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ARTICLE

Increase in brain-derived neurotrophic factor expression in early crack cocaine withdrawal

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Abstract

Recent reports suggest that brain-derived neurotrophic factor (BDNF) could be a biomarker for relapse, drug craving and withdrawal severity. In particular, elevated BDNF levels among former cocaine users have been associated with higher rates of relapse in 90 d. However, no data are available on BDNF levels at baseline and during crack cocaine withdrawal. This study evaluated BDNF among crack cocaine users during inpatient treatment, before and after withdrawal, *vs.* healthy controls. Clinical correlates with changes in BDNF levels were also assessed.

Serum BDNF was evaluated in 49 male crack users on the first and last days of hospitalization and in 97 healthy controls. Serum BDNF was assayed using a sandwich ELISA kit.

BDNF levels were significantly lower upon admission when compared to controls, even after adjustment for age, length of inpatient treatment, number of crack rocks used in the last 30 d, years of crack use and interaction between the latter two variables. At discharge, BDNF levels between patients and controls were similar. Number of crack rocks used in the last 30 d and years of crack use were inversely correlated with the outcome.

Our findings show that BDNF levels increase during early crack cocaine withdrawal, at an inverse correlation with number of crack rocks used in the last 30 d and years of crack use.

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Key words: Brain-derived neurotrophic factor, crack cocaine dependence, neurobiology, neurotrophin, withdrawal.

Introduction

Addiction is a chronic, relapsing disorder, characterized by repetitive and compulsive drug taking, drug-seeking behaviours and loss of control in limiting drug intake, despite the negative consequences of such intake (O'Brien and McLellan, 1996; George and Koob, 2010). This process occurs in three stages, all part of a recurrent cycle: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation (craving) (Koob and Le Moal, 2008). Clinical and pre-clinical studies suggest that this cycle is characteristic of addiction, but not of occasional drug use, suggesting a potential relationship with long-term neuroadaptive changes in the brain (Koob and Volkow, 2009; Parvaz et al., 2011; Volkow et al., 2011).

The notion that addiction is a brain disease is not new, but only very recently have brain biomarkers been investigated regarding the possibility of predicting disease severity and outcome and of helping assess individual underlying vulnerabilities (Mendelson et al., 2011; Sinha, 2011). In this scenario, brain-derived neurotrophic factor (BDNF) has emerged as a potential biomarker in many psychiatric disorders, including drug addiction (Cunha et al., 2006; Shim et al., 2008; Mendelson et al., 2011; Pae et al., 2012). BDNF is the most abundant neurotrophin in the brain, involved in neurogenesis, neuroplasticity and cognitive functioning (Huang and Reichardt, 2001; de Lima et al., 2011). Pre-clinical and clinical studies have suggested an important role of BDNF in drug addiction, particularly in users of alcohol and psychostimulants (Davis, 2008; McGinty

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et al., 2010). In animal models of cocaine addiction, BDNF infusion into the ventral tegmental area potentiated cocaine craving and increased drug-seeking behaviour and self-administration, as well as sensitization to cocaine and cocaine-conditioned cues (Lu et al., 2004; Graham et al., 2007; Bahi et al., 2008). Recent reports in humans are in line with animal studies, suggesting that BDNF could be a biomarker for relapse, drug craving and withdrawal severity (Huang et al., 2010; Costa et al., 2011; D'Sa et al., 2011; Hilburn et al., 2011).

Among cocaine dependents, a recent study has reported that elevated BDNF levels after 3 wk of cocaine withdrawal were associated with higher rates of cocaine relapse in 90 d (D'Sa et al., 2011). Cocaine users had significantly higher serum BDNF levels than controls, but the study had a small sample (35 patients, of which 23 relapsed) and provided no data on baseline BDNF or its pattern during withdrawal (McGinty and Mendelson, 2011). Conversely, in another study with 23 cocaine dependents, BDNF was found to increase after a 2 wk detoxification period, and baseline levels were reduced in relation to the control group (Corominas-Roso et al., 2012). Similarly, among alcohol-dependent subjects, both BDNF levels and the extent of BDNF increase were higher in the abstinent when compared to the relapsed group (BDNF was measured upon hospital admission and 6 months later) (Costa et al., 2011). In methamphetamine abusers, serum BDNF levels were significantly and constantly lower during early withdrawal when compared with results obtained for healthy controls (Chen et al., 2012). These data support the notion that altered BDNF expression during drug withdrawal may be a critical and clinically relevant finding. Nevertheless, both BDNF expression patterns during early cocaine withdrawal and the clinical aspects associated with such patterns remain unknown.

