

Incentive Salience and the Transition to Addiction

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OUTLINE

Drug Addiction, Recovery, and Relapse	391	Sensitization of Incentive Salience	395
The Incentive Sensitization Theory	393	Factors That Influence Sensitization	396
<i>What Psychologically Is Sensitized? Incentive Salience</i>		<i>Cross-sensitization</i>	396
<i>Features</i>	394	<i>Context and Craving</i>	396
What Is Incentive Salience?	395	A Role for Pleasure?	397
Mesolimbic Dopamine as a Common Currency for Incentive Salience	395	Summary	398

DRUG ADDICTION, RECOVERY, AND RELAPSE

Most adults have used a potentially addictive drug at least once in their lifetime, if caffeine, alcohol, and nicotine are included in addition to illicit drugs. In some cases, contact with a substance is so frequent and socially accepted that many in society fail to recognize it as a “drug.” However, relatively few people develop sufficient problems with drug use to meet the formal criteria for addiction, even for potent illegal drugs such as cocaine or heroin. Drug addiction is characterized by compulsive drug seeking, an impairment of social and psychological functions and/or damage to one’s health. It typically involves overwhelming involvement with drug procurement and intake, a loss of control, and a narrowing of interests away from other forms of reward besides the drug of choice. According to a 2004 survey, less than 10% of the US population meet the criteria for alcohol abuse or any illegal drug abuse

disorder, and an even smaller proportion suffer from chronic drug addiction. Yet, the worldwide monetary and social costs associated with drug control measures, corruption, lost productivity, and treatment of drug addiction are enormous.

The chief problem in treating drug addiction is chronic or repeated relapse by those who have become addicted in the above sense. Even after prolonged periods of withdrawal and abstinence, a high percentage of addicted individuals in treatment programs eventually relapse to drug taking. For example, in the case of a study of heroin users, relapse rates to reuse after cessation were approximately 60% within 3 months and at least 75% within 12 months. For this reason, drug addiction is characterized as a chronic relapsing disorder; relapse is the rule rather than the exception and often occurs repeatedly.

There are three reasons frequently suggested to explain relapse: (1) *drug euphoria* – that addicts resume drug taking to experience the intense pleasure

(euphoria) they remember the drug producing; (2) *over-learning habits or predictions* – drug taking becomes such a well-entrenched habit that relapse is almost inevitable or that learning becomes distorted in other ways to create false predictions about drug rewards; and finally (3) *withdrawal escape* – that the withdrawal syndrome that accompanies the cessation of drug intake is so unpleasant that an addict would do anything to stop it and so relapse occurs as an escape from withdrawal. All these explanations certainly play a role in relapse, yet several considerations suggest that they leave out many situations where relapse occurs.

First, drug pleasure or euphoria certainly accounts for the initial pattern of drug use and abuse, but may have more difficulty in accounting for relapse. Some individuals actually have been described to experience a decrease in drug pleasure after prolonged use, due to development of tolerance, yet experience a simultaneous increase in drug craving. Thus, relapse may occur at a moment of reduced drug pleasure but elevated drug craving. Also, relapse happens even in situations when addicts know that their drug will fail to lead to intense pleasure but rather to more misery.

It has also been suggested that the repeated use of drugs creates a learning disorder or makes drug taking an overly ritualized habitual act. This may be true of the act of drug taking, but perhaps less so regarding the preceding flexible acts of drug seeking or drug craving. Learned habits or mispredictions alone cannot account for the excessive motivational attraction that drugs and their cues develop through the course of addiction. The idea that addiction is merely a rigid stimulus–response habit does not account for how motivation imbues the act of drug taking with compulsive overtones that cannot readily be overridden by the resolution to abstain. Other extremely well-learned habits such as tying one's shoes and brushing one's teeth are not compulsive in a motivational sense – those habits can easily be left undone or stopped midway if one wishes, without experiencing a compulsive urge to continue. The learning account as a rigid habit also fails to explain the flexibility and resourcefulness that addicts display when procuring drugs.

