Cognitive reserve mediates the severity of certain neuropsychological deficits related to cocaine use disorder

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Abstract

The concept of cognitive reserve (CR) is being considered in the field of substance use disorder (SUD) by observing that there are individuals whose brain alterations are not related to the cognitive symptomatology they present. Our aims were to characterise the possible neuropsychological deficits in a sample of subjects with SUD compared to healthy controls and to determine whether the degree of CR is a mediator in the cognitive functioning of these patients. To perform these objectives, the study involved a sample of subjects with SUD in outpatient treatment and a healthy control group. A CR questionnaire and a comprehensive neuropsychological assessment were administered, and we also collected data related to drug consumption and psychological well-being. The SUD group showed poorer performance compared to the control group in several cognitive domains (attention, declarative memory, executive functions and emotional perception), as well as in psychological comfort. Interestingly, we observed that the deficits found in attention and processing speed were highly mediated by the CR level of the participants, an effect that we did not observe in the rest of the variables registered. Our results suggest that long-term drug consumption leads to cognitive deficits and affects the psychological well-being of the subjects. Moreover, the CR should be taken into account during the assessment and rehabilitation of patients with SUD due to its protective role against certain neuropsychological deficits.

Keywords: addiction, attention, causal mediation analysis, executive function, memory, neuropsychological assessment

1. Introduction

Substance use disorder (SUD) is a serious public health problem that consists of a compulsive drive to take drugs despite repeated severe adverse consequences (Volkow & Li, 2005). Over the past two decades, neuropsychological research has consistently found that an estimated 30% to 80% of individuals with SUD present impairments in different cognitive functions (Ambrose, Bowden & Whelan, 2001; Bates, Bowden & Barry, 2002; Brewer & Potenza, 2008; Copersino et al., 2009; Gould, 2010; Manning, Verdejo-García & Lubman, 2017). For instance, current evidence indicates that SUD is frequently associated with significant cognitive impairments, especially in attention, working memory, and response inhibition functions (Ambrose et al., 2001; Crean, Crane & Mason, 2011; Gruber, Silveri & Yurgelun-Todd, 2007; Sampedro-Piquero et al., 2019; Shlosberg et al., 2019; Verdejo-García, Perales & Pérez-García, 2007; Wang, Xiao, Zhang, Liang & Zhang, 2008; Woicik et al., 2009). With respect to cocaine, a broad neuropsychological impairment has been described (Vonmoos et al. 2013, 2014). Studies have shown deficits in sustained attention, short-term and working memory, visuospatial abilities, and executive functions, such as abstract reasoning skills, cognitive flexibility, and inhibitory control (Bolla, Rothman & Cadet, 1999; Jovanovski, Erb & Zakzanis, 2005; Spronk, van Wel, Ramaekers & Verkes, 2013; Woicik et al., 2009). Furthermore, research has suggested that dose-related deficits in verbal learning and memory remain over four weeks of abstinence (Bolla, Funderburk & Cadet, 2000). On the other hand, cognitive deficits also occur at a recreational and non-dependent level of cocaine consumption (Vonmoos et al., 2013). In this last study, recreational cocaine users displayed severe alterations in the attention domain, whereas in dependent users the working memory was the most impaired, although this group also presented important deficits in attention and declarative memory.

Nevertheless, despite these findings of a strong association of cognitive deficits with SUD, the clinical implications of this data have received limited attention, owing to variability across individuals, type of drug, comorbidity, and the reversibility of some cognitive deficits after an extensive period of abstinence (Block, Erwin & Ghoneim, 2002; Vonmoos et al., 2014). Unfortunately, most psychologists are only concerned with a reduction or stopping of the drug consumption, and limited attention is given to the individual's cognitive status (Singh, Kaloiya, Dhawan, Balhara & Mishra, 2018). Furthermore, some evidence has generally not shown an association between demographic variables, such as age, substance use variables and risk for onset of neurocognitive impairment in individuals diagnosed with SUD. For instance, although prior literature suggests that greater cognitive decrement may result from numerous years of cocaine consumption and recent, daily cocaine use, results from a recent study did not support these findings. Specifically, these usage characteristics did not modulate performance on tasks of attention, working memory, and episodic memory (Mahoney, Kalechstein, Newton, & De La Garza, 2017). One potential explanation offered by the authors is that after using cocaine for a certain number of years, the deleterious effects on cognition stabilize. This hypothesis may be supported by the findings observed in recreational cocaine users whose cognitive

impairments are similar to individuals with cocaine use disorder (Vonmoos et al., 2013), as we mentioned previously. Nevertheless, methodological aspects may have also accounted for the discrepancy found in these findings, such as sample characteristics or buffering factors which sometimes are difficult to control.

These modulating factors include individual-related factors such as educational level, occupational attainment, the practice of healthy leisure activities, and social support, which seem to attenuate the impact of the drug on cognitive performance and, consequently, to favour a better treatment outcome (Cutuli, Ladrón de Guevara-Miranda, Castilla-Ortega, Santín & Sampedro-Piquero, 2019; Pedrero-Pérez et al., 2014). These variables are known to be proxy measures for the concept of cognitive reserve (CR), which refers to the brain's capacity to cope with damage or compensate for diseases to maintain a stable level of function (Barulli & Stern, 2013; Lara et al., 2017; Scarmeas & Stern, 2003; Stern, 2002, 2009). Other proxy factor which appears to be involved in building CR is the innate and premorbid intelligence of the individual (Alexander et al., 1997). In our study, we have not taken into account this variable because we consider CR as a dynamic and flexible phenomenon across the life span, which can increase or reduce its protective potential depending on our life experiences (Stern, 2012; 2017). Moreover, this construct is a result of the combination of different lifelong experiences, and it cannot be estimated through only the IQ or premorbid IQ of the individual (Grotz, Seron, Van Wissen, & Adam, 2017). On the other hand, it is noteworthy that years of education and occupational attainment are the most studied CR proxies. However, CR proxies such as education, occupation, or leisure activities have limitations. In fact, they can be highly correlated among themselves and not totally accurate since the same value may be associated to different degree of experience across individuals, and they are not dynamic as they do not reflect the current state of CR. Lastly, many other psychosocial factors have shown to be similarly able to provide CR in either disease and health, including exercise and physical activity (Farioli-Vecchioli, Sacchetti, Nicolis di Robilant, & Cutuli, 2018; Phillips, 2017), diet (Farioli-Vecchioli et al., 2017; Martínez-Lapiscina et al., 2013), good sleep (Branger et al., 2016), socioeconomic status (Fotenos, Mintun, Snyder, Morris, & Buckner, 2008) and social stimulation and support (Barnett, Salmond, Jones, Sahakian, 2006, Bennett, Schneider, Tang, Arnold, Wilson, 2006).

The reserve mechanisms have been widely studied in the field of neurodegenerative diseases, mainly in Alzheimer´s disease (Ewers, Insel, Stern & Weiner, 2013; Katzman et al., 1988; Koepsell et al., 2008; Roe et al., 2007; Stern, 2006, 2012; Scarmeas & Stern, 2003; Stern, Alexander, Prohovnik & Mayeux, 1992). However, CR has been studied not only in this type of dementia, but also in other pathologies, such as human immunodeficiency virus infection (Cody & Vance, 2016), schizophrenia (Barnett et al., 2006), bipolar disorder (Andrade, 2017), depression (Evans et al., 2018), stroke, and traumatic brain injury (Nunnari, Bramanti & Marino, 2014; Umarova et al., 2019). Unfortunately, this issue is still a theoretical construct that is not completely assimilated into the clinical routine of the conventional SUD treatments (Serra & Gelfo, 2019). Recently, the CR construct has begun to emerge in the field of SUD, revealing

that a high CR, as well as involvement in healthy activities, led to less severe drug addiction-related problems, longer periods of abstinence, better cognitive performance, and an enhanced daily functioning compared to patients with low scores in this construct (Abbey, Saenz, Buck, Parkhill & Hayman, 2006; Christensen et al., 2017; Pedrero-Pérez et al., 2014; Taylor, Ussher & Faulkner, 2007). Nevertheless, this topic has been only scarcely studied, and controversial results have been also found. For instance, in a recent study, no effect was observed between CR and inhibitory control, which contradicts other existing studies, suggesting that this may be due to low sample size, abstinence periods, or different tests used to assess this function. In contrast, SUD patients with high CR presented a high memory performance (Fernández-Del Olmo et al., 2019). Moreover, some evidence which suggests that CR is not associated with improved performance in all cognitive functions (Lavrencic, Churches, & Keage, 2018). CR has been theorized to affect cognitive performance generally (Stern, 2009), and this has been supported by many papers reporting that those with high CR display better performance on verbal fluency, language, memory, reasoning, executive function, visuospatial abilities, and processing speed tasks (Opdebeeck, Martyr, & Clare, 2016; Ritchie, Bates, & Deary, 2015; Roldán-Tapia, García, Cánovas, & León, 2012; Tucker-Drob, Johnson, & Jones, 2009). More recently, however, it has become evident that CR is likely to differentially affect performance across cognitive domains. For instance, in the Lavrencic and colleagues' study, CR was associated with attention, executive functions, verbal and working memory, and orientation, but not significantly related to emotion perception, processing speed, or motor performance. These results seem to suggest that cognitive domains that start to decline earlier in adulthood (i.e., fluid abilities) are less susceptible to CR, whilst those that remain relatively stable into late adulthood (i.e., crystallized abilities) are most affected.

