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Natural Rewards, Neuroplasticity, and Non-Drug Addictions

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Abstract

There is a high degree of overlap between brain regions involved in processing natural rewards and drugs of abuse. “Non-drug” or “behavioral” addictions have become increasingly documented in the clinic, and pathologies include compulsive activities such as shopping, eating, exercising, sexual behavior, and gambling. Like drug addiction, non-drug addictions manifest in symptoms including craving, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse. These alterations in behavior suggest that plasticity may be occurring in brain regions associated with drug addiction. In this review, I summarize data demonstrating that exposure to non-drug rewards can alter neural plasticity in regions of the brain that are affected by drugs of abuse. Research suggests that there are several similarities between neuroplasticity induced by natural and drug rewards and that, depending on the reward, repeated exposure to natural rewards might induce neuroplasticity that either promotes or counteracts addictive behavior.

Keywords

novelty seeking; addiction; motivation; reinforcement; behavioral addiction; plasticity

1. Introduction

There are now myriad television shows documenting people who compulsively engage in behaviors that may otherwise be considered normal, but do so in a manner that has a serious negative impact on their lives and those of their families. People suffering from what may be considered “non-drug” or “behavioral” addictions are becoming increasingly documented in the clinic, and symptoms include compulsive activities such as shopping, eating, exercising, sexual behavior, gambling, and video games (Holden, 2001; Grant *et al*, 2006a). While the subjects of these television shows may seem like extreme and rare cases, these types of disorders are surprisingly common. Prevalence rates in the United States have been

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estimated at 1–2% for pathological gambling (Welte *et al*, 2001), 5% for compulsive sexual behavior (Schaffer and Zimmerman, 1990), 2.8% for binge-eating disorder (Hudson *et al*, 2007) and 5–6% for compulsive buying (Black, 2007).

Although the DSM-IV acknowledges these disorders and other "addictive" behaviors, they are currently not classified as behavioral addictions. This may be due to the fact that the DSM-IV avoids the term addiction even in reference to drugs of abuse, opting instead for the terms "abuse" and "dependence". Within the DSM-IV, behavioral addictions are grouped under categories such as "substance-related disorders", "eating disorders", and "impulse control disorders not elsewhere classified" (Holden, 2001; Potenza, 2006). More recently, there has been a trend toward thinking about these non-drug addictions to be more like substance abuse and dependence (Rogers and Smit, 2000; Wang *et al*, 2004b; Volkow and Wise, 2005; Grant *et al*., 2006a; Petry, 2006; Teegarden and Bale, 2007; Deadwyler, 2010; Grant *et al*, 2010). In fact, non-drug addictions fit the classical definition of addiction that includes engaging in the behavior despite serious negative consequences (Holden, 2001; Hyman *et al*, 2006). This phenomenon has been appreciated by psychiatrists, and proposed revisions for the DSM-5 include a category of Addiction and Related Behavior ((APA), 2010). Within this category, a Behavioral Addictions category has been proposed, which would include pathological gambling and potentially internet addiction ((APA), 2010; O'Brien, 2010; Tao *et al*, 2010).

Like substance addictions, non-drug addictions manifest in similar psychological and behavioral patterns including craving, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse (Marks, 1990; Lejoyeux *et al*, 2000; National Institute on Drug Abuse (NIDA) *et al*, 2002; Potenza, 2006). Similarities between drugs and non-drug rewards can also be seen physiologically. Functional neuroimaging studies in humans have shown that gambling (Breiter *et al*, 2001), shopping (Knutson *et al*, 2007), orgasm (Komisaruk *et al*, 2004), playing video games (Koepp *et al*, 1998; Hoeft *et al*, 2008) and the sight of appetizing food (Wang *et al*, 2004a) activate many of the same brain regions (i.e., the mesocorticolimbic system and extended amygdala) as drugs of abuse (Volkow *et al*, 2004). This article will review preclinical evidence that natural reinforcers are capable of leading to plasticity in behavior and neurotransmission that is often reminiscent of adaptations seen following exposure to drugs of abuse, especially psychostimulants. For the sake of the present review, plasticity will be broadly defined as any adaptation in behavior or neural function, similar to the usage of the term originally described by William James (James, 1890). Synaptic plasticity will refer to an alteration at the level of the synapse, typically measured using electrophysiological methods (e.g., changes in AMPA/NMDA ratio). Neurochemical plasticity will refer to altered neurotransmission (synaptic or intracellular) measured biochemically by differences in basal or evoked levels of transmitter, receptor, or transporter, or by an enduring change in phosphorylation state of any of these molecules. Behavioral plasticity will refer to any adaptation in behavior (several examples are discussed in Section 1.1).

Neural circuits that underlie encoding of natural rewards are thought to be "hijacked" by drugs of abuse, and plasticity in these circuits is believed to be responsible for the behavioral plasticity (i.e. increased drug seeking and craving) characteristic of addiction (Kelley and Berridge, 2002; Aston-Jones and Harris, 2004; Kalivas and O'Brien, 2008; Wanat *et al*, 2009b). Evidence for this hijacking is seen in several forms of plasticity in brain regions known to affect motivation, executive function, and reward processing (Kalivas and O'Brien, 2008; Thomas *et al*, 2008; Frascella *et al*, 2010; Koob and Volkow, 2010; Pierce and Vanderschuren, 2010; Russo *et al*, 2010). Animal models have given us a snapshot of the profound changes that administration of drugs of abuse can impart. Adaptations range from altered neurotransmitter levels to altered cell morphology and changes in

transcriptional activity (Robinson and Kolb, 2004; Kalivas *et al*, 2009; Russo *et al*., 2010). Several groups have also reported drugs of abuse altering synaptic plasticity in key regions of the brain implicated in drug addiction (for review, see (Winder *et al*, 2002; Kauer and Malenka, 2007; Luscher and Bellone, 2008; Thomas *et al*., 2008). The majority of the neuroadaptations described have been in regions of the mesocorticolimbic system and the extended amygdala (Grueter *et al*, 2006; Schramm-Sapyta *et al*, 2006; Kauer and Malenka, 2007; Kalivas *et al*., 2009; Koob and Volkow, 2010; Russo *et al*., 2010; Mameli *et al*, 2011). Based on known roles of these regions in regulation of mood, processing of natural rewards, and motivated behavior, it is widely believed that this plasticity underlies the maladaptive changes in behavior associated with addiction. In humans, some of these changes include impaired decision making, decreased pleasure from natural rewards (anhedonia), and craving (Majewska, 1996; Bechara, 2005; O'Brien, 2005). In animal models, these altered behaviors can be studied with neurobehavioral measures following a history of drug administration, and analogous brain regions are thought to mediate these measures (Markou and Koob, 1991; Shaham *et al*, 2003; Bevins and Besheer, 2005; Winstanley, 2007). These measures provide the basis for preclinical testing of pharmacotherapies that may be useful in the treatment of addiction.

