Brazilian Journal of Psychiatry
BJP
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2020 Mar-Apr;42(2):214-217
doi:10.1590/1516-4446-2019-0532
Brazilian Psychiatric Association

BRIEF COMMUNICAITON

Effects of childhood trauma on BDNF and TBARS during crack-cocaine withdrawal

Anne O. **Sordi**,[1] Lisia **von Diemen**,[1,2] Felix H. **Kessler**,[1,2] Silvia **Schuch**,[1] Felipe **Ornell**,[1,2] Flávio **Kapczinski**,[2,3,4,5] Bianca **Pfaffenseller**,[4,6] Carolina **Gubert**,[4,6] Bianca **Wollenhaupt-Aguiar**,[4,6] Giovanni A. **Salum**,[2] Flavio **Pechansky**[1,2]

[1]*Centro de Pesquisa em Álcool e Drogas (CPAD), Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.* [2]*Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, UFRGS, Porto Alegre, RS, Brazil.* [3]*Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), HCPA, UFRGS, Porto Alegre, RS, Brazil.* [4]*Laboratório de Psiquiatria Molecular, HCPA, Porto Alegre, RS, Brazil.* [5]*Departamento de Psiquiatria e Medicina Legal, UFRGS, Porto Alegre, RS, Brazil.* [6]*Programa de Pós-Graduação em Ciências Biológicas, Bioquímica, Departamento de Bioquímica, UFRGS, Porto Alegre, RS, Brazil.*

Objective: To evaluate the association between childhood trauma (CT) and serum levels of brain-derived neurotrophic factor (BDNF) and thiobarbituric acid-reactive substances (TBARS) during crack-cocaine withdrawal.
Method: Thirty-three male crack-cocaine users were recruited at admission to a public addiction treatment unit. Serum BDNF and TBARS levels were evaluated at intake and discharge. Information about drug use was assessed by the Addiction Severity Index-6th Version (ASI-6); CT was reported throughout the Childhood Trauma Questionnaire (CTQ). CTQ scores were calculated based on a latent analysis model that divided the sample into low-, medium-, and high-level trauma groups.
Results: There was a significant increase in BDNF levels from admission to discharge, which did not differ across CT subgroups. For TBARS levels, we found a significant time vs. trauma interaction ($F_{2,28} = 6.357$, $p = 0.005$, $\eta_p^2 = 0.312$). In participants with low trauma level, TBARS decreased, while in those with a high trauma level, TBARS increased during early withdrawal.
Conclusion: TBARS levels showed opposite patterns of change in crack-cocaine withdrawal according to baseline CT. These results suggest that CT could be associated with more severe neurological impairment during withdrawal.

Keywords: Childhood trauma; cocaine; drug abuse; BDNF; oxidative stress

Introduction

There is a growing body of evidence implicating possible neurobiological markers in the pathogenesis of substance use disorders (SUD).[1] Whether this is related to early life experiences or to drug use itself is still unknown. Persistently increased oxidative stress (OS), a marker of cell impairment, is a consequence of childhood trauma (CT), and is also observed in SUD.[2] One way of measuring OS is through quantitation of thiobarbituric acid-reactive substance (TBARS) levels. Conversely, neurotrophins are implicated in neuronal protection. Among the neurotrophins, brain-derived neurotrophic factor (BDNF) has the most established evidence of influence on synaptic plasticity, and might act directly on cocaine-induced neuroadaptation.[3] BDNF levels seem to increase during crack-cocaine withdrawal, and later return to normal, which may be an indicative of brain recovery.[1,4] Brain plasticity could also be mediated by early-life experiences, especially in the limbic system, and may be implicated in the development of SUD.[5]

Since crack-cocaine dependence is a subject of major concern worldwide, it is imperative to understand more about its underlying mechanisms. Therefore, the aim of this brief communication is to present some novel findings on how the intensity of CT may be associated with changes in serum BDNF and TBARS levels during early crack-cocaine withdrawal.

Methods

Sample selection and procedures

Thirty-three adult male crack-cocaine users (age $\geqslant$ 18 years) who screened positive for cocaine (Bioeasy® Cocaine-Test, Alere™) were recruited on the first day of hospitalization at a public addiction treatment unit in Porto Alegre, Brazil. The exclusion criteria were: psychotic

Correspondence: Anne Orgler Sordi, Centro de Pesquisa em Álcool e Drogas (CPAD), Hospital de Clínicas de Porto Alegre, Unidade Alvaro Alvim, Rua Prof. Alvaro Alvim, 400, CEP 90420-020, Porto Alegre, RS,Brazil.
E-mail: asordi@hcpa.edu.br
Submitted Jan 09 2019, accepted Aug 28 2019, Epub Dec 05 2019.