Finally, many addictive drugs surely do induce homeostatic responses that oppose the primary drug effects and produce the phenomena of tolerance (when drug is present) and withdrawal (when drug is absent). Withdrawal, in particular, is typically described as an intense negative emotional state accompanied by dysphoria, anxiety, and irritability. Withdrawal may indeed be a potent reason why many addicts relapse and take drugs, at least while the withdrawal lasts. Yet, withdrawal is a relatively short-lived phenomenon and decays substantially within days to weeks. By contrast, while relapse frequently occurs during withdrawal, it

also often occurs much later and even in fully “detoxified” addicts who are no longer experiencing any strong negative symptoms of withdrawal. Even if one adds conditioned withdrawal that sometimes occurs later – symptoms resurrected by drug cues – to the category of withdrawal, long-term feelings of withdrawal remain relatively infrequent and weak as a cause of relapse. For example, McAuliffe reported that only 11 of 40 (27.5%) heroin addicts reported experiencing conditioned withdrawal feelings at all, and only 2 (5%) said that it led them to ever resume drug use. Other reasons for relapse must be more potent to explain why a detoxified addict decides to take drugs again. In addition, addicts will often voluntarily undergo the unpleasant process of withdrawal in detoxification clinics, sometimes again and again, to reduce tolerance and the monetary cost of their addiction and to possibly regain some of the euphoria that comes with taking the drug. In short, withdrawal is not always highly avoided or so bad as to be the chief cause of addictive drug taking, and the end of withdrawal does not signal the end of addiction.

In contrast to these suggestions, the incentive sensitization theory proposes an alternative view – that relapse frequently occurs as a result of drug-induced brain changes that lead to intense incentive motivation for drugs, or pulses of “wanting” often triggered by drug cues, which may control behavior implicitly or sometimes may be experienced as feelings of drug craving. Craving is defined as pathologically intense feelings of wanting, which can be produced when incentive salience (or core “wanting”) is translated into conscious awareness. At its core, the motivation to take drugs is due to the overattribution of incentive salience to drug-related stimuli. It is important to note that incentive salience is a distinct psychological process from withdrawal and drug pleasure.

In particular, the incentive sensitization theory proposed by Robinson and Berridge (1993) suggests that craving and relapse are governed by a sensitized neural system (mesocorticolimbic dopamine and related systems) that normally functions to attribute incentive salience to reward cues. This system transforms ordinary stimuli, such as cues associated with rewards, into incentive stimuli, making them attractive and able to trigger an urge to pursue and consume their reward. Repeated drug use produces sensitization of this brain system, which leads to increased “wanting,” which in turn leads to excessive control of behavior by drug-related incentive stimuli. Addiction can therefore be described as an excessive “wanting” problem. Importantly, excessive “wanting” can occur even in the absence of excessive liking for drugs. In fact, the increasing dissociation that addicts exhibit between how much they “want” drugs and the pleasure drugs produce explains many of the irrational features of

behavior behind their drug-taking and drug-seeking habits. Irrational “wanting” for addictive drugs can lead to persistent taking of drugs again and again despite the adverse consequences and even if the euphoria of drug consumption declines.

The basic mechanisms of the excessive attribution of incentive salience to drugs and drug-related stimuli can even occur as a mostly unconscious process, creating urges to take drugs whether or not a strong subjective feeling of craving is simultaneously present. Such dissociation between acted-on motivation and confusing subjective feelings is what often renders the compulsive quality of an addict’s own behavior astonishing even to him or her.

THE INCENTIVE SENSITIZATION THEORY

A stunning anecdote often arising from clinical settings is that as drugs become wanted more and more, they may become liked less and less. This is compatible with the idea that the basic brain mechanisms of reward “liking” and reward “wanting” are dissociable. In fact, the incentive sensitization theory put forward by Robinson and Berridge partitions drug reward into three components: “liking,” “wanting,” and “learning.” Incentive sensitization suggests that each of these components plays a role in the development of drug use, but that it is primarily a distorted amplification of the “wanting” component alone that makes drug addiction so compulsive and resistant to recovery. The incentive sensitization theory does not deny that drugs produce pleasure, or are learned about, or that drug cessation produces a period of unpleasant withdrawal that prompts some individuals to relapse while it lasts. It simply suggests that the attribution of incentive salience is the critical step that gives rise to “wanting” and that addictive drug use in susceptible people creates very long-lasting brain changes, such as neural sensitization of dopamine-related systems that connect the ventral tegmental area (VTA) to targets in the nucleus accumbens, neostriatum, amygdala, ventral pallidum, and prefrontal cortex. Sensitization of these dopamine-related systems results in the amplification of the neural mechanisms for incentive salience that transform ordinary levels of cue-triggered “wanting” into excessive addicted levels of urges to take drugs and persistent vulnerability to relapse. Although “liking” and “wanting” drugs are strongly linked at the onset of drug use and abuse, only “wanting” becomes sensitized and consequently more intense, as addiction develops. For example, in animal studies, sensitization increases neuronal firing in VTA–accumbens–pallidal pathways that code incentive salience as well as the behavioral ability of reward cues to trigger

frenzied bursts of effort to obtain the reward in Pavlovian-to-instrumental transfer (PIT) experiments. Yet, sensitization does not increase “liking” reactions that reflect the hedonic impact of the reward when it actually arrives. Similarly, in humans who are becoming drug tolerant, incentive motivation to take the drug can grow as they become addicted, so that a single dose of drug can provoke intense urges to take more, even if the person reports that the dose of drug no longer gives as much pleasure as it did initially.

