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Research report

Sensitivity to gains during risky decision-making differentiates chronic cocaine users from stimulant-naïve controls

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ABSTRACT

Background: Chronic cocaine use has been consistently associated with decision-making impairments that contribute to the development and maintenance of drug-taking. However, the underlying cognitive processes of risk-seeking behaviours observed in chronic cocaine users (CU) have so far remained unclear. Here we therefore tested whether CU differ from stimulant-naïve controls in their sensitivity to gain, loss, and probability of loss information when making decisions under risk.

Method: A sample of 96 participants (56 CU and 40 controls) performed the no-feedback version of the Columbia Card Task, designed to assess risk-taking in relation to gain, loss, and probability of loss information. Additionally, cognitive performance and impulsivity were determined. Current and recent substance use was objectively assessed by toxicological urine and hair analysis.

Results: Compared to controls, CU showed increased risk-seeking in unfavourable decision scenarios in which the loss probability was high and the returns were low, and a tendency for increased risk aversion in more favourable decision scenarios. In comparison to controls, CU were less sensitive to *gain*, but similarly sensitive to *loss* and *probability of loss* information. Further analysis revealed that individual differences in sensitivity to *loss* and *probability of loss* information were related to cognitive performance and impulsivity.

Conclusion: Reduced sensitivity to *gains* in people with CU may contribute to their propensity for making risky decisions. While these alterations in *gain* sensitivity might directly relate to cocaine use per se, the individual psychopathological profile of CU might moderate sensitivity to *loss* information.

1. Background

Value-based decision-making facilitates goal-directed behaviour, which is essential for survival. It relates the net returns (i.e., the gains minus the losses) to the risks (e.g., the uncertainty of returns or probability of a loss) of different options with the aim of selecting the option with the highest subjective value [1–4]. Value-based decision processes can be affected by the degree of uncertainty associated with the decision [5], development stage [5], social context [6], and several psychiatric disorders [7]. Specifically, decision-making impairments constitute one of the main behavioural characteristics of substance-related disorders, and contribute both to the impulsive initiation of substance use and to the compulsive maintenance of the addictive behaviour [8]. Such deficits seem to be even more severe when substances with strong addictive potentials are involved [9,10], such as cocaine [11,12].

Despite the negative consequences of chronically using cocaine, it remains one of the most commonly used illicit substances [13,14]. In addition to the immediate risk of overdose and intoxication, cocaine use represents a substantial burden for the individual and their families, as well as for society, because of its associations with cardiovascular [15], neurological [10,16–18], and psychiatric [19] disorders, along with with cognitive deficits [20,21]. The negative consequences of cocaine use include decreases in quality of life and social functioning [3], in addition to increases in high-risk behaviours and drug usage [11,22]. From a clinical perspective, chronic cocaine use is often accompanied by increased forgoing of occupational or recreational activities and by

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an increase in cocaine-seeking behaviours [23], which, from a decision-making viewpoint, suggests changes in the sensitivity of value-based decisions to the risks and returns of different courses of action.

Previous research [23,24] suggests that chronic cocaine users (CU) are less sensitive to gains (i.e., the magnitude of positive outcomes) and losses (i.e., the magnitude of negative outcomes) in everyday situations [25,26]. In particular, CU have been proposed to suffer from a generalised impairment in value representation, reflected in blunted neural responses to non-substance-related (social and non-social) rewards, specifically in value-coding regions such as ventromedial prefrontal cortex [3,27,28]. Based on these findings, we hypothesized that the deficits of chronic CU in risky decision-making would partially arise from alterations in return sensitivity.

Moreover, chronic cocaine use is associated with changes in brain networks involved in executive functioning and risk-taking, as indicated by reduced cortical thickness in the lateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex [20,29,30]. Such alterations may partially explain why CU are more likely to make maladaptive decisions in situations requiring implicit learning about risks, and why they prefer options with high gain, but high risk [31–33]. Thus, it has also been hypothesized that CU may underestimate the risk of being subject to adverse consequences over an extended period, resulting in long-term losses; a phenomenon previously described as "myopia for the future" [34,35]. This tendency to chase short-term reward, potentially at the expense of developing rules that maximize reward over the long term, may be a contributing factor to addiction disorders in general, as it has also been observed in opioid users [36].

Importantly, although the literature suggests that CU may show impaired weighing or estimation of risks and returns in value-based decisions, thus far no study has investigated whether CU show decreased sensitivity specifically to information about gain magnitude, loss magnitude, and/or the probability of loss (i.e., one form of risk). Moreover, it has remained unclear whether such alterations can explain their risk-taking behaviour in decisions with varying expected value. Here, we used the no-feedback ("cold") version of the CCT [37] to investigate whether CU differ from stimulant-naïve controls in the sensitivity to *gain, loss,* and *probability of loss* information when making decisions under risk. The no-feedback CCT version was used because it is designed to trigger deliberative processes, leading participants to base their choices mostly on reasoning instead of affective-emotional processes [38–40]. Based on the blunted neural responses to non-drug rewards observed in CU [27], we hypothesized that CU would be less sensitive to *gain* information compared to the control group.

In addition, we also aimed to investigate the effects of demographic, cognitive, psychopathological, and substance use severity variables on the sensitivity to *gain*, *loss*, and *probability of loss* information. Previous studies indicate that self-reported impulsivity and gambling behaviour are strongly state-dependent in CU [41], and that the often comorbid symptoms of attention deficit hyperactivity disorder (ADHD) aggravate the effects of cocaine use on cognitive impairment [42,43]. We therefore hypothesized that both trait impulsivity and ADHD symptoms would reduce the sensitivity of CU to *gain*, *loss*, and *probability of loss* information. Investigating possible effects of ADHD on information sensitivity is important because reward processing deficits in ADHD are still present during adulthood and have been related to changes in prefrontal activity during decision-making [44]. Finally, using both self-reports and hair samples allowed us to explore whether subjective and objective measures of cocaine use severity relate to the sensitivity to *gain*, *loss,* and *probability of loss* in the CCT. Overall, we investigate how chronic cocaine use, as well as demographic, clinical, and cognitive factors, affect sensitivity to *gain, loss,* and *probability of loss* information in value-based decisions. Our findings provide a basis for allowing a better understanding of the proclivity of CU for risky behaviours. This knowledge may provide new leads towards improving the efficiency and the efficacy of preventive and therapeutic strategies.

