The science of addiction: untangling complex systems
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Recent research has revolutionized our understanding of the structure and function of the genetic, molecular and neural networks that underlie alcohol and substance use disorders. Drugs and alcohol affect multiple circuits in the brain, including those involved in self-regulation, which partly explains the profound behavioral impairments seen in addicted individuals. Inasmuch as the neuronal networks implicated in addiction also process physiological signals involved in survival and optimal performance, it is not surprising that some of those circuits are implicated in other behavioral disorders that impact inhibitory control, such as compulsive eating.

Even faster progress is just around the corner: access to large genetic, epigenetic, biochemical, and brain imaging datasets will provide exciting opportunities in brain research. Real progress, however, will require more powerful analytical tools to investigate the complex organization within and across multilayered systems. Ultimately, these advances will help uncover the biological underpinnings of how the brain works in normal and diseased states, including those triggered by drugs and alcohol.

Who’s at risk and why?
Family history is one of the largest risk factors for developing a substance use disorder. While the genetic risk landscape is still incomplete, genomics research has already provided crucial information on the neurobiology of addiction. A recent discovery of a cluster of nicotinic receptor subunits that influences nicotine addiction risk through effects on anhedonia and negative mood rather than positive reward, has refocused attention on the habenula. At the same time, a better understanding of the genetic programs that influence brain development, structure and connectivity continue to uncover new contributors to the risk of substance use disorders. The impact of COMT variants on dopamine metabolism, prefrontal cortex (PFC) maturation and the risk of substance use and other psychiatric disorders is just one of many examples. Also, since developmental trajectories can also be disturbed by epigenetic processes, there is a robust impetus to investigate the mechanisms through which environmental factors, including drugs and alcohol, can alter behavior by dialing up or down or even silencing transcription.

How do drugs induce the long lasting modifications in brain function?
Drugs of abuse evoke short and long-term neuroplastic changes in the brain akin to the molecular events associated with memory and learning. For example, the long-lasting impairment in cognitive control of goal-directed behaviors that characterizes addicted individuals reflects in part dysregulated synaptic potentiation in the neural pathways connecting the PFC and the nucleus accumbens. Indeed, brain imaging shows that the loss of control over drug intake in addiction stems not only from the disruption of subcortical reward circuits, but also from drug-induced impairments in the PFC. Given the PFC’s role in self-regulation and higher-order executive functions, its disruption by chronic substance use helps explain the self-destructive behaviors and erosion of self-control associated with addiction. Thus, pharmacotherapies and/or behavioral interventions designed to enhance frontocortical function may prove effective. In addition, the increasingly detailed account of how different drugs of abuse modulate synaptic plasticity to induce neuroadaptations in other circuits continues to provide critical insights that will, some day, form the basis for the next generation of addiction therapies.

Why do some substance abusers respond to treatment while others do not?
Identifying the active ingredients of successful treatments will require significant cross-disciplinary efforts to define biological and environmental variables and to tailor treatment interventions on the basis of individual characteristics. Clinical trials of alcoholism medications nicely illustrate the power of this approach: genetic variations in the µ-opioid receptor 1, the serotonin transporter, and the type 4 dopamine receptor genes predict positive drinking outcomes in response to naltrexone, ondansetron and olanzapine, respectively. We must also consider the important mechanistic differences that exist among various drugs when optimizing the development of interventions designed to untangle the considerable co-morbidity in substance use disorders.

The future of imaging
Brain imaging techniques have propelled stunning breakthroughs in neuroscience. New algorithms for faster monitoring of brain activity patterns have enabled researchers to feed real-time information back to subjects in the scanner for biofeedback-mediated neural circuit retraining. This approach, which has proven its utility for chronic pain patients, is being investigated as a possible treatment for addiction and other psychiatric disorders. Another important development is the emergence of resting fMRI, which has already generated large datasets of at rest functional brain connectivity in normal individuals, providing an invaluable baseline against which to compare any abnormalities detected in the diseased brain, monitor biomarkers of treatment effectiveness, or predict clinical outcomes.

Harnessing our growing knowledge for clinical purposes
Though scientific discoveries have expanded the array of evidence-based prevention and treatment options for substance use disorders a major challenge continues to be their implementation; exacerbated by the limited participation of the healthcare system in screening and treating these disorders. In addition, the minimal involvement of the pharmaceutical industry in medication development for addictive disorders has slowed down the translation of promising molecular target into potentially useful medications.

References