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Distinct effects of cocaine and cocaine + cannabis on neurocognitive functioning and abstinence: A six-month follow-up study

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ABSTRACT

Background and Aims: Cannabis use is frequent among individuals with cocaine use disorder. Despite recent non-controlled studies advocating a therapeutic role of smoked cannabis, there is a paucity of evidence-based data on potential therapeutic and cognitive side-effects of this association.

Methods: We examined 63 cocaine-addicted subjects who used cannabis more than 50 times in lifetime (COC + CAN), 24 cocaine-addicted patients who use cannabis less than 50 times (COC), and 36 controls (CON). Participants were evaluated with an extensive battery of neurocognitive tests after two weeks of supervised detoxification in an inpatient treatment program. Patients were followed up in one, three, and six months after discharge.

Results: Both groups of patients performed worse than CON on working memory, processing speed, inhibitory control, mental flexibility, and decision making. COC + CAN performed worse than COC on speed processing, inhibitory control and sustained attention, while COC performed worse than COC + CAN on mental flexibility. Concomitant cannabis use did not decrease relapses to cocaine use after one, three and six months. Among COC + CAN, earlier cocaine and cannabis use, and impaired executive functioning were predictive of relapse on cocaine after six months.

Conclusion: Our results did not support the recommendation of smoked cannabis as a safe therapeutic approach for cocaine-addicted patients due to significant negative cognitive side-effects and absence of efficacy. Further studies investigating frontal brain morphology, neuromaturation, and prescription of the non-psychoactive constituent of cannabis sativa cannabidiol among cocaine-addicted patients who use cannabis are warranted.

1. Introduction

Cannabis use is frequent among individuals with cocaine use disorder. About 192 million and 18 million of people reported, respectively, cannabis and cocaine use in the last year (United Nations Office on Drugs and Crime (UNODC, 2018). Overall, cannabis users are between 4 and 25 times more likely to report the use of cocaine than the general population (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2009). Despite cumulative evidence of specific neuronal pathways in the brain and different subjective properties for each substance of abuse, the association of cannabis with cocaine is a current trend and a relevant phenomenon that includes mixed drug actions and frequently unknown interactions (Deschenau et al., 2016). Most cocaine-addicted individuals who have an overstimulation with cocaine, also report a kind of "compensatory" concomitant use of smoked cannabis due to its relaxing effects (Santos Cruz et al., 2013;

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Andrade et al., 2011).

Cocaine users have a set of negative consequences that include neurocognitive deficits in attention, verbal fluency, verbal memory, immediate and delayed memory, and spatial processing (Cunha et al., 2004; Di Sclafani et al., 2002; Viola et al., 2015; Lima et al., 2019) and high rates of morbidity and mortality (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2017; Han et al., 2019; Kerridge et al., 2019). Also, smoked cannabis has been associated with cognitive deficits in attention, memory, verbal learning, and psychomotor functioning (Thames et al., 2016; Broyd et al., 2016). Particularly, specific patterns of cannabis consumption such as the use of more than 50 times in life is associated with more serious consequences like psychosis, increased mortality, and worse prefrontal cortex damage (Andréasson and Allebeck, 1990; Zammit et al., 2002; Gorey et al., 2019; Price et al., 2015). Conversely, there are reports of improvement in neurocognitive functions with isolated cocaine or cannabis use. A study has also shown improvement in psychological functions such as attention and verbal fluency in smoked cocaine users compared to controls (Hoff et al., 1996). Patients using smoked cannabis prescribed by physicians experienced improvement in measures of executive functioning such as the Stroop test and the Trail Making Test (Gruber et al., 2016).

