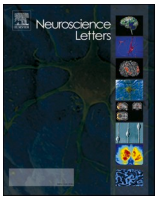
Neuroscience Letters 786 (2022) 136805

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Impact of sleep disorders and disease duration on neurotrophins levels in cocaine use disorder

Andrea Miuli [a,b], Gianluca Mancusi [b], Mauro Pettorruso [a,b,*], Francesco Di Carlo [b], Katia Clemente [c], Ilenia Di Meo [c], Antea D'Andrea [b], Giulia Pernaci [b], Teresa Di Crosta [b], Giacomo d'Andrea [b], Giovanna Bubbico [b,e], Giovanni Martinotti [b,d], Massimo di Giannantonio [a,b]

[a] Department of Mental Health, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy
[b] Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
[c] Unit of Clinical Pathology, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy
[d] Department of Pharmacy, Pharmacology, Clinical Science, University of Hertfordshire, Herts, UK
[e] Department of Neurology, University of California Irvine, US

ARTICLE INFO

Keywords:
BDNF
proBDNF
Neurotrophins
Cocaine use disorder
Insomnia, sleep disturbances

ABSTRACT

Introduction: Brain-derived neurotrophic factor (BDNF) and its precursor proBDNF contribute to brain plasticity and neuronal remodeling. Recently, the ratio between proBDNF and BDNF (RpB) has been proposed as a possible marker in major psychiatric disorders. Convergent lines of evidence suggest neurotrophins alterations could be involved into the pathophysiology of Cocaine Use Disorder (CUD) and insomnia. The aims of the present study are to evaluate the correlations between neurotrophins levels, insomnia and clinical features among CUD patients.

Materials and methods: Subjects with a moderate to severe CUD were recruited. ProBDNF, BDNF and consequently RpB values were analyzed using ELISA technique. Insomnia severity index (ISI) scale was used to assess the severity of insomnia. Sociodemographic characteristics and CUD habits (e.g., years of cocaine use) were also collected.

Results: Twenty-four subjects (mean age 39.3 ± 6.7 years) were recruited. Correlation analysis showed that lower values of RpB were associated with higher ISI score ($r = -0.469$; $p = 0.021$), longer history of cocaine use ($r = -0.584$, $p = 0.022$) and higher amount of cocaine used ($r = -0.655$, $p = 0.004$).

Discussion: These preliminary findings may offer a novel insight on neurobiological alterations sustaining cocaine use. Lower RpB, as observed both in high insomnia levels and in chronic cocaine use, could induce a neuroprotective state as a synaptic homeostatic response to chronic damage. These findings also highlight the important role of neurotrophins balance on neurobiological alterations induced by cocaine misuse and insomnia, suggesting that RpB could be considered as a marker of neurotrophic and metabolic state of neural tissue.

1. Introduction

The protein brain-derived neurotrophic factor (BDNF) is a member of the neurotrophins family of nerve growth factors. Through the pre-synaptic and post-synaptic binding to TrkB receptors, BDNF activates several intracellular pathways [1] which induces dendritic growth and branching, adaptation to stress, and synaptic plasticity [2,3]. BDNF is synthesized starting from its precursor proBDNF, produced by neurons, and stored in secretory vesicles in the pre-synaptic button. ProBDNF serves mainly as a reserve for the mature molecule, but recent studies have revealed an independent biological effect mediated by its link with the $p75_{NTR}$ receptor contributing to the mechanisms of brain plasticity and neuronal remodeling through processes of apoptosis and elimination of damaged, malfunctioning or ineffective neurons [3]. The BDNF-mediated mechanisms of synaptic plasticity and neuromodulation-mediated underpin the pathophysiological processes involved in various psychiatric disorders, including Substance Use Disorders (SUDs). In particular, it has been proposed that BDNF plays a central role in SUDs neural and behavioral adaptations [4]. In this context, the cocaine use enhances the BDNF synaptic production in the nucleus

* Corresponding author at: Department of Neuroscience, Imaging and Clinical Sciences, via dei Vestini, 30 – Chieti, Italy.
E-mail addresses: mauro.pettorruso@hotmail.it, mauro.pettorruso@unich.it (M. Pettorruso).

https://doi.org/10.1016/j.neulet.2022.136805
Received 26 April 2022; Received in revised form 12 July 2022; Accepted 12 July 2022
Available online 16 July 2022

accumbens [5], increasing the neurotrophic factors bioavailability. This condition modifies neuronal connections and the functioning of synapses in the short and long term, inducing adaptive mechanisms such as tolerance, withdrawal and behavioral sensitization [6].

