>
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<tr>
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<td></td>
<td></td>
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<td>Times per week ā</td>
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<td>Grams per week ā</td>
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<td>1.1 (1.4)</td>
<td>7.9 (15.8)</td>
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<td>9.4 (6.5)</td>
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<td>519.7 (751.2)</td>
<td>5500.9 (9635.2)</td>
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<td>27.5 (37.6)</td>
<td>21.0 (33.6)</td>
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<td>Hair analysis Cocaine pg/mg į</td>
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<td>2739 (4628)</td>
<td>22164 (32609)</td>
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<td>Hair analysis Benzoylenponine pg/mg į</td>
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<td>546 (919)</td>
<td>5048 (7711)</td>
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<tr>
<td>Hair analysis Cocaethylene pg/mg į</td>
<td>-</td>
<td>276 (316.)</td>
<td>2006 (3656)</td>
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<tr>
<td>Hair analysis Norcocaine pg/mg į</td>
<td>-</td>
<td>62 (101)</td>
<td>586 (758)</td>
</tr>
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<td>Hair analysis Cocaine total pg/mg į</td>
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<td>3347 (5580)</td>
<td>27798 (40226)</td>
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<td>Urine toxicology (neg/pos) į</td>
<td>68 / 0</td>
<td>57 / 10</td>
<td>18 / 12</td>
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<td><strong>Cannabis</strong></td>
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<td>Grams per week ā</td>
<td>0.5 (1.0)</td>
<td>0.9 (2.1)</td>
<td>1.2 (3.7)</td>
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<td>Years of use</td>
<td>4.7 (6.5)</td>
<td>7.7 (6.0)</td>
<td>10.5 (9.9)</td>
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<td>Cumulative dose (grams)</td>
<td>358.3 (846.2)</td>
<td>1042.8 (1780.0)</td>
<td>3550.3 (5959.0)</td>
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<td>Last consumption (days) į</td>
<td>36.2 (50.1); n=33</td>
<td>22.1 (32.3); n=44</td>
<td>25.7 (32.8); n=20</td>
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<td>Urine toxicology (neg/pos) į</td>
<td>58 / 10</td>
<td>55 / 12</td>
<td>20 / 10</td>
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<td><strong>Amphetamine</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Grams per week ā</td>
<td>0.0 (0.0)</td>
<td>0.1 (0.2)</td>
<td>0.0 (0.2)</td>
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<tr>
<td>Years of use</td>
<td>0.0 (0.1)</td>
<td>1.6 (3.0)</td>
<td>1.5 (3.2)</td>
</tr>
<tr>
<td>Cumulative dose (grams)</td>
<td>0.2 (1.4)</td>
<td>21.2 (56.8)</td>
<td>22.3 (62.8)</td>
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<tr>
<td>Last consumption (days) į</td>
<td>121.6 (0.0); n=1</td>
<td>61.8 (51.3); n=25</td>
<td>78.4 (75.4); n=6</td>
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<tr>
<td>Hair analysis Amphetamine pg/mg į</td>
<td>1 (7)</td>
<td>76 (257)</td>
<td>60 (169)</td>
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**MDMA**

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<th></th>
<th>a</th>
<th>b</th>
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<tr>
<td>Tablets per week</td>
<td>-</td>
<td>0.1 (0.3)</td>
</tr>
<tr>
<td>Years of use</td>
<td>0.3 (1.7)</td>
<td>2.5 (3.8)</td>
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<tr>
<td>Cumulative dose (tablets)</td>
<td>0.9 (2.9)</td>
<td>35.9 (90.5)</td>
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<tr>
<td>Last consumption (days)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>75.1 (84.8); n=20</td>
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<tr>
<td>Hair analysis MDMA pg/mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (16)</td>
<td>545 (1598)</td>
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<td></td>
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<td>255 (653)</td>
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**GHB**

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<table>
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<tr>
<td>Cumulative dose (pipettes)</td>
<td>0.0 (0.0)</td>
<td>1.8 (9.5)</td>
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<td></td>
<td></td>
<td>1.3 (2.9)</td>
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**Hallucinogens**

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<tr>
<td>Cumulative dose (times)</td>
<td>0.9 (2.2)</td>
<td>6.0 (14.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.9 (11.8)</td>
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</table>

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

-<sup>a</sup>Average use during the last 6 months.

