

Brain Changes in Substance Abuse: Implications for Treatment

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Abstract

Because the phenomenon of drug abuse generates a wide range of serious problems within society, much attention has been paid to understanding how the brain reacts to drugs, and how it changes in addicted individuals, as a result of prolonged exposure. Neuroscience research has revealed much about processes underlying drug abuse, and every day the story grows more coherent. This article provides a brief survey of the key changes that occur in the brain as the user progresses through the stages of drug abuse. This is intended to serve as an accessible introduction to the biological basis of drug abuse and addiction. In particular, it is important to have some understanding of the relatively long-lasting brain changes that make the user susceptible to recidivism, clearly one of the most difficult problems related to this topic.

Understanding the mechanisms by which stressful events or drug-related stimuli can reactivate strong cravings is fundamental to designing effective ways to reduce recidivism. The presentation will also discuss how a significant classical conditioning component underlies the activation of cravings, which has important implications for treatment programs.

Brain Changes in Substance Abuse: Implications for Treatment

The plight of the chronic substance abuser lies largely in the fact that chronic abuse of drugs produces profound changes in the brain that appear to be very long lasting, if not permanent. These changes make the abuser highly vulnerable to recidivism, even if he or she has undergone extensive rehabilitation treatment. In this article I will describe the cascade of events that occur in the brain as the abuser takes repeated doses. We will see that long-lasting changes occur in several brain systems as the development of drug dependence progresses.

The brain changes that accompany drug abuse have significant implications for the development of appropriate treatments for drug abuse. The burden of these treatments is not only to promote initial recovery from the condition, but also to reduce the likelihood of recidivism once the initial treatment has been completed. Given the high rate of recidivism (over 90% by some estimates), it is clear that most of our treatments could be materially improved. Understanding the neural condition and mental state of the recovered abuser is a crucial element in devising treatments and, more importantly, in influencing policies so that sufficient resources can be allocated to effective treatments.

The Experience of the Abuser

Before looking at brain changes accompanying the development of drug abuse, it's important to consider the changes that occur in the experience of the drug abuser as the problem develops. Depending on the drug of choice, individuals vulnerable to becoming drug abusers typically experience an intense feeling of euphoria on taking the initial few doses of their drug of choice. Stimulant drugs like amphetamine or cocaine often require an initial few doses to sensitize the user,

at which point the peak pleasure experience occurs. This initial part of the process can be seen as the reward stage, in which the habit of seeking this intense pleasure state is established.

At some point the user experiences the peak effect of the drug, which is described as extremely pleasurable. However, even during that single dose the peak subsides until a lower intensity pleasure plateau is reached. This plateau then persists until the drug effect wears off, and a mild negative state occurs. This intense pleasure then motivates further drug taking.

Here is where the great irony of the phenomenon of drug abuse becomes clear. Although they are motivated to take more of the drug to duplicate the original high, drug abusers will never again attain that intensity of pleasure. Clearly some reaction in the brain has reduced the effect of the drug. It is interesting that this occurs so rapidly; the brain is a quick study.

This reduction signals the onset of the next stage, known as the transition to addiction. At this point, the drug user begins to take a higher dose, in an attempt to increase the now severely diminished pleasure state. This phenomenon, known as drug tolerance, marks the development of physical dependence on the drug. If the drug doses are no longer available, the abuser begins to experience serious physical effects, known as withdrawal symptoms. These symptoms, known collectively as a withdrawal syndrome, become more severe as the number of doses increases.

It's important to note that the withdrawal symptoms are opposite to the original effect of the drug. Heroin and alcohol are classified as depressant drugs because they reduce the activation of the brain and body. However, withdrawal from these drugs produces an activated body state. Symptoms include restlessness, pain, irritability, and muscle cramps and uncontrollable tremors. In contrast, withdrawal symptoms from stimulants like cocaine and amphetamine include apathy, a loss of sex drive, insomnia, a general lack of energy, and, significantly, mental depression.

To the extent that the habit reduces the drug abuser's quality of life, and induces him or her to take desperate measures to obtain the next dose, the abuser is likely to reach the point where treatment is attempted. Assuming that the abuser has received treatment, and is no longer actively taking the drug, he or she is now in the final stage of the process, known as end-stage drug abuse.

Many drug abusers report that they experience a distinct anhedonia. They no longer derive pleasure from stimuli and events that were pleasurable before they began to use the drug. These users are also highly vulnerable to renewed cravings, especially because other sources of pleasure in their lives are severely curtailed.

