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The science of addiction

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Life expectancy in the United States has fallen for the first time in decades, a shocking trend driven by so-called "deaths of despair" involving drug overdoses, suicides, and diseases attributable to substance abuse and stress. The country is in the midst of a veritable epidemic of opioid use. Over 99% of the world's supply of the powerful opioid drug hydrocodone, the active ingredient in Vicodin, is consumed by the United States. Illicit synthetic opioids such as fentanyl are also flooding across the border. Alcohol sales have increased in recent years, while numbers of individuals testing positive for cannabis, cocaine, and methamphetamine in the workplace are at an all-time high. The U.S. Food and Drug Administration (FDA) has approved several treatments for opioid use disorder (OUD). These include the slow-acting opioid receptor agonists (or partial agonists) buprenorphine and methadone that attenuate the intense cravings for opioid drugs during abstinence, and the fast-acting opioid receptor antagonist naloxone that quickly reverses opioid overdose if used in time. The available medications all share one feature in common—they have limited clinical efficacy for the treatment of OUD. As a consequence, treatment-seeking individuals have considerable risk of relapse to opioid use even when treated with the most effective medications and behavioral approaches available. Individuals attempting to quit cannabis, cocaine, or amphetamines face an equally daunting challenge, as they remain vulnerable to relapse for months or even years, yet there are no FDA-approved medications to help maintain abstinence. Thus, there is a pressing need to better understand the pathophysiology of substance use disorders (SUDs) so that more effective treatments can be developed.

Genetic contributions to addiction

Large-scale human genetic association studies have identified gene variants that influence the risk of SUDs. Many of these variants reside within genes that code for potentially "druggable" proteins, which may represent novel targets for medication development. Allelic variation in the *OPRM1* gene, which encodes the μ opioid receptor (MOR), increases OUD risk (*1*). MORs are the principal receptors through which opioid drugs exert their euphorigenic and analgesic properties and are the major targets for the therapeutic actions of methadone, buprenorphine, and naloxone. Other potentially druggable gene variants that influence risk of OUD include *KCNN1* and *FURIN* (*1*). Allelic variation in the *CHRNA2* gene, which encodes the α2 nicotinic acetylcholine receptor (nAChR) subunit, increases risk of cannabis use disorder (*2*). Other nAChR genes, particularly *CHRNA5* encoding the α5 subunit, regulate vulnerability to alcohol, cocaine, and tobacco use disorders (*3*). Studies using cultured human neurons are identifying functional consequences of these risk-associated gene variants, consistent with their involvement in addiction (Fig. *1*). The adoption of electronic health records (EHRs) by many healthcare systems in the United States promises to revolutionize our understanding of the genetics of SUDs. Linking genetic information to the wealth of data contained in EHRs will help identify genes that influence vulnerability to addiction. Such information may also predict the course of the disorder in individual patients and identify those most likely to benefit from specific therapeutic interventions.

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Neural circuitry underlying addiction

Mesocorticolimbic circuits in the brain have been the major focus of addiction research over the past 30 years (Fig. *1*). However, many addiction-associated genes are expressed preferentially or exclusively in brain regions that have received relatively scant attention in the context of SUDs. For example, the highest concentrations of MORs in the brain are found in neurons of the medial habenula that project to the interpeduncular nucleus (IPN). Similarly, the *CHRNA2* and *CHRNA5* genes that influence vulnerability to SUDs are expressed almost exclusively in the habenula–IPN circuit. Little is known about the function of the habenula–IPN circuit, but emerging evidence suggests that it regulates aversive responses to drugs of abuse that reduce the risk of addiction (*4*), and undergoes striking structural and functional adaptations in response to drug use (*5*). MORs are also densely expressed in other aversion-related brain regions, such as the parabrachial nucleus. Notably, the parabrachial nucleus has been implicated in the respiratory depression that contributes to opioid overdose-related deaths (*6*), but its involvement in the motivational properties of opioid drugs is unclear. Hence, human genetics studies are revealing not just gene variants that influence addiction vulnerability, but pointing as well to novel brain circuits that are likely involved. The emergence of new spatial transcriptomics and barcoding technologies, in vivo brain imaging approaches with single-cell resolution, and sensors that can track neurotransmission with unprecedented spatiotemporal precision will facilitate better understanding of the actions of drugs of abuse on brain circuits. Advances in optogenetics, chemogenetics, and other methods of brain modulation, particularly those that are non-invasive, may enable circuit-based approaches for the treatment of SUDs (*7*). Unique small-molecule drugs that modulate neuronal circuits involved in addiction may provide additional treatment options (*8*).

