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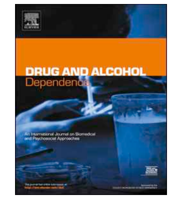

Full length article

The role of neurocognitive functioning, substance use variables and the DSM-5 severity scale in cocaine relapse: A prospective study

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ABSTRACT

Background: The severity of substance use disorder (SUD) is currently defined by the sum of DSM-5 criteria. However, little is known about the validity of this framework or the role of additional severity indicators in relapse prediction. This study aimed to investigate the relationship between DSM-5 criteria, neurocognitive functioning, substance use variables and cocaine relapse among inpatients with cocaine use disorder (CUD).
Methods: 128 adults aged between 18 and 45 years were evaluated; 68 (59 males, 9 females) had CUD and 60 (52 males, 8 females) were healthy controls. For the group with CUD, the use of other substances was not an exclusion criterion. Participants were tested using a battery of neurocognitive tests. Cocaine relapse was evaluated 3 months after discharge.
Results: Scores for attention span and working memory were worse in patients compared to controls. Earlier onset and duration of cocaine use were related to poorer inhibitory control and global executive functioning, respectively; recent use was related to worse performance in inhibitory control, attention span and working memory. More DSM-5 criteria at baseline were significantly associated with relapse.
Conclusions: Recent cocaine use was the most predictive variable for neurocognitive impairments, while DSM-5 criteria predicted cocaine relapse at three months post treatment. The integration of neurocognitive measures, DSM-5 criteria and cocaine use variables in CUD diagnosis could improve severity differentiation. Longitudinal studies using additional biomarkers are needed to disentangle the different roles of severity indicators in relapse prediction and to achieve more individualized and effective treatment strategies for these patients.

1. Introduction

The classification of severity in substance use disorder (SUD) is currently based on clinical observation and self-report information only. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association – APA, 2013) patients meeting two to three criteria are categorized as having mild SUD, four to five as moderate, and six to 11 criteria as severe. Although clinical characterization of SUD is well established, the extent to which the current diagnostic framework can predict outcomes and guide clinical decisions remains unclear.

The severe DSM-5 category is mainly characterized by substantial loss of self-control, also known as "addiction" (Volkow et al., 2016). Addiction has been associated with deficits in reward processing and

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diminished activity in frontal cortex regions, but the clinical application of these findings has been limited (Kwako et al., 2015; Volkow et al., 2016). Executive functions (EF) are required to control drug-seeking behaviors and to achieve long-term goals. Indeed, EF are known to play an important role in determining outcomes in substance addiction (Aharonovich et al., 2006; Czapla et al., 2016; Stevens et al., 2014; Streeter et al., 2008; Verdejo-García et al., 2012). However, EF represent a broad concept composed of different cognitive abilities, and some neurocognitive tests used to evaluate EF might be more sensitive for this population (Turner et al., 2009). Given the complexity and the lack of homogeneity of investigations about EF impairment in chronic substance use, further discrimination of which EF subdomains are associated with relapse vulnerability is warranted.

Substance use variables such as age of onset, intensity and duration of use have been related to the severity of neurocognitive deficits (Adinoff et al., 2014; Bolla et al., 1999; Del Mar Capella et al., 2015; DeVito et al., 2018; Di Sclafani et al., 2002; Moreno-Lopez et al., 2015; Vonmoos et al., 2014) and to the prognosis in SUD (Fleury et al., 2016). Substance abstinence has been shown to predict recovery of important neurocognitive functions such as attention, memory and global cognitive performance (Schulte et al., 2014; Vonmoos et al., 2014). However, the association between neurocognitive functioning, substance use variables and relapse is still poorly understood. Although heavier use has been related to poorer performance in EF (Verdejo-García et al., 2007), the relevance of these results to treatment outcomes is unclear. A cross-sectional study comparing early and late onset substance use (≤16 and > 16 years old) found that individuals in the early onset group had worse neurocognitive functioning, greater duration of drug use, more inpatient treatment, higher rates of polysubstance use and relapses (Del Mar Capella et al., 2015). However, the study was retrospective, so information about patients were based on their clinical history only. On the other hand, another study has shown that greater duration of substance use associated with adherence to the 12-step program six months after discharge (Arbour et al., 2011). However, this study did not use neurocognitive measures or investigate the relationship between severity indicators and relapse. Existing gaps in the literature reinforce the need for additional follow-up studies investigating the role of severity indicators in the prediction of relapse in SUD.