Recent evidence suggests that non-drug addictions may lead to neuroadaptations similar to those reported with long-term drug use. While the majority of these examples of plasticity are emerging from animal studies, reports also include examples from human studies. In this review, we will explore the concept that natural rewards are capable of inducing neural and behavioral plasticity in ways analogous to drug addiction. Future study of this phenomenon may give us insights into behavioral addictions and promote “crossover” pharmacotherapies that could benefit both drug and non-drug addictions (Frascella *et al*., 2010).

1.1. Theories of behavioral plasticity and addiction

In the field of drug addiction, several theories have emerged to explain how neural and behavioral plasticity contribute to addiction. One theory is that of incentive-sensitization (Robinson and Berridge, 1993, 2001, 2008). According to this theory, in susceptible individuals, repeated drug exposure leads to a sensitization (reverse tolerance) of the incentive-motivational properties of drugs and drug-related cues. This alteration is at least in part mediated by sensitized nucleus accumbens (NAc) dopamine (DA) release following exposure to drug-related cues. Behaviorally, this is associated with increased wanting and craving of drugs when one is exposed to cues that are associated with intake (i.e. a crack pipe). In animal models, incentive sensitization can be modeled by measuring drug-seeking behaviors in response to cues paired with drug administration (Robinson and Berridge, 2008). Locomotor sensitization also occurs with repeated administration of several drugs of abuse and may be an indirect measure of incentive sensitization, although locomotor and incentive sensitization are dissociable processes (Robinson and Berridge, 2008). Notably, sensitization processes can also translate between drug and non-drug rewards (Fiorino and Phillips, 1999; Avena and Hoebel, 2003b; Robinson and Berridge, 2008). In humans, the role of dopamine signaling in incentive-sensitization processes has recently been highlighted by the observation of a dopamine dysregulation syndrome in some patients taking dopaminergic drugs. This syndrome is characterized by a medication-induced increase in (or compulsive) engagement in non-drug rewards such as gambling, shopping, or sex (Evans *et al*, 2006; Aiken, 2007; Lader, 2008).

Another theory that has been developed to explain how drug-related plasticity contributes to addiction is the opponent process theory (Solomon, 1980; Koob *et al*, 1989; Koob and Le Moal, 2008). Briefly, this theory of motivation states that there are two processes engaged during repeated experiences: the first involves affective or hedonic habituation, the second process is an affective or hedonic withdrawal (Solomon and Corbit, 1974). An example

provided by Solomon related to opiate use, where tolerance developed to the acute hedonic effects following repeated drug exposure, and negative symptoms of withdrawal would emerge which would further motivate drug use (negative reinforcement) (Solomon, 1980). This early version of the theory was originally developed to explain behavior altered by exposure to both drug and non-drug rewards (for review, see (Solomon, 1980)). An expansion of opponent process theory is the allostatic model of brain motivational systems (Koob and Le Moal, 2001, 2008). Briefly, this model includes the opposing concepts of reward and anti-reward, while the latter involves a failure to return to a homeostatic set point, leading to negative affect and reduction in natural reward, which increases motivation to relieve this state (Koob and Le Moal, 2008). Evidence for neuroplasticity that regulates this altered affective state comes from several findings, including decreased basal NAc DA following drug withdrawal in rats (Weiss *et al*, 1992), decreased striatal D2 receptors in striatum and accumbens of human alcoholics and abstinent heroin addicts (Volkow *et al.*, 2004; Zijlstra *et al*, 2008), and increased intracranial self-stimulation (ICSS) thresholds during cocaine withdrawal in rats (Markou and Koob, 1991). In addition to alterations in mesolimbic DA signaling, central stress systems are also recruited. A particularly robust example is increased CRF signaling in the hypothalamus, central nucleus of the amygdala, and bed nucleus of the stria terminalis following withdrawal of many drugs of abuse (Koob and Le Moal, 2008).

A third theory to describe neuroplasticity contributing to addiction is the recruitment of habit-based neurocircuitry throughout repeated drug exposure (Everitt *et al*, 2001; Everitt *et al*, 2008; Graybiel, 2008; Ostlund and Balleine, 2008; Pierce and Vanderschuren, 2010). For example, non-human primates self-administering cocaine show changes in glucose metabolism and levels of dopamine D2 receptor and dopamine transporter that initially affect the ventral striatum, but with increasing exposure expand into the dorsal striatum (Porrino *et al*, 2004a; Porrino *et al*, 2004b). This expansion “suggests that the elements of the behavioral repertoire outside of the influence of cocaine become smaller and smaller with increasing durations of exposure to drug use resulting in cocaine's dominance over all aspects of the addict's life” (Porrino *et al.*, 2004a). This progressive plasticity from ventral to dorsal striatum parallels an older literature on the transition from goal- to habit-based learning (Balleine and Dickinson, 1998) and has an anatomical correlate that supports the ability of extended reward-based learning to engage progressively more dorsal aspects of the striatum (Haber *et al*, 2000).

2. Food Reward

Perhaps the most extensively studied reward is that of food. Food is the quintessential reward in many rodent studies and has been used as a reinforcer in procedures such as operant (self-administration) tasks, runway tests, maze learning, gambling tasks, and place conditioning (Skinner, 1930; Ettenberg and Camp, 1986; Kandel *et al*, 2000; Kelley, 2004; Tzschentke, 2007; Zeeb *et al*, 2009). In rats that were trained to press a lever to receive intravenous self-administration of drugs, highly palatable foods such as sugar and saccharin were shown to reduce self-administration of cocaine and heroin (Carroll *et al*, 1989; Lenoir and Ahmed, 2008), and these natural reinforcers have been demonstrated to outcompete cocaine in choice self-administration in the majority of rats tested (Lenoir *et al*, 2007; Cantin *et al*, 2010). This would suggest that sweet foods have a higher reinforcing value than cocaine, even in animals with an extensive history of drug intake (Cantin *et al.*, 2010). While this phenomenon could appear as a weakness in current models of cocaine addiction, a minority of rats prefer cocaine to sugar or saccharin (Cantin *et al.*, 2010). It is possible that these animals may represent a “vulnerable” population, which is more relevant to the human condition. This notion is explored more in the Discussion (Section 6.1).

