Psychopharmacology (2014) 231:4179–4187
DOI 10.1007/s00213-014-3563-9

ORIGINAL INVESTIGATION

Decision-making impairment predicts 3-month hair-indexed cocaine relapse

Antonio Verdejo-Garcia · Natalia Albein-Urios · Jose Miguel Martinez-Gonzalez · Ester Civit · Rafael de la Torre · Oscar Lozano

Received: 16 January 2014 / Accepted: 24 March 2014 / Published online: 13 April 2014

Abstract
Rationale One of the key outstanding challenges in cocaine dependence research is determining who is at risk of relapsing during treatment.
Objectives We examined whether cognitive decision-making profiles predict objectively (hair) indexed cocaine relapse at 3-month follow-up.
Methods Thirty-three cocaine-dependent patients commencing outpatient treatment in a public clinic performed baseline decision-making assessments with the original and variant versions of the Iowa Gambling Task, and provided a 3-cm hair sample 3 months afterwards. Based on Iowa Gambling Tasks' performance cut-offs, 5 patients had intact decision-making skills, 17 patients showed impaired sensitivity to reward or punishment (impairment in one of the tasks), and 9 patients showed insensitivity to future consequences (impairment in both tasks). Based on a 0.3 ng/mg cocaine cut-off, 23 patients were classified as relapsers and 10 as non-relapsers at the 3-month follow-up.
Results Eighty percent of patients with intact decision-making were abstinent at follow-up, whereas 90 % of patients with insensitivity to future consequences had relapsed. The two subgroups (relapsers and non-relapsers) showed no significant differences on drug use, comorbidities, or psychosocial function, and significantly differed on verbal but not performance IQ. A regression model including decision-making scores and verbal IQ predicted abstinence status with high sensitivity (95 %) and moderately high specificity (81 %).
Conclusion These preliminary findings demonstrate that decision-making profiles are associated with cocaine relapse. Moreover, combined decision-making and IQ assessments provide optimal predictive values over stimulant relapse, yielding significant opportunities for clinical translation.

Keywords Cocaine · Decision-making · Insensitivity to future consequences · Hair analysis · Iowa Gambling Task

A. Verdejo-Garcia · J. M. Martinez-Gonzalez · O. Lozano
Red de Trastornos Adictivos, Universidad de Granada, Granada, Spain

A. Verdejo-Garcia · N. Albein-Urios
Department of Clinical Psychology & Institute of Neuroscience F. Oloriz, Universidad de Granada, Granada, Spain

A. Verdejo-Garcia (✉)
School of Psychology and Psychiatry, Monash University, 3800 Wellington Rd. Clayton Campus, Melbourne, Australia
e-mail: antonio.verdejo@monash.edu

J. M. Martinez-Gonzalez
Centro Provincial de Drogodependencias, Diputación de Granada, Granada, Spain

E. Civit · R. de la Torre
Human Pharmacology and Clinical Neurosciences Research Group, IMIM-Institut de Recerca Hospital del Mar, Barcelona, Spain

R. de la Torre
CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Santiago de Compostela, Spain

R. de la Torre
Universitat Pompeu Fabra (CEXS-UPF), Barcelona, Spain

O. Lozano
Department of Psychology, Universidad de Huelva, Granada, Spain

Introduction

Relapse is the main challenge faced by stimulant-dependent patients undergoing treatment. Even effective psychosocial treatments are associated with relapse rates of 60 to 70 % in post-treatment follow-ups (Bisaga et al. 2010; Dutra et al. 2008; Knapp et al. 2007). Therefore, an outstanding issue for cocaine addiction treatment research is predicting who is at risk of drug relapse and which strategies can be used to improve treatment outcome in at-risk patients (Garavan et al. 2013; Pattij and De Vries 2013). Predictors of cocaine relapse include socio-demographic factors, comorbidities, and population-specific clinical characteristics (e.g., craving or stress) (Reske and Paulus 2008). Lower socio-economic background/support, alcohol use, personality disorders, stress reactivity, craving, and self-efficacy have been prospectively associated with cocaine relapse in longitudinal studies (Back et al. 2010; Garcia-Fernandez et al. 2011; McKay et al. 2005; McMahon 2001).

In the last years, cognition has been successfully incorporated to prediction of stimulant treatment outcomes. In stimulants addiction, cognitive deficits are malleable to pharmacological and behavioral interventions (Alfonso et al. 2011; Sofuoglu et al. 2011). Therefore, identification of cognitive predictors can be readily translated into therapeutic targets. Cognitive studies have shown that cognitive control measures, including impulsivity, flexibility, and self-regulation tasks, are significant predictors of cocaine treatment retention (Streeter et al. 2008; Turner et al. 2009; Verdejo-Garcia et al. 2012). However, to date, no studies have investigated the impact of cognitive measures on drug relapse in cocaine treatment groups. Such studies have been conducted in users of other substances (alcohol and opiates), and results have shown that decision-making is the strongest cognitive predictor of drug relapse (Passetti et al. 2008; De Wilde et al. 2013; De Wilde et al. 2013). Performance on the Iowa Gambling Task (IGT) alone (De Wilde et al. 2013) or in combination with the more sensitive to risk-taking Cambridge Gamble Task (Passetti et al. 2008) is significantly associated with a 3-month self-reported relapse in alcohol and opiate users, respectively. Other cognitive measures failed to predict this outcome (Passetti et al. 2008; De Wilde et al. 2013). A recent study has further shown that decision-making performance (IGT) predicts stimulants intake in a treatment sample of bipolar patients with comorbid substance use (Nejtek et al. 2013).

