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Childhood physical neglect associated with executive functions impairments in crack cocaine-dependent women

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ABSTRACT

Background: Studies that have investigated the executive functions (EFs) in crack cocaine-dependence have focused on differences between groups of drug users and non-user controls. In this study, however, we employ a promising additional approach that considers individual differences, such as exposure to childhood neglect that might be related to the degree of cognitive impairment associated with addiction.
Objective: We evaluated EFs in crack cocaine-dependent women who have reported a history of childhood physical neglect (CPN) and compared these measures with those of crack cocaine-dependent women who do not reported CPN.
Method: The participants were divided into 2 groups: those with a history of CPN (CPN+) ($n = 37$) and those without a history of CPN (CPN−) ($n = 48$). Cold EFs were assessed with the Stroop Task, the Trail Making Test B, the Verbal Fluency Task, the N-Back Task and the Letter and Number Sequencing task. Hot EFs were assessed with the Iowa Gambling Task (IGT).
Results: The CPN+ group exhibited lower performance in all of the tasks except the IGT. A multivariate analysis of covariance indicated significant group differences in EFs ($F(6,63) = 2.51$, $p = 0.030$), regardless of craving severity and premorbid IQ.
Conclusions: CPN is associated with cognitive impairments in crack cocaine-dependent women specifically regarding EFs and working memory tasks.

1. Introduction

Recent reports have shown that individuals with crack cocaine dependence display multiple cognitive impairments, in particular in executive functions (EFs; Cunha et al., 2011; De Oliveira et al., 2009; Di Sclafani et al., 2002; Hoff et al., 1996). These complex cognitive skills, which interact equally with attention and working memory, have been investigated due to their key role in exerting control over strong drug-seeking behavior (Verdejo-Garcia and Perez-Garcia, 2007). Most recent investigations have focused on differences between drug users and non-user controls (Cunha et al., 2011; Verdejo-Garcia and Perez-Garcia, 2007), but very few have investigated subgroups of drug users.

Specifically the nature and severity of cognitive deficits depend upon many factors, including patterns of drug use and the early development of the individual (Gould, 2010). The "developmental disorder" comprehensive model of substance dependence, according to which gene-environment interactions in childhood or adolescence may be involved in the failure to self-regulate drug use, has focused on the huge impact of early adversity in addiction outcomes (Andersen and Teicher, 2009; Gerra et al., 2010). Stress exposure in the earliest years of life has been shown to increase vulnerability to addiction (Sinha, 2008), which could be related to cognitive impairment (Jaffee and Maikovich-Fong, 2011). There is a strong relationship between cognition, emotion and mood changes during substance withdrawal that increases symptoms such as anxiety, drug craving and depression (George and Koob, 2010). Hence, the challenge of abstinence-based treatment in crack cocaine dependence is also associated with demands on executive control (Kubler et al., 2005; Verdejo-Garcia et al., 2006).

Studies of non-users have assessed the impact of a range of types of childhood maltreatment on specific neuropsychological measures. The greatest deficits in cognitive functioning (e.g., deficits in complex visual attention, learning tasks, planning and problem solving) were observed in individuals who had experienced chronic childhood neglect, particularly childhood physical neglect (CPN; i.e., failure to adequately meet the physical needs of the child, abandonment, educational neglect, medical neglect, or food

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deprivation; Nolin and Ethier, 2007; Pears and Fisher, 2005). Neurobiological data support the idea that separation from the primary caregiver, lack of care and other events related to poor parental care are linked to long-term biological changes, including reduced hippocampus and cortex size and lower levels of brain-derived neurotrophic factor (Grassi-Oliveira et al., 2008; McEwen, 1998; Mueller et al., 2010; Sanchez et al., 2010). These biological markers have been associated with cognitive performance (Gunstad et al., 2008; Oral et al., 2012).

Therefore, it appears that childhood maltreatment is an important factor that might hamper cognitive development. However, there is limited research to confirm these associations between cognition and particular types of maltreatment, including CPN. This topic is even less studied in patients with crack cocaine dependence as there are relatively few studies that have analyzed the impact of early adversity on cognitive outcomes (Narvaez et al., 2012). For this reason, the main goals of this study were to evaluate the EFs of crack cocaine-dependent women who had reported a history of CPN and to compare these measures with the EFs of crack cocaine-dependent women who had not reported CPN.

