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## 13 Medical Models of Addiction

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Biomedical science has been remarkably successful in explaining illness by categorizing diseases and then identifying localizable lesions such as a virus and neoplasm in the body that cause those diseases. Not surprisingly, researchers have aspired to apply this powerful paradigm to addiction. So, for example, in a review of the neuroscience of addiction literature, Hyman and Malenka (2001, 695) acknowledge a general consensus among addiction researchers that "addiction can appropriately be considered as a chronic medical illness," or as Koob and Le Moal (2006, 1) put it, addiction "is a chronically relapsing disorder." Working from this perspective, researchers have put much effort into characterizing the symptomology of addiction and the brain changes that underlie them. Evidence for involvement of dopamine transmission changes in the ventral tegmental area (VTA) and nucleus accumbens (NAc) have received the greatest attention. Kauer and Malenka (2007, 844) put it well: "drugs of abuse can co-opt synaptic plasticity mechanisms in brain circuits involved in reinforcement and reward processing."

Our goal in this chapter is to provide an explicit description of the assumptions of medical models, the different forms they may take, and the challenges they face in providing explanations with solid evidence of addiction.

### What Does a Medical Model Entail?

In its purest or simplest form, a medical model of disease asserts that:

1. there is characteristic set of objectively observable symptoms manifested both synchronically and diachronically;
2. those symptoms are caused by a physical condition that represents a deviation from normal functioning;
3. that deviation can in principle be localized somewhere in the body; and
4. the physical condition is necessary and sufficient to have the disease.

Objectively observable symptoms are those that are not in the eye of the beholder. They do not depend on social conventions. They are measurable by reliable and valid

methods in the technical sense that different observers get the same results and measurements correspond to real phenomena. A medical model also says that there is sufficient understanding of normal biological function and biological systems to identify deviations from normality that cause the disease. The deviation is a state of the physical body that can be localized, is present in all cases of the disease, and when present makes the disease inevitable.

Of course, less simple models may be called for. The localization may not be as simple as a tumor at a specific site; the lesion may only make it probable that the disease will occur; and different lesions in different individuals may produce the same disease (though this latter situation usually calls for finer subdivisions in disease categories).

Note two important implications of medical models for the study of addiction. First, either one has the disease or one does not. Addiction is a categorical, not a dimensional variable: there is a point at which addiction "takes hold." Nosology begins by identifying characteristic symptoms. However, in the end, the key element is a specifiable lesion or malfunction—the etiology of the disease that divides the phenomena into kinds. For addiction, the hope is that changes like those found in the reward system mentioned above will be the "molecular switch" (Adinoff 2004) that does so.

Additionally, if we stick strictly to the medical model, we are committed to localizing the causes of the disease—in this case, addiction—inside the person. This is what Koob and Le Moal (2006, 8) mean when they say addiction is a biological phenomena, not a social one. Of course everybody agrees that addiction results from a complex interplay between genetics, neurobiology, and the environment. Obviously, access to drugs or the relevant activity is presupposed. Social and environmental factors may be involved in acquiring the relevant lesion. Maybe even environmental stimuli may trigger the behavior associated with the disease that is a preexisting state of the body. However, the larger the role of these environmental factors and the more they involve complex social relationships rather than simple external stimuli, the more the spirit of the medical model is being violated. If the factors involved in the transitions from limited use, addiction, remission, and relapse depend significantly on social factors, then we do not have a medical model.

As we noted, researchers often explicitly treat addiction as a disease in the full medical sense. However, at the same time they can be considerably more ambiguous when spelling out details. The language used will be familiar. It will be said that the biological fact is "involved in," "associated with," or "implicated in" the addiction. The part of the brain will be described as a "locus for" or "the substrate for" addiction. The addiction "results from" the biological process identified.

These descriptions are ambiguous when it comes to deciding if the process is necessary and sufficient, and it is quite common never to get a precise statement about what is being claimed. Claims about loci and substrates seem to be more clearly about some-

thing being required or necessary for addiction. Claims about being associated with or implicated in addiction may not be asserting that all cases of addiction include the identified area. Identifying the substrate or locus for addiction may entail that, given normal background conditions, the area in question is sufficient for addiction—that addiction is always present when the process in question is operative.

The pure medical model for addiction described above can be weakened in various ways by relaxing the assumptions we have noted. There might be different neurobiological changes in different addictions or a change common to all that is combined with other type-specific differences.

We think the eventual goal for addiction research should be to formulate clear causal claims about the role of specific neurobiological changes in addiction. Clarity requires stating exactly which of the various different possible claims described above is at stake.

Despite the ambiguous formulations, the medical model is an ideal that is strived for by addiction researchers. It can shape research by providing the background assumptions that are inevitably needed in providing evidence and explanation. Medical models can set the range of hypotheses that are considered plausible possible competitors. They can determine the kinds of causes taken to be important and how they should be described as well as what causes can be ignored. We will detail some of these influences below.

#### What Would a Medical Model Explain?

Addiction is a complex phenomenon with multiple aspects. If a medical model is an ideal to shoot for, we need to be clear what we want the model to explain. We believe that greater precision on these issues can help avoid unnecessary confusion and help show where progress toward a medical style explanation of addiction is most likely and where it is most likely to run into problems. We focus on two issues: the extent to which the commonsense notion of addiction groups together similar phenomena suitable to the same scientific, medical type explanation; and the aspects of the dynamics of addiction that the medical model is supposed to explain.

Medical models of addiction entail that there are in principle clear criteria for the differential diagnosis of addiction. However, types specified in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) may not pick out homogeneous phenomena, as Ross et al. (2008) note for addiction, and as Horwitz (2003) notes in general for DSM. The DSM provides a set of criteria. To have the DSM disorder is to have a specified number of those criteria. The criteria are not weighted. The end result is that individuals with different characteristics can get the same diagnosis.

Furthermore, the screens that are used to operationalize the DSM work in the same way. Take, for example, diagnosis of substance disorder using the common World

Health Organization (WHO) substance-dependency screen. The questions in the screen are:

How often have you had a strong desire or urge to use?

How often has your use led to health, social, financial, or legal problems?

How often have you failed to do what was normally expected of you because of your use?

Has a friend or a relative ever expressed concern about your use?

Have you ever tried and failed to control, cut down, or stop using?

These questions are given either a 5- or 3-element Likert scale for severity and scored. The scores are based on a straight linear combination of the question scores with a cut-off point determining who has a severe problem and who does not. Individuals who have made no attempt to stop but have families and friends who disapprove of all drug use, controlled or not, can be grouped with individuals who make repeated efforts to stop using but who have friends that express little concern over drug use because they are also serious users. The other items can be similarly traded off.

