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Vulnerability to substance abuse: A consideration of allostatic loading factors

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Editorial

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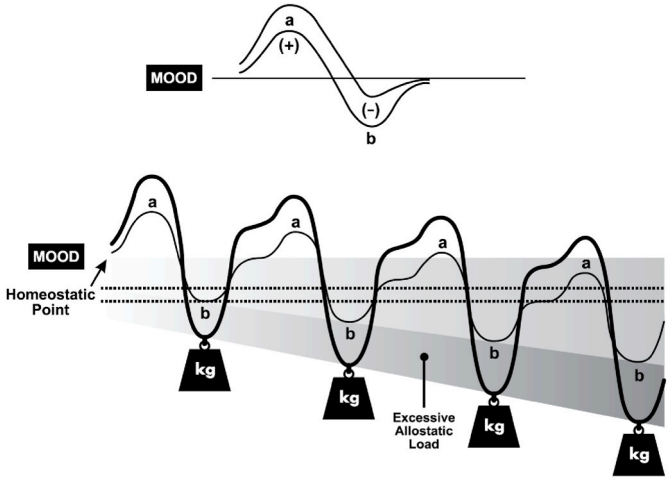
1. Introduction

This Special Issue explores various factors that result in greater vulnerabilities to substance misuse. Vulnerable populations display an array of characteristics that contribute to the formation of substance use disorders (SUDs) that range from biological to social and environmental. The Special Issue also contains primary research articles that explore substance misuse vulnerabilities in preclinical models providing insights into how different neurobiological factors promote the initiation, maintenance and relapse of substance use. Research focused on vulnerability factors can guide the development of more effective treatments for addiction, particularly for persons with co-morbidities, such as diabetes or chronic pain. These reviews highlight the contribution of various factors that disproportionately "weigh" on to a greater likelihood for substance misuse. Indeed, recent work also suggests that the Covid-19 pandemic disproportionately increased drug and alcohol use in certain populations suffering from excessive emotional or physical distress (Koob et al., 2020). An individual may have inherent or acquired factors that facilitate the development of substance misuse. Furthermore, overloading hedonic homeostasis may further propel an individual on a trajectory toward compulsive substance abuse.

2. Allostatic loading factors

The *opponent process theory of addiction* has provided a framework for understanding the motivational factors that result in SUDs (Solomon and Corbit, 1974). Two processes that motivate drug dependence are hypothesized: positive mood states (a-process) and negative affective states (b-process) that emerge over time during withdrawal. Subsequently, the opponent process theory was elaborated to consider the array of factors that enhance "allostatic load" and thereby promote substance use in vulnerable populations (Koob and Le Moal, 2008). Specifically, certain individuals initially might experience stronger substance-induced hedonic mood states (a-process) that promote the initiation of SUDs, as described in this Special Issue. However, with chronic substance use, hedonic mood states recruit opponent processes that grow and facilitate maintenance and promote relapse in SUD. Ultimately, there is a shift of the hedonic set point downward, termed allostasis, that is exacerbated by misguided attempts to return to hedonic homeostasis by drug taking. We suggest that greater allostatic load in vulnerable populations produces excessive recruitment of opponent processes, described in this special issue (see insert). The concept of allostasis is relevant to this Special Issue because it describes an array of factors that shift the allostatic set point, leading to greater vulnerability to misuse drugs. For example, factors such as inherent preference for alcohol, cognitive factors, age and/or sex differences, genetic polymorphisms likely promote the shift in allostatic set point in vulnerable individuals. These individual differences may be common among groups of persons, which may confer greater vulnerability in larger demographic or ethnic populations. In addition to biological factors, there may also be external/social factors that contribute to greater drug misuse, such as systemic racial bias and incarceration. Thus, the presence of greater allostatic load may result in a faster and/or larger downward shift in the set point for developing a SUD. This shift in set point is noted in the figure below by way of the lowering of the dotted line.



3. Summary of contributions in this special issue

Several reviews in the literature have explored the various factors that promote SUD vulnerability. Examples include SUD liability in the context of, sex differences (Becker, 2016; Becker and Koob, 2016; Berry et al., 2016), obesity (Volkow et al., 2013), physical activity (Bardo and Compton, 2015), mental health conditions (Everitt and Robbins, 2016; Szerman and Peris, 2018), epigenetic factors (Ouzir and Errami, 2016; Walker and Nestler, 2018), and developmental factors (Fadus et al., 2019; Spear, 2015, 2018, 2018; Pandey et al., 2017). This special issue provides an exciting extension of these topics and considers novel targets, approaches, and environmental factors believed to be of current impact on drug abuse vulnerability, as follows:

Maldonado et al. (2021) summarized the *brain networks* involved in the vulnerability to addiction and describe the evolution of the

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definition of addiction. They also considered several innovative experimental techniques that, combined with behavioral approaches, have allowed critical advances in understanding the neural circuits involved in addiction.

Two reviews examined *sex differences* in the development of SUDs. Quigley et al. (2021) reviewed evidence for sex differences in vulnerability to addiction with an emphasis on the role of estradiol in promoting drug-seeking in female rodents. The authors review evidence that the actions of gonadal hormones occur within the hypothalamic pituitary adrenal axis via the stress hormone, corticotropin-releasing factor (CRF). Peltier et al. (2021) focused on the impact of trauma on increased vulnerability to alcohol use, an association that is particularly strong in women who drink to cope with stress. The review addresses the therapeutic potential for progestogen- and androgen-derived neurosteroids to target the overlapping symptoms correlated with stress- and alcohol-related disorders.

