## Neuropsychological consequences of alcohol and drug abuse on different components of executive functions


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# Neuropsychological consequences of alcohol and drug abuse on different components of executive functions

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**Abstract**

Several studies have shown alterations in different components of executive functioning in users of different drugs, including cannabis, cocaine and heroin. However, it is difficult to establish a specific association between the use of each of these drugs and executive alterations, since most drug abusers are polysubstance abusers, and alcohol is a ubiquitous confounding factor. Moreover, in order to study the association between consumption of different drugs and executive functioning, the patterns of quantity and duration of drugs used must be considered, given the association between these parameters and the executive functioning alteration degree. Based on the multicomponent approach to executive functions, the aims of the present study were: (i) to analyse the differential contribution of alcohol versus cocaine, heroin and cannabis use on executive functions performance; and (ii) to analyse the contribution made by the severity of the different drugs used (quantity and duration patterns) on these functions in a sample of polysubstance abusers that requested treatment for cannabis-, cocaine- or heroin-related problems. We administered measures of fluency, working memory, analogical reasoning, interference, cognitive flexibility, decision-making and self-regulation to two groups: 60 substance-dependent individuals (SDIs) and 30 healthy control individuals (HCIs). SDIs had significantly poorer performance than HCIs across all of the executive domains assessed. Results from hierarchical regression models showed the existence of common correlates of the use of alcohol, cannabis and cocaine on verbal fluency and decision-making; common correlates of quantity of cannabis and cocaine use on verbal working memory and analogical reasoning; common correlates of duration of cocaine and heroin use on shifting; and specific effects of duration of cocaine use on inhibition measures. These findings indicate that alcohol abuse is negatively associated with fluency and decision-making deficits, whereas the different drugs motivating treatment have both generalized and specific deleterious effects on different executive components.

**Keywords**

alcohol, cannabis, cocaine, executive functions, heroin, severity of use

## Introduction

Drug use has increased notably among the world population, according to the United Nations World Drug Report 2008 (from the United Nations Office of Drugs and Crime, UNODC, 2008). It has been estimated that 4.9% of the world's population aged 15–64 have used drugs at least once over 2007–2008, and 0.6% of the world's population have drug-related problems, poly-consumption of diverse substances, such as heroin, cocaine, cannabis, amphetamines and ecstasy (MDMA), being the predominant abuse pattern (UNODC, 2008) especially in those individuals that demand treatment (European Monitoring Centre for Drugs and Drug Addiction, EMCDDA, 2008). In parallel with the increase of drug-related problems, there is increasing consensus on the notion of addiction as a brain disorder characterized by longstanding changes in cognitive functioning, especially in so-called executive functions (i.e. higher-order skills responsible for selection, monitoring and fine-tuning of goal-directed behaviour) (Goldstein and Volkow, 2002; Lubman et al., 2004). Recent evidence from animal and human studies indicate that specific components of executive functions, including dysfunctional impulsivity and decision-making, may predate initiation of drug use and mediate the transition between drug use and drug dependence (Belin et al., 2008; Dalley et al., 2007; Tarter et al., 2003). Accordingly, human studies have shown mild executive deficits in recreational users of cannabis and psychostimulants (De Win et al., 2007; Leland and Paulus, 2005). On the other hand, there is evidence that intensive exposure leading to dependence to different drugs, including cannabis, psychostimulants and opioids, dose-dependently impair several domains of executive functions (i.e. selective attention, inhibition, flexibility) and prefrontal cortex structure and function in animals (Jentsch et al., 2002; Stalnaker et al., 2009; Verrico et al., 2004; Yang et al., 2007) and humans (Bolla et al., 2003, 2004, 2005;

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Verdejo-Garcia et al., 2004; Whitlow et al., 2004). As compared with recreational users, executive deficits in individuals with substance dependence are more generalized (i.e. affecting mechanisms of access, working memory, inhibition, planning, flexibility and decision-making) and greater in magnitude (i.e. effect sizes ranging 0.5–2.2) (Verdejo-García and Pérez-García, 2007). Executive dysfunction is especially relevant in the context of substance dependence treatment, since performance on indices of executive functioning has been strongly associated with treatment retention and drug relapse (Aharonovich et al., 2006, 2008; Passetti et al., 2008; Streeter et al., 2008). Currently, cannabis, heroin and cocaine are the illegal drugs that generate more treatment demands in the European Union (EMCDDA 2008), and therefore there is a need to better understand the selective effects of these drugs on executive functions among substance dependents.

Despite being traditionally considered as a general cognitive domain (Denckla and Reiss, 1997; Zelazo et al., 1997), the literature agrees on the existence of a number of executive components or sub-functions (such as access, working memory, inhibition, flexibility or decision-making) (Fisk and Sharp, 2004; Miyake et al., 2000; Verdejo-García and Pérez-García, 2007). Evidence from lesion research and functional neuroimaging studies has supported this view by showing that discrete executive mechanisms are endorsed by differentiated neural systems. Hence, there is evidence of the prominent roles of the dorsolateral prefrontal cortex in working memory (D'Esposito et al., 1999), the inferior frontal gyrus and supplementary motor area in response inhibition (Aron et al., 2003; Picton et al., 2007), the lateral orbitofrontal cortex in cognitive flexibility (Cools et al., 2002), the frontal pole (Area 10) in multitasking (Dreher et al., 2008; Gilbert et al., 2006) and the medial orbitofrontal cortex in decision-making (Bechara et al., 1994). Although distinct, these processes are flexibly assembled in response to complex task demands (Collette et al., 2005). Therefore, the abuse of different drugs may both selectively and commonly impair these separate but interrelated executive components. In the last few years, several studies have shown decrements in differentiated components of executive functioning in cannabis, cocaine and heroin abusers/dependents, the type of addicted individuals forming our sample. Studies have found impairments in working memory, decision-making, attention and planning in cannabis abusers/dependents (Bolla et al., 2005; Medina et al., 2007; Verdejo-García et al., 2007a; Wadsworth et al., 2006), impairments in decision-making, working memory and inhibition in cocaine abusers/dependents (Bolla et al., 2003; Fillmore et al., 2002; Kübler et al., 2005; Verdejo-García et al., 2007a) and impairments in decision-making, inhibition and flexibility in heroin abusers/dependents (Brand et al., 2008; Fishbein et al., 2007; Lee and Pau, 2002; Pau et al., 2002; Verdejo-García et al., 2005a). However, it is difficult to establish a selective association between decrements in separate executive tasks and the abuse/dependence of any given drug, since virtually all of these studies have been conducted in polysubstance using groups. Along with the potential detrimental effects of aging and lower education on executive decline (Van der Elst et al., 2006; Verhaeghen and Cerella, 2002), one of the main confusing variables in most of these studies is co-abuse of alcohol, which is ubiquitous among polysubstance abusers. Alcohol abuse and dependence are related to long-lasting executive impairments affecting fluency, working memory, inhibition, flexibility and decision-making, and decreases in prefrontal cortex structure (Chanraud et al., 2007; Loeber et al., 2009; Pitel et al., 2009). Furthermore, there is evidence of dose-dependent effects of severity of alcohol use on executive performance decrements (Glass et al., 2009). More importantly, there is some evidence that alcohol abuse may be more strongly associated with certain aspects of executive dysfunction (i.e. sustained attention, planning or flexibility) than the co-abuse of other drugs, such as cocaine (Bolla et al., 2000; Goldstein et al., 2004) or heroin (Fishbein et al, 2007). Therefore, alcohol co-abuse is a relevant confounding variable that complicates the interpretation of previously observed associations between cannabis, cocaine or heroin abuse and impairment of separate executive processes (Abi-Saab et al., 2005; Di Sclafani et al., 2002; Fishbein et al., 2007; Robinson et al., 1999). Nicotine is also a relevant confounding variable, but its neurocognitive effects appear to be more related to processing speed and memory functioning, with less deleterious effects on executive functions (Swan and Lessov-Schlaggar, 2007). On the other hand, in order to examine the association between abuse/dependence of different drugs and executive functioning, the patterns of quantity and duration of use of these drugs must be considered. As we explained earlier, there is a strong association between the intensity of drug use (in terms of both quantity and duration of use) and the degree of executive functions impairment and frontal cortex dysfunction (see Beveridge et al., 2008). In this regard, several studies have shown consistent associations between the severity of cannabis use and alterations in inhibition, flexibility and decision-making (Bolla et al., 2002, 2005; Verdejo-García et al., 2005b), between the severity of cocaine use and inhibition impairments (Bolla et al., 2000; Fillmore and Rush, 2002; Roselli and Ardila, 1996; Verdejo-García et al., 2005b) and between the severity of opioid consumption and cognitive flexibility decrements (Lyvers and Yakimoff, 2003).

Therefore, based on the multicomponent approach to executive functions, this study is aimed at: (i) analysing the independent impact of the three main drugs motivating treatment demand (cocaine, heroin and cannabis) versus the impact of alcohol co-abuse on polysubstance dependents' executive functions performance, and (ii) analysing the contribution made by the quantity and duration of consumption of the different drugs analysed on executive functions performance. We expect that alcohol and other drugs of abuse have a differential contribution in the separate components of the executive functions analysed. To reach both aims, we chose to make a three-stage multiple regression approach aimed to differentiate between detrimental effects due to the effects of demographic variables (age and education), those related to the effects of alcohol, and those related to the effects of the main drugs of choice motivating treatment (especially after discounting demographic and alcohol effects).