The primary aims of this study were to evaluate BDNF levels in crack cocaine users during inpatient treatment, both before and after withdrawal, and to compare results with those of healthy controls. A second aim was to investigate possible associations between changes in BDNF levels during detoxification and patterns of drug use, psychiatric comorbidities and use of medication.

Methods and materials

Sample selection

Crack cocaine users were recruited at Hospital São Pedro, a public psychiatric hospital that has a specialized unit for the treatment of addiction, located in Porto Alegre, southern Brazil. Inclusion criteria were: being a male crack cocaine user with a positive urine test for cocaine upon admission (Bioeasy® cocaine test, Alere™, Brazil); being 18 yr old or older; and agreeing to provide two blood samples during inpatient treatment. Subjects were excluded if they were considered unable to participate based on clinical evaluation. A total of 78 subjects met the inclusion criteria and agreed to participate; of these, 49 provided two blood samples (at hospital admission and discharge) and were, therefore, included in the sample. For the control group, 97 male non-crack/cocaine users were recruited from records of a primary care centre according to the neighbourhood or geographical area of residence of crack users. Controls were excluded if they reported cocaine use in the last year or if they showed a positive urine screening test for cocaine.

Procedures

Crack cocaine users were interviewed by two previously trained undergraduate psychology students. Patients were invited to enter the study as soon as they had the necessary clinical and mental conditions to understand the study objectives. The research protocol was carried out independently from clinical care. Treatment was conducted 'as usual,' following the routine established at the hospital, including the number of inpatient days for each subject.

One blood sample was collected during the first 24 h of hospitalization, and the other during the 24 h preceding hospital discharge. Whenever the subject was not able to sign the informed consent form upon the first blood collection, the sample was stored until the patient was considered to have mental conditions to understand it. For patients who refused to participate, blood samples already collected were discarded. Interviews were conducted between the 5th and 7th day of detoxification to circumvent potential cognitive impairment on the first days of hospitalization.

In the control group, two other previously trained undergraduate psychology students and one blood collector visited the house of each subject and invited them to participate. When a positive answer was obtained, a urine test for crack/cocaine was performed. All subjects who denied being a crack/cocaine user and who presented a negative urine test were interviewed and had a blood sample collected. Systematic supervision of the interviews and questionnaire review were made by senior investigators to assure and maintain the quality of data collection.

Ethics

The study was approved by the Institutional Review Boards and Ethics Committees of Hospital de Clínicas de Porto Alegre and Hospital São Pedro. All subjects included in the analysis provided written informed consent.

Instruments

Drug use pattern was assessed using the Addiction Severity Index – 6th Version (ASI-6), validated for Brazilian Portuguese (Kessler et al., 2012). Detailed

information about crack use (crack user profile) was obtained using a questionnaire developed by our group, comprised of 27 questions about the intensity, impact, and course of crack use. Psychiatric conditions were assessed using the Mini-International Neuropsychiatric Interview (MINI), validated for Brazilian Portuguese (Amorim et al., 1998). Intelligence quotient (IQ) was estimated using the vocabulary and block design subscales of the Wechsler Adult Intelligence Scale®, third edition. HIV and HCV infection status and medications used during hospitalization were recorded based on hospital records (information was missing in eight cases).

Blood collection and processing

Ten milliliters of blood were collected by venipuncture into an anticoagulant-free vacuum tube for each patient and control included in the study. Immediately after collection, blood samples were centrifuged at 4000 r/min for 10 min and the serum was aliquoted, labeled and stored at −80 °C until assay testing.