Decision-making, as indexed by the IGT, is the ability to select the most advantageous course of action according to both immediate and delayed outcomes (Bechara et al. 2000a, b). Defined as such, decision-making deficits are inherent to addiction pathology (i.e., continued substance use that neglects alternative means and growing negative consequences) (Bechara et al. 2001). However, there are at least two phenotypes linked to decision-making deficits in individuals with substance dependence: hypersensitivity to reward or punishment vs. insensitivity to future consequences (Bechara et al. 2002). These phenotypes were originally described through performance on the original and variant versions of the IGT (Bechara et al. 2000a, b). Deficits in the original version (in which disadvantageous choices involve high immediate reward followed by higher delayed punishment) combined with intact performance in the variant version (in which advantageous decisions involve tolerating high immediate punishment in order to obtain higher delayed reward) are indicative of hypersensitivity to reward. The reversed pattern (intact performance in the original version and impaired performance in the variant version) is indicative of hypersensitivity to punishment. Conversely, deficits in both original and variant versions (involving neglect of both delayed punishment and delayed reward) are indicative of insensitivity to future consequences. The latter phenotype is shared by a subgroup of stimulants-dependent users and patients with ventromedial prefrontal damage (Bechara et al. 2002), who have particularly severe problems to make real-life-type decisions including risk-sensitive choices and forecast-based judgments (Bechara et al. 2000a, b; Gomez-Beldarrain et al. 2004; Studer et al. 2013). Therefore, it is reasonable to hypothesize that insensitivity to future consequences (factored by impairment in both Iowa Gambling Task versions) is particularly associated with relapse in cocaine users, since abstinence during treatment relies on maintenance of long-term commitment against ongoing risks.

In this study, we investigated whether performances in the original and variant versions of the Iowa Gambling Task are longitudinally predictive of a 3-month relapse in a treatment sample of cocaine-dependent individuals. Cocaine use during the 3-month period was objectively measured through hair-indexed cocaine metabolite concentrations. We hypothesized that impaired performance in both versions of the Iowa Gambling Task would be significantly associated with hair-indexed cocaine relapse.

Materials and methods

Participants

The sample was composed of 35 participants (5 females) diagnosed with cocaine dependence and undergoing outpatient community treatment in the public clinic "Centro Provincial de Drogodependencias" (CPD), in Granada (Spain). They performed a baseline cognitive assessment and a follow-up session (scheduled 3 months after baseline) in which they provided a hair sample (~3 cm of hair taken from the back of the head) to be analyzed for cocaine intake. This sample overlaps with the larger sample of the COPERNICO study (n=90), aimed at investigating cognition in cocaine addiction, which baseline results have been published elsewhere (e.g., Albein-Urios et al. 2013). Thirty-five participants completed the follow-up session. There were no significant differences in socio-demographic, drug use, cognitive, or psychosocial variables between the baseline sample and the sample retained at 3 months. Two of the successfully retained participants had insufficient hair to provide a valid hair sample and were subsequently excluded. Therefore, the final sample was composed by the 33 participants with successfully analyzed hair samples.

All cocaine users were recruited through consecutive admissions to the CPD clinic, which provides outpatient psychosocial treatment for substance use disorders. The inclusion criteria for participants were defined as follows: (1) aged between 18 and 50 years old, (2) IQ above or equal 80—as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman 1990), (3) meeting DSM-IV criteria for cocaine dependence—as assessed by the Structured Clinical Interview for DSM-IV Disorders–Clinician Version (SCID-I-CV) (First et al. 1997), (4) being treatment commencers requesting voluntary admission, and (5) abstinence duration >15 days. Abstinence at baseline was confirmed by urine tests conducted two times per week. The exclusion criteria were as follows: (1) the presence of any other DSM-IV Axis I disorders—with the exceptions of alcohol abuse, nicotine dependence, and attention deficit and hyperactivity disorder (ADHD)—as measured by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners 1999), (2) history of head injury or neurological, infectious, systemic, or any other diseases affecting the central nervous system, (3) having followed other treatments within the 2 years preceding study onset, and (4) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID-I-CV. Personality disorders were not exclusionary. They were assessed using the International Personality Disorders Examination (Loranger et al. 1994). All the diagnoses were conducted by a certified clinical psychologist, and all subsequent tests were administered by an independent (blind to clinical status) assessor.

