ORIGINAL ARTICLE

Inhibitory control failures and blunted cortisol response to psychosocial stress in amphetamine consumers after 6 months of abstinence

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Background: Amphetamine abuse has been conceived as an addictive illness where stress regulation and inhibitory control may be crucial factors determining chronicity and relapse. Since amphetamine consumption may disrupt the cerebral systems regulating inhibition and stress behaviors, deregulation on these systems may be expected even after long-term abstinence periods. The present study aimed to evaluate the ability of abstinent amphetamine consumers to regulate stress parameters and to inhibit cognitive patterns under the acute trier social stress test (TSST) paradigm. **Materials and Methods:** A cohort study was conducted in a sample of 44 young individuals (average age: 24.6 years). The sample included 22 amphetamine consumers recruited from an addiction treatment center and 22 healthy nonconsumers belonging to the same sociodemographic conditions. Both groups were exposed to the TSST once the consumers completed 6 months in abstinence. To evaluate stress reactivity, we collected five saliva samples distributed before, during, and after stress exposure. Inhibitory capacity was also assessed before and after stress using the Stroop and d2 cancellation tests. **Results:** Under stress conditions, cortisol measures were significantly lower in amphetamine consumers (1105.34 ± 756.958) than in healthy nonconsumers (1771.86 ± 1174.248) $P = 0.022$. Without stress, amphetamine consumers also showed lower cortisol values (1027.61 ± 709.8) than nonconsumers (1844.21 ± 1099.15) $P = 0.016$. Regarding inhibitory capacity, stress also was associated to consumer's lower scores on the Stroop (5.17 ± 8.34 vs. 10.58 ± 7.83) $P = 0.032$ and d2 tests (190.27 ± 29.47 vs. 218.00 ± 38.08) $P = 0.010$. **Conclusion:** We concluded that both the stress regulatory system and executive function system (attentional/inhibitory control) represent key vulnerability conditions to the long-term effect of compulsive amphetamine consumption.

Keywords: Abstinence, amphetamine, cortisol, executive functions, stress

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INTRODUCTION

Chronic amphetamine use causes mood disturbances, cognitive changes, and neurotoxicity.[1] Following cannabis, amphetamines have become the most used drugs worldwide.[2] Young people are the most affected because of the growing availability of these drugs and the poor capability that they possess to make appropriate decisions. In some countries, the use of amphetamines rises among adolescents and young adults during the last decade.[3] Besides these sociodemographical conditions, periadolescence stages also represent the greatest neurobiological vulnerability to addictive drugs.[4] As a consequence, young people are also the most frequent demanders of detox and rehab treatments. Most frequently, they are detoxified and confined to adapted facilities where they receive treatment and remain in abstinence for periods ranging from 1 to 12 months.

As a brain affecting condition, amphetamine abuse and other addictions involve changes in reward, stress, and executive function systems. Changes in the brain dopaminergic reward system have been extensively demonstrated both in animal models of addiction and

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in morphophysiological studies assessing humans with a history of substance abuse.[5] Stress and executive function systems, on the other hand, remain as less attended conditions.

Stress includes a myriad highly regulated actions that organisms execute to ensure adaptation when adversity compromises its well-being. It is, in fact, one of the most important adaptive systems for all organisms. Most of the stress actions are coordinated and executed by molecules linked to the activity of the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol is the main executor of these actions. When threats challenge the individuals' well-being, a rise in cortisol levels promotes adaptation by moving energy stores, changing immune profiles, reducing unnecessary physiological processes, and activating brain structures indispensable for experience processing.[6] When threats disappear, cortisol inhibits its own liberation by impairing hypothalamic and pituitary secretion of corticotropin-releasing hormone and adrenocorticotropic hormone. Efficient on/off fluctuations in cortisol activity are indispensable for optimal adaptation. Unnadaptive changes on this regulatory system have been reported on a number of diseases including addiction.[7] In alcoholics, for example, HPA hormones become deregulated after chronic ingestion.[8] Then, deregulated HPA systems could make chronic drug consumers less competent to deal with stress.

