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NEUROBIOLOGY OF ADDICTION

This entry provides a general overview of the neurobiology of addiction including (a) background information regarding the state of the field, (b) information regarding the specific neuroimaging techniques and methods used to study addiction in humans, and (c) information about the specific neuroanatomical circuitry and neurochemical changes involved in addiction. Potential risk factors for addiction, implications for addiction treatment, and directions for future work are discussed.

Background

Drug addiction is a process defined by uncontrollable, compulsive drug seeking and use, which persists despite negative health and social consequences. Although addiction is complex, there is consensus on several established principles. First, while sustained exposure to drugs of abuse is a necessary prerequisite for drug addiction, addiction is also influenced by biological and environmental factors, as well as the developmental stage of the affected individual. Second, during the initial stages of drug use, individuals often choose to use drugs to replicate an originally pleasurable experience with the substance. However, as addiction progresses, fundamental motivational shifts take place whereby the drug is no longer consumed to provide pleasure to the consumer but rather to relieve drug craving and withdrawal-associated distress. Third, there is an accumulating amount of evidence regarding the cumulative impact of chronic drug exposure on the human brain.

Although different types of drugs have different pharmacological and pharmacokinetic properties, their

habit-forming effects appear to involve a common denominator, namely, an impact on brain mechanisms involved with reward and motivation. These regions evolved to aid the organism in the search for, and motor approach of, natural rewards, such as food and sexual contact, which are essential to survival and reproduction. Evidence increasingly suggests that drug addiction is a process through which drugs of abuse "hijack" the neural circuitry of reward and motivation and produce a chronic state of drug seeking, which continues even in the face of strong negative consequences of use.

Neuroimaging Methods Used in Addiction Research

Recently the scientific community has witnessed a revolution in the field of human brain imaging. New technology, specifically positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and single photon emission computer tomography (SPECT), allow imaging of brain activity in vivo among human drug users. These advances provide a unique opportunity to understand the processes of addiction through the ability to measure changes in the function of the human brain, including the mapping of molecular kinetics and enzyme reactions over reasonably short time intervals. At the same time, spatially clear neural networks are displayed. Thus, imaging techniques can track neurochemical and neuroanatomical changes that occur due to neural plasticity and the effects of drugs.

Positron Emission Tomography (PET)

PET measures the radioactivity released by radio tracers in the body, such as natural molecules (i.e., oxygen, nitrogen, or glucose) and addictive drug compounds (i.e., amphetamine). This provides a way to measure changes in blood flow, glucose, and oxygen levels in the human brain. This method has been used to study the ways in which addiction and addictive drugs affect the brain neurotransmitters (dopamine, serotonin, opiate, and GABA) through the injection of neurotransmitter-specific tracers. For example, a dopamine-D₂ receptor tracer (i.e., C-raclopride) detects changes in intrasynaptic dopamine. This technology provides a method to track the ways in which addictive drugs bind to various parts of the brain after consumption of labeled

versions of the drug. PET can also be used to measure neurochemical changes after short- or long-term use of abused drugs, such as their effects on receptor density in specific brain regions.

Functional Magnetic Resonance Imaging (fMRI)

fMRI is an imaging method that provides information about the circulation of oxygenated and deoxygenated blood in the brain. This method relies on differences in the magnetic properties of oxygenated versus deoxygenated hemoglobin in the bloodstream at different locations in the brain, which provides a proxy for brain activity in the specific brain regions under study. fMRI can be used to study addiction because it provides information about the ways in which brain activity changes in response to specific types of stimuli (such as drug cues) and how brain responses to stimuli can be altered by drugs. One strength of the fMRI technology is its high temporal resolution, which makes it useful for disentangling the neural systems involved in, for instance, time-dependent subjective responses after drug consumption and specific brain responses to particular stimuli.

Single Photon Emission Computer Tomography (SPECT)

SPECT scanning measures blood flow using the injection of a radioactive substance. Radio-tagging offers the possibility of selecting specific neurotransmitter or binding sites to provide information about localized function and reactivity. Like PET, SPECT is being used to study the neurochemistry of addiction and drug use. Recently, SPECT has been used to trace the GABA receptor system. For example, the GABA_A-benzodiazepine (GABA-BDZ) receptor network is being imaged using the SPECT technology. This tracer elucidates the processes and implications of sedative and memory effects of GABA and benzodiazepines.

