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Liking, Wanting, and the Incentive-Sensitization Theory of Addiction

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Rewards are both "liked" and "wanted," and those 2 words seem almost interchangeable. However, the brain circuitry that mediates the psychological process of "wanting" a particular reward is dissociable from circuitry that mediates the degree to which it is "liked." Incentive salience or "wanting," a form of motivation, is generated by large and robust neural systems that include mesolimbic dopamine. By comparison, "liking," or the actual pleasurable impact of reward consumption, is mediated by smaller and fragile neural systems, and is not dependent on dopamine. The incentive-sensitization theory posits the essence of drug addiction to be excessive amplification specifically of psychological "wanting," especially triggered by cues, without necessarily an amplification of "liking." This is because of long-lasting changes in dopamine-related motivation systems of susceptible individuals, called "neural sensitization." A quarter-century after its proposal, evidence has continued to grow in support the incentive-sensitization theory. Further, its scope is now expanding to include diverse behavioral addictions and other psychopathologies.

Keywords: pleasure, desire, addiction, limbic, dopamine

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It is now widely accepted that brain mechanisms that determine how much a reward is "wanted" are dissociable from those that determine how much the same reward is "liked." However, that idea, which we first proposed in 1989 as a post hoc explanation for some negative results on the role of the brain's mesolimbic dopamine system in pleasure (Berridge, Venier, & Robinson, 1989), originally came as a surprise even to us. At the time, we and most other investigators generally accepted the idea that dopamine mediates reward pleasure: the hedonic impact of tasty food, addictive drugs, and many other rewards. Our early experiment was simply intended to provide another bit of evidence for the dopamine-pleasure hypothesis—but results turned out otherwise.

As background, many studies had found that brain dopamine systems were activated by most rewards, and further that manipulating dopamine altered "wanting" for rewards, for example, changing how much animals preferred, pursued, worked for, or consumed the reward (Koob & Le Moal, 1997; Wise, 1985). Changes in "wanting" were naturally interpreted to reflect corresponding changes in "liking," based on the assumption that "wanting" was proportional to "liking." Our approach to measuring pleasure impact was different, and more similar to how, for millennia, parents have asked their newborn infants whether the taste of a particular food was enjoyable. We used a naturalistic or ethological assay of sweetness pleasure, based on affective facial expressions of "liking" (Steiner, 1973). Sweetness elicits relaxed facial expressions and rhythmic tongue and mouth expressions of "liking," whereas bitterness elicits "disgust" gapes and turning away. Those affective facial expressions to taste are homologous in human infants, apes, and monkeys, and even rats (Grill & Norgren, 1978; Steiner, Glaser, Hawilo, & Berridge, 2001).

In our initial experiment, we hypothesized that depletion of brain dopamine in rats via a neurochemical lesion would reduce "liking" reactions for pleasant tastes, based on the notion that dopamine mediates "liking." We expected this would be reflected as a reduction of hedonic orofacial expressions elicited by sweetness. But that is not what we found. We were surprised to find that liking reactions of rats to sugar taste were completely normal even after depletion of nearly all brain dopamine (Berridge et al., 1989). The dopamine lesions did apparently abolish all motivation—the

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rats were profoundly aphagic and no longer sought or consumed food rewards, confirming what others had described. To make sense of these paradoxical findings, we proposed that mesolimbic dopamine systems mediate "wanting" (in particular, a psychological process called *incentive salience*), but not "liking" for the same reward (Berridge et al., 1989; T. E. Robinson & Berridge, 1993). A follow-up study using implanted electrodes to stimulate the same mesolimbic systems and raise dopamine levels also failed to enhance pleasure "liking," despite quadrupling a rat's "wanting" to eat food rewards (Berridge & Valenstein, 1991). In humans, similar brain stimulation by many so-called "pleasure electrodes," upon closer inspection, may also have turned on "wanting" without "liking," and may have not been so pleasant after all (Berridge & Kringelbach, 2015).