On the other hand, executive functions are highly evolved cognitive processes that also facilitate the individuals' adjustment to challenging conditions. They include a group of mental functions mediated by prefrontal cortices (PFC) and dopaminergic circuits.[9] Attentional and inhibitory control are crucial for these functions because they provide cognitive tools to avoid inappropriate behaviors. Alterations in these capacities are also one of the major contributors to the development and maintenance of addiction.[5] In great part, young people become vulnerable to addiction because of the underdeveloped PFC circuitry that cannot yet properly regulate behavior. People suffering from addiction exhibit impairments in PFC that may reduce their power to resist the desire and stop drug consumption.[10] Alterations in these circuits may explain why addicts cannot stop using drugs even when they are sincere in the intention of maintaining the abstinence and follow a planned rehab treatment.

In the recent years, stress reactivity and inhibitory control have been linked to the dopaminergic reward system suggesting that altered stress and executive function systems might be important factors determining compulsive consumption and relapse. This proposal could be especially relevant when addiction involves drugs (i.e., amphetamines) whose mechanisms interfere directly with the dopaminergic reward system.[11] In this line of thought, it could be expected that chronic amphetamine consumers may exhibit deficits affecting both the HPA hormones and the executive inhibitory systems. Analyzing the few available data produced until now, it can only be confirmed that stress and cognition could be affected as a consequence of drug consumption, but the direction and/or duration (reversibility or irreversibility) of such changes remain controversial. While some studies have reported benefits or no effect of amphetamine consumption,[12] others found short-lasting impairments[13] in one or both of these parameters. Due to the fact that most of the studies investigating this topic have been conducted while addicts are still consuming or shortly after they stop consumption, we believe that evaluating both parameters during abstinence may help to elucidate this controversy. Then, we hypothesize that amphetamine consumers exhibit abnormal patterns of hormone secretions and/or inhibitory capacity even after long periods of abstinence. To test this hypothesis, we exposed a group of abstinent amphetamine consumers to a naturalistic stressing condition (the trier social stress test [TSST]), aiming to evidence whether they could be more or less efficient to regulate hormone secretions and/or to resist cognitive interference under stress conditions.

MATERIALS AND METHODS

Study design and participants

A cohort study was conducted to test the hypothesis that amphetamine consumers are less competent to regulate cortisol secretions and to inhibit behaviors under stress conditions. The protocol established in the TSST was employed to induce stress in participants, and repeated measures related to hormone regulation and cognition were taken at different points as indicated below. We included a total of 44 individuals from both sexes. From these, 22 were former amphetamine consumers and 22 were healthy nonconsumers. Consumers were evaluated in abstinence once they complete a 6-month treatment period. To guarantee the abstinence requirement, former consumers were recruited from a CONADIC's certified addiction treatment center located in Guadalajara, México, between June 2014 and December 2016. All the recruited consumers

Table 1: Demographic characteristics of participants

	Amphetamine (*n*=22) Mean±SD (95% CI)/Frequency	Non-consumers (*n*=22) Mean±SD (95% CI)/Frequency	χ^2	*t*	*P*
Age (years)	24.32±3.12	20.82±2.77		3.932	0.48
Gender (m/f)	18/4	15/7	1.091		0.2
Academic status (years)	10±2.43	13.14±1.58		-4.986	0.09

received the same treatment in strict accordance with the therapeutic communities approach.[14] Only consumers completing their first stay on treatment were included in the study. The 22 healthy nonconsumers were selected considering sex, age, and educational status of amphetamine consumers. Participants were excluded if they reported any psychiatric, somatic, unusual stress event, or medication status affecting HPA axis activity. One week before the test, all participants underwent an initial structured interview for clinic history, intentional assessment, sociodemographic data, and informed consent. Demographic data of participants are summarized in Table 1.

Experimental procedures took place 1 day before the patient left the treatment center (6 months as a minimum). Sessions were always programmed between 14:00 and 16:00 h. Participants were instructed to avoid caffeine, nicotine, and any medication during at least 24 h before the experiment.

All participants were informed that the TSST might be partly unpleasant; so, they were free to leave the study at any time. Once advised, they signed an informed consent before testing. All tests and interventions were planned and performed in accordance with the Declaration of Helsinki regarding ethical principles for medical research in the human subjects.[15] The procedures were evaluated and approved by the Institutional Review Board of the University of Guadalajara, Mexico (identifier C14017).