The advancement of human neuroimaging technologies, together with preclinical research on addiction, has developed a nearly inclusive biological model of addiction. The use of imaging has shown that addiction is coupled with specific changes in neuroanatomy and neurochemistry.

Structures Involved in Addiction

The brain comprises a network of interconnected structures whose evolutionary function is to ensure pursuit of the natural rewards necessary for survival (food) and for survival of the species (sex). Drugs of abuse act through the brain's circuitry for natural rewards, but they activate the system in a much stronger way, providing a "supranormal" stimulus that produces intense subjective effects and strong learning about the association between drug cues and the drug effect. Though the brain circuitry of reward is complex, a large body of imaging work on addiction has focused on the neurotransmitter *dopamine*.

Neurochemistry of Addiction: Dopamine

The dopaminergic brain network plays a fundamental role in the mechanisms of drug addiction. The dopamine system has an important role to play in generating acute drug effects and in the pairing of drug-related cues with responses. Dopamine is a neuromodulator that is involved in reward and motivation, salience attribution and attention, and motor and cognitive function. This system is activated by natural stimuli relevant to evolutionary survival, such as food and sex, as well as nonnatural stimuli that can be addictive, such as gambling. Dopamine is activated by addictive drugs, such as cocaine and alcohol. Dopamine is thought to contribute to a number of drug effects involved with addiction, including reward, craving, and alterations in motivation for the drug relative to other types of reward and the environment.

Reward/Drug "Liking"

There is a relationship between the rewarding effects of drugs and their self-administration. When a drug yields pleasurable effects in people, the chance of taking that drug again increases. This phenomenon of repeated use is guided by the principles of instrumental conditioning that associate contingencies with behavioral outcomes. Most studies investigating the role of dopamine in the experience of pleasure in humans are compatible with the view that dopamine release and high levels of extracellular dopamine in the ventral striatum (located in the forebrain, which receives input from the hippocampus) are associated with the pleasurable effects of drugs of abuse. The

amount of dopamine release required for these processes is unclear, as different substances of addiction have differing effects on the dopamine system.

Craving/Drug "Wanting"

The pleasurable effects of drugs by themselves cannot explain the total spectrum of addictive behaviors, which include use in the face of adverse consequences. Both addicted and nonaddicted persons may experience pleasurable effects of drugs. The focus in addiction research has made a shift from the rewarding aspects of drug use toward the motivational aspects of addictive behavior. The motivational properties of drugs may last for several years after the termination of drug use. Stimuli, or cues, in the environment associated with drug use are still able to trigger motivational circuits and elicit a high motivation to use these drugs, a phenomenon known as cue-elicited craving. This conditioned craving contributes to the continuation of drug use in active drug abusers and to relapse in detoxified abusers.

Based initially on work with rats and future support with human PET scans, research studies suggest that craving involves two separate neurobiological pathways. The first craving pathway (chronic craving) is the result of reduced dopamine activity (reduced dopamine receptor D_2 density in the striatum and orbitofrontal cortex). This reduction results in a chronic state of anhedonia, the inability to experience pleasure. Drugs are used to stimulate the dopamine activity in the striatum and orbitofrontal cortex in an attempt to alleviate this chronic anhedonic state. Essentially, this state can be regarded as a "need for dopamine," which is experienced as chronic craving. The second craving pathway (instant craving) results from a temporary enhanced cue-elicited dopaminergic activity in the striatum, amygdala, and cingulate cortex.

Other Pathways: GABA and Serotonin

Craving also involves other systems such as GABA, which interacts with dopamine. Some drugs, such as opioids, nicotine, and marijuana, affect dopamine indirectly through the stimulation of GABA neurons in the substantia nigra and prefrontal cortex. GABA is an inhibitory neurotransmitter that normally acts through two types of receptors: A and B. The stimulation of receptor A in the hippocampus reduces excessive craving for drugs such as alcohol, which in turn releases noradrenaline in the locus coeruleus, another key area

in the gratification pathway. Type B receptors stimulate the opening of potassium channels that determine the level of inhibition of dopamine release.