BDNF measurement

Serum BDNF concentrations were measured using a sandwich ELISA kit with monoclonal antibodies specific for BDNF from R&D Systems (USA). Human BDNF MAb (Clone 37129), a mouse IgG2a isotype, was used as the capture antibody, and human BDNF biotinylated MAb (Clone 37141), another mouse IgG2a isotype, was used as the detection antibody. Briefly, microtiter plates (96-well, flat-bottom) were coated overnight at 4 °C with the anti-BDNF capture antibody at 4 μg/ml in phosphate buffered saline (PBS). Then, plates were washed with wash buffer (PBS, pH 7.4, with 0.05% Tween-20) and blocked for 1 h at room temperature with PBS containing 5% nonfat milk powder. After washing, plates were coated overnight at 4 °C with the samples diluted 1:200 in PBS with 1% bovine serum albumin; the standard curve of BDNF ranged from 7.8 to 500 pg/ml. Plates were washed and the anti-BDNF detection antibody (0.2 μg/ml) was added for another 2 h incubation. After washing, incubation with streptavidin-peroxidase conjugate (diluted 1:200 in sample diluent) was performed for 20 min at room temperature. Finally, plates were washed again and incubated with a substrate solution for 20 min, followed by a stop solution (H_2SO_4 1 M). BDNF levels were determined by absorbance at 450 nm with correction at 540 nm. The standard curve demonstrated a direct relationship between optical density (OD) and BDNF concentration.

Statistical analysis

Data were expressed as means and standard deviation or as medians and interquartile ranges (25th–75th percentiles), depending on data distribution. The normality of data distribution was assessed using the Shapiro–Wilk test. Variables with normal and asymmetrical distribution were compared using the Student *t*-test and Mann–Whitney test, respectively. Categorical variables were expressed as number of subjects and percentages and compared using the χ^2 test. For repeated measures (only BDNF levels), the *t*-test for paired samples was used. Percentage alterations in BDNF levels were calculated using the formula

$$\{[(\text{BDNF at discharge} - \text{BDNF at admission}) / \text{BDNF at admission}] \times 100\}$$

Number of crack rocks used in the last 30 d was estimated using the formula

$$[\,(\text{rocks per week}/7) \times \text{number of days using crack in the previous 30 d}]$$

Psychiatric disorders were grouped in broad categories (e.g. any anxiety disorder). Generalized estimating equations (GEE) were used to estimate BDNF levels in crack users and controls, adjusted for confounders. Variables showing $p<0.20$ in the bivariate analysis were tested in this model. In all experiments, $p<0.05$ was considered statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18.0.

Results

Demographic characteristics and psychiatric diagnoses in crack users and controls

Crack users had fewer years of education and higher frequencies of alcohol use disorder, drug use disorder (other than crack cocaine), depression or dysthymia, attention deficit hyperactivity disorder (ADHD), and antisocial personality disorder (APD) when compared to controls. The majority of both our cases and controls were Caucasian. Also, there were eight cases (16.3%) and nine controls (9.3%) of African descent, one (2.0%) and five (5.2%), respectively, of indigenous descent, three (6.1%) and 23 (23.7%) *pardo* participants, respectively, and two (4.0%) and one (2.0%) subjects of other ethnicities, respectively. Prevalence of psychiatric disorders was higher among crack users, especially APD, depression/dysthymia, alcohol and drug use disorder (Table 1). Seven patients used antidepressants while hospitalized, as follows: three (6.1%) used amitriptyline, two (4.1%) sertraline and one each (2.0%) fluoxetine and nortriptyline.

BDNF levels in crack users and controls

BDNF levels were significantly lower at admission (28.6±11.0) when compared with discharge (35.5±12.3) and to controls (39.5±10.6). There were no significant differences between BDNF levels on the last day of treatment *vs.* levels in controls, although a tendency toward lower levels was observed (Fig. 1).

Table 1. Demographic characteristics and current psychiatric diagnoses in crack users and controls

	Crack users (n=49) n (%)	Controls (n=97) n (%)	p
Age*	27.9±7.38	30.0±8.37	0.139
Caucasian	35 (71.4)	58 (59.8)	0.231
⩽8 years of education	32 (65.3)	37 (38.5)	<0.05
Years of crack use**	5 (3–7)	–	–
Intelligence quotient*	81.9±9.7	90.0±12.4	<0.001
Drug use disorder (other than crack cocaine)	22 (44.9)	3 (3.1)	<0.001
Depression or dysthymia	30 (61.2)	9 (10.1)	<0.001
Alcohol use disorder	17 (34.7)	4 (4.1)	<0.001
Any anxiety disorder	5 (10.2)	18 (18.6)	0.286
Attention deficit hyperactivity disorder	12 (24.5)	8 (9.2)	<0.05
Antisocial personality disorder	19 (40.4)	3 (3.1)	<0.001
Mania or hypomania	1 (2.0)	0	0.336

* Mean±S.D. ** Median (interquartile range).

