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Neuroeconomic Perspectives on the Potent but Inconsistent Motivations Characteristic of Addiction

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Our goal is to present a case for neuroeconomics as a productive approach to addiction research. The first challenge is that neither the term "addiction," nor "neuroeconomics" has a straightforward definition. We begin by clarifying how we will approach each of these topics.

"Potent but Inconsistent" Motivations in Addiction

Clinical definitions of addiction are complex, generally involving cut-offs based on whether some minimal number of symptoms are present (APA, 2000; WHO, 2004). One implication of this is that individuals with very different symptom profiles can receive the same diagnosis. However, many medical conditions that were once diagnosed on the basis of a complex and heterogeneous symptom presentation came later to be diagnosed on the basis of a singular underlying pathology. Diagnosis (and sometimes misdiagnosis; see Ochola, Vounatsou, Smith, Mabaso, & Newton, 2006) of malaria based on symptom profile was eventually replaced by diagnosis based on the presence of a particular parasite. Could the analog come to pass for addiction neuroscience? Is there something in the brain that marks the transition – a metaphorical flipping switch – between normal motivation and addiction (Leshner, 1997)?

We think the answer to the above question is "no." Even those who meet clinical definitions for addiction remain responsive to other contingencies (Heyman, 2009). In a therapeutic context, a few dollars each day for bio-assay-confirmed drug abstinence is an effective intervention for many who meet criteria for addiction

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(Alessi, Badger, & Higgins, 2004). And, if you try to quit smoking, an assassin paid to follow you around with a contract to shoot if you ever light another cigarette would almost certainly make your cessation attempt fully successful. The key implication is, we suggest, that addiction is a function of the individual's overall set of motivations.

One might object that, while other motivations affect behavior, the *addiction* can still be operationalized on the basis of a particular underlying brain-based pathological motivation. From this point of view, the hypothetical assassin does not make one less addicted; he just prevents one from acting on his addiction. However, this operationalization of addiction on the basis of something about the specific motivation (and/or its neural substrate) implies that one can have a persistent addiction even if one has no problem quitting. Imagine someone who has the underlying "addiction motivation" to smoke. If countering that motivation she also has whatever it takes to quit decisively the moment she sees a reason to do so, would that person nevertheless have a persistent addiction? Not in the clinical or everyday use of the term; but equating addiction with the driving motivation in isolation would require it. Conversely, equating addiction with a particular brain pathology linked to motivation implies that someone who meets most clinical criteria for addiction does not have an addiction, if the clinical symptoms occur despite the hypothetical switch not being flipped. A related problem is that equating addiction with a specific motivational switch lets in behaviors that are almost never considered addictions, for social reasons. Fervent sexual motivations of a happy monogamous young couple, or even the caring behavior of an elderly couple toward each other, would be open for investigation as possible addictions if the disorder was operationalized on the basis of the qualities of the driving motivation (and its neural substrate), in isolation from the individual's other motivations and from societal norms. In reality, motivations that are consistent with the individual's general larger motivations and with societal norms are not thought of this way.

Of course understanding the brain substrates by which an addictive drug like cocaine becomes so compelling is an essential project for addiction neuroscience. But the substrate of strong desire is not synonymous with the substrate of addiction. For this reasons we will focus our discussion of neuroeconomics' application on what we think is a somewhat more encompassing target, and one that neuroeconomics can productively address (although we still do not intend it as a full operationalization of "addiction"). Specifically, we focus our discussion on *behavior that an individual repeatedly seeks out, despite regularly conceiving of it as inconsistent with his or her best interest*: "potent but inconsistent," for short. *Inconsistency* is explicit in some criteria for "syndrome." The DSM criteria include "repeatedly using more than intended" and "repeated unsuccessful attempts to eliminate or reduce use," both of which imply inconsistency (APA, 2000). Indeed, the "unsuccessful efforts" criterion has been proposed to be the *sine qua non* of addiction (Heather, 1998). And adverse consequences like those included in the current DSM, at least for a healthy individual, often provoke ambivalence. By describing the conception of the behavior as *regularly* at odds with one's identified best interest, we do not mean that she needs to view the behavior this way *all of the time* – although some important models we will discuss do view the ambivalence this way.

Inconsistency between What and What? Diachronic versus Synchronic Conflict

As has been noted (Elster, 1979; Ainslie, 1992; Ross, Sharp, Vuchinich, & Spurrett, 2008; Monterosso & Luo, 2010), models that capture the inconsistency of the addict can be divided conceptually into those in which conflict arises between the self at different points in time (think of Stevens's Dr. Jekyll and Mr. Hyde as a pure example) and those in which conflict arises because of clashing output from distinct motivational systems (think of the trope where an angel and the devil sit on your shoulders, urging you to take different courses). These classes of conflict can be referred to as "diachronic" and "synchronic" respectively (Ross et al., 2008). As explanatory frameworks for addiction, they are not mutually exclusive. Diachronic models may be based on underlying system competition and synchronic models generally lead to dynamic inconsistency. Synchronic models are easier to study in neuroscience, but neuroeconomics does provide foundations for diachronic models as well. Indeed we have argued that greater attention to diachronic models is critical for the future of addiction science (Monterosso & Luo, 2010).

What Makes an Approach Neuroeconomic?

Many in the recovery community are ardent consumers of addiction neuroscience. This, we informally observe, appears to be particularly true of brain imaging work that identifies a biological basis for the addict's inconsistency. When someone ruins his life doing what he swore he would not do (and knew full well he *should not* do), it is both tragic and mysterious. The confounding nature provokes interest in, and hunger for, scientific accounts. Where does neuroeconomics fit into the evolving scientific picture? Can neuroeconomics be used to explain potent but inconsistent motivations?

The first step is to clarify what it is that constitutes "neuroeconomics." This is complicated. Attempts to define the discipline see here two distinct research programs (Glimcher, Camerer, Fehr, & Poldrack, 2009; Harrison & Ross, 2010). The first is grounded in "behavioral economics" and emerged as researchers in this area incorporated brain data to inform their theories. We refer to this as "BE neuroeconomics." The second, perhaps less intuitive variant emerged from basic neurophysiology of decision making, which turned to economics (among other "normative" approaches) to provide a framework for modeling neural activity that is far too complex to analyze neuron by neuron. Following Ross (2008), we refer to this as "neurocellular economics." We think there is some controversy regarding what does and does not fit into this latter category, and the controversy is particularly relevant to addiction because the area most in question is reinforcement learning work (which has made major contributions to the neuroscience of addiction). We begin our discussion with the first and more straightforward variant of neuroeconomics – "BE neuroeconomics."

The Emergence of BE Neuroeconomics

In mainstream ("neoclassical") economics, the math is complex, but the approach is elegantly simple. The starting point is observable behavior, which is used to infer an agent's underlying utility functions. These utility functions are nothing more than

whatever functions reconcile all observed behavior. The approach explicitly cleansed the field of psychology, which had been prominent in the classical approach of Adam Smith and Thorstein Veblen. Utility functions capture all the interests of the agent (Samuelson, 1947). She is "rational" in the sense that she holds a complete and internally consistent set of preferences, and all action maximizes the realization of those preferences (Arrow, 1986). The assumption of perfect rationality strikes the noneconomist as bizarre; but, at least in the pure form of neoclassical economics, it is not that the economist thinks that the individual *is* perfectly rational –rather she thinks that the psychology of the individual is none of her concern. In everyday life we think that it is irrational when someone repeatedly does something that she regrets or that makes her unhappy. But those considerations are based on psychological constructs. Once these constructs are pushed aside, there is no reference by which even to consider whether a decision is irrational – other than internal consistency. Since what is really going on in the agent's head is not the domain of the neoclassical economist, she says only that the individual chooses "as if" she were maximizing those utility functions that are derived from her behavior (Friedman, 1971).

Thanks in part to an open market's tendency to correct irrational influences (since these tend to be exploited until they vanish), assumptions of rationality often do surprisingly well in the predictions they generate. Nevertheless, many economists became impressed by the failures of rational maximization, even by its own axiomatic standards. As a result, modeling "fixes" were developed. The train of logic was first to show the presence of behavior that violated an axiom of rationality (often using controlled laboratory setting), and then to propose a function, linked to a psychological process, that matched the anomaly. The name "behavioral economics" was applied to this work. The behavioral economist believes that deviations from rationality are sufficiently large, and sufficiently predictable, for modeling to benefit from abandoning the rational maximization framework (Edwards, 1954; Hirschman, 1985; Kahneman & Tversky, 1979). Behavioral economics does, however, retain the basic tools of utility-function modeling, which has been the basis of criticism from those favoring a more radical departure from neoclassical economics (Berg & Gigerenzer, 2010).

It is worth noting that behavioral economics and neuroeconomics both seek to identify actual mechanisms rather than construct "as if" models; and this has enormous implications. This divergence from mainstream economics makes the behavioral economist and the neuroeconomist more similar to the psychologist in what she is ready to infer from laboratory experiments. For a psychologist, responses to some unusual stimulus devised by the experimenter can up-end entire theories of behavior. It only takes one toddler raised without prior exposure to pictures, for example, to prove that understanding 2D representations is not accomplished through specialized learning (Hochberg & Brooks, 1962). Perception may usually be veridical, but a psychologist studying visual perception may focus on visual illusions to understand how the system works (Rock & Anson, 1979). Similarly, behavioral economists (Tversky & Kahneman, 1981) and neuroeconomists (Gonzalez, Dana, Koshino, & Just, 2005) might challenge people to make hypothetical decisions about saving or killing other people. The fact that framing affects people in this unusual situation is interpreted as revealing something significant about how decisions are and are not made. To the "as if" modeler, however, results from contrived examples are inconsequential. Models are, for him, only abandoned when real-world behavior can be better predicted by an alternative (Friedman, 1971). This is one

reason for a dismissive attitude many economists hold toward behavioral economics and neuroeconomics (Gul & Pesendorfer, 2008).

While neoclassical economics has not completely ignored addiction, its attempts to account for it within its own framework have been wholly unconvincing. Becker and Murphy model what Gordon Winston derisively called "a happy addict, doing what he wants to do so long as he can buy the stuff and stopping effortlessly whenever he thinks he should" (Winston, 1980; and, for a video parody of the Becker and Murphy model, presented as conversation between a trained economist who is addicted to drugs and her father, visit https://www.youtube.com/watch?v=wC1O50az108). The trouble is that the key element – *inconsistency* – is, and must be, defined out of addiction, since the neoclassical framework explicitly presumes perfect consistency (for discussion, see Hanson, 2009). To get off the ground modeling the phenomenon of addiction, the economist had to adopt non-orthodox modeling (for example, see Schelling's work on "egonomics": Schelling, 1978).

Irrational Delay Discounting

Even a modicum of experience with the phenomenon makes clear that the addict is not a consistent maximizer of utility. She is in turmoil – repeatedly cycling through resolutions, transgressions, and regret. One way to characterize the challenge continually faced by individuals struggling with addictions is that they must forgo the relatively immediate reward or relief available from drugs in order to attain the relatively delayed benefits of sobriety (e.g., social, health, financial). The difference in immediacy between the rewards of drug use and sobriety seems relevant – it would be easy to quit smoking if one could arrange it so that the enjoyable aspects of smoking arrived 20 years after the inhalation, but the negative consequences were immediate. "If the headache would only precede the intoxication," Samuel Butler quipped, "alcoholism would be a virtue."