It may be important to note that some neuroscientists initially questioned, after the incentive sensitization theory was proposed, whether there was concrete evidence that neural sensitization of mesolimbic systems occurred in humans, as well as in lab animals. This was despite evidence for incentive sensitization, such as the intense neural activation induced in the brains of drug addicts who view drug-related cues, and the concomitant psychological urge to consume drugs that such cues often trigger. Now, recent neuroscience evidence has emerged to support the postulate that sensitization happens in the brains of vulnerable humans exposed to psychostimulant drugs just as it does in animals. It was long known that amphetamine and cocaine produce psychosis and psychotomimetic effects that can last a long time, and cocaine users who show a sensitized response to psychotomimetic effects also have an elevated incidence of addictive relapse. Just a few administrations of amphetamine is all it may take to potentiate basic emotional mood-elevating responses or simple psychomotor responses such as eye blink for up to 1 year later. Sensitization has also been demonstrated in the brains of ordinary people as direct elevation of the amount of mesolimbic dopamine released in response to an addictive drug. For example, significantly greater amphetamine-induced ventral striatal dopamine release was observed 2 weeks and again 1 year after the administration of three drug doses over a 1-week period. Compelling evidence for neural sensitization of dopamine release has also been shown in Parkinson’s patients with dopamine dysregulation syndrome. This leads to compulsive dopaminergic drug taking, with increased reports of drug wanting, but not drug liking, and increased dopamine release in nucleus accumbens and striatum especially in the combined presence of cues and the dopamine-stimulating drug. Consequent incentive sensitization may also manifest itself by pathological gambling, hypersexuality, food bingeing, and punding (a form of complex behavioral stereotypy). Conversely, there was no apparent sensitization to how much subjects liked amphetamine or other dopamine-stimulating drugs in the aforementioned studies. One report has even shown tolerance to the euphoric effects of psychostimulant drugs in cocaine-dependent abusers despite enhanced

drug seeking. This evidence taken together demonstrates neural sensitization in humans and highlights the dissociation of liking and wanting emphasized by the incentive sensitization theory of addiction.

What Psychologically Is Sensitized? Incentive Salience Features

Incentive salience peaks, expressed as phasic peaks of neural firing or bursts of reward-seeking behavior in laboratory studies, are often triggered by reward cues. In human addicts, a cue-triggered peak of incentive salience would make them urgently “want” to take drugs again. Three fundamental characteristics apply to the cues or conditioned stimuli (CSs) that have been imbued with incentive salience. The first is that the cues act as “motivational magnets” and elicit approach toward them, which can be measured in animal studies of addiction mechanisms by Pavlovian conditioned approach or sign tracking. This feature of an incentive stimulus will serve to bring individuals into the proximity of drugs. In some cases, attribution of incentive salience to reward-predicting cues may make the cues “wanted” as much as the reward itself. Indeed, the cue may become so irresistibly attractive that it can lead the animal away from the reward, which is then lost. Such cues become motivational magnets, sometimes prompting irrational behavior such as interactions with the cue similar to those prompted by the nature of the reward. Consequently, animals are attracted to reward cues and may even try to drink or eat levers or lights that predict water or food, respectively. Similarly crack cocaine addicts can be found inspecting the floor for a white speck that is more likely to be an ordinary pebble than crack cocaine and can be attracted to pick it up, inspect, and put it in the pipe and even try to light or smoke the noncocaine pebble (a phenomenon that has been called “chasing ghosts”).

Secondly, these CSs possess the ability to elicit cue-triggered wanting for their associated unconditioned stimulus reward (“conditioned motivation”), which creates sudden surges of efforts to obtain the real reward, measured in animal experiments by PIT effects. In addicts, cue-triggered “wanting” for a drug reward can cause relapse by reinstating the motivational state that spurs efforts to obtain and take the drug again.

Finally, a CS attributed with incentive salience can reinforce the acquisition of a new instrumental response by acting as a reinforcer in its own right, as measured by conditioned reinforcement. An animal may for example learn to perform a new nose-poking response if that response is followed merely by presentation of a Pavlovian cue previously paired with a drug reward. This action of an incentive stimulus can maintain flexible drug-seeking behavior over long periods of time when the drug itself is not immediately available. All

three of these characteristics are susceptible to further magnification following sensitization of incentive salience by repeated drug treatments.