All participants were of European ancestry, mean age was 33 years old (SD=7.3), and mean years of education was 10.7 (SD=1.8). At baseline, cocaine use was of 18 g per month (SD=22.5), and regular cocaine use had been ongoing for a mean duration of 43.5 months (SD=43). Fifteen participants (45 % of the sample) had comorbid personality disorders: 5 with borderline, 4 with antisocial, 4 with histrionic, 1 with avoidant, and 1 with obsessive-compulsive diagnoses, respectively.

Measures

Drug use and clinical measures

Interview for research on addictive behavior (Verdejo-Garcia et al. 2005) This interview collects information about substance-use behavior. The main parameters collected are the monthly use of each substance (quantity per month), the total duration of use of each substance (duration in years), and age at onset of drug use.

General health questionnaire (GHQ-28) We used the 28-item Spanish-language version of this questionnaire that measures four dimensions of psychosocial function relevant to mental health populations: somatic complaints, anxiety, social dysfunction, and depression. This version has demonstrated sound psychometric properties (Lobo et al. 1986).

Decision-making measures

Iowa Gambling Task, original version (Bechara et al. 2000a, b) This is a computer task measuring reward/punishment-based decision-making. It involves four decks of cards (A, B, C, and D). Each time a participant selects a card, a specified amount of play money is awarded. However, interspersed among these rewards, there are probabilistic punishments (monetary losses). Two of the decks of cards (A and B) produce high immediate gains; however, in the long run, they will take more money than they give, and are therefore considered disadvantageous. The other two decks (C and D) are considered advantageous, as they result in small, immediate gains, but will yield more money than they take in the long run. The performance measure was the net score calculated by subtracting the number of disadvantageous choices (decks A and B) from the number of advantageous choices (decks C and D). Participants were classified as impaired or non-impaired according to a cut-off score of 10 as defined by Bechara et al. (2002).

Iowa Gambling Task, variant version (Bechara et al. 2000b) The appearance and operation of this task is very similar to the original IGT. The only difference is in the schedules of punishment and reward. In this case, each time a participant selects a card, a specified amount of play money is punished, and interspersed among these punishments, there are probabilistic rewards. The schedules were set in such a way that the discrepancy between punishment and reward in the disadvantageous decks (F and H) is rendered larger in the negative direction, i.e., toward a larger loss. By contrast, the discrepancy between punishment and reward in the advantageous decks (E and G) is rendered larger in the positive direction, i.e., toward a larger gain. The performance measure was the net score calculated by subtracting the number of disadvantageous choices—yielding low punishment and progressively lower reward (decks F and H)—from the number of advantageous choices—yielding high punishment and progressively higher reward (decks E and GD). Participants were classified as impaired or non-impaired according to a cut-off score of 8 as defined by Bechara et al. (2002).

A global decision-making impairment index was obtained based on impairment measures from both versions (Bechara et al. 2002). Participants were classified as the following: "intact," if they showed non-impaired performance in both versions; "hypersensitive to reward or punishment," if they showed impaired performance in the original or the variant version; or "insensitive to future consequences," if they showed impaired performance in both the original and variant versions. Two participants failed to complete the EFGH task, and therefore this classification index was obtained for 31 participants.

Outcome measure Cocaine relapse was defined as hair-indexed cocaine concentrations exceeding 0.3 ng/mg. This definition agrees with the current guidelines of the European Workplace Drug Testing Society and the Society of Hair Testing, which recommend cut-off concentrations of 0.5 ng/mg or less of cocaine for reporting positive cases (Agius and Kintz 2010; Cooper et al. 2012). Cocaine and benzoylecgonine were analyzed by gas chromatography coupled to mass spectrometry (Pichini et al. 2004).

Statistical analyses

Analyses were conducted on Stata version 12.1. We conducted preliminary descriptive analyses to examine the distributions of the dependent variables in both groups (relapsers and non-relapsers). Since virtually all variables followed non-normal distributions, we applied *Mann–Whitney U* tests for all continuous variables (demographic, drug use, and IQ; Lehmann 1998). The main contrast of interest (association between Iowa Gambling Tasks impairment and cocaine relapse) was tested with a *chi-square test*. This association was further examined with a stepwise logistic regression model introducing Iowa Gambling Tasks' performances (total net scores) and verbal IQ scores as predictors, and relapse/non-relapse as the dependent variable. The *Hosmer–Lemeshow test* was used to check goodness of fit, $\chi^2=11.91$; $p>0.05$. We also examined the sensitivity and specificity of the model.

Results

Relapse vs. non-relapse

Twenty-one participants (63.6 % of the sample) had cocaine metabolite concentrations above the 0.3 ng/mg cut-off and were classified as relapsers. Twelve participants had concentrations below the specified cut-off and were classified as non-relapsers. Cocaine concentrations in relapsers ranged from 0.31 to 6.31 [CI (2.38–4.21)], whereas cocaine concentrations in non-relapsers ranged from 0 to 0.29 [CI (0.009–0.13)]. We also measured THC, amphetamine, and opiate metabolite concentrations, but none of the participants showed concentrations over 0.5 ng/mg.