Three manuscripts examined *ontogeny* as a vulnerability factor spanning across species, cell types, and substances of abuse. Lees et al. (2021) considered 44 longitudinal studies and found that aberrant neural structure and function within specific brain regions implicated in reward processing, cognitive control, and impulsivity predate the development of SUDs. Laviolette (2021) examined the neurodevelopmental effects of adolescent nicotine exposure on the long-term pathophysiological sequelae that ultimately increases the risk of developing chronic mental health disorders in later life. The authors focus on the mesocorticolimbic circuitry and molecular biomarkers linked to adolescent nicotine exposure and increased risk of developing mood and anxiety-related disorders. Lastly, Silva-Gotay et al. (2021) is a primary research article that revealed sex differences in microglial activation and proinflammatory markers following voluntary alcohol drinking in early adolescence. Their findings give insight into potential mechanisms by which voluntary alcohol intake impacts neural circuits that modulate cognitive function and behavioral control in adulthood.

Two reviews examined the negative impact of *stress* on the development of SUDs. al'Absi (2021) addresses how early life adversity produces blunted stress responsiveness that leads to unstable mood regulation, impulsive behaviors, and reduced cognitive function that promote greater risk for SUDs. Lastly, Bardo et al. (2021) examined the impact of early life adversity on a negative trajectory to SUDs. The authors posit that early life adversity promotes drug abuse vulnerability by strengthening stress CRF systems and weakening oxytocin systems, which may offer novel avenues for intervention strategies to reduce risk of SUDs.

Examination of *genetic factors* of SUDs were presented by Borruto et al. (2021). The authors reviewed pre-clinical work using alcohol-preferring rats to identify genetic variables that are linked to alcohol use. Their assessment identifies important gene targets related to stress as well as sex differences in anxiety- and depressive-like behaviors. Moreover, Brynildsen and Blendy (2021) suggest that the single nucleotide polymorphism (SNP) D398N in the gene *CHRNA5* is a key marker associated with addiction to nicotine, opioids, cocaine, and alcohol. Since *CHRNA5* encodes the α5 subunit of the nicotinic acetylcholine receptor (nAChR), they suggest that cholinergic systems play a role in reward and addiction vulnerability to an array of substances.

Examination of *impulsivity traits* on SUDs were examined by Verdejo-Garcia and Albein-Urios (2021). The authors postulate that non-planning impulsivity, affect-based impulsivity, along with the cognitive processes involved in reward-related valuation are consistent predictors of SUD vulnerability. These cognitive processes appear to be associated with hyperactive dopamine transmission within the orbitofrontal-striatal system. A research report by O'Connor et al. (2021) found that greater sensation seeking in "high responder" rats is associated with greater escalation of intake and more drastic reductions in cocaine demand elasticity. These data suggest that the high responder phenotype is associated with a propensity for addiction.

Two papers addressed the interaction between the *immune system* and the brain in facilitating pathological drug use. Lucerne and Kiraly (2021) suggest a bidirectional communication between both the immune system and the gut microbiome drive changes in neural and behavioral plasticity relevant to SUDs. Cisneros and Cunningham (2021) reviewed emerging data examining the effects of neuroimmune signaling in response to viral infections, namely the impact of SARS-CoV2 (i.e,.Covid-19) on substance use. The authors considered the potential synergy between inflammation and kynurenine pathways activity during Covid that leads to dysregulation of neurotransmitters that are strongly associated with SUDs.

The review by Nazarian et al. (2021) considered factors that mediate *pain-related* risk for opioid use disorders. The authors describe the current consensus on the opioid epidemic, different biological factors that contribute to opioid use in persons with pain, examine alternative strategies to study non-reflexive pain models in rodents, and suggest potential variables that may significantly alter opioid use.

Another review by Serafine et al. (2021) examined converging vulnerability factors that predispose an individual to compulsive *food or drug use*. The authors explore potential therapeutic approaches that might leverage commonalities to provide more effective treatments, particularly in persons displaying metabolic disorder and SUD. Relatedly, Cruz et al. (2021) is a primary research article showing that insulin resistance increases nicotine intake to a greater extent in female versus male rats. Finally, Amaro et al. (2021) evaluated *social factors* that enhance vulnerability to SUDs and reviewed the contribution of different stressors, exposure to socially toxic childhood environments, and racism and discrimination to SUDs. They also address implications for future research that examines the relationships between vulnerability to substance use, related inequities, and potential differences across demographic groups.

4. Concluding remarks

This Special Issue brings to light some of the unique challenges and critical knowledge gaps in our understanding of the factors that promote greater vulnerability to SUDs. Future work is needed to establish best practices for informing clinicians and developing public policies to reduce SUDs in vulnerable populations. Future opportunities may include interrogation of protective factors that produce resilience and reduce the likelihood of SUDs. In addition, future research should capitalize on back translation from the human condition particularly in regard to unique gender and diversity factors that may influence allostatic overload on motivation neurocircuitry. These efforts will be important towards providing novel and specialized approaches that can disentangle the factors that heavily influence greater vulnerability to SUDs.

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The illustration in this introduction was developed by graphic designer, Ernesto Herrera. The cover image was also designed in collaboration with Ernesto Herrera to represent the array of allostatic loading factors that promote drug misuse in vulnerable populations.

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