## Method and materials

### *Participants*

Sixty substance-dependent individuals (SDIs) (eight female), aged 21–49 years, and 30 healthy control individuals (HCIs)

(six female), aged 18–49 years, participated in this study. All participants were Spaniards (European background) and spoke Spanish as their native language. SDIs and HCIs participants were matched for gender, but not for age or education level, which were used as independent variables in regression analyses. In Table 1, we present the main sociodemographic characteristics of both groups. SDIs were selected during their treatment at the 'Proyecto Hombre' rehabilitation centre, an intreatment therapeutic community in Granada, Spain. This centre provides a controlled environment for dishabituation and treatment of drug abuse. SDIs were in a situation of controlled abstinence and urine toxicology screening (One Step Syva rapid tests for alcohol, cannabis-THC, amphetamines, benzodiazepines, cocaine and opiates) was conducted on these individuals weekly, allowing us to rule out drug use throughout the entire period of abstinence. Selection criteria for participants in the SDIs group were: (i) meeting the DSM-IV criteria for substance dependence; (ii) absence of documented comorbid mood or personality disorders as assessed by clinical reports; (iii) absence of documented head injury or neurological disorders; (iv) not being enrolled in opioid substitution treatment; and (v) minimum abstinence duration of 15 days before testing, although the median duration of abstinence for any drug in the group was of 32 weeks, so that it was possible to rule out the presence of alterations associated with the acute or short-term effects of the drugs. The SDIs sample was principally composed of polysubstance abusers who requested treatment for cocaine, heroin or cannabis use. Although five SDIs showed high level of MDMA use (a lifetime consumption of more than 50 pills), none of them requested treatment for this MDMA consumption. In Table 2, we present the consumption characteristics of the SDIs group.

Control participants were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these control participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than six units of alcohol per week); (ii) absence of documented major psychiatric disorders; (iii) absence of documented head injury or neurological disorder; and (iv) not being on any medication affecting the central nervous system (CNS), including antidepressants, mood stabilizers, anxiolytics, antiepileptics or antipsychotics. The mean amount of alcohol use in male HCIs was 5.43 units/month (SD = 5.24) and the mean of alcohol duration consumption was 6.12 years (SD = 6.06). In female HCIs the mean amount of alcohol use was 5.33 units/month (SD = 8.35) and the mean of alcohol duration consumption was 9.00 years (SD = 11.45).

## *Instruments and assessment procedures*

*Background information:* In order to examine the lifetime use of different substances, we used the *Interview for Research on Addictive Behaviour* (IRAB) (López-Torrecillas et al., 2001). This instrument evaluates the dosing, frequency (consumption episodes per month) and duration of use of a number of substances. For every substance the subject had actually consumed, including cannabis, alcohol, cocaine, heroin, amphetamines, benzodiazepines and MDMA, the following information was requested:

(1) The average amount of each target drug taken in each episode of use (number of joints for cannabis; number of grams for cocaine and heroin; and number of units for alcohol, considering that a glass of Scotch whisky equals one unit, while a glass of wine or beer equals 0.5 units), and the frequency of these consumption episodes per month (daily, between one and three times per week, once a week, between one and three times per month or once a month).
(2) The number of years elapsed since the onset of use.

**Table 2.** Descriptive scores for patterns of quantity and duration of drug use in the group of substance-dependent individuals (SDIs)

| | | SDIs | |
|---|---|---|---|
| Substances | Variables | Mean | SD |
| Cocaine | Grams/month | 49.53 | 42.22 |
| | Duration (years) | 8.07 | 5.57 |
| Cannabis | Joints/month | 148.65 | 179.87 |
| | Duration (years) | 8.27 | 7.63 |
| Heroin | Grams/month | 10.90 | 24.05 |
| | Duration (years) | 1.90 | 4.14 |
| Alcohol | Units/month | 506.98 | 445.58 |
| | Duration (years) | 10.40 | 7.17 |
| | Abstinence (weeks) | 33.28 | Median = 32.00 |

**Table 1.** Descriptive scores for the sociodemographic characteristics of substance-dependent individuals (SDIs) and healthy control individuals (HCIs)

| | SDIs | | HCIs | | | |
|---|---|---|---|---|---|---|
| Socio-demographic variables | Mean | SD | Mean | SD | $t/\chi^2$ | *p*-value |
| Age | 30.58 | 7.08 | 26.40 | 8.03 | 2.52* | 0.013 |
| Years of education | 9.88 | 2.48 | 11.63 | 2.04 | −3.33* | 0.001 |
| Gender (%) | | | | | 0.67** | 0.538 |
| Men | 86.7 | | 80 | | | |
| Women | 13.3 | | 20 | | | |

*Value of Student's *t*.
**Value of chi-squared $\chi^2$.

From these data, two independent measures of *quantity* (average amount taken in each episode of use × monthly frequency) and *duration* (years) of consumption were calculated for each drug abused by the participants.

*Neuropsychological tests:* We used a selective battery of neuropsychological tests designed to assess several components of executive functions, including fluency, working memory, analogical reasoning, interference and cognitive flexibility (which have been associated with the functioning of different sections of the lateral prefrontal cortex) (Koechlin and Summerfield, 2007), and decision-making and self-regulation during multitasking (which are proposed to relate to more medial and rostral sections of the prefrontal cortex) (Bechara et al., 2000; Levine et al., 2000). Below we describe the tasks used grouped by executive components.

Fluency tests:

- FAS (verbal fluency) (Lezak, 2004): participants were asked to produce in 1 min the greatest possible number of words that start first with the letter 'F', next with the letter 'A' and finally with the letter "S". The main dependent variable was the sum of the words produced with these three letters.
- Ruff figural fluency test (RFFT) (Ruff, 1996): consists of five parts that present a similar structure, made up of 35 boxes with five dots in each. Participants were required to draw as many different figures as possible joining with straight lines at least two of the five dots each box contains. The main dependent variable used in this test was the total number of original figures produced.

Working memory tests:

- Letter number sequencing (LNS) (Wechsler adult intelligence scale, WAIS-III) (Wechsler, 1997a): the participant is read a sequence in which letters and numbers are combined, and they are asked to reproduce the sequence heard, first placing the numbers in ascending order and then the letters in alphabetical order. The test consists of seven elements, and each element consists of three tries. In each element, the sequence is read at one letter or number per second. The administration is stopped when the participant misses three tries in the same element. The main dependent variable used on this test was the number of correct answers.
- Spatial span (Wechsler memory scale, WMS-III) (Wechsler, 1997b): this task consists of a platform on which a series of 10 three-dimensional cubes are placed and organized according to a pre-determined pattern. The test consists of two parts: forward and backward span. In both cases the evaluator touches a series of cubes (whose number increases in successive trials) with his finger, and the participant must touch the same cubes as the evaluator (1) in the same order (forward span) or (2) in inverse order (backward span). The main dependent variable used in these tests was the total number of correct responses.

Analogical reasoning tests:

- Similarities (WAIS-III) (Wechsler, 1997a): pairs of words that represent common objects or concepts are read, and participants have to indicate how these objects/concepts are similar. This task consists of 19 pairs of words. The administration is stopped when the participant misses four consecutive elements. The main dependent variable analysed in this test was the number of correct answers.
- Category test (DeFilippis, 2002): a computerized version of this test was administered. The task consists of 208 stimuli that have different types of designs (squares, triangles, circles, letters, etc.) grouped in seven subtests with different rules. For all of the stimuli included in the same subtest, there is an underlying rule that determines the appropriateness of the responses throughout this subtest. However, this rule changes in the next subtest, so that the participant's performance on the test depends on the ability to infer these rules, and modify them when they are no longer valid. Test instructions are intentionally ambiguous: we explained to the participant that different types of designs will appear consecutively on the screen, and that each design is associated with one of the first four numbers: 1, 2, 3 or 4. For each stimulus the participant must press the key with the number they think is associated with that design, and the computer provides auditory feedback related to the correctness or incorrectness of the response provided. The main index of performance on the test was the total number of errors on the seven subtests.