In the 1990s, it was a lonely scientific position to maintain that dopamine did not mediate pleasure. But in about a decade, studies of dopamine in human pleasure began to catch up. For example, eventually it was reported that suppressing dopamine neurotransmission in people did not reduce their pleasure ratings of drug rewards, such as cocaine or amphetamine, even when it reduced their desire to consume more drug (Brauer & De Wit, 1997; Leyton, Casey, Delaney, Kolivakis, & Benkelfat, 2005). Similarly, dopamine suppression in ordinary people or in Parkinson's disease was reported to not reduce pleasure ratings of tasting delicious foods (Hardman, Herbert, Brunstrom, Munafò, & Rogers, 2012; Sienkiewicz-Jarosz et al., 2013). Further, neuroimaging studies began to report that changes in brain dopamine neurotransmission in people was correlated more with their subjective ratings of wanting drug and food rewards than with their liking ratings (Evans et al., 2006; Leyton, 2010; C. T. Smith, Dang, Cowan, Kessler, & Zald, 2016; Volkow et al., 2002). In sum, many studies have now accumulated supporting our original conclusion that dopamine mediates desire rather than pleasure (Salamone & Correa, 2012), and it is now rather rare to find an affective neuroscientist studying reward who still asserts that dopamine mediates pleasure "liking."

Psychological Features of Incentive Salience: "Wanting"

Note that our use of the word "wanting" so far is often in quotation marks, because we use that term to refer to a particular form of desire—namely, mesolimbic incentive salience. This type of "wanting" is often triggered in pulses by reward-related cues or by vivid imagery about the reward (Berridge, 2012). The ordinary sense of wanting (without quotation marks) refers to a cognitive desire with a declarative goal. However, incentive salience "wanting" is less connected to cognitive goals and more tightly linked to reward cues, making those cues attention-grabbing and attractive (Anderson & Yantis, 2013; Hickey & Peelen, 2015). The cues simultaneously become able to trigger urges to obtain and consume their rewards (Ostlund, LeBlanc, Kosheleff, Wassum, & Maidment, 2014; Peciña & Berridge, 2013; Zhou et al., 2012). "Wanting" is mediated largely by brain mesocorticolimbic systems involving midbrain dopamine projections to forebrain targets, such as the nucleus accumbens and other parts of striatum (see Figure 1). The intensity of the triggered urge depends both on the cue's reward association and on the current state of dopamine-related brain systems in an individual. This interaction allows "wanting" peaks to be amplified by brain

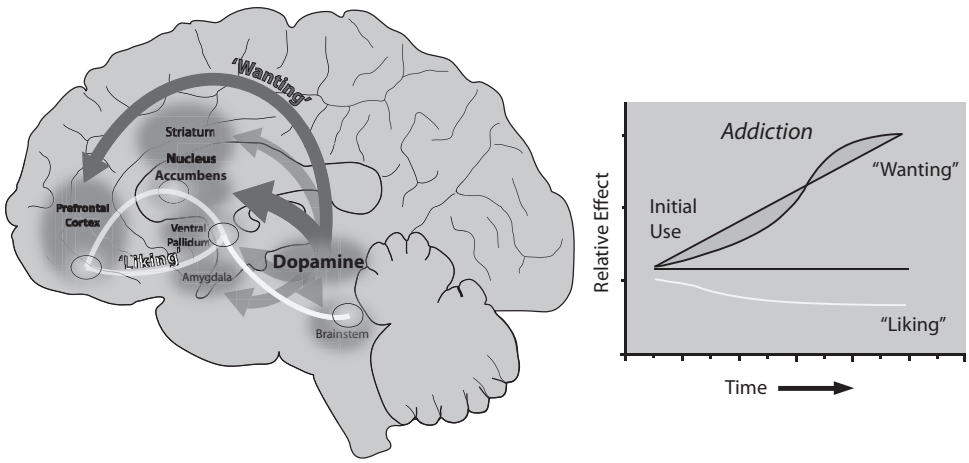

Figure 1. "Liking" and "wanting" in brain and in addiction. "Wanting" is mediated by a robust brain system including dopamine projections (left, dark gray), whereas "liking" is mediated by a restricted brain system of small hedonic hotspots (white; described in Berridge & Kringelbach, 2015). The incentive-sensitization theory of addiction (right) shows how "wanting" may grow over time independently of "liking" as an individual becomes an addict, because of sensitization of brain mesolimbic systems. (This figure was adapted by Shannon Cole and Daniel Castro from T. E. Robinson & Berridge, 1993).