A further complication is that the criteria or questions themselves sometimes are not so clearly objectively observable. The problem comes from the standard inclusion of harmful consequences as a criterion for addiction. Physical harm may be fairly non-controversial. But there many people who act compulsively and make repeated attempts to stop who have not yet done serious physical harm to themselves. Thus the harm in question is almost always defined more broadly as involving harm to relationships and work. This broader conception of harm leaves plenty of room for social conventions and norms as well as other factors such as income to be essential aspects determining what causes harm. A wealthy individual whose drug use is financially inconsequential and whose family and friends do not disapprove may exhibit the same behaviors that in a different individual and social context might indeed cause harm in a sense broader than physical harm. This variability is an obstacle to successful medical models of addiction.<sup>2</sup>

There are at least two worries here: what individuals themselves experience as harm will vary with social context and what practitioners count as social harm will vary from individual to individual and from practitioner to practitioner. We are uncertain how serious these problems are, but believe they are worth keeping in mind. Research in clinical populations in treatment may present fewer problems in practice—particularly for the most severe frequent relapse cases (see below) where the harm is blatantly obvious. For epidemiological research, which is essential for understanding the full range of addiction phenomena such as spontaneous remission in the general population, the problem may be serious. This argues for the importance of longitudinal studies.

We know that many concepts in science are not easily defined in terms of straightforward traditional necessary and sufficient conditions and that nevertheless such con-

cepts do not prevent scientific progress. Yet it is undeniable that clear definitions allowing for clear operationalizations are something to be valued. We think that the problems with DSM-style categorizations of addiction as well as with their specific instantiations are an obstacle to progress in addiction research. That obstacle should be recognized and routes around it pursued.

We would suggest two possible, related paths are worth pursuing in trying to find more scientifically palatable categorizations of addiction. There is nothing to prevent researchers from going beyond the "any five of the following ten criteria" method of categorizing addicts. It is possible to weight components and to determine statistically which components are doing the most work in the classification processes. Researchers have begun to take such steps in the pathological gambling literature. Even when research samples are based on the DSM criteria, it is possible to report on differences in results by differences in which subcriteria are met.

The loose nature of the DSM categorization might also be dealt with by investigating the possibility that the commonsense notion of addiction that underlies the DSM-based categorization covers heterogeneous phenomena that are best separated (Ross et al. 2008). Those who get labeled addicts may fall into two distinct groups: the severe, biochemically challenged individuals, perhaps best picked out by serious (resource-using) repeated failed attempts to quit, and another set of individuals who exhibit a range of behaviors such as episodic use, movement between binge and controlled use, and so on. The individual who uses alcohol daily in a controlled way a large part of the time perhaps should not be classified with the individual who has been in detox repeatedly and who returns to binge drinking each time.

If we are serious about a medical model for addiction, then separating the severe addicts from the others may be essential. Science often takes commonsense notions and then fragments them into components, finding some amenable to some kinds of explanation and not others. Medical models that give relatively minimal place to social and environmental factors in explaining addiction are likely to be more plausible for the severe addicts described above than for the full plethora of behaviors that get labeled as addiction. Pursuing a strong medical model for all behaviors that get labeled as addiction may be letting the medical model dictate hypotheses and possible causes where it should not be doing so.

We have been discussing the extent to which the commonsense notion of addiction groups together similar phenomena suitable to the same scientific, medical type explanation. We also need to look at the aspects of the dynamics of addiction that the medical model is supposed to explain. This is an important complication and one that is probably under-discussed in the research literature where the medical model predominates. The problem is there is not one thing—"addiction"—to explain. This is not the problem raised above by diverse behaviors associated with the commonsense notion of addiction. Rather, this is a problem that would surface even if we had quite clear

necessary and sufficient conditions for being addicted. The problem is that we do not want to explain just the state of being addicted. It would be nice to have an explanation for much more. We want to know what explains onset—what explains the transition of nonproblem user to addict? We also want to explain the course of addiction, in particular the high spontaneous remission rate (though it is unclear if there is evidence about remission among the severe cases—assuming that it is not definitionally impossible on the grounds that if you go into remission you were not a severe addict in the first place).<sup>3</sup>

It should be obvious that what explains one of the various aspects of addiction need not logically explain the other aspects. Indeed, some theories of a current state of addiction are logically incompatible with explaining other aspects. If current-state addiction is explained by a medical model describing a biological transformation in the brain, that very same change cannot explain spontaneous remission. The dearth of discussion of spontaneous remission in medical-model-inspired addiction research is thus not so surprising; it is perhaps another place where strong medical models may be skewing what is investigated in potentially unhelpful ways. *Note that in general a medical model might be a good explanation for one stage of addiction but not another.*

#### To What Extent Have We Gotten a Neurobiological Model?

Up to this point we have been talking about medical models of addiction in the abstract. Addiction, it is said, is a disease of the brain. In this section we ask in what sense addiction has been located as a disease of the brain. Contemporary addiction researchers cling to the hope that all addictions (whether natural, e.g., sex; substance, e.g., cocaine, alcohol; or behavioral, e.g., gambling) may prove to be successfully treated by some *common* therapeutic intervention. So, the predominant goal is to provide what might best be termed a “common pathway account” of the causes of addiction. However, in the literature we encounter multiple idealized common pathway models of addiction pitched at varying levels of analysis. The interesting question, then, is how such models can be fit together into a unified causal account that locates addiction as a disease in the brain. It is the strides that have been made toward such a unified account of the mechanisms of addiction and the challenges that still remain with which we concern ourselves in this section.

The best-articulated systems-level model of addiction consists in the hypothesis that addicts have a dysfunction in “the mesocorticolimbic dopaminergic and glutaminergic pathways” (Adinoff 2004). As Nestler (2005, 1445) claims:

There is now considerable evidence, from animal models and more recently from humans, that all drugs of abuse converge on a common circuitry in the brain's limbic system. Most attention has been given to the mesolimbic dopamine pathway, which includes dopaminergic neurons in the ventral tegmental area of the midbrain and their targets in the limbic forebrain, especially the nucleus accumbens (NAc).