Work from many laboratories has demonstrated examples of plasticity in reward-related circuits following access to palatable food. Neurobehavioral adaptations following a history of palatable food intake have been likened to those observed following drugs of abuse, prompting several scientists to propose that dysregulation of food intake may be similar to addiction (Hoebel *et al*, 1989; Le Magnen, 1990; Wang *et al.*, 2004b; Volkow and Wise, 2005; Davis and Carter, 2009; Nair *et al*, 2009a; Corsica and Pelchat, 2010). The laboratory of Bartley Hoebel has extensive data demonstrating behavioral plasticity following a history of intermittent sugar access, which has led he and his colleagues to propose that sugar consumption that meets criteria for addiction (Avena *et al*, 2008). This notion is supported by the fact that several examples of plasticity seen following repeated drug exposure are also observed following intermittent access to not only sugar, but also fat. Different types of palatable food have been used to study plasticity, including high sugar, high fat, and "Western" or "Cafeteria" diets to try to model different human eating patterns.

During repeated access to sugar, escalation of intake is observed (Colantuoni *et al*, 2001), a phenomenon previously associated with cocaine and heroin self-administration (Ahmed and Koob, 1998; Roberts *et al*, 2007). Escalation is an increase in intake that occurs during the initial phase (e.g. the first hour of a six hour session) of self-administration after a history of repeated sessions, a phenomenon thought to mimic human patterns of drug intake (Koob and Kreek, 2007). Following removal of sugar or fat access, withdrawal symptoms including anxiety- and depressive-like behaviors emerge (Colantuoni *et al*, 2002; Teegarden and Bale, 2007). After this period of "abstinence", operant testing reveals "craving" and "seeking" behavior for sugar (Avena *et al*, 2005) or fat (Ward *et al*, 2007), as well as "incubation of craving" (Grimm *et al*, 2001; Lu *et al*, 2004; Grimm *et al*, 2005), and "relapse" (Nair *et al*, 2009b) following abstinence from sugar. In fact, when given a re-exposure to sugar after a period of abstinence, animals consume a much greater amount of sugar than during previous sessions (Avena *et al.*, 2005). This deprivation effect was originally described for alcohol (Sinclair and Senter, 1968), and is thought to be another preclinical model of craving and relapse (McBride and Li, 1998; Spanagel and Holter, 1999). Finally, following intermittent exposure to a high fat diet, food-seeking was continued despite adverse consequences (Teegarden and Bale, 2007; Johnson and Kenny, 2010), which has been proposed as a animal corollary for risky acquisition of drugs seen in human addicts (Deroche-Gamonet *et al*, 2004).

Another indication of plasticity induced by diet is that a "cross-sensitization" of the locomotor activity between intermittent sugar intake and psychostimulants can be induced in either order of treatment (Avena and Hoebel, 2003b, a; Gosnell, 2005). Cross-sensitization is a phenomenon that occurs following previous exposure to an environmental or pharmacological agent (such as a stressor or psychostimulant, respectively) that results in an enhanced response (typically locomotor) to a different environmental or pharmacological agent (Antelman *et al*, 1980; O'Donnell and Miczek, 1980; Kalivas *et al*, 1986; Vezina *et al*, 1989). Sensitization processes involving psychostimulants involve mesolimbic DA neurons, and cross-sensitization is believed to occur from common mechanisms of action between two stimuli (Antelman *et al.*, 1980; Herman *et al*, 1984; Kalivas and Stewart, 1991; Self and Nestler, 1995). Cross-sensitization to psychostimulants is also seen in animals fed a high sugar/fat diet during perinatal and post-weanling periods (Shalev *et al*, 2010). To determine if exposure to a high fat diet could alter the "rewarding" (reinforcing) effects of a drug of abuse, Davis et al. tested animals fed a high fat diet for altered sensitivity to amphetamine using a conditioned place preference (CPP) paradigm (Davis *et al*, 2008). In this model, animals are first allowed to explore a multi-chamber apparatus (the pre-test) where each chamber has distinct visual, tactile, and/or olfactory cues. During conditioning sessions, the animals are confined to one of the chambers and paired with a reward (e.g. amphetamine injection or food in the chamber). These sessions are repeated and interleaved with

conditioning sessions that involve pairing of another chamber of the apparatus with the control condition (e.g. saline injection or no food). The test phase is done under the same conditions as the pre-test and CPP is demonstrated when animals show a significant preference for the chamber that was paired with the drug or non-drug reward. Davis et al. found that high fat fed rats failed to develop conditioned place preference for amphetamine, suggesting a cross-tolerance between the intake of high fat food and the conditioned reinforcing effects of amphetamine (Davis *et al.*, 2008).

Withdrawal is a phenomenon also seen following repeated exposure to highly palatable foods. Somatic signs of withdrawal commonly associated with naloxone precipitated opiate withdrawal can be also be precipitated by naloxone or food restriction following intermittent sugar (Colantuoni *et al.*, 2002) or a cafeteria style diet (Le Magnen, 1990). Elevated thresholds for brain stimulation reward, which are commonly observed following withdrawal from cocaine, alcohol, amphetamine, and nicotine (Simpson and Annau, 1977; Cassens *et al*, 1981; Markou and Koob, 1991; Schulteis *et al*, 1995; Wise and Munn, 1995; Epping-Jordan *et al*, 1998; Rylkova *et al*, 2009), are observed in rats following 40 days access to a cafeteria diet in addition to regular chow, and this effect persisted at least 14 days following withdrawal of the high fat food (Johnson and Kenny, 2010). This measure has commonly been used to describe a state of relative anhedonia characterized by lower tone of endogenous brain reward systems (Kenny, 2007; Wise, 2008; Bruijnzeel, 2009; Carlezon and Thomas, 2009) and is thought to regulate continued intake of drugs (and perhaps food) to relieve this state (a phenomenon known as negative reinforcement) (Cottone *et al*, 2008; Koob, 2010).