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states that heighten dopamine reactivity, such as stress, emotional excitement, relevant appetites, or intoxication (Anselme, 2016; Berridge, 2012; M. J. Robinson & Berridge, 2013). State-dependent amplification of incentive salience is one reason why many addicts find it so hard to stop at "just one hit." In the face of an amplified urge, the one hit may turn into many hits, or even a lost weekend. It is also a reason why stressful states—or even happy life stresses like winning the lottery—can promote vulnerability to relapse in addiction and related disorders (Sinha, 2013). Addiction is not so much about satisfaction, pleasure, need or withdrawal, by this view, as it is about "wanting."

Ordinarily, cognitive wanting and incentive salience "wanting" go together, so that incentive salience can give heightened urgency to feelings of cognitive desire. But the two forms of wanting versus "wanting" can sometimes dissociate, so that incentive salience can occur either in opposition to a cognitive desire or even unconsciously in absence of any cognitive desire. Incentive salience "wanting," in opposition to cognitive wanting, for example, occurs when a recovering addict has a genuine cognitive desire to abstain from taking drugs, but still "wants" drugs, so relapses anyway when exposed to drug cues or during vivid imagery about them. Nonconscious "wants" can be triggered in some circumstances by subliminal stimuli, even though the person remains unable to report any change in subjective feelings while motivation increases are revealed in their behavior (Childress et al., 2008; Winkielman, Berridge, & Wilbarger, 2005).

Motivational Salience in Desire Versus Dread

For readers interested in the psychology of emotion and motivation, we note another intriguing feature of incentive salience. This is that "wanting" brain mechanisms can also operate in a different neurobiological mode to generate an active coping form of fear (Berridge & Kringelbach, 2015). Although fear seems almost the psychological opposite of desire in valence, fearful salience is generated by the same mesolimbic circuitry as incentive salience. Fearful salience also makes percepts become attention-riveting, but with a negative threatening aspect rather than positive attraction, calling out active coping responses (Richard & Berridge, 2011). This dopamine-related fearful salience has been suggested to contribute to human paranoia symptoms in schizophrenia (Barch, Treadway, & Schoen, 2014; Heinz & Schlagenhauf, 2010; Howes & Kapur, 2009) and in psychostimulant-induced psychosis (Cicero, Docherty, Becker, Martin, & Kerns, 2015).

So Where Does "Liking" Come From in the Brain?

In contrast to the large and robust "wanting" system in the brain, a much smaller and functionally fragile system appears to generate intense pleasure or "liking" reactions. Experiments in the Berridge lab have established that this "liking" system comprises a collection of interactive hedonic hotspots, and this hedonic circuitry may be shared by diverse pleasures ranging from sensory food and drug pleasures to human cultural and social pleasures (Berridge & Kringelbach, 2015). The pleasure-generating hotspots are anatomically tiny, neurochemically restricted, and easily disrupted—perhaps a reason why intense pleasures are relatively few and far between in life compared with intense desires (Castro & Berridge, 2014; Mahler, Smith, & Berridge, 2007; Peciña & Berridge, 2005; K. S. Smith, Berridge, & Aldridge, 2011). Each hedonic hotspot is nestled within its larger limbic structure. For example, a nucleus accumbens hedonic hotspot is only one cubic millimeter in a rat brain, and probably about a cubic centimeter in humans. The hotspot constitutes only 10% of total nucleus accumbens volume: The remaining 90% of the nucleus accumbens lacks any ability to enhance "liking," though still robustly causes intense "wanting."

Hedonic hotspots exist in limbic prefrontal cortex, in orbitofrontal and insula regions, where they may correspond to human sites that code sensory and higher pleasures (Kringelbach, 2010; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001). Other hotspots are buried deeper in subcortical brain structures. Each hedonic hotspot has the special ability when neurochemically stimulated, such as by opioid or endocannabinoid neurotransmitters (the brain's natural heroin-like and marijuana-like signals), to amplify "liking" reactions, and so make sweetness appear even more enjoyable. Dopamine stimulations even in hedonic hotspots, by contrast, always fail to enhance "liking" (Berridge & Kringelbach, 2015; K. S. Smith et al., 2011)—the role of dopamine seems restricted to "wanting."