Much of the available evidence suggests that it is the mesolimbic dopaminergic system of the brain that contributes to the psychological attribution of incentive salience to rewards, often triggered by the cues that have been paired with those rewards in the past. The mesolimbic dopamine system is well known to be a common neural substrate activated by the majority of addictive drugs and can also be nearly permanently changed by drugs when taken by susceptible individuals at doses and in patterns that parallel addictive use. That is, through the repeated consumption of drugs, this brain system will in certain individuals gradually and incrementally become *sensitized*. In neural studies of sensitization mechanisms, drug-induced sensitization can increase the amount of dopamine release elicited by a given dose of drug, cause changes in molecular processing of dopamine and glutamate signals in synapses in the ventral tegmentum, nucleus accumbens, and related brain structures, and even cause microanatomical rewiring of those synapses in the form of changes in the number and complexity of tiny dendrites on neurons that receive inputs from other neurons.

Mesolimbic sensitization in addicts gives rise to a state where drugs and their cues become increasingly “wanted” to the point where the drugs are irrationally craved. It also helps explain why, contrary to the predictions made by a withdrawal avoidance approach to addiction, taking drugs again typically will further increase rather than reduce craving to take even more. Motivation priming by drugs is one reason why many alcoholic treatment programs recommend their members to avoid all subsequent use of alcohol: an attempt to take even a single drink in a social context entails the danger of precipitating an intense binge of further consumption. The incentive sensitization theory also highlights the fact that the neuroadaptations responsible for the sensitization of incentive salience are a long-lasting, if not permanent, phenomenon, potentially persisting for years after the individual stops taking drugs. This, we suggest, is why relapse is so prevalent and persistent despite recovery and regardless of withdrawal and even when strong pleasure is not to be expected from taking a drug.

Embedded in the theory is also the suggestion that sensitization of incentive salience may affect both conscious craving or wanting, in the ordinary sense of those words, and more unconscious forms of “wanting” that motivate drug seeking even in the absence of strong craving feelings, as a more implicit psychological process. Additionally, as mentioned above, sensitized “wanting” may grow independently of any changes to the neural system responsible for drug liking. In fact,

the “liking” system may in some cases display a form of adaptation known as tolerance. The result is a paradoxical state where some drugs are increasingly “wanted” despite not being particularly “liked.” Finally, as the drug addict becomes progressively more consumed with drug-seeking and drug-taking behavior, a narrowing of interests occurs, which tends to exclude all other activities from the addicts life in favor of those linked to the drug. With time, and as a consequence of an ever-growing history of drug intake, the addict comes to associate an expanding number of different stimuli with the experience of the drug. All of which may later become capable of triggering craving and precipitating relapse in certain situations.

All these factors help explain the persistence of drug-taking behavior despite aversive consequences (job loss, health issues, etc.) and account for the discordance often witnessed in drug addicts between drug wanting and drug liking.

WHAT IS INCENTIVE SALIENCE?

In more detail, the attribution of incentive salience is a psychological process thought to be mediated by brain mesocorticolimbic systems to help direct behavior toward naturally sought after rewards, such as food, water, and sex. It heightens perception and focuses attention toward the particular sights, sounds, and smells associated with these rewards in a way that normally promotes well-being and survival. Incentive salience may have evolved to guide behavior in the right direction even prior to having experienced the rewards, but also became able to be recruited by pleasurable experiences and combined with learning to add additional guidance. Incentive salience obeys what are sometimes called Bolles–Bindra–Toates principles of incentive motivation, which posit that Pavlovian cues that predict pleasant rewards trigger motivation, interact with current physiological states, and become wanted and liked in much the same way as the reward itself. However, incentive salience theory further dissociates “wanting” (incentive salience itself) from “liking” (hedonic impact), as different psychological processes with different neural mechanisms, even when those two processes occur simultaneously. “Wanting” in quotation marks is distinct from more cognitive forms of desire associated with the ordinary sense of the word wanting. The two usually occur together; however, cognitive wanting involves explicit goals and declarative expectations of the desired outcome, while core “wanting” does not require conscious awareness, perhaps because it is chiefly a product of subcortical structures involving mesolimbic dopamine systems. Incentive salience bestows even natural reward-related

Pavlovian cues with the ability to trigger powerful peaks of “wanting,” such as when a child walks past the window of a candy store. These peaks in “wanting” are sudden, intense, temporary, reversible yet also repeatable. Amplified further by neural sensitization and focused onto drug rewards as the target, “wanting” peaks can reach compulsive intensities. Normally, pleasure is required to assign incentive salience, but brain stimulation and certain drugs of abuse that directly or indirectly activate primarily dopamine systems can skip this step by directly activating and sensitizing the neural substrate of incentive salience, causing in essence a form of sham reward (“wanting” without “liking”).