Serotonin provides important modulatory influence over neurons and neurotransmitters, such as dopamine, which are critically involved in addiction pathways and substance use disorders. A monoamine neurotransmitter, serotonin, plays a key role in the regulation of anger, aggression, and sexual behavior. Cocaine is a known drug wielding major neurochemical effects by binding to the serotonin, dopamine, and noradrenaline receptors. This blocks reuptake of these neurotransmitters from the extracellular space. Recent research suggests that serotonin and dopamine are necessary prerequisites for the development of cocaine addiction-related behaviors, such as craving. The neurotransmitter pathways involved in addiction suggest chronic adaptations in signaling and receptor responses, which impact specific anatomical circuitry and networks.

Anatomical Substrates of Addiction

Dopamine and other neurotransmitters involved in addiction impact function in a variety of neural circuits, particularly those involved in motivation, the processing of rewards, and making decisions about how to deal with rewards. In these regions, what begins (before drug use) as a normal system in homeostatic balance appears to undergo an allostatic shift (i.e., dysregulation of neurotransmitters) such that equilibrium is later maintained only by the continuing consumption of drugs. Anatomical structures involved in reward, motivated behavior, and acute and chronic drug effects include the following:

- *Orbitofrontal cortex*, which is involved in stimulus evaluation or "telling us what we want"
- *Nucleus accumbens*, located in the ventral base of the human forebrain, which is a key structure for reward, motivation, and addiction and is implicated in learning to predict rewards and to express adaptive behaviors
- *Amygdala*, which responds to the intensity of rewarding and aversive stimuli and also links motivationally relevant events with neutral stimuli and the autonomic and endocrine systems
- *Anterior cingulate*, which has a high concentration of dopaminergic receptors that are interconnected with both higher level structures (e.g., orbitofrontal cortex) and limbic structures (e.g., amygdala)

Neuroanatomical Pathway: Ventral to Dorsal Activation Patterns

At the neurophysiological level, there is a gradual change from ventral to dorsal activation in the nucleus accumbens, with an accompanying shift in activity from the ventral tegmental area to substantia nigra dopaminergic projections. There is also a reduction in orbitofrontal cortex and ventromedial prefrontal cortex activity at rest in addicts, which reflects a switch from prefrontal control, with reflective decision making, to more compulsive striatal control. This switch from drug use, with associated pleasure and liking, to drug dependence, with compulsive drug wanting, is marked by changes in synaptic plasticity and neurotransmitter function. Research suggests a final common pathway consisting of prefrontal cortex/nucleus accumbens/ventral pallidum in drug-craving and drug-seeking behavior. Changes in the strengths of synaptic connections in this pathway can account for the rapid reinstatement of drug use during a relapse from abstinence. Such reinstatement can be triggered by stress, a drug-specific cue, or a single dose of the drug. These changes in synaptic connections depend upon glutamatergic fibers from the prefrontal cortex, which converge on nucleus accumbens dendritic spines with dopaminergic afferents from the ventral tegmental area. Repeated use of drugs may lead to plastic reorganization of these synaptic connections, which then cements changes in neural activity, and so behavior. Molecular changes that affect synaptic connection strengths may occur both presynaptically and postsynaptically in the nucleus accumbens and also in the prefrontal cortex itself, as reflected by changes in activity seen there in neuroimaging studies. Dysfunction in the neural circuitry outlined here may underlie the development and maintenance of addiction in a general sense; however, individual substances disrupt this circuitry in specific ways. This means that different perturbations of the circuitry can give rise to addiction.