Tests of interference and shifting:

- Stroop: this test consists of three forms, each of which contains 100 elements distributed in five columns of 20 elements each. The first form (WORDS condition) is made up of the words 'RED', 'GREEN' and 'BLUE' ordered randomly and printed in black ink. In this condition the participant is asked to read aloud, as quickly as possible, the words written on this page in a time set at 45 s. The second form consists of strings of 'XXXX' (COLORS condition) printed in red, blue or green ink. In this condition, the participant is asked to read aloud as quickly as possible the colour of these elements with a time limit of 45 s. The third form (COLOR-WORD condition) introduces the condition of interference, and it consists of the words from the first form printed in the colours of the second. In this condition, the subject is asked to name the colour of the ink the word is written in, ignoring the word, also in 45 s. The main dependent variable used in this test was the interference score, obtained by subtracting subjects' response latency to WORDS and COLOR (using the formula: WORDS*COLORS/WORDS + COLORS) from their response latency to the COLOR-WORD condition (Golden, 1978).
- Five digit test (5DT) (Sedó, 2005): this consists of four parts of independent application, in which a series of 50 boxes are presented, each of which contains one to five digits (parts 1, 3 and 4) or stars (part 2), organized in

patterns similar to those on domino pieces or playing cards. In part 1 (reading), the participant is asked to read as quickly as possible the digit each box contains. In part 2 (counting), they are asked to count how many stars each box contains. In part 3 (interference), they are asked to count the number of digits each box contains, producing an effect of interference as the boxes present groups of digits that do not correspond to their arithmetic value (e.g. in a box with five twos, the correct response would be five and not two). Finally, in part 4 (shifting), the participant is asked to count, just as in part 3, or read, as in part 1, depending on whether the outline of the box is normal (count, 80% of the stimuli) or of double thickness (read, 20% of the stimuli). Parts 1 and 2 constitute basic measures of attention and processing speed. In contrast, parts 3 and 4 are sensitive to executive processes of inhibition. Therefore, the main dependent variables used in this test were the difference between the performance time on part 3 and the mean of parts 1 and 2 (differential 'interference' score), and the difference between the performance time on part 4 and the means of parts 1 and 2 (differential 'shifting' score).

- Oral Trail Making (OTM) (Sedó et al., 1995): this test includes two independent parts. The first part (OT 1) assesses visuo-spatial and naming abilities. It contains 20 items consisting of numbers (1–20) paired with four familiar fruit images (apple, banana, grapes and orange). The items (containing the number and the paired fruit represented together in 20 little boxes) are spread all over the test form. Participants are asked to visually search for the items by number, and to name the fruit paired with each item (one apple, two orange and so forth). The second part (OT 2) assesses visuo-spatial and cognitive flexibility skills. This portion of the test uses a presentation identical to that in the first part, except that the fruits paired with the numbers are printed in different non-natural colours, in such a way that the shape and the colour of the fruit are always incongruent (e.g. red banana). Participants are asked to visually search for each item by number and to name the fruit paired according to the colour and not the shape (thus, a red banana should be named as 'apple'). The dependent measure was the interference score obtained by subtracting time in part 1 from time in part 2 (OT 2−1).

Decision making:

- Iowa gambling task (IGT) (Bechara et al., 1994): this is a computerized task that factors several aspects of decision-making including uncertainty, risk, and evaluation of reward and punishing events. The IGT involves four decks or cards, decks A′, B′, C′ and D′. Participants were instructed to win as much money as possible by picking one card at a time from each of the four decks in any order until the computer instructed them to stop (after the selection of the 100th card). 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 with different amounts). Two of the decks of cards, decks A′ and B′, produce high immediate gains; however, in the long run, these two decks will take more money than they give, and are therefore considered to be the disadvantageous decks. The other two decks, 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 main dependent variable used on this task was the difference between the number of advantageous and disadvantageous choices [(C + D)−(A + B)] on each of the five blocks of 20 trials of the task.

Self-regulation:

- Revised Strategy Application Test (R-SAT) (Levine et al., 2000; Spanish adaptation by Verdejo-García et al., 2007b): this is an unstructured paper-and-pencil multitasking test sensitive to disturbed self-regulation. It consists of three simple activities: figure tracing, sentence copying and object numbering. Each activity has to be performed in two different stacks (A and B), each containing 10 pages with approximately 12 items each. The items differed in two dimensions: size (they can be large or small) and time required to complete them (they can be brief, taking a couple of seconds, medium or long, taking more than one minute). The different types of stimuli are intermixed within each page, but the number of brief items decreases progressively within each stack. The main goal of the task was to win as many points as possible, considering that large items scored 0 points and small items scored 100 points each. Nonetheless, points were used in the instructions only to see whether participants would respond accordingly, but the dependent variable in this task is the number of items and not points. In order to complete more items, given the limited time, the most efficient strategy (which the participant must discover as they perform the task) is to complete brief items to the exclusion of lengthy items. This requires the inhibition of a tendency to complete all of the items in sequence, which is established on the early pages of each stack, where all of the items are brief. Therefore, the main dependent variable from the R-SAT was the proportion of brief items completed (not including the first page of each stack) with regards to the total number of items attempted.

## Procedure

Participants were assessed individually between April 2003 and November 2007 in a single session that lasted approximately 3 h and 45 min (including breaks) or on two consecutive days, depending on the rehabilitation centre availability. Participants did not consume food, caffeine or nicotine during tests administration, although smoking (a maximum of one cigarette) was allowed during the breaks to avoid nicotine withdrawal effects. SDIs and HCIs were not tested at a fixed time of the day, but to the best of the authors' knowledge there is no consistent evidence of biasing effects of this variable on neuropsychological performance

in this population. The tests included in the study were part of a more comprehensive battery aimed at examining neuropsychological functions in SDIs. Test administration was blocked for all participants and arranged to alternate between verbal and non-verbal tasks and between more- and less-demanding tasks. The order of administration was: FAS, RFFT, LNS, Stroop, Similarities, Category Test, R-SAT, OTM, Spatial Span, 5DT and IGT.

All of the participants in the study were informed about the objectives, benefits and possible inconveniences associated with the research protocol. Likewise, all of the participants signed an informed consent form certifying their voluntary participation. The SDIs and HCIs participants who requested it received a neuropsychological report about their performance on the tests. In addition, the control participants were paid €18 for their participation to ensure motivation.

### Data analysis

First, in order to characterize neuropsychological performance differences between SDIs and HCIs, we conducted independent-samples *t*-tests (for those dependent variables unrelated to age and education: 5DT shifting score, 5DT interference score and R-SAT) or univariate analyses of covariance (ANCOVAs; for those dependent variables significantly associated with age, education or both: FAS, RFFT, LNS, Spatial span, Similarities, Category test total errors, OTM shifting score, Stroop interference score and IGT) using group (SDIs versus HCIs) as a between-subjects factor and age and education as covariates. Next, we explored dependent variables to examine the possible presence of outliers (defined as atypical values by the Explore command of SPSS v.15). Two outliers were detected in the R-SAT proportion of brief items distribution, two outliers were detected in the 5DT–interference score distribution, and three outliers were detected in the 5DT–shifting score distribution. These subjects were removed from further analyses with the corresponding dependent variables; therefore SDIs sample size for R-SAT analyses, $N = 58$, for 5DT interference, $N = 58$ and for 5DT shifting, $N = 57$. Next, we performed a series of multiple regression models to examine the impact of demographic variables, alcohol use and illegal drugs use on executive performance. Since the three illegal drugs motivating treatment demand in this sample were the main focus of the study, we first conducted multiple regression models including only cannabis, cocaine and heroin (both quantity and duration) as predictor variables; these analyses were included to assess the variance attributable to drug use before inclusion of demographics and alcohol. Next, to test the main aim of the study (i.e. to disentangle specific effects of alcohol versus illegal drugs on different executive components and determine the impact of cannabis, cocaine and heroin after discounting the effect of demographics and alcohol abuse), we conducted hierarchical multiple regression analyses. These models were set on three stages: (i) demographic variables associated with executive performance (age and years of education); (ii) total consumption of alcohol, which is the main substance of co-abuse; and (iii) quantity and duration of consumption of cannabis, cocaine and heroin. We developed independent regression model series for the variables quantity and duration of consumption of the different substances, to determine the specific effects of both parameters and avoid collinearity effects. These separate models also allowed us to adjust the number of predictors as a function of sample size: we used a maximum of five predictor variables for a sample size of 90; ratio of 15 cases by predictor variable (a ratio of at least 10 cases by predictor is considered appropriate) (Hair et al., 2000). Therefore, for each analysis we introduced three differentiated blocks of predictor variables in a sequential manner: the first block included the variables of age and years of education, the second block included the total alcohol consumption (i.e. a combined quantity × duration measurement was calculated to avoid that alcohol consumption of healthy control individuals, similar to that of SDIs in duration, yet of quite lower intensity, could slant the contribution of this factor), and finally, the third block included the quantity or duration of consumption of cannabis, cocaine and heroin. The different performance indices of the executive function neuropsychological tests were included as dependent variables. For each new block of variables entered in the regression model, we estimated the $R^2$ of the prediction change associated with that block and its statistical significance, with the aim of determining the differential contribution of each of the blocks to the regression model. To facilitate reading, in text we only present results from hierarchical models showing significant effects of alcohol or drug use after discounting the effects of demographic variables. Data from regression models including only drug use variables are presented in Tables (two first columns), along with hierarchical models.

## Results

### Group differences

SDIs performed significantly poorer than controls on all of the executive indices assessed, with effect sizes ranging from 0.6 (e.g. shifting) to 2.3 (analogical reasoning); see Table 3. All executive indices (with the exception of OTM shifting) yielded effect sizes circa or superior to 0.8 for differences between SDIs and HCIs, which are considered large effects according to Cohen (Zakzanis, 2001).

### Regression models

The coefficients obtained with the hierarchical regression analyses are represented in Table 4, for the models including quantity of consumption, and in Table 5, for the models including duration of consumption. The impact of the entry of each block in each of the steps of the regression model is represented by means of the determination coefficient values ($R^2$). The results of multiple regressions including only drug measures (quantity or duration) are also included in the first two columns of Tables 4 and 5, respectively.