MESOLIMBIC DOPAMINE AS A COMMON CURRENCY FOR INCENTIVE SALIENCE

There is strong evidence that dopamine systems help mediate incentive salience. Cues for rewards such as food, water, a sexual partner, or drug cause an increase in dopamine neurotransmission, activating dopamine neurons in the VTA that project upward to the nucleus accumbens, prefrontal cortex, and related forebrain structures. For example, raising dopamine levels directly in the nucleus accumbens amplifies the ability of reward cues to trigger “wanting.” Conversely, suppressing dopamine levels reduces the motivational value of rewards. Experiments have revealed that the effects of dopamine manipulations are chiefly on reward “wanting” and not on “liking” or hedonic impact of the same reward. For example, studies in our laboratory, using the affective taste reactivity paradigm to specifically measure “liking,” show that pleasure from sweet tastes is increased by hunger and decreased by satiety, but remains unchanged by dopamine manipulations (sensitization, dopamine elevation, pharmacological antagonists, lesions). By contrast, these same manipulations of the dopaminergic system can potently alter the motivation or “wanting” for rewards. This also highlights the fact that naturalistic manipulations such as hunger and satiety typically modulate both “liking” and “wanting” in concert, but drugs of abuse can in some situations key in directly to “wanting” alone, more than to “liking.”

SENSITIZATION OF INCENTIVE SALIENCE

Central to addiction neuroscience is the well-known fact that almost all drugs of abuse share the ability to enhance mesolimbic dopamine transmission. Additionally, sensitization of mesolimbic dopamine neurons causes long-term hyperreactivity in dopamine transmission due to repeated drug-induced sudden bursts of

dopamine triggered by high doses taken in an intermittent pattern, especially in a particular context. Initially, the spotlight focused on the sensitization of psychomotor stimulant effects, but it now seems clear that the incentive motivation effects of drugs also sensitize. As it turns out, the mesolimbic process of attributing incentive salience can become sensitized by drugs in susceptible individuals under particular circumstances relevant to addiction. For example, neurochemically, sensitization leads to an enhanced dopamine elevation produced by an addictive drug in the synapses of the nucleus accumbens in the face of a drug challenge. Anatomically, there are also persistent changes in the brain cells and circuits of the mesolimbic system that respond to drugs and control incentive salience. These include structural changes in the morphology of neurons in brain structures of the nucleus accumbens and prefrontal cortex. The length of dendrites on medium spiny neurons in the nucleus accumbens and on pyramidal neurons in the prefrontal cortex is increased, accompanied by an increase in spine density. Changes seem to occur both pre- and postsynaptically in connectivity in brain reward systems. Increased release of dopamine is a presynaptic consequence of drug sensitization, seen both *in vitro* and *in vivo*, whereas postsynaptically, dopamine D1 receptors show increased sensitivity. In spite of this, there have been reports showing a reduction in the availability of dopamine D2 receptors in cocaine addicts, often suggested to mean either that they have fewer dopamine receptors or that more of their receptors are already occupied by dopamine. Yet, recent findings in animals indicate that cocaine causes an increase in the subpopulation of D2 receptors that are in a state of high affinity, which can occur even in spite of a reduction in overall D2 receptors. An increase in the proportion of dopamine D2 receptors in the high-affinity state would not be evident in human studies because the ligands used in human imaging studies do not discriminate between low- and high-affinity states, but if it does occur in addicts, it would result in dopamine supersensitivity. Psychologically, these neuroadaptations may combine to create pathological levels of “wanting” for drugs and their associated stimuli, although specific cause–effect relations have not yet been elucidated. In animal experiments, sensitization with amphetamine facilitates the later acquisition of a self-administration habit of taking drugs such as cocaine and amphetamine and, in a number of ways, increases the incentive motivational power of drug rewards and their cues.

FACTORS THAT INFLUENCE SENSITIZATION

Sensitization is a complex phenomenon that is influenced by the dose, timing, and spacing of the drug, along

with the context in which it is taken, and individual features of the person who is taking it (including genes, sex, hormonal status, and prior stress). Sensitization is strongest when drugs are taken in high doses and intermittently in spaced pulses (rather than as a continuous stream). Once induced in a brain, sensitization may last for years even if no more drug is taken during that period. The phenomenon of sensitization also displays a tremendous amount of individual variation, with some individuals developing rapid and robust sensitization in contrast to others who sensitize very little if at all. So far it has been shown in animals that there are genetic differences in the propensity of individual brains to undergo sensitization and in the functioning of the mesolimbic dopamine system. There is also evidence suggesting that the genetic variation in acute responsiveness to drugs is different to that responsible for differences in sensitization. Thus, on the whole, relatively few people who take drugs might actually develop sensitization of brain mesolimbic systems, and only those who do develop sensitization might become true addicts with compulsive levels of “wanting” to take drugs that persist long after withdrawal is over. That relative rareness may help account for why although 55% of 18- to 34-year-olds have at one point sampled a potentially addictive drug, only a relatively few become addicts.