There are studies indicating that smoked cocaine-addicted individuals frequently use cannabis products as an alternative treatment. In fact, some of them report a reduction in undesirable cocaine effects, some improvement of sleep and appetite, and reduced craving (Gonçalves and Nappo, 2015). A first preliminary investigation included 26 male cocaine-addicted patients who were also concomitant cannabis users with the intention of reducing cocaine abstinence symptoms (Labigalini et al., 1999). After nine months, 68% of participants reported improvement in withdrawal symptoms, anxiety, sleep, weight gain, and reduced craving to use cocaine. A more recent prospective cohort study (Socías et al., 2017) included 122 participants who had also reported intention of using cannabis to control smoked cocaine use. After three years, subjects reduced cocaine use but increased cannabis consumption, with absence of benefits in global health or quality of life. Despite some initial evidence of supposed beneficial effects of cannabis use on neurocognitive functioning and long-term outcomes, some limitations such as restricted samples (Labigalini et al., 1999; Gonçalves and Nappo, 2015; Gruber et al., 2016), non-controlled environments (Labigalini et al., 1999; Hoff et al., 1996), lack of a control group (Labigalini et al., 1999; Socías et al., 2017), and absence of urine tests to exclude the use of other drugs (Hoff et al., 1996; Socías et al., 2017) make difficult to draw conclusions on the impact of smoked cannabis use among cocaine addicted subjects in terms of neurocognition and long-term outcomes. Also, there is evidence that the use of cannabis at earlier age increase the risk of lower levels of educational attainment, unemployment, use of other drugs; and psychotic symptomatology (Fergusson et al., 2015).

Notwithstanding these significant controversies, many authors still advocate the use of psychoactive cannabinoids compounds and smoked cannabis as harm-reduction therapeutic options for cocaine addiction (Dreher, 2002; Fischer et al., 2015a). That should be a concern since there is an absence of evidence-based data regarding effectiveness, safety, and side-effects of this association in the long-term. A study initially designed to assess the efficacy of baclofen in cocaine addiction has not found differences between cocaine-addicted patients with and without exposure to cannabis in terms of cocaine relapse (Shoptaw et al., 2003). A more controlled study designed with both users of intranasal and smoked cocaine has shown that early age at first cannabis use and long-term exposure to cannabis were associated with more abstinence symptoms and craving for cocaine. Also, long-term cannabis use was associated with higher incidence of rehospitalization after 2.5 years of the first assessment (Viola et al., 2014). Confirming these findings, Giasson-Gariépy et al (2017) reported that cocaine-addicted individuals who also have cannabis abuse or dependence present a more relevant and persistent craving on cocaine.

Although most studies have shown that both substances are associated with negative consequences, there are few and contrasting data on differential cognitive functioning and long-term impact on treatment outcomes between cocaine addicted subjects who use or not cannabis. Also, to the best of knowledge, no study to date has investigated if the association of cannabis in the context of cocaine addiction would be related or not with negative cognitive side-effects, and whether a possible executive dysfunction would play a role on long-term outcomes among cocaine-addicted patients. This study aims: 1) to shed light on the neurocognitive functioning of addicted individuals who frequently use cocaine + cannabis and 2) to clarify if a more frequent pattern of cannabis use could lead to worse prognosis. Based on previous findings, we expect that cocaine users who smoke cannabis more frequently would present a worse performance in executive functions such as attention, mental flexibility and working memory when compared with only cocaine users and controls and that they could be more vulnerable to relapse on cocaine use months later.

2. Method

2.1. Participants, ethical aspects, and procedures

One hundred and twenty-three subjects (105 males) were included in this study, 63 cocaine + cannabis users (COC + CAN), 24 cocaine users without frequent cannabis use (COC), and 36 controls (CON). They were treatment-seeking cocaine-addicted patients in a four-week standard medical inpatient program for treatment of cocaine addiction, which requires a one-month hospitalization in an impulsive behavior ward. All participants were evaluated according to the DSM-IV-TR criteria (American Psychiatric Association, 2000) at the time of admission. The abstinence was verified by self-report and supervised by the clinical staff. Participants were tested for psychoactive drugs when they arrived for treatment and every week until the tests resulted negative. Participants could smoke cigarettes during their stay. Two urine tests were used to verify recent cocaine use (if positive) or their abstinence (if negative). We have enrolled patients who use cannabis more than 50 times in lifetime as frequent cannabis users (COC + CAN) and patients who used cannabis less than 50 times in lifetime as not frequent cannabis users (COC). This criterion was based on the literature that establishes this important cut-point (Kessler et al., 2012).

We excluded patients with: (1) past or current major diagnosis of severe mental disorders according to the DSM-IV-TR, including schizophrenia, dementia, and bipolar disorder; (2) history of any neurological conditions or any medical condition that could affect the central nervous system; (3) history of head traumas with loss of consciousness longer than 30 min; (4) prior diagnosis of learning disorder; and (5) intellectual quotient (IQ) less than 70. The CON group was comprised by volunteers actively recruited in the city of Sao Paulo, including employees from the public hospital where the research center is located, as well as people from the community and from the local police department. We also recruited adult students from a local public school. The exclusion criteria for the CON were: (1) DSM-IV criteria for any psychoactive substance dependence disorder other than nicotine; (2) the same exclusion criteria outlined above. All the participants signed an informed consent and the study was approved by our institutional review board (IRB). The participants were reimbursed for expenses on transports and feeding.