### Quantity of consumption

Fluency: In the FAS test, after controlling for the effects of demographics, the block of total alcohol consumption was a significant predictor of performance. However, the entry of the block of quantity of consumption of other drugs

**Table 3.** Descriptive scores, independent group *t*-tests/univariate analyses of covariance (ANCOVAs), and effect sizes on the neuropsychological measures for substance-dependent individuals (SDIs) and healthy control individuals (HCIs)

| | | SDIs | | HCIs | | | | |
|---|---|---|---|---|---|---|---|---|
| Domain | Task | Mean | SD | Mean | SD | *F/t* | *p*-value | Cohen's delta |
| Fluency | FAS | 33.81 | 10.55 | 51.43 | 9.80 | 46.52[a] | 0.000 | −1.71 |
| | RFFT | 82.86 | 23.72 | 110.33 | 19.94 | 20.11[a] | 0.000 | −1.21 |
| Working memory | LNS | 9.33 | 2.40 | 15.13 | 2.33 | 93.50[a] | 0.000 | −1.57 |
| | Spatial Span | 14.89 | 3.36 | 19.90 | 4.35 | 24.55[a] | 0.000 | −1.35 |
| Reasoning | Similarities | 18.11 | 4.51 | 27.76 | 3.01 | 90.55[a] | 0.000 | −2.37 |
| | CT_tot_errors | 66.89 | 24.01 | 31.80 | 25.32 | 30.86[a] | 0.000 | 1.41 |
| Shifting | 5DT_shift | 25.47 | 9.38 | 20.10 | 5.45 | 2.89[b] | 0.005 | 0.64 |
| | OTM_shift | 21.89 | 15.32 | 14.13 | 7.57 | 2.18[a] | 0.143 | 0.58 |
| Interference | 5DT_interf | 15.74 | 6.46 | 11.10 | 3.77 | 4.28[b] | 0.000 | 0.81 |
| | Strp_interf | −1.67 | 6.07 | 4.15 | 7.24 | 9.63[a] | 0.003 | −0.89 |
| Decision-making | IGT | −2.21 | 22.60 | 37.20 | 26.15 | 47.84[a] | 0.000 | −1.65 |
| Self-regulation | R-SAT | 82.95 | 16.46 | 93.98 | 5.70 | −3.55[b] | 0.001 | −0.79 |

[a]*F*-value.
[b]Student's *t* value.
FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test.

significantly increased the predictive value of demographics and alcohol. The global model revealed that the quantity of cannabis was the most predictive variable of performance on this test. In the RFFT, neither the block of total alcohol consumption nor the block of illegal drugs consumption were predictors of performance on this task.

Working memory: In the LNS test, the block of total alcohol consumption showed a trend to significant effects ($p = 0.057$), but the entry of the block of quantity of consumption of drugs significantly improved the prediction of the former blocks. In the global model we observed that the quantity of cocaine and cannabis use had the highest predictive value of performance. In the Spatial Span task, we observed that the block of total alcohol consumption failed to predict performance on this task. Nevertheless, inclusion of the quantity of consumption of other drugs significantly improved the prediction of demographics and alcohol. The analysis of the global model coefficients showed that the quantity of cocaine use had the highest predictive value of performance on this task.

Reasoning: In the Similarities test, we observed that, after controlling for demographics and alcohol, the block of quantity of consumption of drugs was a significant predictor of performance. The analysis of the global model coefficients showed that the quantity of consumption of cannabis and cocaine were the variables with the highest predictive value of performance on this task. Similarly, in the Category test, the block of quantity of consumption of drugs showed a trend to significantly increase prediction of performance ($p = 0.062$), and the analysis of global model coefficients revealed that the quantity of cocaine was the most predictive variable of performance on this task.

Interference and shifting: In the 5DT (both interference and shifting scores) and the Stroop tests, neither the block of total alcohol consumption nor the block of other drugs had predictive capability of performance on these measures. In the OTM test, the entry of the block of quantity of consumption of drugs improved the prediction of previous blocks significantly, and quantity of heroin consumption was the most predictive variable.

Decision-making: In the IGT we observed that both the block of total alcohol consumption and the block of other drugs significantly predicted performance on this task. When analysing the global model, we observed that total alcohol consumption, quantity of cannabis and quantity of cocaine were the most predictive variables of performance on this task.

Self-regulation: In the R-SAT we observed that only the block of total alcohol consumption showed a trend to significantly predict performance on this task ($p = 0.077$). The inclusion of the block of drug measures failed to increase the prediction of the global model significantly.

*Duration of consumption:* In this section we only refer to the predictive value of the variables of cannabis, cocaine and heroin consumption, since the predictive value of the blocks of total alcohol consumption variable is the same as that of the previously described models.

Fluency: In the FAS test we observed that the block of consumption of drugs (cannabis, cocaine and heroin) improved the predictive value of demographics and alcohol significantly, with duration of cocaine consumption being the

**Table 4.** Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and quantity of cannabis, cocaine and heroin use and neuropsychological performance

| | | Model including only cannabis, cocaine and heroin | | Hierarchical three-stage model including demographics, alcohol and drugs use | | | | |
|---|---|---|---|---|---|---|---|---|
| Domain | Test | $R^2$ adjusted ($p$-value) | Significant contributors | Demographics $R^2$ change ($p$-value) | Alcohol $R^2$ change ($p$-value) | Cannabis/cocaine/ heroin Quantity $R^2$ change ($p$-value) | Full model $R^2$ adjusted ($p$-value) | Significant contributors |
| Fluency | FAS | 0.297 (0.000) | Cann Quant (0.000); Coc Quant (0.027); Heroin Quant (0.039) | 0.096 (0.013) | 0.086 (0.003) | 0.177 (0.000) | 0.313 (0.000) | Cann Quant (0.001) |
| | RFFT | 0.061 (0.038) | Cann Quant (0.066) | 0.133 (0.002) | 0.017 (0.199) | 0.034 (0.399) | 0.124 (0.009) | Educ (0.005) |
| WM | LNS | 0.286 (0.000) | Cann Quant (0.035); Coc Quant (0.000) | 0.171 (0.000) | 0.034 (0.057) | 0.180 (0.000) | 0.341 (0.000) | Educ (0.014); Cann Quant (0.032); Coc Quant (0.001) |
| | Spatial Span | 0.096 (0.009) | Coc Quant (0.015) | 0.109 (0.007) | 0.006 (0.443) | 0.081 (0.049) | 0.137 (0.006) | Coc Quant(0.032) |
| Reasoning | Similarities | 0.207 (0.000) | Cann Quant (0.022); Coc Quant (0.004) | 0.173 (0.000) | 0.030 (0.075) | 0.118 (0.004) | 0.272 (0.000) | Educ (0.005); Cann Quant (0.026); Coc Quant (0.032) |
| | CT_tot_errors | 0.085 (0.016) | Coc Quant (0.027) | 0.074 (0.039) | 0.012 (0.308) | 0.079 (0.062) | 0.103 (0.022) | Coc Quant (0.047) |
| Shifting | 5DT_shift | 0.058 (0.047) | | 0.014 (0.556) | 0.004 (0.558) | 0.079 (0.080) | 0.029 (0.213) | |
| | OTM_shift | 0.130 (0.002) | Coc Quant (0.037); Heroin Quant (0.018) | 0.105 (0.008) | 0.008 (0.375) | 0.092 (0.028) | 0.148 (0.004) | Heroin Quant (0.047) |
| Interference | 5DT_interf | 0.058 (0.046) | | 0.005 (0.814) | 0.011 (0.330) | 0.078 (0.081) | 0.027 (0.225) | |
| | Strp_interf | 0.021 (0.191) | | 0.087 (0.020) | 0.002 (0.667) | 0.036 (0.347) | 0.061 (0.083) | Age (0.073) |
| DM | IGT | 0.260 (0.000) | Cann Quant (0.003); Coc Quant (0.011) | 0.049 (0.111) | 0.127 (0.000) | 0.160 (0.000) | 0.288 (0.000) | Alcoh tot cons (0.037); Cann Quant (0.004); Coc Quant (0.067) |
| Self-regulation | R-SAT | 0.030 (0.136) | Cann Quant (0.084) | 0.011 (0.619) | 0.036 (0.077) | 0.057 (0.168) | 0.038 (0.164) | |

*Note:* WM, Working Memory; DM, Decision-making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Quant, Quantity; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