Measures of EF have been associated with treatment retention and outcomes among patients with cocaine use disorder (CUD) (Turner et al., 2009; Verdejo-García et al., 2012). However, it remains unclear how additional severity indicators, such variables of use and clinical symptoms, associate with relapse. In this context, studies are needed to investigate possible associations between available severity indicators and cocaine relapse in patients admitted for treatment for CUD.

There are no longitudinal studies investigating DSM-5 criteria for CUD, severity of cocaine use, neurocognitive functioning and response to treatment. In addition, investigations of neurocognitive functioning in addiction present important methodological limitations, including different abstinence periods (Verdejo-García et al., 2007), the inclusion of mixed substance use disorder diagnoses or poly-substance use individuals (Schulte et al., 2014) and a lack of standardized neurocognitive test batteries (Verdejo-García and Pérez-García, 2007). These shortcomings limit the conclusions that can be drawn and hinder comparison between studies. To overcome these limitations, abstinence time must be properly described, and neurocognitive tests should be selected based on previous studies with this population.

Furthermore, there is a scarcity of studies examining whether severity as indicated by DSM-5 positive criteria predicts outcomes. Two studies have reported no association between DSM criteria and clinical variables such as cognitive functioning (Tanabe et al., 2009) and relapse (Lima et al., 2015). In addition, the severe DSM-5 category for SUD can be highly heterogeneous (Agrawal et al., 2011; Fazzino et al., 2014; Martin et al., 2014; Preuss et al., 2014); this warrant investigations focused on differentiating these patients for more individualized treatment interventions. Measuring severity using the total DSM criteria count (fully dimensional scale) may predict outcomes better than using a tri-category framework (Fazzino et al., 2014). However, this method still seems insufficient to determine vulnerability and specific treatment needs.

This study aimed to investigate associations between cocaine use severity (age of onset, duration and recent use), number of DSM-5 criteria for CUD (using a dimensional scale) and neurocognitive functioning at admission for treatment. The relationship between these variables and relapse to cocaine three months after discharge was also investigated. The hypothesis was that more severe patients (earlier onset of cocaine use, more years of regular cocaine use, more days of recent cocaine use and more DSM-5 criteria for CUD) would present poorer neurocognitive functioning and would be more likely to relapse.

2. Materials and methods

2.1. Sample and ethical aspects

One-hundred and twenty-eight subjects participated in the study. Males and females, aged between 18 and 45 years were recruited. A minimum of four years of formal education was required to ensure participants were able to read, write and understand instructions throughout the study. Sixty-eight participants meeting the minimum of six criteria for CUD were included in this study. The diagnosis of other substance use disorder other than cocaine was not an exclusion criterion, but all patients reported cocaine as the substance of choice and the main reason for seeking voluntary treatment. Patients were enrolled in a four-week standard inpatient treatment for cocaine addiction in the Psychiatry Institute at the University of São Paulo, Brazil. During this period, they participated in different therapeutic activities, including cognitive-behavioral group therapy and other occupational activities. Patients were allowed to smoke cigarettes at restricted times (more specifically, after breakfast, lunch and dinner) and some patients were also receiving medication as part of the treatment. Urine toxicology screening, obtained at admission, was used as an objective measure of recent cocaine use. After the urine test became negative for cocaine metabolites, baseline assessment, which included a battery of neurocognitive tests, was performed (see Section 2.2.2).