Details of this hypothesis differ across individual advocates, but there are enough common elements to define a common approach and research program. At the systems level, changes in the function of brain systems are appealed to in order to explain at least some of the behavioral phenomena of addiction (e.g., loss of control, relapse). The most prevalent and widely accepted systems-level explanation is in terms of two competing systems. According to Bickel and Yi (this volume), “choices of addicts result from two separate competing processes—one that is hyperactive and one that is hypoactive.” The hypoactive system is executive functioning, which is subserved by the prefrontal cortex. It is claimed that addicts “exhibit a variety of deficits in what is often called executive function.” The hyperactive process is “the impulsive system” or “the reward system.” This system, at this level of analysis, is taken to comprise two pathways: the mesocortical and mesolimbic pathways (described below). Addiction occurs when “the impulsive system overwhelms the executive system”—“if signals triggered by the impulsive system were relatively strong, they would have the capacity to hijack the top-down goal-driven cognitive resources needed for normal operation and exercising the willpower to resist drugs” (Bickel and Yi, this volume).<sup>4</sup> Goldstein and Volkow (2002, 164) put the claim another way: “top-down processes are reduced, releasing behaviors that are normally kept under close monitoring.”

This general picture is multilevel, as it includes reference to brain systems and neuronal networks. But it is pitched at a relatively abstract level. Below we will look at a complementary account that ties addiction more closely to details at the synaptic, cellular, and molecular levels. We believe that such details are important because medical models at the systems level do not by themselves get us very far with respect to identifying the causes of addiction. We worry that the causal stories they provide are dictated too much by what fMRI can measure. It seems to us that the use of the fMRI naturally encourages oversimplification in explanations, as experimental tools are prone to do. What can be measured is treated as an isolable cause despite background knowledge that suggests that the system in question is much more complex. To see this in practice in the addiction literature, look at the reasoning in these two quotations:

“Neuroimaging studies generally observe decreased activity among addicts relative to controls in those regions that compose the prefrontal cortex (PFC), which is an evolutionarily younger brain region found in humans and higher mammals. For example, studies have demonstrated decreased activity or volumetric reduction of the PFC” (Bickel and Yi, this volume).

“The frontal cortex is a brain region that supports logical thinking, goal setting, planning and self control. Numerous MRI studies have documented that addictive drugs cause volume and tissue composition changes in this region. . . . Several structural MRI studies have shown enlargement of the brain's basal ganglia in addicts compared to controls. . . . In one study, methamphetamine dependence and poor decision making correlated with reduced activation of the PFC” (Fowler et al. 2007, 6).

Here the experimental tool, after much data analysis, produces a result—a small probability of seeing a small decrease or increase in blood-oxygen-level-dependent (BOLD) signal by chance in some region of the brain.<sup>5</sup> That is then taken to show that the region in question is “less active.” From “less active” comes the move to the conclusion that the region is dysfunctional, and it is so because, being less active, it is less able to control other brain regions. These hydraulic explanations come from taking what the experiment is able to isolate as an isolable cause. But from a molecular or synaptic perspective, we are not sure that the idea that different parts of the brain are more or less *causally* forceful has a clear sense—there is burst firing, phasic firing, and many other biochemical processes all going on at any one time throughout the brain. The “resting” brain—one that is not engaged in a task or receiving an experimental stimuli—is quite “active” as measured by fMRI (Sonuga-Barke and Castellanos 2007).

There are further issues to worry about with respect to explanations at this level insofar as they are supported by fMRI. First, an important problem calling for further investigation concerns the extent to which brain differences in addicts is the result of addiction or the cause of addiction (or some combination of both). Ideally, we would like to see prospective, longitudinal studies using fMRI to help sort this out. Such studies would be valuable.

We also know that there is high comorbidity in addiction, particularly in the severe cases, with disorders such as depression, and we know that depression is also associated with lower PFC volume and signal. Having been addicted could be a common cause of lower signal in both cases, but the signal could also be the result of prior differences. Moreover, depression is not the only such confounder. The lower PFC and higher striatum activation pattern also show up in antisocial personality disorder, for example (Silbersweig et al. 2007). These are issues that still need to be sorted out if the system-level medical model of addiction is to make progress.

Finally, we note that the fMRI evidence points to a more complicated medical model at the systems level, though these complications are sometimes not fully acknowledged. fMRI results in addicts show that in addition to differences in the orbitofrontal cortex (OFC), VTA, anterior cingulate cortex (ACC), and NAc there are differences between addicts (active and abstinent) and controls in activation in:

Right posterior cingulate, an area that may be “involved in” risky decision making. Parietal cortex, which is involved in attentional, inhibitory, imagery, episodic memory retrieval, and consciousness of self. PET studies have found similar activity differences in these areas.

Occipital-temporal regions, particular the superior temporal gyrus, which is involved in action planning and identifying salient events, among other things. These regions show greater activation in addicts compared to controls.

Thus there is some evidence that the causes of addiction are more widely distributed in the brain than the systems-level executive versus reward systems story allows.

Better medical models at this level will need to take such causal complexity into consideration.

Researchers working in the neurobiology of addiction accept the basic story behind the executive versus reward systems-level model of addiction (e.g., Hyman and Malenka 2001; Kalivas and Volkow 2005; Kauer and Malenka 2007; Nestler 2005). Their task has been predominantly to identify the synaptic, cellular, and molecular mechanisms that play a permissive role in the reward system coming to dominate over executive function in addiction. Or, at least, they are interested in explaining the phenomena they take to be common across addictions including bingeing, withdrawal, recovery, relapse, and the *persistence* that defines addiction. A handful of basic experimental strategies have been employed for this purpose, including behavioral experiments in which organisms are trained in addiction paradigms and the effects of drugs of abuse on behavior, synaptic physiology, and/or molecular activity are investigated. In other experiments, animals are injected with the drug of interest (e.g., cocaine) either one time or repeatedly; their brains are later removed (e.g., 24h following injection) to produce midbrain slices that are used to investigate, *in vitro*, potential physiological and morphological changes at synapses of interest (e.g., VTA-NAc synapse) that occur *in vivo* in response to drugs of abuse (see, e.g., Hyman and Malenka 2001; Kauer and Malenka 2007; Ungless et al. 2001).

The general consensus among neurobiologists is that research efforts ought to be directed at identifying the cellular and molecular mechanisms involved in persistent activity-dependent changes in synaptic strength in those synapses that are assumed to be “hijacked” in addiction, so that treatment strategies may be aimed directly at preventing or reversing such changes (e.g., Kauer and Malenka 2007). Yet, how far has such research gotten us toward a neurobiological medical model of addiction of the kind investigators want?

To date, neurobiological research on the whole has yielded evidence that has been used to substantiate several different neurobiological models of addiction. The common denominator across all models is the important role ascribed to the *mesolimbic dopamine pathway*. This pathway consists of dopamine neurons that originate in the VTA of the midbrain and terminate on medium spiny neurons in the NAc. We want to consider this basic model to determine how good the evidence for it is and to see how far it takes us in explaining addiction. Other, more elaborate models have been introduced to overcome this model's shortcomings, and we will consider the merits of these models with respect to achieving this goal later in this section.