The cravings that assail the end-stage user can arise from a variety of circumstances. Objects and situations associated with their previous drugs are powerful inducers of cravings. For example, if the user employed a belt or necktie as a tourniquet, the sight of these objects would be likely to activate strong cravings. Perhaps not surprising, persistent cravings also arise from another dose of the drug. However, the fact that cravings also arise from any sufficiently intense stressful episode reveals a much more insidious threat to the end-stage user's attempts to avoid taking the drug once again.

There is compelling evidence that vulnerability to cravings may persist in end-stage drug abusers for decades. For example, consider a group of addicted Japanese soldiers from World War II

who stopped taking amphetamine when the war ended. Nearly five decades later, even small doses of amphetamine induced the same effect that they experienced during the war (Sato et al. 1992, 115). Thus, decades after the sensitization process, a single dose was enough to reinstate the cravings, suggesting that the sensitization effect is permanent.

Brain Changes in Drug Abuse

At this point we turn our attention to the brain changes that account for the stages described above. Understanding the neural basis of drug abuse involves answering four key questions that arise from the previous description of the drug abuser's experience. This section addresses these questions in order.

How and where does the drug exert its effect?

Drugs of abuse exert their effects in synapses, the regions where one nerve cell (neuron) is closely opposed to, but does not touch, its target neuron. In the process known as synaptic transmission, the sending neuron releases a chemical called a neurotransmitter into the synapse. The neurotransmitter diffuses across the gap and activates receptors on the receiving neuron, causing it to send the message on in the neural circuit.

Although drugs can influence synaptic transmission in many different ways, our focus here is on the process that underlies the feeling of pleasure produced by drugs of abuse. Most drugs of abuse cause an increase in the release of a neurotransmitter called dopamine. These increases in dopamine activate the brain's reinforcement system which includes two key structures, the ventral tegmental area (VTA) and the nucleus accumbens (NA). Neurons from the VTA project to the NA where they release dopamine. It is well accepted now that addictive drugs gain their reinforcing properties through activating dopamine release in the nucleus accumbens (Pierce and Kumaresan 2006, 216).

As this suggests, rats will learn to self-administer drugs that activate dopamine release in the nucleus accumbens. When a rat is given limited daily opportunities to press a bar that gives drug doses it will show a steady rate of self-infusion. When self-infusing cocaine, rats typically regulate the overall dose they receive. If the dose per bar press is increased they will reduce their responding, and vice versa.

Incidentally, here is where we see the first direct danger of taking drugs on a long-term basis. It turns out that self-administering rats run a significant risk of dying from their drug intake. After 25 days 90% of the rats allowed continuous cocaine self-administration had died (Bozarth and Wise 1985, 81)! In contrast, 35% of those given continuous heroin self-administration died.

Most drugs of abuse either activate the VTA neurons, or directly influence dopamine levels in the NA. For methamphetamine this increased dopamine level occurs during the first dose the subjects experience (Vollm et al. 2004, 1715). Nicotine also activates the release of dopamine in the reward system, supporting the conclusion that nicotine can be addictive (Rice and Cragg 2004, 583). Similarly, ethanol increases dopamine release in the nucleus accumbens in rats (Löf et al. 2007, 148; Imperato and Di Chiara 1986, 219) and also in humans (Boileau et al. 2003, 226).

Cocaine and amphetamine cause a direct increase in the dopamine concentration in the NA. Under normal circumstances, dopamine released into the synapse is cleared away by a process called reuptake, where a molecule called a transporter brings dopamine molecules back into the neuron that released them in the first place. Cocaine and amphetamine block this transporter molecule, which means that the dopamine now remains in the synapse. At the same time, more dopamine is continually released, so the dopamine level steadily increases, leading to the activation of the pleasure sense. Opiates also produce a strong increase in DA release in the nucleus accumbens (Self 2004, 242). Opiate receptors have been found throughout the VTA (Garzón and Pickel 2002, 461) and rats will self-administer opiates directly into the nucleus accumbens and the VTA.

For some drugs, such as amphetamine, it often takes a few doses to reach the maximum effect. This process, known as sensitization, is an important element in the addiction process. In rats, sensitization to amphetamine takes over a week to occur, and consists of a greater than normal release of dopamine in response to a given dose of amphetamine (Paulson and Robinson 1995, 56).