Procedures and variable assessment

Trier Social Stress Test

It has been well documented that psychological stress induces changes on several hormones including adrenocorticotropic hormone and cortisol.[16] The TSST has been proven to be an effective tool in basic studies of cortisol responses to psychosocial stress. It provides a naturalistic exposure to a stressful situation that produces recognizable increases in cortisol, heart rate, and other psychological stress responses previously validated.[17,18]

In our study, participants were first instructed to relax for 20 min in a waiting room adjacent to the testing room. Then, participants received instructions regarding the protocol procedure. Baseline measures for salivary cortisol and inhibitory control were taken at this point (T0).

Next, all participants accomplished the TSST to investigate endocrine and neuropsychological responses to psychological stress. Once in the testing room, they were instructed to prepare the emotive speech knowing that this action would be video recorded and remotely evaluated (stress anticipation period). Ten minutes later, individuals performed the speech for 5 min and answered questions of the jury (3–4 members) for another 5 min. A second salivary cortisol and inhibitory control measure were obtained at this point (T1). Once the individuals completed the postspeech evaluation, they returned to the waiting room where subsequent cortisol measures were taken at three different time points: (i) after the execution of a mental arithmetic task (T2), (ii) 15 min after executing distracting/relaxing tasks (T3), and (iii) once the

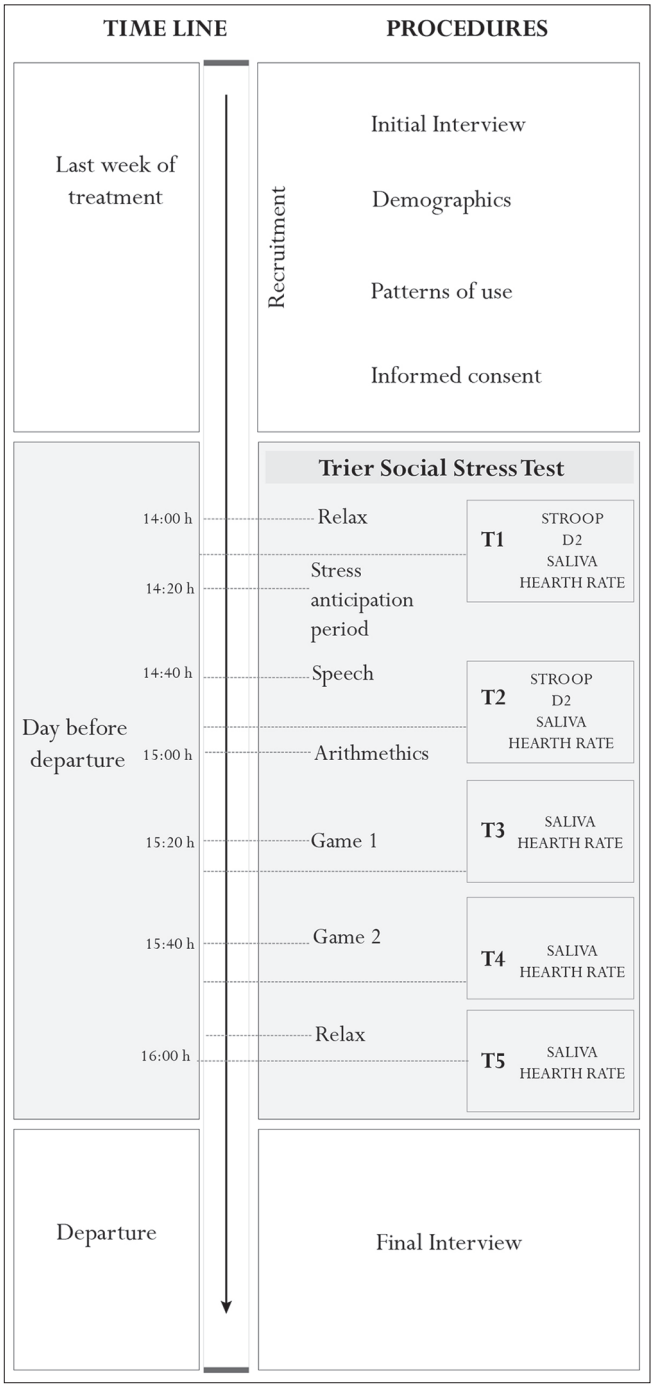

Figure 1: General procedure. Depicts the general procedure followed in our study. Procedures are chronologically depicted from initial interview (upper side of the scheme) to final interview (bottom part of the scheme). The trier social stress test procedure and corresponding measures are detailed at the middle part of the scheme

experiment concluded and individuals received the final instructions (T4) [Figure 1].

