



Adverse Psychosocial Relationships and Substance Use Disorder: a Narrative Review

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RESUMEN

Introducción: el abuso de sustancias es reconocido como un trastorno cerebral que afecta principalmente dos sistemas: el sistema de motivación-recompensa y el sistema de defensa. El primero es responsable de modular comportamientos dirigidos a obtener reforzadores placenteros, como interacciones sociales y comida. El uso frecuente de drogas disminuye la respuesta de este sistema, lo que lleva a la tolerancia de sus efectos hedónicos. Por otro lado, el sistema de defensa, orientado a salvaguardar la integridad física del individuo, responde ante estímulos amenazantes por medio de sensaciones de miedo o ansiedad, y muestra una naturaleza antifragil. **Objetivo:** describir la interacción entre estos sistemas, que se ve alterada por el uso frecuente de drogas, y que conduce a una disminución de la respuesta del sistema de motivación-recompensa y un aumento de la respuesta del sistema de defensa, así como el efecto de las interacciones sociales adversas en estos sistemas. **Método:** se realizaron búsquedas y revisiones críticas de artículos científicos recientes publicados en PubMed y se incluyeron tanto investigaciones en humanos como en animales. **Discusión y conclusiones:** las interacciones sociales adversas, como la negligencia parental y el abuso infantil, promueven una carga alostática y fortalecen la naturaleza antifragil del sistema de defensa, que favorece y mantiene el consumo de drogas. En modelos animales, se ha observado que la privación de cuidados maternos en los primeros días de vida conduce a comportamientos maladaptativos en la edad adulta y un aumento en el consumo de alcohol. De manera similar, los animales subordinados consumen más drogas que sus contrapartes dominantes. Estos hallazgos sugieren una relación compleja entre experiencias adversas tempranas, el desarrollo de los sistemas de recompensa y defensa, y la vulnerabilidad a la adicción.

Palabras clave: trastorno por uso de sustancias, sistema de recompensa, sistema de defensa, carga alostática, interacción social negativa.

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ABSTRACT

Introduction: Substance abuse is recognized as a brain disorder that primarily affects two systems: the motivation-reward system and the defense system. The former is responsible for modulating behaviors aimed at obtaining pleasurable reinforcers such as social interactions and food. Frequent drug use diminishes the response of this system, leading to tolerance to hedonic effects. The defense system, oriented towards safeguarding the individual's physical integrity, responds to threatening stimuli by generating sensations of fear or anxiety and displays an antifragile nature. **Objective:** to describe the interaction between these systems, which is altered by frequent drug use. This leads to a diminished response of the motivation-reward system and an increased response of the defense system, as well as the effect of adverse social interactions between the two. **Method:** recent scientific articles published in PubMed were browsed and critically reviewed; both human and animal studies were included. **Discussion and conclusions:** adverse social interactions, such as neglectful parenting and child abuse, promote an allostatic load and strengthen the antifragile nature of the defense system, favoring and maintaining drug consumption. In animal models, it has been observed that maternal care deprivation in the early days of life leads to maladaptive behaviors in adulthood and increased alcohol consumption. Similarly, subordinate animals consume more drugs than their dominant counterparts. These findings suggest a complex relationship between early adverse experiences, the development of the reward and defense systems, and vulnerability to addiction.

Keywords: substance use disorder, reward system, defense system, allostatic load, negative social interaction.

INTRODUCTION

In 1997, Alan I. Leshner, then director of the National Institute on Drug Abuse (NIDA) in the United States, acknowledged that substance addiction is a brain disorder (Leshner, 1997). Although controversial, this statement provided previously missing context in which present, extensive and rigorous research has been trying to elucidate the brain systems affected by drug abuse and how their physiology changes as a result of high and frequent use over extended periods.

Several groups of researchers worldwide have dedicated their work to unraveling the neurobiological alterations resulting from drug use and abuse leading to a substance use disorder (SUD). Numerous comprehensive reviews (Berridge, 2019; Berridge & Kringelbach, 2015; Koob, 2021 and, 2022; Volkow & Blanco, 2023; Volkow & Morales, 2015) have adeptly expounded upon the primary systems impacted and the mechanisms involved, which include the motivation-reward and the defense systems. In the subsequent paragraphs we will succinctly discuss these fundamental systems in order to establish a framework for examining how adverse psychosocial relationships might contribute to the initiation of substance consumption and the progression to a SUD.

