PERSPECTIVE DE RECHERCHE

Hyperkatifeia, Negative reinforcement and Allostasis in Alcohol Use Disorder: A Theoretical and Translational Perspective

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Abstract: Alcohol misuse and alcohol addiction cost society an enormous amount of suffering to individuals and their loved ones in the form of disability-adjusted life years, deaths, and medical costs. Understanding the neurobiological etiology of alcohol addiction allows for better diagnosis, treatment, and prevention but requires a heuristic framework upon which to focus. The well-established three-stage cycle and three dysfunctional domain heuristic framework (binge/intoxication, incentive salience; withdrawal/negative affect, negative emotionality; preoccupation/anticipation, executive function) has not only identified important neurocircuitry mediators but also identified validated clinical targets for intervention. In the present perspective, a hypothesis is outlined that emphasizes a key and often neglected role for the withdrawal/negative affect stage of the addiction cycle, where opponent process, hyperkatifeia, and negative reinforcement sensitize and drive hedonic allostasis, which in turn leads to severe alcohol use disorder or alcohol addiction. Here, with excessive drug and alcohol use, through opponent processes, a greater quantity and more frequent use of a previously rewarding drug (e.g., alcohol) are needed to maintain or approach euthymia. Then, when alcohol is not used, a deficit emotional state emerges, termed hyperkatifeia, which includes irritability, anxiety, dysphoria, sleep disturbances, and subjective feelings of need. Hyperkatifeia then drives compulsive alcohol intake via negative reinforcement processes because the drug transiently prevents or relieves the hyperkatifeia. Then, such alcohol taking for relief perpetuates a self-defeating opponent-process cycle, thereby creating hedonic allostasis, defined as hedonic stability with a shift in set point. Using this framework, the unique nosology of the Addiction Neuroclinical Assessment is allowing more precise insights and translation into prevention, treatment, and recovery. Altogether a greater focus on hyperkatifeia associated with the withdrawal/negative affect stage of the addiction cycle will allow significant alleviation of human suffering that is associated with severe alcohol use disorder.

Keywords : Alcohol use disorder; Hyperkatifeia; Hedonic allostasis ; Negative reinforcement ; Addiction neurobiology

Résumé: L'usage nocif d'alcool et l'addiction à l'alcool entraînent un coût humain, sanitaire et économique considérable, se traduisant par des années de vie perdues ajustées sur l'incapacité, une mortalité élevée et des dépenses médicales importantes. Mieux comprendre les mécanismes neurobiologiques à l'origine de l'addiction à l'alcool est indispensable pour améliorer son diagnostic, son traitement et sa prévention, mais nécessite un cadre conceptuel structurant. Le modèle désormais bien établi du cycle de l'addiction en trois étapes et de ses trois domaines dysfonctionnels (consommation excessive/intoxication – saillance incitative ; sevrage/affects négatifs – émotionnalité négative ; préoccupation/anticipation – fonctions exécutives) a permis non seulement d'identifier les principaux circuits neuronaux impliqués, mais également de définir des cibles cliniques pertinentes pour les interventions thérapeutiques. Dans cette perspective, nous proposons une hypothèse mettant l'accent sur le rôle central, mais souvent sous-estimé, de la phase de sevrage et d'affects négatifs du cycle de l'addiction. Au cours de cette étape, les processus opposants, l'hyperkatiféia et le renforcement négatif sensibilisent et entretiennent un état d'allostasie hédonique, favorisant ainsi l'installation d'un trouble sévère de l'usage d'alcool. Lors d'une consommation excessive et répétée d'alcool, les processus opposants conduisent progressivement à la nécessité de consommer des quantités plus importantes et plus fréquentes d'une substance auparavant gratifiante afin de maintenir, ou de retrouver, un état émotionnel normal (euthymie). En l'absence d'alcool, apparaît alors un état émotionnel déficitaire, appelé hyperkatiféia, caractérisé notamment par de l'irritabilité, de l'anxiété, une dysphorie, des troubles du sommeil et un besoin subjectif impérieux de consommer. Cet état favorise la prise compulsive d'alcool par un mécanisme de renforcement négatif, la consommation permettant temporairement d'atténuer ou de prévenir ces affects négatifs. Cette consommation motivée par le soulagement entretient à son tour un cercle vicieux fondé sur les processus opposants, conduisant à une allostasie hédonique, définie comme le maintien d'un nouvel équilibre émotionnel autour d'un point de consigne durablement altéré. Dans ce cadre conceptuel, la nosologie originale de l'Addiction Neuroclinical Assessment permet une caractérisation plus précise des dimensions cliniques de l'addiction et favorise leur traduction en stratégies de prévention, de traitement et de rétablissement. Dans son ensemble, cette approche suggère qu'une attention accrue portée à l'hyperkatiféia associée à la phase de sevrage et d'affects négatifs du cycle de l'addiction pourrait contribuer de manière significative à réduire la souffrance humaine liée aux formes sévères du trouble de l'usage d'alcool.