Cross-sensitization

Mechanisms of induction and expression of sensitization may differ across drugs, but sensitization to one drug often will produce a sensitized response to other drugs, an effect otherwise known as cross-sensitization (such as between cocaine and heroin). The implication is that as an individual's drug history increases, the incentive value attributed to the act of drug taking and to drug-related stimuli will progressively be enhanced, which will increase the probability of repeating drug-seeking and drug-taking behavior in the future. Furthermore, cross-sensitization has even been reported between drugs and stress. Notably, pretreatment with amphetamine, cocaine, or morphine will cause hyper-responsiveness to stress, whereas initial sensitization to stress or administration of corticosterone will produce a heightened response to a later drug challenge. Evidence suggests that addictive drugs and stress both activate and sensitize dopamine systems. This highlights a critical role for stress in the occurrence of relapse, whereby stressful life events may act as powerful triggers of drug craving and, if sufficient to produce sensitization, could possibly predispose individuals to subsequent drug addiction.

Context and Craving

Environmental cues associated with the drug-taking experience become powerful triggers of sensitized

“wanting” and relapse into addictive drug taking. The hypersensitive response that addicts may display toward the incentive properties of drug-related cues may be strongest in contexts previously related to drug taking in the past. The context may therefore act as an occasion setter to modulate the incentive power of drug cues, dramatically raising the probability that a sensitized elevated neural response will be expressed in the future in that same place or situation. Different occasion-setting stimuli can either facilitate or inhibit the expression of sensitization in an environment-specific manner. Facilitators do not necessarily elicit conditioned responses but instead control the ability of other stimuli to do so. Conditioned inhibitor properties may be developed by contexts not associated with drug use, thereby preventing the expression of the sensitized response in that context. For example, the presence of relevant stimuli when drug-abusing subjects underwent testing gave rise to a positive correlation between past psychostimulant drug use and the subjects' striatal dopamine response. In contrast, the absence of these cues when the drug was administered, resulted in drug history predicting a smaller striatal dopamine response. This means that the presence of drug-related cues helped unmask the hypersensitivity of their dopaminergic brain systems, induced by prior drug use, which otherwise was hidden in their absence. Other cognitive factors may also function in related fashion as top-down inhibitors. For example, addicted airline pilots or medical anesthesiologists, who, having been identified as addicts, are compelled to pass daily drug tests under threat of losing their careers if they test drug positive, are among the few groups of addicts to have uniformly high success at avoiding relapse.

The presentation of drug-associated cues alone produces an increase in dopamine release in addicted humans, and the magnitude of the dopamine release is closely related to that individual's degree of addiction severity. Consistent with the incentive sensitization theory, there is also evidence that the drug addicts display a bias of attention toward visual drug-associated cues, as if the cues were more attractive and attention grabbing. Similarly, abstinence from smoking for only 24 h can dramatically potentiate neural responses to smoking-related cues. This highlights the importance of drug cues and the exacerbated salience attributed to them. It also emphasizes how the completeness of the contextual picture, by the presence of the myriad of components that make up the drug-associated context (mood, location, drug paraphernalia, etc.), may culminate in uncontrollable levels of craving and further increase the risk of relapse.

In addition, internal factors can fluctuate inside an individual to influence whether a particular cue will trigger intense incentive salience at that moment.

Cue-triggered “wanting” can be dramatically intensified during temporary pharmacological or physiological states that amplify mesolimbic reactivity to the cue. Such states can interact with a pre-sensitized hyperreactivity in mesocorticolimbic systems to create an even greater hyper-hyperreactivity to drug cues while the states last. The simplest example is that taking some of the addictive drug itself creates a much stronger urge to take more of the drug. Having some drug-on-board primes the reactivity of mesolimbic mechanisms to drug cues, creating a synergy that amplifies the intensity of incentive salience during the drugged-plus-sensitized combination to a further elevated level. This phenomenon known as drug priming is referred to by Alcoholics Anonymous as the one drink that leads to the next in an uncontrollable fashion. The combination of drug priming with preexisting sensitization of mesolimbic brain systems may explain why addicts who attempt to “take just one” drink or hit find themselves unable to stop after the one and often are precipitated into a frenzied binge of drug consumption. Once taken, the drug further amplifies the already sensitized levels of incentive salience evoked by the surrounding drug cues to irresistible levels. Emotional events such as stress or emotional excitements may also amplify heightened responsiveness to drug cues that trigger mesocorticolimbic “wanting” systems.