-<sup>b</sup>Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.

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

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

-<sup>e</sup>Cocaine<sub>total</sub> (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs.<sup>48</sup>
Table DS2 Neurocognitive global and domain z-scores and scores of neuropsychological tests

<table>
<thead>
<tr>
<th>Measure</th>
<th>n*</th>
<th>Stimulant-naive controls</th>
<th>Recreational cocaine users</th>
<th>Dependent cocaine users</th>
<th>F</th>
<th>df, df corr</th>
<th>p</th>
<th>Controls vs. RCU</th>
<th>Controls vs. DCU</th>
<th>RCU vs. DCU</th>
<th>Controls vs. RCU</th>
<th>Controls vs. DCU</th>
<th>Cohen's d Controls vs. RCU</th>
<th>Cohen's d Controls vs. DCU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cognitive Index</td>
<td>68/68/30</td>
<td>-0.02 (0.06)</td>
<td>-0.35 (0.06)</td>
<td>-0.67 (0.09)</td>
<td>19.345</td>
<td>2, 161</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.01</td>
<td>0.53</td>
<td>1.04</td>
<td>0.52</td>
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<tr>
<td>Neurocognitive domain scores</td>
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<td></td>
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<tr>
<td>Attention</td>
<td>68/68/30</td>
<td>-0.03 (0.10)</td>
<td>-0.41 (0.10)</td>
<td>-0.68 (0.15)</td>
<td>7.579</td>
<td>2, 161</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.02</td>
<td>.01</td>
<td>.38</td>
<td>0.44</td>
<td>0.74</td>
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<td>Working memory</td>
<td>68/68/30</td>
<td>-0.03 (0.08)</td>
<td>-0.36 (0.08)</td>
<td>-0.81 (0.12)</td>
<td>16.312</td>
<td>2, 161</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<td>.005</td>
<td>.43</td>
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<td>Declarative memory</td>
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<td>-0.02 (0.09)</td>
<td>-0.4 (0.09)</td>
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<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.01</td>
<td>.01</td>
<td>.34</td>
<td>0.43</td>
<td>0.73</td>
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<td>Executive functions</td>
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<td>-0.5 (0.09)</td>
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<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.03</td>
<td>.02</td>
<td>.39</td>
<td>0.92</td>
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<td>Neuropsychological test scores</td>
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<tr>
<td>Attention</td>
<td>67/68/30</td>
<td>0.917 (0.0)</td>
<td>0.899 (0.0)</td>
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<td>6.254</td>
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<td>.04</td>
<td>.004</td>
<td>.43</td>
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<td>0.72</td>
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<td>RVP Total hits</td>
<td>67/68/30</td>
<td>18.3 (0.5)</td>
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<td>15.3 (0.8)</td>
<td>5.561</td>
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<td>.05</td>
<td>.008</td>
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<td>0.67</td>
<td>0.27</td>
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<td>RAVLT Supraspan trial 1</td>
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<td>8.9 (0.2)</td>
<td>8.4 (0.2)</td>
<td>8.0 (0.4)</td>
<td>2.407</td>
<td>2, 161</td>
<td>.09</td>
<td>.31</td>
<td>.13</td>
<td>.81</td>
<td>.25</td>
<td>0.41</td>
<td>0.17</td>
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<tr>
<td>Working memory</td>
<td>68/68/30</td>
<td>15.6 (0.3)</td>
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<td>13.2 (0.5)</td>