In addition to behavioral plasticity, excessive intake of certain types of food has also been associated with neurochemical plasticity. In particular, dopamine and opioid signaling appears to be susceptible to adaptations following intermittent access to high sugar or high fat foods. In the NAc, intermittent feeding episodes with access to sugar and chow increase D1 and D3 receptor content (either mRNA or protein), while decreasing D2 receptors in the NAc and dorsal striatum (Colantuoni *et al*., 2001; Bello *et al*, 2002; Spangler *et al*, 2004). This effect was also observed with extended access to a high fat diet in rats, with the greatest decrease in D2 occurring in the heaviest rats (Johnson and Kenny, 2010). These adaptations in accumbal and striatal dopamine receptors parallel those seen in rodents repeatedly administered cocaine or morphine (Alburges *et al*, 1993; Unterwald *et al*, 1994a; Spangler *et al*, 2003; Conrad *et al*, 2010). Further, reductions in striatal D2 receptors are also seen in human psychostimulant users and alcoholics (Volkow *et al*, 1990; Volkow *et al*, 1993; Volkow *et al*, 1996; Zijlstra *et al*., 2008), and in obese adults, where D2 content was found to negatively correlate with body mass index (Wang *et al*., 2004b). Endogenous opioid signaling is also affected profoundly by diet (Gosnell and Levine, 2009). Intermittent sugar or sweet/fat diet increases mu opioid receptor binding in the NAc, cingulate cortex, hippocampus and locus coeruleus (Colantuoni *et al*., 2001) and decreases enkephalin mRNA in NAc (Kelley *et al*, 2003; Spangler *et al*., 2004). Neurochemical plasticity in mesolimbic DA and opioid signaling has also been demonstrated to occur in the offspring of female mice fed high fat food during pregnancy (Vucetic *et al*, 2010). These offspring have elevated dopamine transporter (DAT) in the ventral tegmental area (VTA), NAc, and prefrontal cortex (PFC), and increased preproenkephalin and mu opioid receptors in the NAc and PFC (Vucetic *et al*., 2010). Interestingly, these alterations were associated with epigenetic modification (hypomethylation) of the promoter elements for all of the proteins affected.

Effects on the corticotropin-releasing factor (CRF) system by high fat/high sugar diets are also reminiscent of those imparted by drugs of abuse. CRF in the amygdala was increased following a 24 hour withdrawal from a high fat diet, while animals maintained on this diet

had unaltered amygdala CRF (Teegarden and Bale, 2007). In preclinical models, this altered CRF signaling is thought to underlie negative reinforcement processes and increased "binge" intake of ethanol (Koob, 2010). As a result, CRF antagonists are being proposed for the treatment of alcoholism and drug addiction (Sarnyai *et al*, 2001; Koob *et al*, 2009; Lowery and Thiele, 2010). Based on these data, CRF antagonists may also be expected to help individuals remain abstinent from high fat/high sugar foods during a transition to a healthier diet.

Transcription factors are another class of molecule implicated in mediating enduring effects of drugs of abuse by directly affecting gene expression (McClung and Nestler, 2008). In support of the idea that food is capable of inducing neural plasticity, several transcription factors are also altered by diet. NAc phospho-CREB was reduced 24 hours following withdrawal from a high carbohydrate diet and both 24 hours and 1 week following withdrawal from a high fat diet, while the transcription factor delta FosB is increased during access to high fat diet (Teegarden and Bale, 2007) or sucrose (Wallace *et al*, 2008). In the NAc, decreased phospho-CREB is also seen during periods of withdrawal from amphetamine and morphine (McDaid *et al*, 2006a; McDaid *et al*, 2006b), and delta FosB is also increased following withdrawal from these drugs as well as cocaine, nicotine, ethanol, and phencyclidine (McClung *et al*, 2004; McDaid *et al*., 2006a; McDaid *et al*., 2006b). Similar to their proposed role in increasing drug seeking behavior, these neuroadaptations may also affect subsequent feeding behavior, as overexpression of delta FosB in the ventral striatum increases motivation to obtain food (Olausson *et al*, 2006) and sucrose (Wallace *et al*., 2008).

Synaptic plasticity in addiction-related circuitry has been linked with *in vivo* administration of numerous drugs of abuse. In the VTA, several classes of addictive, but not non-addictive psychoactive drugs induce synaptic plasticity (Saal *et al*, 2003; Stuber *et al*, 2008a; Wanat *et al*, 2009a). To date, there is very little data directly measuring the effects of food on synaptic plasticity in addiction-related neurocircuitry. Operant learning associated with food (chow or sucrose pellets) increased AMPA/NMDA ratios in the ventral tegmental area for up to seven days following training (Chen *et al*, 2008a). When cocaine was self-administered, the effect lasted up to three months, and this effect was not seen with passive administration of cocaine (Chen *et al*., 2008a). Miniature EPSP frequency in the VTA was also increased for up to three months following cocaine self-administration, and up to three weeks following sucrose (but not chow) self-administration, suggesting that glutamatergic signaling is strengthened pre- and post-synaptically (Chen *et al*., 2008a).

These data suggest that some measures of synaptic plasticity in the mesolimbic system (e.g. AMPA/NMDA ratios) may be associated with appetitive learning in general. This is supported by the fact that Pavlovian learning associated with food reward occluded VTA LTP during acquisition (day 3 of conditioning) (Stuber *et al*, 2008b). Although evidence of plasticity was observed on day 3, it was absent two days later, suggesting that self-administration distinctly leads to more enduring plasticity in these circuits (Stuber *et al*., 2008b). This appears to also be the case for plasticity associated with cocaine self-administration, as repeated non-contingent cocaine-induced plasticity in the VTA is also short-lived (Borgland *et al*, 2004; Chen *et al*., 2008a). The nature of these operant studies does not, however, discount the fact that extended access to palatable food may lead to protracted synaptic plasticity. During typical operant conditioning studies, animals are allowed much less access to food reward than during free-feeding or scheduled access. Future studies will need to be conducted to determine the effects of extended access to highly palatable food on synaptic plasticity.

3. Sexual Reward

Sex is a reward that, much like food, is critical for the survival of a species. Like food and several drugs of abuse, sexual behavior elevates mesolimbic DA (Meisel *et al*, 1993; Mermelstein and Becker, 1995). It is also a behavior that has been measured in terms of reinforcing value by operant (Beach and Jordan, 1956; Caggiula and Hoebel, 1966; Everitt *et al*, 1987; Crawford *et al*, 1993) and place conditioning methods (Paredes and Vazquez, 1999; Martinez and Paredes, 2001; Tzschentke, 2007). Human subjects in treatment for compulsive sexual behavior (categorized as "Sexual Disorder Not Otherwise Specified" in the DSM-IV) have many symptoms associated with drug addiction, including escalation, withdrawal, difficulty in stopping or reducing activity, and continued sexual behavior despite adverse consequences (Orford, 1978; Gold and Heffner, 1998; Garcia and Thibaut, 2010). Considering these adaptations in behavior, it is reasonable to imagine significant neuroadaptations occurring within mesocorticolimbic circuitry. As seen with repeated sugar exposure, repeated sexual encounters in male rats cross-sensitized with amphetamine in a locomotor assay (Pitchers *et al*, 2010a). Repeated sexual encounters also increase sucrose consumption and place preference for low dose amphetamine, suggesting cross-sensitization between sexual experience and drug reward (Wallace *et al*., 2008; Pitchers *et al*, 2010b). Also similar to the sensitizing effects of drugs of abuse (Segal and Mandell, 1974; Robinson and Becker, 1982; Robinson and Berridge, 2008), repeated sexual encounters sensitize the NAc DA response to a later sexual encounter (Kohlert and Meisel, 1999). Cross-sensitization is also bidirectional, as a history of amphetamine administration facilitates sexual behavior and enhances the associated increase in NAc DA (Fiorino and Phillips, 1999).