Especially crucial to the normal capacity for pleasure may be a particular hedonic hotspot located in the ventral pallidum, which lies at the base of the subcortical forebrain (K. S. Smith & Berridge, 2007). In addition to enhancing "liking" for intense pleasure, this ventral pallidal hotspot is the only known site in the brain where a small lesion eliminates normal pleasure, and reverses the hedonic impact of sweet sensation from "liked" to, "disgust" (so that afterward, sucrose elicits bitterness-typical gapes and related negative expressions (Berridge & Kringelbach, 2015; Ho & Berridge, 2014).

Addiction Distorts "Wanting" Versus "Liking"

Our discovery that "wanting" and "liking" are mediated by dissociable brain systems took us halfway toward the incentive-sensitization theory of addiction (T. E. Robinson & Berridge, 1993, 2008). The other half of the journey came from the discovery around the same time that brain dopamine systems can be enduringly "sensitized" by many drugs

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of abuse (cocaine, amphetamine, heroin, alcohol, nicotine, etc.), not just stimulated while those drugs are actually on board (T. E. Robinson & Becker, 1986). Mesolimbic sensitization happens especially if the drugs are taken repeatedly, and at high doses spaced apart (e.g., in weekend binges; Kalivas & Stewart, 1991; Post, 1980; T. E. Robinson & Becker, 1986). Once induced, sensitization is very long lasting, and possibly even permanent.

Early research on sensitization in the T. E. Robinson lab focused particularly on dopamine neurons, and increases in release of dopamine, but it is now clear that mesolimbic sensitization changes other neurotransmitters and neurons as well. For example, drug sensitization also alters glutamate neurons that project from cortex to nucleus accumbens (Wolf, 2010), which interact with dopamine there, and similarly are receiving attention as potential targets of future addiction therapies (e.g. Creed, Pascoli, & Lüscher, 2015; Roberts-Wolfe & Kalivas, 2015). Sensitization also changes the physical structure of mesolimbic neurons, such as altering the shape and number of tiny spines on dendrites of neurons in nucleus accumbens, which act as their "receiving antennae" for incoming signals (T. E. Robinson & Kolb, 2004; Singer et al., 2009; Steketee & Kalivas, 2011). Initially, the main experimental evidence for mesolimbic sensitization by drugs came from studies in rodents, but now sensitization is well-documented in humans as well (Boileau et al., 2007; Paulson & Robinson, 1995; M. J. F. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2016; Vezina & Leyton, 2009).

Functionally, mesolimbic sensitization renders brain "wanting" systems *hyper*reactive to drug cues and contexts, thus conferring more intense incentive salience on those cues or contexts. Consequently, addicts have stronger cue-triggered urges and intensely "want" to take drugs (see Figure 1). "Liking," by contrast, need not increase with sensitization, and may even decrease. Sensitized "wanting" can persist for years, even if the person cognitively does not want to take drugs, does not expect the drugs to be very pleasant, and even long after withdrawal symptoms have subsided (Berridge & Robinson, 2011; T. E. Robinson & Berridge, 2003, 2008). Thus, the central tenet of the incentive-sensitization theory is that addiction becomes compulsive when mesolimbic systems become sensitized and hyperreactive to the incentive motivational properties of drug cues (Childress et al., 2008; Ostlund et al., 2014; Witteman et al., 2015; Zhou et al., 2012). This theory of addiction is specifically meant to explain individuals who have near-compulsive levels of urge to take drugs, and who remain vulnerable to a persisting risk of relapse even after a significant period of drug abstinence.

A sensitized dopamine system is not always hyperactive, but it is hyper*re*active to drug cues and contexts. That hyperreactivity produces pulses of heightened dopamine release, brain activations, and motivation that last seconds or minutes (T. E. Robinson & Berridge, 2008; Tindell, Berridge, Zhang, Peciña, & Aldridge, 2005). Drug contexts powerfully gate the ability of both drugs themselves and of discrete cues to elicit sensitized neural hyperreactivity (Leyton & Vezina, 2013; T. E. Robinson, Browman, Crombag, & Badiani, 1998). This means that surges of intense "wanting" are most likely to be triggered when drug cues are encountered (or imagined) in contexts previously associated with taking drugs.