Mots-clés : Trouble de l'usage d'alcool ; Hyperkatiféia ; Allostasie hédonique ; Renforcement négatif ; Neurobiologie de l'addiction

1. INTRODUCTION

Alcohol misuse can be defined as drinking in a manner, situation, amount, or frequency that could cause harm to the person who drinks or to those individuals around them (niaaa.nih.gov). Alcohol addiction can be defined as a chronic relapsing disorder, characterized by a compulsion to seek and take alcohol, the loss of control in limiting intake, and the emergence of a negative emotional state when access to alcohol is prevented (Koob, 2021). The World Health Organization defines the "harmful use of alcohol" as "drinking that causes detrimental health and social consequences for the drinker, the people around the drinker and society at large, as well as the patterns of drinking that are associated with increased risk of adverse health outcomes" (World Health Organization, 2010).

Alcohol misuse and alcohol addiction cause enormous suffering and pain to individuals, substantial costs to society (including direct and indirect medical pathology), many premature deaths, and enormous burdens to healthcare systems (Sacks et al., 2015). In 2019, the World Health Organization estimated that alcohol consumption resulted in 2.6 million deaths and 115.9 million disability associated life years (DALYs), which represented 4.6% of all DALYs in 2019, largely attributable to the effects of alcohol misuse on noncommunicable diseases, injuries, and mental health conditions (World Health Organization, 2024).

Alcohol addiction, and addiction in general, has been characterized in a heuristic framework of a three-stage cycle (Koob and Le Moal, 1997). Here, the binge/intoxication stage involves gains in reward, incentive salience, and pathological habits that are associated with alcohol seeking, mediated by the basal ganglia and its neurocircuitry (Koob and Volkow, 2010; Koob and Volkow, 2016). The withdrawal/negative affect stage involves a loss of reward and a gain of stress, mediated by the extended amygdala and its neurocircuitry. The preoccupation/anticipation stage involves impairments in executive function and craving, mediated by the prefrontal cortex and its neurocircuitry. The focus of the present perspective is the often neglected withdrawal/negative affect stage of alcohol addiction and how neuroadaptation in this stage can have a powerful effect in driving alcohol addiction.

2. OPPONENT PROCESS

Early on, opponent process-like adaptations were observed in the study of tolerance to the basic physiology of body temperature, heart rate, and respiratory depression (Martin, 1968). Subsequently, in the domain of hedonic processing, a long-standing dynamic neuroadaptation hypothesis was proposed by Solomon and colleagues, namely opponent process theory, where the initial activation of brain circuits that elicit pleasurable emotional states, termed the *a-process* (e.g., euphoria, contentment, well-being, and satisfaction), is followed by opposite effects, such as dysphoria and depressed mood, known as the opponent process or *b-process* (Solomon and Corbit, 1974; Solomon, 1980). In the context of alcohol addiction, the *a-* and *b-processes* were hypothesized to be temporally linked, where alcohol intoxication produces time-limited positive hedonic effects or rewarding effects, termed the *a-process*, followed by negative emotions or negative hedonic effects or negative emotions, termed the *b-process* or opponent process (Solomon, 1980). The *b-process* was argued to have a longer onset latency, slower recruitment, and more inertia and exhibit slower recruitment and a more prolonged decay than the *a-process*. With longer exposure to the drug, the *b-process* gets progressively larger and has been hypothesized to subtract out the *a-process* to produce what has been argued to represent counteradaptive tolerance (Colpaert, 1996; Laulin et al., 1999; Solomon, 1980; Solomon and Corbit, 1974).