As described for food reward, sexual experience can also lead to activation of plasticity-related signaling cascades. The transcription factor delta FosB is increased in the NAc, PFC, dorsal striatum, and VTA following repeated sexual behavior (Wallace *et al*., 2008; Pitchers *et al*., 2010b). This natural increase in delta FosB or viral overexpression of delta FosB within the NAc modulates sexual performance, and NAc blockade of delta FosB attenuates this behavior (Hedges *et al*, 2009; Pitchers *et al*., 2010b). Further, viral overexpression of delta FosB enhances the conditioned place preference for an environment paired with sexual experience (Hedges *et al*., 2009). The MAP kinase signaling pathway is another plasticity-related pathway that is engaged during repeated sexual experience (Bradley *et al*, 2005). In sexually experienced females, a sexual encounter led to elevated pERK2 in the NAc (Meisel and Mullins, 2006). Increases in NAc pERK are induced by several drugs of abuse, but not by non-addictive psychoactive drugs, suggesting that NAc ERK activation may be associated with plasticity associated with addiction (Valjent *et al*, 2004). Further, a recent study found that pERK was induced by sexual activity in the same neurons of the NAc, basolateral amygdala, and anterior cingulate cortex that were previously activated by methamphetamine (Frohmader *et al*, 2010). This unique selectivity suggests that activation of this signaling cascade in NAc and other mesocorticolimbic regions may specifically lead to plasticity that promotes future appetitive behavior (Girault *et al*, 2007).

Neural structure in the mesocorticolimbic system is also altered following sexual experience. Pitchers and colleagues recently reported an increase in dendrites and dendritic spines within the NAc in rats during "withdrawal" from sexual experience (Pitchers *et al*., 2010a). This expands on other data demonstrating that sexual experience can alter dendritic morphology in a manner analogous to repeated drug exposure (Fiorino and Kolb, 2003; Robinson and Kolb, 2004; Meisel and Mullins, 2006).

4. Exercise Reward

Access to a running wheel for exercise serves as a reinforcer in laboratory rodents (Belke and Heyman, 1994; Belke and Dunlop, 1998; Lett *et al*, 2000). Like drugs of abuse and other natural rewards, exercise in rodents is associated with increased DA signaling in the NAc and striatum (Freed and Yamamoto, 1985; Hattori *et al*, 1994). Exercise also elevates brain and plasma levels of endogenous opioids in humans and rodents (Christie and Chesher, 1982; Janal *et al*, 1984; Schwarz and Kindermann, 1992; Asahina *et al*, 2003). One target of these opioids is the mu opiate receptor, a substrate of opiate drugs of abuse such as heroin and morphine. This overlap also appears to extend to behavioral responses to drugs of abuse. Unlike the natural rewards discussed thus far, most studies have found that exposure to exercise attenuates the effects of drugs of abuse. For example, self-administration of morphine, ethanol, and cocaine are all reduced following exercise (Cosgrove *et al*, 2002; Smith *et al*, 2008; Ehringer *et al*, 2009; Hosseini *et al*, 2009). Exercise experience attenuated CPP to MDMA and cocaine and also reduced the MDMA increase in NAc DA (Chen *et al*, 2008b; Thanos *et al*, 2010). Exercise prior to self-administration training was also able to reduce drug seeking and reinstatement, although in this study self-administration of cocaine was not affected (Zlebnik *et al*, 2010). In a similar study, cocaine seeking and cue reinstatement were reduced in rats that exercised during a period of drug abstinence (Lynch *et al*, 2010). In animals with a history of running wheel experience, withdrawal of wheel access leads to drug withdrawal-like symptoms including, increased anxiety and aggression, and susceptibility to naloxone-precipitated withdrawal (Hoffmann *et al*, 1987; Kanarek *et al*, 2009).

In addition to altered behavioral responses to drugs of abuse, there is neurochemical plasticity reflected by increased dynorphin in the striatum and NAc following running, a phenomenon also seen in human cocaine addicts and in animals following administration of cocaine or ethanol (Lindholm *et al*, 2000; Werme *et al*, 2000; Wee and Koob, 2010). Also reminiscent of drug associated neural plasticity, the transcription factor delta FosB is induced in the NAc of animals with wheel running experience (Werme *et al*, 2002). These changes may underlie the state of “withdrawal” that is observed following removal of running wheel access in animals with previous access (Hoffmann *et al*., 1987; Kanarek *et al*., 2009). Conversely, exercise during drug abstinence is also associated with a reduction in reinstatement-induced activation of ERK in the PFC (Lynch *et al*., 2010). This is an especially relevant finding considering the role of ERK in many aspects of addiction (Valjent *et al*., 2004; Lu *et al*, 2006; Girault *et al*., 2007) and the finding that ERK activation within the PFC is associated with incubation of drug craving (Koya *et al*, 2009). Striatal levels of the dopamine D2 receptor have also been reported to increase following exercise (MacRae *et al*, 1987; Foley and Fleshner, 2008), an effect that is opposite to that observed following psychostimulant self-administration in rodents, primates, and humans (Volkow *et al*., 1990; Nader *et al*, 2002; Conrad *et al*., 2010). It is possible that these adaptations may contribute to a “protective” effect of exercise in regards to drug abuse/addiction. Support for this idea comes from studies mentioned earlier in this section demonstrating reduced drug self-administration, seeking, and reinstatement in animals allowed to exercise. There is also support that exercise can “out-compete” drug self-administration, as wheel running reduces amphetamine intake when both reinforcers were concurrently available (Kanarek *et al*, 1995).