The control group was recruited from the public hospital (employees and students) where the research center is located (n = 30), the local police department (n = 12) and a public school (n = 18). Only individuals reporting not using drugs and with similar socio-demographic characteristics to the patients were included. The controls were participating in another study being conducted concurrently at the institution. The exclusion criterion for the control group was: 1) current or past DSM-5 diagnosis for substance use disorder other than tobacco; and, for both groups, exclusion criteria included: 1) past or current major psychiatric disorders (bipolar disorder, depression, and mania); 2) history of neurological disorders, including head injuries, with loss of consciousness for longer than 30 min, strokes, and intracranial hemorrhages; and 4) estimated intelligence quotient (IQ) less than 70.

The sample with CUD was part of a larger study involving a neurorehabilitation program (Gonçalves et al., 2014), registered at ClinicalTrials.gov (NCT01914835) and approved by the local Research Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki (World Medical Association). All 128 participants were volunteers and gave written informed consent.

2.2. Assessments

2.2.1. Baseline clinical assessment

For participants with CUD, information about age of onset, years of cocaine use and days of cocaine use in the last 30 days were collected using the Addiction Severity Index, 6th version (ASI-6) (McLellan et al., 2006). CUD severity was defined according to the sum of DSM-5 criteria met by each patient. The following 11 criteria were assessed: 1. Use of larger amounts and/or for longer periods;2. Unsuccessful efforts to cut down or control use; 3. Great deal of time spent to obtain or recover from substance effects; 4. Craving; 5. Failure to fulfill obligations; 6. Social or interpersonal problems; 7. Giving up or reducing important activities; 8. Hazardous use; 9. Physical or psychological problems; 10. Tolerance; and 11. Withdrawal (APA, 2013). According to the DSM-5 guidelines, patients are considered mild (2 to 3 criteria), moderate (4 to 5 criteria) or severe (6 or more criteria) according to the sum of criteria fulfilled in the last 12 months (APA, 2013).

The study data was collected before the release of the DSM-5. The preceding edition, the DSM-IV, has 10 criteria in common with the DSM-5. Therefore, the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer et al., 1992) was the main source used to assess diagnostic criteria. However, since "craving" was added to the DSM-5, the ASI was used to assess the presence or not of this criterion. However, because the ASI only covers a 30-day period, the investigation was complemented with a more extensive source to cover the preceding 12-month period. Clinical records were used to confirm the presence of cocaine craving among patients during hospitalization. As part of standard treatment, admission and follow up interviews include clinical history and examination, mental state examination, as well as laboratory and other tests (Lima et al., 2015). These data are included in the patient's clinical records. In sum, 67.6% of the sample of patients (n = 46) reported the presence of craving in the 12 months prior to admission. Of these, approximately 97% reported craving on the ASI (n = 44). For the remaining 3%, craving was reported during extensive psychiatric interviews (as detailed above).

2.2.2. Baseline assessment of neurocognitive functioning

A brief battery of neurocognitive tests was administered to all participants with the supervision of a neuropsychological specialist. Patients were evaluated after the urine test became negative for cocaine metabolites (mean time in days: 8.6 ± 2.9 days). In this period they were also abstinent from other substances except tobacco and prescribed medication (if applicable). The selection of tests to evaluate different executive functions was based on previous evidence about: 1.) relevance of EF for cocaine addiction; 2.) sensitivity of a given test for this population; and 3.) feasibility (paper-and-pencil, quick and easy-to-use) of incorporation in routine clinical practice. Based on these criteria, the following tests were selected: the Trail Making Test (TMT), for shifting, measured by time to complete part B minus time to complete part A (Marceau et al., 2017); the Stroop Color-Word Test (SCWT), part C, for inhibitory control, measured by the time to complete the task and number of errors (Gonçalves et al., 2014; Streeter et al., 2008); the Digit Span Forward and Backward task of the Wechsler Memory Scale, for attention span and verbal working memory, respectively, measured by number of correct answers (Gonçalves et al., 2014; Wechsler, 1997); and the Frontal Assessment Battery, for global executive functioning, measured by total score in six subtests (Cunha et al., 2010; Dubois et al., 2000). Measures of estimated IQ were obtained using the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (WASI) and the vocabulary and block design subscales of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Silverstein, 1982; Wechsler, 1981)