Because there is limited evidence available about the role of CR in the cognitive performance of subjects with SUD in treatment, and since this variable could be very important in the planning of rehabilitation programmes according to the cognitive profile of each patient, we established the following aims: to characterise possible neuropsychological deficits in a sample of subjects with SUD compared to a healthy control group; and to determine whether the degree of CR may influence the cognitive functioning of these patients. To date, this is the first study focused on analysing the effect of drug abuse on cognition after a short and controlled period of abstinence. The results were compared with the cognitive performance of a healthy control group, whereas the majority of studies often employ standardized test scores. Furthermore, the methodology carried out to analyse the role of CR on cognitive status allows us to ascertain if this variable mediates the severity of the symptoms.

2. Materials and methods

2.1. Participants

The sample of this study consisted of white Caucasian participants with SUD ($n = 40$) and a healthy control group ($n = 20$). Subjects with SUD were

recruited from outpatient detoxification treatment programmes at Ayuda a la Recuperación de Enfermos Alcohólicos (AREA) and Fundación CESMA Proyecto Hombre, in Málaga, Spain. Healthy controls were recruited by convenience in the same city. After a complete description of the study, all included participants gave written consent to participate. Furthermore, all participants had the opportunity to discuss any questions or issues. For the clinical sample, the inclusion criteria were: 1) aged 25 to 55 years; 2) a diagnosis of SUD, with cocaine as the primary drug (cocaine use >1 g per month); 3) no consumption of opioids; 4) abstinence duration between 2 and 12 weeks (García-Marchena et al., 2018; Hagen et al., 2016; Miller, 1985; Pavón et al., 2013), which was verified weekly by the clinicians belonging to the staff of each outpatient centre (*Proyecto Hombre* and *Ayuda Recuperación Enfermos Alcohólicos* (A.R.E.A.) (Malaga)) using the *Multidrug urine test Instant View* (Alfa Scientific Designs Inc. USA). This test is a rapid qualitative immunoassay for screening the use of one or more drugs. The device detects any combination of the drugs or drugs metabolites at or above the specified cut-off levels; 5) a minimum of four years of formal education; and 6) an absence of comorbid psychotic disorder and characterized depressive episode. Diagnoses of SUD were based on clinical and structured interviews following the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria. For healthy controls, the inclusion criteria were: 1) aged 25 to 55 years; 2) no history of drug abuse, including nicotine and alcohol; 3) a minimum of four years of formal education; and 4) an absence of comorbid characterized depressive episode and psychotic disorder. Volunteers were excluded if they presented severe difficulties in understanding the test instructions, continuous interruptions to talk about their experiences exceeding the time limit on all tests, altered consciousness or agitation, and if they consumed prescription drugs affecting the central nervous system (mainly anxiolytics and antidepressants).

The study and protocols for recruitment were approved by the Ethics Committee of the University of Malaga (CEUMA: 67-2019-H) in accordance with the *Ethical Principles for Medical Research Involving Human Subjects* adopted in the Declaration of Helsinki by the World Medical Association (64th WMA General Assembly, Fortaleza, Brazil, October 2013), Recommendation No. R (97) 5 of the Committee of Ministers to Member States on the Protection of Medical Data (1997), and the Spanish Data Protection Act (*Ley Orgánica 15/1999 de Protección de Datos*, LOPD).

2.2. Procedures

All collected data were coded to maintain privacy and confidentiality. After obtaining the informed consent, trained psychologists conducted a structured interview to obtain data about sociodemographic variables and drug abuse (age of onset, drugs consumed, years of abuse, last consumption, treatment received, drop-outs, etc.), along with a *craving* Likert scale from 0 to 10 to determine the desire for drug use during the present moment, the past week, and the past month (maximum of 30 points). Then, a CR questionnaire was carried out (Rami et al., 2011). This scale is composed of 8 items that evaluate schooling level (from

0 to 5); schooling level of the parents (from 0 to 2); formal courses performed (from 0 to 3); musical training (from 0 to 2); languages (from 0 to 3); reading activity (from 0 to 4); occupational attainment (from 0 to 4); and the practice of intellectual games (from 0 to 2). A high score in these variables would suggest a higher CR, with a 25-point maximum rating (under 10 points is considered a low CR). We selected this questionnaire because it is useful and quick to administer in clinical settings, based on the measurement of the most relevant parameters linked to the construct of CR (education, languages, formal courses, occupational attainment, etc.). Moreover, it is one of the few CR tests that count with normative values in cognitively healthy Spanish population. Another interesting aspect is that its association with cognitive functions has been studied, showing an association with executive performance (Fernández-Del Olmo et al., 2019; Rami et al., 2011). Furthermore, we also considered the frequent practice of moderate or intense physical activity (≥ 2 times per week). Subsequently, participants underwent a single-session comprehensive neuropsychological assessment as described below (approximately 2 h). Participants were allowed to take a break, and they could revoke their consent at any time.

2.3. Neuropsychological assessments

Attentional functioning, psychomotor speed, and visual searching were assessed with the d2 Test (Brickenkamp, 2012) and the Trail Making Test, part A (Reitan & Wolfson, 1985). Verbal and nonverbal declarative memory were measured with the Spain-Complutense Verbal Learning Test (TAVEC) (Benedet & Alejandre, 2014) and the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944), respectively. The copying part of the latter test allowed us to eliminate possible perceptive problems. Executive functioning was tested with different tests such as the D-KEFS Sorting Test (Delis et al., 2001), the Tower Test (Delis et al., 2001), the forward and backwards digit span task of the Wechsler Memory Scale (WAIS-IV; Wechsler, 2008), the Trail Making Test, part B (Reitan & Wolfson, 1985), a verbal fluency test (Delis et al., 2001), the Stroop Test (Golden, 2001), and the Iowa Gambling Task (IGT) (Bechara et al., 1994). In addition, for emotional perception, we used the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001). Finally, we administered a psychological well-being scale (Díaz et al., 2006; Ryff & Keyes, 1995), formed of 6 dimensions (self-acceptance, positive relationships with others, autonomy, environmental mastery, personal growth, and purpose in life) and 39 items. Respondents rated statements on a scale of 1 to 6, with 1 indicating strong disagreement and 6 indicating strong agreement. All neuropsychological assessments were carried out with pencil and paper, except the IGT, which was administered in a computerised version (Google Play, IGTT), and it was administered using a Samsung Galaxy 10.1" tablet. The specific cognitive domains measured with the different tests, along with the mean ± standard error of the mean (SEM) for each group, are displayed in Table 2. More details about the tests employed are shown in the supplementary material.

2.4. Statistical analysis

Descriptive analyses were performed on the demographics, the information related to drug use (age of onset, years of substance use, weeks of abstinence, etc.) (Table 1), the total score of the CR questionnaire, the neuropsychological tests, and the psychological well-being scale (Table 2). More information about group comparisons is displayed in Supplementary Table 1. We reported mean ± SEM and frequency (percentage) for continuous and categorical variables, respectively. Statistical differences between groups were computed by the Student's t test ($p \leq 0.05$).

Based on previous reports (Liu & Lachman, 2019), we applied principal component analysis (PCA) as a method to reduce the data set to a few dimensions (i.e. factors) that are representative of the participants' performance in global cognitive domains, such as attention, executive function, and declarative memory. A total of three PCAs were conducted, including the variables shown in Figure 1. A 'factor score' (i.e. a standardised value that reflects the relative standing of each participant on every factor) was obtained using the regression method in IBM SPSS 20 (IBM Corporation, Armonk, NY, USA). More details about the PCA analysis can be found in the supplementary material.

