Dramatic advances in addiction research

By supporting and disseminating research across a wide range of scientific areas, the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the US National Institute on Drug Abuse (NIDA) are at the forefront of efforts to reduce the impact of alcohol and other drug-related problems on public health.

Recent advances in neuroimaging, optogenetics, genomics, epigenomics and a range of other technologies are providing an increasingly detailed picture of the molecular and neurocircuitry disruptions that underlie substance use disorders (SUDs). These advances have enabled a shift from a historic focus on the behavioural effects of acute drug administration and associated reward mechanisms to the investigation of broader neuroadaptive changes in the brain, including dysphoric components, cognitive consequences and developmental trajectories. This is likely to lead to substantial advances in our ability to predict addiction and relapse as well as to individually tailor interventions for both prevention and treatment.

The addiction cycle

Distinct neural circuits and neurotransmitters (most notably dopamine (DA), glutamate, opioids, cannabinoids, dynorphin and corticotropin-releasing factor) have been identified for three stages in the addiction cycle: binge/intoxication, which involves brain reward regions (that is, the nucleus accumbens and ventral pallidum); withdrawal/negative affect, which involves the extended amygdala and habenula (among others); and craving/preoccupation, which involves the basolateral amygdala, hippocampus, prefrontal cortex, insula and default mode network, among other brain regions.

This broadened perspective highlights the contribution to addiction of both positive and negative reinforcement. Brain scans of addicted individuals have revealed diminished DA signalling through D2 receptors (D2Rs) in the reward neurocircuitry during withdrawal and, surprisingly, during intoxication. By reducing inhibition of the striato-cortical indirect pathway, which in the ventral striatum is associated with aversive responses, this diminished D2R signalling could contribute to the dysphoria of withdrawal, which is transiently relieved by brief DA increases during intoxication.

Clinical and preclinical studies also show that addiction involves the recruitment of stress and negative emotion systems. This ‘anti-reward system’ acts in opposition to reward as part of a larger motivational system that strives to maintain hedonic homeostasis. Addiction reflects a state of dysregulation between the reward and anti-reward systems that progressively favors the latter; individuals are increasingly driven by the imperative to escape intolerable stress and dysphoria more than by the drugs’ pleasures. Perhaps equally compelling is the impaired capacity of the prefrontal cortex to control basal ganglia outputs (resulting in impulsivity) and amygdala outputs (resulting in compulsivity).

This more-detailed neurobiological picture of SUDs is raising the possibility of developing biomarkers (through neuroimaging, genotyping or relevant neurocognitive or behavioural phenotyping) to predict disease susceptibility, status and treatment prospects. This could have enormous clinical application as we move towards more-personalized approaches: the objective of US President Barack Obama's Precision Medicine Initiative. Advances in imaging and genetic technologies, driven in part by the White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, are enabling the characterization of brain function in unprecedented detail. Furthermore, they are allowing more-nuanced characterization of complex patients and are providing insights into the heterogeneous presentation of SUDs and the interplay of poly-SUDs and co-morbidities.

The ABCD study

Collaborative Research on Addiction at NIH (CRAN), which is comprised of the NIDA, NIAAA and US National Cancer Institute in collaboration with other US National Institutes of Health (NIH) partners, is preparing to launch a 10-year longitudinal study that will bring neuroimaging and other research tools to bear on a large United States-wide cohort of children aged 10 and above, before substance use begins. The Adolescent Brain and Cognitive Development (ABCD) study will shed important light on brain maturation in adolescents, whose psychosocial vulnerabilities and ongoing brain development make them particularly vulnerable to SUDs. The study will provide valuable information on the association of SUD trajectories with other mental illnesses and their interactions with physical health and psychosocial stressors. It will also show how genes influence brain development, structure and function.

Technology leading the way

Technology has brought us to a point where the neurobiological and genetic complexities of SUDs can be examined, including the interplay between social and neurobiological factors. New analytical tools, such as machine learning, and ‘open’ access to increasingly large scientific databases (including those that will be generated from the Precision Medicine Initiative) will revolutionize our ability to detect new associations in a hypothesis- and bias-free manner.

NIH-supported genomic and epigenomic studies have identified a number of statistically significant gene variants and pathways that are relevant to addiction. New tools and technologies (for example, clustered regularly interspaced short palindromic repeat (CRISPR) systems and tools related to the BRAIN Initiative) will enable us to probe more deeply into the neurobiological mechanisms involved in the function of a variant, gene or pathway and will provide crucial knowledge for the development of future strategies for preventing, diagnosing and treating SUDs.

References


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