2.2.3. Follow-up assessment

Patients and/or other family members were contacted three months after discharge to verify cocaine abstinence status. A report of any episode of cocaine use during this period was considered as "relapse". The follow up assessment was made by telephone contact or in person for individuals who continued in the outpatient treatment program. Patients who could not be reached three months after discharge were excluded from the follow up analysis. The outcomes "abstinence" and "relapse" were then registered for each patient.

2.3. Statistical analysis

Descriptive, comparative and bivariate correlation analyses were conducted. Comparisons of baseline sociodemographic characteristics between patients and controls were conducted using Student's *t*-test or the Mann–Whitney test for continuous variables. Fisher's Exact Test was used for all categorical variables. Analysis of covariance (ANCOVA) and generalized linear models (GLM) were used to examine differences in neurocognitive functioning between patients and controls at baseline.

The distribution of CUD criteria fulfilled by the patients in the sample was calculated as absolute and relative values. Associations between variables of interest were calculated using parametric and nonparametric tests. Pearson (r) and Spearman (ρ) correlation coefficients were used, according to the data distribution, to investigate associations between neurocognitive performance and cocaine use variables. Because CUD severity values (i.e., criteria sum) assumed a short scale with an irregular distribution, Kendall's (τ) correlation coefficient was used to calculate associations between DSM-5 criteria counts and other variables. Comparisons of follow-up data between patients who had (or had not) relapsed at three months after discharge were made using Student's *t*-test or the Mann–Whitney test for all variables of interest (variables of use, neurocognitive functioning and criteria sum).

Normal distributions for each variable were verified using the Kolmogorov-Smirnov or Shapiro-Wilk tests. Type I error was set at 5%. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 24.

3. Results

3.1. Participants

Sixty-eight patients with CUD were included in the baseline analyses. A similar number of subjects was matched for sociodemographic characteristics to form the control group.

As shown in Table 1, there were no significant differences between groups regarding sex, years of education, or IQ. However, the average age of patients was significantly higher, and both groups contained proportionally fewer women than men. Prevalence of participants reporting tobacco use was also significantly different between patients and controls, with only two participants from the control group reporting the use of tobacco. Handedness among participants was well distributed between groups.

Some patients were taking prescription medication, mostly Benzodiazepines (35.2%). Patients were distributed into patients with CUD-only (26.5%) and those with multiple substance use disorders (MUD) (73.5%), which included patients with cocaine use disorder associated with tobacco, alcohol and/or cannabis use disorder. Population with MUD was more prevalent than CUD-only. The mean age of onset of cocaine use was 18 years and the mean duration of regular cocaine use was 10 years. Patients reported using cocaine on 19.5 out of 30 days before admission. Based on clinical assessment and self-reported symptoms, all patients met six or more DSM-5 criteria for CUD. As such, although there was variation in criteria, all patients were in the "severe" DSM-5 category for CUD.

3.2. Neurocognitive functioning between groups

Because age was significantly different between groups and because women were the minority, both age and sex were included as covariates for the comparison of neurocognitive performance between groups. Overall, neurocognitive performance among patients was poorer than controls (see Table 2). Notably, when controlling for age and sex, patients presented significantly lower scores in the Digit Span Forward and Backward tasks, indicating worse attention span (P = .014) and working memory (P = .014) than controls.

Table 1
Sociodemographics and clinical characteristics among patients and controls.