How to cite this article: Sordi AO, von Diemen L, Kessler FH, Schuch S, Ornell F, Kapczinski F, et al. Effects of childhood trauma on BDNF and TBARS during crack-cocaine withdrawal. Braz J Psychiatry. 2020;42:214-217. http://dx.doi.org/10.1590/1516-4446-2019-0532

symptoms, intelligence quotient < 70, and refusal of consent. Interviews were conducted by trained graduate students in Psychology between the 5th and 7th day of withdrawal. Drug use information was assessed by the Addiction Severity Index – 6th Version (ASI-6).[6] CT was assessed by the Childhood Trauma Questionnaire (CTQ).[7]

Blood collection and assay

A 10-mL blood sample was collected from each participant on the first 24 hours of hospitalization, and again in the 24 hours preceding hospital discharge. TBARS were measured using a commercial assay kit (Cayman Chemical Company, Ann Arbor, MI, USA). BDNF were measured using a sandwich ELISA method with monoclonal antibodies specific for BDNF from R&D Systems (Minneapolis, MN, USA).

Statistical analysis

Since there is no established cutoff point for trauma scores, CTQ scores were calculated on the basis of a previous report suggesting a new second-order structure for the instrument.[8] Factor scores for the five CTQ subscales and a higher-order trauma factor were saved for an analysis using mean- and variance-adjusted weighted least squares (WLSMV) estimator, which presented proper fit in the sample from which our subjects derive: root mean square error of approximation (RMSEA) = 0.049; 90% confidence interval (90%CI) = 0.042-0.055; comparative fit index (CFI) = 0.960; Tucker-Lewis index (TLI) = 0.956; and weighted root mean square residual (WRMR) = 1.058. The fit indices and rules of thumb used were as follows: CFI, good fit if $\geqslant$ 0.95; TLI, good fit if $\geqslant$ 0.90; and RSMEA, good fit if < 0.06. CTQ total scores were then split into a categorical variable based on the sample tertile distribution (low, medium, and high). Differences in BDNF and TBARS from admission to discharge and among trauma groups were tested using repeated-measures analysis of covariance (ANCOVA). Significant results were controlled for severity of crack-cocaine use and days of hospitalization. Significant time vs. trauma interactions were analyzed using paired t-tests stratified by level of trauma. Effect sizes were defined in terms of % of explained variance; 1, 9, and 25% were defined as small, medium, and large effects, corresponding to 0.01, 0.06, and 0.14 partial eta square (η_p^2) values, respectively.[9] Severity of crack use was estimated using a composite of age at first use, duration of use in years, and number of crack rocks consumed in the preceding 30 days (as described elsewhere).[4]

Ethics statement

The study was approved by the institutional review boards and ethics committees of Hospital de Clínicas de Porto Alegre and Hospital São Pedro. All participants provided written informed consent.

Results

All participants were male. Mean age was 27.06 (standard deviation [SD] = 6.94) years, and the mean duration of hospitalization was 18.97 (SD = 4.24) days. There was no significant difference in age, days of hospitalization, years of crack-cocaine use, or severity of crack-cocaine use among the low, medium, and high CT groups (Table 1).

For BDNF levels, we found significant time effects ($F_{1,30}$ = 8.45, p = 0.007, η_p^2 = 0.22), but not trauma effects ($F_{2,30}$ = 2.15, p = 0.134, η_p^2 = 0.125), nor time vs. trauma interactions ($F_{2,30}$ = 0.954, p = 0.397, η_p^2 = 0.06) in repeated-measures ANOVA. Controlling for the effects of potential confounders did not change our results for time ($F_{1,28}$ = 0.273, p = 0.605, η_p^2 = 0.01), trauma ($F_{2,28}$ = 2.0, p = 0.153,