Exercise also has effects within the hippocampus, where it influences plasticity (reflected in elevated LTP and improved spatial learning) and increases neurogenesis and the expression of several plasticity-related genes (Kanarek *et al*., 1995; van Praag *et al*, 1999; Gomez-Pinilla *et al*, 2002; Molteni *et al*, 2002). Decreased hippocampal neurogenesis has been linked with depressive-like behaviors in preclinical studies (Duman *et al*, 1999; Sahay and

Hen, 2007), and consistent with an ability to increase hippocampal neurogenesis, exercise has been demonstrated to have an antidepressant effect in a depressive line of rats (Bjornebekk *et al*, 2006), and to improve depressive symptoms in human patients (Ernst *et al*, 2006). Considering a recently reported link between suppression of hippocampal neurogenesis and increased cocaine intake and seeking behaviors in the rat (Noonan *et al*, 2010) along with previous evidence that exposure to stress (a treatment that reduces hippocampal neurogenesis), increases drug intake (Covington and Miczek, 2005), it is important to consider effects of exercise on hippocampal function in addition to those on mesolimbic function. Because exercise leads to plasticity in both depression-related circuitry (i.e. hippocampal) and drug-seeking related circuitry (i.e. the mesolimbic system), it is difficult to determine where the precise locus of the "anti drug seeking" effects of exercise exists.

Consistent with the effects of exercise on drug rewards, there is also evidence that running can decrease preference for natural reinforcers. Under conditions of limited food access, rats with constant access to running wheel will actually cease to eat to the point of death (Routtenberg and Kuznesof, 1967; Routtenberg, 1968). This extreme phenomenon is observed only when periods of food access occur with continued access to a running wheel, although it may suggest that exposure to exercise may reduce motivation in a general manner for both drug and non-drug reinforcers. A final consideration of the effects of exercise is that a running wheel housed within the animal cage may act as a form of environmental enrichment. While it is difficult to completely dissociate environmental enrichment from exercise (EE housed animals exercise more), dissociable effects of EE and exercise have been reported (van Praag *et al*., 1999; Olson *et al*, 2006).

5. Novelty/Sensory Stimulation/Environmental Enrichment

Novel stimuli, sensory stimulation, and enriched environments are all reinforcing to animals, including rodents (Van de Weerd *et al*, 1998; Besheer *et al*, 1999; Bevins and Bardo, 1999; Mellen and Sevenich MacPhee, 2001; Dommett *et al*, 2005; Cain *et al*, 2006; Olsen and Winder, 2009). Novel environments, sensory stimuli, and environmental enrichment (EE) have all been shown to activate the mesolimbic DA system (Chiodo *et al*, 1980; Horvitz *et al*, 1997; Rebec *et al*, 1997a; Rebec *et al*, 1997b; Wood and Rebec, 2004; Dommett *et al*., 2005; Segovia *et al*, 2010), suggesting overlap with addiction circuitry. In human populations, sensation and novelty seeking have been linked to susceptibility, intake, and severity of drug abuse (Cloninger, 1987; Kelly *et al*, 2006); for review, see (Zuckerman, 1986). In rodents, response to novelty has also been correlated with subsequent drug self-administration (Piazza *et al*, 1989; Cain *et al*, 2005; Meyer *et al*, 2010), suggesting that these two phenotypes covary. Based on these and neurochemical data, there is thought to be overlap in mesocorticolimbic circuitry that underlies response to novelty and drugs of abuse (Rebec *et al*., 1997a; Rebec *et al*., 1997b; Bardo and Dwoskin, 2004). Sensory stimuli (especially visual and auditory stimuli) have been studied for their reinforcing properties (Marx *et al*, 1955; Stewart, 1960; Cain *et al*., 2006; Liu *et al*, 2007; Olsen and Winder, 2010), and we have recently demonstrated an involvement of dopaminergic and glutamatergic signaling in mediating the reinforcing properties of varied sensory stimuli (Olsen and Winder, 2009; Olsen *et al*, 2010). Plasticity following discrete exposure to novelty or sensory stimuli within parameters that would not be aversive is limited, although there is extensive evidence for neural plasticity following strong activation or deprivation of sensory systems (Kaas, 1991; Rauschecker, 1999; Uhlrich *et al*, 2005; Smith *et al*, 2009). However, there is a wealth of data on neural plasticity associated with housing in an enriched environment (which includes aspects of other topics discussed, including novelty and exercise; for more in-depth reviews, see (Kolb and Whishaw, 1998; van Praag *et al*, 2000a; Nithianantharajah and Hannan, 2006)). Hebb's renowned theory of learning was

influenced by results he obtained demonstrating that rats housed in an enriched environment (his own house) performed better at learning tasks than littermates housed in the laboratory (Hebb, 1947). Subsequent studies have identified drastic changes in brain weight, angiogenesis, neurogenesis, gliogenesis, and dendritic structure in response to environmental enrichment (EE) (Bennett *et al*, 1969; Greenough and Chang, 1989; Kolb and Whishaw, 1998; van Praag *et al*, 2000b). More recent data from microarray studies have shown that EE housing induces expression of gene cascades involved with NMDA-dependent plasticity and neuroprotection (Rampon *et al*, 2000). The same group found that exposure to the EE environment for only 3 hours (i.e. exposure to numerous novel stimuli) had similar results, increasing gene expression in pathways associated with neuritogenesis and plasticity (Rampon *et al*., 2000).

Like exercise reward, as a general trend the plasticity induced by EE appears to reduce the sensitivity to drugs of abuse and may impart a “protective phenotype” against drug taking (Stairs and Bardo, 2009; Thiel *et al*, 2009; Solinas *et al*, 2010; Thiel *et al*, 2011). Compared to animals in impoverished conditions, EE produced a rightward shift in the dose-response curve of locomotor activation by morphine, as well as attenuated morphine- and amphetamine-induced locomotor sensitization (Bardo *et al*, 1995; Bardo *et al*, 1997). A similar trend was observed following psychostimulant treatment, where EE attenuated the locomotor activating and sensitization effects of nicotine and reduced cocaine self-administration and seeking behavior (although EE increased cocaine CPP) (Green *et al*, 2003; Green *et al*, 2010). Interestingly, EE did not lead to differences in NAc or striatal DA synthesis or mu opiate receptor binding in several mesocorticolimbic areas investigated (Bardo *et al*., 1997), although Segovia and colleagues did find an increase in basal and K^+-stimulated NAc DA following EE (Segovia *et al*., 2010). In the PFC (but not NAc or striatum), EE rats were found to have reduced dopamine transport capacity (Zhu *et al*, 2005). This resulting increase in prefrontal DA signaling could impact mesolimbic activity, impulsivity, and drug self-administration (Deutch, 1992; Olsen and Duvauchelle, 2001, 2006; Everitt *et al*., 2008; Del Arco and Mora, 2009). More recent work has identified attenuated activity of CREB and reduced BDNF in the NAc following 30 days EE compared to impoverished rats (Green *et al*., 2010), although NAc BDNF levels were similar between EE and control rats following one year of housing (Segovia *et al*., 2010). EE also affects transcriptional activity induced by drugs of abuse. Induction of the immediate early gene *zif268* in the NAc by cocaine is reduced, as is cocaine-induced expression of delta FosB in the striatum (although EE itself was found to elevate striatal delta FosB) (Solinas *et al*, 2009). This “protective” effect is not just seen in the field of addiction. The degree of plasticity induced by EE is so great that it is continuing to be studied in terms of protecting and improving recovery from several neurological diseases (van Praag *et al*., 2000a; Spires and Hannan, 2005; Nithianantharajah and Hannan, 2006; Laviola *et al*, 2008; Lonetti *et al*, 2010), and a recent report even found a hypothalamic-dependent increase in cancer remission when animals were housed in EE (Cao *et al*, 2010). As discussed in regards to exercise, conclusions regarding the effects of EE on drug self-administration should be made while considering the potential anti-depressive effects of enriched housing. Like exercise, EE has been demonstrated to increase hippocampal neurogenesis (van Praag *et al*., 2000b) and reduce the depressive-like effects of stress in rodents (Laviola *et al*., 2008).