Interfering with this dopamine release demonstrates that the nucleus accumbens dopamine system is critical for the pleasure produced by drugs. High doses of drugs that block dopamine receptors completely abolish self-infusion responding. Similarly, damage to the VTA neuron terminals produced a dramatic decline in cocaine self-administration (Roberts and Koob 1982, 901; Roberts, Corcoran, and Fibiger 1977, 615). Similar reductions in self-administration following lesions were found for amphetamine (Lyness, Friedle, and Moore 1979, 553), nicotine (Singer, Wallace, and Hall 1982, 579), and heroin (Spyraki, Fibiger, and Phillips 1983, 278).

What accounts for drug tolerance?

Chronic drug abuse leads to a marked reduction in dopamine activity in the brain. For example, microdialysis studies in rats (which allow analysis of dopamine levels in the NA) have revealed that after the first two doses of cocaine there was a distinct increase in dopamine levels in the nucleus accumbens (Maisonneuve and Kreek 1994, 916). However, the increase in response to the third dose was not as great, suggesting that by this time the brain had produced a countering response and that tolerance was beginning to occur.

This effect becomes more pronounced with repeated doses. After fourteen days of cocaine doses, baseline dopamine levels in the nucleus accumbens of rats then became permanently depressed (Maisonneuve, Ho, and Kreek 1995, 652). At this point, each cocaine dose did produce a very slight rise in dopamine, but now the dopamine levels subsided quickly, suggesting that the brain countering responses had become stronger and their onset more rapid.

It's clear that this reduction underlies drug tolerance, but how and why does it occur? While there are many different theories of drug abuse, most researchers accept that the brain produces responses to counteract the effects of the drug. The easiest way to explain why this happens is to invoke the concept of homeostasis, which is the tendency for the body or brain to maintain internal conditions within optimal limits. In the case of the brain, the increased dopamine release and the consequent intense change in activity in the receiving neurons in the NA are detected as disruptions

of homeostasis. Consequently the brain initiates changes in the synapse to reduce the extent of the activity change caused by the drug.

In other words, the brain tries to counteract the drug effect by producing compensatory responses. These compensatory responses in the synapse are called neuroadaptations. Neuroscientists have discovered a number of mechanisms that function as neuroadaptations in the synapse. One of the easiest examples to explain is a reduction in dopamine receptors on the target nucleus accumbens neurons.

Given that the pleasure sense is activated by an increased level of dopamine in the synapse, reducing the number of receptors means that the increased level of dopamine becomes largely irrelevant. With fewer receptors available, the target neuron synapse will not be as active and the pleasure sense will be decreased.

The brain scanning technique known as PET scanning can reveal the activation of dopamine receptors in different parts of the brain, including the nucleus accumbens. Using this technique Tsukada et al. (1996, 7670) reported a distinct reduction in dopamine receptor concentration after 14 days of cocaine use. This reduction in the activation of NA neurons leads to a reduction in the intensity of the pleasure sense. In other words, tolerance occurs, prompting the user to take a higher dose.

There are also compensatory responses in the emotional state of the abuser. The intense feeling of pleasure derived from drugs like cocaine is seen by the brain as a disruption of emotional homeostasis. This is where the amygdala, the key brain structure that regulates emotions, enters the picture. There are direct pathways between the VTA and the amygdala and there is strong evidence that changes in the activation of the amygdala occur as drug addiction progresses.

In its role as the key emotional regulator in the brain the amygdala controls whether we feel happy or sad. It also controls attaching motivational significance to different stimuli. In other words, it labels stimuli as either reinforcing or aversive. These functions lead it to play a key role in the body's response to excessive use of drugs of abuse. As drug use progresses the amygdala activates anti-reward systems to reduce the reinforcing nature of the drug. In addition the amygdala activates other emotion circuits to produce actual states of emotional depression and the feeling of stress (Koob 2003, 442), adding to the drastically reduced pleasure experienced by chronic users. We can also see how conditioned tolerance plays a role here. Presentation of drug associated cues would activate these anti-reward systems, producing the aversive behavioral state that generates strong cravings, making relapse more likely (See 2006, 140).

The final important factor in generating tolerance is the body's response to the many stimuli that are typically present in the drug-taking ritual performed by the abuser. The ritual may involve using various instruments such as spoons, gram scales, syringes and often a rubber hose to use as a tourniquet to raise a vein for injection. All of these objects, plus the room in which the dosing occurs, and any other cues that regularly occur at this time, are consistently paired with the actual drug dose taken by the user.

This produces a classical conditioning effect called **conditioned tolerance**, first reported by learning theorist Shepard Siegel (1977). Drug-associated stimuli act as conditioned stimuli that signal to the body that the drug is coming. As a result, counter responses are activated when these cues are present. Thus, even before the dose is taken, the counter responses are activated. The net effect is that the overall pleasure feeling is minimal.