Table 1 Sample profile, stratified by trauma groups

	Low (n=11)	Medium (n=11)	High (n=11)	Total
Age (years)	29.64[a] (8.3)	26.09[a] (5.68)	25.45[a] (6.47)	27.06 (6.94)
Length of hospital stay (days)	19.82[a] (4.33)	19.18[a] (4.17)	17.91[a] (4.39)	18.97 (4.24)
Crack-cocaine use (years)	7.00[a] (3.5)	6.91[a] (3.51)	5.82[a] (2.64)	6.56 (3.17)
Severity score	14.27[a] (3.93)	15.09[a] (4.66)	15.18[a] (4.77)	14.85 (4.35)
Standardized trauma levels				
Physical neglect	-0.033[a] (0.189)	0.273[b] (0.127)	0.383[b] (0.179)	0.208 (0.241)
Emotional neglect	-0.025[a] (0.307)	-0.367[a] (0.518)	-0.294[a] (0.179)	-0.229 (0.382)
Sexual abuse	-0.005[a] (0.452)	0.523[ab] (0.590)	0.760[b] (0.549)	0.426 (0.610)
Physical abuse	-0.354[a] (0.275)	0.395[b] (0.299)	0.835[c] (0.409)	0.292 (0.594)
Emotional abuse	-0.177[a] (0.264)	0.386[b] (0.101)	0.710[c] (0.228)	0.306 (0.424)
Total trauma scores	-0.074[a] (0.106)	0.166[b] (0.045)	0.297[c] (0.096)	0.130 (0.177)
Biomarkers				
BDNF (admission)	29.28[a] (11.62)	26.01[a] (13.08)	30.77[a] (8.13)	28.69 (10.97)
BDNF (discharge)	32.48[a] (9.88)	33.86[a] (13.09)	42.99[a] (12.13)	36.44 (12.35)
TBARS (admission)	20.24[a] (14.65)	11.67[ab] (3.64)	7.54[b] (2.27)	13.15 (10.08)
TBARS (discharge)	9.83[a] (4.18)	12.57[a] (5.41)	13.93[a] (7.87)	12.11 (6.08)
Ethnicity (Caucasian), n (%)	10[a] (90.90)	6[a] (54.50)	9[a] (81.80)	25 (75.80)
Marital status (married), n (%)	1[a] (9.10)	5[a] (45.50)	2[a] (18.20)	8 (24.20)

Data presented as mean (SD), unless otherwise specified.
BDNF = brain-derived neurotrophic factor; SD = standard deviation; TBARS = thiobarbituric acid-reactive substances.
Between-group differences were assessed using t-tests and z-tests. Different lowercase superscript letters denote significant differences.

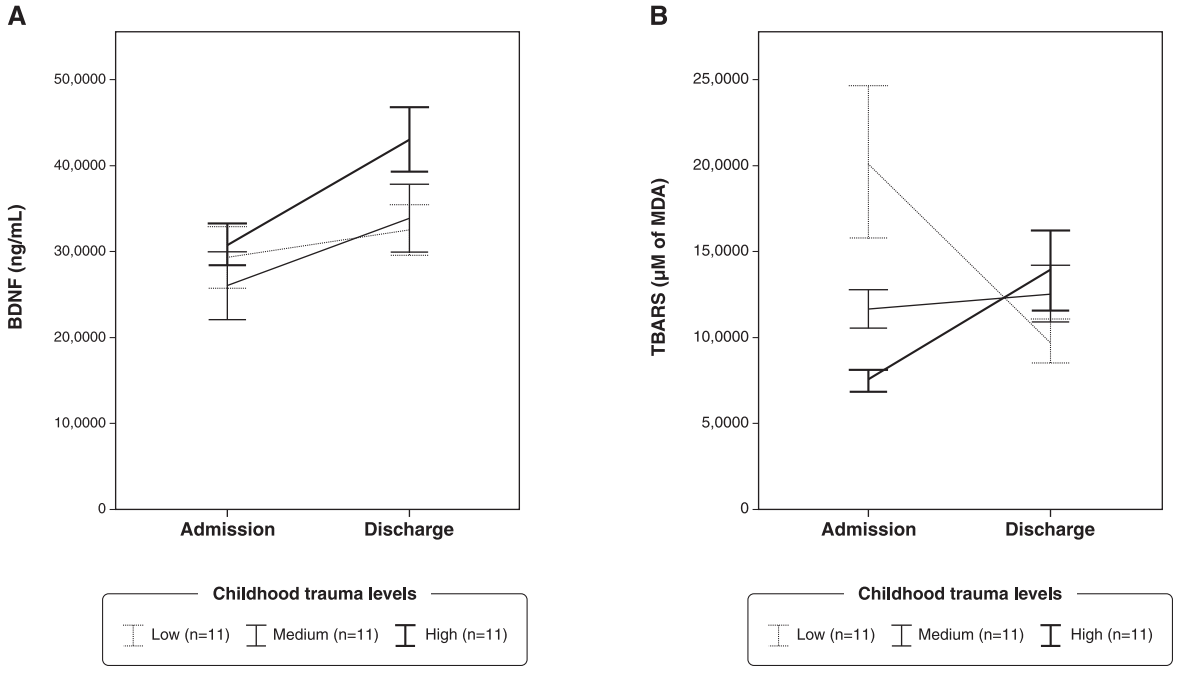

Figure 1 BDNF and TBARS serum levels among trauma groups during withdrawal. A) BDNF levels from admission to discharge stratified by childhood trauma level. B) TBARS from admission to discharge stratified by childhood trauma level. BDNF = brain derived neurotrophic factor; MDA = malondialdehyde; TBARS = thiobarbituric acid reactive substances.

