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Is Addiction a Brain Disease?

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Abstract Where does normal brain or psychological function end, and pathology begin? The line can be hard to discern, making disease sometimes a tricky word. In addiction, normal 'wanting' processes become distorted and excessive, according to the incentive-sensitization theory. Excessive 'wanting' results from drug-induced neural sensitization changes in underlying brain mesolimbic systems of incentive. 'Brain disease' was never used by the theory, but neural sensitization changes are arguably extreme enough and problematic enough to be called pathological. This implies that 'brain disease' can be a legitimate description of addiction, though caveats are needed to acknowledge roles for choice and active agency by the addict. Finally, arguments over 'brain disease' should be put behind us. Our real challenge is to understand addiction and devise better ways to help. Arguments over descriptive words only distract from that challenge.

Keywords Addiction · Desire · Wanting · Liking · Brain · Dopamine

Marc Lewis writes books on addiction that are wonderfully engaging and illuminating [1, 2]. He describes with clarity what it's like to be an addict, and what is scientifically known about addiction's causes and treatments. He ably blends these themes with compelling portraits of the experiences of individual addicts, who have made personal journeys often through depths of despair, yet eventually found the strength to make a positive change in their lives.

Recently Marc has also argued the view that addiction should not be viewed as a brain disease. He gives several reasons in the target article for this commentary [3], as well as in his recent book [2]. First, he notes that some addicts may not regard themselves as diseased. Also, those who eventually do give up drugs may never see themselves as cured or reversed into a pre-addiction state, but rather as having reached an entirely new stage of life. Second, though addiction is accompanied by distinct changes in the brain, many changes in the brain also occur in normal life. Third, he suggests that to view addicts as medical patients is to regard them as passive and so neglect their active agency, and even make less likely their personal act of re-invention that will be required in order to successfully give up drugs. Finally, he points out that brain dopamine mechanisms of addiction overlap not only with those of other behavioral addictions (for example, compulsive gambling, sex addiction, or binge eating), but also with the mechanisms of ordinary desires such as love or hunger that are shared by everyone. So "If addiction is a disease, then so apparently is love", Marc Lewis concludes [3].

Marc and I are friends. We came to know each other while participating in a week-long seminar on craving and addiction with the Dalai Lama several years ago. Also participating in that seminar were Nora Volkow (the director of NIDA), and several other experts on

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addiction and craving. During that week, we discussed some of the issues he raises here. But we may not quite agree on whether it's misleading to call addiction a brain disease.

My own view is that to call addiction a brain disease is not unreasonable. Brain disease is not a label that Terry Robinson and I ever used in our original proposal of the incentive-sensitization theory of addiction [4, 5]. But the disease label can fit, and deserves to be tolerated. That is, the distinct neural changes in the brain involved in addiction are extreme enough to be viewed as pathological. They are problematic enough to qualify as disease because they add a compulsive intensity to addiction that carries deleterious consequences. However, I also believe this neural and psychological 'disease' remains entirely compatible with the person's own free will and ability to make choices. Finally, I am persuaded by Marc that that escaping addiction requires an enormously effortful act of personal agency, and recovery is never passively received from someone else.

Addiction is a brain disease of temptation and of choice itself. Addiction doesn't replace choice, it distorts choice. In particular, the sensitization of brain dopamine mechanisms of 'wanting' (incentive salience) amplifies temptation for addicts to a level more intense than most other people ever face. These intense temptations interact with normal mechanisms of choice, but impose a formidable degree of difficulty. Successful abstinence requires the right choice every time in facing a long series of intense temptations – and many of us would fail that test if faced with sensitization of 'wanting'.

How should we think about addiction? Marc Lewis suggests that addiction is "in a phrase, *motivated repetition that gives rise to deep learning*" [3]. Well, yes, that description does seem right. But the same abstract description might also apply to learning to play a musical instrument, mastering a skilled profession, learning a new language or learning to dance.

Addiction has special features that make it different from other forms of deep learning. Drugs are often the focus of addiction, but the essence of addiction is not in the drug itself. Rather that essence is the addict's own hyper-reactive brain response to drug cues or thinking about drugs, which I believe is psychologically manifest as excessive 'wanting' or incentive salience. Some individuals are particularly susceptible to developing this signature brain response of incentive-sensitization, whereas others are not. The crucial role of this addictive brain signature is why some people never do quite become addicts, even if they take habitually take comparable amounts of drugs such as cocaine, methamphetamine or heroin, or even if they become dependent for a while. They can still quit because they never developed 'wanting' sensitization. This brain signature identity of addiction is also why a few people can develop forms of addiction to other non-drug incentives, even if they haven't taken addictive drugs. Some people are perhaps so vulnerable to incentive sensitization changes that they may develop it almost spontaneously, even without drugs.