The Motivation-Reward System

The function of the motivation-reward system is to modulate behaviors aimed at obtaining reinforcers that induce pleasure, thereby generating positive reinforcement (Olds & Milner, 1954), for example, sex, food, and psychosocial interactions (Prospéro-García et al., 2021). This system consists of the ventral tegmental area (VTA), the anterior region of the nucleus accumbens shell (NAcSa), and the medial prefrontal cortex (mPFC) in humans (Junghofer et al., 2017), and the prelimbic (PL) and infralimbic (IL) areas in rats (Berridge, 2019). SUD has been associated with maladaptive functioning of this circuit, as these substances activate it during user consumption, which induces a positive reinforcement (Volkow & Blanco, 2023). However, frequent drug use diminishes the response of this system, leading to tolerance to the hedonic effects. Consequently, users increase both the quantity (dose) of and the frequency of drug consumption.

A fragile system is defined as one that is quickly weakened or destroyed by a given stimulus. Taleb & Douady (2013) described mathematically the characteristics of such a system. As the motivation-reward system develops tolerance, that is, secondary refrac-

toriness to the pharmacological effects of drugs as a result of its frequent massive activation, it becomes less reactive as the user persists in consuming substances, thereby devaluating both drugs and natural reinforcers. In other words, both drugs and natural reinforcers weaken the system. For example, in the case of food ingestion, the system responds less as the individual consumes more food on the same occasion. The same occurs with sexual activity. In this context, we conclude that this system is fragile, since its response weakens as a consequence of its frequent activation.

On top of the reduced motivation-reward system response, users who suffer from drug addiction and attempt to permanently cease said consumption experience negative-valence emotions in the process of quitting, such as intense craving and withdrawal syndrome. These emotions lead users to relapse into consumption, as substance abuse alleviates these discomforts. In this context, we propose that maintaining a substance addiction primarily depends on the user's desire to avoid these negative emotions, which are related to the activity of the defense system (Koob, 2022; Prospéro-García et al., 2021). Substances of abuse induce negative reinforcement when the user has developed a SUD, as their consumption reduces craving and prevents withdrawal syndrome.

The Defense System

The defense system safeguards the physical integrity and life of the individual, inducing the subjective sensations of fear or anxiety that motivate the person to seek refuge and/or assistance. If the individual possesses strategies that enable him to successfully contend with the threatening stressor by either confronting and neutralizing it or avoiding it through seeking refuge and/or assistance, these strategies will generate negative reinforcement. A significant part of this circuit, specifically the prefrontal cortex (PFC)/amygdala interaction, has been extensively explored in individuals with anxiety traits (Bramson et al., 2023) and in subjects who have suffered from parental neglect during childhood (Korom et al., 2024). The defense system comprises additional components, such as the bed nucleus of the stria terminalis (BNST), the anterior cingulate cortex (aCC), the insular lobe (LOBIN), the paraventricular thalamic (PVT) and hypothalamic (PVN) nuclei, and the autonomic nervous system are among the additional components.

The defense system includes the stress response, which is the hormonal response triggered by the detection of a threat. It promotes hormonal mechanisms

that strengthen the organism's defense and help it contend with the stressor to prevent potential harm. The hypothalamic-pituitary-adrenal (HPA) axis is a crucial component of this response, since it involves the release of the corticotropin-releasing factor (CRF) from the PVN, which induces the release of glucocorticoids from the adrenal cortex (Shin & Liberzon, 2010). The release of CRF by the PVT activates the amygdala, promoting the subjective sensation of fear or anxiety. These stress hormones induce a re-organization of the individual's energy and cognitive resources, preparing them to fight, flee, seek refuge and protection, or, in the most extreme case, faint and feign death.

Unlike a fragile system, an antifragile system is one that is strengthened by stimuli within a certain range of intensity. In other words, such stimuli make the system more efficient. The defense system responds more robustly and efficiently as it faces more adverse stimuli, leading us to conclude that it is antifragile. In essence, stressors strengthen it. Taleb and Douady (2013) have mathematically defined the antifragile system (Figure 1).