Molecular and cellular basis of addiction

Drugs of abuse induce striking structural and functional remodeling of neurons throughout the brain, and addiction is largely considered a disorder of neuroplasticity (*9*). The long-lasting alterations in brain function that drive addiction reflect the ability of drugs of abuse to engage complex programs of gene expression that control such maladaptive plastic changes (Fig. *1*). Groundbreaking studies over the past 15 years have revealed crucial roles for epigenetic and noncoding RNA mechanisms in drug-induced neuroplasticity (*9-12*). Remarkably, recent findings suggest that classical neurotransmitters such as dopamine can be covalently appended to histone proteins to influence gene expression in the brains of animals exposed to drugs of abuse (*13*). These findings suggest that molecular machineries that regulate chromatin function may be novel targets for medication development to treat SUDs. Studies exploring drug-induced changes in gene expression have focused almost exclusively on neurons. Over the past 2 to 3 years, single-cell RNA sequencing (scRNA-seq) technologies have shown that non-neuronal cells are of-

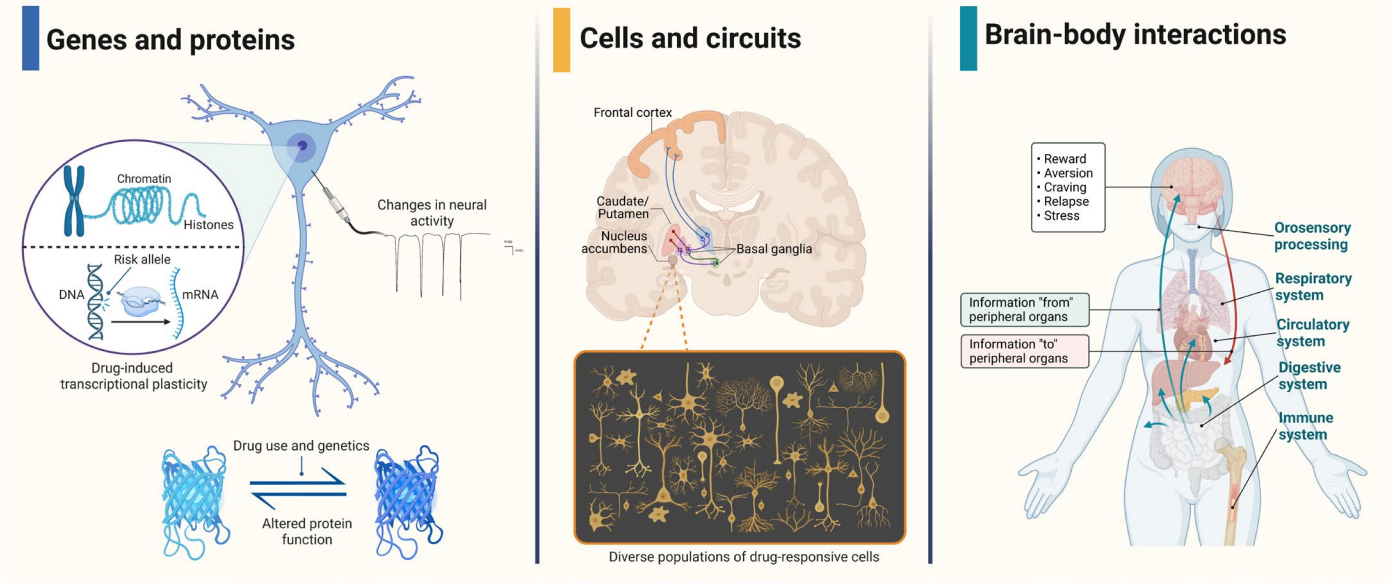

Figure 1. Multiscale actions of addictive drugs drive substance use disorders. Genetic risk factors influence drug-induced changes in gene expression and protein function that precipitate long-lasting alterations in cellular function in the brain (left panel). Drug-induced modifications in the function of neurons and non-neuronal cells alter the activity of brain circuits that influence reward, aversion, and other addiction-related behavioral processes (middle panel). Drugs of abuse remodel addiction-related brain circuits by direct actions in the brain and indirect actions in the periphery (right panel).

ten more transcriptionally responsive to drugs of abuse than neurons, particularly astrocytes and microglia (*14*). Astrocytes maintain glutamate homeostasis in the brain while microglia prune synaptic contacts between neurons and secrete neuroregulatory factors to influence synaptic transmission. Drug-induced perturbations in the function of these glial cells may contribute to the abnormalities in neurotransmission that underlie relapse vulnerability. Intriguingly, scRNA-seq has shown that lesser-studied non-neuronal cells in the brain also demonstrate striking transcriptional responses to drugs of abuse, including periventricular ependymal cells, vascular epithelia, and oligodendrocytes (*14*). Remodeling of these non-neuronal cells may contribute to SUDs through as-yet unknown mechanisms.