Beside the well-investigated role of BDNF in cocaine seeking behaviors in preclinical settings [7], addiction-related variations in serum BDNF levels in subjects with Cocaine Use Disorder (CUD) have been found. Accordingly, it has been proposed BDNF may represent a possible phase-specific biomarker of brain plasticity in this disorder [8]. In fact, a transient increase in BDNF levels has been observed after acute withdrawal. Proportionally with the progression toward chronic addiction pattern, BDNF levels persistently decrease down to the levels of healthy subjects, and below [9]. Moreover, the magnitude of abstinence-related progressive increase of BDNF levels seems to be associated with CUD severity [10], and greater neurotrophins peaks have been proposed to be predictive of relapse in substance use [11]. A work of Corominas-Roso and coll. in 2015 conducted in abstinent CUD subjects explored and confirmed the role of BDNF in relapse to cocaine use, although the underlying neurobiological mechanisms have yet to be elucidated [12].

Some evidences in literature show that some of the neurotrophic deficiencies that characterize schizophrenia and psychosis have also been observed in patients with cocaine-induced psychosis (CIP) who had reduced BDNF levels during a CIP episode [13]. This finding suggests that BDNF plays a role in the transient psychotic symptoms associated with cocaine use [14]; however, studies assessing BDNF involvement in CIP are lacking.

In contrast, to date very little is known about proBDNF role in CUD. ProBDNF and BDNF seem to have opposite, counteracting functions for the maintenance of neuronal cells homeostasis. Furthermore, proBDNF acts as a reserve for mature neurotrophins, but its activation undergoes complex and finely regulated biochemical processes. Recently, research is focusing attention on the proBDNF/BDNF ratio (RpB) as a possible marker of brain neuroplasticity state in psychiatric disorders [15]. Neurotrophins alterations have been observed in many stress-related diseases [16] and in conditions like sleep deprivation and insomnia, which determine chronic stress and the reduction of basal BDNF levels [17]. Interestingly, CUD clinical course is associated with sleep disorders [18], therefore depicting a complex interaction of different neurobiological factors influencing neurotrophins.

There are studies that have examined the interaction between cocaine use and sleep disturbance, however, this relationship remains unclear. A recent review by Bjorness and Greene examined the disturbing influence of cocaine on sleep behavior and the influence of sleep disturbances on reward seeking. We know that the misuse of substances such as cocaine induce acute sleep loss followed by an immediate recovery pattern that is consistent with the normal sleep loss response. Under conditions of chronic cocaine exposure, an abnormal recovery pattern occurs that includes the maintenance of sleep disturbances under abstinent conditions. In contrast, experimentally induced sleep disturbances may increase cocaine seeking; in fact, it has been shown that these sleep disturbances enhance the rewarding properties of cocaine [19]. Therefore, it is expected that treatment of sleep disorders may reduce the risk of relapse. Another study by Hodges et al. shows an interesting phenomenon that has been termed “occult insomnia,” in which during abstinence chronic cocaine users experience an objective worsening of sleep that is perceived as qualitatively better. Perhaps it is not surprising that the misperception of a positive sleep state is associated with chronic cocaine use, if it turns out to be characteristic of any disease or disorder [20].

The primary outcome of the present study was to estimate correlations between insomnia and neurotrophins values and metabolism in a clinical sample of CUD patients. The secondary outcome was to estimate correlation between neurotrophins values and different clinical features of cocaine use, thus investigating the role and reliability of RpB as a possible marker of pathology.

2. Materials and methods

2.1. Design and participants

This is an exploratory correlation study. Each part of the study (ideation, planning, development, recruitment, laboratoristic analysis and data analysis) took place at SS. Annunziata Hospital in Chieti, Abruzzo, Italy. Subjects diagnosed with CUD were recruited on voluntary basis from March 2019 to August 2020. All enrolled subjects were treatment-seeking patients, which responded to advertisements for participating to the Brainswitch project, a double-blind, sham-controlled, repetitive transcranial magnetic stimulation-based protocol to reduce cocaine craving and use in CUD [21,22]. The inclusion criteria were: age 18–65; diagnosis of moderate to severe CUD (DSM-5 criteria); abstinence from cocaine for at least 48 h; no current use of pro-convulsive drugs; absence of epileptic episodes in anamnesis [23]; for female patients: no pregnancy/lactation.