A ROLE FOR PLEASURE?

In contrast to the hypersensitivity that develops in addicts toward the incentive properties of drugs and their cues, the euphoria that drugs produce does not succumb to the same effect. There is no sensitization of “liking” mechanisms in the brain. In fact, it seems that in certain cases, tolerance may occur instead. It is clear that the pleasurable effects that drugs produce are a critical component of the initiation and initial pattern of drug use. Yet, no clear relationship exists between a drug's euphoria and its addictive potential. This is particularly evident for nicotine, which is highly addictive without producing much euphoria. Previous theories of drug addiction often fall short of explaining such dissociations between drug pleasure and drug addiction. The incentive sensitization theory is able to explain the dissociation by shifting the addiction explanation away from drug “liking” and focusing primarily on the role of drug “wanting.” Supporting evidence comes from manipulations of dopamine systems that impact “wanting,” without affecting liking responses in both humans and animals. Drug self-administration can also be maintained in the absence of any subjective pleasure, which supports the view that subjective pleasure is not a critical component for drug taking. One

report has even shown tolerance to the euphoric effects of psychostimulant drugs in cocaine-dependent abusers despite enhanced drug seeking. Similarly, a recent study in humans has shown that subjective ratings of alcohol liking and wanting often are not significantly correlated with each other. It also appears that the subjective effects reported are not functionally equivalent to the reinforcing effects of a drug. Notably, morphine has been shown to concomitantly produce both positive reinforcing and negative aversive effects. Repeated drug use also tends to engender far more negative than positive consequences. Yet, despite this, addicts report almost irrational craving for the drug. Furthermore, "wanting" can also occur not only in the absence of subjective pleasure but also in the absence of any form of cognitive wanting. Awareness only trickles down from the activation of interpretive cognitive processes that usually translate implicit activation into explicit subjective feelings. This would explain why addicts have so little insight into their apparent hunger for drugs and their cues and why they may persist in drug taking despite an array of adverse consequences. Beyond a psychological dissociation, pleasure "liking" also appears to possess a much more restrictive limbic brain circuit, both anatomically and neurochemically, which may predispose us more naturally to states of desire than to states of pleasure. To make matters worse, it appears that the enjoyment related to nondrug-associated pleasurable activities also diminishes. It seems that drug addiction actually narrows the focus to drug seeking at the expense of natural rewards and pleasurable endeavors. This may further reduce the chances of recovered addicts to resume a normal lifestyle away from the drug.

All this allows the maintenance of addiction to be more robustly controlled by drug craving than by pleasure or even by attempts to avoid the negative affective dysphoria that often comes with the cessation of drug use. The previous belief that the avoidance of withdrawal was a critical factor on the road to addiction was in large part due to reliance on observations of opiate abusers. It has since then been noted that drug addiction and even relapse can occur in the absence of withdrawal symptoms.

SUMMARY

The persistence of the neuroadaptations that underlie drug-induced sensitization suggests that recovering from addiction may be a long and slow process. Cognitive and behavioral therapies may gradually reduce some layers of responsiveness to drug cues, but other layers may persist. Drug medications are not yet in view that would selectively reverse the expression of

mesolimbic sensitization without undesirable side effects. As a result, research is increasingly turning its focus toward the factors that determine an individual's susceptibility to sensitization and therefore put them at risk for addiction, as well as to ways of coping with a sensitized "wanting" system.

Once established, by demonstrating how sensitization of the mesolimbic "wanting" system occurs with repeated bursts of large drug doses, producing changes that are almost permanent. With continued drug use at high doses, the dopamine system becomes sensitized in some individuals, progressively amplifying "wanting" for drugs especially in response to drug cues, until drugs become craved more than most other rewards. The sensitization of "wanting" independent of pleasure can produce an addict who wants drugs more and more – without necessarily liking them proportionately as much, and even if liking them less and less. Yet, the incentive sensitization theory does not deny a role for pleasure seeking in initial experimenting with drugs or casual use, or even addictive use, as long as the drugs truly do give intense pleasure. Nor does the incentive sensitization theory deny that ritualized habits contribute to daily addictive drug consumption in many addicts or that withdrawal avoidance may motivate a great deal of addictive drug taking. These explanations are not mutually exclusive. However, the incentive salience theory recognizes that many addicts still persist in taking drugs again, even under conditions when all of those explanations are lacking. That is, some addicts take drugs compulsively even when they do not expect much pleasure from that drug. Addicts often devise new ways to obtain and take drugs, abandoning old habits in favor of motivated pursuit of novel drug opportunities when circumstances demand. Addicts still relapse often even after they have escaped the unpleasantness of withdrawal through a process of detoxification. The critical change underlying addictive relapse, we suggest, is the sensitization or hypersensitivity of brain mesolimbic systems to the incentive motivational effects of drugs and drug-associated stimuli. The result is a bias in attentional processing and incentive motivation value attributed to the drug cue, the act of taking the drug, and the representation of drug effects, which when combined with impaired executive control gives rise to the symptoms of addiction and the bad choices that addicts make regarding drugs.