Cortisol sampling and analysis

To compare cortisol reactivity under stress conditions, five saliva samples (T0, T1, T2, T3, and T4) were collected from each individual as indicated in the TSST protocol. We prohibited food ingestion, chewing gum, brushing teeth, and rinsing mouth with water for 2 h before saliva collection. We used 15-ml salivettes for quick and hygienic sampling. Salivettes containing saliva were stored at −20°C until assay. On thawing, the saliva samples were centrifuged and analyzed following the instructions described on the DetectX® cortisol immunoassay detection kit from Arbor Assays.

Heart rate recording

To obtain an additional stress measure, we registered each individual's heart rate in beats per minute (bpm) using a small pulse oximeter attached to the patient's finger. Heart rate measures were also acquired during the TSST execution at T0, T1, T2, T3, and T4.

Inhibitory control/attentional control assessment

The printed version of the Stroop color and word test was used to evaluate resistance to interference (RI) as a measure of the individual's ability to inhibit an automatic response (inhibitory control).[19] We employed three printed cards (word W, color C, and word-color WC) asking the individuals to read the 100 items included in each one of the cards as fast as possible. Hence, the individual's task was to read aloud the color words on the first card (W), to name the colored patches on the second card (C), and to name the colors of the ink ignoring the printed color word on the third card (WC). They were given 45 s for each card. If the individual finished before time was over, he/she could start again; so, the number of items depended on how fast the individual performed. A single score was calculated to measure RI using the formula RI = WC − WC′ where WC′ = (W × C)/(W + C).[20]

As a complement, we applied the cancellation d2 test to obtain a quick measure of attentional control.[21,22] Participants must cross out any letter "d" with double mark in a card containing "d" and "p" letters provided with surrounding distracters. The individual must scan each one of the total 14 lines as quickly as possible (max 20 s/line) to estimate the concentration performance index (number of correctly marked items minus the number of confusion mistakes).[23] All the individuals executed the Stroop and d2 tasks both under basal conditions (T0) and after the speech stress (T1).

Statistical analysis

Demographic and clinical characteristics of interest were tested for differences using t-tests for continuous variables (age, school, and consumption years) and Chi-square tests for categorical variables (gender male/female). Our primary analysis was based on the repeated measures ANOVAs considering the independent variable as categorical (group: 2 levels [amphetamine consumers and nonconsumers]) and the dependent variables as continuous (heart rate, cortisol, RI, and attentional control). For heart rate and cortisol, there were five measures (T0, T1, T2, T3, and T4) and for RI and attentional control, there were two measures (baseline and stress). The Kolmogorov–Smirnov test was used to evaluate whether variables were normally distributed or not. Levene's test was used to verify that we were working with random samples from populations with the same variance. The Mauchly test was used to test the sphericity assumption. Analyses were performed with commercially available IBM (IBM Corp., SPSS Inc., Chicago, IL, USA) Statistical Package for Social Science 20.

RESULTS

Demographic and clinical characteristics

There were no significant differences between groups in age, gender, or academic status.

Cortisol and heart rate measures

Repeated measures ANOVA analysis of saliva cortisol revealed main effect of time $F_{(4, 96)}$ =11.092, P = 0.000, condition $F_{(1, 24)}$ = 4.245, P = 0.05, and condition × time interaction $F_{(4, 96)}$ = 4.758, P = 0.002. In addition, the analysis of heart rate revealed main effect of condition $F_{(1, 42)}$ = 24.906, P = 0.000011 but not effect of time $F_{(1, 42)}$ = 1.845, P = 0.122 or time × condition interaction $F_{(1, 42)}$ = 0.523, P = 0.713.

Independent samples t-test used to compare the two conditions at single time points (T0, T1, T2, T3, and T4) showed that consumers in general exhibited fluctuations much lesser marked than controls. Cortisol measures were significantly lower in abstinent consumers at T1 $t(14)$ =2.900, P = 0.022, T2 $t(14)$ =4.107, P = 0.004, and T3 $t(14)$ =3.044, P = 0.016 [Figure 2a].