η_p^2 = 0.125), or time vs. trauma interactions ($F_{2,28}$ = 2.25, p = 0.124, η_p^2 = 0.138). This analysis reveals a significant increase in BDNF levels from admission to discharge (time effect), which did not differ among groups (Figure 1A).

For TBARS levels, we found no time effects ($F_{1,30}$ = 0.307, p =0.584, η_p^2 = 0.01) nor trauma effects ($F_{2,30}$ = 1.901, p = 0.167, η_p^2 = 0.112), but we did find a significant time vs. trauma interaction ($F_{2,30}$ = 6.95, p = 0.003, η_p^2 = 0.317). Controlling for the effects of potential confounders did not change our results for time ($F_{1,28}$ = 0.006, p = 0.94, η_p^2 = 0.03), trauma ($F_{2,28}$ = 1.972, p = 0.158, η_p^2 = 0.123), or time vs. trauma interaction ($F_{2,28}$ = 6.357, p = 0.005, η_p^2 = 0.312). This analysis revels that the level of CT moderates changes in TBARS levels during withdrawal. To clarify time vs. trauma interactions for TBARS, we performed a stratified analysis for changes in TBARS levels from admission to discharge among the three groups. We found that, for the low trauma level group, TBARS showed a trend-level decrease across time (mean difference = 10.4, SD = 16.12, 95%CI -0.4 to 21.25, r = -0.230, *t* = 2.14, degrees of freedom [df] = 10, p = 0.058). It did not change for the medium trauma group (mean difference = -0.9, SD = 5.96, 95%CI -4.9 to 3.10, r = 0.178, *t* = -0.503, df = 10, p = 0.626), while it significantly increased for the high trauma group (mean difference = -6.38, SD = 7.25, 95%CI -11.3 to -1.51, r = 0.405, *t* = -2.919, df = 10, p = 0.015) (Figure 1B).

Discussion

To the best of our knowledge, this is the first study to show opposite patterns of changes in TBARS levels in crack-cocaine users with high vs. low CT scores.

Although evidence suggests that CT could decrease BDNF levels in later life, we did not find a difference in this parameter among groups. Previous studies that evaluated how CT might affect BDNF during crack-cocaine withdrawal are consistent with our results. Viola et al. demonstrated that CT did not have an impact on BDNF levels during early withdrawal in a sample of female crack-cocaine users.[10] Overall, BDNF levels increase during withdrawal, but this is related to craving, relapse, and severity of drug use.[1,4,10] Therefore, we controlled for severity of crack-cocaine use.

When we investigated changes in TBARS during crack-cocaine withdrawal, we found a decrease in TBARS among patients with low CT levels, but a sustained increase in TBARS among those with high CT levels. The first finding is in accordance with the literature, which shows that a decrease in OS occurs during abstinence.[1] Cocaine use rapidly increases the production and release of dopamine, and can increase OS because dopamine reuptake is due to self-oxidation.[11] Furthermore, cocaine users have impaired antioxidant defenses.[12]

Different hypotheses might explain our results. Early-life stress could lead to a persistent increase in lipid peroxidation, and antioxidant defenses would ultimately become insufficient to overcome it.[2] Individuals with a history of CT experience allostatic overload of the hypothalamus-pituitary-adrenal axis, which increases symptoms of anxiety, leading to higher cortisol production – which consequently increases OS.[13] In addition, drug use might represent a way to achieve immediate relief of negative feelings.[14] Abstinence would then cause the emergence of traumatic memories, thus increasing OS.

Our findings must be interpreted in light of some limitations. First, the history of CT was collected retrospectively, which is always subject to recall bias. Nevertheless, the CTQ is considered a reliable scientific instrument. We also used a sophisticated latent-variables model which takes into account that different types of trauma contribute differently to overall trauma severity.[8] Second, our analysis was limited to 33 male subjects; our findings may not apply to women. However, the small sample size did not prevent us from finding substantial associations between biomarkers and trauma levels, which indicates sufficient power to detect the most important association under study. Third, we did not evaluate psychiatric comorbidities. However, since CT is a major risk factor for the development of psychiatric disorders, it could be considered a mediator of the results. It is important to note that all patients attended the same treatment program.