2.2. Procedures

All the enrolled patients underwent a detailed structured anamnestic interview with psychometric assessment conducted by a trained psychiatrist at Psychiatric Unit of SS. Annunziata Hospital in Chieti. Then, subjects underwent the evaluation of neurotrophins. Correlations between neurotrophins values, psychometric scores and different clinical features of cocaine use (age of onset, amount of cocaine used on a monthly basis, frequency of cocaine use, previous maximum period of abstinence) were finally calculated.

2.3. Measures

a) Anamnestic and psychometric assessment.

The anamnestic form investigated sociodemographic information (age, employment and family status), previous psychiatric history (presence of a psychiatric diagnosis, current psychopharmacological treatment, cigarette smoking, alcohol and other substance use), and CUD clinical features: age of onset, amount of cocaine use (grams per month), frequency of cocaine use (days per month), previous maximum period of abstinence, failures related to cocaine use, polydrug abuse.

Psychometric assessment included the Insomnia Severity Index (ISI) and the Montgomery-Asberg Depression Rating Scale (MADRS). ISI is a self-administered 7-items questionnaire assessing clinical characteristics and severity of insomnia and its impact on daily life, considering the last month period. Answers range from 0 to 4, and they are added up to get a total score, representing insomnia categories: no clinically significant insomnia (from 0 to 7), subthreshold insomnia (from 8 to 14), moderate clinical insomnia (from 15 to 21) and severe clinical insomnia (from 22 to 28) [24]. MADRS is a ten-item clinician-administered questionnaire assessing severity of depressive symptomatology. Usual cut-offs are symptom absent (from 0 to 6), mild depression (from 7 to 19), moderate depression (from 20 to 34) and severe depression (>34) [25].

b) Laboratory tests.

Evaluations of proBDNF and BDNF values were performed through the collection of venous blood samples. The blood samples were centrifuged at 1000×g for 15 min within two hours of collection, rated and frozen inside the unit of Clinical Pathology of SS. Annunziata Hospital in Chieti. Serum levels of proBDNF and BDNF were detected using the Enzyme-Linked ImmunoSorbent Assay (ELISA) technique performed on plates with 96 pre-coated wells with highly specific monoclonal antibodies. The BDNF-ELISA kit was coated with specific murine monoclonal anti-BDNF antibodies. The human proBDNF-ELISA kit was coated with anti-proBDNF antibodies. Following the addition of serum in the wells, the desired neurotrophin greedily binds to the specific antibody and biotinylated antibodies were used for its detection. Horseradish peroxidase (HRP) conjugated to streptavidin was added to the solution, which binds to the solid phase by the biotin-streptavidin bond. The

samples were then incubated, and the unbound conjugates were washed off. Finally, the substrate 3,3′,5,5′-tetramethylbenzydine (TMB) was added to the solution, which undergoes an enzymatic reaction catalyzed by HRP from which a blue color was produced that turns yellow after adding an acid stop solution. The signal strength was measured on a reader at 450 nm and was quantitatively proportional to the amount of BDNF or proBDNF captured in the well. BDNF values were quantified in relation to a standard curve calibrated with a known amount of protein. The detection limit was 2 pg/mL. Measurements were performed in duplicate and expressed in pg/mL. ProBDNF values were quantified in relation to a standard curve calibrated with a known amount of protein. The detection limit was 0.094 ng/mL. No cross-reactivity or significant interference was observed between BDNF, proBDNF and other neurotrophins.

2.4. Ethics

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki of 2013, and it was approved by the Ethics Committee of the "G. d'Annunzio" University of Chieti-Pescara. All the subjects signed a written informed consent, and all data have been treated confidentially and anonymously. Each recruited subject was assigned a unique code that cannot be directly linked to the patient's identity; only the personal code was used for the collection and management of the data.

2.5. Statistical analysis

SPSS software for Windows v.26.0 was used for the analysis. Frequencies were reported as a value and percentage, while continuous variables were reported as mean ± standard deviation (SD). Data were tested for normality using Shapiro-Wilk test, and a non-parametric analysis was performed. Correlations were assessed by using 2-tailed Spearman rank correlation coefficient. Significance was set at $p < 0.05$.