Conditioned tolerance has serious implications for the possibility of fatal drug overdose. Consider the predictions arising from the conditioned tolerance effect. What would happen if a chronic drug user took his or her usual high dose in unfamiliar surroundings when few of the usual cues were available? Without these cues the counter response that “protects” the user from this high dose will only be weakly activated, and the user would be more likely to overdose.

Because the key factor is the presence or absence of the drug cues, one could test this by removing the drug cues that were present as the addiction state developed. Siegel et al. (1982, 436) administered opiates in a distinctive chamber (Chamber A) until tolerance developed and then administered the same dose to one subgroup of those rats in a distinctly different chamber (Chamber B). There was significantly more mortality in the rats in the new chamber, than in those given the drug in the familiar surroundings,

Studies of human overdoses also support this overdose prediction. For example, a study on non-fatal overdoses showed that non-daily injectors of heroin are much more likely to overdose than daily users (Brugal et al. 2002, 319). In this case, daily use would promote stronger and more consistent conditioned tolerance. These studies strongly support the claim that one would expect most overdoses to occur when the usual drug-taking ritual is disrupted or absent.

Why are withdrawal symptoms opposite to the original effects of the drug?

The same neuroadaptations underlying tolerance also account for withdrawal symptoms. Given that the neuroadaptations, such as reduced receptors, are still present, removing the drug means that the body is only under the influence of the neuroadaptations. Thus, the body is now in solely in the counter response condition. Table 1 shows how reducing dopamine receptors leads to tolerance and withdrawal symptoms. Notice how the first column indicates that the initial conditions generate the intense peak feeling of pleasure, while the last column illustrates why withdrawal symptoms are opposite to the initial effects of the drugs.

Table 1 Brain changes occurring as substance abuse develops

	During 1 st Dose	After Repeated Doses	During Withdrawal
Dopamine level	increased	reduced	reduced to normal or below normal
D2 Receptor numbers	no change	reduced	reduced
Behavioral effect	“rush”	minimal “rush” (tolerance)	severe “crash”

Why its recidivism over 90%?

Even though they may have gone through an intensive detoxification treatment, drug abusers are still at great risk to begin using again. This problem, known as recidivism, or habit reinstatement, suggests that taking the drug in the first place has produced long-lasting, possibly permanent, changes in the brain. For example, recovered cocaine addicts report a distinct persistent anhedonia, which suggests that their cocaine use has produced permanent neuroadaptations in their pleasure system.

These changes begin with the initial sensitization process that we saw above. The permanence of this sensitization effect is amply demonstrated in the study of Japanese World War II veterans described above. Other changes in the brain are also very long-lasting, and make the user vulnerable to the intense cravings that induce recidivism.

In addition to a single dose of the drug, the problem for the end-stage addicted user is that these intense cravings, and the resulting recidivism, can also be activated by the drug-associated stimuli to which the user has now become conditioned (McFarland and Ettenberg 1997, 86). Perhaps even more important, a general intense stressful episode can also activate cravings. For example, in rats reinstatement of dosing was induced by a stressful footshock (McFarland et al. 2004, 1551), or presenting drug-related stimuli (Di Ciano and Everitt 2004, 1661; McFarland and Kalivas 2001, 8655).

As the drug abuser approaches end-stage addiction, there are complex changes that occur in the prefrontal cortex. In general, beginning in Stage 2, several regions in the prefrontal cortex show drastically reduced activity (Volkow et al. 2004, 557), a condition referred to as hypofrontality. This effect is generally attributed to a reduction in the activity of neurons in the prefrontal cortex that in turn activate other brain structures by releasing an excitatory neurotransmitter called glutamate.

The reduced activation of the prefrontal cortex seen during Stage 2 of drug abuse persists in end-stage drug abusers. These individuals show a dramatic reduction in overall activation of the frontal cortex (Volkow et al. 1992, 184). Reducing prefrontal cortex activity has several important consequences. It impairs decision making by reducing the ability to inhibit impulsive acts. Patients

with frontal cortex damage due to tumours or strokes typically do poorly on tasks that present them with the prospect of immediate big rewards, but even bigger future punishments (Bechara, Tranel, and Damasio, 2000, 2189; Damasio 1994, 154). They tend to restrict their thinking and focus on the more salient immediate reward.