The dampening effect that delay has on the motivations elicited by expected outcomes (we will use the phrase "delay discounting") is among the most well-studied topics in behavioral economics and neuroeconomics. A main reason for this effect is that, when it comes to weighing the present and the future, people appear highly irrational in both the technical and the everyday senses of the word. Consider the exam or the deadline one month away. It just does not move us to action with the same force as the deadline that is imminent. There are, of course, some justified bases for discounting an expected future gain or loss. There is always at least some uncertainty associated with additional delay. What a shame, for example, to have squandered your time struggling to meet a deadline if you are flattened by a bus before the deadline arrives! But delay discounting goes well beyond what can be attributed to the level of uncertainty associates with the future. A "commonsense" perspective on this issue focuses on degree: everyone is less moved by the distant future than by the imminent future, but someone is faulted for being *extreme* in his delay discounting (e.g., for always waiting to the very last minute to do things). This diverges from the perspective of neoclassical economics. Steepness of discounting is not the issue for axiomatic rationality – one can be perfectly rational while exhibiting extremely steep discounting. Such is her preference, and neoclassical economics is mute on the origin or reasonableness of preferences (Stigler & Becker, 1977).

Instead the key issue is the functional form of the delay discounting, because of its implication for consistency. The machinery of mainstream economic modeling requires that any discounting based on delay happen at a fixed rate per unit of time – that it be "exponential discounting" (equation 1). The exponential functional form is critical because it entails no dynamic inconsistency, and therefore no violation of rationality axioms. An individual can discount the future steeply; so long as she does so by a single fixed rate (exponentially) she can still be modeled as the optimization of a single set of utility functions. Just as the larger of two bank accounts opened on different days will always be larger as both accrue interest, the preferred of two delayed options will, if discounting is exponential, remain the preferred one as time passes. If on day 0 an exponential discounter prefers $20 in 11 weeks over $15 in 10 weeks, she will continue to prefer the $20 even on day 70, when the $15 is immediately available. This can be represented as exponential discounting of a consumption stream over time:

$$V = \sum_{t=0}^{\infty} \delta^t u\,(c_t) \tag{1}$$

where each period's utility is multiplied by a fit parameter δ that is less than (but generally quite close to) 1. The further off in time (t), the smaller the utility.

The problem with exponential discounting is that it generally does not match the behavior of actual people (Myerson & Green, 1995) or other organisms (Ainslie, 1975; Mazur, 1987). The key observation and its implication for neoclassical economics were noted more than a half century ago (Ainslie, 1975, 1992, 2001; Strotz, 1955). In the above example, a common pattern is to prefer the $20 in 11 weeks. "Why not, what is one more week." However, if given the same alternatives on day 70, many switch preference to the immediate $15. The intuition is obvious – the difference between 70 and 77 days of delay is trivial, but the difference between 0 days of delay and 7 days of delay is not trivial (especially not to the individual whose stream of consumption is affected by such a windfall). This pattern implies dynamic inconsistency and violates rationality axioms. It implies that preference between two fixed alternatives switches as a function of the passage of time. Moreover, since the inconsistency in the individual's preference is systematic, she may know that this preference reversal is coming and may orient strategically against it (Ainslie, 1975, 1992, 2001). Thus, rather than the individual moving through time and maximizing a single set of preferences, this individual is broken into momentary selves with sometimes conflicting preferences. Her own future self may be the obvious obstacle to her current preference gaining the day, which results in a state of conflict between selves over time (Ainslie, 1992). The inconsistency entailed by non-exponential delay discounting may contribute to the inconsistency of the addict.

If delay discounting is not exponential, what form does it take? Two modeling alternatives deserve mention because they are important to neuroeconomics and addiction research. The conceptually simplest modeling alternative (Laibson, 1997) makes "now" special by multiplying any expectancy that is not imminent by a fit parameter ( ) between 0 and 1. It amounts to a fixed percentage reduction in potency of motivation associated with any expectancy that is not immediate. Discounting beyond this categorical devaluation for any delay is modeled exponentially. For a

stream of consumptions (c1, c2, …), this can be represented as a quasi-hyperbolic discounting of a consumption stream over time:

$$V = u(c_0) + \beta \sum_{t=1}^{\infty} \delta^t u(c_t) \quad (2)$$

where u is the utility function and parameters β and δ both serve as discount parameters. Note that lower values of β indicate a greater devaluation of all outcomes that are not immediate, and lower values of δ indicate a greater fixed-rate discounting across all periods (identical to equation 1). Because of its distinct (and functionally discontinuous) two-fit parameters, the model is often referred to as beta–delta discounting. The functional discontinuity between delay 0 and 1 describes a dynamically inconsistent individual but preserves space in which standard rationality assumptions prevail (all discounting beyond period 1).

The above beta–delta function is sometimes alternatively referred to as "quasi-hyperbolic" discounting, with reference to its similarity with a second non-exponential functional form – the simple hyperbolic function (Ainslie, 1975; Mazur, 1987). This is the most widely used discounting function within psychology. The hyperbolic discount function describes the dynamic inconsistency like that in the above example, with a value function that includes delay in the denominator. This results in value that is inversely proportional to the delay. In order to allow fitting, a free parameter (typically denoted as k) is attached to time. A constant, usually 1, is added to the denominator in order to avoid the function's approaching infinity as delay approaches 0. The hyperbolic discount function matches the general pattern of the above example. The impact of a difference between two times is small when the more immediate time is far away, but the impact of the same difference is large when the more immediate time is near (or immediate). More generally, motivation is inversely proportional to delay (Strotz, 1955; Ainslie, 1975, 1992, 2001). Present value for a stream of consumptions (c1, c2, …) discounted hyperbolically can be represented as:

$$V = \sum_{t=0}^{\infty} \frac{u(c_t)}{K^* t + 1} \quad (3)$$

where u is the utility function and higher values of the discount parameter k indicate steeper hyperbolic discounting.

Delay Discounting and Addiction

Because, as noted above, the contingencies associated with drug use often entail short-term benefit and long-term costs, it has been repeatedly suggested that individual differences in the steepness by which value is discounted as a function of delay might predict individual differences in drug use and susceptibility to addiction (Ainslie, 1975; Mitchell, 1999; Bickel et al., 2007). Since the theoretical writings on this topic focus on the shape of the discount function as the determiner of rational (exponential) or irrational (hyperbolic and quasi-hyperbolic) choice, it might be anticipated that empirical work would examine whether individual differences in functional form relate to variance in addiction vulnerability. Maybe some people are

exponential – or nearly exponential – discounters and others are more hyperbolic or quasi-hyperbolic, the latter being susceptible to addiction. However, this has generally not been the focus of addiction research. Where it has been considered, researchers have been satisfied to say that the hyperbolic functional form fits better than the exponential form for both drug-naïve and problem drug users (Madden, Bickel, & Jacobs, 1999; Bickel & Marsch, 2001). It is worth noting, however, that there is strong empirical evidence that in fact some individuals do look more exponential in their behavior than others, and recent econometric techniques allow models that include blends of both exponential and hyperbolic discounting as separate data-generating processes (Coller, Harrison, & Rutstrom, 2012). This may open a new area of applied addiction work. However, existent applications of the discounting construct to addiction generally assume hyperbolic discounting, and then look at the fit parameter that best matches the individual or group. The notion is that everyone discounts hyperbolically, but the important difference is how compressed that function is along the X-axis plotting time (Ainslie, 1992; Mitchell, 2003). Thus the focus is more in line with "commonsense" emphasis on the steepness of discounting.

On the basis of these strong theoretical ties, more than 100 studies have been published where the relationship between addiction and discounting was at least one of the comparisons of interest, if not the primary one (Mackillop et al., 2011). A recent meta-analysis of 64 comparisons (from 46 published journal articles) between degree of discounting of addicts and/or heavy users and controls and/or light users observed an effect size with a Cohen's d = .15, while a more restricted analysis of 57 comparisons that excluded less precise methods of measuring discounting produced an effect size of d = 0.58. Correlations to higher levels of delay discounting have been observed in comparing controls to participants dependent on or heavily using alcohol (Petry, 2001), cigarettes (Johnson et al., 2007), cocaine (Bickel et al., 2011), and methamphetamine (Monterosso et al., 2007), but they failed to show an effect for marijuana (Johnson et al., 2010).

BE neuroeconomics of delay discounting and addiction: Beta–delta in the brain?

The short history of neuroimaging investigation of delay discounting provides a clear example of the promise of BE neuroeconomics for understanding addiction. McClure, Laibson, Loewenstein, and Cohen (2004) conducted the first study that paired the typical methodology of intertemporal choice investigation with functional magnetic resonance imaging (fMRI). In their study, which was a collaboration between cognitive neuroscientists and behavioral economists, participants made choices from rewards with values ranging from $5 to $40. The "smaller sooner" option varied in delay between the same day ("today") and a 4-week delay; the "larger later" option was always either 2 or 4 weeks after the "smaller sooner" option. The analytic approach brought to these data was based on the beta–delta model. Recall that this model treats the value of something imminent (now) as discontinuous with value for all future expectancies. The theorists asked whether the modeling duality of beta–delta discounting (equation 2) might correspond to an underlying duality in the neural substrates of valuation. As they put it: "Our key hypothesis is that the pattern of behavior that these two parameters summarize … *stems from the joint influence of distinct neural processes, with [beta] mediated by limbic structures and [delta] by the*

lateral prefrontal cortex and associated structures supporting higher cognitive functions" (McClure et al., 2004, 504). The results seemed to fit the group's prediction, brain regions of the limbic/paralimbic network exhibiting more activity when an immediate reward was present than not, and also more when the immediate reward was chosen than when not. Following the economic model, the group referred to this the "beta" network and contrasted it with regions that were recruited during choice, but not more so when there was an immediate reward (primarily in the lateral prefrontal cortex and parietal cortex), which, following suit, was referred to as the "delta" network (McClure et al., 2004). In a follow-up experiment (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007), the group used brain-imaging data to develop a natural modification of beta–delta that removed the conceptual problematic discontinuity between 0 delay and "any delay" (i.e., what counts as 0 delay?). In the modification, present value for a stream of consumptions (c1, c2, …) is represented as the double exponential discount function:

$$V = \mathrm{w}\sum_{t=0}^{\infty} \beta^t u\,(c_t) + (1-w)\sum_{t=0}^{\infty} \delta^t u\,(c_t) \qquad (4)$$

where u is the utility function and discount parameters β and δ are bounded between 0 and 1, lower values indicating steeper exponential discounting for each of the hypothesized systems, and a weighting parameter *w*, also bounded between 0 and 1, parameterizes the relative contribution of beta and delta systems. The aggregated result is non-exponential, since the differential rates of the two exponential components result in non-uniformity of discount rates across time. From the standpoint of BE neuroeconomics, the proposal from McClure et al. (2007) suggests a potentially dramatic modeling advance, particularly if the parameter *w* (the weighting of the two systems) can be operationalized anatomically (e.g., metabolism, connectivity, or receptor density measures). This back-and-forth between economic modeling and neuroscience is the promise of neuroeconomics. Within addiction research, the above BE neuroeconomic formulation is a highly constructive hypothesis (see Bickel et al., 2007 for discussion). It connects the behavioral literature on steep discounting among addicts to the addiction neuroscience literature that identifies drug-related impairment of prefrontal cortical inhibition of the limbic system (Jentsch & Taylor, 1999; Goldstein & Volkow, 2002). It suggests a clear synchronic competition framing of the addict's ambivalence, and brings the discounting addiction literature in direct contact with neurology-based competing system perspective on addiction (Bechara, 2005). It also suggests a novel way to approach the steep discounting repeatedly reported among addicts. Perhaps the observed steep discounting is a manifestation of an on-average difference in the balance between these systems (captured by *w* in equation 4). Assays measuring the function of these systems could, in principle, be used for both diagnostic purposes, and could identify appropriate therapeutic targets in addiction treatment.