Adolescence: Development and Drug Use

Distinct age-related responses and developmental differences to drug use indicate that adolescence may constitute a critical period of vulnerability for addiction. Age-specific behavioral responses following repeated drug exposure include motivation and performance deficits that suggest the existence of

age-dependent differences in the vulnerability to addiction. The prefrontal cortex, the limbic system (i.e., amygdala and nucleus accumbens), anterior cingulate, and orbital-frontal cortices undergo significant and widespread refinement and maturation during adolescence, which include development of global and white matter volume, synaptic density, and oxygen uptake. Each of these structures is heavily innervated by ascending dopamine fibers, and each is involved in addiction.

Research suggests that a failure of executive functioning is coupled with addiction. Recently this connection has piqued interest, as it is linked with normally slow maturation of the prefrontal cortex in human adolescents. Thus, the integration of addiction research and neuroanatomical research might indicate adolescent risk for drug use and addiction processes. Additionally, it is possible that the impairment of higher-order cognition prolongs abuse or relapse.

Studies looking at the composition of gray matter in the human brain have found negative trends in gray-matter volume and age in drug-dependent individuals. In the temporal lobe, the drug-dependent individuals show a significant age-linked decline in gray-matter volume. Additionally, frontal lobe gray-matter volume tends to be negatively correlated with age in normal, drug-dependent subjects. The implication of gray-matter volume reductions as related to age suggests a potential biological link to addictive and risky behaviors, which statistically also decreases with age.

Treatment Implications

Treatment for addictions most often includes behavioral and pharmacological interventions. Based on clinical research, there is hope for the development of treatments that combine a variety of techniques, such as cognitive behavioral therapy and pharmacological therapy.

As noted earlier, research indicates that different neural networks and neurotransmitter systems are involved in different stages of the addiction pathway. The focus of current pharmacological treatment options looks to "reset," or alter, the neurotransmitter systems that are affected by drug addiction processes. Toward this end, several behavioral and medication interventions are being assessed. Relevant behavioral interventions include cognitive behavioral therapy, which seeks to increase mastery and control over stressors, as well as teaching strategies for coping

with cue-induced craving. These strategies include alternative responses, aversive imagery, mastery imagery, and cognitive techniques.

There are many pharmacological interventions that seek to correct the neurotransmitter imbalances that appear due to addiction. In the treatment of cocaine, alcohol, and opioid dependence, the GABA_B agonist baclofen has shown some promise. Additionally, there are many promising treatments against nicotine dependence, such as bupropion (Wellbutrin, Zyban), which inhibit norepinephrine and dopamine reuptake and act as nicotine antagonists. These treatments work to reduce craving and withdrawal symptoms associated with nicotine abuse.

Additionally, there are treatments for a variety of drug addictions that replace, at lower levels, the drug currently in the system. For example, with nicotine addiction, the use of the nicotine patch replaces nicotine in the bloodstream at lower doses and a slower rate than one would get through smoking a cigarette. Similarly, with heroin addiction, methadone is given as a treatment. Methadone is an opioid replacement therapy that uses a substance that is slow to metabolize. Therefore, methadone has long-lasting effects on reducing craving and withdrawal symptoms.

Future Directions

The pace of identifying drug-induced molecular changes in the ventral tegmental area–nucleus accumbens and in the many other brain regions important for addiction has increased dramatically over the past 5 years with the advent of neuroimaging and genomic tools. Studies have indicated that multiple drugs of abuse produce common, chronic actions in reward regions in the brain, in addition to a given drug's specific effects. One challenge for future drug-addiction research is to better understand the ways in which molecular and cellular changes in neurons in the reward circuitry in the brain contribute to the behavioral phenomena of reward and addiction. For example, it is unknown how decreased excitability of nucleus accumbens neurons specifically contributes to an alteration in the sense of reward and how altered activity of these cells contributes to craving and relapse. Such understanding requires additional appreciation of how the nucleus accumbens and its interrelated brain-reward structures function as complex neural circuits.

An important area of future research is investigation of between-person risk factors for addiction, which will increase our understanding of the ways in which some individuals are particularly vulnerable to addiction. Available data indicate that approximately 50% of the risk of drug addiction (including addiction to opioids, cocaine, nicotine, and alcohol) appears to be genetically influenced, but the specific genes involved have not yet been identified. Identification of the specific genes involved will elucidate the ways in which genetic and nongenetic factors may interact to influence an individual's risk for an addictive disorder. Wide genomic associations for addiction will enhance the ability to identify vulnerable populations and enable individually tailored treatments of those afflicted by addiction.