2. Methods

2.1. Participants

The data were collected in the context of the "*Stress and Social Cognition Study*" (SCPP) at the Psychiatric Hospital of the University of Zurich. In this study, a total sample of 123 participants (69 chronic CU and 54 stimulant-naïve controls) was assessed (for detailed information on recruitment procedures, please see Supplementary Material). CU were included in the study if cocaine was the primary illegal drug they used, if a lifetime cumulative consumption of at least 100 g of cocaine was estimated by self-report and if their current abstinence duration was < 6 months. Exclusion criteria comprised a family history of genetically mediated psychiatric disorders ($h^2 > 0.5$, e.g., autism, schizophrenia, and bipolar disorder); any severe neurological disorder or brain injury; a current diagnosis of infectious diseases or severe somatic disorder; a history of autoimmune, endocrine, and rheumatoid arthritis; intake of medication with potential action at the central nervous system during the last seven days; participation in a large previous study from our lab, the *Zurich Cocaine Cognition Study* [42,45]; and for women being pregnant or breastfeeding. Controls were excluded if they had DSM-IV-R Axis I adult psychiatric disorders, or recurrent illegal substance use (> 15 occasions lifetime, with the exception of cannabis for reasons of participant matching). We excluded CU with regular use of illegal substances other than cocaine, such as heroin or other opioids (with the exception of cannabis use), a polysubstance use pattern according to DSM-IV-R, or a DSM-IV axis I adult psychiatric disorder diagnosis (e.g., schizophrenia, bipolar disorder, current major depressive episode, eating disorders, current anxiety disorder) except for cocaine, cannabis, and alcohol abuse/dependence, previous depressive episodes, and ADHD.

After applying the exclusion criteria, a total sample of 99 participants (59 chronic CU and 40 stimulant-naïve controls) was considered. However, two participants could not perform the CCT for technical reasons and one participant was excluded because the CCT data revealed random responses, suggesting that they did not understand the task or were not sufficiently motivated to perform. Therefore, 96 participants (56 chronic CU and 40 stimulant-naïve controls) matched for sex, age, smoking status, and weekly alcohol use (average number of times people drink per week) were analysed in this study. The study was approved by the *Cantonal Ethics Committee of Zurich* (BASEC ID 2016-00278) and preregistered with an *International Standard Randomised Controlled Trial Number* (ISRCTN-10690316). All participants provided written informed consent in accordance with the Declaration of Helsinki and were compensated for their participation.

2.2. Clinical and substance-related assessment

The psychopathological assessment was carried out with the Structured Clinical Interview I (SCID-I) according to DSM-IV-R [46]. ADHD symptoms were collected with the ADHD self-rating scale (ADHD-SR) [47]. Trait impulsivity was measured with the Barratt Impulsiveness Scale (BIS) [48]. Self-reported drug use was assessed with the structured and standardized Interview for Psychotropic Drug Consumption [49].

2.3. Urine and hair toxicological analysis

Urine analyses using a semi-quantitative enzyme multiplied immunoassay method targeted the following substances: amphetamines, barbiturates, benzodiazepines, cocaine, methadone, morphine-related opiates, and tetrahydrocannabinol. In addition, quantitative analysis of hair samples using liquid chromatography tandem mass spectrometry (LC–MS/MS) was used to investigate substance consumption over the last 4 months as represented in the proximal 4 cm-segment of the hair samples. In total 88 compounds were assessed. For a complete

description of all compounds assessed, please see Supplementary Material.

2.4. General cognitive assessment

The German vocabulary test *Mehrfachwahl-Wortschatz-Intelligenztest* (MWT-B) was applied to estimate premorbid verbal intelligence [50]. General cognitive performance was assessed with three tasks from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB, http://www.cantab.com). These tasks included the *Spatial Working Memory* task (SWM) (to assess working memory and executive functioning), the *Match to Sample Visual Search* task (MTS) (a visual matching test involving a trade-off of speed and accuracy), and the *Rapid Visual Information Processing* task (RVP) (to assess sustained attention capacity). For detailed information about these tasks, please see the Supplementary Material.

2.5. Columbia card task

Due to our primary focus on understanding how the sensitivity to *gain*, *loss*, and *probability of loss* information can explain people's behaviour in different decision scenarios, participants performed the no-feedback condition of the CCT (see Supplementary Material). In the CCT, participants view a deck with 32 facedown cards and three explicit information cues (i.e., scenario properties). These properties include the number of losing cards hidden in the deck (i.e., *probability of loss*: 1 or 3), the amount associated with each losing card (i.e., *loss*: -250 or -750 points) and the amount associated with each winning card (i.e., *gain*: 10 or 30 points). The different combinations of *gain*, *loss,* and *probability of loss* form eight possible decision scenarios that can be sorted from the most favourable to the least favourable, according to the expected value.

2.5.1. Risk-attitude

*In every round, participants decided how many cards the computer would randomly select and turn over, knowing that the round would end immediately if the computer selected one of the losing cards. The primary outcome of the CCT is the average number of cards chosen, which can be interpreted as a general proxy of risk-seeking behaviour, with a higher number of cards corresponding to greater risk-proneness [37,51–53]. We also analysed the risk-seeking behaviour separately for each decision scenario in order to assess risk-taking in a more fine-grained fashion.

2.5.2. Sensitivity to gain, loss, and probability of loss

Concerning sensitivity to the scenario properties (i.e., *gain*, *loss,* and *probability of loss*), a normative analysis of the CCT suggests that participants should choose the number of cards so as to maximize subjective value [37]. An optimal strategy takes into account *gain*, *loss,* and *probability of loss*. Data can be analysed at both the group and the individual level [37].

At the group level we performed a linear mixed effect model (LMM) [54] including group (CU or stimulant-naïve controls), *gain* (10, 30), *loss* (-250, -750), and *probability of loss* (1, 3 loss cards) as fixed-effects. This model allowed us to extract regression coefficients for both group and scenario properties. The LMM accounted for the random-effects of each participant slope and intercept associated with the different scenario properties [54]. Because the regression coefficients represent the slope of the function (i.e., the weighting that *gain*, *loss,* and *probability of loss* received in determining the number of cards), we used these values as measures for the sensitivity to *gain, loss,* and *probability of loss*.

At the individual level, LMM analyses were performed for each participant separately to investigate how the sensitivity to *gain*, *loss*, and *probability of loss* influenced his/her risk-taking. Given that the 24 rounds of the task were randomly presented among three blocks, the blocks and the rounds were included as random effects in the model. The number of cards chosen was mean centred according to the control group. Similar to the group analysis, three coefficients were extracted for each participant, capturing how the participant weighted *gain*, *loss,* and *probability of loss*.