However, careful subsequent attempts to test the beta–delta system competition hypothesis have raised significant doubts about the model (Kable & Glimcher, 2007; Kable & Glimcher, 2010). In one intertemporal choice study, Kable and Glimcher (2007) observed that activation within the network McClure and colleagues identified as "beta regions" was not differentially sensitive to immediacy, but rather tracked overall value. Our own research on value-tracking brain response for immediate and

delayed rewards (Luo, Ainslie, Giragosian, & Monterosso, 2011) was also inconsistent with the beta–delta neural system model. It would be going too far to infer from the unsupportive data that a beta–delta system duality does not exist – delay-discounting tasks are rather tedious for participants and might be ill suited to capture the competition between hypothesized "hot" and "cool" (Metcalfe & Mischel, 1999) systems. Moreover, fMRI is only sensitive to differences based on regional metabolic effects of a particular spatial and temporal scale. Our perspective is that a more circumscribed conclusion is warranted – the field has yet to identify distinct value-tracking networks that differ in their delay discounting during standard intertemporal choice tasks. Others, we should note, view the balance of evidence more favorably for the beta–delta network theory (e.g., Bickel et al., 2007).

One aspect of the McClure et al. (2007) proposal has been repeatedly supported: the functioning of the lateral prefrontal cortex during intertemporal decisions tends to bias choice toward later but larger alternatives. Preference for later larger over sooner smaller options is associated with more activation within the dorsolateral prefrontal cortex (dlPFC; inclusive of BA9) (Weber & Huettel, 2008; Christakou, Brammer, & Rubia, 2011; Luo, Ainslie, Pollini, Giragosian, & Monterosso, 2012). Moreover, evidence outside of neuroimaging suggests that the association between this region and delayed choice may be causal. Using transcranial magnetic stimulation (TMS), Figner and colleagues (2010) observed reduced preference for larger later alternatives when functioning of the left dlPFC was temporarily disrupted. In another relevant study (Cho et al., 2010) where continuous theta burst stimulation (cTBS) was applied to *excite* the dlPFC, the discounting rate was reduced by comparison with a sham condition. In all, the evidence is quite convincing that lateral sectors of the prefrontal cortex do play a role in far-sighted choice.

Subsequent to McClure and colleagues' original paper modeling delay discounting in the brain, a number of research groups have investigated neural correlates of intertemporal choice in populations with abuse of substances like methamphetamine (Monterosso et al., 2007; Hoffman et al., 2008), cocaine (Meade, Lowen, MacLean, Key, & Lukas, 2011), nicotine (Mackillop et al., 2012; Clewett et al., 2014), and alcohol (Boettiger et al., 2007; Boettiger, Kelley, Mitchell, D'Esposito, & Fields, 2009; Claus, Kiehl, & Hutchinson, 2011; Amlung, Sweet, Acker, Brown, & Mackillop, 2012). Like behavioral studies of discounting among similar populations, most of these studies compare participants with substance disorders to groups of one or more types, not limited to controls (including recovered or subclinical participants). The basic question that these studies seek to answer is whether the brain activity during intertemporal choice suggests a possible cause of steep discounting in substance users. In general, the findings reported across these studies have not been consistent with one another. Reasons why this might be include (1) different substances; (2) differences in periods of abstinence before testing; (3) differences in the procedure used (e.g., fixed-choice sets vs. choice sets tailored to the individual's discounting); (4) different models used (e.g., some include regressors for value and/or RT and some do not); and (5) most of the studies are rather underpowered for purposes of group comparison. In light of this, rather than try to summarize the disparate findings, we highlight the largest of these studies. Claus and colleagues (2011) paired a delay discounting with neuroimaging in a sample of 151 individuals who were all at least moderately heavy drinkers (they had five episodes of five or more drinks over the past month). In the primary analyses, the severity of drinking problem was used as a

continuous measure. Severity of drinking was significantly correlated with steeper discounting, where $r(149) = .24$, $p = .003$. Across the entire sample, during the selection of delayed over immediate alternatives, greater discounting and greater drinking severity were both associated with increased recruitment of the anterior orbitofrontal gyrus or anterior insula. Interestingly, a recent study by our group using a similar design with 72 participants (39 of them being nicotine-dependent) also suggested the anterior insula as a possible correlate of the steep discounting associated with addiction. In particular, we observed greater functional connectivity among smokers than among nonsmokers between the anterior insula and the frontoparietal network recruited during decision making. Moreover, greater functional connectivity between the left anterior insula and the frontoparietal network was associated with steeper delay discounting (Clewett et al., 2014). Taken together, we think these results constitute suggestive correlational evidence that the anterior insula and its connectivity play some role in the steep discounting associated with addiction.

Neuroeconomics and Genetics: The Pursuit of Endophenotypes

Pharmacological addictions are considered among the most heritable of psychiatric conditions, ranging between .39 for hallucinogens and .72 for cocaine (Goldman, Oroszi, & Ducci, 2005). The integration of economic behavior and genetics (a field known as geno-economics) is relatively recent, and its application to addiction is still in its infancy (for a recent review, see MacKillop, 2013). There is, however, promising work being done attempting to integrate genetics and behavioral economics as potential endophenotypes for addiction. The moderately high heritability of delay discounting (Anokhin, Golosheykin, Grant, & Heath, 2011) raises the possibility that it may contribute to the overall heritability of addiction. One interesting way to approach this matter is to assess whether family history of addiction (in the absence of problem use for the individual assessed) is associated with steeper discounting. Currently the evidence is mixed (Crean, Richards, & de Wit, 2002; Petry, Kirby, & Kranzler, 2002; Herting, Schwartz, Mitchell, & Nagel, 2010).

Regarding molecular genetic work, the current focus is on dopamine genes, especially in relation to dopamine hypofunction. In a nonclinical sample of young adults, discounting was found to be related to two genetic variants, the possession of at least one DRD2/ANKK13-Taq IA single nucleotide polymorphism (SNP; rs1800497) being related to greater discounting, and the variable number of tandem repeats polymorphism in exon 3 of the dopamine D4 receptor gene (DRD4 VNTR) in combination with the DRD2 A1 allele leading again to greater discounting, though this D4 finding conflicts with work in knock-out mice (Eisenberg et al., 2007). A separate study looking at adults who were C allele carriers of the DRD2 C957T (rs6277) SNP (which is associated with reduced striatal D2 binding) found faster response times, despite no differences in discounting (White, Lawford, Morris, & Young, 2009). Similarly, the COMT val158met SNP (rs4680) has shown a promising relation to discounting. This val allele is associated with greater enzymatic metabolism of dopamine, further implicating a dopamine hypofunction endophenotype (Savitz, Solms, & Ramesar, 2006; MacKillop, 2013). In line with results on variants similarly altering dopamine functioning, alcoholics who are homozygous for this val variant have been

shown to exhibit more impulsive discounting (Boettiger et al., 2007). Additionally, Paloyelis, Asherson, Mehta, Faraone, and Kuntsi (2010) examined genetic variation in DAT1 (the dopamine transporter gene) and showed that people with two copies show more impulsive discounting than those with fewer than two copies.

Animal models have some advantage over human models because they allow researchers to use techniques that are too invasive for human research. In line with human research, rats and mice from alcohol-preferring strains exhibit significantly greater delay discounting when compared to rats and mice from low alcohol-preference strains (Wilhelm & Mitchell, 2008; Oberlin & Grahame, 2009). Additionally, Helms, Gubner, Wilhelm, Mitchell, and Grandy (2008) found no differences in discounting between D4 receptor knock-out mice and wild-type controls. To further demonstrate the genetic link to discounting, researchers have looked at differences between isogenetic inbred strains of rodents with identical rearing environments. Despite some mixed results among studies, results have indicated that there are between strain differences in discounting (Wilhelm & Mitchell, 2009). Overall, work in this area seems to have focused on the dysfunction of dopamine; however, other neurotransmitters have been shown to be involved in the expression of impulsivity and addiction – for example, the administration of a selective serotonin re-uptake inhibitor has been found to reduce impulsivity (Black, Monahan, & Gabel, 1997) – and genetic variants affecting these chemical systems are also worth investigating as potential endophenotypes for addiction. However, given the poor replicability of candidate gene findings (Bearden, Jasinska, & Freimer, 2009), these results should be taken with more than a little caution.

Prospect Theory: Behavioral Economics Most Successful Model

Although we began our discussion of BE neuroeconomics with delay discounting because of its strong links with addiction, the most elaborated and successful BE proposal is Kahneman and Tversky's (1979) prospect theory. Prospect theory provides a general framework for the valuation of possible outcomes ("prospects") without consideration of delay, and so it is conceptually complementary to delay-discounting work. Prospect theory's application to addiction, while theoretically compelling, has not been well developed. We will briefly summarize prospect theory and move quickly to related neuroeconomic work and summarize its relatively sparse application to addiction.

Like hyperbolic discounting, prospect theory was developed to describe behavior that diverges systematically and dramatically (at least in the lab setting) from the tenets of rationality. Prospect theory has been expanded greatly over the years; however, its relation to the neurobiology of addiction primarily falls under the four main tenets of the theory:

1 reference dependence: prospects are valued as gains and losses relative to the perceived status quo;
2 loss aversion: the value function for loss is steeper than the value function for gains (approximately by a factor of 2);
3 diminishing sensitivity: the marginal value of gains and losses decreases with their distance from the reference point.

4 nonlinear probability weighting: people tend to systematically deviate from normative linear probability weighting. In particular, people overweigh very low probabilities (P = .0001 is treated as a greater increase over P = 0 than it should be), they show hyposensitivity to probability differences between low probabilities and near certainty (slope less than 1), and they show hyperdifferentiation between near certainty and certainty.

Tenets 1 through 3 are visually captured in Figure 19.1.

Prospect theory characterizes substantial violations of rationality. The actor's behavior under prospect theory is affected by her point of reference. A point of reference can be shaped by the framing of events, whether externally imposed (as when the discrepancy between a store's price for cash versus credit purchases is described as a discount for cash customers rather than as a surcharge on credit customers) or self-imposed (as when someone who wants to spend money while on holiday without feeling pangs of loss sets an amount aside ahead of time as a planned "fun money" expenditure). It is hard to overstate how powerful reference dependence is. For better and for worse, we have a capacity to adjust relatively quickly to a vast range of circumstances (e.g., (Brickman, Coates, & Janoff-Bulman, 1978), and we react sharply only to changes. If someone with $1,000,000 in savings loses $10,000 and someone else with $0 savings gets a $500 windfall, the latter is likely to be feeling more pleased about her finances, at least briefly.

It is worth noting that prospect theory retains the basic structure of modeling choice through utility functions, albeit utility functions that are inconsistent with neoclassical economics. It is consistent with otherwise anomalous behavior both within (Kahneman & Tversky, 1979) and outside (Gooding, Goel, & Wiseman, 1996) of laboratory contexts, and is, at least by the standards of behavioral economics, parsimonious. Prospect theory's penetration into the mainstream of economics is evidenced by the Nobel Prize in Economics awarded to Kahneman in 2002 (in fact coawarded to him and Vernon Smith – to the latter also for work on a behavioral phenomenon that violates neoclassical models).