To investigate whether CR mediated the association between clinical condition and cognitive performance, we carried out mediation analyses using the PROCESS macro (Hayes, 2013) in IBM SPSS 20 (IBM Corporation) as previously reported (Ladrón de Guevara-Miranda et al., 2019). The implemented mediation models included the clinical condition (controls versus SUD) as a predictor, the factor score in a given cognitive domain (Fig.1) as a criterion, and the standardised score [i.e. mean (=0) ± standard deviation (=1)] in the CR questionnaire as a mediator. Analyses were conducted according to the causal steps approach (Baron & Kenny, 1986; more details in supplementary material, page 3). Effect sizes were tested using bias-corrected bootstrapping with a 95% confidence interval (CI; Shrout & Bolger, 2002) based on 5000 interactions. P values ≤ 0.05 were considered statistically significant, and a 95% CI excluding the 0 value was used for interpretation of bootstrapping.

3. Results

3.1. Demographics and substance abuse history

A summary of the demographic and drug abuse variables is presented in Table 1. The SUD and the healthy control groups were similar in age, years of formal education, sex, and marital status [$t(58) = 0.97$, $p = 0.33$; $t(58) = 0.10$, $p = 0.72$; $t(58) =- 1.85$, $p = 0.07$; $t(58) = -0.63$, $p = 0.53$, respectively]. Within the SUD condition, we divided the participants into two groups based on the CR questionnaire score (≤10 points was considered a low CR, and >10 points a medium/high CR). As a result, we found that only individuals with a low CR had higher scores in the craving scale [$t(38) = -2.07$, $p = 0.04$].

3.2. The SUD group had worse cognitive performance in several neuropsychological domains, as well as low psychological well-being compared to the control group

An overview of the performance on CR, cognitive tests, and the psychological well-being scale for the control and SUD groups is presented in Table 2. Regarding the CR questionnaire, firstly we calculated the Cronbach's alpha index, observing an acceptable internal consistency of the CR questionnaire (α=0.71). Then, both in the total CR score and the proxy measures registered, the control group had a higher score in most of them compared to the patient group, but significant differences were found only in the total CR score and in the occupational attainment [$t(58)$ = -3.41, p = 0.001; $t(58)$ = -2.70, p = 0.01, respectively].

In the case of the neuropsychological measures, the healthy control group significantly outperformed the SUD group on the attentional domain (d2), verbal and nonverbal declarative memory (TAVEC and Rey Complex Figure), executive functioning [working memory (digit span, backwards version), phonological and semantic verbal fluency, problem resolution (D-KEFS Sorting Test), and inhibitory control (Stroop Interference Test)], and emotional perception (RMET). Finally, the SUD group had a low result in most of the dimensions tested by the psychological well-being scale compared to the control participants. Due to limited space, the t and p values for these measures are displayed in Table 2.

3.3. CR level mediated the impact of drug abuse on cognitive performance

The first mediation model tested whether the drug-related deficit in attention and processing speed was mediated by CR deterioration in the SUD group (Fig. 2A). The results showed that SUD predicted poor performance in this cognitive dimension (path c), as well as low scores in the CR questionnaire (path a). In turn, the level of CR directly predicted the score in the 'attention and processing speed' factor after controlling for the influence of the clinical condition (path b). Our results suggest complete mediation, as the negative effect of SUD on attention and processing speed ceased to be significant after controlling for CR (path c'). Consistently, bootstrapping yielded significance for the mediating effect of CR (a x b = -0.26, CI: [-0.62, -0.04]), but not for the direct effect of SUD (c' = -0.46, CI: [-1.01, 0.08]). The second and third mediation models tested whether drug-related deficits in executive function (Fig. 2B) and declarative memory (Fig. 2C), respectively, were mediated by CR deterioration in patients with SUD. Our results showed that SUD predicted worse performance in these cognitive dimensions (path c), as well as low CR scale scores (path a). Furthermore, indirect effects were found, since the level of CR directly predicted scores in both cognitive factors after controlling for the clinical condition (path b). However, mediation was partial, since the direct effect of SUD on tasks measuring executive function and declarative memory remained significant but closer to zero after controlling for CR (path c'). Bootstrapping consistently yielded significance for both indirect and direct effects of SUD over performance in tasks related to executive function (a x b = -0.28, CI: [-0.55, -0.09]; c' = -0.73, CI: [-1.24,

-0.22]) and declarative memory (*a* x *b* = -0.27, CI: [-0.63, -0.07]; *c'* = -0.71, CI: [-1.22, -0.19]). We found no direct or CR-mediated effects of the clinical condition on emotional perception (data not shown).

4. Discussion

Our first aim was to examine whether the long-term use of drugs, mainly cocaine, was associated with a worse neuropsychological functioning in a sample of subjects in outpatient treatment at 1-3 months of abstinence. As expected, we found that the participants with SUD had a poorer cognitive performance in most of the functions assessed, compared with the healthy control group. This finding is in line with previous results in which cognitive deficits have been related to drug abuse (Madoz-Gúrpide & Ochoa-Mangado, 2012; Sholsberg et al., 2019; Spronk, van Wel, Ramaekers & Verkes, 2013; Vonmoos et al., 2014). Nevertheless, it is important to consider that the relationship between substance use and cognitive impairment is not necessarily linear, as pre-existent neurodevelopmental factors or behavioural traits cannot be excluded (Ersche et al., 2011, 2012; Sampedro-Piquero et al., 2019). Hence, the absence of a characterized depression and non-consumption of antidepressants has been considered as exclusion criteria to control for the fact that the cognitive deficits observed through the neuropsychological assessment were related to the diagnosis of SUD and not depression. Several studies have shown that depression, above all, major depressive disorder, involves not only emotional symptoms, but also cognitive deficits in attention, memory and learning, executive function, and processing speed (Culpepper, Lam & McIntyre, 2017; Roca, Vives, López-Navarro, García-Campayo & Gili, 2015; Russo, Mahon, & Burdick, 2015; Semkovska et al., 2019). In our study, owing to limited time to administer all the neuropsychological tests, we did not administer specific tests for subclinical depression or anxiety. Instead, we received a medical report from each patient specifying whether or not they had some kind of psychopathological disorder. On the other hand, in our interview administered to all the subjects (control and experimental groups), we asked them about whether they had suffered from anxiety or depression in the last 6 months or if they were suffering from it at the time of the evaluation session. Besides, we also asked them about the quality of their sleep and if they were consuming some medication which could affect the cognitive performance. Nevertheless, this aspect will be considered in future studies.

In our study, attentional function, specifically, selective and sustained attention, was altered in our patient sample. Regarding this, cocaine abuse has been shown to be associated with a lower performance on cancellation tests, as employed in our study (Bolla, Rothman & Cadet, 1999). Moreover, it has also been found that cocaine polydrug users showed – compared to cocaine-free polydrug users – a reduced visual attention and a compromised ability to control their attentional focus (Colzato, van den Wildenberg & Hommel, 2009; Kübler, Murphy & Garavan, 2005). In addition, the SUD group showed a poorer performance on an auditory-verbal memory test that is sensitive to attentional problems. In particular, the TAVEC test consists of the presentation of a 16-word list over five trials; altered performance was observed on trial 1, which could

suggest attentional deficits due to stimulus overload, as well as on trial 5, showing memory retention deficits, as well (Bolla, Funderburk & Cadet, 2000; Benedet & Alejandre, 2014). Interestingly, a semantic strategy can be used in the TAVEC test to recall a high number of words, but the SUD group showed a lower use, as well as no benefit in the short-term and long-term, recalling trials when semantic cues were provided. This could be related to a deficit in the acquisition of the list of words rather than a failure in memory recall. Furthermore, the high number of intrusions committed by the SUD group is probably due to a random search for words when not remembering the original list.