3. Results

3.1. Descriptive analysis of the sample

Twenty-four Caucasian subjects with diagnosis of CUD (DSM-5 criteria) were recruited for this study. Mean age was 39.3 ± 6.7 years; twenty-three (97 %) were male. Eight subjects (36.4 %) were following psychopharmacological treatment, mainly with antipsychotics (n = 3; 13.6 %; Olanzapine and Aripiprazole), mood stabilizers (n = 2; 9.1 %), benzodiazepines (n = 2; 9.1 %; Alprazolam), antidepressant (n = 4; 17.4 %; (Paroxetine, Trazodone, Vortioxetine, Buproprion) and methadone (n = 2; 9.1 %), either in monotherapy or in combined therapy. Three (13.6 %) subjects experienced almost one hospitalization in a psychiatric ward and nine (39.1 %) received a psychiatric diagnosis other than CUD lifetime.

Twenty-one subjects (95.5 %) used cocaine snorting, and five (23.8 %) smoked crack crystals. The mean dose of cocaine used was 17.3 ± 21.2 g per month, with a mean frequency of 18.8 ± 11.2 days of use per month. In association with cocaine consumption, nineteen subjects (86.4 %) occasionally used alcohol, eleven (50 %) people occasionally smoked cannabis and three (13.6 %) people occasionally used heroin.

Detailed information about cocaine use patterns, neurotrophins serum levels (BDNF, proBDNF and RpB), ISI and MADRS scores are reported in Table 1.

3.2. Primary outcome: correlation analysis between neurotrophins and insomnia

Correlations between neurotrophins values, ISI scores and MADRS scores were calculated. ISI scores showed a negative correlation with RpB (r = -0.469; p = 0.021). Correlation analysis is detailed in Table 2.

Table 1
Cocaine use pattern, laboratory and psychometric results.

Cocaine use patterns		
	Mean	**SD**
Cocaine grams/month	17.3	21.2
Days of use/month	18.8	11.2
Years of use	14.6	7.3
Age at first use	22.3	6.9
Longer abstinence period (days)	296.1	627.4
Neurotrophins analysis		
	Mean	**SD**
BDNF	18.57	7.11
proBDNF	87.85	34.98
RpB	0.00458	0.00081
Psychometric assessment		
	Mean	**SD**
MADRS	10.5	9
ISI	7.5	4.3

BDNF and proBDNF: expressed in pg/ml. ISI: Insomnia Severity Index. MADRS: Montgomery-Asberg Depression Rating Scale.

Table 2
Correlations between psychometric scales and neurotrophins values.

		BDNF	**proBDNF**	**RpB**
ISI	r	0.051	−0.040	**−0.469**
	p	0.814	0.854	**0.021**
MADRS	r	0.111	0.069	−0.215
	p	0.614	0.753	0.325

Statistic: Spearman correlation coefficient. ISI: Insomnia Severity Index. MADRS: Montgomery-Asberg Depression Rating Scale.

3.3. Secondary outcome: correlation analysis of neurotrophins and features of cocaine use

Correlations between neurotrophins values and clinical features of cocaine use were calculated. Both grams of cocaine used per month and total years of cocaine use showed negative correlations with RpB (r = −0.655, p = 0.004; r = −0.584, p = 0.022). Correlation analysis is detailed in Table 3.

4. Discussion

Increasing evidence highlights the preeminent role of BDNF in stress-related diseases and insomnia. However, little is known about alterations occurring in proBDNF blood concentration, as well as about the potential role of RpB imbalance. To our knowledge, this study represents

Table 3
Correlations between clinical features of cocaine use and neurotrophins values.

		BDNF	**proBDNF**	**RpB**
Age (years)	r	−0.147	−0.201	−0.289
	p	0.493	0.347	0.170
Grams/month	r	0.021	−0.073	**−0.655**
	p	0.936	0.782	**0.004**
Days of use/month	r	−0.171	−0.324	−0.326
	p	0.513	0.205	0.201
Years of use	r	0.346	0.262	**−0.584**
	p	0.207	0.346	**0.022**
Age at first use	r	0.151	0.264	0.115
	p	0.592	0.342	0.684
Longer abstinence period (days)	r	0.047	0.017	−0.064
	p	0.879	0.957	0.836

Statistic: Spearman correlation coefficient.

the first exploration of the relationships between neurotrophins alterations and insomnia in CUD. Other studies evidenced a significant reduction of BDNF blood concentration in relation to insomnia severity, thus hypothesizing BDNF could be investigated as an insomnia severity marker [17,26]. Interestingly, we reported a significant alteration in RpB in CUD subjects with more severe insomnia. Despite the absence of significant differences in absolute neurotrophins levels, subjects without insomnia showed a neurotrophins ratio imbalanced towards proBDNF. In contrast, in CUD subjects with higher insomnia, a BDNF-imbalanced RpB has been reported. These findings are novel and may be interpreted considering the complex, modulating neurotrophins role.