While, as noted above, links between prospect theory and addiction have not been well elaborated, we think there are exciting possibilities. Addictive behavior can be

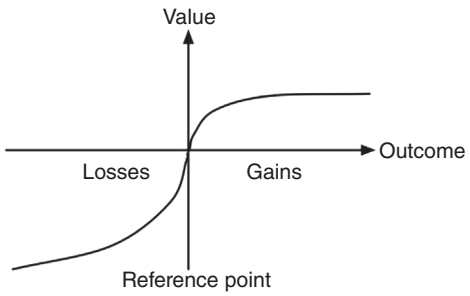

Figure 19.1 Schematic illustrating prospect theory's referenced-based (i.e., gains and losses) utility function. The figure describes risk aversion in the domain of gains, risk affinity in the domain of losses, and a general hypersensitivity to losses relative to gains. Source: Reproduced from Wikipedia (http://commons.wikimedia.org/wiki/File:Valuefun.jpg) and released under the GNU Free Documentation License.

looked at as a series of decisions with shifting reference points, and prospect theory predicts that those shifting reference points can produce dynamic inconsistency. Initiation of drug use involves uncertainty of both gains and potential losses, since the positive feelings that motivate use are unknown, and virtually all possible negative consequences are uncertain. For the moderately experienced (but not addicted) individual, decisions involve certain gains (he knows the pleasure or relief of getting high) with uncertain losses (continued use may or may not lead to an unwanted consequence). For the addict, use has become the status quo, and recovery is based on decisions that involve certain losses (e.g., withdrawal) with uncertain gains ("Can I maintain sobriety? Is there any hope for getting back what was lost?"). Frame-based changes provide a potential *diachronic conflict* mechanism that may contribute to the inconsistency of the addict, since preference between the same alternatives (e.g., to smoke or not smoke) can switch on the basis of changing reference points. Considering the changing frame from the perspective of prospect theory may be particularly useful for understanding the assets and vulnerabilities associated with initial versus extended abstinence during cessation (e.g., considering the changing frame when one, as is often said, *has* X amount of abstinence). Prospect theory suggests a *synchronic conflict* mechanism as well, at least indirectly. The irrationalities of prospect theory may be driven by one system (or collection of systems) that is fast and computationally undemanding, which competes with a more rational but slow and resource-demanding system (Kahneman, 2011). This is similar to the beta–delta formulation discussed in the context of delay discounting. A person who has seen his life fall apart but who still thinks about all he had as the reference point may be so far to the left of zero on the X-axis of Figure 19.1 that the negative value of further loss or the positive value of any new gain in life is minimal. If the frame of reference is changed to the current situation (i.e., acceptance) then the motivational potency of gain and loss may increase. Although empirical work is limited, there is some evidence that general insights from prospect theory can be used to make interventions more effective (e.g., Toll et al., 2007).

Prospect theory is explicitly an account of on-average behavior; there is a specific function mapping objective probability to subjective probability, and gains and losses to value. However, the model invites the possibility of parameterizing individual differences along the same dimensions. Perhaps the relative steepness of gain and loss functions differs meaningfully across people, and perhaps these differences can explain some variance in drug use and addiction. In addiction research, the most extensively studied decision tasks do not allow individual parameterization of prospect theory functions, but can nevertheless be considered from this perspective. We briefly discuss two of these tasks, which are likely sensitive to risk aversion: the Iowa gambling task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994) and the balloon analog risk task (BART) (Lejuez et al., 2002). Unlike in typical behavioral economic tasks, the maximizing alternative is not identifiable on the basis of information presented on individual trials of the IGT and BART. Learning is a critical determinant of performance during these tasks.

The IGT was originally developed to capture the functional deficits among ventromedial prefrontal lesion patients – patients who were largely spared in terms of cognitive functioning, but who experienced marked deficits in social and life functioning (e.g., difficulty maintaining employment and close relationships). Clinically, the patients were described as being insufficiently moved by the contingencies that

guide healthy people (Damasio, 1994). The IGT requires participants to repeatedly choose (typically 100 times) between four decks of cards to earn points. The task explicitly segregates outcomes into gains and losses (e.g., "you gain 50" followed by "but you lose 30") and looks at preference between decks with modest gains but even more modest losses (good decks) and decks with high gains but even higher occasional losses (bad decks). Other things being equal, an individual with greater risk aversion (steeper value function in the domain of losses relative to gains) would be expected to avoid risky decks. If low-risk aversion is associated with substance abuse, relatively high preference for the risky decks would be expected. This result has been generally reported among individuals dependent on various substances including alcohol, cocaine, opioids, and marijuana (Bartzokis et al., 2000; Bechara et al., 2001; Bechara & Damasio, 2002; Mintzer & Stitzer, 2002; for a review, see Buelow & Suhr, 2009).

A second relevant task, the BART, lets participants blow up a computerized balloon by repeatedly pressing a response key. Each simulated pump (1) increases the points that will be received when the participant decides to stop, but also (2) carries a small risk that the balloon will burst, losing any potential reward accumulated for that balloon. A participant who is more averse to risk will cash out sooner (fewer pumps per balloon.) In line with the basic natural prediction for drug abuse and addiction, several studies reported abnormally high numbers of pumps on the BART in relevant populations, including cigarette smokers (Lejuez et al., 2003; Lejuez, Aklin, Bornovalova, & Moolchan, 2005), heavier drinkers (Holmes et al., 2009; Fernie, Cole, Goudie, & Field, 2010) and individuals using illicit drugs (Crowley, Raymond, Mikulich-Gilbertson, Thompson, & Lejuez, 2006; Hopko et al., 2006; though see Dean, Sugar, Hellemann, & London, 2011 for a recent report in which *smokers* exhibited progressively *greater* risk aversion than nonsmokers).

Although risk aversion is a conceptually plausible link between the key constructs of prospect theory and performance on both the IGT and the BART, the tasks require learning, and so the degree to which variance in risk behavior on these tasks relates to variance in risk preference versus learning is unclear. Also, like the delay-discounting literature, longitudinal studies are particularly valuable for distinguishing between the possibilities that low-risk aversion precedes drug taking and the possibility that low-risk aversion is a consequence of chronic drug use. Presently longitudinal data with these tasks are scarce.

The Neuroeconomics of Reference-Dependent Decision Making

Does the fundamental tendency to adjust to the status quo and respond to gains and losses reflect the functioning of biologically distinct systems? We will refer to this possibility broadly as the *approach versus withdrawal* separation hypothesis, although similar designations are used elsewhere, such as approach versus inhibit, approach versus avoid, or reward versus punishment systems (Craig, 1918; Schneirla, 1959; Lang, Bradley, & Cuthbert, 1990; Gray, 1994; Knutson & Greer, 2008). It is, of course, a primarily synchronic possible mechanism for the conflict of addiction.

In order to accommodate the gain–loss asymmetry (and implied risk aversion), a withdrawal system must, on average, be more sensitive than the approach system (e.g., the motivational withdrawal response elicited by the anticipation of losing $10

must be greater than the approach response elicited by the prospect of gaining $10). Neuroscience investigation of these systems can be conceived of as neuroeconomic, since it naturally can be linked to the reference-based decision making (characterized in Figure 19.1). There are two critical components to the hypothesis: first, that there is neurobiological *heterogeneity between* these categories of motivation (i.e., that the two have distinct neural substrates); and, second, that there is some degree of *homogeneity within* these categories (e.g., sexual and food approach share commonality). Like the previously discussed beta–delta hypothesized dissociation, this systems-level dissociation between approach and withdrawal remains controversial. From the standpoint of addiction, as with intertemporal choice, the idea of separate systems for approach and withdrawal motivations is attractive, because individual differences in the relative potency of the systems could explain differential vulnerability to addiction. We briefly summarize some of the relevant evidence related to the hypothesized approach – withdrawal dissociation (for a detailed and compelling synthesis, see Knutson & Greer, 2008).

The approach system

"Approach motivation" or "wanting" (Berridge & Robinson, 1998; Kelley & Berridge, 2002) has been extensively applied to addiction. Wanting appears to be linked to mesolimbic dopamine signaling. Midbrain dopamine neurons projecting from the ventral tegmental area to the nucleus accumbens are strongly implicated in approach motivation (Schultz, 1998; Setlow, Schoenbaum, & Gallagher, 2003).[1] Additional components of what has been characterized as the basic "approach module" (Schultz, 1998; Setlow et al., 2003; Ikemoto, 2010) include the supramammillary nucleus (Olds & Olds, 1963), the rostromedial tegmental nucleus (Jhou, Geisler, Marinelli, Degarmo, & Zahm, 2009), and the median and dorsal raphe nuclei (Miliaressis, Bouchard, & Jacobowitz, 1975; Rompre & Miliaressis, 1985). One of the most striking demonstrations in the human literature of the mesolimbic dopamine system's involvement in approach motivation comes from the use of the dopamine precursor L-dopa for the treatment of Parkinson's disease. Some patients receiving this treatment develop both abuse of the drug itself and secondary maladaptive excessive approach behaviors such as binge eating and compulsive gambling (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000). These syndromes are generally manifest in patients who respond to the drug with greater ventral striatal dopamine release, which is also correlated with self-reported "wanting" of the medication (Evans et al., 2006). FMRI studies using a range of reinforcers also implicate regions of the mesolimbic dopamine system (for a recent meta-analysis, see Garrison, Erdeniz, & Done, 2013). In a meta-analysis that used activation likelihood estimation (ALE) to synthesize results from 12 studies, the anticipation of possible gains (relative to a neutral period) was associated with greater likelihood of activation than was anticipation of possible losses (also relative to neutral) in several regions, including the nucleus accumbens (bilaterally), the right putamen, and the medial frontal gyrus (Knutson & Greer, 2008); the result implicated these regions in approach motivation. Although fMRI does not allow for the measurement of specific neurotransmitter activity, there is evidence that change in the nucleus accumbens' blood oxygen level-dependent (BOLD) signal can be driven by dopamine signaling, probably through agonism of postsynaptic D1 receptors (Knutson & Gibbs, 2007; Schott et al., 2008).

Hypothesized withdrawal system

Several studies appear to implicate the periaqueductal gray, the anterior insula, and the amygdala as particularly important to the withdraw/loss side of the suggested approach–withdrawal motivational divide (Kahn et al., 2002; Kuhnen & Knutson, 2005; De Martino, Camerer, & Adolphs, 2010). To give one particularly compelling example from the human fMRI literature, Mobbs and colleagues had participants play a videogame reminiscent of Pac-Man, in which participants pressed buttons to move within a simple maze so as to avoid a character who was giving chase. In some conditions, the consequence of being caught was electric shock. When the player was close to being caught, there was a robust signal increase within the periaqueductal gray. Also, within subjects, the signal increase in the periaqueductal gray was greater in a high-shock than in a low-shock condition. And, further, between-subject variance in signal within the periaqueductal gray activity in association with the shock conditions was positively correlated with greater reports of subjective dread of being caught during the task (Mobbs et al., 2007). The set of findings is consistent with reports of fear and anxiety in humans during electrical stimulation of the periaqueductal gray (Nashold, Wilson, & Slaughter, 1969; Iacono & Nashold, 1982). Also of interest, in the previously mentioned ALE-based meta-analysis comparing gain and loss anticipation, the anticipated loss was more likely than the anticipated gain to recruit significant signal change in regions that included the bilateral anterior insula (though on the right a neighboring cluster was more associated with approach), the bilateral caudate, and the rostral sector of the midbrain (the right red nucleus) (Knutson & Greer, 2008).

In addition to the evidence presented above for a partial dissociation of approach and withdrawal motivation, it has also been suggested that there is prefrontal hemispheric asymmetry, the left cortical hemisphere being differentially involved in approach motivation and the right being involved in withdrawal drives (Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Sutton & Davidson, 1997). Although most of the supporting evidence for this hypothesis came from electroencephalography (EEG) work (Davidson et al., 1990), some recent fMRI studies (Herrington et al., 2005; Berkman & Lieverman, 2010) also observed prefrontal cortex (PFC) asymmetries for approach and withdrawal motivation. No evidence of cortical hemispheric asymmetry was observed in the aforementioned ALE meta-analysis (Knutson & Greer, 2008).