**Table 5.** Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and duration of cannabis, cocaine and heroin use and neuropsychological performance

| | | Model including only cannabis, cocaine and heroin | | Hierarchical three-stage model including demographics, alcohol and drugs use | | | | |
|---|---|---|---|---|---|---|---|---|
| Domain | Test | $R^2$ adjusted ($p$-value) | Significant contributors | Demographics $R^2$ change ($p$-value) | Alcohol $R^2$ change ($p$-value) | Cannabis/cocaine/ heroin Duration $R^2$ change ($p$-value) | Full model $R^2$ adjusted ($p$-value) | Significant contributors |
| Fluency | FAS | 0.160 (0.000) | Coc Durat (0.012) | 0.096 (0.013) | 0.086 (0.003) | 0.130 (0.002) | 0.262 (0.000) | Age (0.002); Educ (0.026); Coc Durat (0.012) |
| | RFFT | 0.093 (0.010) | Coc Durat (0.007) | 0.133 (0.002) | 0.017 (0.199) | 0.179 (0.033) | 0.179 (0.001) | Educ (0.003); Coc Durat (0.015) |
| WM | LNS | 0.179 (0.000) | Coc Durat (0.020) | 0.171 (0.000) | 0.034 (0.057) | 0.113 (0.005) | 0.269 (0.000) | Educ (0.001); Coc Durat (0.069) |
| | Spatial Span | 0.098 (0.008) | Cann Durat (0.025) | 0.109 (0.007) | 0.006 (0.443) | 0.080 (0.050) | 0.137 (0.006) | Educ (0.012); Cann Durat (0.014) |
| Reasoning | Similarities | 0.193 (0.000) | Coc Durat (0.004) | 0.173 (0.000) | 0.030 (0.075) | 0.144 (0.001) | 0.300 (0.000) | Educ (0.000); Coc Durat (0.009) |
| | CT_tot_errors | 0.106 (0.006) | Cann Durat (0.090) | 0.074 (0.039) | 0.012 (0.308) | 0.073 (0.084) | 0.096 (0.028) | |
| Shifting | 5DT_shift | −0.003 (0.432) | | 0.014 (0.556) | 0.004 (0.558) | 0.052 (0.224) | 0.000 (0.430) | Coc Durat (0.074) |
| | OTM_shift | 0.223 (0.000) | Coc Durat (0.002); Heroin Durat (0.002) | 0.105 (0.008) | 0.008 (0.375) | 0.167 (0.001) | 0.228 (0.000) | Educ (0.062); Coc Durat (0.016); Heroin Durat (0.003) |
| Interference | 5DT_interf | 0.064 (0.035) | Coc Durat (0.066) | 0.005(0.814) | 0.011(0.330) | 0.098(0.036) | 0.048(0.124) | Coc Durat (0.036) |
| | Strp_interf | 0.102 (0.007) | Coc Durat (0.089) | 0.087(0.020) | 0.002(0.667) | 0.076(0.065) | 0.104(0.019) | Educ (0.065) |
| DM | IGT | 0.125 (0.002) | Coc Durat (0.076) | 0.049 (0.111) | 0.127 (0.000) | 0.060 (0.099) | 0.181 (0.001) | Alcoh tot cons (0.013) |
| Self-regulation | R-SAT | −0.019 (0.710) | | 0.011 (0.619) | 0.036 (0.077) | 0.006 (0.916) | −0.017 (0.602) | |

*Note:* WM, Working Memory; DM, Decision Making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Durat, Duration; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

variable with the highest predictive value. In the RFFT the block of duration of drug consumption improved prediction of previous blocks significantly, and duration of cocaine consumption was the variable with the highest predictive value.

Working memory: In the LNS test, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly. Duration of cocaine consumption was the best predictor variable of performance on this task. In the Spatial span task, the block of duration of drug consumption improved prediction of demographics and alcohol significantly, but in this case the variable with the highest predictive value was duration of cannabis consumption.

Reasoning: In the Similarities task, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly, and duration of cocaine consumption was the best predictor of performance on this task. In the Category test, we observed that the block of durations of drugs consumption failed to significantly predict performance on this measure.

Interference and shifting: In the Stroop test, the block of duration of drug consumption was only marginally significant for prediction of performance on this task, and none of the individual drug variables (cannabis, cocaine or heroin) showed significant $\beta$-coefficients. In the 5DT, we observed that, for the interference score, the block of duration of drugs consumption produced a significant improvement in prediction, being the duration of cocaine consumption the best predictor of performance. As for the shifting score, the block of duration of drugs use failed to significantly predict performance, and only duration of cocaine use had a marginally significant effect ($p = 0.074$). In the OTM test, we observed that the block of drugs produced a significant improvement in prediction, with duration of heroin and cocaine being the variables with the highest prediction of performance.

Decision-making: In the IGT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

Self-regulation: In the R-SAT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

### *Summary*

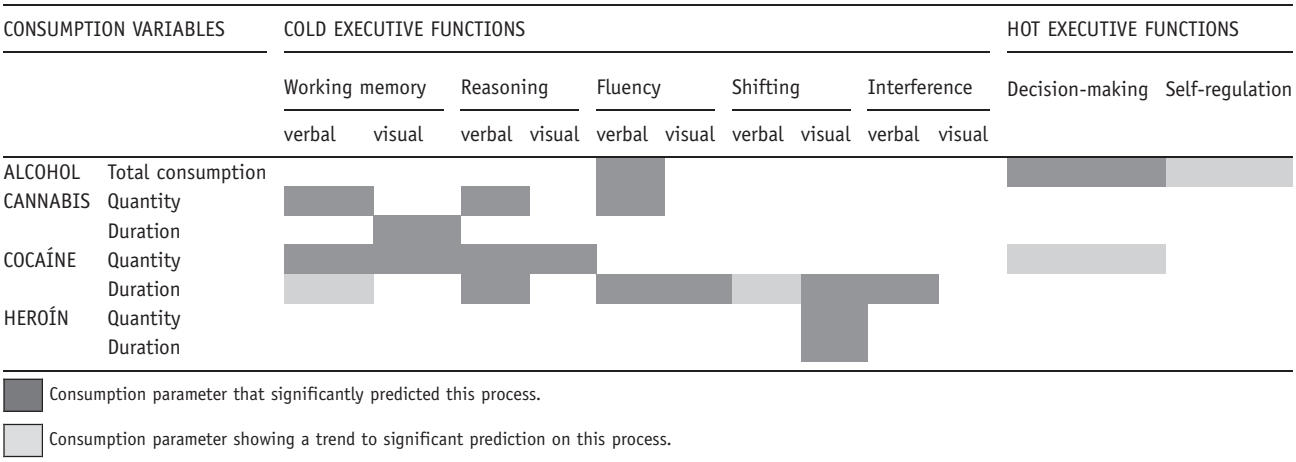
Group comparisons showed that SDIs performed significantly poorer than controls on all of the executive indices assessed, showing large effect sizes for differences on tests of fluency, working memory, reasoning, inhibition and decision-making. The hierarchical regression models showed a significant contribution of total alcohol consumption on verbal fluency and decision-making. As for quantity of consumption of the drugs that motivated treatment, we observed that: (i) the quantity of cannabis consumption predicts performance on verbal working memory, verbal reasoning, verbal fluency and decision-making; (ii) the quantity of cocaine consumption predicts performance on verbal and visual–spatial working memory, verbal and visual reasoning, and decision-making; and (iii) the quantity of heroin consumption predicts performance on visual–spatial shifting. As for duration, we observed that: (i) the duration of cannabis consumption predicts performance on visual working memory only; (ii) the duration of cocaine consumption predicts performance on verbal working memory and reasoning, both verbal and non-verbal fluency and shifting, and interference-based inhibition; and (iii) the duration of heroin consumption predicts performance on visual-spatial shifting (Table 6).

## Discussion

Results showed that SDIs have a broad range of executive impairments, including fluency, working memory, reasoning, inhibition, shifting and decision-making deficits, of moderate to large magnitude according to effect sizes (Cohen's *d* range: 0.6–2.4). Importantly, these decrements are observed in SDIs with a median abstinence duration of 8 months, and therefore they should be regarded as long-term effects with relevant implications for the notion of addiction as a chronic brain disorder associated with frontal systems dysfunction (Goldstein and Volkow, 2002). Previous studies had obtained similar results (see the review by Verdejo-García et al., 2004), but the fact that virtually all SDIs are polysubstance abusers complicates the attribution of specific or generalized executive deficits to the effects of alcohol or any given drug. In this respect, the results from regression models revealed that severity of alcohol use is robustly associated with verbal fluency and decision-making decrements. As for the main drugs motivating treatment (cannabis, cocaine and heroin), results showed that quantity of cannabis and cocaine use have common detrimental effects on verbal working memory, analogical reasoning and decision-making measures, and that duration of cocaine and heroin use have common detrimental effects of visual–spatial shifting measures. On the other hand, we found specific effects of duration of cannabis use on visual–spatial working memory, and of duration of cocaine use on response inhibition.