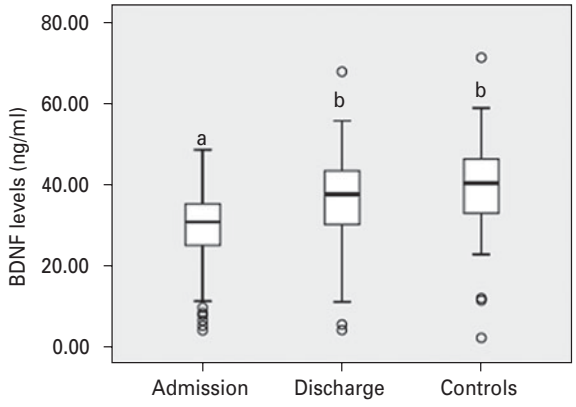

Fig. 1. BDNF levels in crack users during inpatient treatment (at admission and discharge) and in controls. Different letters indicate statistical differences between groups (p<0.001).

Alterations in BDNF levels varied greatly, ranging from −82.8 to 504.2% (median=33.0%; interquartile range=−1.8–51.2%). Fourteen subjects (28.6%) showed reductions in their BDNF levels during inpatient treatment. Age, body mass index, number of days using marijuana, tobacco and alcohol in the 30 d preceding inpatient treatment were not associated with modifications in BDNF levels during hospitalization. Psychiatric comorbidities and medications used during hospitalization did not show significant associations with changes in BDNF levels either, except for suicide risk and treatment with valproate, respectively. Patients with a suicide risk upon admission and those who did not use valproate presented an increase in BDNF levels during hospitalization, however at a lower rate when compared with patients with no suicide risk and who had used valproate (Table 2). Years of crack use was not associated with changes in BDNF levels, but number of crack rocks used in the last 30 d was negatively correlated with increased BDNF. Only one subject tested positive for both HIV and HCV among crack users; his BDNF upon admission was 17.74, compared with 34.77 at discharge.

Adjusted BDNF levels

Estimated IQ, suicide risk, use of valproate and use of topiramate reached p<0.20 in the bivariate analyses, but lost significance after adjustment and were therefore excluded from the final model. Age was included in the final model because of its relevance for BDNF levels and for model adjustment. The final GEE model included hospitalization days, age, number of crack rocks used in the last 30 d, years of crack use, and interaction between the latter two variables. The control group was adjusted for age only. Following adjustment for these variables, the differences between groups remained the same as those observed in the unadjusted analysis (Fig. 2).

Discussion

To the authors' knowledge, this is the first clinical study to show that alterations in BDNF levels during early crack cocaine withdrawal are associated with number of crack rocks used in the last 30 d, years of crack use and length of inpatient treatment. In our sample, BDNF levels increased in early crack cocaine withdrawal, i.e. were lower at the time of admission when compared to hospital discharge and to the control group, even after controlling for confounding variables.

Our findings showed that serum BDNF levels indeed increase during crack cocaine withdrawal, but the extent of such increase seems to vary greatly across subjects. Variation patterns seem to be associated with severity of drug dependence: number of crack rocks and years

Table 2. Association between selected variables and increased BDNF levels during inpatient treatment of crack users