When we hear the term 'brain disease' we may think of pathological lesions or shriveling neurons, the sort of thing that produces holes in the brain in tumors or strokes, or that shrinks the cortex in Alzheimer's disease. In some extreme cases, lesion-type neuronal damage in prefrontal cortex is known to occur in addicts. But such cortical damage may be relatively rare, and I agree with Marc that it is probably unfair to consider most addicts as significantly brain *damaged*.

However, other forms of neural pathology don't involve damage, but rather occur as extreme values of some normal neuronal parameter. It is the extremity of those changes in neural-psychological parameter values that causes problems. Those changes are pathological partly in the sense that hardly anyone else has parameters that extreme, and also in the sense that the extremity of those values causes bad consequences. They make the addiction so compulsive and hard to quit.

Brain Ups and Downs in Addiction

Alterations in brain dopamine-related circuitry of addicts distort choices about drugs. This is experienced as a 'software pathology' in craving and behavior, but has roots in underlying extreme-parameter brain changes that are the 'hardware pathology'. Two forms of extreme-parameter changes occur in brains of addicts, and the two are almost opposite to each other. The opposites do not cancel each other out, but can co-exist simultaneously. That's because their mechanisms lie in parallel molecular cascades within the neurons of dopamine-related circuits that can occur in the same brain.

One of these brain changes is mesolimbic suppression: due to down-regulation of dopamine receptors, or down-regulated release of dopamine release that especially occurs in situations where addicts have never before taken drugs (such as a hospital neuroimaging scanner) [6]. Mesolimbic suppression is a relatively

short-term consequence of addictive drug taking. Many have thought these suppressive brain changes essentially were the essence of addiction [7]. But I believe the mesolimbic suppressions, while mechanisms of tolerance and withdrawal, are relatively temporary, more a consequence than cause of drug taking, and not the essence of addiction. Mesolimbic dopamine suppression is most evident while still taking drugs as drug-tolerance (needing higher doses of the drug to get high), or immediately after giving up drugs as withdrawal symptoms in the absence of drug. Neurobiologically, part of the brain dopamine suppression is due to loss of the D2 type of dopamine receptors after continual bombardment with drug-evoked dopamine (and of other mesolimbic receptors too, but D2 has been most studied). D2 receptor loss is a partial compensation to the too-high levels of dopamine stimulation that neurons encountered when the drug was being taken. Bombardment with high levels of repeated dopamine release causes the receiving neurons to lose some their D2 receptors, as a cellular attempt to rebalance to a normal level of dopamine signal. However, most of this D2 dopamine receptor loss in addiction is only temporary. Many of the D2 receptors eventually come back when a person stops taking the drug, so that the tolerance pretty much goes away, and withdrawal symptoms come to an end. A few individuals – who may be especially predisposed to developing addictions – may naturally over-stimulate their D2 receptors with high dopamine release, and consequently undergo a more permanent suppression of D2 receptors as a partially-compensating consequence.

But all of this D2 suppression above is mostly a consequence of the addiction and of drug-taking, rather than the essential cause of addiction. Even withdrawal feelings – unpleasant as they are – eventually go away after a month or so of drug abstinence. Yet many addicts remain vulnerable to relapse afterwards. Weeks or months of successful abstinence is no guarantee against future relapse. The problem of addiction is not solved when the brain suppressions go away.

Incentive-Sensitization as Excessive 'Wanting'

In my view the essential cause of addiction and persistent relapse danger is the second type of brain change in addiction: mesolimbic hyper-reactivity to drug cues and drug-imagery [5]. Incentive-sensitization or mesolimbic hyper-reactivity is induced by a history of drug binges in vulnerable individuals, and then elicited by drug cues or by thinking vividly about drugs. Mesolimbic hyper-reactivity creates a too-high pulse of dopamine stimulation, caused by increased excitability in the midbrain neurons that stimulate dopamine neurons to fire, by extra amounts of dopamine released from dopamine-containing neurons, and by increased sensitivity to dopamine signals in the forebrain target neurons that receive dopamine signals. Those cue-triggered hyper-reactivity increases are all mechanisms of incentive-sensitization, induced by the previous drugs, and manifest psychologically as excessive 'wanting' or incentive salience.

