



The Addicted Human Brain: An Overview of Imaging Studies and Their Treatment Implications

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Abstract

Addiction is characterized by loss of control over substance use, often operationally defined as continued use of substances despite knowledge of adverse consequences. The exact cause of addiction is not known, but it's hypothesized that both environmental and genetic factors play a crucial role in the predisposition of this disease. When an individual abruptly stops using a drug or an addictive substance, withdrawal symptoms often take place, which include vomiting, nausea, loss of appetite and depression. Not much is known about the neurobiology of addiction and treatment remains a huge challenge. Current research aims at identifying the neurological circuit of addiction as well as the key neurotransmitters and biological markers involved in this disease. In this paper, I will first begin by giving you an overview of the major substances that cause addiction as well as the most common addictive behavior patterns. Second, I will discuss the major findings that have been done using animal models of addiction, and describe in more details the role that brain imaging technology plays in improving our understanding of drug abuse. Finally, a closer look will be taken at the behavioral and pharmacological approaches frequently employed to treat addiction.

Keywords

Addiction, Brain Imaging Technology, Drugs, Neurobiology, Withdrawal Symptoms

Subject Areas: Animal Behavior, Neurology, Neuroscience, Psychiatry & Psychology

1. Introduction

Addiction is characterized by a continued repetition of a behavior despite adverse consequences, and can be classified as behavioral addiction or chemical addiction. Behavioral addiction is some form of dependence not

caused by the use of drugs, such as Internet addiction, gambling and obsession. In contrast, chemical addiction, also known as substance dependence, is a disease characterized by chronic exposure to drugs that causes significant molecular and cellular changes in brain circuits. While treatment for behavioral addiction is relatively easy, it's much more difficult with chemical addiction. Drugs such as nicotine and cocaine have reinforcing effects that are associated with an initial blockade of dopamine transporters, resulting in an increased in the extracellular level of dopamine [1]. Other studies using electrical brain stimulation have shown that opioids, such as heroin and morphine, and psychostimulants, such as amphetamine, can activate the brain reward system and lead to the development of addiction [2]. Advances in brain imaging technologies have shaped our understanding of the neurobiology of drug dependence, and have provided a new perspective on the molecular effects of addictive drugs. While the exact neurological mechanisms of addiction is not well known, it's hypothesized that addictive behaviors are the results of both genetic and environmental factors [3]. Several studies have shown that a single mutation in a gene that regulates addictive behaviors can lead to an increase in alcohol consumption [4]. Moreover, a variety of environmental factors including stress, sexual abuse, and drug availability, contribute to a person's propensity to use drugs. Across the world, around 140 million people suffer from alcohol dependence, and there are approximately 17 million users of heroin, morphine and other synthetic drugs [5]. Because addiction is a complex disease influenced by numerous factors, treatment remains a big challenge. However, there exist some medications such as methadone and buprenorphine that could be useful in treating drug dependence [6]. Other approaches include rehabilitation programs and adherence to behavioral groups that prevent drug relapse and improve the health of individuals [7].

2. Substance Abuse and Behavioral Addiction

Drug abuse, or substance dependence, is a chronic disorder defined as the use of a drug in excessive amount despite significant negative consequences [8]. It is also characterized by a loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is denied. While this disease can have devastating effect on an individual's health, it is also associated with significant damage to the society in terms of monetary costs [8]. Examples of addictive drugs include alcohol, nicotine, amphetamines, benzodiazepines, cocaine, and opioids like heroin and morphine. **Table 1** shows a list of the psychostimulants and opioids that can be addictive. Chronic use of these drugs can cause a variety of neurological changes in specific areas of the brains, leading to severe damage to the individual. Moreover, withdrawal of drugs of abuse is often associated with side effects, such as depression, increased anxiety, nausea, vomiting and stress [9] [10].

In contrast, behavioral addiction, also known as non-substance-related addiction, consists of an urge to constantly follow a pattern of behavior that eventually takes an important place in someone's life and could lead to negative consequences [11] [12]. Examples of behavioral addiction most often include treatable forms of addiction, such as gambling, food-related addiction, as well as the use computers and Internet [13]. Gambling, which is one of the most common forms of behavioral addiction, shares similar characteristics to drug dependence [14]. It was shown that gamblers have significant lower amounts of norepinephrine in the brain compared to healthy individuals. Another very common type of non-substance-related addiction is compulsive buying, which is characterized by a habit of buying more than one can afford, most often unneeded items [15]. Although there are no standard treatments for compulsive buying disorder, research is currently being pursued in order to develop novel psychopharmacological therapies [16].