2.2. Psychiatric symptoms

Mental disorders were assessed through a structured clinical interview based on the DSM-IV-TR criteria. Also, all subjects were assessed through the Beck Depression Inventory (BDI) (Beck et al., 1961) and the State-Trait Anxiety Inventory (Spielberger et al., 1970). Childhood attention deficit/hyperactivity disorder (ADHD) symptoms were assessed through the abbreviated version of the Wender-Utah Rating Scale

(WURS) (McCann et al., 2000). Patterns of alcohol, tobacco, cannabis, cocaine and other substance use, as well as a previous history of child maltreatment were investigated using the Addiction Severity Index (ASI-6) (Kessler et al., 2012).

2.3. Neurocognitive functioning

First, we used short forms of the Wechsler Adult Intelligence Scale – Revised and the Wechsler Abbreviated Scale of Intelligence (WASI) to estimate IQ (Wechsler, 1999) and to exclude those with an IQ < 70. Then, the participants were assessed in a variety of cognitive domains: Digits forward test (DF) was used to measure attention span and Digits Backward (DB) to evaluate working memory. The Stroop Color Word Test (SCWT) was used to measure speed processing and inhibitory control. Iowa Gambling Test (IGT) was used to measure decision-making and impulse control (Bechara et al., 1994). The short form of the Wisconsin Card Sorting Test (WCST) with 64 cards was applied to measure mental flexibility (ability to use environmental feedback to adjust cognitive sets), abstract reasoning, sustained attention, and self-monitoring (Lezak et al., 2004). Frontal Assessment Battery (FAB) was applied to evaluate specific subdomains covering six distinct executive abilities: abstraction/conceptualization, mental flexibility (verbal phonological fluency/self-monitoring), motor programming, sensitivity to interference, inhibitory control, and environmental autonomy (Dubois et al., 2000). All the instruments were translated and adapted to our context.

2.4. Follow-up

Both COC and COC + CAN were contacted by phone or in person one, three, and six months after discharge to investigate their cocaine abstinence status ("relapsed or not"). Some of the patients were engaged in an outpatient treatment program so they were considered "retained". A limited number of patients was not found on the follow up due to difficulties to reach the patient or family members at the time of each follow up. The proportion of reached to non-reached participants on the follow-up was similar across groups [(COC + CAN = 60, 57, and 58; COC = 23, 23, and 21, in the one, three and six months, respectively)]. Participants were stimulated to remain in an outpatient treatment and received personalized advice for seeking health assistance and coming back to our service if they had a relapse.

2.5. Statistical analyses

Homoscedasticity and normality of variables were assessed with Levene's Test and inspection of QQ plots, respectively. Comparative analysis of sociodemographic characteristics, considering the three groups was conducted using an Analysis of Variance (ANOVA) model. Differences in substance use variables were analyzed with Student's *t* test. Categorical variables were evaluated using chi-square and Fisher's exact tests. The raw scores on neuropsychological tests of all participants in this study were converted in Z-scores (Cunha et al., 2010; Oliveira et al., 2018). Differences in performance on neurocognitive tests between the three groups were assessed with Analysis of Covariance (ANCOVA) controlling for age and education. Effect sizes were calculated using *Cohens'd*. The level of statistical significance was set at $p \leq .05$. Pairwise comparisons of groups were performed with Fisher´s Least Significance Difference. The results were adjusted for multiple comparisons with the False Discovery Rate procedure (Benjamini and Hochberg, 1995). This method controls the error rates of tests among *a priori* significant results. It has been consistently tested over years and is considered a useful tool in health studies (Glickman et al., 2014). Differences between groups in the follow-up were assessed through chi-square and Fisher´s exact tests and mean comparisons with Student's *t* test. For all statistical analyses, we used the Statistical Package for the Social Sciences (SPSS) 14.0.