This neuroscience work dissociating approach and withdrawal systems was, of course, largely unconcerned with prospect theory or addiction. But the potential implications for both are obvious. The central component of prospect theory's gain–loss valuation may be rooted in a fundamental dissociation of brain architecture. If so, then one might be able to use neurobiological measurements to fit the parameters of prospect theory. Perhaps the relative potency of the approach and withdrawal systems would predict variance in individuals' degree of risk aversion in binary-choice gambles. Perhaps it might be applied to understand variability in addiction vulnerability both across individuals and within the same individual at different points in time. The separation between approach and withdrawal systems could in principle be linked with synchronic motivational conflict. Moreover, changes in the relative potency of these systems may create diachronic conflict. Understanding such changes (for example, caused by emotion or by pharmacological intervention) may lead to intervention targets.

However, one important study should be considered, which gives pause with regard to the optimistic characterization above. Tom, Fox, Trepel, and Poldrack (2007) used a procedure specifically designed to investigate the neural correlates of prospect theory's loss aversion. They endowed participants with money, and then presented them with gambles that they could either accept or reject. Because the potential gains and the potential losses were orthogonal and varied parametrically, distinct regions tracking the potential gain (approach) and the potential loss (withdrawal) components of the gambles could, in principle, be identified. Instead the authors observed an activation that tracked the overall expected value of the gambles (that is, the integration of gains and losses). Moreover, this value tracking matched the preferences, as well as the basic asymmetry of prospect theory's gain–loss value function. They observed no "withdrawal regions" – no regions that specifically tracked the potential loss of gambles.

It would be going too far to infer from Tom et al.'s (2007) findings that human risk preferences do not involve inputs from distinct approach and withdrawal networks. One possibility is, again, that approach and withdrawal systems were relevant, but did not produce the type of signal to which BOLD fMRI is sensitive (large changes in the ratio of oxygenated to deoxygenated hemoglobin). Suggestively, a recent investigation of two amygdala lesion patients with previously documented deficits in fear response observed abnormally low sensitivity to the loss component of binary-choice lotteries (De Martino et al., 2010).

Another possibility with regard to the implications of Tom et al.'s (2007) data is that perhaps there are withdrawal-specific neural pathways, but that the particular task used did not recruit them. Consider the sense of risk one might experience when picking a stock for the very first time. Compare this person with someone who trades stocks on a daily basis. The latter might develop a global strategic orientation that becomes the only process robustly engaged during decision making. Presumably realization that there is a very promising opportunity would engage the systems that track value. But the sense of imminent risk experienced by the first-time investor may be attenuated or altogether absent. It may still be true that withdrawal networks engaged at an earlier point shaped the strategic orientation, even if they are no longer engaged regularly during the task (which would be consistent with the amygdala lesion finding related to risk aversion, discussed above).

Relevant Neurobiological Abnormalities in Substance Abuse and Dependence

Have approach-neutral versus withdrawal-neural systems been linked to addiction? Going beyond the evidence already cited benefits from brain imaging probes that separately tax these systems. The IGT (discussed above) is not designed to separate between approach motivation and withdrawal motivation, since the key independent variables of potential gain and potential loss are confounded (e.g., possible high-gain decks are also possible high-loss decks). However, neuroimaging work with the task may provide some suggestions with regard to links between addiction and individual differences in the parameters used in prospect theory. Abnormal performance on the IGT has been strongly linked with ventral medial PFC dysfunction, and substance dependent individuals perform poorly on the task (Bechara et al., 2001). Cousijn

et al. (2012) found that heavy cannabis users show enhanced activation during wins when contrasted with loss in the right orbitofrontal cortex, right insula, and left superior temporal gyrus. Furthermore, they observed a positive relationship between degree of cannabis use and win versus loss activity disparity in the right insula, right caudate, and right ventral lateral PFC – and, additionally, a higher disparity in the right superior frontal gyrus that predicted increased cannabis use at a 6-month follow-up. Wesley, Hanlon, and Porrino (2011) used the same task and found no functional differences between marijuana users and controls during gain. However, when looking at gain + loss response compared with baseline, controls had an enhanced activity of the anterior cingulate cortex (ACC) and medial frontal cortex. During loss evaluation (loss contrasted with baseline), marijuana users showed reduced activity of the ACC and medial frontal cortex. In contrast to the work by Cousijn et al. (2012), this paper found that marijuana users did not improve their performance over time and that in controls (but not in marijuana users) the magnitude of response in the ACC, medial prefrontal cortex, and rostral prefrontal cortex during the early portion of the task positively correlated with an increased choice of the "good" decks.

The monetary incentive delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005) is better suited for differentiating anticipatory responses to gains versus losses and has been repeatedly used in addiction research (though mostly in variants that focus on gains). In each trial of the task, the individual is first shown a potential gain or (in some versions) a potential loss. They then must wait a few seconds for a target to appear. When it does, they respond as quickly as they can with a button press. A fast press is rewarded with either receipt of the gain or avoidance of the loss. Analyses focus on the anticipation period – the few seconds when the participant is anticipating and trying to realize a possible gain, or anticipating and trying to avoid a possible loss. Although there is some evidence of striatal hyperactivity during reward anticipation among chronic marijuana smokers (Nestor, Hester, & Garavan, 2010), most evidence is consistent with the opposite, perhaps surprising, conclusion: during the anticipation of non-drug reward, drug users exhibit hypoactivity in the ventral striatum (Wrase et al., 2007; Beck et al., 2009; van Hell et al., 2010; Peters et al., 2011). In relation specifically to cigarette smoking, where the issue has been most thoroughly examined, evidence is mixed with regard to the basis of the observed association between low reward anticipation and smoking. Müller and colleagues recently reported that adolescents who had been exposed to maternal smoking *in utero* exhibited low reward anticipation (Muller et al., 2013). Although the authors emphasize the possibility that fetal exposure played a causal role, it is possible that the association was related to other factors (including genetic ones) associated with maternal smoking. Interestingly, among monozygotic twins discordant for smoking, lower reward-anticipation activity during the task was observed in the smoking co-twins (Lessov-Schlaggar et al., 2013). However, other pieces of evidence are more consistent with the idea that hyporesponsivity during reward anticipation precedes smoking. Most directly, adolescents who had tried smoking but had smoked on fewer than 10 occasions (so who were unlikely to have exposure effects) also exhibited hyporesponse in the ventral striatum during reward anticipation (Peters et al., 2011). Also more in line with the risk-factor hypothesis, low reward anticipation has been repeatedly observed among nonsmoking adolescents with ADHD (Plichta & Scheres, 2014), itself a risk factor for smoking (Milberger, Biederman, Faraone, Chen, & Jones, 1997). However, in order to directly link this

work with prospect theory, it is necessary to measure *loss*-anticipation sensitivity as well. Although there is some work on this topic (e.g., Bjork, Knutson, & Hommer, 2008), more is needed before a general conclusion can be reached.

Neurocellular Economics and Reinforcement Learning

As noted at the outset, there is a "neuroeconomics" that is quite distinct from the BE neuroeconomics area we have thus far covered. This alternative perspective was developed by neurophysiologists interested in decision making, who looked to economics for a framework for modeling the behavior of populations of neurons. Following Ross and Harris, we refer to this as neurocellular economics. Within this area, work on value-based reinforcement that produces "habit" responses is most directly relevant to addiction. But, as was alluded to earlier, there is disagreement over whether this area should be considered part of neuroeconomics. For example, van der Meer and Redish (2010) suggest applying the term only to deliberative/goal-directed behavior. Habit-based motivation is, on this view, outside the explanatory domain of neuroeconomics. One justification for this position is that work on habits is not closely tied to economics. Indeed, there is an extensive literature on "reinforcement learning" (RL) neuroscience that substantially predates the term "neuroeconomics," so post-hoc classification of this area as "neuroeconomics" may strike the RL researcher as odd (or worse, since some of what gets classified as neuroeconomics is viewed by many as overhyped).

However, those good arguments notwithstanding, many prominent RL researchers have embraced the term (Montague, 2007; Schultz, 2008), and RL is well covered in treatments of neuroeconomics (see Chapters 15, 16, and 17 in). Indeed much interesting work associated with neuroeconomics deals directly with the interplay between goal-directed motivations and value-based outputs from other systems, including the habit system (Daw, Niv, & Dayan, 2005; Rangel, Camerer, & Montague, 2008). We therefore include discussion of this literature in our review of neuroeconomics. Although its classification in neuroeconomics is debatable, the relevance of this area – whatever its label – to addiction is widely accepted.

Neuroeconomics and Reinforcement Learning of the Habit System

Deliberative action based on models of the world is among the nervous system's most impressive capacities. The capacity allows us (and other mammals) to carry out approximate simulations before taking potentially costly action. But this type of processing has important limitations. Foremost, it is slow and demanding of attentional resources. We may be fully capable of working out the shortest driving path to some new destination, but doing so will take a bit of time and concentration. Compare this with the action selections necessary to go to work along the same old route you have taken almost daily for years. Navigating here is effortless – it can be done even as music or conversation fills conscious awareness. The action sequence has become a habit.

The habit system is thought to be dependent on the dorsolateral striatum and its dopaminergic afferents (Yin, Knowlton, & Balleine, 2004; Balleine, 2005). Habitual behavior does not require attention – and indeed, in the absence of attention, it will

occur even if is is incongruent with actual goals, as when one finds oneself entering the highway absent-mindedly when the intended destination is elsewhere. Indeed, habitual behavior can be operationally defined by this insensitivity to predictable outcomes (Dickinson & Balleine, 2002). When the driver suddenly realizes, "oops, I am going the wrong way," there is a corresponding transfer of control out of the habit system. At least at a superficial level, "insensitivity to predictable outcomes" fits the behavior of the addict. This suggests diachronic conflict as a candidate model for addiction; perhaps the "potent but inconsistent" motivations of addiction relate to a habit system that overpowers the deliberative system.

As in delay discounting and prospect theory, a "value" construct is central to work on habits. The habit system is thought to operate through the association of an action or situation with its *value*. It is sometimes referred to as a "caching" system, since it allows value to be directly accessed in later encounters, without forward modeling of how a particular action might unfold. Research in this area has generated a rich back-and-forth between computational modeling and neurophysiological measurement (Montague, Dayan, & Sejnowski, 1996; Schultz, Dayan, & Montague, 1997; Barto, Sutton, & Anderson, 2012). The class of "temporal difference reinforcement learning" (TDRL) models is particularly relevant to addiction, since dopamine signaling within the mesolimbic "reward pathway" is thought to be critical to both (Di Chiara & Imperato, 1988; Montague et al., 1996; Barto et al., 2012). In TDRL models, "prediction error" is the difference between the value received (usually following a choice) and the value expected given the prior state and action and given the organism's prior learning history (Di Chiara & Imperato, 1988). It is reasonable, therefore, to expect that RL models might inform mathematical hypotheses to explain addiction as a learning phenomenon (Montague, Hyman, & Cohen, 2004).

In RL work value is singular, all specific rewards being placed on the same scale. When a reward is of greater value than anticipated, prediction error is positive, and when a reward is of lower value, prediction error is negative. Normatively, prediction error has long been specified as a formalization that could be used to model learning associations among stimuli or between stimuli and responses (Rescorla & Wagner, 1972). Formally, an RL model is a mathematical formulation designed to capture features of learning. An environment is defined, and the model attempts to learn actions by trial and error. Thus, if the model chooses action α_t on the t trial and receives reward or punishment r_t, then the prediction error for a transition between states t and t+1 is expressed as:

$$\delta = r_t + \gamma V(s_{t+1}) - V(s_t) \tag{5}$$

where $V(s_t)$ is the estimated value for state s_t and $0 < \gamma < 1$ is a discounting factor indicating the effects of delay for one time unit in observing the next state, s_{t+1}. The model observes s_t and receives r_t as its outcome. So the estimated value for s_t after this observation can be r_t (the immediate outcome) plus the value of the following state (s_{t+1}). By contrast, the estimated value for s_t before this observation is $V(s_t)$. So, in fact, prediction error is the difference between the estimated value for s_t after observing its outcome, $r_t + V(s_{t+1})$, and the estimated value before this observation, $V(s_t)$. The estimated value is updated with this prediction error and the estimated value before this observation, V(st):

$$V(s_t) \leftarrow V(s_t) + \alpha\delta \tag{6}$$

where α is the learning rate, which indicates the speed of learning. This simple reinforcement model "learns" the values of states with prediction error computed on each trial. After enough time, when the estimations of state values of the model approach the realized values, the prediction error approaches zero.