Differences between relapsers and non-relapsers in socio-demographic, drug use, and psychosocial characteristics

Results are shown in Table 1. There were no significant differences between relapsers and non-relapsers in age, years of education, age of onset of cocaine use, and cocaine, alcohol and tobacco use. Groups did not significantly differ either in personality comorbidities (seven participants had personality comorbidities in the non-relapsing group, eight in the relapsing group; $\chi^2=0.44$; $p>0.05$) or any domain of psychosocial function: anxiety, depression, somatic complaints, or social dysfunction. There were no significant differences between groups on performance IQs. However, verbal IQs were significantly lower (8 points lower) in relapsers vs. non-relapsers.

Differences between relapsers and non-relapsers in decision-making

Results are shown in Fig. 1. In the relapsing group, 8 participants had impaired performance in the two decision-making tasks, 11 participants had impaired performance in one of the decision-making tasks, and 1 participant performed normally in both tasks. In the non-relapsing group, 4 participants had intact performance in the two decision-making tasks, 6 participants had impaired performance in one of the tasks, and only 1 participant had impaired performance in both tasks. Therefore, 89 % of participants with impaired performance in both tasks (the profile characterized by insensitivity to future consequences) had relapsed after 3 months, whereas 80 % of participants with intact performance in both tasks maintained abstinence after 3 months ($\chi^2=6.66$, $p<0.05$). The use of more conservative cut-offs to define relapse produced very similar results.

The individual analysis of each task showed that impairment in the variant version was significantly associated with relapse ($\chi^2=3.95$, $p<0.05$), whereas impairment in the original version was not significantly associated with relapse ($\chi^2=2.23$, $p=0.14$).

Prediction of abstinence status

Inter-correlations between verbal IQ, Iowa Gambling Tasks' net scores, and cocaine relapse (relapse/non-relapse) are displayed in Table 2. The regression model, including Iowa Gambling Tasks' net scores and IQ, yielded a *pseudo* $R^2=0.312$, $\chi^2=7.03$, and $p<0.05$. This model resulted in 90.3 % of participants correctly classified as relapsers/non-relapsers, with sensitivity and specificity of 95 and 81.2 %, respectively (Tables 3). The main predictors retained in the model were the net scores from the variant version, $\beta=-0.03$, Wald test=4.45, and $p<0.05$, and verbal IQ scores, $\beta=-0.15$, Wald test=4.34, and $p<0.05$.

Table 1 Descriptive data for the subpopulations of relapsers and non-relapsers in socio-demographic, drug use, and psychosocial characteristics

	Non-relapse	Relapse	Mann–Whitney *U*	*p*
Demographic/psychosocial				
Age	33.3 (7.2)	32.7 (7.6)	116.0	0.707
Years of education	10.5 (1.5)	10.7 (1.9)	125.0	0.967
Somatic complaints[a]	1.81 (1.78)	1.63 (1.77)	98.0	0.800
Anxiety[a]	2.45 (2.16)	3.16 (2.65)	92.5	0.611
Social function[a]	1.73 (1.68)	1.36 (2.21)	74.0	0.200
Depression[a]	1.45 (1.57)	1.78 (2.57)	96.5	0.735
Verbal IQ	107 (7.6)	99.1 (7.1)	49.5	0.004
Performance IQ	100.7 (12.3)	94.8 (9.2)	78.5	0.075
Drug use				
Cocaine monthly use (gr.)	19.1 (27.4)	17.4 (19.8)	109.5	0.535
Cocaine duration (months)	33.7 (26.2)	49.1 (49.8)	57.5	0.523
Cocaine use onset (age)	22.8 (7.2)	19.4 (4.3)	82.5	0.102
Alcohol monthly use (SAU)	59.60 (66.12)	55.05 (74.18)	64.0	0.309
Alcohol duration (months)	80.4 (63.45)	105.7 (95.15)	81.5	0.863
Alcohol use onset (age)	18 (4.19)	18.41 (4.39)	78.5	0.749
Tobacco monthly use (cigarettes)	681.13 (372.43)	460.56 (309.81)	48.0	0.196
Tobacco duration (months)	122 (90.33)	129 (126.06)	65.5	0.724
Tobacco use onset (age)	16.7 (4.83)	15.3 (3.59)	66.5	0.765

Drug use measures refer to regular use before treatment onset

gr. grams; *SAU* standard alcohol units

[a] Range between 0 and 3

Discussion

We found a significant association between the decision-making profile of insensitivity to future consequences and objectively indexed cocaine relapse in a 3-month follow-up. Relapsers and non-relapsers did not significantly differ on demographic variables, comorbidities, or psychosocial adjustment. There were, however, significant differences between subgroups on verbal but not performance IQ. The regression model including the net scores from the two decision-making tasks and verbal IQ predicted abstinence status with very high sensitivity and moderate specificity. These findings indicate that cocaine-dependent users showing decision-making profiles compatible with insensitivity to future consequences at treatment onset are at significantly higher risk of drug relapse down the line. The significant association between decision-making and 3-month cocaine relapse is in agreement with previous findings in alcohol and opiate users (De Wilde et al. 2013; Passetti et al. 2008). We extend these findings by identifying specific decision-making profiles that are