6. Discussion

In some people, there is a transition from “normal” to compulsive engagement in natural rewards (such as food or sex), a condition that some have termed behavioral or non-drug addictions (Holden, 2001; Grant *et al*., 2006a). As research in non-drug addiction progresses, knowledge gained from the fields of drug addiction, motivation, and obsessive-compulsive disorder will contribute to the development of therapeutic strategies for non-

drug addictions. There is emerging clinical evidence that pharmacotherapies used to treat drug addiction may be a successful approach to treating non-drug addictions. For example, naltrexone, nalmefine, N-acetyl-cysteine, and modafanil have all been reported to reduce craving in pathological gamblers (Kim *et al*, 2001; Grant *et al*, 2006b; Leung and Cottler, 2009). Opiate antagonists have also shown promise in small studies in the treatment of compulsive sexual behavior (Grant and Kim, 2001), and topirimate has shown success in reducing binge episodes and weight in obese patients with binge eating disorder (McElroy *et al*, 2007). The success of these treatments for non-drug addictions further suggests that there are common neural substrates between drug and non-drug addictions.

Animal models of motivated and compulsive behavior will also help provide insight into neural mechanisms underlying non-drug addictions (Potenza, 2009; Winstanley *et al*, 2010). Some types of non-drug addictions are more easily modeled in rodents than others. For example, paradigms using access to highly palatable foods have provided an excellent framework for the study of the transition to compulsive or excessive food intake. Rodent models using access to high fat, high sugar, or “cafeteria style” diet result in increased caloric intake and elevated weight gain, principal components of human obesity (Rothwell and Stock, 1979, 1984; Lin *et al*, 2000). These treatments can increase future motivation for food reward (Wojnicki *et al*, 2006) and lead to alterations in neural plasticity in the mesolimbic dopamine system (Hoebel *et al*, 2009). Food self-administration models have further found that food-associated cues and stressors can lead to relapse to food seeking (Ward *et al*., 2007; Grimm *et al*, 2008; Nair *et al*., 2009b), a phenomenon also reported for human dieters (Drewnowski, 1997; Berthoud, 2004). Thus, these types of models have high construct validity and may result in neuroadaptations that give us insight into human conditions such as compulsive food intake or relapse to excessive eating habits following a beneficial change in diet.

Another area of recent progress has been in the development of rodent models of gambling and risky choice (van den Bos *et al*, 2006; Rivalan *et al*, 2009; St Onge and Floresco, 2009; Zeeb *et al*., 2009; Jentsch *et al*, 2010). Studies have demonstrated that rats are capable of performing the Iowa gambling task (IGT) (Rivalan *et al*., 2009; Zeeb *et al*., 2009) and a slot machine task (Winstanley *et al*, 2011). One study found that rats that performed suboptimally on the IGT had higher reward sensitivity and higher risk taking (Rivalan *et al*., 2009), similar to traits that have been associated with pathological gambling and drug addiction in human patients (Cloninger, 1987; Zuckerman, 1991; Cunningham-Williams *et al*, 2005; Potenza, 2008). Using rodent models, studies are also focusing on neural mechanisms underlying the “drive to gamble” and the development of pathological gambling which may provide insight into development of pharmacotherapies for pathological gambling (Winstanley, 2011; Winstanley *et al*., 2011).

Mechanistic studies using sensory stimuli as a reinforcer have found overlap of the molecular mechanisms that modulate self-administration of sensory reinforcers and drugs of abuse (Olsen and Winder, 2009; Olsen *et al*., 2010). While research in this field is in its infancy, these and future experiments may give insight into potential therapeutic strategies for the treatment of compulsive internet use or video gaming.

While these and other advancements in behavioral models are beginning to give us potential insight into processes underlying non-drug addictions, there are several challenges and limitations when attempting to model such behavior. One limitation is that in most models, there is no significant consequence of maladaptive decision-making or excessive engagement in the behaviors. For example, rodent gambling tasks use smaller rewards or increased delay between rewards in response to poor decisions, but the animal doesn't risk losing his home after a losing streak. Another limitation is that excessive engagement in

behaviors such as food or drug self-administration in laboratory conditions may be a consequence of animals not having access to other non-drug rewards (Ahmed, 2005). This unique situation has been proposed to model risk-prone individuals in human populations (Ahmed, 2005), although it still represents a caveat for these types of studies.

Continued study of excessive, compulsive, or maladaptive performance in eating, gambling, and other non-drug behaviors will be key in advancing our understanding of non-drug addictions. Results from preclinical studies using these methods combined with research in human populations will promote “crossover” pharmacotherapies that could benefit both drug and non-drug addictions (Grant *et al*., 2006a; Potenza, 2009; Frascella *et al*., 2010).