Presynaptic proBDNF pools represent the main source of bioavailability of BDNF; it is synthetized and stocked into vesicles in presynaptic boutons, waiting for specific extracellular stimuli to be processed to mature BDNF [27]. A possible explanation to RpB moving towards BDNF in higher insomnia levels could be the pathophysiological attempt to increase synaptic BDNF levels in response to chronic neurobiological damage induced by sleep deprivation. This could occur increasing metabolic processes of conversion of proBDNF into mature BDNF. Considering the chronic BDNF decrease associated to insomnia [28], enhancing in maturation speed could be a response to the needing of re-elevate BDNF levels in brain tissue by utilizing available proBDNF presynaptic reservoir, thus raising synaptic BDNF levels. These results support the hypothesis that RpB could be investigated as an insomnia severity marker in CUD patients.

This study also highlighted interesting negative correlations between RpB and both years of cocaine use and total amount of cocaine used per month. It has already been observed that absolute blood levels of BDNF tend to decrease during chronic cocaine abuse [29] and, more specifically, the more years of cocaine use, the less BDNF increases during early abstinence and lower blood neurotrophins levels will be observed after cocaine withdrawal [30]. This study observed that, independently from absolute neurotrophins values, novel cocaine users have a RpB balanced in favor of proBDNF, indicating a bigger precursor bioavailability, while years of use cause this ratio to switch towards the mature neurotrophin, showing a slow and progressive depletion of proBDNF. Other studies observed that neurobiological damage caused by chronic cocaine use triggers a BDNF production as neuroprotective response of brain tissue [31]. A possible interpretation of concomitant RpB decrement observed in this study could be the increase of proBDNF maturational processes, obtained through positive regulation of BDNF metabolism, in the attempt to induce a state of neuroprotection.

Moreover, this study contributes to emphasize the potential role of the ratio between proBDNF and BDNF as a marker of neural tissue physiological state. To date, an increase in RpB has been observed to be associated to neuronal negative regulation mechanisms and to a reduction of LTP phenomenon, correlating with lower cognitive performances in mild cognitive impairment [15]. This mechanism is triggered by the prevalence of negative neuroplastic effects of proBDNF against BDNF. This study suggested that a lower RpB, as observed both in high insomnia levels and in chronic cocaine use, could be considered as an indicator of a neuroprotective state induced by the synaptic homeostatic response to chronic damage.

Modulation in RpB has been also observed during different phases of neural development: during first years of life neurotrophins balance leans toward proBDNF, while in adulthood BNDF is prevalent [32]. However, specific changes of RpB during aging has not yet been observed, while it is known that BDNF tends to be lower in older people. This study did not reveal any significant relationship between age and RpB, suggesting that neurotrophins alterations determined by CUD and insomnia could have a deeper impact compared to aging.

Finally, in previous literature BDNF modulation has been proposed as a possible therapeutic strategy in reducing addiction-related behaviours [8,33] allowing not only the “symptomatic” treatment of craving and other psychopathological alterations typical of CUD, but being able to treat in a more deep way the neurobiological alterations related to CUD. It can be speculated a better understanding about neurotrophins metabolism by RpB examination could provide new therapeutic tools in insomnia management and CUD-related behaviours.

The main limitation of our study is represented by the small sample size. Therefore, the results are preliminary, and they need further confirmation in larger sample. Moreover, previous studies reported alterations in neurotrophins levels of CUD patients, which could have influenced the insomnia-related outcome. It should be considered that some of the recruited subjects were assuming drugs of different groups during the study, and these could have influenced BDNF and proBDNF levels in unpredictable manner. This could represent a limitation to this study, being difficult to determine the effect of drugs interaction with neurotrophins. Finally, the observation of insomnia only in the last month (ISI scale) could be a limitation in the discussion of the results obtained.