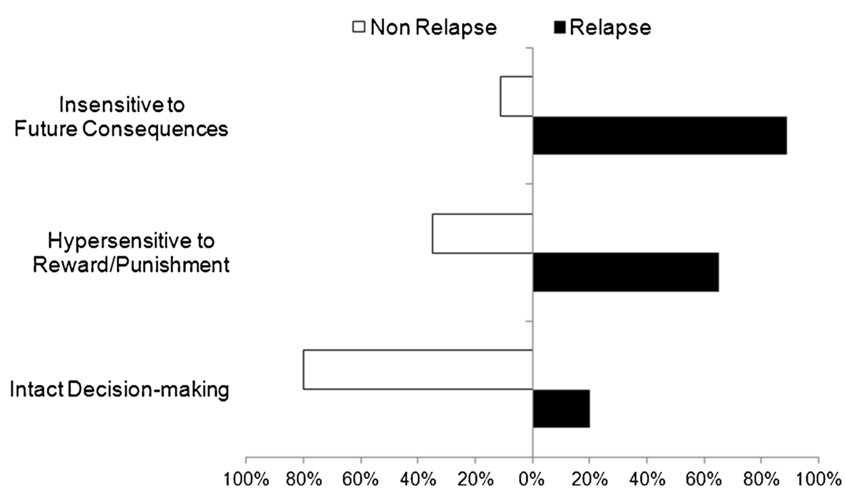

Fig. 1 Proportion of relapsing and non-relapsing participants within each of the decision-making profiles: insensitive to future consequences (n=9), hypersensitive to reward/punishment (n=17), or intact decision-making (n=5)

Table 2 Inter-correlations (Spearman's *Rho* and *p* values) between verbal IQ, Iowa Gambling Task indices, and cocaine relapse

	Verbal IQ, *Rho* (*p*)	IGT original version net score, *Rho* (*p*)	IGT variant version net score, *Rho* (*p*)	Global impairment in original and variant IGTs, *Rho* (*p*)
Relapse	−0.51 (0.003)	−0.20 (0.26)	−0.47 (0.008)	0.45 (0.01)
Verbal IQ		0.55 (0.001)	0.19 (0.30)	−0.50 (0.004)
IGT original version net score			−0.05 (0.77)	−0.53 (0.002)
IGT variant version net score				−0.67 (0.0001)

predictive of cocaine treatment relapse, and by incorporating an objective and sensitive biomarker of long-term drug relapse, in contrast to previous studies relying on retrospective self-reports.

Based on the decision-making profiles defined by Bechara et al. (2000b, 2002), we found that the performance pattern characterized by impaired sensitivity to future consequences (regardless of their reward or punishment nature) is strongly associated with cocaine relapse: 90 % of cocaine users with this profile relapsed. This profile was originally observed in a subpopulation of alcohol and stimulants polysubstance users (23 % of the original sample, in fitting with 29 % of the current sample) who showed deficits to adjust behavioral choices to both delayed punishments and rewards, and blunted physiological responses before making decisions about risky options (Bechara et al. 2002). This decision-making profile was strikingly similar to that of patients with ventromedial prefrontal cortex lesions (Bechara et al. 2000a, b; Bechara et al. 2002), who are prominently characterized by poor judgment in real-life decisions (Bechara et al. 2000a, b). Therefore, this subpopulation of cocaine users share poor judgment characteristics with ventromedial prefrontal lesion patients, and these characteristics are specifically associated with relapse in the context of stimulant addiction. Ventromedial prefrontal cortex lesions have been associated with deficits in future time perspective, forecast-based choices, and risk-sensitive decisions (Fellows and Farah 2005; Gomez-Beldarrain et al. 2004; Studer et al. 2013). Patients with ventromedial prefrontal lesions are also more prone to make choices that are inconsistent with previously revealed preference values (Camille et al. 2011). By analogy, this subpopulation of cocaine users may have poor ability to foresee/appraise risk and future harmful outcomes and be more prone to display behaviors that are incompatible with pre-committed values (e.g., abstinence). Likewise, in fitting with Bechara et al.'s (2002) results, we found that approximately half of the sample was characterized by impairment in only one version of the Iowa Gambling Task, either the original or the variant version. This pattern was linked to relapse in >60 % of this subpopulation, an association that was significantly driven by impairment in the variant version, in which immediate punishments can blur the prospect of attaining long-term rewards. In the opposite pole of our classification, most of cocaine users with intact performance in the two decision-making tasks (80 %) maintained abstinence after 3 months, suggesting that preserved decision-making skills contribute to resilience to relapse. Since decision-making deficits are at least partly malleable (Alfonso et al. 2011), our findings suggest that behavioral and pharmacological interventions targeting these deficits can substantially improve outcomes in the at-risk subpopulation. Emerging interspecies evidence suggests that opioid molecules warrant further investigation as "cognitive enhancers" for decision-making deficits (Lutz and Kieffer 2013). In rats, mu opioid receptors in the nucleus accumbens mediate goal-driven decisions (Laurent et al. 2012), and in humans, buprenorphine (a mu opioid agonist/kappa antagonist) treatment has shown to improve decision-making in opiate users (Pirastu et al. 2006).