Executive deficits were also found in our SUD group. In particular, we found a poorer performance in concept formation skills, modality-specific problem-solving skills (verbal/nonverbal), and the ability to explain sorting concepts abstractly (D-KEFS Sorting Test), as well as complex working memory (backwards digit span), the verbal fluency test, and inhibitory control (Stroop Test). However, significant differences were not observed in planning ability (D-KEFS Tower Test), simple working memory (forward digit span), and decision making (IGT). Along with this, an impaired performance on the Rey Complex Figure Test could be associated with executive deficits, since planning and organisational abilities are also required in this task, in addition to declarative memory (Lezak, Howieson & Loring, 2004). It is well known that executive functions are cognitive domains that rely heavily on the prefrontal cortex (Miller & Cohen, 2001), and neuroimaging studies have often reported hypofrontality in abstinent subjects with SUD performing these sorts of tasks, especially in cocaine-abstinent users (Bolla et al., 2004; Tomasi et al., 2007). Interestingly, several studies have pointed out that an accurate executive functioning seems to be a predictor of a successful treatment outcome. Thus, the lack of inhibitory control has been a factor in the probability of relapse (Czapla et al., 2016). For instance, low performance in this cognitive domain predicted alcohol use six months after treatment (Czapla et al., 2015), and neurocognitive indices related to this measure, such as delay discounting task and impulsive decision making, significantly predicted short-term relapse in a heterogeneous sample of 70 individuals with SUD (Stevens et al., 2015). Furthermore, higher verbal fluency skills led to a lower rate of drug relapse (Wehr & Bauer, 1999), and decision making has been proposed as an essential factor for understanding relapse (Barreno et al., 2019). Contrary to expectation, and consistently with Woicik and colleagues (2009), we did not find significant differences between groups in decision making measured with the IGT task. As these authors mentioned, this result might be attributed to sample differences between the studies due to the heterogeneity of patients with SUD.

Finally, emotional perception was assessed by the RMET (Baron-Cohen et al., 2001), showing that patients with SUD had more difficulties in recognising the emotion expressed by the eyes of different faces. This task has demonstrated effectiveness in detecting alterations in the social cognition of cocaine and methamphetamine users (Kemmis, Hall, Kingston & Morgan, 2007; Henry, Mazur & Rendell, 2009). This deficit could negatively affect the establishment of positive social interactions, which is one of the dimensions of the psychological well-being

scale that had a lower score in our SUD sample. Furthermore, emotion recognition is one of the core components of theory of mind (Ahmed & Miller, 2010; McDonald et al., 2013), and it has been related to other cognitive functions, particularly working memory, verbal fluency, and executive functions (Ahmed & Miller, 2010; Corcoran & Frith, 2003), which were also altered in our sample.

In view of that, we found several cognitive deficits in our SUD sample compared to the healthy control group. Cognitive status has been considered to predict SUD treatment retention, as cognitive impairment is one of the most consistent risk factors for addiction treatment dropout identified across recent studies (Bates, Buckman, & Nguyen, 2013; Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013). For instance, performance in a variety of cognitive domains (attention, reasoning, verbal memory, spatial processing, etc.) are significant predictors of addiction treatment completion and attendance at follow-ups (Aharonovich, Amrhein, Bisaga, Nunes, & Hasin, 2008; Streeter et al., 2008; Teichner, Horner, Roitzsch, Herron, & Thevos, 2002; Verdejo-Garcia et al., 2014, 2012). Furthermore, cognitive measures may also predict relapse, since patients with SUD with impairments in verbal memory and executive skills, such as decision making, are more likely to resume drug use (Fox, Jackson, & Sinha, 2009; Passetti, Clark, Mehta, Joyce, & King, 2008; Wehr & Bauer, 1999). Additionally, cognitive decline may hamper SUD treatment because engaging in therapeutic change and assimilating behavioural interventions demand cognitive effort (Aharonovich et al., 2006; Brorson et al., 2013; Perry & Lawrence, 2017; Torregrossa, Corlett, & Taylor, 2011).

The second purpose of this study was to determine whether CR might play a mediating role in the cognitive abilities of subjects with SUD. Taken together, our results suggest that the adverse effects of drug use on cognitive performance were mediated (to a greater or lesser extent) by the level of CR. Thus, these findings highlight the relevance of CR as a potential modulator of drug-induced cognitive deficits. Consistently, subjects with a high level of CR (or neural reserve) have been shown to be able to engage different brain networks in order to more effectively use the cognitive functions withstanding cerebral alterations (Serra et al., 2018). This is also congruent with the 'brain maintenance' concept introduced by Stern (2017), which postulates that life experiences (including cognitive, social, and physical activities) reshape the brain, increasing the ability to maintain the cognitive integrity. Specifically, statistical mediation revealed that the performance in tasks measuring attention and processing speed was reliant on CR integrity, which was lower in subjects with SUD. Consistent with this, previous studies have found that tasks that require greater attentional capacity appear to be strongly influenced by CR (Lavrencic, et al., 2018; Le Carret et al., 2003). Concerning the performance in the executive function and declarative memory domains, we found a significant, but partial, mediating effect of CR. Hence, other variables not contemplated in this study should also be considered. It is relevant to note that CR did not mediate the performance in emotional perception. In this sense, Lavrencic and colleagues (2015) found that CR was not related to emotion evaluation or theory of mind. Thus, despite the complexity of

social cognition, the advantage afforded by CR does not appear to extend to such abilities.

Interestingly, the degree of CR not only influenced cognitive performance, but those subjects with high CR also showed reduced levels of craving compared to the subjects with low CR (Table 1). Concerning this, in our recent review, we described that the different proxy measures associated with CR can be included and trained as a complement to conventional SUD therapies, showing positive effects on drug-related measures such as craving (Cutuli et al., 2019; Buchowski et al., 2011; Silverman, 2011).

On the other hand, we must consider that a factor which appears to be involved in building CR is the innate and premorbid intelligence of the individual (Alexander et al., 1997). There are studies in which lower premorbid IQ seems to be a negative variable related to cognitive impairment and, consequentially, to poor treatment outcomes (Mahoney et al., 2017; 2019). Regarding this, Mahoney and colleagues (2017) observed that premorbid IQ negatively mediated performance on neurocognitive tests in individuals diagnosed with cocaine use disorder. One possible explanation for these findings is that individuals with higher intellectual functioning may be less susceptible to the detrimental cognitive effects produced by cocaine. Another possible explanation is that higher IQ may serve as a protective factor, in other words, slowing cognitive decline related to cocaine use, supporting the theory of CR.

In our study, we have not taken into account this variable because we consider CR as a dynamic and flexible phenomenon across the life span, which can increase or reduce its protective potential depending on our life experiences throughout all stages of life (Stern, 2012; 2017). Furthermore, this construct is a result of the combination of different lifelong experiences, and it cannot be estimated through only the IQ or premorbid IQ of the individual (Grotz, Seron, Van Wissen, & Adam, 2017). Therefore, CR can be considered as a measure per se rather than being represented singly by education level, work attainment, or premorbid intelligence. Moreover, IQ is not supposed to change significantly across our life, while our life experiences (i.e. lifestyle factors, cognitively stimulating behaviours, and social activities) can change in every stage of life, even in those individuals who are not supposed to raise their education level or to improve their IQ anymore. Thus, it is possible that improving life span experiences, such as leisure activities, could mitigate the effects of lower premorbid IQ and education level on cognitive efficiency. Regarding this, in our recent review about CR and SUD (Cutuli et al., 2019), we also discussed how variables involved in CR (healthy leisure, social support, or job-related activities, among others) could be trained and included as complementary activities of SUD treatments.

Finally, this paper has important limitations. The sample size is small, and this hinders the generalization of our results. Another problem related to our sample is that, although cocaine was the main substance consumed in our experimental group, this group shows a high proportion of multi-drugs users. For

instance, comorbid alcohol abuse is common in cocaine users which is itself associated with cognitive impairment in multiple neuropsychological domains (Stavro, Pelletier, & Potvin, 2013). Hence, this potential confounding factor would need to be addressed in future studies. For instance, several studies did not exclude individuals who also abused alcohol (Cunha, Nicastri, Gomes, Moino, & Peluso, 2004; De Oliveira, Barroso, Silveira, Sanchez, De Carvalho Ponce, Vaz, et al., 2009; Woicik et al., 2009), or only excluded individuals whose alcohol intake met criteria for abuse/dependence (Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Madoz-Gurpide, Blasco-Fontecilla, Baca-Garcia, & Ochoa-Mangado, 2011; Ruiz Sánchez de León et al., 2009).