5. Conclusions

The results of our study highlight the pivotal role of neurotrophins balance and metabolism on the neurobiological alterations induced by cocaine use and insomnia. In particular, we suggest that RpB could be considered as a valuable marker of neurotrophic and metabolic state of neural tissue in CUD. It could also provide a better understanding of complex, multi-factorial, pathophysiological processes underlying insomnia. To date, proBDNF/BDNF ratio is a promising but still poorly known neurobiological indicator, and it appears necessary that its relations to different behavioral and psychiatric diseases should be further investigated. Integrating proBDNF/BDNF ratio analysis as a disease-related biomarker may contribute to improve the accuracy and the outcome in the management of CUD clinical course, possibly integrating conventional therapies with innovative interventions directed to neurotrophins modulations [8,33].

Funding

None.

CRediT authorship contribution statement

Andrea Miuli: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Visualization, Project administration. **Gianluca Mancusi:** Formal analysis, Investigation, Data curation, Writing – original draft. **Mauro Pettorruso:** Conceptualization, Methodology, Writing – review & editing, Project administration. **Francesco Di Carlo:** Formal analysis, Data curation. **Katia Clemente:** Resources, Data curation, Writing – original draft. **Ilenia Di Meo:** Resources, Data curation. **Antea D’Andrea:** Investigation, Writing – original draft. **Giulia Pernaci:** Data curation, Writing – original draft. **Teresa Di Crosta:** Data curation, Writing – original draft. **Giacomo d’Andrea:** Investigation, Data curation. **Giovanna Bubbico:** Writing – review & editing, Visualization. **Giovanni Martinotti:** Visualization, Supervision, Project administration. **Massimo di Giannantonio:** Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

References

[1] H. Fang, J. Chartier, C. Sodja, A. Desbois, M. Ribecco-Lutkiewicz, P.R. Walker, M. Sikorska, Transcriptional activation of the human brain-derived neurotrophic factor gene promoter III by dopamine signaling in NT2/N neurons, J. Biol. Chem. 278 (2003) 26401–26409, https://doi.org/10.1074/jbc.M211539200.

[2] D.R. Kaplan, F.D. Miller, Signal transduction by the neurotrophin receptors, Curr. Opin. Cell Biol. 9 (1997) 213–221, https://doi.org/10.1016/s0955-0674(97)80065-8.

[3] P. Kowiański, G. Lietzau, E. Czuba, M. Waśkow, A. Steliga, J. Moryś, BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity, CellMol. Neurobiol. 38 (2018) 579–593, https://doi.org/10.1007/s10571-017-0510-4.

[4] J.W. Grimm, L. Lu, T. Hayashi, B.T. Hope, T.-P. Su, Y. Shaham, Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving, J. Neurosci. 23 (2003) 742–747, https://doi.org/10.1523/JNEUROSCI.23-03-00742.2003.

[5] F.E. Pontieri, G. Tanda, F. Orzi, G. Di Chiara, Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs, Nature 382 (1996) 255–257, https://doi.org/10.1038/382255a0.

[6] G. Schoenbaum, T.A. Stalnaker, Y. Shaham, A role for BDNF in cocaine reward and relapse, Nat. Neurosci. 10 (2007) 935–936, https://doi.org/10.1038/nn0807-935.

[7] G. Sadri-Vakili, V. Kumaresan, H.D. Schmidt, K.R. Famous, P. Chawla, F. M. Vassoler, R.P. Overland, E. Xia, C.E. Bass, E.F. Terwilliger, R.C. Pierce, J.-H.-J. Cha, Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine, J. Neurosci. 30 (2010) 11735–11744, https://doi.org/10.1523/JNEUROSCI.2328-10.2010.

[8] A. Miuli, G. d'Andrea, M. Pettorruso, G. Mancusi, A. Mosca, F. Di Carlo, G. Martinotti, M. di Giannantonio, From a cycle to a period: the potential role of BDNF as plasticity and phase-specific biomarker in cocaine use disorder, Curr. Neuropharmacol. (2022), https://doi.org/10.2174/1570159X20666220114152052.

[9] F. Angelucci, V. Ricci, M. Pomponi, G. Conte, A.A. Mathé, P. Attilio Tonali, P. Bria, Chronic heroin and cocaine abuse is associated with decreased serum concentrations of the nerve growth factor and brain-derived neurotrophic factor, J Psychopharmacol. 21 (2007) 820–825, https://doi.org/10.1177/0269881107078491.