2.6. Statistical analysis

2.6.1. Demographic characteristics and substance use

All statistical analyses were performed with the open source statistical software R [55]. Regarding demographic, clinical, cognitive, and substance-related variables, frequency data were analysed by means of Pearson's chi-squared tests. Group data were compared by Student's t-tests or, when data were non-normally distributed, Wilcoxon rank sum tests (i.e., Shapiro–Wilk $W < .001$, and skew and kurtosis divided by 2 standard errors < 2).

2.6.2. Overall and scenario-specific risk-attitude

To assess potential group differences in overall risk-attitude, independent of the decision scenario, we used several LMM analyses including different random intercepts and slopes and tested them with the model fitting function "anova" [56]. The best model included a random slope and intercept for each participant and scenario properties (i.e., *gain*, *loss*, and *probability of loss*). Then, using a similar strategy of testing different random intercepts and slopes with the same model fitting function, the effect of group on the average number of cards chosen at each decision scenario was investigated including a random intercept for participant only.

2.6.3. Sensitivity to gain, loss, and probability of loss

Secondly, to investigate group differences in the sensitivity to scenario properties, we first performed a LMM analysis including group (CU or stimulant-naïve controls) and the expected value of each decision scenario as fixed-effects, and a random slope and intercept for each participant and the three scenario properties (*gain*, *loss*, and *probability of loss*). Then, as mentioned, a LMM analysis including group, *gain*, *loss*, and *probability of loss* as fixed-effects and a random slope and intercept for each participant and the three scenario properties was performed. To explore within-group variance explained by the use of information, the same model was also analysed for both groups separately. Effect sizes were calculated ($0 \leq |r| < .10$ small effect size; $0.10 \leq |r| < .30$ medium effect size; $.30 \leq |r| < .50$ large effect size), which have been suggested as versatile measures of the strength of an experimental effect with an intuitive interpretation – absolute values of "r" are constrained to lie between 0 (no effect) and 1 (maximal effect) [57].

2.6.4. Impact of demographic, cognitive, and clinical variables on gain, loss and probability of loss sensitivities

In a third step, we examined whether the reported demographic, cognitive and clinical group differences contributed to sensitivity to *gain, loss,* and *probability of loss* for each participant individually. To do so, we performed hierarchical linear models including years of education, verbal IQ, SWM Strategy score, SWM Total error score, meta-efficiency index, trait impulsivity, and ADHD symptoms. To test for multicollinearity between predictors we performed a set of Spearman's rank correlations over all participants. Based on the cut-offs suggested by Cohen [57], predictors with large effect size correlations were not included together in the same model. Then, to identify the subset of variables with the highest explanatory power we incorporated the predictors into the model 'one by one'. As before, models were compared using the model fitting function "anova" [56]. Subsequently, linear regressions were performed within both groups to relate individual sensitivity to *gain*, *loss,* and *probability of loss* to the average number of cards chosen in each decision scenario, controlling for the predictors with which a significant effect was found in the hierarchical linear models.

Table 1
Demographic, cognitive and clinical data.

	Controls (n = 40)	Cocaine Users (n = 56)	Test Statistics	df	*p*
Demographics					
Age, y	29.3 (7.1)	32.3 (7.9)	t = -1.9	89.0	.060
Sex, f/m	17 / 23	17 / 39	x^2 = 1.5	1	.220
Verbal IQ [a]	100.6 (6.5)	95.4 (5.8)	t = 3.9	77.7	**.000**
School education, y	10.2 (1.4)	9.4 (.89)	W = 1415	–	**.009**
Cognition					
SWM - Between errors	15.9 (13.7)	26.0 (17.3)	W = 723	–	**.003**
SWM - Within errors	.85 (2.3)	1.1 (2.1)	W = 952	–	.151
SWM - Total errors	16.3 (14.1)	26.4 (17.4)	W = 729	–	**.003**
SWM - Strategy score	29.0 (6.4)	32.5 (5.8)	t = -2.7	78.9	**.007**
RVP - Response A'	.92 (.06)	.88 (.05)	W = 1638	–	**.000**
RVP - Response bias B'	.89 (.32)	.93 (.10)	W = 1121	–	.655
RVP - Mean latency, ms.	405.9 (196.1)	425.4 (91.4)	t = -.94	76.1	.350
RVP - Total false alarms	1.2 (1.4)	2.3 (5.2)	W = 835	–	**.028**
RVP - Impulsivity Index	.00 (.93)	.66 (3.5)	W = 1005	–	.392
RVP - Efficiency Index	.00 (1.7)	−1.0 (4.1)	W = 1477	–	**.007**
MTS - Correct, %	96.1 (5.0)	93.8 (6.8)	W = 1306	–	.097
MTS - Correct reaction time, ms.	2568 (623.9)	2662 (737.3)	t = -.67	90.8	.504
MTS - Time change 2–8, ms.	146.0 (303.5)	139.2 (434.2)	W = 1193	–	.480
MTS - Impulsivity Index	.00 (1.5)	−.29 (3.1)	t = .61	84.3	.543
MTS - Efficiency Index	.00 (1.3)	−1.1 (2.9)	t = 2.55	80.2	**.012**
BIS subscales					
Total Score	64.2 11.1	70.0 12.0	t = -2.4	87.8	**.016**
Attention Impulsiveness	14.6 (3.8)	16.9 (4.4)	t = -2.7	90.6	**.007**
Motor Impulsiveness	23.4 (5.1)	24.4 (5.2)	t = -.94	85.0	.346
Non-planning Impulsiveness	26.1 (4.8)	28.6 (4.9)	t = -2.4	84.8	**.014**
Clinical					
ADHD, y/n [b]	7/33	43/13	x^2 = .46	1	.496
ADHD sum score	10.5 (9.7)	14.6 (10.1)	W = 827	–	**.029**

Note. Table reports counts or means with standard deviations in brackets. Significant group differences are shown in bold. t = Student t-test; x^2 = Pearson chi-square; W = Wilcoxon rank sum test. (a) Verbal intelligence quotient estimated by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B); (b) Cut-off DSM-IV criteria as assessed by the ADHD-SR questionnaire. RVP, Rapid Visual Information Processing task; SWM, Spatial Working Memory task; MTS, Match to Sample Visual Search task. BIS, Barratt Impulsiveness Scale. ADHD, Attention deficit hyperactivity disorder.