Sensitization in Human Addiction

Laboratory neuroimaging studies have shown that even the oral administration of relatively low doses of amphetamine can produce mesolimbic sensitization in people without a history of drug use (Boileau et al., 2006; Leyton & Vezina, 2013). Furthermore, in nondependent cocaine users, the ability of self-administered cocaine (taken by the intranasal route) to increase dopamine levels in the ventral striatum is positively correlated with amount of lifetime cocaine use, suggesting past use sensitized their dopamine systems (Cox et al., 2009). However, there is reason to expect even stronger sensitization from higher street-typical doses, or by intravenous or smoking routes of consumption (which deliver drugs to the brain more rapidly than swallowing or snorting), based on animal studies (Allain, Minogianis, Roberts, & Samaha, 2015). Indeed, addicts tend to prefer to smoke or inject drugs, because those routes deliver drugs to the brain more rapidly. Consequently, real-life addicts may have greater mesolimbic sensitization than so far demonstrated by laboratory studies in nonusers.

Do human addicts actually show the brain hyperreactivity to drug cues that is posited by incentive sensitization? The short answer is "yes." There have been many reports over the past 10 years that mesolimbic brain responses to drug cues, such as viewing photos of drug paraphernalia or of other people taking drugs, are enhanced in individuals with addiction (Kühn & Gallinat, 2011). Furthermore, "more years of cocaine use [are] associated with greater activation to cocaine cues in ventral striatum" (Prisciandaro et al., 2014), indicating progressively intense sensitization. Similar findings have been reported with alcohol use (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011).

We note as a caveat that most reports of such hyperreactivity used functional MRI (fMRI) measures, which do not directly measure dopamine, but rather oxygenated blood signals (BOLD), which are used to infer neural activity. However, recent research confirms that dopamine release does cause striatal BOLD activations (Ferenczi et al., 2016), supporting the interpretation that fMRI hyperreactivity to drug cues in addicts reflects a higher dopamine surge, and indicates incentive sensitization. Further, several studies that have used more direct PET measures of dopamine release in people (i.e., via dopamine displacement of radio-

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active raclopride from D2 receptors) also confirm that drug cues do trigger higher increases in dopamine release, and in fact, "the greater the cue-induced dopamine release the greater the craving" to take more drugs (Leyton & Vezina, 2013, p. 2004). These intense cue-triggered neural signatures are very much what one would expect based on the incentive-sensitization theory of addiction.

Disentangling Reports of Mesolimbic Suppression Versus Sensitization in Addiction

As another caveat, it is only fair to note that some studies have reported nearly the opposite of sensitized brain responses as described in the Sensitization in Human Addiction section that is, neural suppression or *blunted* rise in dopamine displacement elicited when an addict takes a drug. Suppressed brain responses are typically not to the drug cues that trigger urges, but rather to drugs themselves once actually taken, such as amphetamine or methylphenidate (Volkow, Koob, & McLellan, 2016). However, we caution that two points need to be considered before jumping to a conclusion that addicts have too little brain dopamine, as some have suggested. First, suppression of drug-elicited brain activation to drugs is by no means a universal finding. For example, as mentioned, sensitized or increased dopamine rises elicited by exposure to a drug are also sometimes reported. For instance, alcohol is reported to elicit greater dopamine release in the striatum of alcoholics than in social drinkers (Yoder et al., 2016). Still, suppression of drug-induced dopamine is found often enough in addicts to have led some observers to suggest that the essence of addiction is primarily too-little dopamine in nucleus accumbens and striatum (Volkow et al., 2016). That dopamine-deficit suggestion is quite a contrast to incentive sensitization, and is often wrapped together implicitly with the older assumption that lower dopamine causes reduced pleasure and that addicts simply seek pleasure (despite the emerged consensus that the dopamine pleasure hypothesis not true). Second, however, partial compensations to excessive dopamine stimulation may occur in the brain after heavy drug use, which at least for a while can mask the expression of neural sensitization. We would agree that compensatory neural suppressions (e.g., receptor downregulation) do accompany heavy drug use, while drug-taking continues. Suppressions produce tolerance to drug highs (and to the aversive effects of some addictive drugs—which permits the person to take higher doses, inducing even more tolerance). Neural suppressions also produce withdrawal for a while, once the drug is finally stopped.