Sample characteristics (n = 128)		CUD n = 68	Controls n = 60	*P-value*
Age (years), mean (SD)		32.0 (6.6)	27.80 (5.1)	< .001[a]*
Gender, male, n (%)		59 (86.8)	52 (86.7)	.987[b]
Years of education, mean (SD)		11.9 (3.1)	12.8 (2.7)	.163[a]
*Handedness, right/other***		62/6	55/5	.588[b]
Estimated Intelligence Quotient, mean (SD)		97.9 (14.5)	102.3 (11.3)	.056[a]
Tobacco use		23 (33.8)	2 (3.3)	.013[b]*
Prescribed medication				
Antipsychotics, n (%)		21 (16.4)	–	–
Antidepressants, n (%)		20 (15.6)	–	–
Benzodiazepines, n (%)		45 (35.2)	–	–
Mood stabilizers, n (%)		11 (8.6)	–	–
Substance use characterization of the CUD group				
CUD-only, n (%)		18 (26.5)	–	–
Multiple Substance Use (MUD), n (%)		50 (73.5)		
Age of onset of cocaine use, mean (SD)		18.0 (3.6)	–	–
Years of regular cocaine use, mean (SD)		10.4 (7.1)	–	–
Days of recent cocaine use, mean (SD)		19.5 (9.0)	–	–
Distribution of severity for CUD by number of DSM-5 criteria fulfilled	Sum of criteria	n (%)		
	6	1 (1.5)	–	–
	8	10 (14.7)	–	–
	9	9 (13.2)	–	–
	10	27 (39.7)	–	–
	11	21 (30.9)	–	–

Note: CUD: Patients with cocaine use disorder; SD: Standard deviation; ** Left-handed and ambidextrous; MUD: Patients with multiple substance use disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition; [a] Student *t*-test; [b] Qui-Square test; (*) *P*-values < 0.05.

Table 2
Comparison of neurocognitive performance among patients (n = 68) and healthy controls (n = 60) controlling for age and gender.

Neurocognitive Tests	CUD Mean (SE)	Controls Mean (SE)	*P-value* *
TMT part B-part A, *Time*	44.2 (3.8)	38.6 (3.5)	.219
SCWT, part C, *Time*	25.6 (1.0)	25.0 (1.0)	.842
SCWT, part C, *Errors*	1.9 (0.1)	1.7 (0.1)	.755
Digit Span Forward, *Score*	**6.6 (0.3)**	**7.7 (0.3)**	**.014**
Digit Span Backwards, *Score*	**5.1 (0.2)**	**5.9 (0.3)**	**.014**
FAB, *Score*	15.9 (0.2)	16.4 (0.2)	.061

Note: CUD: Patients with cocaine use disorder; SE: Standard Error; TMT: Trail Making Test; SCWT: Stroop Color-Word Test; FAB: Frontal Assessment Battery; (*) *P*-value < 0.05.

3.3. Neurocognitive functioning, cocaine use and clinical criteria

There were significant correlations between cocaine use variables and performance on certain neurocognitive tests (see Table 3). Younger age of cocaine use was associated with more errors in the SCWT, indicating worse inhibitory control among these individuals. Duration of cocaine use was negatively correlated with FAB scores. As such, those with more years of lifetime cocaine use displayed poorer overall performance in executive tasks. The number of days of recent cocaine use was positively correlated with time taken to complete the SCWT and negatively correlated with scores in the Digit Span Forwards and Backwards. These correlations indicate that heavier recent use of cocaine was associated with poorer inhibitory control, attention span and working memory. The sum of DSM-5 criteria was not correlated with any of the neurocognitive domains evaluated.

3.4. Follow up

The follow up analysis included 65 patients with CUD (18 with CUD-only and 47 with MUD). Three patients could not be reached and were excluded. Patients who remained abstinent three months after discharge (n = 14) had less DSM-5 criteria for CUD when compared to the non-abstinent group (n = 51) (*P* = .006). None of the other baseline variables were significantly associated with “cocaine abstinence/relapse” at 3 months (Table 4).