In addition, because executive functions are often subdivided, we included in our neuropsychological battery tests of "cold" EFs (cognitive processes that tend not to involve much emotional arousal and are relatively "mechanistic" or "logically" based; Chan et al., 2008), and a "hot" EF task (which involve more "emotional", "belief" or "desire" states, that include experiences of reward, punishment or decision-making; Bechara et al., 1994). We hypothesized that women with crack cocaine dependence and a history of CPN would show deficits on all measures of EF, both hot and cold, relative to those without a history of neglect.

2. Methods

Our comparative, cross-sectional study included a total of 120 crack cocaine-dependent, female inpatients. All of the participants were recruited within the same locked detoxification treatment facility for female drug and alcohol abusers in Porto Alegre, Brazil, 3 weeks after admission. These women were in an abstinence-controlled situation. They had no access to alcohol, cigarettes or drugs. In addition, all patients had prescribed symptomatic cocaine detoxification protocol, including neuroleptics, analgesics, antidepressants and mood stabilizers. However benzodiazepines were not prescribed during treatment. The inclusion criteria were as follows: women aged 18–50 years, a diagnosis of substance use disorder – physiological dependence of crack cocaine type, a minimum of four years of formal education and an absence of co-morbid psychotic syndromes. The exclusion criteria were as follows: the presence of previously undetected psychotic symptoms ($n = 2$), neurological diseases ($n = 1$), infectious and metabolic disorders ($n = 8$) or either severe cognitive deficits that resulted in an altered state of consciousness or agitation or a Mini Mental State Examination (MMSE) < 18 and IQ < 55 ($n = 24$). Although the sample was composed of poly-substance users, crack cocaine was their self-reported drug of choice, and crack cocaine dependence was the primary diagnosis. Furthermore, the Structured Clinical Interview for DSM Disorders (SCID I; Del-Ben et al., 2001) was used to determine the participants' diagnoses and comorbid syndromes.

Histories of CPN were assessed with the Childhood Trauma Questionnaire – Short Form (CTQ; Grassi-Oliveira et al., 2006). The CTQ is a widely used self-report instrument that examines childhood maltreatment, including childhood neglect. All of the items are rated on a 5-point Likert-like scale, representing the frequency with which the participants had to wear dirty clothes, had insufficient food to eat, had no one to care for them during an illness or to otherwise protect them or were exposed to episodes of parental drug or alcohol intoxication. The presence or absence of CPN was rated from moderate to extreme according to the cutoff point postulated by Bernstein et al. (2003). As a result, the participants were divided into 2 groups: one composed of 37 participants with a presence of CPN (CPN+) and another composed of 48 participants without a history of childhood neglect (CPN−).

To better characterize the participants and to evaluate other important variables that could also affect EFs, we administered supplementary clinical assessments. Depression severity was evaluated with the Beck Depression Inventory (BDI-II; Gorenstein and Andrade, 1996). The severity of craving and withdrawal symptoms was rated with The Cocaine Selective Severity Assessment (CSSA; Kampman et al., 1998). The Addiction Severity Index (ASI-6; Kessler et al., 2012), a semi-structured interview that has been widely used for large-scale substance abuse evaluation, was also administered. The ASI-6 assessed the severity of substance use problems in various functional domains. This instrument also assessed an individual's pattern of substance use, including the frequency, quantity and severity of drug use behavior. All of the instruments were administered by an expert psychiatrist and three well-trained clinical psychologists. The current research was approved by the Ethical Committee of the enrolled institutions, and all of the participants provided written informed consent.

2.1. Executive functions assessment

The battery of tests was designed to assess multiple EFs, including verbal fluency, inhibition, working memory, cognitive flexibility, and selective attention (all cold EFs) and decision making (one of the hot EFs). The EF battery was administered individually over 2 sessions, each approximately 2 weeks after the participant's enrollment in the treatment program, when the participants were no longer in the acute phases of withdrawal. 2 trained neuropsychologists administered the EF evaluations. The evaluators were blind to the subjects' clinical status and CTQ history. No sedative medication was administered for 24 h before assessment. The data from the participants who did not complete a specific task were excluded from the task's analyses.