Interaction between the Motivation-Reward/Defense Systems

The opponent-process theory for the control of motivation (Solomon & Corbit, 1974) suggests that brain systems regulating positive emotions (happiness, pleasure) decrease the activity of brain systems regulating negative emotions (fear and anxiety), and vice versa. This model provides a conceptual framework for understanding the interaction between the motivation-reward system and the defense system, particularly in the context of substance addiction (George et al., 2012; Koob & Le Moal, 2008). As mentioned earlier, drugs activate the motivation-reward system of the user. Drugs shift a naive user from a state of anhedonia to one of euphoria, resulting in positive reinforcement. It has been shown that the VTA projects to the amygdala by inhibiting it through the dopamine D2 receptors (Hernández-Mondragón et al., 2023). This effect may reduce the subjective sensation of fear or anxiety, facilitating the subjective sensation of pleasure induced by natural reinforcers and drugs.

During periods when the user is not consuming drugs, however, the defense system strengthens because the hyperactivity of the motivation-reward system caused by drugs is no longer present; hence the dopamine inhibitory action on the amygdala is reduced. Simultaneously, the CRF is released in big quantities into the amygdala, facilitating a compen-

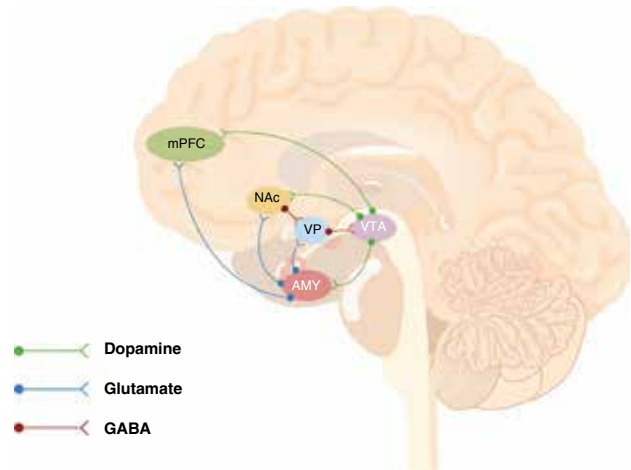


Figure 1. This diagram depicts the motivation-reward and defense systems, illustrating their reciprocal interactions and highlighting key neurotransmitters involved. Dopaminergic projections originating from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) appear implicated in motivation for obtaining reinforcers. Conversely, projections from the amygdala to the NAc seem associated with motivation to avoid stressors. Projections from the VTA to the medial prefrontal cortex (mPFC) are implicated in the generation of subjective sensations of satisfaction or pleasure, while projections from the amygdala to the mPFC may contribute to the generation of subjective sensation of anxiety. Inhibitory interactions between these systems appear to occur, in part, through VTA projections inhibiting the amygdala, and amygdala projections activating the ventral pallidum, which subsequently inhibits the VTA.

satory hyperactivity of the defense system for the user to return to homeostasis (Koob & Le Moal, 2008; Prospéro-García et al., 2021; Solomon & Corbit, 1974). An interaction between the basolateral amygdala (BLA) with the ventral pallidum (PV) to inhibit the VTA when a natural reinforcer or a drug has activated it, leading to restoring the balance between these two systems has also been described (Guo et al., 2023; Salin et al., 2023).

With high and frequent drug consumption, the fragile motivation-reward system weakens its response over time (Prospéro-García et al., 2021; Volkow et al., 2010; Willuhn et al., 2014), while the antifragile defense system strengthens itself, generating *hyperkatifeia*, defined as hypersensitivity to internal and external noxious stimuli (Koob, 2022), thereby facilitating anxiety, irritability, physical pain, and anhedonia during periods of abstinence.

All these affective consequences are logical within the framework of the opponent-process model.

Therefore, we postulate that once the drug is removed from the brain and stops hyperactivating the reward system, the defense system is the one becoming hyperactive. With initial drug use, the defense system's function is to reduce the activity of the motivation-reward system for the individual to return to homeostasis. With prolonged drug use, however, the fragile motivation-reward system weakens due to molecular changes, such as reducing dopamine synthesis in the VTA, endocytosis of receptors and/or reducing their synthesis (e.g., D2/D3 receptors and the dopamine transporter [DAT]). Cannabinoid receptor 1 (CB1R) in terminals afferent to the nucleus accumbens (NAc) increase their expression. Simultaneously, the anti-fragile defense system strengthens, due to an increase in both CRF and CRF receptor type 1 (CRFR1) in the amygdala and a reduction of CB1R expression, as well as modifications in the conductance of glutamatergic receptors, such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Castro-Zavala et al., 2021; George et al., 2012; Volkow et al., 2010). This creates a state with negative emotions that sustains drug consumption and facilitates addiction (Figures 2 and 3).