3. Results

3.1. Demographics

The three groups (COC + CAN, COC, and CON) were similar regarding gender ($p > .05$). They were predominantly male, 25–35 years-old and had ± 10 years of education. However, both COC + CAN and COC were older ($p < .01$), had less years of education ($p < .01$), and lower IQ when compared with controls ($p < 01$). Patients were more homogeneously distributed between white and black participants, while CON was predominantly composed by white participants (85%) ($p < .01$). COC + CAN and COC did not differ in terms of the occurrence of childhood physical ($p = .75$) and sexual abuse ($p = .75$).

3.2. Substance use

There were no differences between COC + CAN and COC at the age of onset of cocaine ($p = .49$) and cannabis use ($p = .65$). Also, there were no differences between groups in years of cocaine use ($p = .31$) or recent cocaine use defined as days of use in the last month ($p = .56$). Compared with COC, COC + CAN reported more years of cannabis use and more days of cannabis use in the last month ($p < .01$). COC + CAN and COC did not differ in terms of alcohol ($p = .29$) and tobacco ($p = .29$) use.

3.3. Psychiatric symptoms

COC + CAN and COC were similar in terms of depressive symptoms, anxiety (trait and state), and ADHD symptoms (Table 1).

3.4. Neurocognitive functioning

COC + CAN and COC performed worse than CON in Forward and Backward Digits ($p < .01$), STROOP A ($p < .01$) and C ($p < .05$), IGT ($p < .01$), and WCST perseverative errors ($p < .01$). COC + CAN also performed worse than controls in STROOP B ($p < .01$) (Table 2). When directly compared with COC, COC + CAN performed worse on STROOP A and C ($p \leq .05$), STROOP B ($p < .01$), and had more failures to maintain set in the WCST ($p < .05$). COC had more perseverative errors on the WCST than COC + CAN ($p \leq .05$). COC + CAN did not differ from COC in Forward and Backward Digits, IGT, WCST categories, and FAB.

3.5. Follow-up

COC + CAN and COC were similar in terms of relapses on cocaine (Fig. 1) and retention to treatment after one, three and six-months ($p > 0.1$). Despite the lack of significant differences between groups, an apparent and slightly higher percentage of COC + CAN participants remained abstinent in the first month after discharge, but they were somewhat more likely to relapse than COC after three and six months. We only had two patients with COC + CAN who dropped out due to unspecified causes. Finally, earlier age at onset of cocaine or cannabis use and impaired executive functioning (verbal fluency/mental flexibility) were predictive of relapse on cocaine use after three and six months, respectively ($p < .05$) (Table 3). After one month, one participant from both groups were non-respondent. After three months, COC + CAN and COC had 4 and 1 non-responders respectively, and, finally, after six months COC + CAN had 2 and COC had 3 non-responders.

4. Discussion

In this study, both groups COC + CAN and COC presented significant neurocognitive impairments in attention span, working memory, speed processing, inhibitory control, mental flexibility, and

Table 1
Demographics, drug use, and psychiatric disorders among cocaine and heavy cannabis users (COC + CAN), cocaine users (COC), and control subjects (CON).

	COC + CAN n = 63	COC n = 24	CON n = 36	F	p	COC + CAN vs. CON	p – values (Cohen´s d) COC vs. CON	COC + CAN vs. COC
Demographics								
Age (SD)[a]	32.17 (6.21)	31.91 (8.09)	25.75 (6.40)	11.42	.01*	.01* (1.01)	.01* (.84)	1.0 (.03)
Male (%)[b]	58 (92.0)	18 (75.0)	29 (80.5)	–	.08	–	–	–
Race (%)[b]								
White	7 (11.1)	0 (.0)	17 (85.0)	–	.01*	.01*	.01*	.43
Black	46 (73.0)	18 (75.0)	0 (.0)	–				
Other	10 (15.9)	6 (25.0)	3 (15.0)					
Education (SD)[a]	11.95 (3.35)	11.79 (2.94)	14.77 (2.02)	12.13	.01*	.01* (1.02)	.01* (1.18)	1.0 (.05)
IQ (SD)[a]	97.47 (16.21)	93.04 (15.56)	111.50 (11.68)	14.09	.01*	.01* (.99)	.01* (1.34)	.65 (.27)
Cocaine use[c] (SD)								
Age at first use	17.79 (3.46)	18.41 (4.65)	–	–	–	–	–	.49
Use in years	10.71 (6.73)	9.04 (7.27)	–	–	–	–	–	.31
Recent use[d]	19.36 (8.88)	18.04 (11.03)	–	–	–	–	–	.56
Number of DSM criteria	9.83 (1.15)	9.88 (1.08)	–	–	–	–	–	.89
Cannabis use[c]	15.03 (2.17)	14.17 (9.33)						.65
Age at onset								
Use in years	10.90 (7.67)	.29 (.90)	–	–	–	–	–	.01*
Recent use[d]	11.01 (12.84)	.20 (.59)	–	–	–	–	–	.01*
Other substance[b]								
Alcohol (%)	20 (31.7)	6 (25.0)	–	–	–	–	–	.79
Tobacco (%)	22 (34.9)	5 (20.8)	–	–	–	–	–	.29
Child maltreatment[b]								
Physical abuse (%)	27 (42.8)	13 (54.1)	–	–	–	–	–	.47
Sexual abuse (%)	9 (14.2)	4 (20.0)	–	–	–	–	–	.75
Psychiatric symptoms[c](SD)								
WURS[1]	26.90 (21.18)	28.83 (19.91)	–	.15	–	–	–	.70
BDI[2]	13.34 (9.46)	14.59 (10.80)	–	.26	–	–	–	.61
STAI[3] trait	42.73 (8.89)	45.56 (13.36)	–	1.26	–	–	–	.26
STAI[3] state	47.40 (11.16)	48.21 (9.47)	–	.09	–	–	–	.75