In addition, a wider view of neurobehavioral chemistry and behavioral development during adolescence is needed to better characterize and understand the differential vulnerability seen at this age. This should include the scope and extent of drug-induced changes in neural systems—for instance, where changes occur, how persistent are age-related changes, and the links between these changes and short-term and long-term behavior. Second, in understanding the neurobiology of addiction, attention on nondopaminergic processes, including contributions of other neurotransmitter systems, such as glutamate, 5-HT, and opioids, may facilitate understanding of the neural bases of the full spectrum of addiction outcomes, including the compulsion to use in the face of adverse consequences. In addition, the neurobiology of many current treatments has not been fully characterized to date.

Advances in brain imaging, neurochemistry, and molecular biology are adding crucial depth to the understanding of the complex pathophysiology involved and revealing new targets for pharmaceutical, behavioral, and combined treatments. The implications of such developments are likely to be profound, given the large societal, personal, and interpersonal costs of addiction.

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See also Brain Chemistry and Addiction; Craving; Neurotransmitters; Pharmacological Approaches to Treatment; Physiological Aspects of Drug Use

Further Readings

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NEUROCOGNITIVE EFFECTS OF ALCOHOL AND OTHER DRUGS

As understanding increases regarding the effects of alcohol and other drugs on the brain, it is becoming increasingly apparent that the use of most drugs is accompanied by short- and long-term changes in cognitive abilities such as attention, learning, memory, and problem solving. The term *neurocognitive* is often used to describe these abilities in order to reflect the link between biology and behavior—in this case the link between the brain and the complex cognitive abilities (behaviors) that it supports. New discoveries have demonstrated that the manner in which individual substances affect neurocognitive function is very complex. Not only does each substance have its own influence on brain function, with some having few demonstrable long-term effects and others having devastating effects; it is also apparent that the brain can be compromised in multiple ways by chronic substance use. Compromised brain function and resulting alterations in neurocognitive function can occur as a result of the direct effects (e.g., agonist or antagonist) of substances on neurotransmitter function during

intoxication. Neurocognitive deficits can also become evident during withdrawal, where the chronic effects of substance use have caused upregulation or downregulation of various neurotransmitter systems. Alterations in neurocognition as a result of intoxication and withdrawal effects are transient in nature and typically resolve as the symptoms of intoxication and withdrawal resolve. It is also the case that some substances are neurotoxic, causing damage to the brain itself as more and more of the substance is used. Deficits in neurocognitive abilities resulting from neurotoxic effects persist after withdrawal is complete, and although they may demonstrate some improvement over the long term, some also may continue to persist for many years following cessation of substance use. The brain can also be negatively affected through the indirect influences of substances by at least two mechanisms. In these cases, the neurotoxic effects of the substances are not responsible for brain damage per se. First, some substances can damage organ systems other than the brain, which in turn compromises brain function. Liver damage, which is common in alcoholism, is an example of this type of indirect effect. A second means by which substances can indirectly affect brain function is by causing or exacerbating neurological disorders. For example, because cocaine increases blood pressure and causes blood vessels to constrict, it can cause cerebrovascular accidents or “strokes,” which significantly impact brain function and cognition. Seizures that occur during withdrawal from alcohol or barbiturates are another example of this type of influence. Finally, some psychiatric and medical disorders that occur at increased frequency in individuals with substance use disorders may have their own negative effects on neurocognitive abilities. Depression and HIV infection are two such conditions. Thus, neurocognitive deficits resulting from substance use are complex in that they may be transient or enduring in nature, result from direct or indirect effects on the brain, are associated with neurotoxic effects that are unique to each substance, and are oftentimes difficult to separate from other coexisting psychiatric or medical disorders. The following sections review the assessment of neurocognitive impairments and describe impairments that have been associated with use of specific substances that have received the most attention in the research literature, including alcohol, cannabis, cocaine, amphetamines and MDMA, opioids, and benzodiazepines.