Neural sensitization is nearly the opposite of tolerance. That is, neural sensitization makes brain mesolimbic dopamine systems hyper-responsive, even to drug-cues that initiate drug taking before the drug is actually taken again. That sensitized response to cues triggers the stronger urge to relapse and actually take drugs. A drug-sensitized brain reacts more strongly than normal to drug-related cues, and the dopamine-receiving system responds at an extreme high intensity with an urge to take drugs again. A sensitized dopamine system is not hyper-active all the time, but rather momentarily hyper-RE-active to particular events and stimuli. Sensitized hyper-reactivity can be further amplified to even higher levels if cues are encountered at certain moments by states of stress, emotional excitement – or after taking a hit of drug again – creating a special window of heightened vulnerability to relapse and binging. The state-dependent amplification of incentive-sensitization hyper-reactivity is a reason why many addicts find it so hard to stop at 'just one hit'. It is also a reason why stressful states – or even happy life stresses like winning the lottery – can promote vulnerability to relapse in addicts.

Neural sensitization can happen in many of the same brain neurons that undergo drug tolerance: the dopamine neurons themselves, their midbrain excitatory input neurons that trigger dopamine neurons to fire, and the target forebrain neurons in nucleus accumbens or striatum that receive the dopamine. Sensitization and tolerance can happen in the same neurons because the two changes proceed through parallel chains of molecular events within those neurons, almost like ships passing in the night [6, 8, 9]. In the short run, tolerance and withdrawal often win and mask sensitization as long as the drugs have been recently taken.

But unlike tolerance and withdrawal, neural sensitization doesn't go away when the person stops taking the drugs. Instead, neural sensitization grows, and emerges

with even more visibility. This is sometimes called 'incubation of craving': an actual increase in motivation to cue-triggered relapse that can emerge after a month or so of abstinence from drugs, despite disappearance of withdrawal symptoms by then [10]. Neural sensitization of dopamine systems renders addicts vulnerable for months or years to intense urges [4, 5], especially when drug-cues are encountered in stressed or emotionally excited states [11].

But Is Sensitized 'Wanting' Pathological?

Marc Lewis points out that normal love and normal hunger activate our same brain dopamine circuitry as do addictive drugs. Those natural motives are why brain mesolimbic circuitry evolved. But while seeing a delicious food activates brain dopamine circuitry in nearly anyone, most of us would have to starve for weeks in order for food to evoke as intense a level of brain reaction as drug cues could trigger in a sensitized addict. People who starve for weeks begin to obsess about food, and to dream of food. Their brain dopamine circuitry reacts with higher intensity to any food cues than in the rest of us, creating a more intense urge to eat than most of us ever experience in our well-fed lives. That starved brain reaction to food is somewhat like the intense level of temptation created by a sensitized addict's brain who encounters drug cues by surprise in an emotionally excited state.

Is Compulsive Incentive-Sensitization Vompatible with Free Choice and Agency?

Despite its intensity, incentive-sensitization doesn't override free will. Sensitized 'wanting' creates only a probabilistic form of compulsion. On any given occasion, the person is free to say no to temptation, and may succeed in doing so despite the higher temptation. An addict truly committed to abstinence from drugs may succeed in saying no many times in a row. But success versus failure is probabilistic when temptations are very strong, and success in escaping addiction may require saying no every time a temptation occurs. Asking a starving person to resist the temptation of a modern feast – and to keep saying no to the next hundred offers of delicious food as weeks go on – seems rather a lot to ask. Many of us might fail that test in the end. Yet that test may be what we ask the addict with a sensitized brain dopamine system to pass.

The task is not insurmountable. Marc Lewis and many other addicts have passed the test and overcome the temptations. But the task is difficult, and the situation deserves our sympathy. Overcoming such addictive temptations may well require a special act of personal agency by the addict in resolving to seek a better life, as described for the individuals in Marc's book [2].

Beware of Unintended Consequences

I suspect that if those who wish to banish the 'brain disease' view of addiction ever succeeded, they would not like what would follow. At best, therapy for addicts would fossilize into the few strategies currently available (e.g., 12-step programs, cognitive-behavioral therapy, mindfulness training). Those are helpful to some, but often not enough to many others. In my view, we need to continue research to find improved therapies. However, quite possibly the result would be worse than simply maintaining current therapies. Quite possibly in rejecting the disease view that encourages sympathy, society would revert to the older view of addiction as a 'moral failing' and blame addicts for their choices. If so, support for therapy would decline too.

