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EDITORIAL

Editorial Special Issue on "Nature vs nurture in addiction research"

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Introduction

The idea of this special issue organized by Charles W Bradberry came from a symposium entitled "Nature, nurture and redemption: how human cross-sectional imaging studies of cocaine users are informed by longitudinal clinical and preclinical research " at the biennial meeting of the European Behavioural Pharmacology Society (EBPS) held in Braga (Portugal) in 2019. Here is below the presentation of the whole issue collected since on the related topic.

This special issue of Psychopharmacology on Nature vs Nurture in Addiction Research addresses an enduring question that applies to our observations of most of the natural world. Where does the balance lie between inherited risk and environmental influence? Inevitably, it is a combination of the two, but trying to ascertain the distinction between the two can better inform our understanding of where societies can ameliorate influences that contribute to drug use that crosses into the realm of injury. There is an increasing awareness that injury is in the eye of the beholder, and that its extent is hugely dependent on how society at large frames the legal context in which drug use occurs. The significance of this framing effect and its justification (or not) is eloquently addressed in Hanna Pickard's article: "Is addiction a brain disease? A plea for agnosticism and heterogeneity." Therein are strong statements on the fallacy of interpreting differences to indicate dysfunction and an elegant analysis of "Brain Disease as a Model of Addiction (BDMA)" articulated by Alan Leshner. She addresses the risks associated with the good intention of destigmatizing addiction in the hope of greater compassion toward those who harm themselves with substance use and increased funding for research into the neurobiology of drug use and abuse. Ironically, she presents evidence that the intended effect of reducing stigma is actually not achieved. When introduced, BDMA coincided with the War on Drugs in the 80 s and 90 s, whose battle lines often paralleled those of race. She notes that, perhaps not coincidentally, as the current opioid epidemic damages society more broadly, there is a more sympathetic view of those whose lives are damaged. She also addresses the conceptually critical question of what is a brain disease because "few advocates or critics of the view that addiction is a brain disease have provided an account of what a brain disease is."

Driving the question of nature vs nurture is the observation of individual differences. In their study, "Investigating Individual Differences in Opioid-taking and Opioid-seeking Behavior in Male Rats," Chang et al., address the commonality of individual differences in response to novelty and sign-tracker/goal-tracker status to both cocaine and opioid self-administration. Acquisition of self-administration and the propensity to relapse in response to cues were examined. The opioid used, remifentanil, is a particular strength of this study because, like cocaine, it also has short half-life. A strong study design shows that those traits that confer the initiation of cocaine use and the propensity to reinstate cocaine-seeking behavior following abstinence appear to be distinct from those that confer the initiation of opioid use and the propensity to reinstate opioid-seeking behavior. These clear differences in contextual effects bring to mind the striking differences demonstrated in translational studies from the Badiani lab distinguishing cocaine and opioid reinforcement.

Another study from the Flagel lab, "Inhibition of a Cortico-Thalamic Circuit Attenuates Cue-induced Reinstatement of Drug-seeking Behavior in "Relapse Prone" Male Rats," Kuhn et al. examine the role of the prelimbic cortex (PRL) to paraventricular thalamus (PVT) circuit, implicated in cue-reward learning. This was studied in relation to individual differences in propensity to relapse to

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cocaine self-administration. The sign-tracker/goal tracker groups were compared in both cue-induced and drug prime induced relapse. Chemogenetic inhibition of the PRL/PVT circuit reduced cue-induced relapse in the sign-trackers, with no effect on goal-trackers. It had no effect on drug prime induced relapse. Comparing groups of rats with high and low locomotor responses to novelty showed no effect on either type of relapse in either group, demonstrating a unique selectivity of this circuit in environmentally induced relapse in a specific subset of behaviorally distinct animals. Their results address the nature vs nurture emphasis of this issue in that the effects of cocaine on neuronal plasticity within the PrL, and specifically within the PrL-PVT pathway, are dependent on an inherent tendency to attribute incentive motivational value to reward cues.

Environmental influences on methamphetamine self-administration were investigated by Nicolas et al. in their study "Prevention of Relapse to Methamphetamine Self-administration by Environmental Enrichment: Involvement of Glucocorticoid Receptors." They demonstrated that following an extended period of methamphetamine self-administration, a three week exposure to an enriched environment reduced seeking for the drug relative to a standard environment. Post-mortem evaluation of glucocorticoid receptors (GR) revealed that the enriched environment prevented a methamphetamine-induced increase in GR levels in dorsal and ventral hippocampus. In the amygdala, enriched environment by itself decreased GR levels in the amygdala, but this effect was blocked by methamphetamine self-administration. To further demonstrate the effects on drug seeking were likely mediated by anti-stress effects of an enriched environment, they demonstrated that the GR antagonist mifepristone (RU-486) dramatically reduced methamphetamine seeking in a separate group of rats.