Over time, drug users develop an allostatic state (Sterling & Eyer, 1988) which, in the context of addiction, is a state of chronic imbalance in the brain's defense and reward systems (Koob & Le Moal, 2008). The allostatic state suggests that the brain adapts to chronic drug consumption by establishing a new set point in these systems, leading to an increased threshold for feeling reward and a reduced threshold for feeling hyperkatifeia/anxiety, making negative emotions the motivation for substance abuse.

The reviewed evidence suggests that the high and frequent use of substances of abuse alters the homeostatic interaction of the motivation-reward and defense systems. This alteration would lead the motivation-reward system to develop a state of secondary refractoriness, resulting in a weak response to the pharmacological stimulus of such substances. Meanwhile, the defense system, due to its antifragile nature, would respond increasingly robustly to the absence of such stimuli. If this were the underlying pathophysiological condition of addiction, then we must conclude that substance addiction depends on the defense system and consequently on negative reinforcement.

Adverse Psychosocial Interactions as Vulnerability Factors to Develop SUD

Allostatic load, defined as the accumulation of wear and tear on physiologic systems as a product of adaptation (McEwen, 1998), has been related to sever-

al psychiatric and systemic disorders (Twait et al., 2023) and drug use (Fan et al., 2023). Neglectful parenting and child abuse are powerful stressors that promote allostatic load, thereby strengthening the individual's defense system and preparing them to face a hostile environment (Korom et al., 2024). It has been observed that child abuse or negligent parenting can lead an individual to develop adaptive defense and aggression strategies as they frequently perceive their environment as hostile even when there is no hostility in the immediate surroundings. As these strategies persist even in friendly settings, the individual may face social rejection and stigmatization, strengthening their defense system even more and making them vulnerable to developing a SUD (Ruiz-Contreras et al., 2023). In essence, stressful events during critical periods of life strengthen the defense system (Korom et al., 2024), and as a result, many substance users often experience comorbidities with other psychiatric disorders such as anxiety and depression (Nederhof & Schmidt, 2012).

The motivation-reward system also undergoes changes in response to stressful events. For example, individuals with less social success and/or a reduced support network have lower levels of dopamine D2/D3 receptors in the NAc, compared to individuals who enjoy these social benefits (Martinez et al., 2010). It is plausible that these changes may be a contributing factor to being vulnerable to developing a substance use disorder. For instance, in an interview with individuals using marijuana for medicinal purposes in the United States, and individuals in Mexico using different kind of drugs, they reported using them to manage pain, anxiety, depression, loss of appetite, or insomnia (Hazekamp et al., 2013; Ruiz-Contreras et al., 2023). Some of these physiological and psychiatric conditions, anxiety, depression, loss of appetite, or insomnia are precipitated by social isolation, solitude and/or loneliness (Lawrence & Marini, 2024; Shorer et al., 2024; Suzuki et al., 2024).

Animal Studies That Support This Hypothesis

Maternal Care. The mother-child relationship, considered one of the most fundamental psychosocial connections during early developmental stages in animals, including humans, induces changes in the brain that may facilitate drug ingestion if not developed normally. In animal models, it has been observed that rats subjected to maternal care deprivation (MCD) during the postnatal days (PD) 2 to 16 exhibit maladaptive behaviors in adulthood (PD90). For example, they exhibit behaviors suggesting anxiety and depression, in addition to voluntarily

consuming more alcohol than rats that have not undergone MCD (Amancio-Belmont et al., 2020; Romano-López et al., 2012). MCD also induces a brain reprogramming in the expression of endocannabinoid receptors, such as a reduction in the CB1R receptor in the prefrontal cortex and an increase in the NAc. Significant changes are also observed in dopamine receptors D1, D2, and D3, and in the glucocorticoid receptor (GR), and changes in the dendrite arborization in both the prefrontal cortex and the NAc (Amancio-Belmont et al., 2020; Romano-López et al., 2016). MCD followed by social isolation in adolescent rats also increases alcohol consumption in adult rats and alters the expression of CB1R and dopaminergic receptors (Amancio-Belmont et al., 2020).