Explanations of addiction that appeal to this synapse span multiple levels of organization (e.g., cells, synapses, and molecules). First, VTA dopamine neurons in this pathway are ascribed several different functional roles under “normal” or “natural” conditions. For example, they burst fire (i.e., release a number of action potentials within a very short temporal window, and consequently release a significant amount of dopamine into the synaptic cleft, which remains there for a prolonged period of

time, given the time it takes for the reuptake of such a large amount of dopamine) in response to stimuli considered to be naturally rewarding for an organism, such as food and sex. Second, they burst fire in response to stimuli that predict the occurrence of such rewarding stimuli, or in response to stimuli that have come to be associated with such stimuli (e.g., via classical conditioning) (see, e.g., Schultz 2000). Third, their firing pattern reflects when an expected reward differs from the actual reward received (see, e.g., Schultz 2002). A fourth function is also ascribed to dopamine neurons and the dopamine signal. In reinforcement learning paradigms, increased release of dopamine into the synaptic cleft is hypothesized to act as a primary reinforcer, making it more likely that those behaviors that preceded its release into the synaptic cleft will be repeated (see, e.g., Hyman and Malenka 2001). It is also supposed that medium spiny neurons in the NAc "[are] involved in responding to the motivational significance of stimuli" whereas "the dorsal striatum is involved in the learning and execution of behavioral sequences that permit an efficient response to those cues" (Hyman and Malenka 2001, 697).<sup>6</sup>

One basic explanation for addiction offered on this neurobiological model is as follows. Drugs of abuse and certain kinds of behaviors cause VTA dopamine neurons to burst fire and release a significant amount of dopamine for a sustained period of time into the synaptic cleft. Repetitive drug use causes the repetitive significant and prolonged release of dopamine into the synaptic cleft, which repeatedly activates NAc neurons. Such repetition is accompanied by a *strengthening* of this synapse, because VTA dopamine neurons repeatedly cause NAc neurons to fire, and according to the Hebbian rule, "cells that fire together wire together." The organism exposed to the drug is motivated to take it again, given the reinforcing properties of dopamine. In turn, plastic changes downstream of the VTA-NAc synapse are also hypothesized to occur in order to explain the changes in behavior that accompany addiction. Such changes are used to explain repetitive drug use and the phenomenon of bingeing. Furthermore, following repeated drug use, natural rewards (e.g., food, sex) no longer elicit the same kind of dopamine release of which they were previously capable (i.e., they become *less* rewarding). This contributes to the organism subsequently engaging in drug-seeking behaviors. Overall basal levels of dopamine or tonic release of dopamine in the synaptic cleft between the VTA and NAc (i.e., release that occurs in the absence of rewarding stimuli) are decreased, yet, stimuli that are associated with the drug of abuse or behavior and the use of the drug or engagement in the behavior itself both continue to result in a significant release of dopamine into the synaptic cleft. On Robinson and Berridge's (1993, 2001, 2003) model, the synapse becomes "hypersensitized" to the drug. Such hypersensitivity is also appealed to in order to explain drug-seeking behavior and relapse. Furthermore, stimuli that often co-occurred with drug-taking and subsequent dopamine release come to be associated with the drug experience or its effects; this is taken to occur via the co-release of (1) glutamate from pyramidal cells that syn-

apse onto medium spiny neurons in the NAc from limbic structures traditionally involved in associative learning (e.g., hippocampus, bed nucleus of the stria terminalis [BNST] and the amygdala) and (2) dopamine (i.e., the "reward" signal) from VTA dopamine neurons. Subsequent exposure to such stimuli may then come to trigger dopamine release in the absence of the drug or, during periods of withdrawal and even recovery, trigger relapse and repeated drug use. All of these causal factors are taken to contribute to addictions being so difficult to treat and beat.

Yet neurobiological explanations for addiction do not stop at the synaptic level. For such synaptic level changes are thought to require changes in cells and molecules. Neurobiologists, accepting the aforementioned synaptic model of addiction, have recently been concerned with investigating the cellular and molecular mechanisms that result in hypersensitization or strengthening of the VTA-NAc dopamine synapse. Long-term potentiation (LTP), an activity-dependent *increase* in synaptic strength, and long-term depression (LTD), an activity-dependent *decrease* in synaptic strength, are the two candidate mechanisms that have been identified as causally responsible for such drug-induced changes at this synapse. It is supposed that drugs of abuse, in part because they lead to persistent changes in behavior, co-opt the synaptic, cellular, and molecular machinery traditionally involved in learning and synaptic plasticity and that, in fact, "addiction represents a pathological, yet powerful form of learning and memory" (Kauer and Malenka 2007, 844).

Activity-dependent changes in synaptic strength occurring under "natural" learning conditions have been predominantly studied in glutamatergic synapses in brain structures such as the hippocampus and amygdala. LTP and LTD are produced by artificial stimulation, but cellular and molecular research on these two forms of synaptic plasticity has been used to shed light on how those plastic changes that are thought to underlie learning are achieved in the brain. In one form of LTP, NMDA-receptor-dependent LTP, (NMDA-LTP), activation of NMDA receptors following artificial stimulation results in  $Ca^{2+}$  influx into postsynaptic neurons. This is thought to trigger the activation of second-messenger signaling cascades (e.g., extracellular signal-regulated kinase [ERK]), which are poised to send signals from the synapse to the nucleus and ultimately result in downstream physical changes at the synapse (e.g., new spine growth, AMPA and NMDA receptor trafficking) that mediate changes in synaptic strength. So, addiction research at the molecular level has been primarily directed at identifying the kinds of extracellular and intracellular changes in molecular activity that occur in VTA neurons in response to drugs of abuse (see Thomas, Kalivas, and Shaham 2008). More recent work has sought to move beyond the VTA to study changes in synaptic strength at the VTA-accumbens synapse, as well as in projections from the amygdala to the accumbens.