The first of the RL model of addiction was suggested by Redish (2004). In his framework, the direct neuropharmacological effect of abused drugs on striatal dopamine partly mimics the dopamine activity that encodes the "prediction error." *Bona fide* prediction errors reinforce a behavior only as long as the rewards are unpredictable. In Schultz's landmark work, when a tone was followed by juice, the VTA dopamine neurons projecting to the nucleus accumbens initially fired only to the juice (Schultz et al., 1997). However, after many tone–juice pairings, the same cells began to fire to the tone and *not* to the juice. This is consistent with prediction error models: after sufficient reinforcement, the tone signaled a transition to a state with greater value, while the subsequent delivery of juice was fully predicted. At this point learning has reached its peak. However, if instead of juice the reward is a drug that pharmacologically causes an increase in striatal dopamine activity that mimics prediction error, then reinforcement will continue ad infinitum. Hence the habit strength can grow beyond what natural rewards can produce. This simple and abstract model proposes a computational way to explain why dependency on a drug increases with the duration of exposure to that drug. It obviously addresses the "potency" side of "potent but inconsistent." And, since outcome-based (goal-directed) motivation diverges from the hypothesized pathologically strong habits, the model indirectly addresses the "inconsistent" quality as well.

Of course, the account above is specific to drugs with some DA agonist component. This entails two related major limitations. First, it is not clear from the model why some people would be able to use a dopamine agonist drug for a long time without developing an addiction. Second and more importantly, since the crucial mechanism of the model is an exogenously produced faux prediction error, the model has no explanation for the addiction to natural rewards (Ahmed, 2004) such as food (Volkow, Wang, Fowler, & Telang, 2008) and gambling (Potenza, 2008). If one is impressed by the similarity of non-drug and drug addictions, then one has reason to doubt the faux prediction error explanation of either. Nevertheless, the back-and-forth between normative models and experimental data has evident momentum.

Neuroeconomics and Recovery

We have thus far focused on neuroeconomic approaches to understanding problematic motivations, ignoring the process by which the majority of individuals who face these problems eventually overcome them, to varying degrees. How can neuroeconomics address self-control and recovery from addiction? For synchronic models, this is at least conceptually very straightforward. Self-control is conceived of as a particular brain-based motivational system prevailing over another – delta-network over beta-network; goal-directed output over habit output; withdrawal motivation (perhaps) over approach motivation. There is now a large and productive literature that focuses on the neuroscience of self-control from a synchronic competition perspective (Jentsch & Taylor, 1999; Bechara & van der Linden, 2005; Goldstein & Volkow, 2011). Neuroeconomics provides measurement tools that are beginning to be exploited to

sharpen work on these types of models (Hare, Camerer, & Rangel, 2009). However, the diachronic perspective on recovery has not been as well integrated into neuroeconomics. And thus we wish to briefly note this essential project for the field.

What happens when someone tries to overcome a "potent but inconsistent" motivation? The inconsistency of the addict trying to quit is accompanied by a protracted internal battle. Informally, the individual who decides to quit forms a plan in her mind about her behavior into the extended future – for example, "I will never smoke again." Often the plan is conceived with awareness that it may be undermined by one's future self. And so the plan is made with some special emphasis that gets called a "resolution." Although it of course often fails, the resolution is an attempt by the individual to affect or manipulate her future self. If it has any effect, the resolution must somehow impact the value-related activity of neural systems during the moment when the individual make the critical decision, in this case, to smoke or not smoke. But by what mechanism does this happen?

We think there have been some convincing suggestions made (see Ainslie, 1992; Hare & Bodner, 2003). The heart of these suggestions lies in the individual's capacity to affect her future self's perceived contingencies by linking the problematic behavior with some added implication. Smoking the cigarette after resolving never to smoke again does not merely entail the negative consequences of one cigarette (which are small and remote). My larger expectation that I will become a former smoker, or even that I am a strong person, is now riding on the decision. Forgoing the cigarette has taken on extra incentive, because it has become a test case of *something*. While this is of course a loose characterization, it can be formally modeled using the tools of economics (see Prelec & Bodner, 2003). Neuroeconomics can take formalizations of this process and use them to identify the critical neural substrates. Doing so would begin to address the great distance between reductionist neuroscience accounts of willpower and the rich and complex internal experiences that go with efforts to overcome addiction.

Note

1 Although prospect theory does not address learning, Ikemoto (2010) argues that reward is ultimately best defined operationally as whatever leads to approach motivation. This view makes reinforcement learning and approach motivations ultimately two sides of the same coin.

References

Ahmed, S. H. (2004). Addiction as compulsive reward prediction. *Science*, 306: 1901–1902.

Ainslie, G. (1975). Specious reward: A behavioral theory of impulsiveness and impulse control. *Psychological Bulletin*, 82(4): 463–496.

Ainslie, G. (1992). *Picoeconomics: The strategic interaction of successive motivational states within the person*. Cambridge: Cambridge University Press.

Ainslie, G. (2001). *Breakdown of will*. Cambridge: Cambridge University Press.

Alessi, S., Badger, G., & Higgins, S. (2004). An experimental examination of the initial weeks of abstinence in cigarette smokers. *Experimental and Clinical Psychopharmacology*, 12(4): 276–287.

Amlung, M. T., Sweet, L. H., Acker, J., Brown, C. L., & Mackillop, J. (2012). Dissociable brain signatures of choice conflict and immediate reward preferences in alcohol use disorders. *Addiction Biology*, 19(4): 1–11. doi: 10.1111/adb.12017.

Anokhin, A. P., Golosheykin, S., Grant, J. D., & Heath, A. C. (2011). Heritability of delay discounting in adolescence: A longitudinal twin study. *Behavioral Genetics*, 41(2): 175–183.

APA. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association.

Arrow, K. (1986). Rationality of self and others in an economic system. *The Journal of Business*, 59(4): S385–S399.

Balleine, B. (2005). Neural bases of food-seeking: Affect, arousal and reward in corticostriatolimbic circuits. *Physiology & Behavior*, 86(15): 717–730.

Barto, A. G., Sutton, R. S., & Anderson, C. W. (2012). Neuronlike adaptive elements that can solve difficult learning control problems. *IEEE Transactions on Systems, Man, and Cybernetics*, 13(5): 834–846.

Bartzokis, G., Beckson, M., Lu, P. H., Edwards, N., Rapoport, R., Wiseman, E., & Bridge, P. (2000). Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: Implications for addiction research. *Psychiatry Research: Neuroimaging*, 98(2): 93–102.

Bearden, C., Jasinska, A., & Freimer, N. (2009). Methodological issues in molecular genetic studies of mental disorders. *Annual Review of Clinical Psychology*, 5: 49–69.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience*, 8(11), 1458–1463. doi: 10.1038/nn1584.

Bechara, A., & Damasio, H. (2002). Decision-making and addiction. Part I: Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia*, 40(10): 1675–1689.

Bechara, A., & van der Linden, M. (2005). Decision-making and impulse control after frontal lobe injuries. *Current Opinion in Neurology*, 18(6): 734–739.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1–3): 7–15.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, 39(4): 376–389.

Beck, A., Schlagenhauf, F., Wustenberg, T., Hein, J., Kienast, T., Kahnt, T., … Wrase, J. (2009). Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biological Psychiatry*, 66: 734–742.

Berg, N., & Gigerenzer, G. (2010). As-if behavioral economics: Neoclassical economics in disguise? *History of Economic Ideas*, 18(1): 133–166.

Berkman, E., & Lieverman, M. (2010). Approaching the bad and avoiding the good: Lateral prefrontal cortical asymmetry distinguishes between action and valence. *Journal of Cognitive Neuroscience*, 22(9): 1970–1979.

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

Bickel, W. K., & Marsch, L. A. (2001). Toward a behavioral economic understanding of drug dependence: Delay discounting processes. *Addiction*, 96(1): 73–86.

Bickel, W. K., Christensen, D. R., Jackson, L., Jones, B. A., Kurth-Nelson, Z., & Redish, A. D. (2011). Single and cross commodity among cocaine addicts: The commodity and its temporal location determine discounting rate. *Psycopharmacology*, 217(2): 177–187.

Bickel, W. K., Miller, M. L., Yi, R., Kowal, B. P., Lindquist, D. M., & Pitcock, J. A. (2007). Behavioral and neuroeconomics of drug addiction: Competing neural systems and temporal discounting processes. *Drug and Alcohol Dependence*, 90: S85–S91.

Bjork, J. M., Knutson, B., & Hommer, D. W. (2008). Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction*, 103(8): 1308–1319.

Black, D. W., Monahan, P., & Gabel, J. (1997). Fluvoxamine in the treatment of compulsive buying. *The Journal of Clinical Psychiatry*, 58(4): 159–163.

Boettiger, C. A., Kelley, E. A., Mitchell, J. M., D'Esposito, M., & Fields, H. L. (2009). Now or Later? An fMRI study of the effects of endogenous opioid blockade on a decision-making network. *Pharmacology, Biochemistry and Behavior*, 93(3): 291–299. doi: 10.1016/j.pbb.2009.02.008.

Boettiger, C. A., Mitchell, J. M., Tavares, V. C., Robertson, M., Joslyn, G., D'Esposito, M., & Fields, H. L. (2007). Immediate reward bias in humans: Fronto-parietal networks and a role for the catechol-O-methyltransferase 158Val/Val Genotype. *The Journal of Neuroscience*, 27(52): 14383–14391. doi: 10.1523/JNEUROSCI.2551-07.2007.

Brickman, P., Coates, D., & Janoff-Bulman, R. (1978). Lottery winners and accident victims: Is happiness relative? *Journal of Personality and Social Psychology*, 36(8): 917–927.

Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the Iowa gambling task. *Neuropsychology Review*, 19(1): 102–114. doi: 10.1007/s11065-009-9083-4.

Cho, S. S., Ko, J. H., Pellecchia, G., Van Eimeren, T., Cilia, R., & Strafella, A. P. (2010). Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. *Brain Stimulation*, 3(3): 170–176.

Christakou, A., Brammer, M., & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *Neuroimage*, 54(2): 1344–1354.

Claus, E. D., Kiehl, K. A., & Hutchinson, K. E. (2011). Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, 35(7): 1209–1219. doi: 10.1111/j.1530-0277.2011.01455.x.

Clewett, D., Luo, S., Hsu, E., Ainslie, G., Mather, M., & Monterosso, J. R. (2014). Increased functional coupling between the left fronto-parietal network and anterior insula predicts steeper delay discounting in smokers. *Human Brain Mapping*, 35(8): 3774–3787. doi: 10.1002/hbm.22436.

Coller, M., Harrison, G. W., & Rutstrom, E. E. (2012). Latent process heterogeneity in discounting behavior. *Oxford Economic Papers*, 64(2): 375–391.

Cousijn, J., Wiers, R., Ridderinkhof, R., van den Brink, W., Veltman, D., Porrino, L., & Goudriaan, A. (2012). Individual differences in decision making and reward processing predict changes in cannabis use: A propsective functional magnetic resonance imaging study. *Addiction Biology*, 18: 1013–1023.

Craig, W. (1918). Appetites and aversions as constituents of instincts. *The Biological Bulletin*, 34(2): 91–107.

Crean, J., Richards, J. B., & de Wit, H. (2002). Effect of tryptophan depletion on impulsive behavior in men with or without a family history of alcoholism. *Behavioral Brain Research*, 136(2): 349–357.