The Stroop Color-Word Interference Test – Golden Version (Golden, 2002) measured the domains of selective attention and inhibitory control (Alvarez and Emory, 2006). The dependent variable used in the analyses was the interference score (described in Section 2.2).

The Trail Making Test B (Goul and Brown, 1970) assessed cognitive flexibility and inhibitory control (Chan et al., 2008; Royall et al., 2002). In Part B of the Trail Making Test, the participants were instructed to connect randomly distributed numbers (from 1 to 13) and letters (from A to M) in an alternating sequence (1-A-2-B-3-C. . .). Any participants who commit an error were instructed to correct it. The dependent measure of interest in the Trail Making Test B was the time needed to finish the task.

The Letter Number Sequencing Task (WAIS-III; The Psychological Corporation, 2002) measured working memory function (Chan et al., 2008). The dependent measure of interest in the Letter Number Sequencing Task was the number of correct answers.

The auditory N-Back Task (Callicott et al., 1998) also evaluated working memory. In the auditory N-back task (Dobbs and Rule, 1989), the participants heard a series of digits at a rate of one digit per second. After each digit, they were instructed to indicate which letter was heard "*N*" positions back in the series. In the first learning phase, $N = 0$, the participants had to repeat the digit that they had just heard. In the next condition, $N = 1$, they had to repeat the digit immediately prior to the one that they had just heard. In the $N = 2$ condition, the participants had to say "no" after the first 2 items; then, after hearing the third digit, they were instructed to repeat the first digit, advancing one number at a time afterward for the duration of the trial. Then, in the $N = 3$ condition, the participants had to say the first number of the sequence when they heard the fourth number, and so on. The main dependent variable was the sum of correct responses in each series and a final score that represented the sum of all of the series.

The Verbal Fluency Task assessed phonemic and semantic verbal fluency (Benton, 1994). The participants were asked to list the greatest possible number of words that started with a specific letter ("F", "A" and "S) within a 1-min period. Finally, the participants were asked to list the greatest possible number of animal words, regardless of the letter that began the word. The main dependent variable was the sum of the words produced in each stage of the task and a final score that represented the sum of all of the words produced during the task.

The Iowa Gambling Task (IGT; Bechara et al., 1994) measured decision-making. The IGT is a computerized task in which subjects are asked to choose between four decks of cards that result in a theoretical monetary reward at different payout rates, for 100 trials. Interspersed within these trials, however, are punishments (monetary losses of different amounts). Two decks (C and D) have a greater long-term reward than the other two decks (A and B). The dependent measure of interest in the IGT was the total number of cards selected from the advantageous decks minus those selected from the disadvantageous decks.

The Wechsler Abbreviated Scale of Intelligence (WASI; The Psychological Corporation, 1999) was used to assess the general intelligence quotient (IQ), which was obtained from 2 subtests, including Vocabulary and Matrix Reasoning.

2.2. Statistical analysis

All of the variables were tested for normality by means of the Shapiro–Wilke test. The demographic, clinical and EF variables were examined using Chi-Squared tests, unpaired *t*-tests or Wilcoxon–Mann–Whitney tests, as appropriate. To explore the Stroop Interference effect, an analysis of covariance (ANCOVA) was performed. The Stroop Word Test score was a covariate variable used with the Stroop Color-Word Test score. This analysis is an alternative to traditional measurement of the Stroop Interference score as it corrects for general task slowing to a considerable extent (Capitani et al., 1999; Lansbergen et al., 2007). Correlations between measures of EFs and clinical variables were assessed by the Spearman correlation coefficient. A multivariate analysis of covariance (MANCOVA) model was created to determine whether group affected any EF outcome measures, including post hoc Bonferroni correction and controlling for potential moderating effects of clinical variables, such as craving symptoms. The level of statistical significance was set at $\alpha = 0.05$. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1
The demographic, clinical and psychosocial characteristics of the groups.