[10] M. Corominas-Roso, C. Roncero, F.J. Eiroa-Orosa, B. Gonzalvo, L. Grau-Lopez, M. Ribases, L. Rodriguez-Cintas, C. Sánchez-Mora, J.-A. Ramos-Quiroga, M. Casas, Brain-derived neurotrophic factor serum levels in cocaine-dependent patients during early abstinence, Eur. Neuropsychopharmacol. 23 (2013) 1078–1084, https://doi.org/10.1016/j.euroneuro.2012.08.016.

[11] C. D'Sa, H.C. Fox, A.K. Hong, R.J. Dileone, R. Sinha, Increased serum brain-derived neurotrophic factor is predictive of cocaine relapse outcomes: a prospective study, Biol. Psychiatry 70 (2011) 706–711, https://doi.org/10.1016/j.biopsych.2011.05.013.

[12] M. Corominas-Roso, C. Roncero, C. Daigre, L. Grau-Lopez, E. Ros-Cucurull, L. Rodríguez-Cintas, C. Sanchez-Mora, M.V. Lopez, M. Ribases, M. Casas, Changes in brain-derived neurotrophic factor (BDNF) during abstinence could be associated with relapse in cocaine-dependent patients, Psychiatry Res. 225 (2015) 309–314, https://doi.org/10.1016/j.psychres.2014.12.019.

[13] C. Roncero, R.F. Palma-Álvarez, E. Ros-Cucurull, C. Barral, B. Gonzalvo, M. Corominas-Roso, M. Casas, L. Grau-López, Cocaine-induced psychosis and brain-derived neurothrophic factor in patients with cocaine dependence: report of two cases, Clin. Psychopharmacol. Neurosci. 14 (2016) 109–113, https://doi.org/10.9758/cpn.2016.14.1.109.

[14] M. Corominas-Roso, C. Roncero, F.-J. Eiroa-Orosa, M. Ribasés, C. Barral, C. Daigre, N. Martínez-Luna, C. Sánchez-Mora, J.A. Ramos-Quiroga, M. Casas, Serum brain-derived neurotrophic factor levels and cocaine-induced transient psychotic symptoms, Neuropsychobiology 68 (2013) 146–155, https://doi.org/10.1159/000353259.

[15] K. Cechova, F. Angelucci, H. Markova, T. Nikolai, V. Matuskova, J. Laczó, Z. Nedelska, M. Vyhnalek, J. Hort, Ratio of serum proBDNF to BDNF and its association with cognitive performance and brain morphometry in mild cognitive impairment, Alzheimer's & Dementia. 16 (2020) e046340. https://doi.org/10.1002/alz.046340.

[16] G. Martinotti, G. Sepede, M. Brunetti, V. Ricci, F. Gambi, E. Chillemi, F. Vellante, M. Signorelli, M. Pettorruso, L. De Risio, E. Aguglia, F. Angelucci, C. Caltagirone, M. Di Giannantonio, BDNF concentration and impulsiveness level in post-traumatic stress disorder, Psychiatry Res. 229 (2015) 814–818, https://doi.org/10.1016/j.psychres.2015.07.085.

[17] M. Giese, E. Unternährer, H. Hüttig, J. Beck, S. Brand, P. Calabrese, E. Holsboer-Trachsler, A. Eckert, BDNF: an indicator of insomnia? Mol. Psychiatry 19 (2014) 151–152, https://doi.org/10.1038/mp.2013.10.

[18] G.A. Angarita, N. Emadi, S. Hodges, P.T. Morgan, Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review, Add. Sci. Clin. Practice 11 (2016) 9, https://doi.org/10.1186/s13722-016-0056-7.

[19] T.E. Bjorness, R.W. Greene, Sleep deprivation enhances cocaine conditioned place preference in an orexin receptor-modulated manner, ENeuro 7 (6) (2020), https://doi.org/10.1523/ENEURO.0283-20.2020.

[20] S.E. Hodges, B. Pittman, P.T. Morgan, Sleep perception and misperception in chronic cocaine users during abstinence, Sleep 40 (2017), https://doi.org/10.1093/sleep/zsw069.