Together with decision-making, verbal but not performance IQ scores differed between relapsers and non-relapsers. The regression model incorporating verbal IQ provided the best estimates of relapse prediction, and therefore, our results suggest that verbal IQ should be taken into account when estimating risk of relapse. The relevance of verbal IQ in predicting relapse is in agreement with previous findings (Wehr and Bauer 1999) and expectable, considering that verbal IQ brings together a constellation of demographic factors (e.g., age, education, occupation; Crawford et al. 1989) that

Table 3 Sensitivity and specificity of the regression model involving Iowa Gambling Tasks' net scores and IQ scores as predictors and cocaine relapse as dependent measure

Observed	Predicted group membership		Negative/positive predictive value
	Non-relapse	Relapse	
Non-relapse	9 (90)	2 (9.5)	81.8
Relapse	1 (10)	19 (90.5)	95
Overall			90.3

are linked to poorer addiction treatment outcome (Reske and Paulus 2008). Conversely, performance IQ was not associated with relapse. In contrast to verbal IQ, performance IQ is substantially less influenced by demographic factors (Crawford et al. 1989). Moreover, it has been specifically associated with the function of dorsomedial and dorsolateral prefrontal-striatal brain networks (Burgaleta et al. 2013; Gong et al. 2005). These brain networks are primarily involved in executive control skills (Bissonette et al. 2013; Monchi et al. 2001) and are relatively independent from brain networks involved in value-based decision-making (Glascher et al. 2012). Interestingly, executive control skills have been significantly associated with addiction treatment *process* outcomes (treatment retention or treatment commitment; Aharonovich et al. 2003, 2006, 2008; Streeter et al. 2008; Turner et al. 2009) but not with relapse (Passetti et al. 2008). Conversely, the opposite is true for decision-making measures, which are predictive of relapse (De Wilde et al. 2013; Passetti et al. 2008; Paulus et al. 2005) but not of treatment process indicators (Verdejo-Garcia et al. 2012). Therefore, our results, together with previous findings, point to the existence of separate pathways, with executive control measures linked to treatment process (but not relapse) and decision-making measures linked to long-term relapse (but not treatment process). This dissociation is reminiscent of findings from the preclinical literature, in which impulsive choice (but not impulsive action) is predictive of cue-induced stimulant relapse (Broos et al. 2012; Diergaarde et al. 2008).

Overall, this study shows that cocaine-dependent users with decision-making profiles characterized by insensitivity to future consequences are at higher risk of relapse. These findings provide novel insights about decision-making profiles associated with relapse. Our findings as well show that the combined use of two decision-making tests and an IQ test can provide accurate detection of treatment participants at risk of relapse. Both decision-making and IQ tests can be easily implemented in clinical settings, and therefore, our findings have clear potential for translation. Moreover, our results identify an important target for behavioral and pharmacological interventions for cocaine dependence. This study has important strengths. First, we recruited and examined a carefully selected and clinically representative sample of cocaine users without other substance dependences or medical comorbidities. The study sample (followed up at 3 months) was extracted from a larger cohort of treatment commencers that performed comprehensive diagnostic assessments and baseline cognitive measures under supervised abstinence. Although there was a risk of a self-selection bias in the retained subsample, preliminary analyses showed that there were no significant differences between non-retained and retained participants on demographic, clinical, or cognitive variables. Second, we incorporated an objective assessment of cocaine relapse. This is an important advantage relative to self-report, since empirical and meta-analytic studies comparing the two methodologies have revealed significant underreporting of cocaine use in clinical samples of cocaine users (Hjorthoj et al. 2012; Ledgerwood et al. 2008). A potential disadvantage of hair-indexed relapse is the debatable nature of cut-offs. Therefore, we established a stringent cut-off (<0.3 ng/mg) based on the current legal European standards (≤0.5 ng/mg) (Agius and Kintz 2010). Moreover, the use of more conservative cut-offs did not change the results, supporting the reliability and validity of this approach. Third, our results were fairly consistent with previous findings collected by different groups on diverse treatment samples, including alcohol, opiates, or methamphetamine users (De Wilde et al. 2013; Passetti et al. 2008; Paulus et al. 2005), and patients with bipolar diagnoses and concurrent cocaine use (Nejtek et al. 2013). Replication across studies emphasizes the reliability of decision-making measurements for prediction of relapse and the generalizability of this linkage. The main limitation of the study refers to the limited sample size and to the fact that the main findings apply to a fraction of that sample (about one-third of participants). To address this limitation and to avoid the risk of type I error, we have conducted the most appropriate statistical analyses for the data distributions (Lehmann 1998), and we have checked the fulfillment of required assumptions for all statistical analyses. Moreover, in support of validity, there is previous evidence about the existence of this subpopulation of stimulant-dependent users with poor decision-making skills in larger samples (Bechara et al. 2002) and evidence about the impact of decision-making on relapse in different populations. Here, we provide novel findings about the clinical relevance of this particular decision-making profile for identifying at-risk patients and fostering tailored interventions.