	CPN+ ($n=37$)		CPN− ($n=48$)		Statistics	p
	Mean	SD ± (n)	Mean	SD ± (n)		
Demographic						
Age (years)	31.51	7.83	28.89	8.72	$t=1.66$	0.10
Education (years)	7.83	2.92	8.72	2.78	$t=1.43$	0.15
Income (US$/month)	567.38	627.55	707.21	610.95	$t=0.96$	0.34
Occupation					$\chi^2=2.73$	0.25
With paid employment	27%	(10)	35.4%	(17)		
Unemployment	73%	(27)	60.4%	(29)		
Comorbidities						
Mood disorders	48.4%	(15)	48.8%	(21)	$\chi^2=0.01$	0.97
Anxiety disorders	2.3%	(1)	10%	(3)	$\chi^2=1.93$	0.16
PTSD	23.3%	(7)	11.6%	(5)	$\chi^2=1.76$	0.18
Clinical						
BDI-II	19.91	12.96	16.32	12.41	$U=717.5$	0.46
CSSA	17.43	11.14	12.69	9.00	$t=2.25$	0.028
CTQ – CPN score	13.63	3.78	6.30	1.48	$U=0.00$	<0.001
Emotional abuse	91.8%	(34)	66.6%	(32)	$\chi^2=7.66$	0.006
Emotional neglect	91.8%	(34)	53.2%	(25)	$\chi^2=14.83$	<0.001
Physical abuse	70.2%	(26)	46.8%	(22)	$\chi^2=4.65$	0.031
Sexual abuse	52.7%	(19)	37.5%	(18)	$\chi^2=1.94$	0.16

Notes: PTSD = Posttraumatic Stress Disorder; BDI-II = Beck Depression Inventory; CPN = Childhood Physical Neglect subscale score; CSSA = Cocaine Selective Severity Assessment total score; CTQ = Childhood Trauma Questionnaire; t = unpaired t test; χ^2 = chi-square test; U = Wilcoxon–Mann–Whitney test. History of other forms of childhood abuse and neglect were expressed as the frequency of moderate to extreme exposure.

3. Results

Both groups were similar with respect to age, years of education and the use of medications. No group differences were found in comorbidities or depressive symptoms; however, there were differences in the severity of craving symptoms. The estimated IQ (WASI) ranged from 58 to 115 in the CPN+ group and from 56 to 116 in the CPN− group; no significant differences between the groups were found (see Table 1).

No significant differences were found in the onset of substance use or in the severity of drug problems as measured with the ASI-6 and in pattern of polysubstance use in the last 30 days (see Table 2).

3.1. Executive functions data

The data from the Verbal Fluency tests were not normally distributed and were therefore log transformed. All of the other tests showed normal distributions of responses. Table 3 shows that the CPN+ group presented with significantly lower scores on five of the six EF measures. In general the CPN+ group showed impairments in cognitive flexibility, inhibitory control, selective attention, working memory and verbal fluency in comparison with CPN− group.

To generate an EF variable that comprised all individual measures, our MANCOVA model included the N-Back Task total score, Trail Making Test B time, Stroop Color-Word Test score, Letter Number Sequencing Task score, Verbal Fluency total score and IGT net score as dependent variables. Group was a fixed factor, and CSSA total score and premorbid IQ were covariates. The MANCOVA indicated significant group differences in EFs ($F(6,62)=2.64$, $p=0.024$). However the between group effects were: N-Back Task total score ($F(1,70)=3.28$, $p=0.075$); Trail Making Test B time ($F(1,70)=3.00$, $p=0.080$); Stroop Color-Word Test score ($F(1,70)=3.91$, $p=0.052$); Letter Number Sequencing Task score ($F(1,70)=9.12$, $p=0.004$); Verbal Fluency total score ($F(1,70)=7.00$, $p=0.010$) and IGT net score ($F(1,70)=0.16$, $p=0.688$).