2.6.5. Impact of cocaine use severity on gain, loss and probability of loss sensitivities

Linear regression analyses were performed within CU to examine how cocaine-related variables (cocaine hair metabolites, cocaine abstinence period, cocaine years of use, and cocaine estimated cumulative lifetime dose) related to *gain, loss,* and *probability of loss* sensitivities. These analyses were run with and without controlling for the predictors with which a significant effect was found in the hierarchical linear models. Due to the highly right-skewed distribution and the resulting deviation from the normal distribution we ln10-transformed hair metabolite measures.

3. Results

3.1. Demographic characteristics and substance use

As intended by our matching procedure, the groups did not differ in age or sex, as well as nicotine and cannabis smoking status (Tables 1 and 2), although on average CU had fewer years of education than stimulant-naïve controls and lower verbal IQ. As expected, CU displayed higher ADHD-SR scores and higher trait impulsivity in the BIS. Moreover, CU exhibited worse working memory and executive functioning, measured by the SWM between/total errors and SWM strategy score, respectively. CU also showed lower signal detection/sustained attention in the RVP and lower efficiency indices in the RVP and MTS.

Hair samples revealed a clear dominance of cocaine compared with all other illegal drugs, as set out by the inclusion criteria (on average 12 times more cocaine than MDMA and 25 times more cocaine than amphetamines) (Table 2). SCID-I revealed a higher frequency of alcohol and cannabis-related disorders in CU compared to stimulant-naïve controls. Correlation analyses revealed that total hair concentrations of cocaine metabolites ($Cocaine_{total}$) were associated with self-reported estimated cumulative dose (r = .366, $p < .01$, n = 56), duration of use (r = .326, $p < .05$, n = 56), days of abstinence before measurement (r = -.333, $p < .05$, n = 56), and urine concentrations for cocaine (r = .542, $p < .001$, n = 56).

3.2. Decision-making

3.2.1. Overall and scenario-specific risk-attitude

To investigate group differences in overall risk-attitude, we performed a LMM including group as a predictor and a random slope for each participant at each scenario property. The analysis revealed that CU (Mean = 12.37, SD = 8.1) did not differ from stimulant-naïve controls (Mean = 11.67, SD = 8.5) concerning the average number of cards chosen over all decision scenarios (ß = .008, 95 %CI = -1.84 to 1.86, t[94] = .008, p = .993, r = .0009).

Next, we investigated risk-taking for each scenario independently by modelling a random intercept for each participant. We found that CU chose more cards than stimulant-naïve controls in high risk, low return scenarios (i.e., the most unfavourable decision scenario: ß = 3.67, 95 %CI = 1.05–6.30, t[94] = 2.76, p = .006; Fig. 1). This finding remained after including verbal IQ, years of education, and ADHD symptoms as covariates (ß = 3.50, 95 %CI = 3.98–4.86, t[91] = 2.31, p = 0.022; Fig. 1). Additionally, we found that CU tended to choose fewer cards than stimulant-naïve controls in low risk, high return scenarios (i.e., the most favourable decision scenario: ß = -2.56, 95 %CI = -5.27 to .14, t[94] = -1.87, p = .064; Fig. 1), although this finding did not reach significance. Thus, CU were more risk-taking than controls in unfavourable decision scenarios but tended to decide more cautiously in favourable decision scenarios.

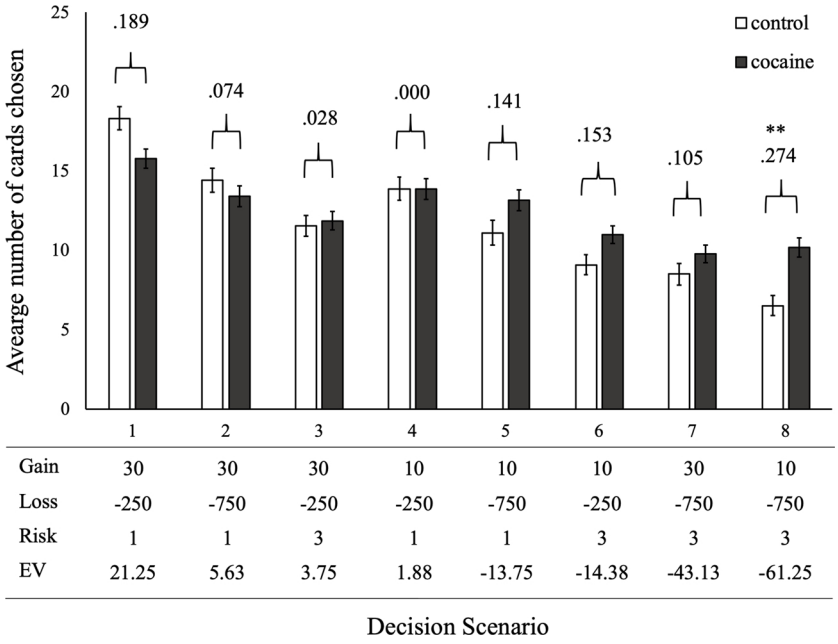
3.2.2. Sensitivity to gain, loss, and probability of loss

To investigate group differences in overall sensitivity to the expected value, we performed a LMM analysis including group and expected value as fixed effects, as well as random slopes and intercepts for each participant and each scenario property. The data revealed that CU were significantly less sensitive to expected value (ß = -.052, 95 %CI = -.08 to -.02, t[2206] = -3.55, p = .0004, r = .075) than stimulant-naïve controls. Subsequently, to investigate group differences in the use of scenario properties, we performed a LMM analysis including group, *gain*, *loss*, and *probability of loss* as fixed-effects and random slopes and intercepts for each participant and each scenario property. As shown in Fig. 2, we found a significant interaction of group with *gain* and a marginally significant interaction of group with *loss*. These interactions suggest that when *gain* is high and, to a lesser degree, when *loss* is low, CU select fewer cards than stimulant-naïve controls. We found no interaction of group with *probability of loss*. Moreover, as expected from

Table 2
Substance use related disorders and drug consumption pattern.