[21] G. Martinotti, M. Pettorruso, C. Montemitro, P.A. Spagnolo, C. Acuti Martellucci, F. Di Carlo, F. Fanella, M. di Giannantonio, Repetitive transcranial magnetic stimulation in treatment-seeking subjects with cocaine use disorder: a randomized, double-blind, sham-controlled trial, Prog. Neuropsychopharmacol. Biol. Psychiatry 116 (2022), 110513, https://doi.org/10.1016/j.pnpbp.2022.110513.

[22] M. Pettorruso, G. Martinotti, C. Montemitro, A. Miuli, M.C. Spano, M. Lorusso, F. Vellante, M. di Giannantonio, Craving and other transdiagnostic dimensions in addiction: toward personalized neuromodulation treatments., J ECT. 36 (2020) e8. https://doi.org/10.1097/YCT.0000000000000643.

[23] M. Pettorruso, G. Martinotti, R. Santacroce, C. Montemitro, F. Fanella, M. di Giannantonio, rTMS reduces psychopathological burden and cocaine consumption in treatment-seeking subjects with cocaine use disorder: an open label, feasibility study, Front. Psychiatry 10 (2019) 621, https://doi.org/10.3389/fpsyt.2019.00621.

[24] C.M. Morin, G. Belleville, L. Bélanger, H. Ivers, The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response, Sleep 34 (2011) 601–608, https://doi.org/10.1093/sleep/34.5.601.

[25] S.A. Montgomery, M. Asberg, A new depression scale designed to be sensitive to change, Br. J. Psychiatry 134 (1979) 382–389, https://doi.org/10.1192/BJP.134.4.382.

[26] T.-T. Fan, W.-H. Chen, L. Shi, X. Lin, S. Tabarak, S.-J. Chen, J.-Y. Que, Y.-P. Bao, X.-D. Tang, J. Shi, L. Lu, H.-Q. Sun, J.J. Liu, Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role, Sleep 42 (2019), https://doi.org/10.1093/sleep/zsy192.

[27] Y.-C. Wu, R. Williamson, Z. Li, A. Vicario, J. Xu, M. Kasai, Y. Chern, E. Tongiorgi, J. M. Baraban, Dendritic trafficking of brain-derived neurotrophic factor mRNA: regulation by translin-dependent and -independent mechanisms, J. Neurochem. 116 (2011) 1112–1121, https://doi.org/10.1111/j.1471-4159.2010.07166.x.

[28] K. Schmitt, E. Holsboer-Trachsler, A. Eckert, BDNF in sleep, insomnia, and sleep deprivation, Ann. Med. 48 (2016) 42–51, https://doi.org/10.3109/07853890.2015.1131327.

[29] T.G. Pianca, R.L. Rosa, K.M.M. Ceresér, B.W. de Aguiar, R.C. de Abrahão, P. M. Lazzari, F. Kapczinski, F. Pechansky, L.A. Rohde, C.M. Szobot, Differences in biomarkers of crack-cocaine adolescent users before/after abstinence, Drug Alcohol Depend. 177 (2017) 207–213, https://doi.org/10.1016/j.drugalcdep.2017.03.043.

[30] L. von Diemen, F. Kapczinski, A.O. Sordi, J.C. de Magalhães Narvaez, L.S. P. Guimarães, F.H.P. Kessler, B. Pfaffenseller, B.W. de Aguiar, C. de Moura Gubert, F. Pechansky, Increase in brain-derived neurotrophic factor expression in early crack cocaine withdrawal, Int. J. Neuropsychopharmacol. 17 (2014) 33–40, https://doi.org/10.1017/S146114571300103X.

[31] I. Riezzo, C. Fiore, D. De Carlo, N. Pascale, M. Neri, E. Turillazzi, V. Fineschi, Side effects of cocaine abuse: multiorgan toxicity and pathological consequences, Curr. Med. Chem. 19 (2012) 5624–5646, https://doi.org/10.2174/092986712803988893.

[32] J. Yang, C.-J. Siao, G. Nagappan, T. Marinic, D. Jing, K. McGrath, Z.-Y. Chen, W. Mark, L. Tessarollo, F.S. Lee, B. Lu, B.L. Hempstead, Neuronal release of proBDNF, Nat. Neurosci. 12 (2009) 113–115, https://doi.org/10.1038/nn.2244.

[33] M. Corominas, C. Roncero, M. Ribases, X. Castells, M. Casas, Brain-derived neurotrophic factor and its intracellular signaling pathways in cocaine addiction, Neuropsychobiology 55 (2007) 2–13, https://doi.org/10.1159/000103570.