nature neuroscience

The neuroscience of addiction

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The burden of substance abuse and addiction to society is enormous, with an estimated annual economic impact in the United States of approximately half a trillion dollars arising from medical consequences, loss of productivity, accidents and crime[1]. The impact of drugs and alcohol on children is particularly problematic, as adolescents are significantly more vulnerable than adults to substance abuse and to addiction[2]. Also, because many of the molecular targets affected by drugs are involved with brain development, substance abuse during childhood and adolescence has the potential to be particularly deleterious. Indeed, it has been shown that children who begin using alcohol early in childhood (ages 14 or younger) are four times more vulnerable to becoming addicted to alcohol later in life than are those who begin drinking at 20 years of age or older[3].

Scientists are now able to portray addiction as a medical disease with physiological and molecular changes thanks to the scientific and technological advances that have occurred over the past decade. The articles in this issue highlight some of the remarkable progress that has revolutionized our understanding of the neurobiology of addiction and the way we treat it. Here we highlight some of the compelling neuroscientific questions about substance abuse, the answers for which will further improve prevention and treatment of addiction.

In this editorial we use the term addiction rather than drug dependence, which is the clinical term favored by the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM-IV), to avoid confusion with physical dependence. Physical dependence refers to the adaptations that result in withdrawal symptoms when drugs such as alcohol and heroin are discontinued. Those are distinct from the adaptations that result in addiction, which refers to the loss of control over the intense urges to take the drug even at the expense of adverse consequences.

Why do some people become addicted and others do not?

Addiction has a significant genetic component. In fact, it is estimated that 40–60% of the vulnerability to addiction can be attributed to genetic factors[4,5]. These estimates of heredity include the percentage of the variance attributed to genetic factors by themselves as well as the percentage of the variance that is attributed to gene-environment interactions. Genotypic vulnerability for addiction is often suggested to reflect both variability in metabolism of the drug and variability in the sensitivity to the reinforcing effects of the abused substance[6]. However, addiction-prone and addiction-resistant phenotypes may also reflect sensitivity to the various stressors and alternative reinforcers in an individual's environment[7,8]. As we gain knowledge of the individual differences in genes and the gene-environment interactions that make a person more vulnerable to addiction, we will be able to tailor interventions for those at high risk.

Why does addiction begin most frequently during adolescence?

Experimentation with drugs and alcohol often starts in adolescence, and so does the process of addiction[1]. This could reflect normal adolescent-specific behaviors (risk-taking, novelty-seeking, response to peer pressure) that increase the probability of someone experimenting with drugs and alcohol, and perhaps could also reflect the incomplete development of brain regions involved in the processes of executive control and motivation (for example, myelination of frontal lobe regions)[9]. Furthermore, preclinical studies indicate that the neuroadaptations that occur in adolescents exposed to certain drugs such as nicotine or cannabinoids are different from those that occur during adulthood[10–12]. Much research is currently focused on finding out whether the sensitivity to neuroadaptations during adolescence generalizes to other drugs and to alcohol, and whether this phenomenon could underlie the greater vulnerability to addiction in individuals who start using alcohol, nicotine and marijuana early in life[13,14]. Better knowledge of the adolescent brain, its normal functioning and how it responds to social stressors and reinforcers will allow us to develop strategies to engage adolescents in productive and creative ways that will minimize their chances of experimenting with drugs.

Why do addicted people often have other mental illnesses?

Individuals suffering from a variety of different disorders (such as depression, anxiety disorder, ADHD and schizophrenia) are at a much higher risk of abusing drugs and alcohol. Similarly, substance abusers and addicted individuals have a higher prevalence of mental disorders than the rest of the population. These robust comorbidities are likely to reflect overlapping environmental, genetic and neurobiological factors that influence substance abuse and mental illness. Comorbidities may emerge, in certain instances, when individuals afflicted by a mental disorder attempt to self-medicate (for example, when individuals with depression or schizophrenia use nicotine and alcohol). A more controversial interpretation, for which there is still not sufficient evidence, is the possibility that early exposure to certain drugs of abuse might increase the vulnerability to other mental disorders, particularly in those genotypes that confer increased susceptibility.

What are the neural consequences of environmental risks?

Drug availability is the most obvious environmental factor that influences addiction. Indeed, increased availability of cocaine and methamphetamine has contributed to the recent epidemics of addiction to these drugs. Low socioeconomic class and poor parental support are two other factors that are consistently associated with a propensity to self-administer drugs, and stress might be a common feature of these environmental factors. The mechanisms responsible for stress-induced increases in vulnerability to

drug use and to relapse in those addicted are not yet well understood. However, there is evidence that corticotropin-releasing factor (CRF) might play a linking role through its effects on the mesocorticolimbic dopamine system and the hypothalamic-pituitary–adrenal axis[15,16]. Additional preclinical studies have provided tantalizing insights on how environmental factors affect the brain and how these, in turn, affect the behavioral responses to drugs of abuse. For example, in nonhuman primates, social status affects dopamine (DA) D2 receptor expression in the brain; low status decreases expression and increases the propensity for cocaine self-administration[17]. Also, animal studies have shown that an increase in DA D2 receptors in the nucleus accumbens markedly decreases drug consumption, and this could provide a mechanism by which a social stressor modifies the propensity to self-administer drugs. If we understand the neurobiological consequences underlying the adverse environmental factors that increase the risks for drug use and for addiction, we will be able to develop interventions to counteract these changes

How can we repair the brain circuits disrupted by drugs?

The adaptations in the brain from chronic drug exposure seem to be long-lasting and implicate multiple brain circuits (reward, motivation, learning, inhibitory control, executive function). This suggests that new interventions for drug addiction should include strategies that enhance the saliency value of natural reinforcers (including social support), strengthen inhibitory control and executive function, decrease conditioned responses and improve mood if disrupted. An interesting approach is the development of medications that act synergistically with an effective behavioral intervention. Although not yet evaluated for addiction, a proof of principle for such a concept has been recently established in a report showing that D-cycloserine administration facilitates the extinction of fear in phobic individuals through the pharmacological strengthening of the relearning events triggered during a desensitization session[18].

What is volition and how do drugs disrupt it?

Remarkable scientific advances have emerged in the neuroscience of addiction that offer new insights into how chronic drug use affects the inner workings of the brain and how this leads to the aberrant behavioral manifestations of addiction. We have learned how some drugs and alcohol can disrupt volitional mechanisms by hijacking the brain mechanisms involved in seeking natural reinforcement and weakening brain mechanisms that inhibit these processes[19]. This new knowledge has started to provide explanations of why the addicted person relapses even in the face of dire consequences such as loss of a child's custody or incarceration. However, despite these advances in understanding the neuroplastic changes to drugs and alcohol, addicted individuals continue to be stigmatized by the pernicious yet enduring popular belief that their affliction stems from voluntary behavior. The loss of behavioral control in the addicted individual should spur a renewed discussion of what constitutes volition, challenge us to identify the neurobiological substrates that go haywire, and influence our evolving strategies to direct our efforts to prevent and treat substance abuse and addiction more effectively.

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