<td>8.320</td>
<td>2, 160</td>
<td>&lt;.001</td>
<td>.07</td>
<td>&lt;.001</td>
<td>.07</td>
<td>.34</td>
<td>0.78</td>
<td>0.44</td>
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<tr>
<td>SWM Total errors</td>
<td>68/68/30</td>
<td>20.1 (1.9)</td>
<td>23.3 (1.9)</td>
<td>34.5 (2.9)</td>
<td>8.727</td>
<td>2, 160</td>
<td>&lt;.001</td>
<td>.53</td>
<td>&lt;.001</td>
<td>.05</td>
<td>.19</td>
<td>0.84</td>
<td>0.65</td>
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<tr>
<td>PAL First trial memory score</td>
<td>68/68/30</td>
<td>15.6 (0.4)</td>
<td>14.1 (0.4)</td>
<td>13.4 (0.6)</td>
<td>6.575</td>
<td>2, 160</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.02</td>
<td>.02</td>
<td>.05</td>
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<tr>
<td>Declarative memory</td>
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</tr>
<tr>
<td>RAVLT Learning performance (Σ trials 1-5)</td>
<td>68/68/30</td>
<td>62.0 (0.9)</td>
<td>58.0 (0.9)</td>
<td>54.9 (1.4)</td>
<td>9.612</td>
<td>2, 161</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.09</td>
<td>.09</td>
<td>.45</td>
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<td>RAVLT Adjusted recognition performance p(A)</td>
<td>68/68/30</td>
<td>0.873 (0.0)</td>
<td>0.858 (0.0)</td>
<td>0.823 (0.0)</td>
<td>2.076</td>
<td>2, 161</td>
<td>.13</td>
<td>.83</td>
<td>.12</td>
<td>.39</td>
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<td>RAVLT Delayed recall trial 7</td>
<td>68/68/30</td>
<td>13.1 (0.3)</td>
<td>11.9 (0.3)</td>
<td>11.4 (0.5)</td>
<td>6.046</td>
<td>2, 161</td>
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<td>.02</td>
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<tr>
<td>PAL Total errors adjusted</td>
<td>68/68/30</td>
<td>10.6 (1.4)</td>
<td>15.1 (1.4)</td>
<td>16.9 (2.2)</td>
<td>3.852</td>
<td>2, 160</td>
<td>.02</td>
<td>.08</td>
<td>.05</td>
<td>.88</td>
<td>.35</td>
<td>0.49</td>
<td>0.14</td>
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<tr>
<td>PAL Total trials adjusted</td>
<td>68/68/30</td>
<td>8.5 (0.3)</td>
<td>9.5 (0.3)</td>
<td>10.1 (0.5)</td>
<td>4.231</td>
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<td>.02</td>
<td>.09</td>
<td>.03</td>
<td>.72</td>
<td>.34</td>
<td>0.53</td>
<td>0.19</td>
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<tr>
<td>Executive functions</td>
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<td></td>
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<tr>
<td>IED Total errors adjusted</td>
<td>68/68/30</td>
<td>30.3 (4.1)</td>
<td>31.3 (4.1)</td>
<td>32.3 (6.3)</td>
<td>.039</td>
<td>2, 161</td>
<td>.96</td>
<td>1.00</td>
<td>.99</td>
<td>.03</td>
<td>.06</td>
<td>0.03</td>
<td>0.03</td>
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<tr>
<td>IED Total trials adjusted</td>
<td>68/68/30</td>
<td>104.1 (7.2)</td>
<td>107.3 (7.3)</td>
<td>108.5 (11.2)</td>
<td>.075</td>
<td>2, 161</td>
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<td>.98</td>
<td>.98</td>
<td>.05</td>
<td>.07</td>
<td>0.02</td>
<td>0.02</td>
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<tr>
<td>SWM Strategy score</td>
<td>68/67/30</td>
<td>32.7 (0.6)</td>
<td>33.4 (0.6)</td>
<td>34.9 (0.9)</td>
<td>1.867</td>
<td>2, 160</td>
<td>.15</td>
<td>.84</td>
<td>.15</td>
<td>.43</td>
<td>.12</td>
<td>0.42</td>
<td>0.30</td>
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<tr>
<td>RAVLT Recall consistency in %</td>
<td>68/68/30</td>
<td>92.3 (1.1)</td>
<td>88.1 (1.1)</td>
<td>83.3 (1.6)</td>
<td>11.004</td>
<td>2, 161</td>
<td>&lt;.001</td>
<td>.02</td>
<td>&lt;.001</td>
<td>.05</td>
<td>.43</td>
<td>0.92</td>
<td>0.49</td>
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</table>