Our first aim was to separate the effects of alcohol versus drugs use on different components of executive functions. Severity of alcohol use showed significant detrimental effects on verbal fluency and decision-making (on the IGT), and a trend to significant effects on working memory, but not on other executive components. Previous studies had proposed that severity of alcohol abuse was significantly associated with decrements on executive components of planning and flexibility in psychostimulants and heroin abusers co-abusing alcohol (Bolla et al., 2000; Fishbein et al., 2007; Goldstein et al., 2004). However, these studies were conducted in short-term abstinent SDIs (range of 2–4 weeks),

**Table 6.** Summary of significant associations between the different substances analysed and the different components of cold and hot executive functions




whereas one of the few studies available in long-term abstinent alcoholics found that decision-making performance (measured with the IGT) was impaired pervasively in these individuals even after six years of sobriety; being the magnitude of disadvantageous decision-making associated with the duration of peak alcohol use (Fein et al., 2004). Moreover, the alcoholic individuals who had impaired IGT performance had significant grey matter reductions in the amygdala, a key region for the operation of decision-making processes (Bechara et al., 2003). A recent structural magnetic resonance study have also provided evidence of significant structural reductions of grey matter (up to 20% lower) in the bilateral dorsolateral prefrontal cortex of alcoholics (Chanraud et al., 2007). This region has been proposed to be involved in verbal fluency and other executive operations associated with the updating of information in working memory (D'Esposito and Postle, 2002; Gauthier et al., 2009). Functional imaging studies have also demonstrated dysfunctional frontotemporal activation during verbal fluency performance using functional spectroscopy (Schecklmann et al., 2007), and significant correlations between PET-indexed left dorsolateral prefrontal hypometabolism and reduced verbal fluency performance in abstinent alcoholics (Dao-Castellana et al., 1998). There is also evidence that acute ethanol administration decreases left dorsolateral prefrontal cortex activation and impairs verbal fluency performance in healthy individuals (Wendt and Risberg, 2001). Overall, these studies support our results showing a prominent association between severity of alcohol use and poorer fluency and decision-making skills. Although fluency and decision-making are independent executive components (Verdejo-García and Pérez-García, 2007) they have in common being complex multifaceted operations encompassing access to long-term memory, clustering, monitoring and switching of information (in the case of fluency) (Fisk and Sharp, 2004; Troyer et al., 1998), and episodic/working memory, motivation and feedback processing and reversal learning (in the case of decision-making) (Bechara et al., 2005; Busemeyer and Stout, 2002; Gupta et al., 2009). Therefore, we may speculate that alcohol severity specifically affects some of the component operations of fluency and/or decision-making (e.g. working memory updating), or alternatively affects in a broad sense to multi-component executive processes.

Our second aim was to determine the contribution of quantity and duration of consumption of the main drugs that motivated treatment to decrements on executive components functioning. In this regard, we found common detrimental effects of quantity of cannabis use and cocaine use on measures of verbal updating of working memory, analogical reasoning and decision-making. A principal component analysis performed on a comprehensive battery of executive functions tests concluded that measures of working memory and analogical reasoning (along with fluency measures) load together on a factor that we and others have labelled 'updating' (Verdejo-García and Pérez-García, 2007); which consists of continuous refreshing/updating of working memory contents in order to set task demands and optimize performance (Miyake et al., 2000; Stuss and Alexander, 2007; Verdejo-García and Pérez García, 2007). These results are consistent with several sources of evidence, including animal studies showing cocaine and cannabinoid dose-related modulation of working memory performance (Deadwyler et al., 2007; Egerton et al., 2006; George et al., 2008), human studies showing dose-related negative effects of severity of cannabis and cocaine use on updating measures in polydrug abusers (Medina et al., 2007; Verdejo-García et al., 2007a), and the conclusions of a recent meta-analysis of neuropsychological studies in cocaine abusers showing moderate effect sizes for updating indices, which are durable across abstinence (Jovanovski et al., 2005). Functional imaging studies have linked these updating deficits to prefrontal cortex, cingulate cortex and superior parietal cortex dysfunctions (Jager et al., 2006; Kübler et al., 2005). Nonetheless, there is also intriguing evidence showing that cannabis users have abnormally increased hippocampal activation in response to executive tasks demands (Eldreth et al., 2004; Nestor et al., 2008). Moreover, a recent structural magnetic resonance imaging study has revealed significant volumetric reductions (circa 12%) in the hippocampus of long-term cannabis users (Yücel et al., 2008). Therefore, hippocampal dysfunction may also play a prominent role on cannabis-induced updating deficits. In fact, duration of cannabis was also linked to

poorer spatial working memory, a process that has been associated with the hippocampal endocannabinoid system activation in animal models (Deadwyler et al., 2007). Similarly, for decision-making, very recent studies have shown that both cannabis and cocaine abuse have dose-related detrimental effects on IGT performance (Bolla et al., 2003, 2005; Verdejo-García et al., 2007a). However, results from functional imaging and cognitive models studies suggest that both groups may fail to make advantageous decisions for different reasons: cannabis abusers display PET-indexed prominent activation in non-specialized areas (e.g. cerebellum and occipital cortex) during IGT performance (Bolla et al., 2005), whereas cocaine abusers exposed to the same paradigm show dysfunctional activation of regions typically involved in reward processing and decision-making (e.g. striatum and orbitofrontal cortex) (Bolla et al., 2003). Moreover, cognitive decision models of the IGT have shown that cannabis abusers fail the task because they place more attention on recent than distal outcomes, whereas cocaine abusers fail because they place more attention on gains than on losses (Busemeyer and Stout, 2002).

Regression models have also shown common effects of cocaine and heroin duration of use on cognitive shifting. Animal models have shown that repeated administration of cocaine produces impairments in cognitive flexibility, specifically in perseveration and reversal learning linked to orbitofrontal cortex functioning (Jentsch et al., 2002; Schoenbaum et al., 2004; Stalnaker et al., 2006, 2009). These findings have been nicely translated to humans by several studies showing relatively specific effects of cocaine abuse on cognitive shifting (Ersche et al., 2008; Verdejo-García and Pérez-García, 2007) and electrophysiological indices of decreased error-related processing and impaired behavioural correction of errors in cocaine abusers (Franken et al., 2007). Although there is no equivalent body of animal research on the opioid modulation of cognitive shifting, a number of human neuropsychological studies have shown that heroin abusers have significant impairments in intradimensional set-shifting, perseveration, risk-taking and decision-making tasks (Fishbein et al., 2007; Lyvers and Yakimoff, 2003; Ornstein et al., 2000; Verdejo-Garcia et al., 2005a; see also the review by Gruber et al., 2007), which have been attributed to grey matter decrements in the medial and inferior prefrontal cortex, insula and temporal cortex (Lyoo et al., 2006) and dysfunctional activation of the rostral anterior cingulate cortex in response to error feedback (Forman et al., 2004). Therefore, abnormal error processing and subsequent failure of 'quality control' executive mechanisms may underlie flexibility deficits in both cocaine and heroin abusers.

Finally, we found specific effects of duration of cocaine abuse on one inhibition measure, the 5DT interference index. Previous results from our lab and others have supported relatively specific deleterious effects of psychostimulants on a number of neuropsychological indices of response inhibition, including the Stroop test, the Go–No Go, the Continuous Performance test or the Stop-Signal task (Bolla et al., 2004; Colzato et al., 2007; Li et al., 2008; Verdejo-García et al., 2007c). Furthermore, these deficits have been linked to patterns of severity of drug use (Bolla et al., 2004; Verdejo-García et al., 2005b) and to brain measures of reduced activation of the anterior cingulate and lateral prefrontal cortices during inhibition trials (using PET or fMRI) (Bolla et al., 2004; Li et al., 2008), and white matter decrements in the genu of the corpus callosum (using diffusion tensor imaging) (Moeller et al., 2005). These effects may be explained by a more intense neuromodulatory effect of psychostimulants on the cingulate cortex-striatal system (Bolla et al., 2003; Paulus et al., 2002, 2003, 2005; see also the review by Li and Sinha, 2008). However, this result may be interpreted with caution for several reasons. First, there is growing evidence that disinhibition deficits may predate initiation of drug use and constitute a liability marker for substance use disorders (see Dalley et al., 2007 and Belin et al., 2008 for animal evidence; see Verdejo-García et al., 2008 for a review of human evidence); therefore, we cannot draw conclusions on the causality of inhibition deficits. Second, there is no consistency between our findings on the 5DT and the results of other inhibition tests, such as the Stroop. We think this may be due to the fact that Stroop performance is more influenced by age and educational factors (Kaplan et al., 2009), making it harder to establish a drug-related effect. However, more research is warranted to investigate the specific effects of cocaine and other psychostimulants on inhibitory control processes.

Overall, these results obtained in mid-term abstinent substance abusers may have important implications for their quality of life and their ability to take advantage of cognitive behavioural therapy-based treatment programs. Deficits in working memory, reasoning, fluency and cognitive flexibility may be associated with difficulties in retaining complex instructions, selecting relevant information from clinical sessions or group interactions, and generalizing specific learning to other familiar and social interactive activities. On the other hand, treatment headways require that addicted individuals reverse strong habits and over-rehearsed decision patterns. Cognitive deficits have been associated with poorer clinical progression levels (Leber et al., 1985), a lower level of participation and implication in the treatment (Fals-Stewart and Lucente, 1994) and higher rates of treatment dropout and drug relapse (Aharonovich et al., 2003, 2006, 2008; Passetti et al., 2008; Streeter et al., 2008; Teichner et al., 2002). In this respect, our results stress the need to promote rehabilitation programs targeted to restore or compensate executive dysfunction in SDIs.