	n (%)	% increase BDNF$*	*p*
Depression or dysthymia			
Yes	30 (61.2)	28.2 (−1.3 to 53.3)	
No	19 (38.8)	33.0 (−11.5 to 42.2)	0.710
Alcohol use disorder			
Yes	17 (34.7)	10.3 (−10.3 to 52.9)	
No	32 (65.3)	36.0 (3.6 to 52.1)	0.294
Any anxiety disorder			
Yes	5 (10.2)	41.3 (35.5 to 47.8)	
No	44 (89.8)	17.1 (−4.4 to 52.1)	0.278
Attention deficit hyperactivity disorder			
Yes	12 (24.5)	25.2 (7.4 to 39.8)	
No	37 (75.5)	35.9 (−3.8 to 59.9)	0.710
Suicide risk			
Yes	19 (40.4)	16.9 (−8.0 to 38.4)	
No	30 (59.6)	36.1 (−0.9 to 82.9)	0.08
Antisocial personality disorder			
Yes	27 (55.1)	35.6 (−9.7 to 42.2)	
No	19 (40.4)	34.2 (−2.2 to 54.0)	0.795
Carbamazepine			
Yes	27 (55.1)	13.9 (−9.0 to 49.4)	
No	14 (28.6)	40.2 (14.2 to 57.2)	0.545
Topiramate			
Yes	4 (8.2)	11.7 (−0.3 to 35.8)	
No	37 (75.5)	35.4 (−2.9 to 53.6)	0.131
Valproate			
Yes	7 (14.3)	46.6 (41.3 to 164.0)	
No	34 (69.4)	15.0 (−6.0 to 43.3)	0.008
Antidepressants			
Yes	7 (14.3)	16.7 (−9.0 to 54.3)	
No	34 (69.4)	34.2 (−1.3 to 50.3)	0.678
Diazepam			
Yes	27 (55.1)	16.7 (−2.6 to 46.6)	
No	14 (28.6)	35.7 (3.9 to 63.7)	0.912
Chlorpromazine			
Yes	37 (75.5)	33.0 (−1.8 to 51.2)	
No	4 (8.2)	29.0 (−14.2 to 62.6)	1.00
Lithium			
Yes	7 (14.3)	35.0 (−24.5 to 41.3)	
No	34 (69.4)	25.2 (−1.3 to 53.3)	0.782
		Correlation with increased BDNF#	
Age	27.9±7.4**	−0.235	0.108
Body mass index	22.4±3.8**	0.114	0.446
Intelligence quotient	81.4±9.7	−0.241	0.110
Inpatient days	18.3±4.1**	0.362	0.01
Crack rocks used last month	120.0 (28.6–285.7)	−0.303	0.048
Years of crack use	6.0 (4.0 to 8.0)	−0.240	0.122
Days of marijuana use (last 30 days)	2.5 (0 to 28.8)	−0.019	0.900
Days of alcohol use (last 30 days)	2.0 (0 to 15.0)	0.107	0.475
Days of tobacco use (last 30 days)	30.0 (16.5 to 30.0)	−0.061	0.680

BDNF=brain-derived neurotrophic factor. $% increase BDNF=((BDNF at discharge – BDNF at admission)/BDNF at admission)×100. *Median (25th–75th percentiles). ** Mean±S.D. # Spearman correlation coefficient.

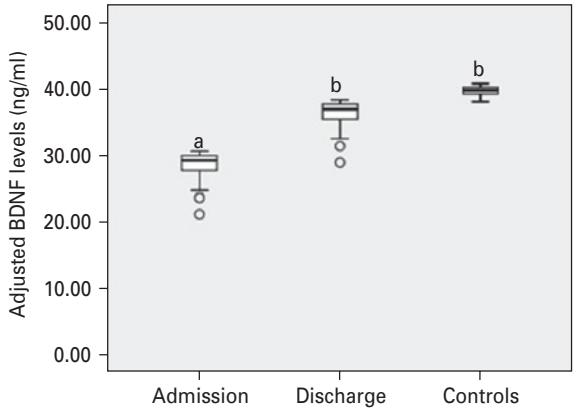

Fig. 2. Adjusted BDNF levels in crack users during inpatient treatment (at admission and discharge) and in controls *$p<0.001$ at admission *vs.* discharge **$p<0.001$ at admission *vs.* control and at discharge *vs.* control. Adjusted for length of inpatient treatment, age, number of crack rocks used in the last 30 d and years of crack use. Control group adjusted for age.

of use were inversely correlated with increased BDNF. These findings corroborate the increase in BDNF levels in early cocaine withdrawal reported by Corominas-Roso et al. (2012), but add to the currently available body of evidence by suggesting a key role of drug use pattern in this relationship. Also, our results are in line with studies involving alcohol-dependent subjects, which have reported increased BDNF levels after withdrawal as well as an association between the extent of increase and prognosis (Huang et al., 2008; Lee et al., 2009). Greater risk of cocaine relapse in subjects with higher BDNF levels (D'Sa et al., 2011) is inconsistent with our results and with findings reported for cocaine dependents (Corominas-Roso et al., 2012), alcohol dependents (Costa et al., 2011) and patients carrying other psychiatric disorders (Autry and Monteggia, 2012).