4. Discussion

In this study, patients displayed poorer performance in attention span and working memory compared to controls. Interestingly, scores in both domains were negatively associated with the number of days of recent cocaine use. Recent use was the most predictive variable of neurocognitive performance. More days of recent cocaine use and an earlier age of onset were associated with poorer inhibitory control. There was also a negative association between years of regular use and scores in a global measure of executive functioning. Furthermore, patients who relapsed three months after discharge presented a higher number of DSM-5 criteria for CUD at admission. These results contribute to the literature by demonstrating a possible role of variables of cocaine use on cognition, as well as evidencing the validity of the DSM-5 severity scale in relapse prediction.

The relationships between recent cocaine use and aspects of neurocognitive functioning highlights the importance of this information to conjecture about possible impairments related to cocaine addiction when patients are admitted for treatment. However, neurocognitive alterations can be due to acute intoxication or withdrawal effects due to cocaine (Verdejo-García et al., 2007). To overcome these limitations, patients were referred for neurocognitive evaluation only after urine toxicology for cocaine metabolites became negative. Therefore, the present study reinforces the observation that more intense recent cocaine use affects negatively neurocognitive functions such as attention span, working memory and inhibitory control.

Previous studies have linked impulsivity traits with poorer outcomes in SUD, meaning that deficits in response inhibition can be significant relapse predictors among these patients (Czapla et al., 2016; Garrison and Potenza, 2014; Stevens et al., 2014). Considering the importance of this executive subdomain for abstinence, cocaine use variables could help identify patients more vulnerable to relapse. Self-control functions such as the ability to plan and exercise attention, working memory and cognitive control enable a person to resist temptations in favor of long-term goals (Stevens et al., 2014). In this perspective, years of cocaine use objectively indicate chronicity of addiction and this information may also be useful for clinical purposes. In this study, more years of cocaine use were correlated with lower FAB scores. FAB is a brief battery for evaluation of executive functioning and it has shown good sensibility for patients with SUD (Cunha et al., 2010; Pombo et al., 2008). These results are in line with previous studies that have reported frontal impairments among individuals with chronic cocaine use (Del Mar Capella et al., 2015; Madoz-Gúrpide et al., 2011; Verdejo-García et al., 2007).

Furthermore, the concept of chronicity in addiction can encompass the age of onset of substance use. Earlier onset of substance use has been related to more severe psychosocial and conduct problems, and with greater risk of subsequent diagnosis of SUD followed by worst outcomes (Grant and Dawson, 1998; Lynskey et al., 2003; Schulte et al., 2014; Weiss and Petry, 2014). In fact, early onset of cocaine use has been related to poorer performance in tests evaluating working memory, declarative memory, sustained attention, divided attention and executive functioning (Lopes et al., 2017). Early initiation of cocaine use may also negatively influence spontaneous improvements in

Table 3
Associations between neurocognitive performance, cocaine use variables and sum of DSM-5 criteria for cocaine use disorder (CUD) among patients (n = 68) at baseline.

Neurocognitive tests, *Measures*	Age of onset		Years of regular use		Recent use		DSM-5 Criteria	
	Correlation Coefficient	*P-value*	Correlation Coefficient	*P-value*	Correlation Coefficient	*P-value*	Correlation Coefficient	*P-value*
TMT part B-part A, *Time*	.090[a]	.464	.076[a]	.537	.132[b]	.283	.040[c]	.668
SCWT, part C, *Time*	−.141[b]	.256	.218[b]	.077	**.327**[b]	**.007***	.014[c]	.882
SCWT, part C, *Errors*	**−.339**[b]	**.005***	.169[b]	.172	.157[b]	.205	−.111[c]	.295
Digit Span Forward, *Score*	.146[a]	.235	−.153[a]	.212	**−.258**[b]	**.034***	−.129[c]	.190
Digit Span Backwards, *Score*	.105[a]	.395	−.207[a]	.090	**−.366**[b]	**.002***	−.049[c]	.625
FAB, *Score*	−.107[a]	.385	**−.290**[a]	**.017***	−.164[b]	.183	−.031[c]	.759