	Controls (n = 40)	Cocaine Users (n = 56)	Test Statistics	df	*p*
Nicotine					
Smoking, y/n	37/3	53/3	x^2 = .18	1	.668
Cigarettes per week [a]	67.0 (47.1)	111.6 (68.2)	W = 575.5	–	**.000**
Years of use	11.7 (6.1)	17.2 (16.1)	W = 710	–	**.026**
Alcohol					
Times per week [a]	2.7 (2.2)	3.3 (3.5)	W = 1052	–	.719
Grams per week [a, b]	22796 (24,922)	59,247 (117,708)	W = 972	–	.334
Years of use	14.1 (6.9)	16.8 (7.0)	t = -1.88	84.81	.062
Estimated cumulative lifetime dose, *g* [b]	65609 (51,775)	284,749 (428,576)	W = 707	–	**.002**
Cocaine					
Cocaine lifetime experience, y/n [c]	5/35	56/0	–	–	–
Times per week [a]	–	2.4 (2.4)	–	–	–
Grams per week [a]	–	3.9 (5.76)	–	–	–
Years of use	–	12.0 (7.5)	–	–	–
Estimated cumulative lifetime dose, *g*	–	1919 (2290)	–	–	–
Abstinence period, days	–	14.3 (23.7)	–	–	–
Cocaine, ng/mg in hair [n] [d]	–	19,388 (26,967) [56]	–	–	–
Benzoylecgonine, ng/mg in hair [n] [d]	–	11,197 (15,907) [56]	–	–	–
Cocaethylene, ng/mg in hair [n] [d]	–	960.8 (1943) [50]	–	–	–
Norcocaine, ng/mg in hair [n] [d]	–	447.8 (654.5) [56]	–	–	–
$Cocaine_{total}$, ng/mg in hair [n] [d, e]	–	31,034 (41,770) [56]	–	–	–
Urine toxicology, n/p in hair [n] [f]	40/0	33/22	x^2 = 33.5	2	**.000**
Cannabis					
Cannabis lifetime experience, y/n [c]	35/5	50/6	x^2 = .07	1	.395
Grams per week [a]	.86 (1.9)	2.0 (7.0)	W = 798	–	.493
Years of use	7.8 (6.0)	12.7 (9.0)	W = 594	–	**.012**
Estimated cumulative lifetime dose, *g*	142.8 (370.0)	3341 (5608)	W = 385	–	**.000**
Abstinence period, days	1159.0 (2222.1)	1005 (2216)	W = 1012	–	.221
THC, ng/mg in hair [n]	36.4 (43.5) [5]	137.0 (258.9) [16]	W = 26.5	–	.264
CBD, ng/mg in hair [n]	16.0 (-) [1]	32.1 (35.8) [8]	W = 4	–	1
CBN, ng/mg in hair [n]	16.6 (18.7) [3]	54.5 (74.5) [14]	W = 14	–	.376
Urine toxicology, n/p [f]	38/2	46/10	x^2 = 5.4	–	.066
MDMA					
MDMA lifetime experience, y/n [c]	9/31	49/7	x^2 = 41.2	1	**.000**
Grams per week [a]	.00 (-) [1]	.04 (.08)	W = 131	–	.054
Years of use	1.8 (1.6)	7.8 (7.6)	W = 108	–	**.015**
Estimated cumulative lifetime dose, *g*	.34 (.46)	50.4 (154.1)	W = 40.5	–	**.000**
Abstinence period, days	1771 (3033)	993.5 (1965.9)	W = 233.5	–	.780
MDMA, ng/mg in hair [n] [d]	109.0 (55.5) [4]	2579 (4976) [36]	W = 38.5	–	.130
MDA, ng/mg in hair [n] [d]	6.6 (3.0) [3]	189.2 (436.4) [29]	W = 19.5	–	.120
Amphetamine					
Amphetamine lifetime experience, y/n [c]	4/36	42/14	x^2 = 39.5	1	**.000**
Grams per week [a]	.01 (.02)	.17 (.63)	W = 54	–	.241
Years of use	.04 (.08)	7.4 (6.5)	W = 7.5	–	**.002**
Estimated cumulative lifetime dose, *g*	2.1 (3.8)	162.8 (369.8)	W = 39	–	.079
Abstinence period, days	1771 (3033)	993.5 (1965.9)	W = 233.5	–	.780
Amphetamine, ng/mg in hair [n] [d]	- (-) [0]	1222 (1700) [13]	–	–	–
SCID-I diagnosis					
Alcohol dependency current, y/n	0/40	8/48	x^2 = 6.2	1	**.012**
Alcohol dependency past, y/n	0/40	18/38	x^2 = 15.8	1	**.000**
Alcohol abuse current, y/n	1/39	18/38	x^2 = 12.9	1	**.000**
Alcohol abuse past, y/n	4/36	26/30	x^2 = 14.4	1	**.000**
Cocaine dependency current, y/n	0/40	36/20	x^2 = 41.1	1	**.000**
Cocaine dependency past, y/n	0/40	39/17	x^2 = 46.9	1	**.000**
Cocaine abuse current, y/n	0/40	36/20	x^2 = 41.1	1	**.000**
Cocaine abuse past, y/n	0/40	36/20	x^2 = 41.1	1	**.000**
Cannabis dependency current, y/n	0/40	1/55	x^2 = .72	1	.395
Cannabis dependency past, y/n	0/40	9/46	x^2 = 7.2	1	**.007**
Cannabis abuse current, y/n	0/40	4/52	x^2 = 2.9	1	.084
Cannabis abuse past, y/n	5/35	17/38	x^2 = 4.4	1	**.035**

Note. Table reports counts or means with standard deviations in brackets. Significant differences are shown in bold. t = Student t-test; x2 = Pearson chi-square; W = Wilcoxon rank sum test. Here we specifically reported the most prevalent substances and metabolites: THC, Tetrahydrocannabinol; CBD, cannabinoid; CBN, cannabinol; MDMA, 3,4-Methylenedioxymethamphetamine; MDA, 3,4-Methylenedioxyamphetamine; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders. (a) Average use of the current consumption period. (b) Pure alcohol estimation; (c) Self-report: Have you ever consumed this substance, at least once, in your life? (d) Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg (Cooper et al., 2012). (e) $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs (Hoelzle et al., 2008). (f) Urine toxicology (neg/pos) are based on cut-off value for Cocaine =150 ng/ml and for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).