Data reported as mean and standard deviation (SD) or frequencies (%). Recent use was defined as drug use in the last month; 1 - WURS: Wender Utah Rating Scale (for childhood symptoms of the Attention Deficit Hyperactivity Disorder); 2 - BDI: Beck Depression Inventory; 3 - STAI: State-Trait Anxiety Inventory; * Significance at $p < .01$; a - p-values were calculated using *Oneway* ANOVA; b – p-values were calculated using *Fisher Exact or Pearson Chi-square tests;* c - p-values were calculated using Student's t test; d - Days of use in the last month.

decision-making when directly compared with controls (CON). When directly compared with COC, COC + CAN had more significant impairments in speed processing, inhibitory control and sustained attention. On the other hand, COC had more deficits in cognitive flexibility than COC + CAN. The concomitant use of cocaine + cannabis did not reduce relapses or increase retention to treatment in a long-term perspective. The main predictive variables associated with relapses on cocaine after 3 and 6 months were executive dysfunction and early age at onset of cocaine and cannabis use, respectively.

Both COC + CAN and COC presented a worse performance in neurocognitive tests when compared with CON presenting significant neurocognitive impairments in attention span, working memory, speed processing, inhibitory control, mental flexibility, and decision-making. Our findings are in line with previous studies that reported impaired attention (Woicik et al., 2009), learning and memory deficits (Fox et al., 2009), and executive dysfunction among cocaine-addicted patients (Spronk et al., 2013; Jovanovski et al., 2005). Despite the absence of a "cannabis-only" group in our study that limits comparisons between the groups in terms of impairments associated with each drug, cannabis users present deficits in decision-making similar with cocaine users

Table 2
Mean differences in neurocognitive measures among COC + CAN, COC, and CON.

Measures	COC + CAN n = 63 M	SD	COC n = 24 M	SD	CON n = 36 M	SD	F	p	COC + CAN vs. CON	p-values (Cohen´s d) COC vs. CON	COC + CAN vs. COC
Executive functioning*											
Forward Digits	−.39	.76	−.40	.80	.93	.84	15.33	.01**	.01** (1.64)	.01** (1.62)	.99 (.01)
Backward Digits	−.22	.85	−.48	.70	.70	1.04	4.67	.01*	.02* (.96)	.01** (1.33)	.19 (.89)
STROOP A	−.42	.56	−.01	.86	.71	1.24	19.79	.01**	.01** (1.17)	.01** (.67)	.05* (.56)
STROOP B	−.19	.99	.37	1.10	.07	.87	9.87	.01**	.01**(.27)	.20 (.30)	.01* (.53)
STROOP C	−.22	.93	.21	.89	.23	1.10	10.88	.01**	.01**(.44)	.03* (.01)	.05* (.47)
IGT	−.21	.74	−.25	.65	.99	1.41	12.36	01**	.01** (1.06)	.01** (1.12)	.85 (.05)
WCST[a] Pers.Errors	−.29	.92	−.64	.91	.94	.21	10.79	.01**	.01** (1.84)	.01** (2.39)	.05* (.38)
WCST Categories	−.19	.97	−.22	.95	.49	.92	.72	.48	.44 (.71)	.44 (.74)	.89 (.03)
WCST Set (failures)	−.14	1.12	.36	.65	.01	.91	2.45	.05	.48 (.14)	.43 (.44)	.04* (.54)
FAB[b] Total	.01	.95	−.46	1.12	.51	.72	2.78	.06	.66 (.59)	.08 (1.03)	.08 (.45)
Verbal Fluency Test	.02	1.0	−.32	.85	.17	1.0	.83	.43	.48 (.15)	.87 (.52)	.23 (.36)