Table 1. List of most common opioids and psychostimulants involved in addiction.

	Class	Drugs
Psychostimulants	Phenethylamine	Amphetamine, Pseudoephedrine
	Sympathomimetic	Ephedrine, Methylphenidate
	Phenethylamine	Methamphetamine, Phenylpropanolamine, Pseudoephedrine
Opioids	Natural Opiates	Morphine, Codeine, Thebaine
	Semi-Synthetic	Buprenorphine, Hydrocodone, Hydromorphone, Oxycodone,
	Fully Synthetic	Fentanyl, Levorphanol, Methadone

Drug dependence and behavioral addiction share several similarities in terms of neurobiology and molecular mechanisms [17]. The triggering of the addicted behavior seen in these two diseases relies on the action of dopamine. Moreover, both drug reinforcement and behavioral reward induce neurological changes in specific regions of the brain, including the amygdala and the prefrontal cortex. However, drug addiction affects more individuals and causes more devastating consequences than behavioral addiction, and will therefore be the focus of this review paper. Drug addiction is a complex disease, and more work need to be done to help us better understand its neurobiological mechanisms. Animal models of addiction play a critical role in this area of research, and will be discussed in more details in the following paragraph.

3. Animal Models of Addiction

Much of the recent progress in understanding the biology and pathophysiology of addiction has been derived from the study of animal models of addiction [18]. Several models have been developed in order to mimic the different stages of human addiction, which are the following: intoxication, withdrawal, and drug-seeking stage [19]. An animal model of drug abuse is often used for the purpose of studying a specific biological phenomenon in humans, or to test the efficiency of potential pharmacological treatments for addiction. The primary stage of addiction is characterized by a binge or intoxication due to the reinforcing effects of drugs, such as opiates, psychostimulants and alcohol. This change in reward can be measured by direct self-stimulation. Several studies in rodents have used intravenous drug self-administration to understand how addictive drugs could alter motivational behavior [20]. In these studies, the animal is implanted with intravenous catheters and is placed in a cage with a lever. When the animal presses the lever, this automatically delivers an intravenous infusion of drugs, like cocaine and heroin. It was shown that self-administration of cocaine in rodents produces a characteristic pattern of addictive behavior: the animal increases the number of lever presses to maintain a high rate of drug infusion [21]. This animal model of intravenous drug self-administration will definitively help us predict the abuse potential of drugs, and their effects on motivation and behavioral actions.

When an individual stops taking a drug after continuous and excessive use, symptoms of withdrawal effects takes place, which often drives the individual to continue seeking the drug [22]. Symptoms of drug withdrawal typically include a general state of anxiety, and a feeling of emotional unhappiness. The first approach in studying the symptoms of withdrawal in an animal model is the drug discrimination methodology, which can be used to identify specific and nonspecific aspects of withdrawal [22] [23]. In this experiment, subjects are trained to distinguish administration of a particular drug from the vehicle, usually saline. Either vehicle or a dose of drug is injected prior to training, and subjects are allowed to respond while the drug is producing its effect. The animal is put in a cage with two levers and can decide which one to selectively press and activate: one lever sends a reward following drug administration, while the other lever following administration of the vehicle [24]. When the dose of drug is administered, the animal presses on the drug-designated lever to produce reinforcement. In this way, the presence or absence of the drug differentially controls responding, and helps characterize the anxiogenic component of the withdrawal syndrome. Another strategy lies in the studying of animal models of anxiety to understand the effects of drug withdrawal. This model is a powerful tool for studying addiction since withdrawal from many drugs generates anxiety and stress [22]. Several scientists have studied the behavioral measures of anxiety during drug and alcohol withdrawal in order to elucidate the mechanisms and biological manifestations that take place [22] [24].