Some might regard this forecast as overly dismal. Marc Lewis might suggest there is no reason why society can't abandon the biomedical view, yet continue to be sympathetic toward addicts. After all, he might ask, why can't society instead adopt a nuanced 'deep learning' view of addiction, viewing it as a habit or a life stage, yet still support paying for addicts' therapy and perhaps even for further research into addiction mechanisms (with hopes for their eventual reversal)?

Well, good luck with that. I see no clear path to a more enlightened view of addiction as a form of deep learning or life stage that will be able to muster societal support. Rejection of the brain disease label may be also to reject any grounds for societal sympathy needed to shift policy from punishment or abandonment of addicts and toward therapy. This would lose the baby with the bathwater, even for 'brain disease' critics.

Words, Words Words

It can be fun to argue about words, such as which ones are the best to describe addiction. But I think that arguments about words, like whether to say 'brain disease' – rather than focus on the actual features and mechanisms of addiction itself –too easily become traps that distract us from more important aims. Those aims should be to identify the essential features and mechanisms of addiction, and think about better ways to help addicts.

Here are a few interesting issues for addiction: In what way is addiction compulsive, and in what way a choice? How do individuals differ in susceptibility to developing addiction? What are the crucial brain mechanisms underlying the transition to addiction, the essential mechanisms that cause addicts to be addicts? Are there are different ways of being addicted – or different types of addict – or does addiction always involve a common core of mechanisms? Why are some former addicts capable of controlled use and others not? What is the special act of agency necessary to escape from addiction? How can that act of agency be facilitated?

Less interesting than any of these issues is the semantic question of whether to call addiction a 'disease' or 'choice', 'habit' or 'life stage' or something else. All those words are just linguistic tools to be used in service of the questions above.

In my view, we who study addiction should choose our words carefully, and do our best to capture the features, brain substrates, or therapies of addiction we are trying to describe. With luck, we can use those words to reveal something new or useful about addiction. Marc Lewis takes wonderful steps in that direction in his illuminating books. But let's not mind too much the words that other people choose in their own quest to describe addiction, or expend too much effort in trying to stop them from using certain words. They may be describing an aspect of reality too. Addiction as a phenomenon is a hard nut to crack. Better understanding of the nature of addiction and better therapy should be the focus of all our efforts – a difficult enough aim already, without wasting time on squabbles about words.

References

1. Lewis, Marc. 2011. *Memoirs of an addicted brain*. New York: Public Affairs Perseus Books.
2. Lewis, Marc. 2015. *The biology of desire*. Philadelphia: Perseus books.
3. Lewis, Marc. 2017. Addiction and the brain: development, not disease. *Neuroethics* (this issue)
4. Robinson, T.E., and K.C. Berridge. 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research. Brain Research Reviews* 18(3): 247–291.
5. Robinson, Terry E., and Kent C. Berridge. 2003. Addiction. *Annual Review of Psychology* 54(1): 25–53.
6. Leyton, M., and P. Vezina. 2013. Striatal ups and downs: their roles in vulnerability to addictions in humans. *Neurosci Biobehav Rev* 37(9 Pt A): 1999–2014. doi:10.1016/j.neubiorev.2013.01.018.
7. Volkow, N.D., G.F. Koob, and A.T. McLellan. 2016. Neurobiologic advances from the brain disease model of addiction. *The New England Journal of Medicine* 374(4): 363–371. doi:10.1056/NEJMra1511480.
8. Steketee, J.D., and P.W. Kalivas. 2011. Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. *Pharmacological Reviews* 63(2): 348–365.
9. Wolf, M.E. 2010. The Bermuda triangle of cocaine-induced neuroadaptations. *Trends in Neurosciences* 33(9): 391–398. doi:10.1016/j.tins.2010.06.003.
10. Bossert, J.M., N.J. Marchant, D.J. Calu, and Y. Shaham. 2013. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. *Psychopharmacology* 229(3): 453–476. doi:10.1007/s00213-013-3120-y.
11. Berridge, Kent C. 2012. From prediction error to incentive salience: mesolimbic computation of reward motivation. *European Journal of Neuroscience* 35(7): 1124–1143. doi:10.1111/j.1460-9568.2012.07990.x.