Accordingly, bpm were also significantly lower in abstinent consumers at T0 $t(42)$ =3.002, P = 0.004, T1 $t(42)$ =4.767, P = 0.000030, T2 $t(42)$ =3.689, P = 0.001, T3 $t(42)$ =2.677, P = 0.011, and T4 $t(42)$ =4.662, P = 0.000032 [Figure 2b]. Results of cortisol and heart rate measures are summarized in Table 2.

Inhibitory/attentional control measures

As pointed above, we also assessed the effect of drugs on Stroop and the d2 test to obtain measures of inhibitory and attentional control, respectively. We conducted two evaluations of each one. The first one was under basal conditions (T0) and the second one after the speech

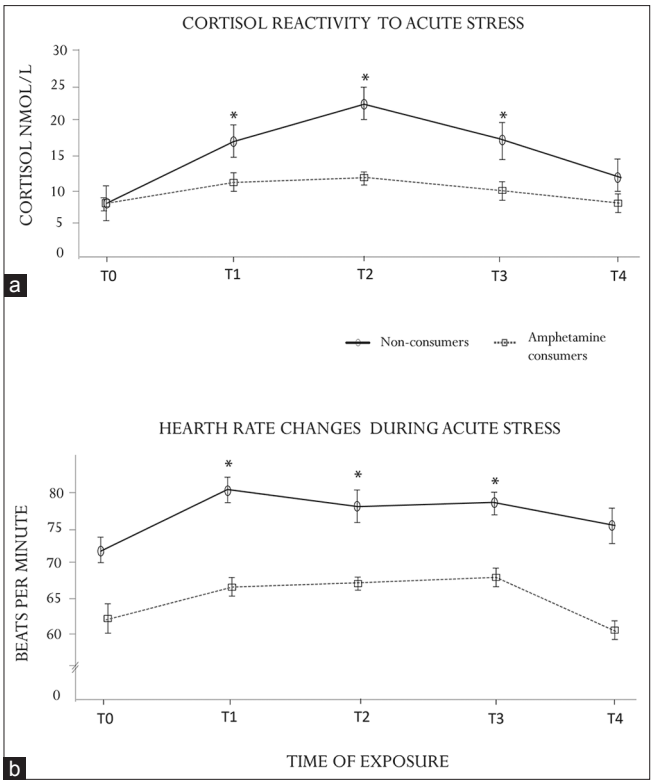

Figure 2: (a) The mean level of free salivary cortisol during the trier social stress test. T0–T4: Time points at which samples were collected in both, control and addicts. *P = 0.01 (t Student's). (b) The mean values of heart rate in beats per minute during trier social stress test. T0–T4: Time points at which the measures were taken in both groups. *P = 0.001, (t Student's). Error bars indicate standard errors of the mean

stress (T1). Regarding the Stroop interference, the analysis of repeated ANOVAs revealed main effect of time $F_{(1, 42)} = 20.252$, $P = 0.000053$ but neither effect of condition $F_{(1, 42)} = 2.303$, $P = 0.137$ nor condition × time interaction $F_{(1, 42)} = 2.467$, $P = 0.124$. On the other hand, the analysis of attentional control in d2 test revealed main effect of time $F_{(1, 41)} = 28.525$, $P = 0.000004$ and condition $F_{(1, 41)} = 6.624$, $P = 0.014$ but no effect of condition × time interaction $F_{(1, 42)} = 0.605$, $P = 0.441$.

Independent samples t-tests revealed significant differences between the groups at specific points. When executed the Stroop paradigm under stress conditions (T1), nonconsumers exhibited greater RI compared to amphetamine consumers $t(42) = 2.216$, $P = 0.032$ [Figure 3a]. Nonconsumers also obtained greater number of correct answers in the attention d2 test compared with consumers both at baseline (T0) $t(41) = 2.031$, $P = 0.049$ and under stress conditions (T1) $t(42) = 2.701$, $P = 0.010$ [Figure 3b]. Results of Stroop and d2 tests are summarized in Table 3.