Crowley, T. J., Raymond, K. M., Mikulich-Gilbertson, S. K., Thompson, L. L., & Lejuez, C. W. (2006). A risk-taking "set" in a novel task among adolescents with serious conduct and substance problems. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(2): 175–183.

Damasio, A. R. (1994). *Descartes' error*. New York: G. P. Putnam's Sons.

Davidson, R., Ekman, P., Saron, C., Senulis, J., & Friesen, W. (1990). Approach–withdrawal and cerebral asymmetry: Emotional expression and brain physiology. *Journal of Personality and Social Psychology*, 58(2): 330–341.

Daw, N., Niv, Y., & Dayan, P. (2005). Uncertainty-based competition between frontal and dorsolateral striatal systems for behavioral control. *Nature Neuroscience*, 8: 1704–1711.

De Martino, B., Camerer, C. F., & Adolphs, R. (2010). Amygdala damage eliminates monetary loss aversion. *Proceedings of the National Academy of Sciences*, 107(8): 3788–3792.

Dean, A., Sugar, C., Hellemann, G., & London, E. (2011). Is all risk bad? Young adult cigarette smokers fail to take adaptive risk in a laboratory decision-making test. *Psychopharmacology*, 215(4): 801–811.

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences*, 85(14): 5274–5278.

Dickinson, A., & Balleine, B. (2002). The role of learning in the operation of motivational systems. In H. Pashler & R. Gallistel (Eds.), *Steven's handbook of experimental psychology, Vol. 3; Learning, motivation and emotion*, pp. 497–533. New York: John Wiley.

Edwards, W. (1954). The theory of decision making. *Psychological Bulletin*, 51(4), 380–417.

Eisenberg, D. T., MacKillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., … Wilson, D. S. (2007). Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavior and Brain Functions*, 3, 2. doi:10.1186/1744-9081-3-2.

Elster, J. (1979). *Ulysses and the Sirens: Studies in rationality and irrationality.* Cambridge: Cambridge University Press.

Evans, A. H., Pavese, N., Lawrence, A. D., Tai, Y. F., Appel, S., Doder, M., … Piccini, P. (2006). Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Annals of Neurology*, 59(5): 852–858.

Fernie, G., Cole, J. C., Goudie, A. J., & Field, M. (2010). Risk-taking but not response inhibition or delay discounting predict alcohol consumption in social drinkers. *Drug and Alcohol Dependence*, 112(1–2): 54–61.

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience*, 13(5): 538–539.

Friedman, M. (1971). *Essays in positive economics.* Chicago, IL: University of Chicago Press.

Garrison, J., Erdeniz, B., & Done, J. (2013). Prediction error in reinforcement learning: A meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, 37(7): 1297–1310.

Giovannoni, G., O'Sullivan, J. D., Turner, K., Manson, A. J., & Lees, A. J. L. (2000). Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *Journal of Neurology, Neurosurgery & Psychiatry*, 68(4): 423–428.

Glimcher, P., & Fehr, E. (2013). *Neuroeconomics, Second Edition: Decision Making and the Brain*. London: Academic Press.

Glimcher, P. W., Camerer, C. F., Fehr, E., & Poldrack, R. A. (2009). Introduction: A brief history of neuroeconomics. In P. W. Glimcher, C. F. Camerer, E. Fehr, & R. A. Poldrack (eds.) *Neuroeconomics: Decision Making and the Brain*, pp. 1–13. New York: Academic Press.

Goldman, D., Oroszi, G., & Ducci, F. (2005). The genetics of addictions: Uncovering the genes. *Nature Reviews Genetics*, 6: 521–532.

Goldstein, R. Z., & Volkow, N. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159(10): 1642–1652. doi: 10.1176/appi.ajp.159.10.1642.

Goldstein, R., & Volkow, N. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, 12: 652–669.

Gonzalez, C., Dana, J., Koshino, H., & Just, M. (2005). The framing effect and risky decisions: Examining cognitive functions with fMRI. *Journal of Economic Psychology*, 26: 1–20.

Gooding, R., Goel, S., & Wiseman, R. (1996). Fixed versus variable reference points in the risk-return relationship. *Journal of Economic Behavior & Organization*, 29(2): 331–350.

Gray, J. A. (1994). *Three fundamental emotion systems. In The nature of emotion: Fundamental questions.* Oxford: Oxford University Press.

Gul, F., & Pesendorfer, W. (2008). The case for mindless economics. In A. Caplin and A. Schotter (Eds.), *The foundations of positive and normative economics: A handbook*, pp. 3–42. Oxford: Oxford University Press.

Hanson, C. (2009). *Thinking about addiction: Hyperbolic discounting and responsible agency*. Amsterdam, Netherlands: Rodopi.

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*, 324(5927): 646–648.

Harrison, G., & Ross, D. (2010). The methodologies of neuroeconomics. *Journal of Economic Methodology*, 17(2): 185–196.

Heather, N. (1998). A conceptual framework for explaining drug addiction. *Journal of Psychopharmacology*, 12(1): 3–7.

Helms, C. M., Gubner, N. R., Wilhelm, C. J., Mitchell, S. H., & Grandy, D. K. (2008). D4 receptor deficiency in mice has limited effects on impulsivity and novelty seeking. *Pharmacology, Biochemistry and Behavior*, 90(3): 387–393.

Herrington, J., Mohanty, A., Koven, N., Fisher, J., Stewart, J., Banich, M., … Heller, W. (2005). Emotion-modulated performance and activity in left dorsolateral prefrontal cortex. *Emotion*, 5(2): 200–207.

Herting, M. M., Schwartz, D., Mitchell, S. H., & Nagel, B. J. (2010). Delay discounting behavior and white matter microstructure abnomalities in youth with a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 34(9): 1590–1602.

Heyman, G. M. (2009). *Addiction: A disorder of choice*. Cambridge, MA: Harvard University Press.

Hirschman, A. (1985). Against parsimony: Three easy ways of complicating some categories of economic discourse. *Economics and Philosophy*, 1(1): 7–21.

Hochberg, J., & Brooks, V. (1962). Pictorial recognition as an unlearned ability: A study of one child's performance. *The American Journal of Psychology*, 75(4): 624–628.

Hoffman, W. F., Schwartz, D. L., Huckans, M. S., McFarland, B. H., Meiri, G., Stevens, A. A., & Mitchell, S. H. (2008). Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology*, 201(2): 183–193. doi: 10.1007/s00213-008-1261-1.

Holmes, K. M., Bearden, C. E., Barguil, M., Fonseca, M., Serap Monkul, E., Nery, F. G., … & Glahn, D. C. (2009). Conceptualizing impulsivity and risk taking in bipolar disorder: importance of history of alcohol abuse. *Bipolar Disorders*, 11(1): 33–40.

Hopko, D. R., Lejuez, C. W., Daughters, S. B., Aklin, W. M., Osborne, A., Simmons, B. L., & Strong, D. R. (2006). Construct validity of the balloon analogue risk task (BART): Relationship with MDMA use by inner-city drug users in residential treatment. *Journal of Psychopathology and Behavioral Assessment*, 28(2), 95–101.

Iacono, R. P., & Nashold, B. S., Jr. (1982). Mental and behavioral effects of brain stem and hypothalamic stimulation in man. *Human Neurobiology*, 1(4): 273–279.

Ikemoto, S. (2010). Brain reward circuitry beyond the mesolimbic dopamine system: A neurobiological theory. *Neuroscience & Biobehavioral Reviews*, 35(2), 129–150. doi: 16/j.neubiorev.2010.02.001.

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the of behavior by reward-related stimuli. *Psychopharmacology*, 146(4), 373–390.

Jhou, T. C., Geisler, S., Marinelli, M., Degarmo, B. A., & Zahm, D. S. (2009). The mesopontine rostromedial tegmental nucleus: A structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. *The Journal of Comparative Neurology*, 513(6): 566–596.

Johnson, M. W., Bickel, W. K., & Baker, F. (2007). Moderate drug use and delay discounting: A comparison of heavy, light, and never smokers. *Experimental and Clinical Psychopharmacology*, 15(2): 187–194.

Johnson, M. W., Bickel, W. K., Baker, F., Moore, B. A., Badger, Q. J., & Budney, A. J. (2010). Delay discounting in current and former marijuana-dependent individuals. *Experimental and Clinical Psychopharmacology*, 18: 99–107.

Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, 10(12): 1625–1633.

Kable, J. W., & Glimcher, P. W. (2010). An "as soon as possible" effect in human intertemporal decision making: Behavioral evidence and neural mechanisms. *Journal of Neurophysiology*, 103: 2513–2531.

Kahn, I., Yeshurun, Y., Rotshtein, P., Fried, I., Ben-Bashat, D., & Hendler, T. (2002). The role of the amygdala in signaling prospective outcome of choice. *Neuron*, 33(6): 983–994.

Kahneman, D. (2011). *Thinking, fast and slow*. London: Macmillan.

Kahneman, D., & Tversky, A. (1979). Prospect theory: An analysis of decision under risk. *Econometrica*, 47(2): 263–292.

Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: Relevance to addictive drugs. *The Journal of Neuroscience*, 22(9): 3306–3311.

Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, 21(16): 159–172.

Knutson, B., & Gibbs, S. E. (2007). Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology*, 191(3): 813–822.

Knutson, B., & Greer, S. M. (2008). Anticipatory affect: Neural correlates and consequences for choice. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1511): 3771–3786.

Knutson, B., Taylor, J., Kaufman, M., Peterson, R., & Glover, G. (2005). Distributed neural representation of expected value. *The Journal of Neuroscience*, 25(19): 4806–4812.

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. *Neuron*, 47(5): 763–770.

Laibson, D. (1997). Golden eggs and hyperbolic discounting. *Quarterly Journal of Economics*, 112(2): 443–477.

Lang, P., Bradley, M., & Cuthbert, B. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, 97(3): 377–395.

Lejuez, C. W., Aklin, W. M., Bornovalova, M. A., & Moolchan, E. T. (2005). Differences in risk-taking propensity across inner-city adolescent ever-and never-smokers. *Nicotine & Tobacco Research*, 7(1): 71–79.

Lejuez, C. W., Aklin, W. M., Jones, H. A., Richards, J. B., Strong, D. R., Kahler, C. W., & Read, J. P. (2003). The balloon analogue risk task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology*, 11(1): 26–33.

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., … Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: The balloon analogue risk task (BART). *Journal of Experimental Psychology: Applied*, 8(2): 75–84.

Leshner, A. (1997). Addiction is a brain disease, and it matters. *Science*, 278(5335): 45–47.

Lessov-Schlaggar, C., Lepore, R., Kristjansson, S., Schlaggar, B., Barnes, K., Petersen, S., … Barch, D. (2013). Functional neuroimaging study in identical twin pairs discordant for regular cigarette smoking. *Addiction Biology*, 18(1): 98–108.

Luo, S., Ainslie, G., Giragosian, L., & Monterosso, J. R. (2011). Striatal hyposensitivity to delayed rewards among cigarette smokers. *Drug and Alcohol Dependence*, 116(1): 18–23.

Luo, S., Ainslie, G., Pollini, D., Giragosian, L., & Monterosso, J. R. (2012). Moderators of the association between brain activation and farsighted choice. *Neuroimage*, 59(2): 1469–1477.

MacKillop, J. (2013). Integrating behavioral economics and behavioral genetics: Delayed reward discounting as an endophenotype for addictive disorders. *Journal of the Experimental Analysis of Behavior*, 99(1): 14–31.

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafo, M. R. (2011). Delayed reward discounting and addictive behavior: A meta-analysis. *Psychopharmacology*, 216: 305–321. doi: 10.1007/s00213-011-2229-0.