However, even the same investigators that report suppression of responses to drugs often also report the same addicts show intense neural hyperactivations—not suppressions—to the drug cues that trigger urges to take drugs. That is, compensatory suppressions of drug-elicited reactions as consequences of overstimulation need not contradict incentive sensitization as the primary mechanism for the compulsive craving in addiction, consistent with incentive sensitization. Further, many tolerance-related neural suppressions are merely temporary. Suppressions are partial compensatory responses to the high levels of mesolimbic stimulation induced by drugs, essentially a temporary cellular effort by neurons to turn down their levels of neurochemical overstimulation. Sensitization and tolerance can develop simultaneously in the same brain while drug is being taken, because they have parallel mechanisms involving different intracellular signaling cascades. But many tolerance/withdrawal suppressions are apt to fade within weeks if drug-taking is stopped. By contrast the neural changes that cause incentive sensitization do not fade over months of drug abstinence—if anything, sensitization grows for some time during abstinence (Paulson & Robinson, 1995), a phenomenon sometimes called "incubation of drug craving," which is an increase in relapse vulnerability after a month or so of drug abstinence (Pickens et al., 2011). Incubation of craving is impossible to explain by a neural suppression or withdrawal view of addiction, because those fade, over a month of abstinence, but is entirely plausible in light of incentive sensitization. Finally, suppression of neural responses to drugs may occur mostly in test situations that are very different from situations in which drugs were usually taken—such as while in a neuroimaging scanner in a hospital setting (Leyton & Vezina, 2013). By contrast, neural suppression may be converted into sensitized hyperreaction when neuroimagers take efforts to provide realistic drug-related cues and contexts during the neuroimaging test (Leyton & Vezina, 2013). Early animal studies showed that giving a drug in a test environment in which it never before was experienced can completely prevent the expression of sensitization, even when it clearly has been induced. By contrast, a previously drug-associated context enables the sensitized response to fully reappear again when drug is retaken (T. E. Robinson et al., 1998). That is, sensitized "wanting" urges are much more likely to occur in drug-associated contexts than in biomedical neuroimaging situations. Recent neuroimaging evidence indicates that drug-related contexts gate sensitized brain reactions in humans as well (Leyton & Vezina, 2013). Therefore, it may be crucial that PET studies of drug-elicited brain responses take steps to better recreate drug-related contexts and cues in order to reveal sensitized hyperreactive brain responses to drugs that would occur in real-life drug situations, and which may underlie addictive urges to take more drugs. Of course, how addicts perceive contexts is likely complex, so it might help to let addicts also actively engage in their drug-taking rituals (e.g., preparing lines of cocaine to sniff, or preparing an injection), or to experience diverse drug-related auditory, smell, taste, or other sensations in order to unmask sensitized hyperreactivity in mesolimbic systems (Cox et al., 2009). It might also be useful to test with the same drug an

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addict most commonly takes rather than with an unfamiliar drug (such as methylphenidate, which has been substituted for an addict's habitual drug in some neuroimaging studies).

Individual vulnerability. Another important point that any addiction explanation must deal with is that most people who take drugs never become addicts. For example, only about 30% of people who take cocaine actually go on to become long-term addicts. Accordingly, individuals also differ considerably in their susceptibility to mesolimbic sensitization, even when exposed to the same drugs and doses (Becker, Perry, & Westenbroek, 2012; T. E. Robinson & Berridge, 2008). Genetic factors are important determinants of susceptibility to sensitization in rodents, and genes also contribute strongly to addiction vulnerability in humans (Franklin et al., 2011; Hoft, Stitzel, Hutchison, & Ehringer, 2011; Hutchison et al., 2008; Moeller et al., 2013). Other determinants of sensitization vulnerability include gender and the presence of sex hormones, and whether the individual has had major stresses in life before taking drugs (Becker et al., 2012; T. E. Robinson & Berridge, 2008). Individuals with combinations of these several factors may be most at risk to develop incentive sensitization and addiction. Finally, among those who experiment with drugs in the first place, important situational factors can facilitate incentive sensitization or, alternatively, make it less likely. These include how long drugs have been taken, whether dose has escalated, and whether the person took drugs by routes that resulted in drug rapidly reaching the brain (i.e., inhalation or intravenous use).