Funding and disclosure This study has been funded by the grants from the Spanish Ministry of Health: project grant COPERNICO, Drug Abuse Plan (Plan Nacional sobre Drogas Convocatoria 2009) and program grant RETICS, Carlos III Health Institute (Instituto de Salud Carlos III, Red de Trastornos Adictivos).

References

Agius R, Kintz P (2010) Guidelines for European workplace drug and alcohol testing in hair. Drug Test Anal 2:367–376

Aharonovich E, Nunes E, Hasin D (2003) Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. Drug Alcohol Depend 71:207–211

Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV (2006) Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend 81:313–322

Aharonovich E, Amrhein PC, Bisaga A, Nunes EV, Hasin DS (2008) Cognition, commitment language, and behavioral change among cocaine-dependent patients. Psychol Addict Behav 22:557–562

Albein-Urios N, Martinez-Gonzalez JM, Lozano-Rojas O, Verdejo-Garcia A (2013) Executive functions in cocaine-dependent patients with cluster B and cluster C personality disorders. Neuropsycholoy 28:84–90

Alfonso JP, Caracuel A, Delgado-Pastor LC, Verdejo-Garcia A (2011) Combined goal management training and mindfulness meditation improve executive functions and decision-making performance in abstinent polysubstance abusers. Drug Alcohol Depend 117:78–81

Back SE, Hartwell K, DeSantis SM, Saladin M, McRae-Clark AL, Price KL et al (2010) Reactivity to laboratory stress provocation predicts relapse to cocaine. Drug Alcohol Depend 106:21–27

Bechara A, Damasio H, Damasio AR (2000a) Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 10:295–307

Bechara A, Tranel D, Damasio H (2000b) Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 123(Pt 11):2189–2202

Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE (2001) Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia 39:376–389

Bechara A, Dolan S, Hindes A (2002) Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? Neuropsychologia 40:1690–1705

Bisaga A, Aharonovich E, Cheng WY, Levin FR, Mariani JJ, Raby WN et al (2010) A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. Drug Alcohol Depend 111:97–104

Bissonette GB, Powell EM, Roesch MR (2013) Neural structures underlying set-shifting: roles of medial prefrontal cortex and anterior cingulate cortex. Behav Brain Res 250:91–101

Broos N, Diergaarde L, Schoffelmeer AN, Pattij T, De Vries TJ (2012) Trait impulsive choice predicts resistance to extinction and propensity to relapse to cocaine seeking: a bidirectional investigation. Neuropsychopharmacology 37:1377–1386

Burgaleta M, Johnson W, Waber DP, Colom R, Karama S (2013) Cognitive ability changes and dynamics of cortical thickness development in healthy children and adolescents. NeuroImage 84C:810–819

Camille N, Griffiths CA, Vo K, Fellows LK, Kable JW (2011) Ventromedial frontal lobe damage disrupts value maximization in humans. J Neurosci 31:7527–7532

Conners CK (1999) Clinical use of rating scales in diagnoses and treatment of attention deficit- hyperactivity disorder. Pediatr Clin North Americ 46:857–870

Cooper GA, Kronstrand R, Kintz P (2012) Society of Hair Testing guidelines for drug testing in hair. Forensic Sci Int 218:20–24

Crawford JR, Stewart LE, Cochrane RH, Foulds JA, Besson JA, Parker DM (1989) Estimating premorbid IQ from demographic variables: regression equations derived from a UK sample. Br J Clin Psychol 28(Pt 3):275–278

De Wilde B, Verdejo-Garcia A, Sabbe B, Hulstijn W, Dom G (2013) Affective decision-making is predictive of three-month relapse in polysubstance-dependent alcoholics. Eur Add Res 19:21–28

Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer AN et al (2008) Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. Biol Psychiatry 63:301–308

Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW (2008) A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry 165:179–187

Fellows LK, Farah MJ (2005) Dissociable elements of human foresight: a role for the ventromedial frontal lobes in framing the future, but not in discounting future rewards. Neuropsychologia 43:1214–1221

First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I). Biometric Research Department, New York

Garavan H, Brennan KL, Hester R, Whelan R (2013) The neurobiology of successful abstinence. Curr Opin Neurobiol 23:668–674

Garcia-Fernandez G, Secades-Villa R, Garcia-Rodriguez O, Alvarez-Lopez H, Sanchez-Hervas E, Fernandez-Hermida JR et al (2011) Individual characteristics and response to contingency management treatment for cocaine addiction. Psicothema 23:114–118

Glascher J, Adolphs R, Damasio H, Bechara A, Rudrauf D, Calamia M et al (2012) Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. Proc Natl Acad Sci U S A 109:14681–14686

Gomez-Beldarrain M, Harries C, Garcia-Monco JC, Ballus E, Grafman J (2004) Patients with right frontal lesions are unable to assess and use advice to make predictive judgments. J Cogn Neurosci 16:74–89