BDNF levels were found to be reduced in patients at the time of admission *vs.* discharge and *vs.* controls. This finding is in disagreement with a report describing similar BDNF levels between injecting cocaine users and control subjects (Angelucci et al., 2007), but is similar to the results reported by Corominas-Roso et al. (2012). Among methamphetamine abusers abstinent for a minimum of 30 d, one report found increased BDNF levels (Kim et al., 2005), whereas another study found a reduction (Chen et al., 2012). Taken together, these findings suggest that extremely complex mechanisms regulate the impact of stimulants on BDNF levels.

Psychiatric comorbidities, especially mood disorders, were frequent in our sample. Notwithstanding, we do not believe that this has had a significant impact on the changes in BDNF levels observed during withdrawal. First, changes in BDNF levels were not associated with psychiatric disorders in the bivariate analysis. Second, only seven patients were under treatment with antidepressants. Third, the prevalence of these disorders may have been overestimated, as some cocaine withdrawal symptoms may confound a correct diagnosis.

Animal studies have shown that BDNF levels have an important role in cocaine addiction, craving, sensitization, and relapse (Graham et al., 2007; Bahi et al., 2008). Exogenous BDNF infusion can enhance cocaine seeking behaviour when injected in the ventral tegmental area (Lu et al., 2004) or suppress it when injected in the prefrontal cortex (Whitfield et al., 2011). In humans, BDNF levels may be increased or reduced in different brain areas, and it has been suggested that the frequency and amount of cocaine use could impact results (Filip et al., 2006; Fumagalli et al., 2007). Thus, the apparently inconsistent data found in the literature could be the result of serum BDNF levels reflecting its expression from different brain areas, in addition to differences in the type, frequency and amount of drug used and psychiatric comorbidities diagnosed. Also, some other studies have investigated the association between brain and peripheral BDNF levels, and have found a strong correlation between both measures (Rasmussen et al., 2009; Sartorius et al., 2009; Klein et al., 2010).

In this scenario, the allostatic load theory emerges as a useful tool to help elucidate these divergent results, and should, therefore, be investigated in future studies. The theory was initially proposed by McEwen to explain adaptations that take place in the body and brain in response to stressors, working as a protection mechanism in the short term (allostasis), but causing changes that may lead to disease in the long run (allostatic load) (McEwen, 1998). The fundamentals of the allostatic load theory have been translated into psychiatry and have helped achieve a better understanding of psychiatric diseases (Kapczinski et al., 2008), including addiction (George et al., 2012). Cocaine produces a widespread but transient induction of BDNF protein expression in many brain areas related to addiction and reward (Fumagalli et al., 2007; Graham et al., 2007). This response could be deregulated as a result of chronic exposure to cocaine, aggravated by factors such as compulsive drug use, psychiatric comorbidities, abuse of other drugs, genetic vulnerability and others. Our data support this theory, since we observed great variability in basal and delta BDNF levels and an inverse correlation between these levels and number of crack rocks used in the last 30 d and years of crack use. Further studies are warranted to further explore and confirm these findings.

One strength of our study is that we used a community control sample with demographic characteristics similar to those of the clinical sample. Controls lived in poor areas, marked by high violence rates and probably submitted to similar life stressors, except for crack use. Conversely, among the limitations of our study is the fact that we evaluated only male patients, preventing the extrapolation of our findings to females. Also, whereas all crack users used medications while hospitalized, no information on the use of medications was

available for this group before inpatient treatment or for the control group.

There is a growing body of evidence suggesting that BDNF is strongly implicated in drug craving, severity of withdrawal and drug addiction and prognosis. A caveat in drug addiction treatment, especially among crack cocaine users, is the lack of efficacy of the behavioural and pharmacological treatments currently available (Henskens et al., 2008; Dias et al., 2011). Biomarkers could help tailor individualized treatments and thus improve treatment outcomes, and BDNF seems to be a promising candidate in this regard (Mendelson et al., 2011). Further studies are warranted to explore in more detail the clinical correlates of BDNF levels and BDNF response to drug use and withdrawal.

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Statement of Interest

None.

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