DISCUSSION

Our study investigated the effects of experimental stress on cortisol reactivity and inhibitory/attentional control in a sample of young amphetamine consumers that remained in abstinence during 6 months for rehab treatment. We collected repeated samples of saliva and heart rate to obtain physiological parameters of stress reactivity under the TSST. We also applied the Stroop and d2 tests to gain knowledge on how these individuals resist to interference in the presence or absence of psychosocial stress.

Table 2: Repeated measures ANOVA for cortisol and Hearth Rate

Factor	*F*	df	*P*
Cortisol: time	11.092	4,96	0.000
Cortisol: condition	4.245	1,24	0.05
Cortisol: time x condition	4.758	4,96	0.002
Hearth rate: time	1.845	1,42	0.122
Hearth rate: condition	24.906	1,42	0.000011
Hearth rate: time x condition	0.523	1,42	0.713

First, we found that stress reactivity was altered in amphetamine consumers that completed a 6-month residential treatment. They exhibited diminished salivary cortisol levels before, during, and after stress exposure (T0–T4). Impairments on stress reactivity were also recognized by less pronounced fluctuations on heart rates. Thus, we confirmed that amphetamine abuse coexists with alterations in stress responsiveness.

The line of thought arguing alterations in the stress regulatory system of addicts was previously established on reports suggesting that alcohol and other drugs might disrupt the HPA axis after chronic or heavy intakes.[24] It has been recognized that drugs initially act as acute stressors that activate the HPA axis and subsequently deregulated its function.[7,25] In line with this, other reports showed that chronic smokers and alcoholics had deficient cortisol secretions during withdrawal.[26-28] Then, it may be argued that hormone secretions related to stress regulatory systems tend to decline over drug withdrawal or abstinence periods. Our results show strong consistency with this and suggest that these alterations may persist for periods longer than previously reported (at least 6 months according to the minimum registered in our study). Furthermore, our results also agree with the idea that deficiencies in cortisol secretions could be a featuring defect affecting the most common forms of substance abuse and support the hypothesis that addicts turn out less competent to face stressful events. Therefore, addicts could be in a clear disadvantage when dealing with quotidian stress since the hormonal flexibility required to exert adequate responses to adversity seems to be damaged. Such disadvantage could explain why addicts tend to relapse soon after the occurrence of emotional or physical stress.[29] It remains, however, unclear if this diminished hormonal flexibility also correlates with higher incidence of relapse once the

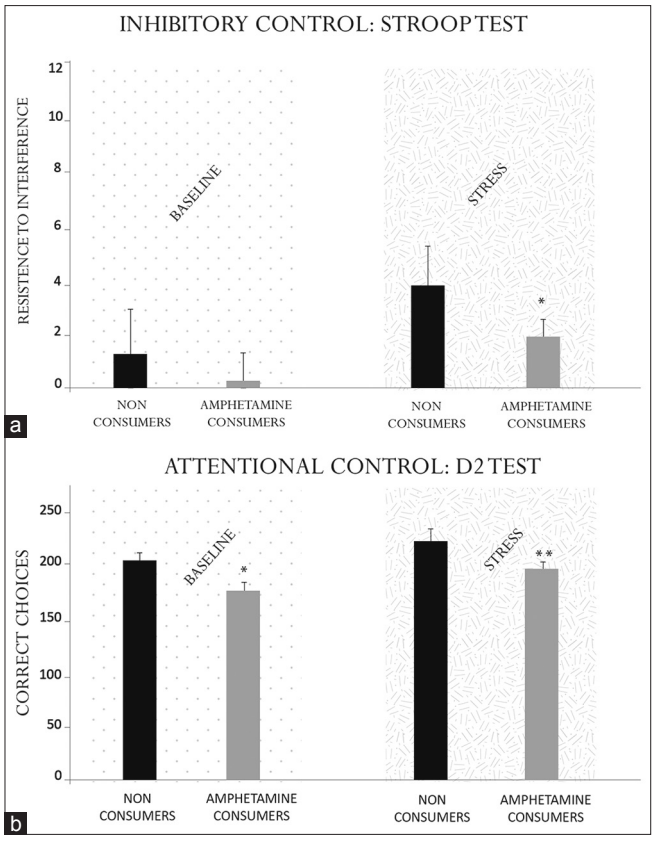

Figure 3: (a) The mean resistance to interference registered when individuals executed the trier social stress test. The measures of interference resistance in basal and stress conditions are from the Stroop test (Golden, 2001). *N* =44 (22 addicts and 22 control). **P* < 0.05 (*t* Student's). Error bars indicate standard errors of the mean. (b) The number of correct choices registered on D2 test when individuals executed the trier social stress test. *N* =44 (22 addicts and 22 control). **P* < 0.05, ***P* < 0.01 (*t* Student's). Error bars indicate standard errors of the mean