3. HYPERKATIFEIA

Hyperkatifeia is defined as the greater intensity of negative emotional/motivational symptoms and signs that are observed during withdrawal from drugs of addiction (Shurman et al., 2010) and essentially represents the phenotype of both opponent processes and the motivational component of alcohol withdrawal (Koob, 2021). The word was derived from the Greek word *katifeia* for dejection, sadness, or negative emotional state. As such, hyperkatifeia is hypothesized to represent such elements as dysphoria, irritability, alexithymia, or simply symptoms that are often described as ill at ease, uncomfortable within one's own skin, or simply not hedonically normal, symptoms that have been historically difficult to define. Hyperkatifeia has been proposed to worsen with repeated experience and to represent the motivation and driving force for negative reinforcement in acute and protracted withdrawal not only from alcohol and opioids but also all major drugs of addiction (Koob, 2021).

4. NEGATIVE REINFORCEMENT

Ultimately, as one enters the withdrawal/negative affect stage of the addiction cycle or joins the addiction cycle via the withdrawal/negative affect stage (e.g., alcohol as self-medication), one engages an additional and powerful source of motivation, negative reinforcement. Positive reinforcement is defined as the process by which the presentation of a stimulus (drug) increases the probability of a response (nondependent drug-taking paradigms). Negative reinforcement is defined as the process by which the removal of an aversive stimulus increases the probability of a response. Thus, negative reinforcement is driven by hyperkatifeia, where a greater amount and more frequent use of the initially rewarding alcohol is needed to maintain or approach euthymia (Vendruscolo and Koob, 2026).

5. ALLOSTASIS

Historically, one may extrapolate hedonic homeostasis from the basic precepts of physiological homeostasis, defined as a self-regulating process for maintaining stability within physiological systems while holding the parameters of the organism's "milieu interieur" within prescribed limits that allow an organism to survive (Bernard, 1865; Cannon, 1932). However, as outlined above with opponent process, repeated drug taking does not allow time for the hyperkatifeia that is produced by opponent processes to return to the normal hedonic range.

In contrast to homeostasis, the construct of allostasis, defined as the process of maintaining stability or "apparent stability" with change but at a cost (Sterling and Eyer, 1988), has been applied to explain the dysregulation of hedonic homeostasis that is associated with compulsive drug seeking. Here, affect regulation fails to return to homeostatic levels because of a lack of sufficient time for neural emotional systems to recalibrate in the context of maintaining function. Under this framework, hyperkatifeia becomes the driving force for hedonic allostasis and maintenance of the addiction cycle. In alcohol addiction, such allostatic shifts have long been hypothesized to be mediated by the loss of reward function in basal ganglia neurocircuits and the gain of brain stress or anti-reward function in the extended amygdala (Koob and Le Moal, 1997; Koob and Le Moal, 2001; Koob, 2021; Koob and Volkow, 2010; Koob and Volkow, 2016; Vendruscolo and Koob, 2026).