This condition also accounts for the state of mind shown by a drug abuser. They typically show a mind set narrowly focused on their next dose, and they are highly likely to give in to impulses to engage in risky or illegal acts to obtain the drug they are driven to take (Goldstein and Volkow 2002, 1642). During cognitive tasks involving making decisions, drug-dependent subjects showed less activation of the prefrontal cortex (Verdejo-Garcia et al. 2006, 405; Paulus et al. 2003, 65; Bechara and Damasio 2002, 1675; Paulus et al. 2002, 53). The same reduction has also been reported during cognitive tasks requiring response inhibition (Goldstein et al. 2001, 2595). Thus drug-dependent individuals tend to have reduced prefrontal cortex activation most of the time. This suggests that addicted subjects do not pay as much attention to normal cognitive or even emotional stimuli, which could help to account for the persistent anhedonia seen in end-stage addicted subjects.

In fact, the anhedonia is probably more directly due to the reduced overall prefrontal cortex activity. This reduction means that the PFC no longer controls activation of the nucleus accumbens as it once did. The reduced excitatory glutamate transmission in the nucleus accumbens results in significantly reduced feelings of pleasure to normally pleasurable stimuli, accounting for the anhedonia experienced by many users.

Unfortunately, for drug abusers in end-stage addiction, these frontal lobe neurons are not always inactive. To the contrary, while they are insensitive to many normal stimuli and events, they are hypersensitive to drug-related stimuli and doses of the abused drug. A single drug dose leads to a strong activation of the nucleus accumbens that generates at least some pleasure, while drug cues activate the intense cravings felt by the user. In the presence of these stimuli, there is enhanced glutamate transmission from the amygdala and the prefrontal cortex (Kalivas 2004, 23; Kalivas et al. 2004, 169; McFarland, Lapish, and Kalivas 2003, 3531; Kalivas 1995, 95).

This enhanced activity in response to a drug dose, or to drug-related cues, is crucial in the reinstatement process. When enhanced glutamate transmission from the prefrontal cortex to the nucleus accumbens occurs following a dose of cocaine, the drug habit may be re-established (Park et al. 2002, 2916). In contrast, lesioning the glutamate pathways from the prefrontal cortex, or blocking glutamate receptors abolished this effect (Cador et al. 1999, 705).

A clear example of this habit reinstatement effect can be seen in a rat study involving extinction of a drug self-administration habit. Rats were trained to run to a goal box to receive an injection of heroin when they smelled an odor that signaled the drug was available. Following this, the running response was fully extinguished over seven days by removing the odor. After extinction a single presentation of the odor was enough to reinstate significant running to the goal box (McFarland and Ettenberg 1997, 86). Even more interesting, pretreatment with a dopamine receptor blocking drug had no effect on this finding, suggesting that the dopamine system is not required for

this reinstatement effect. Thus, while increased DA release in the nucleus accumbens is essential for the initial development of tolerance, other brain systems control the reinstatement process.

One of these is clearly the prefrontal cortex. While prefrontal cortex activity is reduced in general, where drug-related stimuli are concerned the prefrontal cortex becomes strongly activated. For example, when addicted subjects were engaged in interviews about themes related to cocaine, they reported intense cravings. At the same time brain scans indicated strong activation of the prefrontal cortex (Wang et al. 1999, 775). Use of other drug-related cues also produced prefrontal activation that correlated with the intensity of the cravings reported by the addicted subjects (Bonson et al. 2002, 376). Clearly these drug cue-induced changes in the prefrontal cortex underlie the persistent intense cravings that make reinstatement of the habit so probable.

Drug-related cues are a constant problem for most drug abusers. Consider the consequences for a treated drug addict who goes back to the same surroundings from which he or she came. The familiar cues will activate neuroadaptations, producing an aversive condition in the body as well as intense cravings for the drug. This presents a very real risk of reinstating drug use, and appears to be a major factor in the high rate of recidivism seen in drug abusers.

Unfortunately for addicts, this means that there is a relatively high rate of recidivism, even after they have undergone a course of complete withdrawal. Because most recovered addicts return to the same surroundings and social influences that were present when they became addicts, these sights and sounds become powerful factors inducing them to take drugs once more.

It is crucial for policy makers and funders of programs to understand these vulnerabilities to familiar cues. They mean that rehabilitation must go beyond a temporary departure of the drug abuser from familiar surroundings. Simply allowing or requiring the user to return to his or her home environment, which is what occurs in most cases, results in high recidivism. Somehow we must go beyond this in our rehabilitation programs. Here, of course, is where further research is needed. As we learn more about these drug-related effects and the neural events that produce them, we will learn to treat drug abusers with increasing effectiveness.

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