Finally, several limitations of this study should be mentioned. First, there is evidence of age-related cognitive decline from the thirties onwards (Herndon et al., 1997; Salthouse, 2009), and therefore some of the executive declines in our sample may be related to normal aging. However, our regression models adequately controlled for the effects of age and education, and all of the drug effects reported were obtained after removing the effect of these variables. Second, due to a lower prevalence of female inpatients during recruitment, our sample was predominantly composed of males. Future studies should investigate how these findings may or may not generalize to a female population of SDI. Third, some executive indices that were impaired in SDI failed to show any association with alcohol or drug use (e.g. the R-SAT). It is possible that in these cases the relatively medium sample size (further limited after outliers exclusion) may have contributed to type

II error or, alternatively, that these deficits relate to different aspects of the addiction phenomenon (e.g. age of first use, personality patterns). Furthermore, there is an inherent limitation linked to the reliability of self-reports of drug use; nonetheless, when considering the limitations of other methods, such as toxicological analyses or structured interviews categorical approaches, to catch the time line, peak effects and dimensional aspects of drug history, self-reports end up as the approach with highest face validity (see Verdejo-García et al., 2004 for a discussion of this methodological challenge of drug abuse cognitive studies). Finally, as mentioned above, the current cross-sectional data do not allow us to determine whether these alterations preceded drug use and contributed to higher severity patterns, or if they occur as a consequence of persistent drug use. Longitudinal studies are warranted to address this relevant question.

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## References

Abi-Saab D, Beauvais J, Mehm J, Brody M, Gottschalk C, Kosten TR (2005) The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. *Am J Addict* 14: 166–178.

Aharonovich E, Brooks AC, Nunes EV, Hasin DS (2008) Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. *Drug Alcohol Depend* 95: 279–283.

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

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci* 6: 115–116.

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

Bechara A, Damasio H, Damasio AR (2003) Role of the amygdala in decision-making. *Ann N Y Acad Sci* 985: 356–369.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50: 7–15.

Bechara A, Damasio H, Tranel D, Damasio AR (2005) The Iowa Gambling Task and the somatic marker hypothesis: Some questions and answers. *Trends Cogn Sci* 9: 159–162.

Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ (2008) High impulsivity predicts the switch to compulsive cocaine taking. *Science* 320: 1352–1355.

Beveridge TJR, Gill KE, Hanlon CA, Porrino LJ (2008) Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Phil Trans R Soc B* 363: 3257–3266.

Bolla KI, Brown K, Eldreth BA, Tate K, Cadet BA, Cadet JL (2002) Dose-related neurocognitive effects of marijuana use. *Neurology* 59: 1337–1343.

Bolla KI, Eldreth DA, London ED, et al. (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *NeuroImage* 19: 1085–1094.

Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2005) Neural substrates of faulty decision-making in abstinent marijuana users. *NeuroImage* 26: 480–492.

Bolla K, Ernst M, Kiehl K, et al. (2004) Prefrontal cortical dysfunction in abstinent cocaine abusers. *J Neuropsychiatry Clin Neurosci* 16: 456–464.

Bolla KI, Funderburk FR, Cadet J (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology* 54: 2285–2292.

Brand M, Roth-Bauer M, Driessen M, Markowitsch HJ (2008) Executive functions and risky decision-making in patients with opiate dependence. *Drug Alcohol Depend* 7: 64–72.

Busemeyer JR, Stout JC (2002) A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychol Assess* 14: 253–262.

Chanraud S, Martelli C, Delain F, et al. (2007) Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology* 32: 429–438.

Collette F, Olivier L, Van der Linden M, et al. (2005) Involvement of both prefrontal and inferior parietal cortex in dual-task performance. *Cognitive Brain Res* 24: 237–251.

Colzato LS, Van den Wildenberg WPM, Hommel B (2007) Impaired inhibitory control in recreational cocaine users. *PLoS ONE* 2: e1143.

Cools R, Clark L, Owen AM, Robbins TW (2002) Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci* 22: 4563–4567.

Dalley JW, Fryer TD, Brichard L, et al. (2007) Nucleus accumbens d2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* 315: 1267–1270.

Dao-Castella MH, Samson Y, Legault F, et al. (1998) Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. *Psychol Med* 28: 1039–1048.

Deadwyler SA, Goonawardena AV, Hampson RE (2007) Short-term memory is modulated by the spontaneous release of endocannabinoids: evidence from hippocampal population codes. *Behav Pharmacol* 18: 571–580.

DeFilippis NA (2002) *Category Test: Computer Version Research Edition*. Lutz, FL: Psychological Assessment Resources.

Denckla MB, Reiss AL (1997) Prefrontal-subcortical circuits in developmental disorders. In: Krasnegor NA, Lyon GR, Goldman-Rakic PS (eds) *Development of the Prefrontal Cortex: Evolution, Neurobiology, and Behaviour*. Baltimore, MD: Brookes.

D'Esposito M, Postle B (2002) The organization of working memory function in lateral prefrontal cortex: evidence from event-related functional MRI. In: Stuss DT, Knight RT (eds) *Principles of Frontal Lobe Functioning*. New York: Oxford University Press.

D'Esposito M, Postle BR, Ballard D, Lease J (1999) Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain Cogn* 41: 66–86.

De Win MML, Reneman L, Jager G, et al. (2007) A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology* 32: 458–470.

Di Sclafani V, Tolou-Shams M, Price LJ, Fein G (2002) Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug Alcohol Depend* 66: 161–171.

Dreher JC, Koechlin E, Tierney M, Grafman J (2008) Damage to the fronto-polar cortex is associated with impaired multitasking. *PLoS ONE* 3: e3227.

Egerton A, Allison C, Brett RR, Pratt JA (2006) Cannabinoids and prefrontal cortical function: insights from preclinical studies. *Neurosci Biobehav Rev* 30: 680–695.

Eldreth DA, Matochik JA, Cadet JL, Bolla K (2004) Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *NeuroImage* 23: 914–920.

Ersche KD, Roiser JP, Robbins TW, Sahakian BJ (2008) Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. *Psychopharmacology* 197: 421–431.

EMCDDA (2008) *Annual Report 2008: the State of the Drugs Problem in the European Union*. Available at http://www.emcdda.eu. Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

Fals-Stewart W, Lucente S (1994) The effect of neurocognitive status and personality functioning on length of stay in residential substance abuse treatment: An integrative study. *Psychol Addict Behav* 8: 1–12.

Fein G, Klein L, Finn P (2004) Impairment on a simulated gambling task in long-term abstinent alcoholics. *Alcohol Clin Exp Res* 28: 1487–1491.

Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend* 66: 265–273.

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug Alcohol Depend* 67: 157–167.

Fishbein DH, Krupitsky E, Flannery BA, et al. (2007) Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. *Drug Alcohol Depend* 90: 25–38.

Fisk JE, Sharp CA (2004) Age-related impairments in executive functioning: Updating, inhibition, shifting and access. *J Clin Exp Neuropsychol* 26: 874–890.

Forman SD, Dougherty GG, Casey BJ, et al. (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry* 55: 531–537.

Franken IHA, Nijs IMT, Muris P, Van Strien JW (2007) Alcohol selectively reduces brain activity during the affective processing of negative information. *Alcohol Clin Exp Res* 31: 919–927.

Gauthier CT, Duyme M, Zanca M, Capron C (2009) Sex and performance level effects on brain activation during a verbal fluency task: A functional magnetic resonance imaging study. *Cortex* 45: 164–176.

George O, Mandyam CD, Wee S, Koob GF (2008) Extended access to cocaine self-administration produces long-lasting prefrontal cortex-dependent working memory impairments. *Neuropsychopharmacology* 33: 2474–2482.

Gilbert SJ, Spengler S, Simons JS, Frith CD, Burgess PW (2006) Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain–behavior associations. *Cereb Cortex* 16: 1783–1789.

Glass JM, Buu A, Adams KM, et al. (2009) Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction* 104: 38–48.

Golden CJ (1978) *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Wood Dale, IL: Stoelting Co.

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 159: 1642–1652.

Goldstein RZ, Leskovjan AC, Hoff AL, et al. (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia* 42: 1447–1458.

Gruber SA, Silveri MM, Yurgelun-Todd DA (2007) Neuropsychological consequences of opiate use. *Neuropsychol Rev* 17: 299–315.

Gupta R, Duff MC, Denburg NL, Cohen NJ, Bechara A, Tranel D (2009) Declarative memory is critical for sustained advantageous complex decision-making. *Neuropsychologia* 47: 1686–1693.

Hair JF, Jr, Anderson RE, Tatham RL, Black WC (2000) *Análisis Multivariante*, Quinta edición (in Spanish). Prentice Hall.

Herndon JG, Moss MB, Rosene DL, Killiany RJ (1997) Patterns of cognitive decline in aged rhesus monkeys. *Behav Brain Res* 87: 25–34.

Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF (2006) Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. *Psychopharmacology* 185: 358–368.

Jentsch JD, Olausson P, De la Garza R, Taylor JR (2002) Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. *Neuropsychopharmacology* 26: 183–190.

Jovanovski D, Erb S, Zakzanis K (2005) Neurocognitive deficits in cocaine users: A quantitative review of the evidence. *J Clin Exp Neuropsychol* 27: 189–204.

Kaplan RF, Cohen RA, Moscufo N, et al. (2009) Demographic and biological influences on cognitive reserve. *J Clin Exp Neuropsychol* 31: 1–9.

Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. *Trends Cogn Sci* 11: 229–235.

Kübler A, Murphy K, Garavan H (2005) Cocaine dependence and attention switching within and between verbal and visuospatial working memory. *Eur J Neurosci* 21: 1984–1992.

Leber WR, Parsons OA, Nichols N (1985) Neuropsychological test results are related to ratings of men alcoholics' therapeutic progress: A replicated study. *J Stud Alcohol* 46: 116–121.

Lee TM, Pau CW (2002) Impulse control differences between abstinent heroin users and matched controls. *Brain Inj* 16: 885–889.

Leland DS, Paulus MP (2005) Increased risk-taking decision-making but not altered response to punishment in stimulant-using young adults. *Drug Alcohol Depend* 78: 83–90.

Levine B, Dawson D, Boutet I, Schwartz ML, Stuss DT (2000) Assessment of strategic self-regulation in traumatic brain injury: Its relationship to injury severity and psychosocial outcome. *Neuropsychology* 14: 491–500.

Lezak MD (2004) *Neuropsychological Assessment*, 4th edn. New York: Oxford University Press.

Li CS, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R (2008) Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology* 33: 1798–1806.

Li CS, Sinha R (2008) Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal–limbic dysfunction in psycho-stimulant addiction. *Neurosci Biobehav Rev* 32: 581–597.

Loeber S, Duka T, Welzel H, et al. (2009) Impairment of cognitive abilities and decision making after chronic use of alcohol: The impact of multiple detoxifications. *Alcohol Alcohol* 44: 372–381.

López-Torrecillas F, Godoy JF, Pérez-García M, Godoy D, Sánchez-Barrera M (2001) Variables modulating stress and coping that discriminate drug consumers from low or not drug consumers. *Addict Behav* 25: 161–165.

Lubman DI, Yucel M, Pantelis C (2004) Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction* 99: 1491–1502.

Lyoo K, Pollack MH, Silvery MM, et al. (2006) Prefrontal and temporal gray matter density decreases in opiate dependence. *Psychopharmacology* 184: 139–144.

Lyvers M, Yakimoff M (2003) Neuropsychological correlates of opioid dependence and withdrawal. *Addict Behav* 28: 605–611.

Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007) Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc* 13: 807–820.

Miyake A, Friedman NP, Emerson MJ, Witzky AH, Howerther A (2000) The unity and diversity of executive function and their contribution to complex frontal lobe tasks: A latent variable analysis. *Cogn Psychol* 41: 49–100.

Moeller FG, Hasan KM, Steinberg JL, et al. (2005) Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. *Neuropsychopharmacology* 30: 610–617.

Nestor L, Roberts G, Garavan H, Hester R (2008) Deficits in learning and memory: Parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. *NeuroImage* 40: 1328–1339.

Ornstein TJ, Iddon JL, Baldacchino AM, et al. (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology* 23: 113–126.

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.

Pau CWH, Lee TMC, Chan SF (2002) The impact of heroin on frontal executive functions. *Arch Clin Neuropsychol* 17: 663–670.

Paulus MP, Hozack N, Frank L, Brown GB, Schuckit MA (2003) Decision-making by methamphetamine-dependent subjects is associated with error-rate independent decrease in prefrontal and parietal activation. *Biol Psychiatry* 53: 65–74.

Paulus MP, Hozack N, Zauscher BE, et al. (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology* 26: 53–63.

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

Picton TW, Stuss DT, Alexander MP, Shallice T, Binns MA, Gillingham S (2007) Effects of focal frontal lesions on response inhibition. *Cereb Cortex* 17: 826–838.

Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F (2009) Changes in the episodic memory and executive functions of abstinent and relapsed. Alcoholics over a 6-month period. *Alcohol Clin Exp Res* 33: 490–498.

Robinson JE, Heaton RK, O'Malley SS (1999) Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *J Int Neuropsychol Soc* 5: 10–19.

Roselli M, Ardila A (1996) Cognitive effects of cocaine and polydrug abuse. *J Clin Exp Neuropsychol* 18: 122–135.

Ruff RM (1996) *Ruff Figural Fluency Test: Professional Manual*. Lutz, FL: Psychological Assessment Resources.

Salthouse TA (2009) When does age-related cognitive decline begin? *Neurobiol Aging* 30: 507–514.

Schecklmann M, Ehlis AC, Plichta MM, Boutter HK, Mezger FG, Fallgatter AJ (2007) Altered frontal brain oxygenation in detoxified alcohol dependent patients with unaffected verbal fluency performance. *Psychiatry Res Neuroimaging* 156: 129–138.

Schoenbaum G, Saddoris MP, Ramus SJ, Shaham Y, Setlow B (2004) Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions. *Eur J Neurosci* 19: 1997–2002.

Sedó M, Levenson R, Leonard A (1995) Reading-free Stroop Interference Tests: automatic and effortful processing. In *Proceedings of the 17th Midyear Conference of the International Neuropsychological Society*, Angers, France.

Sedó M (2005) *Test de los Cinco Dígitos: Five Digit Test*. Madrid: TEA Ediciones.

Stalnaker TA, Roesch MR, Franz TM, Burke KA, Schoenbaum G (2006) Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. *Eur J Neurosci* 24: 2643–2653.

Stalnaker TA, Takahashi Y, Roesch MR, Schoenbaum G (2009) Neural substrates of cognitive inflexibility after chronic cocaine exposure. *Neuropharmacology* 56: 63–72.

Streeter CC, Terhune DB, Whitfield TH, et al. (2008) Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology* 33: 827–836.

Stuss DT, Alexander MP (2007) Is there a dysexecutive syndrome? *Philos Trans R Soc Lond B Biol Sci* 29: 901–915.

Swan GE, Lessov-Schlaggar CN (2007) The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev* 17: 259–273.

Tarter RE, Kirisci L, Mezzich A, et al. (2003) Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am J Psychiatry* 160: 1078–1085.

Teichner G, Horner MD, Roitzsch JC, Herron J, Thevos A (2002) Substance abuse treatment outcomes for cognitively impaired and intact outpatients. *Addict Behav* 27: 751–763.

Troyer AK, Moscovitch M, Winocur G, Alexander MP, Stuss D (1998) Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia* 36: 499–504.

UNODC (2008) *United Nations World Drug Report 2008*. United Nations Office of Drugs and Crime.

Van der Elst W, Van Boxtel MPJ, Van Breukelen GJP, Jolles J (2006) The Stroop color-word test. Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 13: 62–79.

Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI (2007a) The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend* 90: 2–11.

Verdejo-García A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev* 32: 777–810.

Verdejo-García A, López Torrecillas F, Aguilar de Arcos F, Pérez García M (2005b) 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-García A, López-Torrecillas F, Orozco C, Pérez-García M (2004) Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant and opioid abuse. *Neuropsychol Rev* 14: 1–41.

Verdejo-García A, Perales JC, Pérez-García M (2007c) Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav* 32: 950–966.

Verdejo-García A, Pérez-García M (2007) Profile of executive deficits in cocaine and heroin polysubstance users: common and differential effects on separate executive components. *Psychopharmacology* 190: 517–530.

Verdejo-García A, Rivas-Pérez C, Vilar-López R, Pérez García M (2007b) Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug Alcohol Depend* 86: 139–146.

Verdejo-Garcia A, Toribio C, Orozco K, Puente K, Pérez García M (2005a) Neuropsychological functioning in methadone

maintenance patients versus abstinent heroin abusers. *Drug Alcohol Depend* 78: 283–288.

Verhaeghen P, Cerella J (2002) Aging, executive control, and attention: a review of meta-analyses. *Neurosci Biobehav Rev* 26: 849–857.

Verrico CD, Jentsch JD, Roth RH, Taylor JR (2004) Repeated, intermittent $\Delta^9$-tetrahydrocannabinol administration to rats impairs acquisition and performance of a test of visuospatial divided attention. *Neuropsychopharmacology* 29: 522–529.

Wadsworth EJK, Moss SC, Simpson SA, Smith AP (2006) Cannabis use, cognitive performance and mood in a sample of workers. *J Psychopharmacol* 20: 14–23.

Wechsler D (1997a) *Wechsler Adult Intelligence Scale*, 3rd edn.

Wechsler D (1997b) *Wechsler Memory scale*, 3rd edn.

Wendt PE, Risberg J (2001) Ethanol reduces rCFB activation of left dorsolateral prefrontal cortex during a verbal fluency task. *Brain Lang* 77: 197–215.

Whitlow CT, Liguori A, Livengood LB, Hart SL, Mussat-Whitlow BJ, Lamborn CM (2004) Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend* 76: 107–111.

Yang L, Sun ZS, Zhu YP (2007) Proteomic analysis of rat prefrontal cortex in three phases of morphine-induced conditioned place preference. *J Proteome Res* 6: 2239–2247.

Yücel M, Solowij N, Respondek C, et al. (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65: 694–701.

Zakzanis KK (2001) Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effects size analyses for neuropsychological researchers. *Arch Clin Neuropsychol* 16: 653–677.

Zelazo PD, Carter A, Reznick JS, Frye D (1997) Early development of executive function: A problem-solving framework. *Rev Gen Psychol* 1: 198–226.