Means and standard errors. ANCOVA (all groups, corrected for age and verbal IQ). Significant P are shown in bold. GC1 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 \( p_{\text{post-hoc}} = .08 \)).

*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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Attention</th>
<th>Working memory</th>
<th>Declarative memory</th>
<th>Executive functions</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>RVP A'</td>
<td>RVP Hits</td>
<td>RAVLT Trial 1</td>
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</tr>
<tr>
<td>Cumulative dose (grams) log*</td>
<td>-.23</td>
<td>-.22</td>
<td>**.38</td>
<td></td>
</tr>
<tr>
<td>Cumulative dose (grams) log, adj.</td>
<td>**.27</td>
<td>**.26</td>
<td>**.35</td>
<td></td>
</tr>
<tr>
<td>Times per week a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grams per week log b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of use a</td>
<td>-.25</td>
<td>-.21</td>
<td>**.32</td>
<td>**.22</td>
</tr>
<tr>
<td>Years of use, adj. age b</td>
<td>-.19</td>
<td>.23</td>
<td>-.25</td>
<td>-.25</td>
</tr>
<tr>
<td>Maximum dose (grams/day) a</td>
<td>-.21</td>
<td>-.21</td>
<td>-.20</td>
<td>-.20</td>
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<tr>
<td>CCQ sum score (0-70) a</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair analysis Cocaine pg/mg a,c</td>
<td>-.18</td>
<td>.19</td>
<td>-.24</td>
<td>-.19</td>
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<tr>
<td>Hair analysis Benzoylecgonine</td>
<td>-.24</td>
<td>-.23</td>
<td>-.23</td>
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<td>Hair analysis Cocaethylene pg/mg a,c</td>
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<td>**.27</td>
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<td>Hair analysis Norcocaine pg/mg a,c</td>
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<td>**.29</td>
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<td>Hair analysis Cocaine total pg/mg a,c,e</td>
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<td>-.26</td>
<td>-.20</td>
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<tr>
<td>Severity of cocaine use Index a,f</td>
<td>**.31</td>
<td>**.26</td>
<td>**.44</td>
<td>**.25</td>
</tr>
</tbody>
</table>

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.

- Pearson’s product-moment correlation.
- Partial Correlation corrected for age.
- Hair samples were voluntary and are deficient for 1 recreational cocaine user.
- Two cocaine users were missing either SWM or PAL parameters due to technical problems.
- **Cocaine_{total} = Cocaine + Benzoylecgonine + Norcocaine.**
- **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

<table>
<thead>
<tr>
<th>Model 1: Cumulative dose</th>
<th>Model 2: Years of use</th>
<th>Model 3: Weekly use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B</strong></td>
<td><strong>SE</strong></td>
<td><strong>β</strong></td>
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<tr>
<td>Constant</td>
<td>.26</td>
<td>.33</td>
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<tr>
<td>Age</td>
<td>-.01</td>
<td>.01</td>
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<tr>
<td>Depression</td>
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<td>ADHD</td>
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<td>.01</td>
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<tr>
<td>Craving for cocaine</td>
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<td>.01</td>
</tr>
<tr>
<td>Urine sample (neg/pos)</td>
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<td>.14</td>
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<tr>
<td>Cocaine cumulative dose (grams)</td>
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<td>.00</td>
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<tr>
<td>MDMA cumulative dose (tablets)</td>
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<tr>
<td>Amphetamine cumulative dose (grams)</td>
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<td>.00</td>
</tr>
<tr>
<td>Cannabis cumulative dose (grams)</td>
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<td>Cocaine years of use</td>
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<td>.02</td>
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<tr>
<td>MDMA years of use</td>
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<td>.01</td>
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<tr>
<td>Amphetamine years of use</td>
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<td>.02</td>
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<tr>
<td>Cannabis years of use</td>
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<tr>
<td>Alcohol years of use</td>
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<td>Nicotine years of use</td>
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<td>Cocaine grams per week</td>
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<td>MDMA tablets per week</td>
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<tr>
<td>Amphetamines grams per week</td>
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<td>.02</td>
</tr>
<tr>
<td>Alcohol grams per week</td>
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<td>.00</td>
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<tr>
<td>Cigarettes per week</td>
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<td>.00</td>
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</tbody>
</table>

\(R^2\) .22 \(F\) **2.80 \(p\) .006

\(F\) 1.83 \(p\) .06

\(F\) 3.20 \(p\) .001

\(F\) 3.20 \(p\) .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.
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.
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.
Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset

Matthias Vonmoos, Lea M. Hulka, Katrin H. Preller, Daniela Jenni, Markus R. Baumgartner, Rudolf Stohler, Karen I. Bolla and Boris B. Quednow

BJP 2013, 203:35-43.
Access the most recent version at DOI: 10.1192/bjp.bp.112.118091

Supplementary material can be found at: http://bjp.rcpsych.org/content/suppl/2013/05/20/bjp.bp.112.118091.DC1.html

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