In summary, the animal models discussed above can efficiently validate some of the key characteristics of addiction, and will definitively help scientists target homologous genes or biological mechanisms found in humans that could render a person more susceptible to drug addiction. Other models not discussed earlier are also extensively used to study drug dependence. For instance, a genetic animal model has been developed to study alcohol related disorders [25], and it has been shown that these genetically modified animals are able to drink more amount of alcohol compared to the normal strain, which enable them to attain physical dependence [26]. Much remains to be explored about the efficiency of animal models of addiction. A better understanding of the changes that take place in the central nervous system of these models will provide insights into the reinforcing effect of drug addiction, which might be useful for the development of novel therapeutic strategies.

4. Brain imaging Technology

Brain imaging studies have provided enough evidence that neurological changes in specific circuits and struc-

tures of the brain occur as a result of the triggering effects of addictive drugs [1] [27]. Physicians are now able to rely on several techniques that can help them visualize the structure and activity of the brain, which is crucial for a better understanding of the causes and mechanisms of drug use and addiction. Positron emission tomography (PET) imaging is a technique used in functional human brain to detect regional changes in cerebral blood flow as well as alterations in glucose metabolism. The mapping of glucose utilization can identify which brain areas become more active following drug administration, and determine the brain structures that are interrelated. PET is also used to measure the gamma rays emitted by a radiotracer labeled with positron-emitting isotopes that bind to specific receptors [1] [28]. Radiolabeled ligands for dopamine, serotonin, and nicotinic acetylcholine receptors are available for PET imaging, and have helped scientists better visualize the neuroreceptors in the context of psychiatric disorders such as addiction and drug abuse [29]. PET imaging studies have shown that dopamine receptors are up-regulated in psychostimulant and nicotine users [30], and that administration of cocaine inhibits the reuptake of dopamine, leading to an increase in its extracellular level.

Magnetic resonance imaging (MRI) is another imaging technique commonly used to visualize the brain of addicted individuals. By providing information about the size, shape and anatomy of brain structures, structural MRI can examine the effects that addictive drugs have on the central nervous system [28]. It is a noninvasive technique that allows the study of the chemical composition and biochemistry of the central nervous system, and has been proven to be efficient in the detection of neurological changes that occurs during addiction. Using MRI, it was demonstrated that alcoholic patients have diminished gray matter in the prefrontal cortex compared to healthy individuals [31]. Moreover, MRI studies have shown that a decreased in hippocampal volume, as well as serious damage to the cingulate-limbic cortex and the temporal lobe, are observed in individuals with chronic methamphetamine abuse [33]. While MRI is useful to visualize areas of the brain and identify pathologies that may be present, it does not detect changes in brain function. Functional magnetic resonance imaging (fMRI) is a new tool that has been developed recently that is very sensitive to alterations in brain activity. fMRI is very efficient in measuring the activity of brain circuits and their association with the reinforcing effects of drugs [28]. It has proven to be more useful than PET because of its higher spatial resolution. fMRI can determine the areas of the brain that are active by detecting changes in blood oxygenation and flow. Studies using functional magnetic resonance imaging have shown that drug intoxication significantly alter the function of the subcortical striatum, which leads to an increase in reward and gratification [32]. **Table 2** provides a brief summary of the imaging techniques discussed earlier, and explain how they are used in medical research.

5. Behavioral and Pharmacological Treatments

The primary goal of treating addiction is to allow the patient to manage their excessive use of drugs, and to enhance its ability to function normally. There exist several treatments, both behavioral and pharmacological, and the best type of treatment often depends on factors such as age, personality, drugs of choice, and the severity of physical and mental illness. Interventions consisting of as little of a single session have been shown to be effective in helping the patient control his addictive behaviors [34]. Not only do these motivational approaches help individuals cope with drug addiction, but they also are very efficient in a wide variety of behavioral diseases such as gambling and eating disorder [35]. When it comes to alcohol addiction, many individuals with severe problem seek advice from a psychotherapist who can help them cope with their self-control and passive dependence. An alternative to individual psychotherapy is treatment in a clinical setting with the help of family physicians and clinical psychologists, as well as adherence to a group of alcoholics, where every member can share his personal experience. Moreover, there is strong evidence that cognitive behavioral therapy could serve as a

Table 2. Medical imaging techniques and their applications.