So, at the molecular level the hypothesis is that the same molecular mechanisms that are operative in traditional forms of LTP and LTD are recruited in response to

drugs of abuse, and ultimately result in persistent changes at the VTA-NAc synapse that underlie systems-level accounts of addiction and the behavioral phenomena of addiction (see, e.g., Hyman, Malenka, and Nestler 2006; Hyman 2005). The consensus is that interventions exclusively at the molecular level may prevent those changes in synaptic plasticity at the VTA-NAc synapse that accompany addiction. It should also be noted, however, that this traditional causal story is typically supplemented by noting that individuals who become addicts have certain "early" molecular vulnerabilities to addiction, such as low availability of D2 or D3 dopamine receptors in the ventral striatum (see, e.g., Everitt et al. 2008 [review]; Dalley et al. 2007).<sup>7</sup>

To summarize, the predominant working medical model of addiction based on the mesolimbic dopamine system spans multiple levels from molecules to behavior. It attributes primary roles in the etiology of addiction to the VTA-NAc synapse, dopamine neurons in the VTA and medium spiny neurons in the NAc, dopamine molecules/release, and cellular and molecular machinery implicated in synaptic plasticity at the VTA-NAc synapse. It hypothesizes a role for glutamatergic inputs from limbic association areas to medium spiny neurons in the NAc in both addiction and relapse, and it acknowledges that there must be consequences downstream of this synapse that result in changes in behavior. It is, in itself, a bold, interesting, and parsimonious hypothesis that is the result of an integration of research findings and methodologies across multiple levels of analysis. It, in some form or other, currently plays a crucial role in all medical models of addiction and drives neurobiological research on addiction. But how far does it actually take us toward a robust medical model that localizes addiction in the brain? How good is the evidential support for this model, and what types of phenomena is it actually able to explain?

Remember that a medical model of a disease ideally requires that the disease in question be identified by a set of objectively verifiable symptoms. It must be the result of a physical condition that represents a deviation from normal functioning. This condition must be in principle localizable somewhere in the body and it must be both necessary and sufficient to have the disease. We have suggested that two problems may arise with respect to providing a traditional medical model of addiction. First, the model may fail to be exhaustive with respect to identifying the phenomena of addiction. It may identify some phenomena, while remaining silent about or placing less weight on others. Second, descriptions of the causes of addiction phenomena may suffer from ambiguity or vagueness.

Since the explanation of addiction that is offered on this model makes reference to at least some of the stages of addiction observed at the level of the behaving organism, it seems worthwhile to approach our analysis of this model with respect to these stages and with respect to the type of evidential support offered for each stage.

First, an obvious prerequisite for becoming an addict is exposure to a drug of abuse. The best evidence to suggest that drugs of abuse elicit persistent changes at the VTA-

NAc synapse in response to a one-time exposure to a drug of abuse is data obtained from *in vitro* midbrain slices prepared from the brains of mice 24h after administration (via injection) of cocaine or saline (control) (Ungless et al. 2001). The type of plastic change observed in such cases was a change in excitatory postsynaptic currents in VTA dopamine neurons. This was shown to be mediated in part by increased expression of AMPA receptors at the cell surface in these neurons. There are several things worthy of note about such data. First, as Kauer and Malenka (2007) point out, these studies only investigated changes in VTA dopamine neurons and were not concerned with investigating whether other types of plastic changes had taken place in the brains of these mice as a result of the cocaine injection. So, these data do not rule out the possibility that the onset of addiction involves more brain areas than just the VTA-NAc synapse. What is required to validate this explanation of the onset of addiction on the VTA-NAc model would be data that demonstrated that these plastic changes in response to drugs of abuse were unique to the VTA, and this would have to be shown for each and every drug of abuse, not just cocaine.<sup>8</sup> So, one suggestion, which is aligned with Kauer and Malenka's admission of the limitations of this study, would be to investigate whether plastic changes are observed in brain structures upstream and downstream of the VTA following acute exposure to each drug of abuse.

Of course, few investigators are committed to the idea that an individual becomes an addict after a one-time exposure to a drug of abuse. It is thought to take *multiple* trials. In fact, the predominant method employed to study addiction in rodent and primate models is the self-stimulation paradigm, in which rat or monkey subjects come to develop what is identified as an addiction only over *repeated* self-controlled exposure to a drug. But, if repetition is necessary for addiction (at least in some if not all cases), what is the threshold? How many times is enough for the requisite plastic changes to take place to make an individual an addict? Or how much of the drug is enough? This is not so odd a question, given that activity-induced synaptic plasticity in other brain structures, such as the hippocampus, is thought to require stimuli of a particular frequency, intensity, and duration. A further question we may ask is whether the thresholds for the induction, expression, and maintenance of plasticity vary or are consistent across different drugs of abuse and different people. For example, might there be synaptic, cellular, or molecular changes that can be appealed to in order to explain why some individuals never develop an addiction even after repeated exposure to a drug, whereas other individuals do? Do thresholds for addiction vary across individuals? These are merely some of the questions that may be raised with respect to onset. And investigators have sought to provide answers to such questions, but this does not mean that they have considered all of the potential causes that may contribute to variability in the onset and expression of addiction across individuals.

There is an additional issue relative to the specific methodology of studying drug-induced plasticity one set of synapses at a time. We may anticipate that the kinds of



plastic changes observed when an animal is administered a drug via injection will differ from those plastic changes observed in the brain of an animal that has been trained in a self-stimulation paradigm, in which it learns to lever-press to receive a drug stimulus. In the latter case, other brain areas besides the VTA are likely to be involved in the process of the animal becoming an addict, given that it is in an operant learning situation. The activation of other brain areas that send neuronal projections to the VTA and NAc will most likely have an impact on the kind of plastic changes that are observed at the VTA-NAc synapse. This is an obvious and worthwhile avenue for exploration, namely, to tease apart plastic changes caused by the drug alone versus plastic changes that may occur in addition to such changes as a result of the learning. In any case, experimentalists will face obvious challenges in trying to link data obtained from these two methodologies up into a neat causal story of addiction that validates the current working medical model.<sup>9</sup>

Another issue with respect to the onset of addiction relative to this model presents itself. As Kauer and Malenka (2007) acknowledge, recent neurobiological research has been directed at understanding plastic changes that occur at the VTA-NAc synapse—that is, to understand postsynaptic changes in NAc medium spiny neurons in response to drugs of abuse. Little to date is known about plastic changes in these neurons and the story will presumably be complex for several reasons. First, these neurons have multiple dendritic spines, which each receive inputs from multiple different neuronal types originating in multiple different brain systems (e.g., hippocampus, amygdala, VTA, prefrontal cortex [PFC]). NAc medium spiny neurons are integrators of information coming from each of these different regions. Types of information include (1) the reward or any number of other signals from dopamine neurons in the VTA, (2) spatial and temporal information from pyramidal cells (GLU) originating in the hippocampus, and (3) emotional information from pyramidal cells (GLU) originating in the amygdala. Now, the VTA-NAc model makes it seem as if at the time that an individual is presented with or takes a drug of abuse for the first time, that is, prior to the onset of addiction, there is nothing going on in his or her brain apart from the reward signal from dopamine neurons—and that the only time that these other brain areas exert their influence in addiction is at the stages of drug-seeking and withdrawal, resulting in relapse. But there are several interesting questions we may raise for this model: First, how is it that the dopamine signal comes to be rewarding if these other brain structures and neurotransmitter systems are not operative prior to onset? Isn't "reward" dimensional—having emotional, temporal, and even spatial dimensions? Some investigators have suggested so (e.g., Berridge and Robinson 2003). And aren't organisms learning all the time? But if these other brain areas are operative from the get-go, then isn't it possible that important changes in synaptic plasticity are happening in these regions as early as the first exposure to a drug of abuse? And if so, then, what role do they play? Sometimes, when addiction is explained in light of the working model, the role

of these other systems tends to be overlooked. Yet it is not obvious that the key to solving addiction isn't in these other brain areas as well as in the reward system—or that maybe the area currently designated as the reward system should be more broadly circumscribed.