Furthermore, although the abstinence was controlled in our participants, there was a significant heterogeneity regarding alleged duration of abstinence (between 2 and 12 weeks). On the other hand, the CR questionnaire used in this study has shown indicators of psychometric goodness that allow for its employment (Cronbach's alpha index: α=0.71), but because of its shortness, it is difficult that it covers the diversity of activities involved in the CR construct. Moreover, information of other complementary factors moderating the cognitive performance, such as the IQ or complementary CR questionnaires, could have given more details about our results. Despite this, our preliminary results point to the need to consider the CR in the field of addiction treatment and prevention. On the one hand, the degree of CR reached by subjects can operate as a protector, even in the case of substance consumption, as it can attenuate its impact on cognitive performance. On the other hand, the offer of novel and stimulating activities, job opportunities, and healthy leisure activities as an alternative to drug consumption, while at the same time recharging the CR, can also improve cognitive performance (Cutuli et al., 2019; Pedrero-Pérez et al., 2014). Finally, since CR seems to be more associated with certain cognitive domains, these could be more malleable to lifetime experiences and interventions.

5. Conclusions

In summary, cognitive assessment must be considered a key element of the SUD treatment. Determining the neuropsychological deficits of this population could be useful to understand the altered cognitive functioning that may underlie or maintain drug use. Hence, there is a need to routinely include neuropsychological evaluation in the conventional treatment regimens, as well as to monitor cognitive functions at follow-up. In addition, SUD patients seem to be a heterogeneous group, and CR level should be considered because it appears to be protective, attenuating certain cognitive deficits. Hence, this must be taken into account when treatment groups are established, and the measures associated with this construct should be included and trained as a complement to conventional SUD therapies.

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Figure legends

Figure 1. General cognitive dimensions extracted in principal component analyses. (A) A domain related to attention and processing speed was obtained from measures registered in $d2$ and TMT (version A). (B) A factor revealing executive function was extracted from variables assessed in the Sorting Test, the Tower Test, digit span, the verbal fluency test and the Stroop Test. (C) A dimension indicating declarative memory was obtained from measures registered in TAVEC (verbal) and Rey Complex Figure (non-verbal). High factor scores indicate better performance in each dimension. Values represent factor loadings. Class., classification; delay., delayed score; LTM, long-term memory; rec., recognition; STM, short-term memory; v.a, version A.

Figure 2. Mediation models implemented. (A) SUD-related deficits in attention and processing speed were completely mediated by CR deterioration, as evidenced by significant a and b paths and non-significant path c'. Deficits in executive function (B) and declarative memory (C) in subjects with SUD were partially mediated by CR impairment, as shown by significant a, b and c' paths. Data are displayed as regression coefficient (standard error), with signs indicating the direction of correlations. Significant correlation values: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

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Highlights

-Subjects with SUD showed neuropsychological deficits.

-Psychological well-being was lower in subjects with SUD in outpatient treatment.

-Higher CR was related to lower levels of drug craving.

-CR seems to attenuate certain cognitive deficits.

-CR related activities should be considered as a complement of conventional treatments.

29

A

'Attention and processing speed' factor

d2-TOT

.850

- .632   .844

TMTv a (s)   d2-CON

B ■ **'Executive function' factor**

Sorting test class.
.780

Stroop color/word   .570   .788   Sorting test rec.

Verbal fluency (animals)   .737   .599   Tower test

.643   .574

Verbal fluency FAS   Digit span (backward)
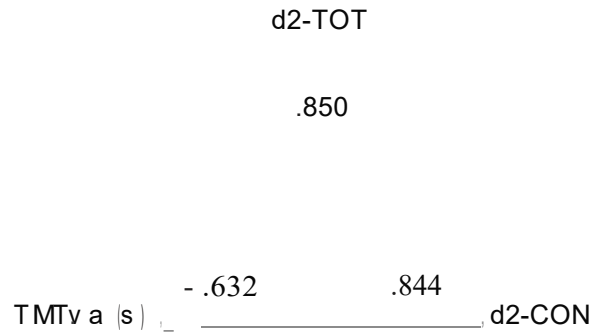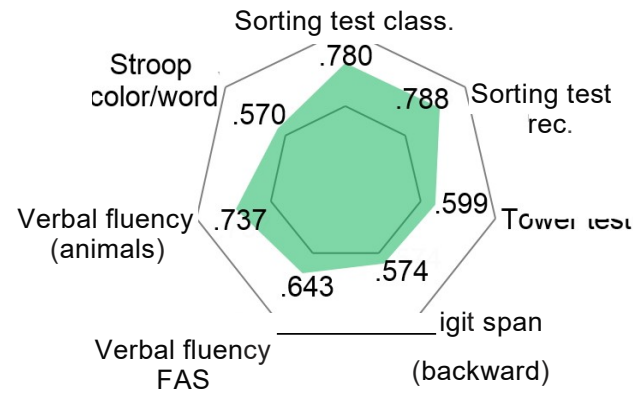
e   **'Declarative memory' factor**
TAVEC Trial 5

Rey Complex Figure delay.   **.848**

.411   .913   TAVEC STM

TAVEC LTM+cues   .937   .892   TAVEC STM+cues

.953

TAVEC LTM

A

| Clinical condition
Control (O)
SUD (1) | $e= -0.724^{**} (0.259)$ | Attention and
processing speed
(factor score) |

| Clinical condition
Control (O)
SUD (1) | $a= -0.861^{**} (0.252)$ | CR level
(standardized
score) | $b = 0.302^{*} (0.130)$ | Attention and
processing speed
(factor score) |

$$e'= -0.465 (0.274)$$

B

| Clinical condition
Control (O)
SUD (1) | $e = -1.008^{***} (0.249)$ | Executive
function
(factor score) |

| Clinical condition
Control (O)
SUD (1) | $a= -0.780^{**} (0.256)$ | CR level
(standardized
score) | $b = 0.358^{**} (0.128)$ | Executive
function
(factor score) |

$$e' = -0.729^{**} (0.254)$$

e

| Clinical condition
Control (O)
SUD (1) | $e = -0.973^{***} (0.245)$ | Declarative
memory
(factor score) |

| Clinical condition
Control (O)
SUD (1) | $a = -0.861^{**} (0.252)$ | CR
(standardized
score) | $b = 0.309^{**} (0.122)$ | Declarative
memory
(factor score) |

$$e'= -0.707^{**} (0.257)$$

Table 1. Demographic, substance use characteristics of participants.

	SUD group		Healthy control group
DEMOGRAPHICS			
-Age $\pm$ SEM	37.9 $\pm$ 1.40		35.4 $\pm$ 2.5 (p=0.33)
-Sex % male	95% (38/40)		80% (16/20) (p=0.07)
-Years of education	16.2 $\pm$ 0.5		17.7$\pm$0.8 (p=0.72)
-Marital status (single) - % (n)	57.5 % (23/40)		65% (13/20) (p=0.53)
SUBSTANCE USE	**SUD-high CR**	**SUD-low CR**	
-Onset age	16.9$\pm$1.3	19.1$\pm$1.2 (p=0.22)	-
-Duration of cocaine use (years)	16.6$\pm$1.9	17.3$\pm$2.1 (p=0.83)	-
-Weeks since last used drug	6.9$\pm$0.5	5.9$\pm$0.6 (p=0.26)	-
-Number of relapses	0.8$\pm$0.5	1.5$\pm$0.5 (p=0.30)	-
-Number of drugs consumed	3.1$\pm$0.4	3.3$\pm$0.4 (p=0.82)	-
-Cocaine used per month (g)	11.4$\pm$0.5	8.3$\pm$0.4 (p=0.25)	-
-Route of administration % intranasal	100%	100%	
-Reported tobacco use -% (n)	75%(11/16)	54.17% (13/24)	
-Tobacco cigarettes per day	11$\pm$2.3	7$\pm$1.6 (p=0.14	-
-Reported alcohol use -%(n)	68.75%(11/16)	70.83% (17/24)	
-Reported cannabis use -%(n)	62.50%(10/16)	70.83% (17/24)	
-Reported amphetamine/MDMA use-% (n)	37.5%(6/16)	41.67% (10/24)	
-Score craving scale (maximum 30)	5.5+1.8	10.8+1.7 (p=0.04)*	-

Values are means $\pm$ SEM or percentages. SUD group, n=40 (High CR, n=16; Low CR, n=24); Control group, n=20.
* t (38) = -2.07, p=0.04.

Table 2. Neuropsychological tests results.