Imaging technique	Application
Positron emission tomography—PET	Used to quantify processes such as glucose metabolism, drug distribution and pharmacokinetics. Useful in for the study of the physiology, anatomy, and biochemical properties of brain structures.
Magnetic resonance imaging—MRI	A non-invasive technique used to map tissue morphology and anatomical composition. Can detect tumors in the brain and differentiate between white matter and grey matter.
Functional magnetic resonance imaging—fMRI	A technique used to observe brain structures and assess their activity during cognitive tasks. It can visualize changes in oxygenation and blood flow associated with brain activities.

potential approach for treating addiction [34]. It is a type of psychotherapy that encourages the patient to recognize and think about the behavioral patterns and motivations that lead him to become addicted. This approach often helps the patient learn more about his disease, which enables him to develop new strategies to change his behavior [34] [36] [37].

An alternative to behavioral approaches for treating addiction is the use of pharmacological therapies. Methadone has proven to be very effective in treating drug abuse. It is an analgesic that is mainly used in the treatment of opioid dependence because of its ability to abolish the drug-seeking behavior and relieve the patient from narcotic craving [38]. It also acts by attenuating opioid withdrawal symptoms. Studies have found that methadone can suppress heroin use in addicted individuals, while significantly improving their social life and general productivity [39]. Although this compound is itself addictive, the withdrawal symptoms are relatively mild compared to those following withdrawal of other opiates. Another treatment for opiate dependence is the use of narcotic antagonists such as naloxone. By blocking the effects of opioids, naloxone can reverse the lethal respiratory depression and reduce rates of fatal drug overdose like heroin or morphine [40]. Treatment of psychostimulants, such as cocaine, nicotine, and caffeine, involves the use of dopamine agonists and various serotonin reuptake inhibitors. Bromocriptine is a potent agonist at dopamine D2 receptors that is frequently used in the treatment of cocaine addiction [41]. It is hypothesized that cocaine withdrawal lead to the depletion of dopamine, and that the use of agonist such as bromocriptine could restore the level of DA and reduce drug use and mood symptoms. Fluoxetine, a medication used for the treatment of major depressive disorders, is a serotonin reuptake inhibitor that is also effective at reducing the use of cocaine in dependent individuals. Fluoxetine is also useful in reducing alcohol consumption, as demonstrated in animal models of alcohol addiction [42].

6. Conclusion

Addiction is a neurological disorder that causes profound changes in an individual's behavior, which can lead to loneliness, marginalization, stress and depression. This review primarily discussed the use of animal models to study the neurobiology of addiction, and to examine the reinforcing effects of drugs as well as the symptoms that occurs following withdrawal. Promising results from animal studies and clinical trials have helped scientists pinpoint the main neurotransmitters and brain structures involved in addiction, and have helped identify the neurocircuit of motivation and reward. The review also talked about the advances in imaging technology with a special focus on PET, MRI and fMRI. These brain imaging technologies have made possible the visualization of specific brain structures and the detection of anatomical and functional changes that follow drug intoxication. As indicated in this paper, addiction leads to significant changes in several areas of the brain, including the prefrontal cortex and the amygdala. Imaging techniques such as PET can also aid in the identification of the neuroreceptors and neurotransmitters involved in drug addiction. However, more research needs to be done to detect the anatomical and neurobiological differences among specific subgroups of addiction, which will definitively help in the design of novel pharmacological treatments. As outlined in this paper, treating addiction remains a big challenge for physicians. Although behavioral approaches have proven to be successful in treating some addicted individuals, the chances of relapse are still very high. Nowadays, most patients use prescribed medications to help attenuate their addictive symptoms. Pharmacological treatment of opiate dependence mainly relies on methadone maintenance and narcotic antagonists like naloxone, while alcohol and psychostimulant addiction can be treated with dopamine agonists and serotonin reuptake inhibitors. Nonetheless, there are still several limitations about the current treatments available. The use of combination strategies, including both behavioral and pharmacological approaches, needs to be studied in order to provide a more effective and safe treatment for the patient. Moreover, when deciding which treatment is most suitable, physicians must take into account the genetic profile of each individual. Future research in drug addiction needs to seek a better understanding of the genes implicated in the predisposition for drug abuse, which will help identify molecular targets and open up new directions for therapeutic strategies.

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