Brain–body interactions in addiction

Finally, drugs of abuse can modulate brain function through indirect actions in the periphery (Fig. *1*). MORs, nAChRs, and other addiction-relevant receptors are expressed in peripheral tissues such as the mouth, lungs, and heart that come into direct contact with drugs of abuse before they enter the brain (*15*). Peripheral actions of addictive drugs contribute to their interoceptive properties that influence drug-taking behavior. Nevertheless, remarkably little is known about how drug-related sensory information is routed to the brain and processed by circuits that control drug-seeking (see article in this booklet by Swirski). The emergence of whole-body activity mapping procedures, such as vDISCO, will facilitate better understanding of the peripheral actions of addictive drugs. This may reveal peripherally located targets for medication development, thereby avoiding difficulties associated with getting medications across the blood–brain barrier.

In summary, SUDs and other neuropsychiatric abnormalities are perhaps the least well understood and most difficult to treat of any health affliction. Progress in the development of new treatments depends on the continued incorporation of cutting-edge technologies to better understand the long-lasting molecular, cellular, circuit, behavioral, and whole-body actions of drugs of abuse that cause addiction.

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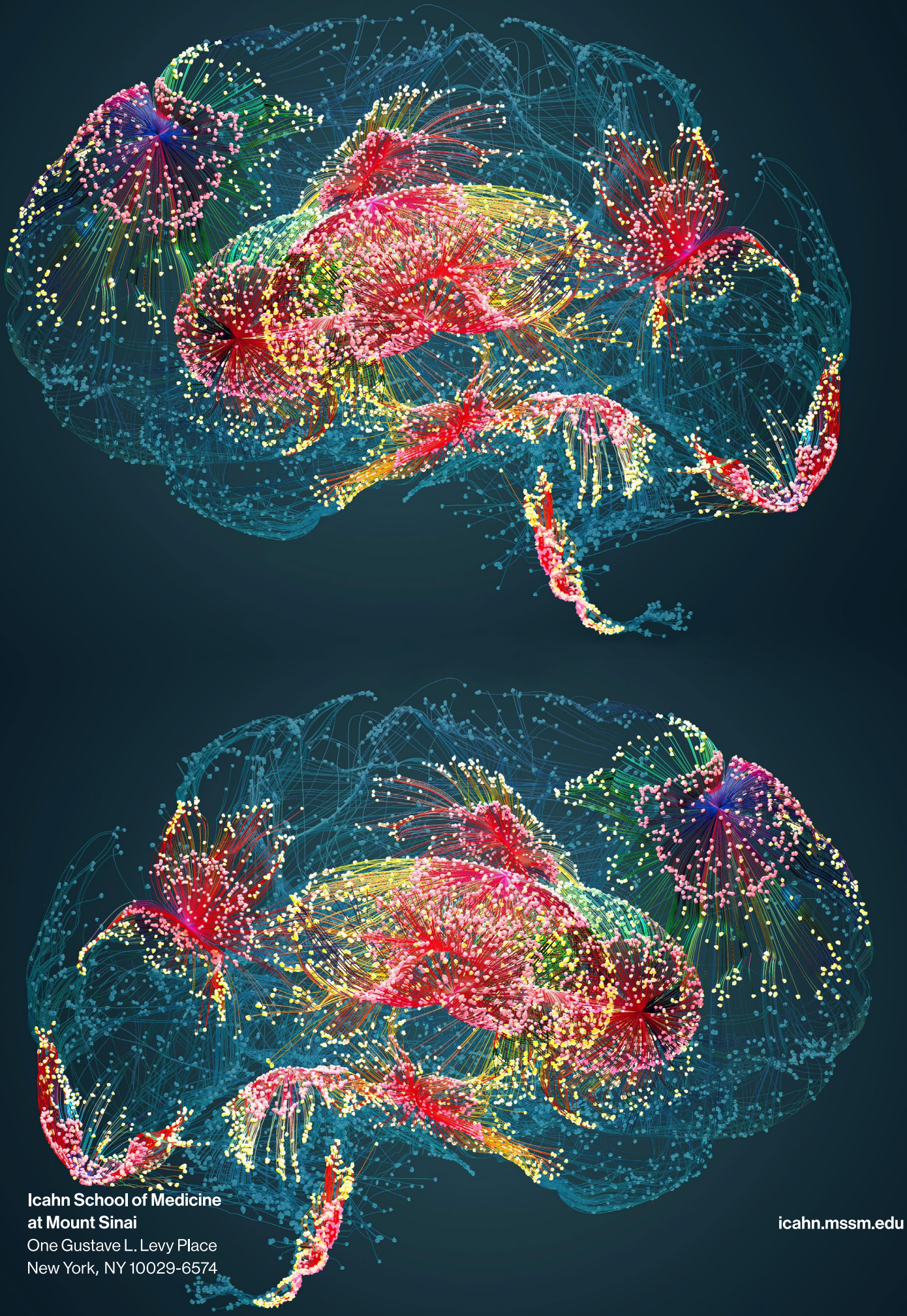

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