Another type of individual difference concerns neuropsychological traits of incentive salience that might predispose toward either drug taking or addiction. For example, even animals differ as individuals in their propensity to attribute incentive salience to discrete predictive reward cues (T. E. Robinson, Yager, Cogan, & Saunders, 2014). For example, some rats come to rapidly approach a discrete Pavlovian cue that predicts delivery of a food or drug reward (such as sudden appearance of a lever), and will work avidly to get the cue (these individuals are called sign-trackers). However, other rats will instead go directly to the location of impending delivery of a food reward when its predictive cue appears (called "goal trackers"). Studies in the T. E. Robinson lab have found that discrete cocaine or opioid cues acquire greater incentive salience in sign trackers than in goal trackers, and in some situations sign trackers are also more likely than goal trackers to show cue-triggered relapse of drug-taking behavior (T. E. Robinson et al., 2014). However, both types of individuals eventually show addictive-type patterns of high drug intake when they have weeks of intermittent access to cocaine, in binge-like periods, and develop robust incentive sensitization (Kawa, Bentzley, & Robinson, 2016). Thus, being relatively attracted to discrete reward cues may make some individuals more susceptible to develop addiction when they initially start to use drugs (Mahler & de Wit, 2010; van Hemel-Ruiter, de Jong, Ostafin, & Oldehinkel, 2015; Vollstädt-Klein et al., 2012), though most individuals may develop neural incentive sensitization eventually if they take drugs for long enough and at high enough doses.

Is incentive sensitization a brain disease? Addiction has sometimes been called a "brain disease" (Leshner, 1997). Yet recently that label has come under criticism on the grounds that some addicts may not regard themselves as diseased, incentives often still can influence drug use as though it were an ordinary choice, and because believing that one has a "brain disease" could encourage a fatalistic acceptance of the condition (Hall, Carter, & Forlini, 2015; Lewis, 2015). Also, though addiction is accompanied by distinct changes in the brain, some critics also note that related changes in the brain can occur in normal life: Indeed, the brain mechanisms of addiction do overlap the mechanisms of ordinary desires such as love or hunger that are shared by everyone.

Although these objections have some validity, we do believe that incentive sensitization can make the temptations faced by addicts harder to resist than those most other people are called upon to face. This is because the underlying neural sensitization can distort psychological incentive salience function to a pathological degree, with deleterious consequences. If success versus failure is probabilistic when temptations are very strong, and if success in escaping addiction requires saying "no" every time a temptation occurs, then a dopamine-sensitized person who faces a series of hundreds of intense temptations may eventually be expected to fail. Such features may make the "brain disease" label a reasonably fair description.

Other Behavioral Addictions?

Various "behavioral addictions" have emerged in recent years that do not involve drugs at all: eating addiction, gambling addiction, sex or pornography addiction, Internet addiction, shopping addiction, and so on (Davis & Carter, 2009; Gearhardt et al., 2011; Hartston, 2012; Linnet et al., 2012; S. S. O'Sullivan et al., 2011; Ray et al., 2012; Voon et al., 2014). Although drugs were central to mechanisms underlying the original incentive-sensitization hypothesis, perhaps, surprisingly, neural sensitization of "wanting" mechanisms may, in some cases, occur without drugs. In support, evidence is emerging that individuals with these behavioral addictions may have some sensitization-like patterns of brain hyperreactivity to cues related to their own personal addictions (Davis & Carter, 2009; Gearhardt et al., 2011; Hartston, 2012; Linnet et al., 2012; O'Sullivan et al., 2011; Ray et al., 2012; Voon et al., 2014). Conceivably, sensitization-related brain changes arise in some highly susceptible individuals to produce these addictions without need of drugs, through mechanisms not yet understood.