SEE ALSO

Neurobiological Mechanisms of Drug Addiction: An Introduction, Neuroadaptive Changes that Result from Chronic Drug Exposure, The Mesolimbic Dopamine Reward System and Drug Addiction

List of Abbreviations

CS conditioned stimulus
PIT Pavlovian-to-instrumental transfer
VTA ventral tegmental area

Glossary

Conditioned stimulus (CS) a learned cue or originally neutral event that has been paired with an US and comes to elicit a response similar to that elicited by the US.

D2 high-affinity receptors D2-type dopamine receptors that are in a reversible state of sensitivity to dopamine. This state is thought to be required in order for dopamine to produce functional consequences via D2 receptors.

Incentive a reward-related stimulus that is attributed with salience, becoming attractive and eliciting goal-directed behavior.

Pavlovian-to-instrumental transfer (PIT) a process designed to assess incentive salience as cue-triggered “wanting” for associated reward, reflected in the ability of a Pavlovian reward-associated cue to induce an increase in incentive motivation to obtain reward as measured in instrumental responding.

Psychotomimetic effects effects of a drug (especially at high doses) that mimic the symptoms of psychosis, including delusions and/or hallucinations.

Sensitization (of mesolimbic substrates for incentive salience) progressively greater neural or psychological response of incentive salience attribution caused by exposure to repeated administration of drug.

Tolerance progressively smaller neural or behavioral response to a drug with repeated administration.

Unconditioned stimulus (US) here, a reward or drug event that spontaneously elicits a hedonic response.

Withdrawal unpleasant physiological changes that occur when a drug is discontinued abruptly or when its effect is counteracted by a specific agent, such as a drug antagonist.

Further Reading

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews* 28 (3), 309–369.

Berridge, K.C., Robinson, T.E., 2003. Parsing reward. *Trends in Neurosciences* 26 (9), 507–513.

Berridge, K.C., Robinson, T.E., Aldridge, J.W., 2009. Dissecting components of reward: ‘liking’, ‘wanting’, and learning. *Current Opinion in Pharmacology* 9 (1), 65–73.

Boileau, I., Dagher, A., Leyton, M., Welfeld, K., Booij, L., Diksic, M., et al., 2007. Conditioned dopamine release in humans: a positron emission tomography [¹¹C]raclopride study with amphetamine. *Journal of Neuroscience* 27 (15), 3998–4003.

Flagel, S.B., Akil, H., Robinson, T.E., 2009. Individual differences in the attribution of incentive salience to reward-related cues: implications for addiction. *Neuropharmacology* 56 (Suppl. 1), 139–148.

Flagel, S.B., Clark, J.J., Robinson, T.E., Mayo, I., Czuj, A., Willuhn, I., Akers, C.A., Clinton, S.M., Phillips, P.E.M., Akil, H., 2011. A selective role for dopamine in stimulus-reward learning. *Nature* 469, 53–57.

Milton, A.L., Everitt, B.J., 2010. The psychological and neurochemical mechanisms of drug memory reconsolidation: implications for the treatment of addiction. *European Journal of Neuroscience* 31 (12), 2308–2319.

Ostafin, B.D., Marlatt, G.A., Troop-Gordon, W., 2010. Testing the incentive-sensitization theory with at-risk drinkers: wanting, liking, and alcohol consumption. *Psychology of Addictive Behaviors* 24 (1), 157–162.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews* 18 (3), 247–291.

Robinson, T.E., Berridge, K.C., 2008. Review. The incentive sensitization theory of addiction: some current issues. *Philosophical Transactions of the Royal Society B: Biological Sciences* 363 (1507), 3137–3146.

Vezina, P., Leyton, M., 2009. Conditioned cues and the expression of stimulant sensitization in animals and humans. *Neuropharmacology* 56 (Suppl. 1), 160–168.