	1	2	3	4	5	6	7	8
Gain	30	30	30	10	10	10	30	10
Loss	-250	-750	-250	-250	-750	-250	-750	-750
Risk	1	1	3	1	1	3	3	3
EV	21.25	5.63	3.75	1.88	-13.75	-14.38	-43.13	-61.25

Fig. 1. Average number of cards selected in each scenario. EV, Expected Value. Effect sizes |r| < .10 correspond to small effects; 0.10 ≤ |r| < .30 to medium effects; .30 ≤ |r| < .50 to large effects. ** *p*-value < .01.

the preceding analysis (Section 3.2.1), main effects were found for *gain*, *loss,* and *probability of loss* but not for group. Confirming our hypothesis, these findings suggest that, compared to controls, CU are less sensitive to the expected value (i.e., the "favourableness" of the decision scenarios). In particular, CU are less sensitive to *gain* information, choosing fewer cards than controls at high *gains*.

To explore within-group variance explained by the use of scenario properties, we analysed the number of cards chosen for CU and stimulant-naïve controls separately. The control group displayed a significant effect of all scenario properties (*gain*: ß = 3.30, 95 %CI = 1.70–4.91, t[913] = 4.03, $p < .001$, r = .132; *loss*: ß = 2.76, 95 %CI = .99–4.54, t[913] = 3.04, $p = 0.002$, r = .100; *probability of loss*: ß = -4.60, 95 %CI = -6.47 to -2.74, t[913] = -4.82, $p < 0.001$, r = .157). Thus, controls chose more cards when *gain* was high and *loss* or *probability of loss* were low (condition $R^2 = .59$; marginal $R^2 = .16$). Within the CU group we found a significant effect for *probability of loss* (ß = -2.97, 95 %CI = -4.48 to -1.47, t[1281] = -3.86, $p = 0.000$, r = .107). In contrast, there was no effect of *gain* (ß = .25, 95 %CI = -1.08 to 1.58, t[1281] = .36, $p = .714$, r = .010) or *loss* (ß = -.71, 95 %CI = -.63 to 2.06, t[1281] = -1.03, $p = .299$, r = .028; condition $R^2 = .50$; marginal $R^2 = .05$). Together, these results suggest that CU were predominantly sensitive to *probability of loss*, while controls were sensitive also to *gain* and *loss* information.

3.2.3. Impact of demographic, cognitive, and clinical variables on gain, loss and probability of loss sensitivities

To examine whether the reported group differences (Table 1) relate to differential weighing of *gain, loss,* and *probability of loss* information, we used hierarchical linear models. Since the SWM Strategy score and the SWM Total error score revealed large effect sizes, as well as the BIS total score and the ADHD sum score, these variables were entered into separate models (see Supplementary Table S1). As shown in Table 3, *gain* and *loss* sensitivity were best explained by a model that included group and years of school education (F[93] = 8.36; $R^2 = .134$; $p = .055$; and F[93] = 4.12; $R^2 = .61$; $p = .054$, respectively), suggesting that longer education leads to higher sensitivity to *gains* and *losses*. With regard to *probability of loss* sensitivity, we found that the model with group, IQ, SWM Strategy score, and ADHD symptoms explained more variance than the other models (Table 3) (F[91] = 5.40; $R^2 = .156$; $p = .053$). Additional multiple regressions did not reveal any effect for sex and age. Together, these data suggest that while *gain* sensitivity was explained primarily by cocaine use status (and also by years of school education), *loss* and *probability of loss* sensitivity were better explained by additional demographic, cognitive (i.e., executive functioning and working memory) and clinical variables.

Next, we aimed to investigate how *gain, loss,* and *probability of loss* sensitivity correlate with risk-attitude in each decision scenario, after

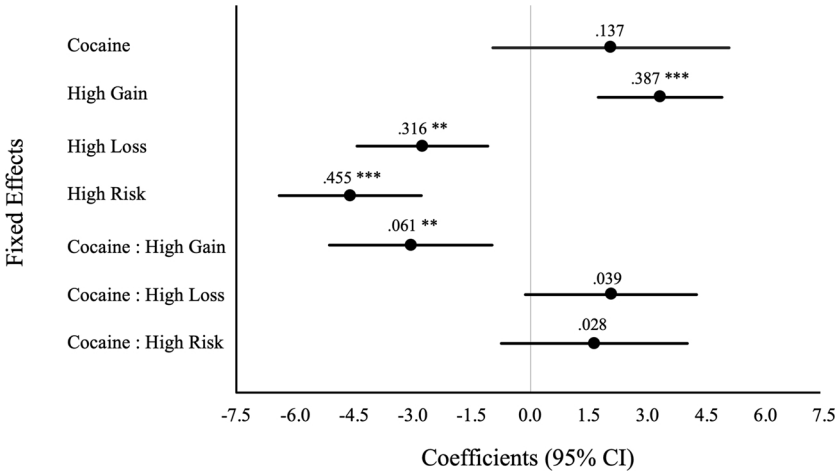


Fig. 2. Regression coefficients for the main fixed effects and interactions of the linear mixed model. The model included random slopes and intercepts for each participant and each scenario property (i.e. *gain*, *loss* and *probability of loss*). Stimulant-naïve control group, at low *gain*, low *loss* and low *probability of loss* served as reference group. Of note, CU were less sensitive to *gain* than control participants. "Cocaine Group" refers to the main effect of group on the overall number of cards chosen. "Cocaine Group : High Gain" refers to the interaction effect of the variable group and the gain information; "Cocaine Group : High Loss", refers to the interaction effect of the variable group and loss information; "Cocaine Group : High Risk" refers to the interaction effect of the variable group and risk information. Conditional $R^2 = .54$, marginal $R^2 = .10$. CU, chronic cocaine users. *** *p*-value < .001; ** *p*-value < .01.

Table 3
Hierarchical multiple linear regression models for gain, loss and risk sensitivity.