	Healthy controls	SUD group	Student's *t test* and *p* values for comparisons	Cohen´s *d*
CR questionnaire	12±0.7	9.1±0.5	T(58)=-3.41, *p*=.001*	0.9
-Schooling	4.1±0.1	3.7±0.1	*t*(58)=-1.91, *p*=.07	
-Parents schooling	1.1±0.1	0.9±0.1	*t*(58)=-1.29, *p*=.20	
-Formal courses	1.9±0.2	1.5±0.1	*t*(58)=-1.25, *p*=.22	
-Occupational attainment	1.6±0.2	0.9±0.1	*t*(58)=-2.69, *p*=.01*	0.7
-Music knowledge	0.9±0.1	0.9±0.1	*t*(58)=-0.32, *p*=.75	
-Languages	0.4±0.2	0.3±0.1	*t*(58)=-0.59, *p*=.56	
-Reading activity	1.6±0.3	0.9±0.2	*t*(58)=-1.79, *p*=.08	
-Brain games	0.5±0.2	0.4±0.1	*t*(58)=-0.76, *p*=.45	
-Physical activity %	60	57.5	*t*(58)=-0.18, *p*=.86	
Attention, psychomotor speed and visual searching				
d2				
-Total response	436.4±16.6	396.5±13	*t*(58)=-1.83, *p*=.07	
-Correct answers	158±7.9	135.3±7	*t*(58)=-2.01, *p*=.04*	0.6
-Omissions	25.8±4.6	32.7±5.6	*t*(58)=0.82, *p*=.41	
-Commissions	7±1.3	13.2±3.6	*t*(58)=1.21, *p*=.23	
-Effectiveness index	403.6±17.8	354.9±11.8	*t*(58)=-2.34, *p*=.02*	0.8
-Concentration index	150.4±8.7	119±7.5	*t*(58)=-2.56, *p*=.01*	0.7
-Variability index	14.3±1.5	16.9±1	*t*(58)=1.45, *p*=.15	
Trail making test				
-Version A (s)	24.2+1.3	26.5+1	*t*(58)=1.38, *p*=.17	
-Version B (s)	63.8+5.2	82.3+7.7	*t*(58)=1.60, *p*=.11	
Declarative memory				
TAVEC				
-Trial 1	7.4±0.4	6.1±0.3	*t*(58)=-2.40, *p*=.02*	0.6
-Trial 5	14±0.5	11.6±0.3	*t*(58)=-4.09, *p*=.0001*	1.1
-Trial B	6.1±0.3	4.1±0.2	*t*(58)=-3.38, *p*=.001*	0.9
-Free STM	12.7±0.5	10.2±0.4	*t*(58)=-3.70, *p*=.0005*	1.04
-STM with semantic cues	12.6±0.8	10.8±0.4	*t*(58)=-2.35, *p*=.02*	0.6
-Free LTM	13.2±0.6	10.3±0.5	*t*(58)=-3.73, *p*=.0004*	1.05
-LTM with semantic cues	13.3±0.6	10.6±0.5	*t*(58)=-3.48, *p*=.001*	0.9
-Semantic strategy use during the list acquisition	17.7±2.4	10.6±1.2	*t*(58)=-2.97, *p*=.004*	0.8
-Semantic strategy use during free STM	5.4±0.7	3.3±0.4	*t*(58)=-2.71, *p*=.009*	0.7
-Semantic strategy use during LTM	6.4±0.8	3.6±0.4	*t*(58)=-3.31, *p*=.002*	0.9
-Serial strategy use during the list acquisition	4.5±0.8	5.4±0.6	*t*(58)=0.84, *p*=.40	
-Serial strategy use during free STM	1±0.3	0.7±0.1	*t*(58)=-1.01, *p*=.32	
-Serial strategy use during free LTM	1.1±0.4	0.9±0.2	*t*(58)=-0.46, *p*=.64	
-Intrusions during free memory	3.2±0.7	6.7±0.9	*t*(58)=2.61, *p*=.01*	0.8
-Intrusions during memory with semantic cues	1.3±0.4	3.4±0.4	*t*(58)=3.31, *p*=.002*	0.9
-Recognition	15.5±0.1	15±0.2	*t*(58)=-1.77, *p*=.08	
Rey Complex Figure				
-Copy score	35.2±0.4	33.3±0.8	*t*(58)=-1.67, *p*=.10	
-Delayed score	23.7±1.5	18.5±1	*t*(58)=-2.93, *p*=.005*	0.8
Executive functions				
D-KEFS Sorting test				
-Classifications	10.9±0.8	8.2±0.4	*t*(58)=-3.29, *p*=.002*	0.9
-Descriptions	43.6±3.1	30.7±1.8	*t*(58)=-3.80, *p*=.0004*	1.02
-Recognition	43.6±2	31.1±2	*t*(58)=-4.20, *p*=.0001*	1.2
D-KEFS Tower test				
-Achievement score	17.8±0.8	16.5±0.6	*t*(58)=-1.22, *p*=.23	

Digit span

-Forward	6+0.3	6.2+0.2	*t*(58)=0.8, *p*=.43	
-Backward	5.2+0.3	4.3+0.2	*t*(58)=-2.67, *p*=.01*	0.7

D-KEFS verbal fluency test

-FAS total	45.6+1.8	37.2+1.9	*t*(58)=-2.86, *p*=.006*	0.8
-Animals	23.1+0.7	20.4+0.8	*t*(58)=-2.16, *p*=.003*	0.6

Stroop test

-Word	100.2+4.9	99.3+2.5	*t*(58)=-0.17, *p*=.86	
-Color	68.6+2.9	63.2+2	*t*(58)=-1.52, *p*=.13	
-Total Color/Word	53.1+5.8	37.7+1.9	*t*(58)=-3.18, *p*=.002*	0.8
-Interference Index	13.1+5.45	-0.72+1.5	*t*(58)=-3.17, *p*=.002*	0.8

IGT

-1-20	-1.4+1.1	-1.5+1.1	*t*(58)=-0.06, *p*=.96	
-20-40	0.3+1.4	-0.3+1	*t*(58)=-0.32, *p*=.75	
-40-60	1.7+1.4	1.2+1.1	*t*(58)=-0.24, *p*=.81	
-60-80	4.1+1.5	1.7+0.9	*t*(58)=-1.40, *p*=.17	
-80-100	3.8+1.5	3.7+1	*t*(58)=-0.04, *p*=.97	

Emotional perception

RMET

-Correct answers	23.4+0.8	19.7+0.7	*t*(58)=-0.06, *p*=.002*	0.9

Psychological well-being scale

-Self-acceptance	28.6+0.8	20.7+1	*t*(58)=-5.28, *p*=.0001*	1.6
-Positive relationships	28.2+1.4	24.4+1.1	*t*(58)=-2.02, *p*=.05*	0.6
-Autonomy	40.3+0.9	33.1+1.1	*t*(58)=-4.25, *p*=.0001*	1.3
-Environmental mastery	29.3+0.7	25.5+0.7	*t*(58)=-3.28, *p*=.002*	0.9
-Personal growth	33.2+1.2	30.3+1.1	*t*(58)=-1.66, *p*=.10	
-Purpose in life	28.8+0.7	25.4+1.1	*t*(58)=-2.08, *p*=.04*	0.6

Values are means + SEM or percentages. STM: Short-term memory; LTM: Long-term memory.

*Asterisks represent significant differences between groups (*p*≤0.05).

Role of Funding Sources

Conflict of Interest

Authors declare no conflict of interest.

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Contributors

Authors S.V., A.P.R. and P.S.P. performed neuropsychological and clinical assessments. Author D.L.G.M. conducted statistical analysis. Authors P.S.P. and L.S. designed the study and protocol and wrote the first version of the manuscript. All authors have approved the final manuscript.

Vicario et al.

Cognitive reserve mediates the severity of certain neuropsychological deficits related to cocaine use disorder

SUPPLEMENTARY MATERIAL

1. Description of the neuropsychological tests

Attention, psychomotor speed and visual searching

-*d*2 test: In this test, participants have to cross out any letter "*d*" with two marks around, above, or below it in any order. There are also surrounding distractors that are similar to the target stimulus, e.g. a "*p*" with two marks or a "*d*" with one or three marks. The time limit per line of the test is 20 seconds (Steinborn, Langner, Flehmig & Huestegge, 2018).

-Trail Making Test: The test consists of two parts in which the task is to connect randomly distributed points. In part A, all objectives are numbers (1 to 25) and the participant must join them up (1-2-3 . . .), while in part B, they must alternate between numbers and letters of the next level (1-A, 2-B, 3-C. . .). The total score is the number of seconds that the participant needs to complete the task, with a time limit of 60 and 150 seconds for TMT-A and TMT-B, respectively (Llinàs-Reglà et al., 2017).