Another important point is that when an individual crosses the threshold from non-addict to addict, there is an obvious behavioral signature: the individual engages in drug-seeking behaviors even when doing so is to his or her own or others' detriment. In order to establish that such changes in behavior are the result of plastic changes in brain synapses, neurobiological investigators have intimated that it would be helpful to understand how changes at the VTA-NAc synapse actually lead to these downstream behavioral consequences. Whereas the hypothesis at the systems-level is that there is an inhibition of executive function that explains this apparent loss of control, and that this is mediated in part by changes in synaptic plasticity in dopaminergic projections from the VTA to the PFC, plastic changes occurring at the VTA-PFC synapse have yet to undergo investigation; merely establishing that VTA cells exhibit some plastic changes in response to drugs of abuse does not provide insight into the downstream consequences of such plastic changes. Furthermore, neurobiological investigators seem more interested in understanding the synaptic events occurring directly downstream of the NAc. For example, evidence to date suggests that the excitability of NAc neurons is depressed in response to chronic drug exposure, yet the downstream behavioral consequences of such depression are not well known. It is supposed that such changes occur rapidly in response to repeated drug exposure and are crucial for the persistence of addiction. But although the pathways via how such changes may occur have been identified, the mechanisms are not yet known.

We take it that it is in response to considerations like these that other circuit models of addiction have begun to proliferate in the neurobiology of addiction literature. Although some of the components of these models are not appealed to in order to explain the early stages of addiction, researchers have at least agreed that more complex models<sup>10</sup> necessarily have to be posited in order to explain the later stages of addiction, which include the phenomena of withdrawal and relapse. Withdrawal is said to be accompanied by responses typically classified as "emotional." Relapse may be the result of stress, or the result of encountering contextual stimuli that have become previously associated with the drug during use.

What these more complex models really suggest, however, is that the causes of addiction could potentially be distributed throughout the whole brain. And this casts doubt on the feasibility of a strict localization of the causes of addiction across all types of addictions and across all persons who are addicts, as is required by a strict understanding of the medical model in combination with the goals of contemporary addiction research. Furthermore, these newer models, insofar as they suggest a diffuse interaction among different brain systems, cell types, and neurotransmitter systems,

make the prospect of a very localized therapeutic intervention in addiction unlikely. This does not mean that the project of finding one is doomed from the start, but rather that investigators must continue to be more inclusive in their search for a cure. And this may mean, as we claim in the next section, considering causal factors outside of the brain.

We want to draw the reader's attention to a final issue that we mentioned in the previous section. The rates of spontaneous remission among diagnosed addicts are actually quite high. Although neurobiological models identify potential causes involved in becoming addicted, being addicted, and staying addicted, these models are silent with respect to these phenomena. And, there is no obvious mechanism in the context of such models to which we might appeal to explain them. If such remission is the result of plastic changes somewhere in the brain, where are such plastic changes taking place and what is the impetus for them? Even if we claim that there is still an underlying addiction, there must be something that we can point to in order to accommodate the lack of expression of addiction in the individual's behavior. We think it is worthwhile to raise such questions, given that understanding why some addicts go into spontaneous remission—that is, understanding what the mechanisms are—may shed light on novel avenues to pursue in the search for effective treatments for addiction.

#### How Far Can a Medical Model Get Us without Bringing in the Social?

A final challenge for medical models of addiction is to incorporate a richer picture of the social environment when that is needed. Whether it is needed is, of course, an open question. There is little direct discussion in the papers in this volume of social factors in addiction, whereas there is much attention to the kind of neurobiological detail of medical models we have sketched above. However, that does not preclude us from asking if and how we would add social elements to our explanations of addiction if those factors do indeed play a causal role.

We should remember that this question must be refined along two dimensions: according to the various aspects or stages in the course of addiction and perhaps according to whether we are focusing on addiction in its broad sense or only the most severe addicts. That social factors determine accessibility of addictive drugs is uncontroversial. What role they play in ongoing addiction, spontaneous remission, relapse, and treatment is more controversial. We saw Koob and Le Moal (2006) expressing the hardest line, namely, that after onset, the explanation is biological, not social. In this final section we sketch reasons for thinking things are not this simple and identify some open issues about social influences that we think might usefully be pursued.

There are some general considerations that make it likely that social and cultural factors have to be an important part of the story. As MacKillop, McGeary, and Ray (this volume) point out for alcoholism, genetic findings about addiction always point to

gene-environment interactions, and social and cultural factors are likely to be part of that environment. We also know from neurobiology that the amygdala is strongly involved in addiction and that the amygdala plays a central role in the emotions. Emotions, however, are often shaped and elicited by social relations.

Aside from such general considerations, there is significant research on the importance of specific social factors:

1. Both smoking and heroin use can be learned substance use (use that takes effort prior to addiction) in that both can be initially very unpleasant and individuals have to make repeated efforts before they find anything pleasurable about the activity. The learning is usually done with the help, support, and peer pressure of friends and family. Social factors in this case are importantly involved in the transition from use to addiction.
2. Stress is a major contributor to relapse (Sinha 2007). Stress is very much social in nature. It works through family, peer group, and work relationships. Life events such as the loss of a job or the breakup of a relationship are prime ways to undergo stress.
3. Access to resources is a key factor in determining whether a regular or past user experiences major problems of the sort that are used to define addiction—individuals with extensive financial support can sometimes lead fairly normal lives without the disruption of social roles.
4. Heavy heroin users in Vietnam mostly transitioned to abstinence or controlled use on their return from the war. Change in the social environment—family and work responsibilities, for example—was probably part of the explanation.
5. Hajema and Knibbe (1998) found that drinking in a Dutch sample declined significantly after marriage and employment.
6. Frankenstein, Hay, and Nathan (1985) found that alcoholics in marital therapy spoke more often to each and more positively after consuming alcohol. Apparently alcohol use can sometimes have positive social functions.
7. Steady but nonbinging drinkers tend to live in families with positive family environments (Dunn et al. 1987).
8. Substance abusers score lower on relationship functioning than controls (Wright and Wright 1990).
9. Deliberate and planned family rituals—regular meals, holiday celebrations together—among married individuals whose parents were alcoholics and who themselves drank show less alcoholism among their offspring (Bennett and Wolin 1990).
10. Spouse coping skills predict transition to problem drinking (Hurcom, Copello, and Orford 2000).
11. Bandura's social learning theory based on individual "modeling" behavior of others led to research supporting the finding that such learning occurs in drug use onset (Rotgers, Morgenstern, and Walters 2006).