Crack-cocaine dependence is a multifactorial disorder which involves biological as well as environmental factors, and causes great impact on the lives of users, their families, and wider society.[15] Our study sheds light on how CT could interfere with specific biological markers that seem to be involved in the pathogenesis of crack-cocaine dependence. Understanding these underlying mechanisms can help design different targeted treatment options which take patients' early-life experiences into account.

In conclusion, childhood abuse or neglect can influence how the brain of a crack-cocaine user behaves during the withdrawal process, increasing oxidative stress in those with a higher level of trauma.

Acknowledgements

Funding was provided by Secretaria Nacional de Políticas sobre Drogas (SENAD) and Fundo de Incentivo à Pesquisa e Eventos (FIPE).

Disclosure

The authors report no conflicts of interest.

References

1 Sordi AO, Pechansky F, Kessler FH, Kapczinski F, Pfaffenseller B, Gubert C, et al. Oxidative stress and BDNF as possible markers for the severity of crack cocaine use in early withdrawal. Psychopharmacology (Berl). 2014;231:4031-9.
2 Schiavone S, Jaquet V, Trabace L, Krause KH. Severe life stress and oxidative stress in the brain: from animal models to human pathology. Antioxid Redox Signal. 2013;18:1475-90.
3 Fumagalli F, Di Pasquale L, Caffino L, Racagni G, Riva MA. Repeated exposure to cocaine differently modulates BDNF mRNA and protein levels in rat striatum and prefrontal cortex. Eur J Neurosci. 2007;26:2756-63.
4 von Diemen L, Kapczinski F, Sordi AO, de Magalhães Narvaez JC, Guimarães LS, Kessler FH, et al. Increase in brain-derived neurotrophic factor expression in early crack cocaine withdrawal. Int J Neuropsychopharmacol. 2014;17:33-40.
5 Cirulli F, Francia N, Berry A, Aloe L, Alleva E, Suomi SJ. Early life stress as a risk factor for mental health: role of neurotrophins from rodents to non-human primates. Neurosci Biobehav Rev. 2009; 33:573-85.
6 Kessler F, Cacciola J, Alterman A, Faller S, Souza-Formigoni ML, Cruz MS, et al. Psychometric properties of the sixth version of the Addiction Severity Index (ASI-6) in Brazil. Braz J Psychiatry. 2012; 34:24-33.
7 Grassi-Oliveira R, Stein LM, Pezzi JC. [Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language]. Rev Saude Publica. 2006;40:249-55.
8 Grassi-Oliveira R, Cogo-Moreira H, Salum GA, Brietzke E, Viola TW, Manfro GG, et al. Childhood Trauma Questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. PloS One. 2014;9:e87118.
9 Cohen J. Statistical power analysis for the behavioral sciences. 2º ed. Abingdon: Routledge; 1988.
10 Viola TW, Tractenberg SG, Levandowski ML, Pezzi JC, Bauer ME, Teixeira AL, et al. Neurotrophic factors in women with crack cocaine dependence during early abstinence: the role of early life stress. J Psychiatry Neurosci. 2014;39:206-14.
11 Dietrich JB, Mangeol A, Revel MO, Burgun C, Aunis D, Zwiller J. Acute or repeated cocaine administration generates reactive oxygen species and induces antioxidant enzyme activity in dopaminergic rat brain structures. Neuropharmacology. 2005;48:965-74.
12 Walker J, Winhusen T, Storkson JM, Lewis D, Pariza MW, Somoza E, et al. Total antioxidant capacity is significantly lower in cocaine-dependent and methamphetamine-dependent patients relative to normal controls: results from a preliminary study. Hum Psychopharmacol. 2014;29:537-43.
13 Badanes LS, Watamura SE, Hankin BL. Hypocortisolism as a potential marker of allostatic load in children: associations with family risk and internalizing disorders. Dev Psychopathol. 2011;23: 881-96.
14 Ramos Sde P. What can we learn from psychoanalysis and prospective studies about chemically dependent patients? Int J Psychoanal. 2004;85:467-87.
15 Kessler F, Woody G, De Boni R, Von Diemen L, Benzano D, Faller S, et al. Evaluation of psychiatric symptoms in cocaine users in the Brazilian public health system: need for data and structure. Public Health. 2008;122:1349-55.