A correlation analysis showed strong associations among the tasks that assessed specific EF components. The correlations between the specific EF tests were as follows: the N-Back Task with the Letter Number Sequencing Task ($r=.54$, $p<0.001$), the Trail Making Test B with the Stroop Test ($r=-.40$, $p<0.001$), and the Verbal Fluency Task with both the Trail Making Test B ($r=-.38$, $p<0.001$) and the Letter Number Sequencing Task ($r=.35$, $p<0.001$). The only IGT significant correlation was with the Stroop Test ($r=.24$, $p<0.030$). Craving severity was associated with the

Table 2
Drug addiction characteristics of groups.

	CPN+ ($n=37$)		CPN− ($n=48$)		Statistics	p
	Mean	SD ± (n)	Mean	SD ± (n)		
ASI-6 – drugs	61.23	9.74	63.76	11.04	$U=629$	0.35
Withdrawal prior admission (days)	4.47	6.61	2.09	3.38	$U=586$	0.13
First drug use (years)						
Alcohol	14.10	6.06	13.58	6.11	$t=0.23$	0.81
Marijuana	14.50	6.69	15.36	5.01	$t=0.63$	0.52
Cocaine	16.80	10.17	18.78	6.29	$t=0.93$	0.35
Crack cocaine	23.26	10.15	23.36	6.73	$t=0.16$	0.86
Drug use last 30 days						
Alcohol	8.70	10.39	6.28	9.84	$t=-1.08$	0.28
Marijuana	4.08	9.58	5.80	10.56	$t=0.73$	0.46
Crack/cocaine	15.32	13.1	18.55	12.5	$t=1.10$	0.27
Others[a]	5.4%	(2)	2.1%	(1)	$\chi^2=0.67$	0.41

Notes: ASI-6 = Addiction Severity Index – Drugs subscale,

[a] Opioids, Stimulants, Sedatives and Hallucinogens; t = unpaired t test; χ^2 = chi-square test; U = Wilcoxon–Mann–Whitney test. Mean number of days regarding alcohol, marijuana and crack/cocaine use.

Table 3
Descriptive scores of the groups on the measures of executive functions.

	CPN+ mean (SD)	CPN− mean (SD)	Statistics	*p*	Effect size
Trail Making Test B	161.34 (74.92)	127.27 (54.49)	$t = 2.35$	0.021	0.52
Stroop Test					
Word test	67.00 (15.71)	74.52 (13.08)	$t = 2.36$	0.020	0.52
Color test	45.35 (11.57)	48.84 (12.02)	$t = 1.33$	0.185	NS
Color-word test	25.38 (8.45)	30.02 (8.89)	$t = 2.39$	0.019	0.53
Interference effect	25.57 (SE = 1.45)	29.66 (SE = 1.27)	$F = 4.34$	0.040	0.48
Verbal Fluency					
Phonemic	24.88 (9.52)	27.64 (8.28)	$t = 1.72$	0.089	NS
Semantic	12.91 (3.76)	15.83 (3.66)	$t = 3.58$	0.001	0.78
Total score	37.10 (12.49)	43.68 (10.08)	$t = 3.16$	0.002	0.69
N-Back Task					
N = 1 task	13.10 (5.65)	14.85 (4.94)	$t = 1.51$	0.133	NS
N = 2 task	4.18 (3.47)	5.81 (3.62)	$t = 2.08$	0.040	0.45
N = 3 task	2.37 (3.36)	4.71 (4.50)	$t = 2.70$	0.008	0.58
Total score	20.80 (9.11)	25.71 (10.78)	$t = 2.17$	0.033	0.49
Letter number sequencing task	5.38 (1.97)	6.95 (2.75)	$t = 3.04$	0.003	0.65
IGT net score	−8.61 (24.45)	−1.82 (20.24)	$t = 1.38$	0.171	NS

Notes: Alpha, *t* and *F* levels and effect sizes (Cohen's delta) of between-group comparisons. Degrees of freedom for Trail Making Test B (78), Stroop Test (80), Verbal Fluency (82), N-Back Task (79), Letter Number Sequencing Task (82) and IGT (81); NS = non significant.