12. Sobell et al. (1993) found that spousal support was an important factor in spontaneous remission among problem drinkers.
13. Several clinical trials have shown that voucher programs providing rewards for being drug free are effective (Budney et al. 2000).
14. The price of valued, nondrinking rewards influence relapse (Vuchinich and Tucker 1996), with social interaction being a substitute commodity (Rachlin 1997). Addicts are price sensitive. Smokers, for example, are quite price sensitive, showing elasticities of .8.

We have some specific causal claims here with some supporting evidence about the role of social factors in onset, current addiction, remission, and relapse. These are piecemeal causal claims. There is a more systematic story about social interaction in addiction that would nicely incorporate these claims. The story falls into the domain of suggestive but imprecise social science, but it is worth keeping in mind as we think about the social side of addiction.

The more systematic account comes primarily from the social interactionist literature in sociology as well as the behavioral learning tradition in psychology and behavioral economics. On this picture, individuals come to their self-identity in interaction with and negotiation with others who do the same. They have roles that are identified by the expectations of others, and they have different levels of commitment to their roles. Roles may expand in that a subject may identify it with in a wide range of circumstances. Reference groups are those whose expectations define the role. Roles can conflict. Roles require expenditures of effort, and individuals can have difficulty in achieving them. Some roles are more similar than others, and the more similar the role, the easier it is to adopt it. Adopting roles involves learning of various kinds. Classical conditioning, operant learning, Bandura's modeling processes, and higher-order cognitive decision making can all be involved.

From this perspective, being an addict is a role. Individuals assume the addict role in part to the extent that families and friends label them as such—the labeling process is part of the learning process. Moreover, it is not just the drug experience that is rewarding. The role itself can be rewarding—although addicts may forgo certain kinds of social interaction and that is a cost, there are nonetheless various social interactions built into being addict that can themselves be rewarding. Spontaneous remission can result from what social scientists call role strain—the costs of being an addict—and from the extent to which the addict can commit to new and past nonaddict identities. One way this can happen is through 12 step programs. Addiction in disadvantaged individuals occurs in part because of the restricted number of roles there are for them to occupy.

This picture is suggestive but sketchy. Nonetheless, it seems clear that social processes of some sort are importantly involved in addiction. How are medical models to incorporate them? The pure medical models, which explain only via localizable inter-

nal dysfunctions, will not do the job. However, we take it that the social processes we describe can be complements to the kind of neurobiological details that medical models emphasize. The effect on the dopamine system helps explain why the addict role can be rewarding and how individuals learn to adopt that role, and thus why the role may be hard to abandon. The success of voucher programs suggests that rewards differ in their ability to compete with drugs, and this fact ought to have a neurobiological substrate if not a complete explanation. Such explanations could also help flesh out how family relations make a difference to various aspects of addiction. There is no reason that the biological and the social have to be competing as Koob and Le Moal claim—unless one persists in requiring a full-on, pure medical model.

It is also important to remember our distinction between the broad common sense-based varieties of addictive behavior and that of the most severe addicts who make serious repeated attempts to quit and fail. It is possible that for the latter the medical model is closer to the truth and that social factors are much more important for the less severe addictive phenomena. If no contingencies in the environment short of incarceration will deter the addictive behavior, then the environment drops out for these individuals after the onset of addiction. At that point it would not be the case that the kinds of factors that influence human behavior in general explain ongoing addiction as Heyman (this volume) asserts they can.

Ross et al. (2008) provide some evidence for thinking that there are such severely addicted individuals for whom the medical model is appropriate. We think there are some further interesting empirical issues about this hypothesis that could be fruitfully pursued. We would like to know if people fall on a continuum of failed times attempting to quit or if there is sharp cutoff—a sharp peak in the frequency histogram pointing to a distinct group. Do we see successes at stopping after  $X$  number of tries but never at some larger  $X$ ? That would give us further evidence that the severe addicts are a distinct group and represent a homogeneous phenomenon. A related empirical question is whether the social factors that seem to influence remission and relapse such as social support, for example, are irrelevant for these individuals—do they show repeated failed attempts to quit despite high social support or other social factors that might explain remission and relapse in the less severe addicts, picked out by the broad sense of addiction? These questions call for going beyond the DSM-based screens and regressions based on them, for they are not set up to find such differences even if they exist.

Finally, if there is a distinct group of severe addicts where the medical model is plausible, they will probably be individuals with other axis I comorbidities such as depression. What is the causal relation between the two? How are the neurobiological causes of the two related? Of course, these are big questions, but the ideal medical model that we might aspire to would provide us with their answers.

### Conclusion

Medical models of addiction as exemplified by the dysfunctional dopamine reward system hypothesis are bold, interesting, and parsimonious accounts. They have served to direct a research program that has produced many important results. However, we think that progress requires, first, being clearer on what exactly they claim and to what extent they actually are medical models, and second, trying to incorporate the more complex causal nexus that is involved in addiction running from the neurobiological to the social. We hope to have contributed in a small way to that enterprise.

### Notes

1. The listing of authors is alphabetical.
2. See Manson, this volume, for a discussion of related problems applied specifically to problem gambling.
3. Orthogonal to these dimensions, if we think there is a genetic component to addiction—and the evidence for this is strong, if not perhaps for the large effects claimed—it will surely be an effect that consists in a vulnerability. If you live in an alcohol-free environment, your alcoholism gene is not going to make martinis for you at happy hour. So we may explain the vulnerability for each of the above aspects of addiction cited above. On our view, explaining behavioral tendencies more generic and fundamental than addiction may be a better target for medical models. See MacKillop, MacKillop, McGeary, and Ray, this volume.
4. For example, “compulsive cocaine use has been hypothesized to result from a failure in top-down executive control over maladaptive habit learning,” which is hypothesized to “reflect the diminishing influence of prefrontal cortical function, as behavioral control devolves from the ventral to dorsal striatum” (Belin et al. 2008, 1352).
5. Sometimes it is claimed that the activation is “significant.” This is the elementary fallacy of confusing statistical significance with clinical causal significance.
6. It should be noted that the functions that we are itemizing for dopamine neurons here are only a small sample of the many functions that have been attributed to dopamine in the literature. Wolfram Schultz (2007, 277) puts it best in claiming: “Scholars have numerous and mutually exclusive views on dopamine function based on the fallacy that there should be only one major role for every brain system. Results from individual experiments using different methods suggest a role in movement, reward, punishment, salience, learning, cognition, and many other processes.” He adds that dopamine may serve all these diverse functions in light of the different time courses at which dopamine neurons can operate.
7. One possible explanation as to why persons with low D2/D3 receptors are more vulnerable to becoming addicts is that following acute exposure to a drug of abuse, the reuptake of dopamine in the ventral striatum is slow due to the low number of reuptake receptors. In turn, the dopamine

remains in the synaptic cleft for a longer duration of time, causing the repeated firing of accumbens neurons after a one-trial exposure. This will make such individuals more likely to become drug abusers. Yet, after chronic exposure to a drug of abuse (e.g., shown for cocaine), low D2 and/or D3 dopamine receptor availability has been observed in dorsal striatum.