Gong QY, Sluming V, Mayes A, Keller S, Barrick T, Cezayirli E et al (2005) Voxel-based morphometry and stereology provide convergent evidence of the importance of medial prefrontal cortex for fluid intelligence in healthy adults. NeuroImage 25:1175–1186

Hjorthoj CR, Hjorthoj AR, Nordentoft M (2012) Validity of timeline follow-back for self-reported use of cannabis and other illicit substances—systematic review and meta-analysis. Addict Behav 37: 225–233

Kaufman AS, Kaufman NL (1990) Kaufman Brief Intelligence Test. American Guidance Service, Circle Pines

Knapp WP, Soares BG, Farrel M, Lima MS (2007) Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders. Cochrane Database Syst Rev CD003023

Laurent V, Leung B, Maidment N, Balleine BW (2012) mu- and delta-opioid-related processes in the accumbens core and shell differentially mediate the influence of reward-guided and stimulus-guided decisions on choice. J Neurosci 32:1875–1883

Ledgerwood DM, Goldberger BA, Risk NK, Lewis CE, Price RK (2008) Comparison between self-report and hair analysis of illicit drug use in a community sample of middle-aged men. Addict Behav 33: 1131–1139

Lehmann E (1998). Nonparametrics—statistical methods based on ranks (Revised First Edition). San Francisco: Holden-Day Inc

Lobo A, Perez-Echeverria MJ, Artal J (1986) Validity of the scaled version of the General Health Questionnaire (GHQ-28) in a Spanish population. Psychol Med 16:135–140

Loranger AW, Sartorius N, Andreoli A, Berger P, Buchheim P, Channabasavanna SM et al (1994) The International Personality Disorder Examination. The World Health Organization/Alcohol, Drug Abuse, and Mental Health Administration international pilot study of personality disorders. Arch Gen Psychiatry 51:215–224

Lutz PE, Kieffer BL (2013) The multiple facets of opioid receptor function: implications for addiction. Curr Opin Neurobiol 23:473–479

McKay JR, Foltz C, Stephens RC, Leahy PJ, Crowley EM, Kissin W (2005) Predictors of alcohol and crack cocaine use outcomes over a 3-year follow-up in treatment seekers. j Subst Abuse Treat 28(Suppl 1):S73–S82

McMahon RC (2001) Personality, stress, and social support in cocaine relapse prediction. J Subst Abuse Treat 21:77–87

Monchi O, Petrides M, Petre V, Worsley K, Dagher A (2001) Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J Neurosci 21:7733–7741

Nejtek VA, Kaiser KA, Zhang B, Djokovic M (2013) Iowa Gambling Task scores predict future drug use in bipolar disorder outpatients with stimulant dependence. Psychiatry Res in press.

Passetti F, Clark L, Mehta MA, Joyce E, King M (2008) Neuropsychological predictors of clinical outcome in opiate addiction. Drug Alcohol Depend 94:82–91

Pattij T, De Vries TJ (2013) The role of impulsivity in relapse vulnerability. Curr Opin Neurobiol 23:700–705

Paulus MP, Tapert SF, Schuckit MA (2005) Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. Arch Gen Psychiatry 62:761–768

Pichini S, Ventura M, Pujadas M, Ventura R, Pellegrini M, Zuccaro P et al (2004) HAIRVEQ: an external quality control scheme for drugs of abuse analysis in hair. Forensic Sci Int 145:109–115

Pirastu R, Fais R, Messina M, Bini V, Spiga S, Falconieri D et al (2006) Impaired decision-making in opiate-dependent subjects: effect of pharmacological therapies. Drug Alcohol Depend 83:163–168

Reske M, Paulus MP (2008) Predicting treatment outcome in stimulant dependence. Ann N Y Acad Sci 1141:270–283

Sofuoglu M, Waters AJ, Poling J, Carroll KM (2011) Galantamine improves sustained attention in chronic cocaine users. Exp Clin Psychopharmacol 19:11–19

Streeter CC, Terhune DB, Whitfield TH, Gruber S, Sarid-Segal O, Silveri MM et al (2008) Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. Neuropsychopharmacology 33:827–836

Studer B, Manes F, Humphreys G, Robbins TW, Clark L (2013) Risk-sensitive decision-making in patients with posterior parietal and ventromedial prefrontal cortex injury. Cereb Cortex.

Turner TH, LaRowe S, Horner MD, Herron J, Malcolm R (2009) Measures of cognitive functioning as predictors of treatment outcome for cocaine dependence. J Subst Abuse Treat 37:328–334

Verdejo-Garcia AJ, Lopez-Torrecillas F, Aguilar de Arcos F, Perez-Garcia M (2005) Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav 30:89–101

Verdejo-Garcia A, Betanzos-Espinosa P, Lozano OM, Vergara-Moragues E, Gonzalez-Saiz F, Fernandez-Calderon F et al (2012) Self-regulation and treatment retention in cocaine dependent individuals: a longitudinal study. Drug Alcohol Depend 122:142–148

Wehr A, Bauer LO (1999) Verbal ability predicts abstinence from drugs and alcohol in a residential treatment population. Psychol Rep 84: 1354–1360