individuals leave the residence or if these blunted cortisol responses were either a preexisting condition or whether a consequence of the chronic consumption. Nevertheless, it seems clear that the efficiency to accurately turn "on" and "off" the stress regulatory system may be downregulated in former amphetamine consumers long after they have suspended the drug use.

On the other hand, we also found that consumers were cognitively less efficient to resist the interference and avoid distracters. Both Stroop and d2 tests evidenced that consumers possess deficient abilities to execute inhibitory control tasks under stress conditions. Individuals that consumed amphetamines at juvenile stages and completed 6 months of residential treatment remained incompetent to inhibit irrelevant stimuli under stress. Our results are consistent with previous reports showing that active addicts exhibit severe difficulties to inhibit irrelevant stimuli.[30,31] These deficits seem to be key factors behind the impulsivity and poor decision-making that characterizes the excessive use during the active phases of addiction.[32] Active addicts may be less competent to solve inhibitory/attentional control tasks because they possess dysfunctional cognitive

Table 3: Repeated measures ANOVA for Stroop and D2 Tests

Factor	*F*	df	*P*
Stroop: time	20.252	1,42	0.000053
Stroop: condition	2.303	1,42	0.137
Stroop: time x condition	2.467	1,42	0.124
D2: time	28.525	1,41	0.000004
D2: condition	6.624	1,41	0.014
D2: time x condition	0.605	1,42	0.441

systems whose neural correlate seems to rest over prefrontal cortices.[33] Accordingly, brain disorders affecting prefrontal areas negatively interfere with the execution of Stroop and d2 tests.[23,34]

While results regarding active consumers show consistency on negative effects,[35] it is not clear, however, on which extend abstinent individuals still exhibit deficiencies on inhibitory/attentional control. The few available literature on this topic has typically investigated short-term abstinence and has confirmed deficits on inhibitory control.[13] In contrast, recent studies evaluating long-term abstinent cocaine (12) and amphetamine (36) addicts found no detectable differences after longer abstinence periods. Our results showed that under stress conditions, deficits on attentional/inhibitory control become widely manifest. Individuals exposed to the TSST performed worse on the two tests. Hence, we believe that deficits in stress regulatory systems may exacerbate inhibitory/attentional control deficiencies. It may be possible that advantages that normal individuals obtain from mild stress when performing cognitive tasks disappear in abstinent amphetamine users whose stress reactions are impaired. Then, decision-making, impulse control, and other abilities necessary to resist amphetamine use may result negatively affected and lead to relapse when individuals deal with stressing conditions.

To properly judge our results, it is important to mention that our sample could be relatively small when we consider the great variation that age, duration of consumption, sex, or treatment may represent for cognition and/or cortisol fluctuations. Moreover, it must be pointed that we included only individuals completing 6 months of abstinence; so, the conclusions obtained after this period does not exclude the possibility that individuals recuperate after prolonged abstinence as reported recently.[36] If well, the recruitment method used here (all individuals were recruited from the same institution and were treated under the same clinical scheme) represents a methodological advantage by ensuring homogeneity and adding certainty for abstinence; it is also disadvantageous when we consider that other treatment methods may confer variations to the analyzed variables. Then, we believe that expanding the sample and including individuals from different institutions and abstinence

periods; the results could be statistically and clinically more robust and reliable.

CONCLUSION

Thereafter, we concluded that young addicts remain less competent to deal with stress during abstinence. The hormonal system that physiologically regulates stress exhibits deficiencies that affect the addict behavior during at least the first 6 months living in abstinence. The executive functions implicated in inhibitory/attentional control also exhibit deficiencies that make amphetamine users less efficient to resist interference and attend relevant stimuli when stressing conditions demand such abilities. Hence, we provide evidence supporting the idea that stress regulation and cognitive control are crucial elements affecting the start, maintenance, and/or progression of amphetamine addiction.

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Conflicts of interest

There are no conflicts of interest.

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