* Data reported as mean and standard deviation; a - Wisconsin Card Sorting Test, b - Frontal Assessment Battery; *Significance at $p \leq .05$using ANCOVA controlling for age and educationwith FDR adjustment.

** Significance at $p < .01$ using ANCOVA controlling for age and education with FDR adjustment.

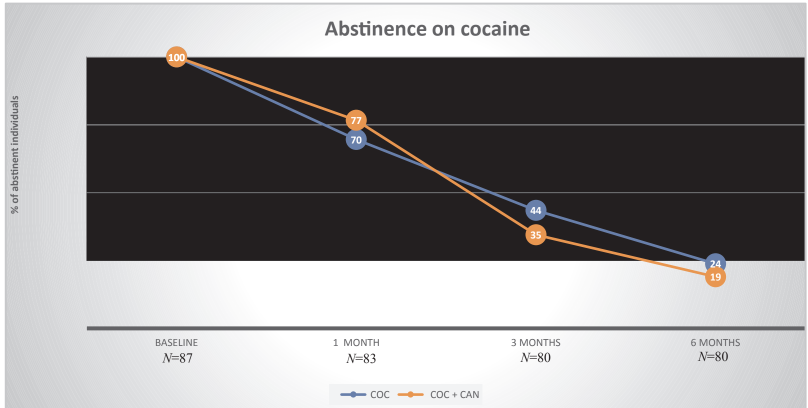

Fig. 1. Abstinence on cocaine use after 1, 3 and 6 months.
Note: There were no statistically significant differences between COC + CAN and COC after one, three, and six months.

(Verdejo-Garcia et al., 2018).

Our findings revealed a worse executive performance among COC + CAN participants in terms of inhibitory control, which is consistent with previous studies that show executive functioning impairments for both drugs (Broyd et al., 2016; Bloomfield et al., 2018; Di Sclafani et al., 2002; Fillmore and Rush, 2002). Cocaine use is associated with neurocognitive impairments in important domains such as attention, verbal fluency, verbal memory, visual memory, and learning ability (Cunha et al., 2004). Also, recently we found that smoked cocaine is associated with worse neurocognitive impairments in inhibitory control and general executive functioning when compared with intranasal cocaine (Oliveira et al., 2018). Contrary to previous studies that reported neurocognitive impairments specifically associated with cocaine independently of a moderate cannabis use (Vadhan et al., 2014), our finding that COC + CAN participants had a worse performance on speed processing, sustained attention, and inhibitory control reinforces the additive negative side-effect of cannabis on cognition.

We have found a distinct performance on the Wisconsin Card Sorting Test by COC + CAN when compared to COC. WCST is a widely used neurocognitive test that assesses frontal lobe functions, being a gold standard tool to assess relevant and different subdomains of executive functioning, such as abstraction, planning, mental flexibility and sustained attention (Barceló et al., 1997). COC + CAN presented more failures to maintain set in the WCST, meaning that COC + CAN were found to have more pronounced deficits in sustained attention than COC. In fact, sustained attention deficits have been reported among cannabis and cocaine users, being associated with heavy cannabis users (Ganzer et al., 2016). On the other hand, COC had more limited cognitive resources to provide alternative behavioral responses to adapt to new demands and contexts. Perseverations and errors in WCST have been associated with problems in behavioral modulation in cocaine addiction (Woicik et al., 2011), impaired dopaminergic tonus in striatum (Hsieh et al., 2010), and with prefrontal lesions (Nagahama et al., 2005). According to the DSM 5 criteria, persistence of substance use despite negative consequences is an essential characteristic of drug addicted patients.