8. Of course, this is true only if the assumption is made that drugs of abuse share common cellular and molecular pathways. It is, however, possible that different drugs of abuse will set different kinds of synaptic changes in motion—that is, even if the functional consequences (i.e., addiction and the behaviors associated with it) of such changes are ultimately identical across different drugs of abuse or even types of addiction. Nestler (2005) points to the possibility of there being a common molecular pathway for addiction.

9. Note that a common way to infer a causal relationship between a drug-of-abuse-induced form of synaptic plasticity and a change in behavior at the level of an organism is to reverse, via pharmacological interventions, the drug-induced synaptic plasticity and then subsequently observe a corresponding change in the behavior. As Thomas, Kalivas, and Shaham (2008, 328) claim in reference to experiments using cocaine, “a stringent criterion to infer causality between a specific physiological process that underwent cocaine-induced neuroplasticity and a specific behavioural effect of cocaine is that reversal of cocaine-induced neuroplasticity of the physiological process to a drug-naïve state leads to decreases in the behavioral effect of cocaine.” Of course, though we may accept this criterion for establishing causality, in all of the cases cited by Thomas et al. (2008), plastic changes at the synapse (e.g., increases in AMPA receptor surface expression) are assumed to be blocked because the activity of certain molecules that are upstream of such plastic changes at the synapse (e.g., ERK), when blocked, is accompanied by a cessation of a drug-related behavior (e.g., drug-seeking). However, such data are only correlational—although suggestive, they are insufficient to establish that changes in synaptic plasticity actually *cause* the changes at the level of behavior.

10. For example, Goldstein and Volkow (2002, 1642) posit what they refer to as “an integrative model of drug addiction that encompasses intoxication, bingeing, withdrawal, and craving,” which includes the mesocortical (VTA-PFC) as well as the mesolimbic dopamine system (VTA-NAc) and takes into account the possible pathways via which these two systems may interact. For example, dopamine projections from the VTA are sent directly to the NAc, the medial dorsal thalamus (via the ventral pallidum), and the medial prefrontal cortex (mPFC or anterior cingulate). The model takes into account the fact that both the PFC and the NAc receive glutamatergic inputs from the amygdala and hippocampus. It also acknowledges reciprocal projections from the PFC to the VTA (glutamatergic), the PFC to the NAc (glutamatergic), and the NAc to the VTA (GABAergic). This model suggests that the neurons contained in the different brain areas identified may interact in complex ways, which might make it difficult to understand which neurotransmitter systems and physiological signals are implicated in the purported plastic changes that underlie addiction. Yet even this model is an idealized model that abstracts away from the actual connectivity of these different systems and neuron types.

Kalivas and Volkow (2005) have put forward another model, namely, the extended amygdala model, that takes into account GABAergic/neuropeptide projections from the extended amygdala (including the central nucleus of the amygdala [CeA], stria terminalis, and shell of the NAc),

which can serve to regulate the activity of dopamine neurons. It also acknowledges an important role for the ventral pallidum, a structure intermediary between the NAc, VTA, and medial dorsal thalamus. This structure sends GABA projections to the VTA and NAc and also receives a GABAergic projection from the NAc. This suggests that there are various points of control in the network, and understanding the plasticity of one may necessarily involve understanding the plasticity of the others. On this model, "plasticity in [those] neural systems converging on the nucleus accumbens and dorsal striatum" are "usurped by chronic drug self-administration" (Everitt and Wolf 2002, 3312). Yet even this model, though more complex than the interactive and mesolimbic models, remains an idealization compared to the actual neural circuitry that is likely to become activated or play a role in addiction. Furthermore, within these systems-level models are distinct neurotransmitter and neuromodulator systems that have become targets of neurobiological investigations. For example, some investigators (e.g., Koob 2008; Koob and Le Moal 2008) aim to understand the role of molecular pathways involved in stress (e.g., corticotrophin-releasing factor [CRF] within the extended amygdala) that contribute to addiction.

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## 14 Addiction and the Diagnostic Criteria for Pathological Gambling

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### Introduction

A philosophical question divides the field of addiction research. Can a psychological disorder count as an addiction absent a common underlying physical basis (neurological or genetic) for every case of the disorder in the category? Or is it appropriate to categorize a disorder as an addiction if the symptoms of and diagnostic criteria for it are sufficiently similar to those of other disorders also classified as addictions—regardless of whether there is some underlying physical basis common to each case of the disorder? The question concerns the scope and validity of the scientific concept of addiction and, more broadly, what is required for a psychological concept to count as scientific.

The case of pathological gambling (PG) raises this question nicely. “Should pathological gambling be considered an addiction?” asks Howard Shaffer (2003, 176). He specifies the question further (2003, 177–178): “When clinicians and scientists identify a behavior pattern as an addiction, even if they can identify it reliably according to DSM criteria, how do they know that it is indeed an addiction?” He warns that, as it stands, “the concept of addiction represents a troublesome tautology” (2003, 178): a subject *S* is addicted if and only if *S* engages in repetitive behavior with negative consequences against *S*'s better judgment. The problem with this concept is that it provides no way to distinguish behavior that cannot be controlled from behavior that is merely in fact not controlled. This “lay” concept is of little scientific value, Shaffer (2003, 179) argues, saying that “for addiction to emerge as a viable scientific construct . . . investigators need to establish a ‘gold standard’ against which the presence or absence of the disorder can be judged.” PG has no such gold standard, says Shaffer. What would such a gold standard be? Shaffer suggests “neurogenetic or biobehavioral attributes” (ibid.). Such attributes will have to be identified because “if pathological gambling represents a primary disorder orthogonal both to its consequences and the laws of probability, then clinicians and scientists should be able to identify the disorder without knowing the winning or losing status of the gambler” (ibid.).