	Cocaine	Years of Education	IQ	SWM Strategy	SWM Total Errors	Meta-Efficiency Index	BIS	ADHD	[df] F	R^2	Model Comparison	*p*
Gain												
Model 1	−.11 (-3.54) ***								[94] 12.59	.109	1 vs. Null	**.000**
Model 2	−.09 (-2.76) **	.02 (1.94) *							[93] 8.36	.134	2 vs. 1	**.055**
Model 3	−.11 (-3.01) **	.03 (2.14) *	−.00 (-1.22)						[92] 6.09	.138	3 vs. 2	.225
Model 4	−.09 (-2.57) *	.02 (1.59)		−.00 (-.75)					[92] 5.74	.130	4 vs. 2	.449
Model 5	−.09 (-2.65) **	.02 (1.85)			−.00 (-.11)				[92] 5.51	.124	5 vs. 2	.909
Model 6	−.08 (-2.45) *	.02 (1.90)				.00 (.1.01)			[92] 5.92	.134	6 vs. 2	.311
Model 7	−.10 (-2.81) **	.02 (2) *					.00 (.60)		[92] 5.65	.128	7 vs. 2	.545
Model 8	−.09 (-2.64) **	.02 (1.91)						−.00 (-.36)	[92] 5.56	.126	8 vs. 2	.716
Full model [a, b]	−.10 (-2.69) **	.02 (1.87)	−.00 (-1.21)	−00 (-.60)	–	−.00 (-.62)	.00 (.62)	–	[89] 3.26	.124	Full vs. 2	.558
Loss												
Model 1	−.00 (-2.08) *								[94] 4.33	.033	1 vs. Null	**.040**
Model 2	−.00 (-1.35)	.00 (1.94) *							[93] 4.12	.061	2 vs. 1	**.054**
Model 3	−.00 (-1.19)	.00 (1.85)	.00 (.24)						[92] 2.74	.052	3 vs. 2	.806
Model 4	−.00 (-1.03)	.00 (1.30)		−.00 (-1.78)					[92] 3.88	.083	4 vs. 2	.076
Model 5	−.00 (-.99)	.00 (1.57)			−.00 (-1.50)				[92] 3.54	.074	5 vs. 2	.135
Model 6	−.00 (-1.10)	.00 (1.91)				.00 (.94)			[92] 3.04	.060	6 vs. 2	.349
Model 7	−.00 (-1.45)	.00 (2.01) *					.00 (.67)		[92] 2.88	.056	7 vs. 2	.501
Model 8	−.00 (-1.47)	.00 (1.97) *						.00 (.83)	[92] 2.97	.058	8 vs. 2	.406
Full model [a, c]	−.00 (-.95)	.00 (1.27)	.00 (.19)	−.00 (-1.64)	–	.00 (.42)	–	.00 (.99)	[89] 2.10	.065	Full vs. 2	.364
Risk												
Model 1	1.08 (2.41) *								[94] 5.84	.017	1 vs. Null	**.017**
Model 2	.97 (2.04) *	−.13 (-.70)							[93] 3.15	.043	2 vs. 1	.480
Model 3	.67 (1.42)		−.07 (-2.21) *						[93] 5.50	.086	3 vs. 1	**.029**
Model 4a	.42 (.88)		−.07 (-2.02) *	.08 (2.38) *					[92] 5.74	.130	4a vs. 3	**.019**
Model 4b [a]	41 (.84)		−.07 (-2.21) *	–	.02 (2.04) *				[92] 5.19	.116	4b vs. 4a	–
Model 5	.40 (.82)		−.07 (-2.02) *	.08 (2.20) *		−.02 (-.21)			[91] 4.27	.121	5 vs. 4a	.828
Model 6	.62 (1.30)		−.06 (-1.97) *	.09 (2.56) *			−.03 (-1.96) *		[91] 5.40	.156	7 vs. 4a	**.053**
Model 7 [c]	.61 (1.31)		−.07 (-2.05) *	.09 (2.71) **			–	−.05 (-2.58) *	[91] 6.25	.181	7 vs. 6	–
Full model [a, c]	.64 (1.30)	.07 (.38)	−.07 (-2.07) *	.09 (2.53) *	–	−.01 (-.10)	–	−.05 (-2.54) *	[88] 4.11	.164	Full vs. 8	.921

Note. IQ, Intelligence Quotient assessed with the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B); SWM, Spatial Working Memory task; BIS, total sum score from Barratt Impulsiveness Scale; ADHD, Attention deficit hyperactivity disorder total sum score from ADHD self-rating scale. *p*-value $\leq$ .05 *; *p*-value < .01 **; *p*-value < .001 ***. The table reports adjusted R^2. Bold *p*-values indicate models with more favourable fit. (a) Due to multicollinearity, EF was not included in the same model as WM. (b) Due to multicollinearity, BIS total score but not ADHD was included in the model. (c) Due to multicollinearity, ADHD total sum score but not BIS was included in the model. (d) Efficiency Index is the average of the efficiency indices from the Rapid Visual Information Processing task and the Match to Sample Visual Search efficiency task.

Table 4
Correlations between gain, loss and risk sensitivity and risk-attitude at each decision scenario.

	Non-Stimulant Controls			Cocaine Users		
	Gain [a]	Loss [a]	Risk [b]	Gain [a]	Loss [a]	Risk [b]
Average nº of cards						
Scenario 1	.538 ***	.559 ***	−.583 ***	.193	.184	−.554 ***
Scenario 2	−.135	−.239	−.503 **	−.416 **	.012	−.472 ***
Scenario 3	−.011	−.394 *	−.144	−.157	−.320 *	−.485 ***
Scenario 4	.456 **	−.574 ***	.099	−.406 **	−.455 ***	−.357 **
Scenario 5	.088	−.217	.258	.025	.203	.094
Scenario 6	−.530 ***	−.402 *	.417 *	−.557 ***	−.067	.125
Scenario 7	−.244	−.591 ***	.465 **	−.057	−.510 ***	.060
Scenario 8	−.439 **	−.743 ***	.469 **	−.523 ***	−.338 *	.120

Note. *p*-value < .05 *; *p*-value < .01 **; *p*-value < .001 ***. (a) Corrected for years of school education; (b) Corrected for IQ, executive functioning and ADHD symptoms;

correcting for the significant effects found in the best explanatory hierarchical linear models (Table 4). Specifically, *gain* and *loss* correlations were corrected for years of school education and *probability of loss* correlations were corrected for IQ, executive functioning, and ADHD symptoms. Our data revealed that, within the control group, in the most and the least favourable decision scenarios, risk-attitude correlated with the sensitivity to *gain*, *loss* and *probability of loss* information. However, within the CU group, only sensitivity to *gain* and *loss* correlated with risk-attitude in the least favourable decision scenario, while only the sensitivity to *probability of loss* correlated with risk-attitude in the most favourable decision scenario.