Peer Relationships. Social interaction with peers modifies the expression of CB1 in the mPFC and NAc, and promotes seeking and ingestion of substances of abuse in rats. Non-human primates and rats behaving as subordinates in their respective groups have low

D2/D3 receptors in the NAc, as it has been described in humans with low social success and support (Martinez et al., 2010; Wiers et al., 2016). In addition, subordinate monkeys and rats consume more cocaine than their dominant counterparts (Heilig et al., 2016; Jupp et al., 2016). Similar results have been observed when rats consume amphetamine: subordinate rats consume more amphetamine compared to dominant ones (Migliaro et al., 2022). This evidence supports the fact that adverse psychosocial interactions may lead to changes in the activity of both the motivation-reward and defense systems, thereby generating in the subject a vulnerability to drug consumption in a way that leads to SUD.

DISCUSSION AND CONCLUSIONS

Numerous scientific investigations validate the implication of the motivation-reward system in the

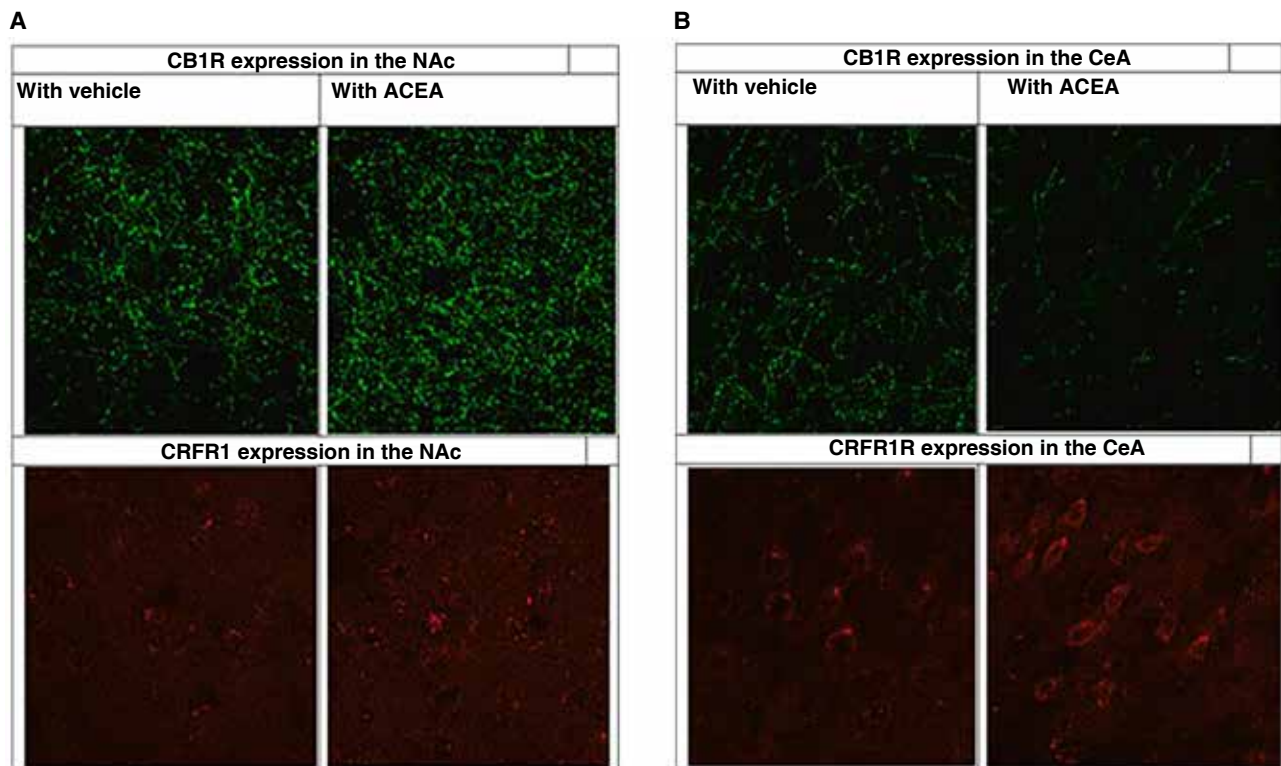


Figure 2

A. This figure illustrates the increase in expression of CB1R and CRFR1 (immunofluorescence micrography) in the NAc in rats treated with vehicle (intraperitoneal ip, 30 continuous days) or ACEA, a highly specific CB1R agonist (4 continuous days of vehicle followed by 1 day of 100 mcg/Kg of ACEA ip, for 30 days).

