



## Genetics and epigenetics approaches as a path to the future of addiction science

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Addiction is a complex and intractable disorder that exacts huge costs from both its sufferers and their communities. The opioid crisis has brought the lethal cost of substance use disorders into clear view, but remedies to the problem remain to be discovered. It is the mission of the National Institute on Drug Abuse (NIDA) to “advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health,” and it is clear that some out-of-the-box thinking will be needed to reach this goal.

The Avenir Award for Genetics or Epigenetics of substance abuse is a NIDA award program designed to bring new, young investigators and their innovative ideas into the field of addiction research. We, the authors of this perspective, have been privileged to be a part of this initiative as proposal reviewers and as one of the earliest award recipients (Day). To highlight advances in the science of substance use disorders, we invited the Avenir award winners to contribute an article to this special issue. Contributions from 16 of the Avenir recipients are included in this collection, covering the full range of supported research in the areas of genetic variation, epigenetic regulation and transcriptional networks, RNA regulation, single cell and cellular tagging methods, computational approaches, and development.

This series is introduced in an associated Preview by NIDA Director Nora Volkow together with Genetics, Epigenetics, and Development (DNB) branch chief Jonathan Pollock, and DNB Coordinator for Trans-NIH Programs and Activities, John Satterlee (Satterlee et al., 2023). The people who work at NIH make a huge difference in how initiatives are translated into research reality and having worked with this NIDA trio for the past decade, we are pleased to have the opportunity to highlight the impact of their program on progress in this field.

The articles in this collection address some of the most important facets of the genetics and epigenomics of substance use disorder.

Like many other neuropsychiatric conditions, individuals show distinct degrees of susceptibility and resilience to the development of substance use disorders. Though environment plays a significant role in the vulnerability to addiction, there is a genetic component to risk as well. However, the contributions of specific gene variants to addiction susceptibility remain to be fully understood. Four articles in this collection highlight new computational methods and conceptual models for

identifying how genetic variation across human populations is linked to increased risk for addiction to different substances.

**Rohan Palmer** describes how his group has worked to identify genes associated with alcohol withdrawal, including how they leveraged cross-species integration with gene expression data from animal models of alcohol exposure (Benca-Bachman et al., 2023). **Qian Peng** presents a study using machine learning algorithms to identify genomic loci related to cannabis use disorder severity (Peng et al., 2023), and **Shuo Chen** describes how they are using methods derived from graph theory to narrow in on the specific genetic variants that associate with nicotine dependence (Mo et al., 2023). Finally **Steve Oghumu** raises a novel idea that addresses sex differences in addiction head on in his review of the evidence for how regulation of genes on the X chromosome can contribute to sex-differences in animal models of addictive-like behaviors (Krueger et al., 2023).

The persistence of addictive behaviors even after drug use has ceased has driven the search for molecular mechanisms that can support long-term, drug-induced memories in the brain. One promising candidate is the epigenome, which is comprised of the histone and DNA modifications that define the regulatory state and physical structure of chromatin across genomic DNA. Chromatin can be modified by signaling pathways activated by sensory experiences to change the programs of gene expression in neurons and other brain cells and thus has the potential to translate environmental exposures like drug use into changes in regulation of gene transcription. Many of the papers in this collection use leading edge methods for sequencing RNA and chromatin in the context of drug exposures to reveal the impact of epigenomic regulation on the brain transcriptome.

**Erin Calipari** asks how the transcriptional response to cocaine changes based on an animal's history of prior drug exposure. Her study identifies a program of genes that flip their direction of regulation in mice that were withdrawing from cocaine compared with naïve animals, revealing the importance of experiential context in the brain response to these drugs (Emerson et al., 2023). Though the Calipari study found a common pattern of gene regulation between brain regions, a major direction of transcriptional research has been focused on cell-type specific responses to stimuli. **William Renthal** uses single nucleus sequencing of

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chromatin accessibility in the mouse nucleus accumbens to find cell-type specific transcription factor binding sites that they interrogate for overlap with genetic variants associated with different neuropsychiatric disorders (Bhatia et al., 2023). **Jeremy Day** uses single cell RNA sequencing to identify a specific subpopulation of dopamine D1 receptor expressing neurons in the nucleus accumbens of rats that show the predominant transcriptional response to cocaine (Phillips III et al., 2023), whereas **Luis Tuesta** reviews the evidence that drugs of abuse act via transcriptional and epigenomic regulation of microglia (Vilca et al., 2023). As an alternative to the heterogeneity of the brain, **Albert Keung** shows that human embryonic stem cells can be differentiated to striatal-like neurons in culture in order to assess the transcriptional responses to different neurotransmitters applied for distinct durations that mimic acute and chronic exposure to drugs of abuse (Tam and Keung, 2023). **Stephanie Sullivan** reminds us that protein-coding messenger RNAs are not the only RNAs in the brain, and she reviews the evidence that induction of circular RNAs by drugs of abuse can have a regulatory impact on neural substrates that regulate drug seeking behaviors (Sullivan and Gillespie, 2023). Finally, **Ian Maze** shares the latest in his fascinating investigation of the role played by the ability of dopamine to directly post-translationally modify histones, showing here a brain-region specific function for this chromatin modification in cocaine seeking (Stewart et al., 2023).

Several of the Avenir winners featured in this collection, as well as the two newest award winners in 2023, have focused their work on opioids given the urgency of this public health problem. Their studies include those seeking to understand the fundamental functional organization of the opioid system in the brain or to discover novel understanding of mechanisms that can lead to non-opioid methods for pain reduction.

**Drew Kiraly's** contribution focuses on gut-brain interactions in the neural transcriptional response to opioids, which is a topic of great interest given the potential of the gut microbiome as a druggable target (Sens et al., 2023). **Christina Woo** reviews how opioids can be chemically modified to use as probes to study opioid receptor distributions and function, advancing neurobiological understanding of the action of these drugs (Leon Duque et al., 2023). Excitingly, she also describes how functionalized opioids are being used in vaccines to prevent the development of opioid use disorder. Finally, **Megan Matthews** reports how her lab is using click chemistry to find new targets for pain therapeutics by exploiting novel mechanisms of drugs with anti-pain and anti-abuse potential (Bustin et al., 2023).

The final set of articles focus how experiences that occur during brain development may set the stage for the later risk of substance use disorders. Understanding the sensitive time periods and mechanisms by which early life experience influences risk offer hope for interventions that can offset genetic or social predispositions to future addiction.

**Liz Heller** reviews preclinical studies that show how adverse early life experiences including stress and drug exposure can change brain transcription in ways that predispose to addictive behaviors (Winter et al., 2023). **Mathieu Wimmer** looks into the important idea of transgenerational transfer of risk for substance use disorders as he presents the results of a study showing how paternal morphine exposure can influence the adolescent behavior of their male offspring (Zeid et al., 2023).

This article collection represents only a fraction of the research that has emerged from the NIDA Avenir award program in genetics and epigenetics of substance abuse, yet even this snapshot shows how this program has led to fundamental advances in understanding of sex differences, cell-type specific brain functions, neuropsychiatric therapeutics, and genome function. "Avenir" means "future" in French and derives from the phrase *temps à venir* ("time that is to come"). Thus, the

selection of this name for an early career investigator award platform is entirely appropriate, and we could not be more excited by the bold and innovative ideas that have been supported by the program. This is where the future of addiction science will be found - in the fundamental understanding of brain function.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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