Environmental factors were further examined by Webb et al., in their paper "The Effect of Adolescent Social Isolation on Vulnerability for Methamphetamine Addiction Behaviours in Female Rats," by studying the effect of social isolation stress during adolescence on a range of measures relevant to DSM criteria for substance use disorder in females. As the authors note, females are "the understudied sex," though hopefully mandates to include both males and females will help correct this moving forward. The point is made that while female rats are affected by adolescent stress more than males, and show more behavioral indices of methamphetamine dependence, the effects of social isolation stress on behavioral markers of methamphetamine dependence and stress induced relapse have almost solely been studied in males. The results observed present a complex picture of reduced initial intake in isolation stressed females vs controls, but more pronounced acute stress induced relapse using a yohimbine challenge, potentially implicating noradrenergic mechanisms.

Another paper that utilizes isolation as a stressor is by Singh et al., "Early Social Isolation Stress Increases Addiction Vulnerability to Heroin and Alters c-Fos Expression in the Mesocorticolimbic System." They examine the effects of early social isolation stress on measures relevant to addiction, this time in mice, using both sexes for self-administration studies of heroin self-administration. The early life stressor had no effect on acquisition for sucrose or heroin self-administration, but in a vertical shift of the dose response curve, increased the amount of heroin self-administered in female mice. When using c-Fos as a marker of neural activity, they observed that the social stress decreased c-Fos expression in prelimbic cortex, infralimbic cortex, and the nucleus accumbens after a fourteen day forced abstinence. However, social isolation stress augmented the neuronal responses to heroin-associated cues in infralimbic cortex and nucleus accumbens, and disrupted an association between c-Fos expression in the prelimbic cortex and responding during a heroin seeking test.

In their translational paper, "Peer Presence and Familiarity as Key Factors to Reduce Cocaine Intake in Both Rats and Humans: an Effect Mediated by the Subthalamic Nucleus," Giorla et al. examine the protective effect of peer presence at reducing cocaine consumption. Parameters examined include familiarity and non-familiarity of the peer, as well as drug-taking experience of that peer. Cross-sectional clinical comparisons corroborated the protective effect of peer presence at reducing cocaine consumption. Importantly, the role of the subthalamic nucleus (STN) in the peer effects was also examined, because extensive prior work has shown the importance of the STN in the value distinction between drug and non-drug reward. Here, it was observed that reducing STN activity further enhanced the protective effect of peer presence, regardless of the familiarity of the peer. This involvement of the STN was further demonstrated by an ability of STN lesion to remove the influence of dominance status of the peer in a social conditioned place preference.

In a study characterizing individual differences in ethanol consumption, Smeets et al., present "On the Interrelation Between Alcohol Addiction–Like Behaviors in Rats." Here they explore the interrelationship between four different behavioral measures in rats believed to be reflective of alcohol use disorder (AUD) in humans. These were total consumption (measured during intermittent access), habit formation (outcome devaluation), motivation to consume (progressive ratio), and insensitivity to negative consequences (consumption of quinine adulterated alcohol). A subset of 11% of all subjects scored high on all four of the measures, and were deemed to show AUD like behavior. That subset significantly differed from the others on all measures except that of habit formation. Among all animals, only total consumption and insensitivity to quinine

were correlated. The results are interpreted to indicate the procedures offer an opportunity to study the heterogeneity of behaviors related to AUD clinically.

In a clinically relevant study by Vandaele and Ahmed, "Choosing Between Cocaine and Sucrose Under the Influence: Testing the Effect of Cocaine Tolerance," the authors delved into a potential mechanism for why preference for cocaine over non-drug reward shifts so dramatically once rats are under the pharmacological influence of the drug. In order to evaluate if anorexic effects drive the observation, "contingent tolerance," to those effects was induced through an active learning process. However, contrary to expectation, tolerance did not alter the observed preference. Potential mechanisms underlying their results are thoughtfully discussed in the context of the clinically important distinction between relapse in the absence of drug and subsequent consumption in its presence.

Deficits in emotion recognition have been observed in addiction, but the effects of cocaine use have been mixed. Rabin et al. examine this issue further in their paper, "Emotion Recognition in Individuals with Cocaine Use Disorder: the Role of Abstinence Length and the Social Brain Network." This study clarifies these effects, and using a cross-sectional approach, examines the potential role of altered brain structure using groups of current users, short- and long-term abstinent users, and controls. Deficits in the recognition of happiness, fear, and sadness were observed in the current users. Structural imaging and voxel-based morphometry revealed that, collapsed across all subjects, poorer recognition of happiness was associated with reduced gray matter volume in the right cerebellum. Pertinent to the question of nature vs nurture focus of this issue, there was a significant positive relationship between duration of abstinence and gray matter volume in cerebellum, however, abstinence duration did not mediate the relationship between gray matter volume and emotion recognition.

Hopefully this collection of outstanding contributions to the literature, covering a broad range of behavioral, neurobiological, and philosophical approaches, will help inform those interested in the question of the relative contributions of inherent, vs environmentally conferred differences in measures of drug use.

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