The identification of predictive variables as early use for prognosis in the addiction field is another important topic. Factors such as gender (McCance-Katz et al., 1999), comorbid psychiatric disorders (Ford et al., 2009), and even the presence of more DSM 5 criteria among cocaine-addicted patients (Lima et al., 2019) have also been associated with a worse prognosis. The association we found between early age at onset of cocaine use and executive dysfunction with worse prognosis is in line with previous studies (Lopes at al., 2017; Lopes-Rosa et al., 2017). An early age at onset of cannabis use has also been associated with alterations in executive functioning (Fontes et al., 2011) due to an influence on brain pruning that impacts brain maturation and cortical architecture in important prefrontal cortex regions such as the dorsolateral prefrontal cortex (Filbey et al., 2015). Thus, early age at onset of cannabis or cocaine use, alterations in brain maturation, and executive

Table 3
Cannabis use and neurocognitive tests among individuals who were abstinent or relapsed after one, three, and six months after discharge.

Substance Use and Measures[a]	One month N = 60		p	Three months N = 57		p	Six months N = 59		p
	Abstinent n = 46	Non-abstinent n = 14		Abstinent n = 20	Non-abstinent n = 37		Abstinent n = 11	Non-abstinent n = 48	
Cocaine use									
Age at first use	18.2 (3.9)	17.7 (3.8)	.62	18.2 (3.3)	17.9 (4.2)	.70	19.7 (4.8)	17.5 (3.6)	.04*
Years of use	10.1 (6.7)	9.8 (7.4)	.84	10.4 (7.3)	10.2 (6.8)	.90	7.5 (6.7)	10.8 (6.7)	.07
Recent use[b]	18.8 (9.6)	19.3 (10.1)	.83	19.0 (9.5)	19.5 (9.4)	.83	18.0 (10.3)	19.5 (9.3)	.55
Cannabis use									
Age at first use	15.1 (2.3)	15.0 (1.6)	.84	15.7 (2.2)	14.8 (2.1)	.84	16.4 (2.9)	14.8 (2.0)	.03*
Years of use	11.0 (7.3)	10.1 (8.6)	.71	9.8 (6.9)	10.9 (7.9)	.71	9.0 (7.6)	11.3 (7.8)	.37
Recent use[b]	11.0 (13.0)	12.5 (8.6)	.70	8.9 (12.8)	12.4 (13.6)	.70	8.2 (13.0)	12.2 (13.1)	.37
Executive Functioning									
STROOP C	−.22 (.72)	−.15 (1.4)	.82	−.38 (.66)	−.08 (1.0)	.26	−.42 (.55)	−.15 (1.0)	.39
IGT	−.14 (.71)	−.30 (.75)	.46	−.19 (.68)	−.24 (.74)	.80	−.21 (.74)	−.24 (.74)	.33
WCST Pers. Errors	.25 (.90)	.38 (1.0)	.65	.13 (.80)	.37 (1.0)	.36	.53 (1.0)	.27 (.91)	.42
WCST Categories	−.15 (.98)	−.26 (.93)	.71	−.08 (.92)	−.24 (1.0)	.55	−.31 (1.1)	−.21 (.93)	.77
WCST Set (failures	.17 (1.2)	.03 (.79)	.68	.23 (1.3)	.02 (1.0)	.52	−.18 (.86)	.20 (1.1)	.52
Verbal Fluency Test	−.02 (1.0)	.22 (.91)	.43	.44 (1.1)	−.19 (.90)	.02*	.53 (1.2)	−.13 (.89)	.04*

[a] Statistical tests with *t* of Student; b- Days of cannabis use in the month prior to the evaluation. *Significance at $p < .05$.

dysfunction might be common pathways leading to worse prognosis and relapses. The additive neurocognitive side-effects of cannabis + cocaine that we have found highlight the critical role of the association of both drugs on prefrontal cortex functioning. Our finding is coherent with a vast literature showing frontal lobe dysfunction in addiction due to disrupted dopaminergic function (Goldstein and Volkow, 2011; Volkow and Boyle, 2018). Cocaine and cannabis use acutely increases dopamine availability while chronic cocaine and cannabis use is associated with a decrease in dopaminergic tonus and impairment in executive functions such as attention and vigilance due to hypoactivation of the mesencephalon, putamen, anterior cingulate, parahippocampal gyrus, and amygdala (Tomasi et al., 2007; Bloomfield et al., 2016). In this regard, chronic cannabis use has been associated with impaired motivation (Lac and Luk, 2018) that could also have some impact on cognitive performance in the group of patients using both substances (cocaine + cannabis).