Trail Making Test B Test ($r = .23$, $p = 0.033$) and with the Stroop Test ($r = -.26$, $p = 0.016$). We did not find any association between depressive symptoms and either the severity of drug problems or the EF tasks. We did not find any significant correlations between any EF measures and any medications. In addition, there were no significant mood disorders or anxiety disorders effects on EF measures, including PTSD. There were no significant effect regarding other forms of childhood abuse on EF measures, except for the presence of history of emotional neglect that significantly increased the time needed to finish the Trail Making Test B ($F(1,79) = 6.42$, $p = 0.013$).

4. Discussion

The current study shows that CPN might constitute an important factor in EF deficits in a sample of female crack cocaine users. A more widespread impairment in the CPN+ group was linked to working memory and verbal fluency, both of which are associated with cold EF domains. Cohen's delta demonstrated effect sizes higher than 0.68 for these measures. Furthermore, there were significant deficits with regard to inhibitory control, selective attention and cognitive flexibility in the CPN+ group, with effect sizes greater than 0.48. These effect sizes should be noted in light of the sample context, in which both groups exhibited extremely poor performance in the tasks. For example, in the Stroop Color-Word test, the CPN+ group scored on average in the 5th to 10th percentile, and the CPN− group scored in the 20th to 30th percentile, according to normative data for an elderly population (Ivnik et al., 1996). On the Trail Making Test B, the scores for the CPN+ group ranged from the 10th to 20th percentile, and scores for the CPN− group ranged from the 20th to 30th percentile relative to elderly age normative data (Tombaugh, 2004). On the Letter Number Sequencing Task, the scores for the CPN+ group ranged from the 10th to the 15th percentile, and the scores for the CPN− group ranged from the 20th to the 25th percentile, according to WAIS-III Brazilian normative data regarding working memory (The Psychological Corporation, 2002). On the Phonemic Verbal Fluency Task, the scores for the CPN− group ranged from the 10th to the 20th percentile, and the scores for the CPN+ group ranged from the 5th to the 10th percentile relative to Tombaugh et al. (1999) normative data study. These comparisons may reflect the fact that both groups had significant deficits in EFs. Furthermore, one prior study also demonstrated that crack cocaine addiction and childhood trauma are both related to EF impairments, although this prior research did not focus specifically on the consequences of childhood neglect (Narvaez et al., 2012).

Our correlation analyses revealed pairwise associations between the cold EF tasks, including correlations between the N-Back Task and the Letter Number Sequencing Task, the Trail Making Test B and the Stroop Test and the Verbal Fluency Task and the Letter Number Sequencing Task. Cold EFs are thought to involve a great deal of "top-down" processing, in which the dorsolateral pre-frontal cortex exerts control over subcortical regions and over the flow of information, resulting in a great demand for cognitive resources (Millan et al., 2012). Therefore, the EF deficits in our data could be a direct consequence of the effects of early life stress on the brain maturation of relevant cortical areas (Hanson et al., 2012). Consistent with this hypothesis, a previous study showed that neglected children, including those experiencing both emotional and physical neglect, demonstrated significantly lower IQs, poorer neurocognitive performances in cold EFs, and lower academic achievements than non-neglected children (De Bellis et al., 2009). It appears that, even though continuous drug use may lead to cognitive impairments, early life stressors, including CPN, may result in an important cognitive vulnerability that anticipates and fosters addiction and may be related to the executive control that is associated primarily with cold cognitive functioning.

Several studies have shown that IGT measures are not associated with other cognitive domains (Bechara et al., 2000; Verdejo-Garcia and Perez-Garcia, 2007). The present study showed that only Stroop Test was correlated with the IGT, indicating that so-called "hot" EFs are clearly distinguished from "cold" EFs. In addition, we suggest that a history of drug abuse alone most likely plays a key role in poor overall IGT outcomes, given that both groups were very similar in their patterns of drug use and in their decision-making outcomes.