Declarative memory

-TAVEC: TAVEC is a test to assess episodic verbal memory and learning ability. The task consists of learning a 16-word list that is read 5 times by the experimenter. Specifically, the TAVEC consists of 3-word lists that are presented to the learner as a *shopping list*: a learning list (A), an interference list (B) and a recognition list. Subjects can use semantic or serial clues to facilitate the recall (Chirivella, Ferri, Villodre & Noe, 2003).

-Rey-Osterrieth Complex Figure: This is a neuropsychological test in which examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory after 30 minutes (recall) (Shin, Park, Park, Seol & Kwon, 2006).

Executive functions

-D-KEFS Sorting Test: This is a test exploring the ability of reasoning, categorisation abilities, problem solving, flexibility of thinking and abstraction. It includes a practise set card, free sorting set card and a sort recognition set. The practice set card is used with the main purpose of allowing the participants to become familiar with the ST procedure. In this practice set, six cards are shown to the participant, and the neuropsychologist explains the ST rules by showing how the cards could be classified, based on perceptive criteria (namely, the round or square shape of the cards) or verbal criteria (namely, the male or female name printed on the cards). In free sorting, the participant is presented with six mixed-up cards that display both perceptual features and printed words. The participant is asked to sort the cards into two groups, with three cards per group, according

to as many different concepts or rules as possible, and to describe the concepts employed to generate each sort. Each of the two card sets has a maximum of eight target sorts. The participant has at maximum 4 minutes (for each card set) to find as many categorisations as possible. In sort recognition, the examiner sorts the same sets of cards into two groups, with three cards per group, according to the eight target sorts. After each sort is made by the examiner, the examinee attempts to identify and describe the correct rules or concepts used to generate the sort. The participant has at maximum 45 seconds (for each group of cards) to verbalise the reason why the cards have been sorted in that way (Mattioli et al., 2014).

-<u>D-KEFS Tower Test</u>: This test requires subjects to rearrange disks on pegs in order to create a tower that the examiner indicates. There are nine different towers to be completed that range in difficulty, beginning with simple towers that require only 1–3 moves and becoming gradually more difficult, with towers requiring up to 26 moves (Larochette, Benn & Harrison, 2009).

-<u>Digit span</u>: This task is used to measure the working memory's number storage capacity. Participants hear a sequence of numbers and are required to recall the sequence correctly, with increasingly longer sequences being tested in each trial. Digit span tasks are given forwards or backwards, meaning that once the sequence is presented, the participant is asked to recall the sequence in either normal or reverse order (Woods et al., 2011).

-<u>D-KEFS verbal fluency test</u>: In phonological VFT, the participant is required to produce in 60 seconds as many words as she/he can beginning with certain letters (in this study F, A and S). However, in semantic VFT, the participant is required to produce in 60 seconds as many words as she/he can belonging to a particular category (in this study, animals). The score obtained is the number of words in each category (Aita et al., 2019).

-<u>Stroop Test</u>: This consists of three pages, each with 100 components randomly organised into five columns. In the first page, the participant must read aloud the words "red", "green", and "blue" printed in black ink. In the second one, "colour naming", the colour (blue, green or red) of each element "XXXX" must be named. In the last one, "interference", the task is to name the colour of the ink, inhibiting the reading of the word, which corresponds to the name of another colour. The subject has 45 seconds to read aloud, as quickly as possible, the columns from left to right. Finally, the interference index is calculated with the formula $WC - [(W \times C)/(W + C)]$, and this indicates the degree to which the person has control over interference (Scarpina & Tagini, 2017).

-<u>IOWA Gambling Test (IGT)</u>: This is a test which simulates real-life decision making. Participants are presented four virtual decks of cards on a computer screen. They are told that each deck holds cards that will either reward or penalise them, using game money. The goal of the game is to win as much money as possible. The decks differ from each other in the balance of reward versus penalty cards. Thus, some decks are "bad decks", and other decks are "good

decks", because some decks will tend to reward the player more often than other decks. The test ends when 100 trials are completed (Jaracz & Borkowska, 2012).

Emotional perception

-Reading the mind in the eyes test (RMET): This is considered a valid test to assess theory of mind. Participants must attribute a feeling to the people he/she sees in the photos based on the emotional expression of the eyes. In each gaze, participants have 4 possible answer options (Warrier, Bethlehem & Baron-Cohen, 2017).

2. Statistical analysis

Principal component analysis

Principal Component Analysis (PCA) was conducted in order to reduce the data set of the neuropsychological assessment (Table 2) into global dimensions (i.e. factors). We performed three independent PCAs with a fixed extraction criterion of a single factor, each of which included those measures indicative of the same cognitive domain (i.e. attention and processing speed, executive function, or declarative memory; Fig. 1). The 'emotional perception' dimension was excluded from the analysis since it was evaluated by a single task (REMT). The factor obtained in the first PCA (~61% of variance explained) represented the degree of attention and processing speed as it included measures indicative of high performance in the *d2* test (concentration –CON– and effectiveness –TOT– indexes) and TMT (version A; Fig. 1A). The dimension extracted in the second PCA (~46% of variance explained) represented the level of executive function since it included variables indicative of high performance in the Sorting test (classifications and recognition), the Tower test (achievement score), Digit span (backward), the verbal fluency test (FAS and animals), and the Stroop test (colour/word interference: Fig. 1B). Lastly, the factor obtained in the third PCA (~71% variance explained) represented the level of declarative memory (verbal and non-verbal), as it included measures indicative of high performance in TAVEC (trial B, STM, and LTM with and without semantic cues) and Rey Complex Figure (delayed score; Fig.1C).

It is important to note that our data were adequate to perform PCA, as indicated by Kaiser-Meyer Olkin (KMO) sample adequacy tests over 0.5 value and significant Bartlett's sphericity tests (X^2; *'attention and processing speed'* factor: KMO = .603; $X^2(3) = 33.16$, $p < .001$; *'executive function'* factor: KMO = .888; $X^2(10) = 300.80$, $p < .001$; *'declarative memory'* factor: KMO = .747; $X^2(21) = 108.75$, $p < .001$).

Mediation analysis

Statistical mediation was conducted according to the causal steps approach (Baron & Kenny, 1986) in order to assess whether CR impairment mediated drug-related cognitive deficits in outpatients. Simple mediation analyses tested bivariate (a, c) and multiple (b, c') regression models depicted in a path diagram

form. Path c represents a regression coefficient quantifying the total effect of the clinical condition (i.e. the predictor) on performance in each cognitive factor (i.e. the outcome). Path a represents a regression coefficient predicting CR level (i.e. the proposed mediator) from the clinical condition, while path b represents a regression coefficient predicting cognitive performance from the CR level when the clinical condition is statistically controlled. The product a x b estimates the indirect effect by which the clinical condition influences cognitive performance via CR modulation. Path c' indicates a regression coefficient quantifying the direct effect of the clinical condition on performance in each cognitive factor when the level of CR is statistically controlled. Mediation exists when c, a, and b are significant. Complete or partial mediation occurs when c' is or is not significant, respectively.

Supplementary Table 1. Comparisons among the groups in the different neuropsychological tests.