Note: CUD: Patients with Cocaine use disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth version; TMT: Trail Making Test; SCWT: Stroop Color-Word Test; FAB: Frontal Assessment Battery; (*) *P*-values < 0.05.
[a] Values calculated using Pearson Correlation Coefficient (r).
[b] Values calculated using Spearman Correlation Coefficient (ρ).
[c] Values were calculated using Kendall Correlation Coefficient (τ).

Table 4
Severity indicators and outcomes (cocaine abstinence and relapse) three months after discharge.

Severity indicators	Cocaine abstinence n = 14	Cocaine relapse n = 51	*P-value*
Age of onset of cocaine use	19.1 (2.7)	17.8 (3.9)	.250
Years of regular use of cocaine	9.7 (8.3)	10.6 (6.9)	.677
Days of recent use of cocaine	16.8 (9.5)	20.4 (8.8)	.188
Sum of DSM-5 criteria	**8.8 (1.4)**	**10.1 (0.9)**	**.006***
TMT part B minus part A, *time*	57.2 (40.1)	42.0 (26.4)	.096
SCWT part C, *time*	24.5 (12.6)	27.4 (11.2)	.404
SCWT part C, *errors*	1.0 (1.4)	2.7 (12.2)	.925
Digit Span Forward, *scores*	6.6 (2.1)	6.5 (2.0)	.921
Digitos Span Backwards, *scores*	5.5 (1.6)	4.9 (1.7)	.270
FAB, *scores*	16.0 (1.9)	15.8 (1.4)	.641

Note: DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth version; TMT: Trail Making Test; SCWT: Stroop Color-Word Test; FAB: Frontal Assessment Battery; Results are shown in raw average per group and standard deviation; (*) *P*-value < 0.05.

working memory after one year of abstinence (Vonmoos et al., 2014). In one cross-sectional study, patients who started using substances before the age of 17 performed worse in neurocognitive tasks and displayed other severity indicators, such as more inpatient stays, years of use and relapses (Del Mar Capella et al., 2015).

It is known that earlier substance use initiation may have a negative effect on brain maturation, especially during adolescence (Lopes et al., 2017). The use of substances such as alcohol and cannabis at a younger age can be also problematic, given that usually these substances are consumed before cocaine initiation. A previous study has demonstrated that earlier cannabis use was associated with worse performance in attention, impulse control and executive functioning (Fontes et al., 2011). Interestingly, a sub-analysis conducted among patients with MUD (including cannabis use disorder) showed that earlier onset of cannabis use was predictive of cocaine relapse (see Tables S5 and S6 in the Supplementary Material).[1] Taken together, these data reinforce the idea that failure in inhibitory control, traits of impulsivity and other prefrontal abnormalities are important to consider for the achievement of long-term abstinence (Moreno-López et al., 2012; Stevens et al., 2014).

Because this study was conducted in a high-complex treatment facility, the distribution of patients' DSM-5 criteria clustered towards the most severe end. However, the use of a fully dimensional scale for severity characterization was helpful in detecting differences between patients with less and more CUD criteria within the same DSM-5 category. Overall, patients who relapsed three months after discharge presented more severe CUD in terms of cocaine use, neurocognitive dysfunction and sum of criteria at admission. However, only the association with the DSM-5 criteria was statistically significant. The initial hypothesis was that criteria sum would also be related to measures of neurocognitive functioning, given that most criteria are related to the patient's inability to control use. This was not found to be the case. Given the lack of objectivity in the current diagnostic system to differentiate more severe patients, the identification of neurocognitive deficits such as poor inhibitory control in early stages of abstinence may be relevant.