6. CLINICAL IMPLICATIONS : ADDICTION NEUROCLINICAL ASSESSMENT FRAMEWORK

The identification of an overall heuristic framework for the neurobiology of alcohol addiction (and addiction in general) that involves a three-stage/three-domain/three-neurocircuitry model led to the development of the Addictions Neuroclinical Assessment to validate the three domains of dysfunction that were hypothesized in the three-stage cycle framework and to unravel the heterogeneity and etiology of alcohol use disorder (Kwako et al., 2019; Gunawan et al., 2024). In an early study, measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected from 454 patients from the U.S. National Institutes of Health Clinical Center (Kwako et al., 2019). The study confirmed the relevance of the three neurofunctional domains to alcohol use disorder. Using a multiple indicators, multiple causes approach, early life stress and sociodemographic factors were identified as predictors. Thus, in a large, diverse clinical sample that represents the spectrum of alcohol use disorder, the three neurobiological domains that are hypothesized to be critical to the addiction cycle (incentive salience, negative emotionality, and executive function) were identified through factor analysis (Kwako et al., 2019). Subsequently, the Addiction Neuroclinical Assessment has been clinically validated and has formed a framework for novel preclinical-to-clinical translation.

For example, among heavy drinkers, three factors (executive function, incentive salience, and emotionality) were all associated with current alcohol use disorder. Significant predictors included a history of alcohol use disorder, a positive family history of alcohol dependence, an earlier age of first drink, and a history of childhood emotional abuse and physical neglect (DeMartini et al., 2021). In another study of heavy drinkers, four core constructs were identified: incentive salience, negative emotionality, executive function, and negative alcohol-related consequences (Nieto et al., 2021).

In nontreatment seekers, deep phenotyping, combined with factor analytic techniques, implicated three intercorrelated neurofunctional domains that mapped onto the proposed Addiction Neuroclinical Assessment domains with methamphetamine use (Nieto and Ray, 2022), and in nontreatment seekers, subjects who were undergoing functional

magnetic resonance imaging after exposure to alcohol-related cues and negative cues showed functional changes in the nucleus accumbens and amygdala that were associated with incentive salience and negative emotionality domains (Al-Khalil et al., 2021).

A subsequent cross-sectional observational study assessed the three domains in an independent prospective clinical sample. Receiver operating characteristic curves showed that alcohol motivation and alcohol insensitivity factors from incentive salience domain, internalizing factors from the negative emotion domain, and impulsivity factors from executive function domain had the greatest ability to classify individuals with alcohol use disorder (Gunawan, et al., 2024). In addition, in a study among treatment seekers with alcohol use disorder, the incentive salience domain showed construct validity and greater predictive validity for drinking outcomes compared with preexisting scales (Stein et al., 2021). In a secondary analysis of individuals with alcohol use disorder who participated in two alcohol clinical trials, the negative emotionality domain showed construct validity and demonstrated concurrent associations with more frequent and heavier drinking and drinking to regulate negative affect (Votaw et al., 2020), and greater relief/negative emotionality at baseline predicted greater drinking intensity and more frequent heavy drinking during recovery (Witkiewitz et al., 2023).

7. SUMMARY: ALLOSTASIS, OPPONENT PROCESS, HYPERKATIFEIA, AND NEGATIVE REINFORCEMENT

In excessive drug and alcohol use, through opponent processes, a greater quantity and more frequent use of a previously rewarding drug (e.g., alcohol) are needed to maintain or approach euthymia (termed tolerance). Then, when alcohol is not used, negative emotional signs of withdrawal emerge, such as irritability, anxiety, dysphoria, sleep disturbances, and subjective feelings of need. This deficit emotional state, or hyperkatifeia (Shurman et al., 2010), sensitizes and becomes persistent with repeated use, known as protracted hyperkatifeia. Under this conceptualization, drug intake is compulsively escalated or renewed (in relapse) via negative reinforcement processes because the drug transiently prevents or relieves the hyperkatifeia. Drug taking for relief ultimately becomes self-defeating because it worsens and perpetuates the vicious opponent-process cycle, thereby creating hedonic allostasis (hedonic stability with a shift in set point). Using this framework and the unique nosology of the Addiction Neuroclinical Assessment, more precise insights into prevention, treatment, and recovery will promote the translation of basic preclinical research to clinical utility and will allow significant alleviation of human suffering that is associated with alcohol use disorder.

8. REFERENCES

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