Related proof-of-principle evidence for the idea that diverse compulsive motivations such as gambling can be

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caused by hyperstimulation of dopamine-related systems also comes from Parkinson's patients, about 15% of whom develop what is called dopamine dysregulation syndrome when treated with newer dopamine-stimulating medications that directly activate their brain dopamine receptors (i.e., direct agonist medications; Callesen, Scheel-Krüger, Kringelbach, & Møller, 2013; Friedman & Chang, 2013; Ondo & Lai, 2008; Politis et al., 2013). These patients can develop intense compulsive motivations to pursue gambling, shopping, sex, Internet use, excessive hobbies, or similar activities (O'Sullivan, Evans, & Lees, 2009). Some patients may even take excessive amounts of their medication in a more classic drug-addiction fashion. Usually, the compulsive motivations rapidly fade if the dopamine-stimulating medications are stopped. This pattern demonstrates intense and idiosyncratically diverse "wants" arising from dopamine-stimulating medications, and is also a further contradiction of the notion that dopamine-suppression causes addictions (i.e., because Parkinson's patients are in dopamine suppression states prior to medication or if taken off medication, but no longer have compulsive motivations at those times). It provides further support for the sensitization idea that dopamine overstimulation is the more likely culprit behind addictive compulsions (i.e., while taking high doses of medications that stimulate dopamine receptors). Finally, such patients with intense motivations have virtually never been reported to experience intense pleasure from their medications or compulsions, any more than individuals with spontaneous behavioral addictions—or some drug addicts (Pettorruso et al., 2016). In short, evidence continues to build that dopamine hyperreactivity produces intense reward "wanting" but not "liking," and can cause addictions.

Treatment Implications

At present, most addiction medications are of quite limited efficacy. Opioid blockers (e.g., naltrexone) conceivably help somewhat blunt "wanting," as well "liking," peaks. Antidepressants take the edge off negative mood-based reasons to take drugs again, and opioid-substitutes prevent withdrawal symptoms. Immune-based vaccines help reduce drug-induced highs, though can be circumvented by taking higher doses or different drugs. Psychological approaches, such as cognitive and behavioral therapies, 12-step programs, contingency management, and mindfulness therapy, arguably remain more effective than any medications available today. Still, although those psychological approaches are quite useful in helping some individuals to escape addiction, they are still not sufficient for many others.

We suggest that a more effective neurobiological treatment would need to reverse the neuroadaptations underlying sensitized mesolimbic hyperreactivity to drug cues, yet not impede normal motivations nor induce adverse side effects. In practice, this may be difficult to achieve, though, in principle, not impossible. Encouragingly, some recent findings from animal studies have suggested it may be possible to rather specifically reverse sensitized mesolimbic hyperreactivity by new neurobiological techniques, without adverse other effects (Creed et al., 2015). Although human applications are still a long way off, such findings give at least some reason to hope that more effective sensitization-reversing treatments might be developed in future.

Conclusion

In summary, a quarter-century after we proposed the incentive-sensitization theory of addiction, we conclude that its key tenets still seem well supported. In addicts, mesolimbic circuits are hyperresponsive to drug cues, which may cause strong cue-triggered "wanting" to take drugs, leading to relapse. Our journey into understanding addiction began with basic science investigations of brain systems and their psychological functions in animals. The insights from those studies have proven remarkably applicable to humans. Those insights were that the psychological process of motivationally "wanting" a reward has distinct brain mechanisms from hedonically "liking" the same reward, and that sensitization of dopamine-related hyperreactivity specifically promotes excessive "wanting." Gradually, substantial evidence from both human and animal studies has emerged to further support and refine those conclusions. Finally, the scope of clinical applications has extended in the past decade beyond drug addiction to other behavioral addictions, schizophrenia, depression, Parkinson's disease, and other forms of psychopathology. This story is still being written, and it seems likely that future findings will continue to reveal exciting facets of normal reward processes in the brain, how their distortion can impact psychological disorders, and how new therapies might someday overcome distortions to improve function again.

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