	Healthy controls	High CR SUD group	Low CR SUD group	ANOVA *test* and *p* values for comparisons
CR questionnaire	12±0.7	12.1±0.5	7.2±0.4	*F*(2,57)=30.4, *p*<0.001 +#*p*<0.001
-Schooling	4.1±0.1	4.1±0.1	3.3±0.2	*F*(2,57)=8.3, *p*<0.001 +#*p*<0.001
-Parents schooling	1.1±0.1	1.3±0.2	0.5±0.1	*F*(2,57)=5.9, *p*=0.004 +*p*=0.01; #*p*=0.002
-Formal courses	1.9±0.2	1.9±0.2	1.2±0.2	*F*(2,57)=3.5, *p*=0.04 +*p*=0.04; #*p*=0.02
-Occupational attainment	1.6±0.2	1.3±0.3	0.7±0.1	*F*(2,57)=5.9, *p*=0.005 +*p*=0.001; #*p*=0.04
-Music knowledge	0.9±0.1	1±0.1	0.8±0.1	*F*(2,57)=0.9, *p*=0.4
-Languages	0.4±0.2	0.5±0.2	0.1±0.1	*F*(2,57)=2.5, *p*=0.09
-Reading activity	1.6±0.3	1.7±0.4	0.3±0.1	*F*(2,57)=6.3, *p*=0.003 +#*p*=0.004
-Brain games	0.5±0.2	0.7±0.2	0.1±0.1	*F*(2,57)=3.5, *p*=0.04 #*p*=0.01
-Physical activity %	60	56.3	58.3	*F*(2,57)=0.02, *p*=0.9
Attention, psychomotor speed and visual searching				
***d*2**				
-Total response	436.4±16.6	396.6±15.9	396.4±19.1	*F*(2,57)=1.6, *p*=0.2
-Correct answers	158±7.9	134.4±9.9	135.9±9.6	*F*(2,57)=1.9, *p*=0.1
-Omissions	25.8±4.6	29.6±8.9	34.8±7.3	*F*(2,57)=0.5, *p*=0.6
-Commissions	7±1.3	9.2±2.3	15.9±5.7	*F*(2,57)=1.4, *p*=0.3
-Effectiveness index	403.6±17.8	357.9±17.4	352.9±16.1	*F*(2,57)=2.7, *p*=0.06
-Concentration index	150.4±8.7	124.6±11.5	115.2±9.9	*F*(2,57)=3.5, *p*=0.04 +*p*=0.01
-Variability index	14.3±1.5	16.4±11.5	17.1±1.4	*F*(2,57)=1.1, *p*=0.3
Trail making test				
-Version A (s)	24.2±1.3	26.8±1.6	26.4±1.3	*F*(2,57)=0.9, *p*=0.4
-Version B (s)	63.8±5.2	72.2±1.7	89±11.1	*F*(2,57)=2.1, *p*=0.1
Declarative memory				
TAVEC				
-Trial 1	7.4±0.4	6.7±0.5	5.6±0.4	*F*(2,57)=4.4, *p*=0.02 +*p*=0.005
-Trial 5	14±0.5	11.9±0.6	11.4±0.4	*F*(2,57)=8.6, *p*<0.001 +*p*<0.001; # *p*=0.005;**p=0.01
-Trial B	6.1±0.3	5.1±0.4	3±0.8	*F*(2,57)=7.3, *p*=0.001 +*p*<0.001; # *p*=0.03
-Free STM	12.7±0.5	10.7±0.7	9.9±0.9	*F*(2,57)=7.4, *p*=0.001 +*p*<0.001; # *p*=0.02;**p=0.04
-STM with semantic cues	12.6±0.8	11.9±0.6	10±0.4	*F*(2,57)=5.1, *p*=0.01 +*p*=0.003; # *p*=0.04
-Free LTM	13.2±0.6	10.9±0.9	9.8±0.5	*F*(2,57)=7.6, *p*=0.001 +*p*<0.001; # *p*=0.02;**p=0.03

-LTM with semantic cues	13.3±0.6	11.6±0.8	9.9±0.6	*F*(2,57)=7.9, *p*<0.001 +*p*<0.001
-Semantic strategy use during the list acquisition	17.7±2.4	11.9±1.9	9.7±1.6	*F*(2,57)=4.7, *p*=0.01 +*p*=0.004
-Semantic strategy use during free STM	5.4±0.7	3.9±0.7	2.7±0.4	*F*(2,57)=4.2, *p*=0.02 +*p*=0.005
-Semantic strategy use during LTM	6.4±0.8	3.3±0.8	3±0.5	*F*(2,57)=5.5, *p*=0.006 +*p*=0.007; # *p*=0.004;**p*=0.01
-Serial strategy use during the list acquisition	4.5±0.8	5.8±1.3	5.1±0.6	*F*(2,57)=0.5, *p*=0.6
-Serial strategy use during free STM	1±0.3	0.7±0.2	0.8±0.2	*F*(2,57)=0.5, *p*=0.6
-Serial strategy use during free LTM	1.1±0.4	1.3±0.5	0.7±0.2	*F*(2,57)=0.7, *p*=0.5
-Intrusions during free memory	3.2±0.7	4.6±1.2	8.1±1.1	*F*(2,57)=0.7, *p*=0.5
-Intrusions during memory with semantic cues	1.3±0.4	2.9±0.6	3.9±0.5	*F*(2,57)=6.4, *p*=0.003 +*p*=0.001; # *p*=0.02;**p*=0.05
-Recognition	15.5±0.1	15.3±0.3	14.8±0.3	*F*(2,57)=2.5, *p*=0.09
Rey Complex Figure				
-Copy score	35.2±0.4	34.2±0.7	32.6±1.2	*F*(2,57)=2.1, *p*=0.1
-Delayed score	23.7±1.5	19.7±1.3	17.6±0.4	*F*(2,57)=4.8, *p*=0.01 +*p*=0.003

Executive functions

D-KEFS Sorting test

-Classifications	10.9±0.8	8.3±0.8	8.2±0.5	*F*(2,57)=5.3, *p*=0.008 +*p*=0.005; # *p*=0.01;**p*=0.03
-Descriptions	43.6±3.1	30.5±3.3	30.8±2.2	*F*(2,57)=7.1, *p*=0.002 +*p*=0.001; # *p*=0.003;**p*=0.01
-Recognition	43.6±2	31.1±2.6	31±2.9	*F*(2,57)=8.7, *p*<0.001 *+# *p*=0.001

D-KEFS Tower test

-Achievement score	17.8±0.8	16.4±1.1	16.6±0.7	*F*(2,57)=0.7, *p*=0.5

Digit span

-Forward	6±0.3	6.4±0.2	6±0.2	*F*(2,57)=0.6, *p*=0.5
-Backward	5.2±0.3	4.2±0.3	4.1±0.3	*F*(2,57)=3.6, *p*=0.03 +*p*=0.03; # *p*=0.02;**p*=0.01

D-KEFS verbal fluency test

-FAS total	45.6±1.8	42.3±2.6	33.8±2.4	*F*(2,57)=7.7, *p*=0.001 +*p*<0.001; # *p*=0.01
-Animals	23.1±0.7	21.3±1.7	18.7±0.8	*F*(2,57)=2.9, *p*=0.06
Stroop test				
-Word	100.2±4.9	103.2±1.2	96.6±4	*F*(2,57)=0.3, *p*=0.7
-Color	68.6±2.9	64.5±1.6	61.3±3.6	*F*(2,57)=1.4, *p*=0.2
-Total Color/Word	53.1±5.8	37.8±2.7	37.37±2.3	*F*(2,57)=4.9, *p*=0.01 +#*p*=0.01;**p*=0.03
-Interference Index	13.1±5.45	0.19±2.1	-1.3±2	*F*(2,57)=4.9, *p*=0.01 +*p*=0.004; # *p*=0.02;**p*=0.05

IGT

-1-20	-1.4±1.1	-3±0.9	-0.5±1.6	*F*(2,57)=0.7, *p*=0.5
-21-40	0.3±1.4	-1.1±1.4	0.3±1.3	*F*(2,57)=0.3, *p*=0.7
-41-60	1.7±1.4	0.9±1.2	1.4±1.6	*F*(2,57)=0.1, *p*=0.9
-61-80	4.1±1.5	1±1.6	2.2±1.1	*F*(2,57)=1.2, *p*=0.3
-81-100	3.8±1.5	2.5±1.5	3.5±1.3	*F*(2,57)=0.5, *p*=0.6

Emotional perception

RMET

-Correct answers	23.4±0.8	19.5±1.1	19.8±1.1	*F*(2,57)=5.1, *p*=0.01 *+*p*=0.01; # *p*=0.02

Psychological well-being scale

-Self-acceptance	28.6±0.8	20.5±1.5	20.9±1.3	*F*(2,57)=13.7, *p*=0.001 *+# *p*<0.001
-Positive relationships	28.2±1.4	25.8±1.9	23.5±1.4	*F*(2,57)=2.6, *p*=0.08

-Autonomy	40.3±0.9	32.3±1.9	33.6±1.4	$F(2,57)=13.7$, $p=0.001$ *+# $p<0.001$
-Environmental mastery	29.3±0.7	25.8±0.9	25.4±1.1	$F(2,57)=5.1$, $p=0.01$ +$p=0.003$; # $p=0.01$;*$p=0.03$
-Personal growth	33.2±1.2	31.3±1.3	29.5±1.6	$F(2,57)=1.7$, $p=0.18$
-Purpose in life	28.8±0.7	24.6±1.6	26±1.6	$F(2,57)=2.4$, $p=0.1$ *$p=0.01$

Values are means ± SEM or percentages. STM: Short-term memory; LTM: Long-term memory.

*Asterisks represent significant differences between the Healthy control group and SUD group with High CR ($p\leq0.05$).

+ Symbol represent significant differences between the Healthy control group and SUD group with Low CR ($p\leq0.05$).

Symbol represent significant differences between the SUD group with High and Low CR ($p\leq0.05$).

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