Our data showed that the CPN+ group exhibited more craving symptoms on the day prior to the EF assessment. In addition, the craving levels were correlated with inhibition, selective attention and cognitive flexibility, indicating that more symptoms resulted in worse cognitive outcomes. Previous findings suggested that brain substrates underlying drug-cue-elicited cravings are similar to those associated with inhibitory control and selective attention (Garavan and Hester, 2007; Lubman et al., 2004). Indeed, drug cues often attract an individual's attention, increasing cravings (Weiss, 2005). In this sense, certain specific EFs might be associated with craving responses, primarily during drug withdrawal periods. Thus, we argued that increased levels of craving symptoms in the CPN+ group could be a consequence of disrupted inhibitory control. These data can also contribute to the debate over the role of drug cravings in cognitive outcomes because our results are opposed to other recent findings that show that craving states

may actually improve cognitive performance (Constantinou et al., 2010; Verdejo-Garcia et al., 2012). Nevertheless, the MANCOVA showed that the presence of CPN was related to EF impairments in all of the cognitive domains, regardless of the severity of craving symptoms.

Our study has some limitations. First, considering that our sample was recruited by convenience sampling in a women's psychiatric unit, we just included female patients in our study. Therefore we cannot conclude whether these findings could be applied to male samples. Second, estimated IQ of 55 is considerably under the limit for diagnosing intellectual disability. Although groups were in similar in premorbid IQ, inclusion of abusers with low IQ may bias the relation between previous history of child neglect and EF, however we included premorbid IQ as a covariate in our analysis which can reduce this possible effect. Therefore, we believe that further research should also include samples with higher education for most likely include participants with higher IQ. Third, considering that the sample was supposed to be composed of patients with crack cocaine dependence, it is noteworthy that almost half the sample had a comorbid psychiatric diagnosis. Fourth, the lack of Brazilian normative data regarding neuropsychological tests used limited the conclusion regarding whether the performance of our sample is still in the normal range considering the culture, however, according to the low scores of both groups in the tasks it is presumable that all sample had considerable deficits in Executive Functions. Fifth, the measures of hot EFs were limited to one task, the IGT, though IGT is an extensively used measure of decision making. Sixth, it is important to consider that the participants of CPN+ group also presented significantly more childhood physical and emotional abuse, as well as emotional neglect moderate to severe exposure, although there were no significant effects regarding these other forms of childhood abuse on EF measures. It should be noted that despite the CTQ subdivides neglect and abuse into distinct categories, it is presumable that exposure to such events may occur simultaneously or associated (Bernstein et al., 2003; Briere and Runtz, 1988). Even with these limitations, however, the current study was conducted with a careful methodological design in which clinical factors that could bias the results were controlled and the neuropsychologists had no access to the clinical data. Nevertheless, further studies with larger samples, more tasks tapping EF and longitudinal follow-up will be needed to investigate the impact of childhood neglect in long-term cognitive development and addiction outcomes and to overcome these limitations.

Finally, our findings support the role of CPN in impairments in EF associated with crack cocaine addiction. In accordance with previous studies, our data contribute to the understanding of crack cocaine addiction in three ways. First, as mentioned above, components of the executive system could control key addiction processes, such as reward, emotion and craving, increasing the likelihood of drug-seeking behavior and relapse (Brewer et al., 2008; George and Koob, 2010). Second, deficits in EFs could affect the capacity of patients with crack cocaine dependence to understand and assimilate information during treatment programs (Johnson-Greene et al., 2002; Lundqvist, 1995). Finally, early life stress is an important factor that is related to individual differences that may increase vulnerability to drug dependence and may mediate the transitions between addiction stages (Andersen and Teicher, 2009). Hence, our work emphasizes the need to take into account the presence of childhood neglect and parental care privation in the pathological underpinnings of crack cocaine dependence. These findings fit well with a growing body of evidence showing that childhood maltreatment is a key environmental factor that could alter neurodevelopment and mediate the route to addiction, aggravating its consequences.

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Contributors

Authors Viola T.W., Pezzi J.P., Kristensen C.H., Grassi-Oliveira R. designed the study and wrote the protocol. Authors Viola T.W. and Tractenberg S.G. managed the literature searches and summaries of previous related work. Authors Viola T.W. and Grassi-Oliveira R. undertook the statistical analysis, and authors Viola T.W. and Tractenberg S.G. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All other authors declare that they have no conflicts of interest.

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