B. This figure illustrates a decrease of CB1R and an increase of CRFR1 (immunofluorescence micrography) expression in the central amygdala (CeA) in rats treated with vehicle (30 continuous days) or ACEA (4 continuous days of vehicle followed by 1 day of 100 mcg/Kg of ACEA, for 30 days).

(Original Creation - Data from Our Lab).

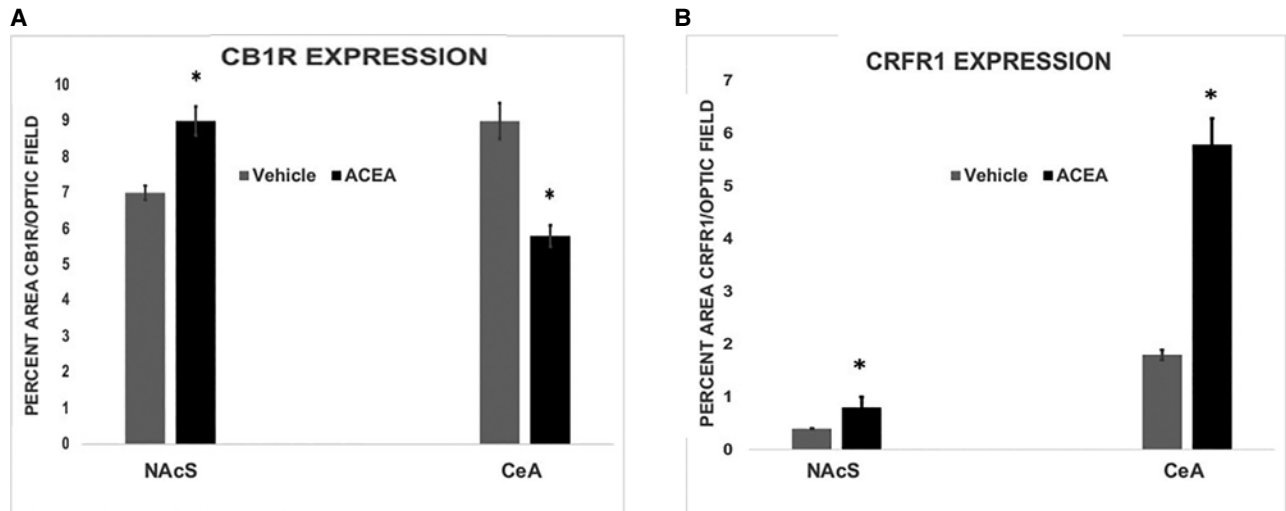


Figure 3

A. This graph depicts CB1R changes in the nucleus accumbens (NAc) and in the amygdala in rats under the effects of vehicle or ACEA. There is a significant increase in the NAc while there is a significant reduction in the CeA (* $p < .05$).

B. This graph depicts CRFR1 changes in the nucleus accumbens (NAc) and in the amygdala in rats under the effects of vehicle or ACEA. There is a significant increase in the NAc (* $p < 0.05$), but there is a massive increase in the CeA (* $p < .001$).

initiation of substance addiction through positive reinforcement. Nevertheless, empirical evidence supports the involvement of the defense system, contributing to negative reinforcement and thereby sustaining the addictive process. The heightened and repetitive administration of substances appears to induce an imbalance between these two systems, culminating in the establishment of an allostatic state that perpetuates substance addiction. It is crucial to acknowledge that allostatic load induced by parental neglect and adverse psychosocial interactions, such as verbal, physical, or sexual abuse, rejection, bullying or abusive subordination, may precipitate such an allostatic state before any drug consumption. This allostatic load reinforces the defense system, rendering individuals susceptible to substance consumption and the development of SUD.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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