The associations identified in this study between impaired frontal functioning, severity of cocaine use, clinical criteria and relapse vulnerability reinforce the importance of specific treatment options, such as neurocognitive rehabilitation strategies for patients with CUD (Aharonovich et al., 2006; Gonçalves et al., 2014; Kopak et al., 2014; Turner et al., 2009). However, severity of cocaine use can be difficult to measure, given the absence of uniform indicators of consumption and differences in purity level for cocaine and other illicit drugs (Hasin et al., 2013). Therefore, the use of short, easy-to-use, evidence-based instruments to assess neurocognitive functions integrated with detailed information about substance use may offer a more complete diagnostic assessment. Importantly, this approach would retain the simplicity of the DSM framework (Hasin et al., 2013).

The strengths of this study include a systematic control of abstinence promoted by a safe clinical environment, the use of urine toxicology, detailed investigation of clinical symptoms for CUD according to DSM-5 guidelines, and the exclusion of individuals with severe psychiatric disorders. However, some limitations should be noted. First, since patients were formally evaluated only at treatment entry and three months after discharge, causality cannot be inferred, nor is it possible to identify additional factors that could have influenced abstinence maintenance. Continued contact with a treatment provider, participation in aftercare services and other sources of support can represent important factors in remission and relapse. However, in a sub-analysis, there was no significant difference in relapse rates between patients who continued contact with the outpatient program and those who ceased contact (see Table S1 in the Supplementary Material).[1] Second, the sample was composed of severely affected patients, with most men and reporting the use of other substances. This could hinder the generalization of results. Regarding sex differences, a predominance of men at specialized treatment facilities has been reported in other studies (Faller et al., 2014; Wechsberg et al., 2008) and distribution of sex was similar between groups in this study. In addition, the inclusion of more severe manifestations of cocaine addiction, which usually includes polysubstance use, represents an effort to detect "real-

[1] Supplementary material can be found by accessing the online version of this paper at https://doi.org/10.1016/j.drugalcdep.2019.01.013.

life" impairments among individuals admitted for inpatient treatment. On the other hand, the inclusion of patients with MUD (including tobacco, alcohol and/or cannabis) could have influenced baseline comparisons as well as outcomes. However, patients with CUD-only performed worse in attention span when compared with those with MUD, and patients with CUD-only did not differ from MUD with respect to cocaine relapse (see Tables S2 and S3 in the Supplementary Material).[1] Finally, the follow up investigation relied on self-report only and cocaine abstinence as the main outcome.

Prospective studies including less severe patients and/or pure cocaine users are warranted in order to better understand the impact of severity indicators and different interventions on relapse. Additional outcome measures could expand conclusions regarding the utility of the severity indicators investigated in this study.

5. Conclusions

In this study, the sum of DSM-5 criteria predicted vulnerability to cocaine relapse three months after discharge. The significant relationships between cocaine use severity and neurocognitive functioning support further investigation of these indicators when patients are admitted for treatment. Further studies are needed that include patients with less severe CUD in order to evaluate the extent to which DSM-5 criteria and other factors predict progression to severe cocaine use and other vulnerabilities, such as relapse.

Objective measures of severity in the diagnostic context for SUD are needed to complement current clinical characterization. Prospective studies using neurocognitive functioning, neuroimaging and other known biomarkers for cocaine and other substance addiction could help disentangle the main factors related to relapse, helping design more evidence-based treatment strategies for these patients.

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Contributors

DRL, PJC, and PDG were responsible for the study conception and design. PDG, MO, AM, RAA, MC, TMCA, MHS, LRKF, FLSD, MVZ contributed with assessments and acquisition of data. BS performed the main analysis. DRL, PJC, AGA, SN, GFB and BS assisted with data analysis and with interpretation of the results. GFB, DRL, PDG and PJC were responsible for the initial drafted of the manuscript. All authors provided critical revision of the manuscript and offered important intellectual content having, thereafter, approved the final version submitted for publication.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.01.013.

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