Finally, even though observational studies have reported a therapeutic potential of smoking cannabis among cocaine users, and some clinicians advocate the role of psychoactive cannabinoids in the “stimulant treatment gap” along with the recommendation of lower-risk cannabis use guidelines (Fischer et al., 2015b), our data suggest that the use of smoked cannabis is not a valuable therapeutic option for cocaine users, especially considering its lack of efficacy and significant negative cognitive side-effects. Our findings are in line with Viola et al. (2014) which indicated that cannabis use was associated even with a worse prognosis among cocaine-addicted patients. Our findings are also strongly in line with recent systematic reviews of medical cannabis that demonstrate limited efficacy based on low quality evidence (Whiting et al., 2015; Wong and Wilens, 2017).

Our study has some strengths which include a homogeneous sample of inpatient cocaine-addicted individuals, urine tests to exclude the use of other drugs, an extensive battery of neurocognitive tests, and information about treatment retention and relapses on cocaine after 1, 3, and 6 months. However, our study has some limitations. First, there was a significant difference in ethnic groups between groups and CON but a *post hoc* analysis (data not shown) did not reveal differences in neurocognitive tests between white, black, and others cocaine-addicted participants. Second, groups of patients differed in terms of age, years of education and IQ when compared with the control group. Nevertheless, we decided to control our analyzes with the covariables age and education, considering that IQ was strongly correlated with education (data not shown) and that IQs from the three groups were qualitatively similar (all of them fell in the average range, see Table 1). Third, we enrolled “occasional” and “regular” cannabis users as distinct groups based on the use of cannabis more than 50 times in lifetime. One can hypothesize that this could not be effective in order to discriminate regular from non-regular users, or if patients might use cannabis as a recreative drug or in order to cope with cocaine abstinence or craving. In fact, a more detailed analysis of cannabis use showed significant differences between groups, evidencing that the group COC + CAN had a significant recent and more prominent lifetime cannabis use (Table 1). Fourth, our study lacks a cannabis-only group that could bring a better understanding of a “pure” cannabis impact on cognition. Fifth, we did not assess other variables that could interfere with cognitive function, such as sleep quality (Bolla et al., 2008). Finally, we were not able to investigate the question whether samples of cannabis with a different ratio of Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) could modulate its negative association with cognition. There is evidence that CBD, the second most abundant non-psychoactive component of cannabis, is associated with anxiolytic, antipsychotic, and neuroprotective actions (Prud’homme et al., 2015; Yücel et al., 2016; Osborne et al., 2017). Also, recent studies have shown possible therapeutic effects of CBD in substance abuse (Gonzalez-Cuevas et al., 2018; Wall et al., 2019). Further studies investigating a possible therapeutic/medicinal role of isolated CBD administered for COC and COC + CAN could be relevant to disentangle whether there is or not a therapeutic potential of CBD in the addiction field.

5. Conclusion

In conclusion, our study has found that both groups COC + CAN and COC had significant executive and decision-making deficits when compared to the control group. When directly compared to COC, COC + CAN had more deficits in information processing speed, inhibitory control, and sustained attention, while COC had more impaired cognitive flexibility. Our results add to the literature that cocaine addicted patients who also use cannabis have a distinct and worse prefrontal dysfunction when directly compared with cocaine addicted patients. Also, we did not find any evidence supporting the indication of cannabis use to improve outcomes among cocaine-addicted patients in a long-term perspective. On the contrary, we have found that an early age at onset of cannabis and cocaine use, combined with executive dysfunction were predictive of relapse to cocaine months later. Despite the urgency for new therapeutic and effective strategies for stimulant use disorders, this study suggests that the prescription of smoked cannabis could be worse for cocaine-addicted patients due to significant negative implications on cognition and absence of long-term efficacy. Further longitudinal studies and controlled clinical trials should be designed to investigate a possible therapeutic potential of isolated non-psychoactive CBD and the neurobiological underpinnings of the association of cannabis and cocaine on brain maturation process impacting on cognition and prognosis.

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Contributors

HPOJ and PJC wrote the manuscript, PJC, PDG, MO and BS performed the assessments and statistical analysis. PJC, PDG, AM, RAA, SN and AGA were responsible for study concept and design and provided significant intellectual content in the writing of the report.

Declaration of Competing Interest

No conflict declared.

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