3.2.4. Impact of cocaine use severity on gain, loss and probability of loss sensitivities

Finally, we investigated possible associations of *gain, loss,* and *probability of loss* sensitivity with cocaine-related metabolites and self-reported cocaine consumption in CU. We found no effect for the self-reported estimated cumulative lifetime dose of cocaine, abstinence period and years of cocaine consumption. In contrast, benzoylecgonine (r = -.298, p = .025, n = 56), norcocaine (r = -.302, p = .023, n = 56) and cocaine (r = -.278, p = .037, n = 56) metabolites, as well as the sum of these three metabolites, $Cocaine_{total}$ (r = -.291, p = .029, n = 56), correlated negatively with *probability of loss* sensitivity. This finding indicates that severe cocaine consumption coincides with lower *probability of loss* sensitivity. However, these effects did not remain significant after including IQ, executive functioning, and ADHD symptoms in the model, in accordance with the hierarchical linear models (Table 3). Regarding *gain* and *loss* sensitivity, no effect was found for the self-reported estimated cumulative lifetime dose of cocaine, abstinence period, years of cocaine consumption, or cocaine metabolites (with and without including years of school education in the models).

4. Discussion

Our study extends current knowledge on decision-making deficits in CU by analysing risky decisions with a more fine-grained approach in the context of the CCT. We investigated whether chronic CU differed from stimulant-naïve controls in the use of *gain, loss,* and *probability of loss* information during decision-making under risk. CU were more risk-seeking than controls in less favourable decision scenarios, where returns were low and risk was high (i.e., lower expected value). By looking at the use of information over all decision scenarios, the data confirmed our hypothesis that chronic CU are not as sensitive to *gains* as stimulant-naïve controls. Indeed, CU were less sensitive to the expected value, suggesting that they are not able to fully integrate all of the available information. We also found a marginally significant group effect for *loss* sensitivity; however, no group effect was found for *probability of loss* sensitivity. Furthermore, the main group difference in *gain* sensitivity was not explained by additional predictors (i.e., IQ, executive functioning, working memory, visual processing efficiency, impulsivity traits or ADHD symptoms), although years of school education also had an effect. By contrast, *loss* sensitivity was related to years of education, but not group and, for *probability of loss* sensitivity, we found an effect for IQ, executive functioning and ADHD symptoms, but not for group. Finally, the correlation analyses between risk-attitude and the sensitivity to *gain, loss,* and *probability of loss* showed that, relative to stimulant-naïve controls, chronic CU more often fail to consider all available information on returns (i.e., *gain* and *loss*) and *probability of loss*.

From a clinical perspective, the reduced *gain* sensitivity in CU is not surprising, since one of the core criteria of all substance-related disorders is the withdrawal from social, occupational, and recreational activities with high value in order to use the substance [58]. This pattern of behaviour has been proposed to reflect a shift in the subjective value of ordinary life events to substance-related rewards [23]. Our study suggest that this shift extends to the domain of taking risks in well-controlled laboratory settings.

In contrast to reduced *gain* sensitivity in the CU group, *loss* and *probability of loss* sensitivity were better explained by demographic and intellectual differences as well as psychiatric comorbidities than by chronic cocaine use. These results demonstrate that the interpretation of deficits in decision-making findings needs to take the specific demographic and clinical background that which is typically associated with cocaine-related disorder [59]. Given that, within the CU group, 90 % met the criteria for current or past cocaine dependency or abuse according to DSM-IV-R, we expected to find higher self-reported impulsivity and ADHD symptoms and worse general cognitive performance in the CU than the control group. Although our findings suggest that severe cocaine use is not directly linked to a decrease in sensitivity to *loss* and *probability of loss* information, they nevertheless point at impairments of CU in the processing of *loss* and *probability of loss* information.

Our data also suggest that CU may not integrate all the available information as fully as controls when making risky decisions, as shown by the interaction effect of group and expected value on risky behaviour. Such impairments in integrating all of the available information could be related to vmPFC dysfunction, as this brain region has been associated with the integration of subcortical signals within a single representation of net value, which is accumulated over time until the individual decides to accept or reject an option [60]. Indeed, in the Iowa Gambling Task, CU showed impaired performance that resembled the maladaptive behaviour of patients with vmPFC lesions [61,62]. More specifically, CU also showed reduced vmPFC activation to social and object reward [27], in line with a *gain* processing function of this region and mirroring the reduced *gain* sensitivity of CU found in the current study.

Of note, it has been recently shown that individuals with opiate dependence also differ in their use of available information during decision making, relative to controls [53]. In that study, heroin-dependent patients took more risks than controls irrespective of whether

the situation was favourable or unfavourable, suggesting that heroin users may not attend to environmental contingencies when making decisions [53]. Although we cannot generalize to other substance use disorders, our findings support the hypothesis that deficits in integrating the available information when making decisions might be investigated as a general behavioural marker for severe substance use disorders.

Some limitations should be considered when interpreting our findings. First, the cross-sectional design of this study does not allow us to clearly determine the causal relationship between cocaine use and alterations in *gain* sensitivity, especially because we found no correlation with subjective and objective cocaine use severity markers. Accordingly, it is also possible that a lower sensitivity to *gain* predicts the onset of substance use. Nevertheless, it seems to be more likely that variations in *loss* and *probability of loss* sensitivities precede chronic cocaine use, as indicated by the significant effects of demographic, clinical, and cognitive variables (i.e., performance on tests of executive function and working memory). Future studies might consider investigating whether changes in cocaine consumption can affect sensitivity to *gain*, *loss,* and *probability of loss* information during decision-making. Remarkably, this finding complements one of our previous studies that investigated decision-making under risk without feedback using a different definition of risk and found that risk proneness was associated with higher cocaine concentrations in the hair [63]. The different definition of risk may also explain why, in contrast to Wittwer, et al. [63], we found an effect of IQ, executive functioning, and ADHD symptoms on *risk* in terms of *probability of loss* sensitivity, but no effect for sex and age. Finally, our data (see Fig. 1) and the hierarchical multiple regressions (see Table 3) showed only small-to-medium effect sizes for risk-taking and several marginal differences with low R^2. This may suggest that substantial variance in information sensitivity arises from individual differences or additional uncontrolled variables. Having said this, we also found converging evidence for a significant effect of cocaine use on *gain* sensitivity with the linear-mixed model (see Fig. 2), which accounts for individual differences.

Taken together, our findings open avenues for future applied research that aims to improve the efficiency and the efficacy of preventive and therapeutic strategies for chronic substance users. For instance, decreased sensitivity to *gain* might partially explain the lack of adherence to long-term treatments and detoxification programs, since chronic CU are insensitive to the advantages of maintaining abstinence. In addition, our findings support the necessity of considering demographic, clinical, and cognitive variables when providing therapeutic strategies, an approach that has well-known benefits, but is frequently not applied.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2019.112386.

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