Mackillop, J., Amlung, M. T., Wier, L. M., David, S. P., Ray, L. A., Bickel, W. K., & Sweet, L. H. (2012). The neuroeconomics of nicotine dependence: A preliminary functional magnetic resonance imaging study of delay discounting of monetary and cigarette rewards in smokers. *Psychiatry Research: Neuroimaging*, 202(1): 20–29. doi: 10.1016/j.pscychresns.2011.10.003.

Madden, G. J., Bickel, W. K., & Jacobs, E. A. (1999). Discounting of delayed rewards in opioid-dependent outpatient: Exponential or hyperbolic discounting functions? *Experimental and Clinical Psychopharmacology*, 7(3): 284–293.

Mazur, J. E. (1987). An adjusting procedure for studying delayed reinforcement. *Quantitative Analyses of Behavior*, 5: 55–73.

McClure, S. M., Laibson, D. I., Loewenstein, G., & Cohen, J. D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, 306(5695): 503–507. doi: 10.1126/science.1100907.

McClure, S. M., Ericson, K. M., Laibson, D. I., Loewenstein, G., & Cohen, J. D. (2007). Time discounting for primary rewards. *Journal of Neuroscience*, 27(21): 5796–5804. doi: 10.1523/JNEUROSCI.4246-06.2007.

Meade, C. S., Lowen, S. B., MacLean, R. R., Key, M. D., & Lukas, S. E. (2011). fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. *Psychiatry Research: Neuroimaging*, 192(3), 167–175. doi: 10.1016/j.pscychresns.2010.12.011.

Metcalfe, J., & Mischel, W. (1999). A hot/cool-system analysis of delay of gratification: Dynamics of willpower. *Psychological Review*, 106(1): 3–19.

Milberger, S., Biederman, J., Faraone, S., Chen, L., & Jones, J. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(1): 37–44.

Miliaressis, E., Bouchard, A., & Jacobowitz, D. M. (1975). Strong positive reward in median raphe: Specific inhibition by para-chlorophenylalanine. *Brain Research*, 98(1): 194–201.

Mintzer, M. Z., & Stitzer, M. L. (2002). Cognitive impairment in methadone maintenance patients. *Drug and Alcohol Dependence*, 67(1): 41–51.

Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology*, 146(4): 455–464. doi: 10.1007/PL00005491.

Mitchell, S. H. (2003). Discounting the value of commodities according to different types of cost. In N. Heather and R.E. Vuchinich (Eds.), *Choice, Behavioral Economics, and Addiction*, pp. 339–357. Oxford: Elsevier.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., … Frith, C. D. (2007). When fear is near: Threat imminence elicits prefrontal–periaqueductal gray shifts in humans. *Science*, 317(5841): 1079–1083. doi: 10.1126/science.1144298.

Montague, P. R. (2007). Neuroeconomics: A view from neuroscience. *Functional Neurology*, 22(4): 219–234.

Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *The Journal of Neuroscience*, 16(5): 1936–1947.

Montague, P. R., Hyman, S. E., & Cohen, J. D. (2004). Computational roles for dopamine in behavioural control. *Nature*, 431(7010): 760–767.

Monterosso, J. R., & Luo, S. (2010). An argument against dual valuation system competition: Cognitive capacities supporting future orientation mediate rather than compete with visceral motivations. *Journal of Neuroscience, Psychology, and Economics*, 3(1): 1–14.

Monterosso, J. R., Ainslie, G., Xu, J., Cordova, X., Domier, C. P., & London, E. D. (2007). Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Human Brain Mapping*, 28(5): 383–393.

Muller, K., Mennigen, E., Ripke, S., Banaschewski, T., Barker, G., Buchel, C., … Smolka, M. (2013). Altered reward processing in adolescents with prenatal exposure to maternal cigarette smoking. *Journal of the American Medical Association Psychiatry*, 70(8): 847–856.

Myerson, J., & Green, L. (1995). Discounting of delayed rewards: Models of individual choice. *Journal of the Experimental Analysis of Behavior*, 64(3): 263–276.

Nashold, B. S., Jr, Wilson, W. P., & Slaughter, D. G. (1969). Sensations evoked by stimulation in the midbrain of man. *Journal of Neurosurgery*, 30(1): 14–24. doi: 10.3171/jns.1969.30.1.0014.

Nestor, L., Hester, R., & Garavan, H. (2010). Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage*, 49(1): 1133–1143.

Oberlin, B. G., & Grahame, N. J. (2009). High-alcohol preferring mice are more impulsive than low-alcohol preferring mice as measured in the delay discounting task. *Alcoholism: Clinical and Experimental Research*, 33(7): 1294–1303.

Ochola, L., Vounatsou, P., Smith, T., Mabaso, M., & Newton, C. (2006). The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard. *The Lancet Infectious Diseases*, 6(9): 582–588.

Olds, M. E., & Olds, J. (1963). Approach–avoidance analysis of rat diencephalon. *The Journal of Comparative Neurology*, 120(2): 259–295.

Paloyelis, Y., Asherson, P., Mehta, M. A., Faraone, S. V., & Kuntsi, J. (2010). DAT1 and COMT effects on delay discounting and trait impulsivity in male adolescents with attention deficit/hyperactivity disorder and healthy controls. *Neuropsychopharmacology*, 35(12): 2414–2426.

Peters, J., Bromberg, U., Schneider, S., Brassen, S., Menz, M., Banaschewski, T., … & Buechel, C. (2011). Lower ventral striatal activation during reward anticipation in adolescent smokers. *American Journal of Psychiatry*, 168(5): 540–549.

Petry, N. M. (2001). Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology*, 154: 243–250.

Petry, N. M., Kirby, K. N., & Kranzler, H. R. (2002). Effect of gender and family history of alcohol dependence on a behavioral task of impulsivity in healthy subjects. *Journal of Studies on Alcohol*, 63(1): 83–90.

Plichta, M. M., & Scheres, A. (2014). Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: A meta-analytic review of the fMRI literature. *Neuroscience & Biobehavioral Reviews*, 38: 125–134.

Potenza, M. N. (2008). The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1507): 3181–3189.

Prelec, D., & Bodner, R. (2003). Self-signaling and self-control. In G. Loewenstein, D. Read, and R. Baumeister (Eds.), *Time and Decision: Economic and Psychological Perspectives on Intertemporal Choice*, pp. 277–298. New York: Russell Sage Foundation.

Rangel, A., Camerer, C., & Montague, R. (2008). A framework for studying the neurobiology of value-based decision making. *Nature Reviews Neuroscience*, 9: 545–556.

Redish, A. D. (2004). Addiction as a computational process gone awry. *Science*, 306(5703): 1944–1947.

Rescorla, R., & Wagner, A. (1972). Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical conditioning II: Current research and theory*, pp. 64–99. New York: Appleton-Century-Crofts.

Rock, I., & Anson, R. (1979). Illusory contours as the solution to a problem. *Perception*, 8(6): 665–681.

Rompre, P. P., & Miliaressis, E. (1985). Pontine and mesencephalic substrates of self-stimulation. *Brain Research*, 359(1–2): 246–259.

Ross, D. (2008). Two styles of neuroeconomics. *Economics and Philosophy*, 24(03), 473–483.

Ross, D., Sharp, C., Vuchinich, R., & Spurrett, D. (2008). *Midbrain mutiny: The picoeconomics and neuroeconomics of disordered gambling*. Cambridge, MA: MIT Press.

Samuelson, P. (1947). *Foundations of economic analysis*. Cambridge, MA: Harvard University Press.

Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: Dopamine, COMT and BDNF. *Genes, Brain, and Behavior*, 5: 311–328.

Schelling, T. (1978). Egonomics, or the art of self-management. *The American Economic Review*, 68(2): 290–294.

Schneirla, T. C. (1959). An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In M. Jones (Ed.), *Nebraska symposium on motivation*, Vol. 7, pp. 1–42. Lincoln: University of Nebraska Press.

Schott, B. H., Minuzzi, L., Krebs, R. M., Elmenhorst, D., Lang, M., Winz, O. H., … & Baure, A. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *The Journal of Neuroscience*, 28(52): 14311–14319.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, 80(1): 1–27.

Schultz, W. (2008). Neruoeconomics: The promise and the profit. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1511): 3767–3769.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, 275(5306): 1593–1599.

Setlow, B., Schoenbaum, G., & Gallagher, M. (2003). Neural encoding in ventral striatum during olfactory discrimination learning. *Neuron*, 38(4): 625–636.

Simon, H. A. (1967). The logic of heuristic decision making. In N. Rescher (ed.), *The logic of decision and action*, pp. 1–20. Pittsburgh, PA: University of Pittsburgh Press.

Stigler, G. J., & Becker, G. S. (1977). De gustibus non est disputandum. *The American Economic Review*, 67(2): 76–90.

Strotz, R. H. (1955). Myopia and inconsistency in dynamic utility maximization. *The Review of Economic Studies*, 23(3): 165–180.

Sutton, S., & Davidson, R. (1997). Prefrontal brain asymmetry: A biological substrate of the behavioral approach and inhibition systems. *Psychological Science*, 8(3): 204–210.

Toll, B., O'Malley, S., Katulak, N., Wu, R., Dubin, J., Latimer, A., … & Salovey, P. (2007). Comparing gain- and loss-framed messages for smoking cessation with sustained-release bupropion: A randomized controlled trial. *Psychology of Addictive Behaviors*, 21(4): 534–544.

Tom, S. M., Fox, C. R., Trepel, C., & Poldrack, R. A. (2007). The neural basis of loss aversion in decision-making under risk. *Science*, 315(5811): 515–518.

Tversky, A., & Kahneman, D. (1981). The framing of decision and the psychology of choice. *Science*, 211: 453–458.

van der Meer, M. A. A., & Redish, A. D. (2010). Expectancies in decision making, reinforcement learning, and ventral striatum. *Frontiers in Neuroscience*, 4. doi: 10.3389/neuro.01.006.2010.

van Hell, H., Vink, M., Ossewaarde, L., Jager, G., Kahn, R., & Ramsey, N. (2010). Chronic effects of cannabis use on the human reward system: An fMRI study. *European Neuropsychopharmacology*, 20(3): 153–163.

Volkow, N. D., Wang, G. J., Fowler, J. S., & Telang, F. (2008). Overlapping neuronal circuits in addiction and obesity: Evidence of systems pathology. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1507): 3191–3200.

Weber, B. J., & Huettel, S. A. (2008). The neural substrates of probabilistic and intertemporal decision making. *Brain Research*, 1234: 104–115.

Wesley, M., Hanlon, C., & Porrino, L. (2011). Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. *Psychiatry Research: Neuroimaging*, 191: 51–59.

White, M. J., Lawford, B. R., Morris, C. P., & Young, R. M. (2009). Interaction between DRD2 c957T polymorphism and an acute psycholosocial stressor on reward-related behavioral impulsivity. *Behavioral Genetics*, 39(3): 285–295.

WHO. (2004). *International classification of diseases and related health problems: Tenth revision*. 2nd ed. Geneva, Switzerland: World Health Organization.

Wilhelm, C. J., & Mitchell, S. H. (2008). Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes. *Genes, Brain, and Behavior*, 7(7): 705–713.

Wilhelm, C. J., & Mitchell, S. H. (2009). Strain differences in delay discounting using inbred rats. *Genes, Brain, and Behavior*, 8: 426–434.

Winston, G. C. (1980). Addiction and backsliding: a theory of compulsive consumption. *Journal of Economic Behavior & Organization*, 1(4): 295–324.

Wrase, J., Schlagenhauf, F., Kienast, T., Wustenberg, T., Bermpohl, F., Kahnt, T., … & Heinz, A. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage*, 35(2): 787–794.

Yin, H., Knowlton, B., & Balleine, B. (2004). Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *European Journal of Neuroscience*, 19(1): 181–189.