6.1 Remaining Questions

One question that remains is whether the same populations of neurons are activated by drug and natural rewards. While there is ample evidence that there is overlap in the brain regions affected by natural rewards and drugs of abuse (Garavan *et al*, 2000; Karama *et al*, 2002; Childress *et al*, 2008), there is conflicting data regarding overlap in neural populations that are affected by natural rewards and drugs. Single unit recordings from rat and non-human primate ventral striatum indicate that different neural populations are engaged during self-administration of natural rewards (food, water, and sucrose) vs. cocaine or ethanol, although there was a high degree of overlap between the different natural rewards used in these studies (Bowman *et al*, 1996; Carelli *et al*, 2000; Carelli, 2002; Robinson and Carelli, 2008). There is also evidence that drugs of different classes engage distinct neural ensembles within the mesocorticolimbic system. Single unit recordings from the medial PFC and NAc of rats self-administering cocaine or heroin revealed that different populations of neurons were differentially engaged during both the anticipatory and post-infusion periods (Chang *et al*, 1998). The distinction between natural and drug reward may not be so absolute, however, as there is also evidence for the contrary. Following timed exposure to methamphetamine and sexual experience, there was significant coincidence of neurons activated by these two rewards in the NAc, anterior cingulate cortex, and basolateral amygdala (Frohmader *et al*., 2010). Thus, recruitment of neural populations by particular drugs of abuse may overlap with that of some natural rewards, but not others. Future studies using more comprehensive batteries of natural and drug rewards will be needed to address this issue.

Another question that arises is to what degree the study of natural reward processing can help us understand drug and non-drug addiction. Recent evidence suggests that exposure to some non-drug rewards can impart “protection” from drug rewards. For example, sugar and saccharin can reduce self-administration of cocaine and heroin (Carroll *et al*., 1989; Lenoir and Ahmed, 2008), and these natural reinforcers have been demonstrated to outcompete cocaine in choice self-administration in a large majority of rats (Lenoir *et al*., 2007; Cantin *et al*., 2010). In a retrospective analysis of animals across studies, Cantin *et al*. reported that only ~9% of rats prefer cocaine over saccharin. An interesting possibility is that this small proportion of animals represents a population that is susceptible to “addiction”. Studies using cocaine self-administration have attempted to identify “addicted” rats using criteria modified to model DSM-IV criteria for drug dependence (Deroche-Gamonet *et al*., 2004; Belin *et al*, 2009; Kasanetz *et al*, 2010). These studies have found that approximately ~17–20% of animals self-administering cocaine meet all three criteria, while estimates for rates of cocaine dependence in humans previously exposed to the drug range from ~5–15% (Anthony *et al*, 1994; O'Brien and Anthony, 2005). Thus, in the majority of animals sugar and saccharin appear to be more reinforcing than cocaine. A question of great interest is whether the minority of animals that find the drug reinforcer to be preferred represent a “vulnerable” population that is more relevant to the study of addiction. Thus, comparing individual animals' preferences for drug versus natural rewards may yield insight into vulnerability factors associated with drug addiction.

A final question is whether the pursuit of natural rewards can help prevent or treat drug addiction. Environmental enrichment has been proposed as both a preventative and a treatment measure for drug addiction based on preclinical studies with several drugs of abuse (Bardo *et al*, 2001; Deehan *et al*, 2007; Solinas *et al*, 2008; Solinas *et al*., 2010). Studies of human inmates suggest that environmental enrichment through the use of "therapeutic communities" is in fact an effective treatment option both for reducing future crime and substance abuse (Inciardi *et al*, 2001; Butzin *et al*, 2005). These results are promising and suggest that environmental enrichment could potentially improve neuroadaptations associated with chronic drug use. Similar to environmental enrichment, studies have found that exercise reduces self-administration and relapse to drugs of abuse (Cosgrove *et al*., 2002; Zlebnik *et al*., 2010). There is also some evidence that these preclinical findings translate to human populations, as exercise reduces withdrawal symptoms and relapse in abstinent smokers (Daniel *et al*, 2006; Prochaska *et al*, 2008), and one drug recovery program has seen success in participants that train for and compete in a marathon as part of the program (Butler, 2005).

7. Concluding Remarks

There are many parallels between non-drug addictions and drug addictions, including craving, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse (Marks, 1990; Lejoyeux et al., 2000; National Institute on Drug Abuse (NIDA) et al., 2002; Potenza, 2006). As I have reviewed, there is a glut of evidence that natural rewards are capable of inducing plasticity in addiction-related circuitry. This should not come as a surprise, as 1) drugs of abuse exert actions within the brain that are similar to, albeit more pronounced than natural rewards (Kelley and Berridge, 2002), and 2) learned associations between things such as food or sexual opportunities and the conditions which maximize availability is beneficial from a survival standpoint and is a natural function of the brain (Alcock, 2005). In some individuals, this plasticity may contribute to a state of compulsive engagement in behaviors that resembles drug addiction. Extensive data suggests that eating, shopping, gambling, playing video games, and spending time on the internet are behaviors that can develop into compulsive behaviors that are continued despite devastating consequences (Young, 1998; Tejeiro Salguero and Moran, 2002; Davis and Carter, 2009; Garcia and Thibaut, 2010; Lejoyeux and Weinstein, 2010). As with drug addiction, there is a transition period from moderate to compulsive use (Grant *et al*., 2006a), although it is difficult to draw a line between "normal" and pathological pursuit of reward. One potential approach to make this distinction is to test patients using DSM criteria for substance dependence. Using this approach, reports have been made that these DSM criteria can be met when applied to patients that compulsively engage in sexual activity (Goodman, 1992), gambling (Potenza, 2006), internet usage (Griffiths, 1998), and eating (Ifland *et al*, 2009). Taken with the fact that the DSM-5 is expected to include categories of moderate and severe within "addiction and related disorders" (American Psychiatric Association, 2010), it would perhaps serve addiction researchers and clinicians well to consider addiction as a spectrum disorder. In other fields, this type of nomenclature has helped to raise awareness that disorders such as autism and fetal alcoholism have numerous levels of severity. In the case of addiction (drug or non-drug), identification of symptoms even below the threshold of "moderate" may help identify at-risk individuals and allow for more effective interventions. Future studies will continue to reveal insights into how the pursuit of natural rewards can become compulsive in some individuals and how best to treat non-drug addictions.

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Table 1

Summary of Plasticity Observed Following Exposure to Drug or Natural Reinforcers.

	Reinforcer Type					
	Opiates	**Psychostimulants**	**High Fat/High Sugar Food**	**Sex**	**Exercise/EE/Sensory Reinforcement**	**References**
Behavioral Plasticity						
Escalation of intake	✓	✓	✓			(Colantuoni *et al.*, 2001; Koob and Kreek, 2007; Clark *et al*, 2010)
Withdrawal effects	✓	✓	✓		✓	(Aghajanian, 1978; Christie and Chesher, 1982; Markou and Koob, 1991; Colantuoni *et al.*, 2002; Teegarden and Bale, 2007)
Cross-sensitization with psychostimulants	✓	N/A	✓	✓	(attenuated)	(Vezina *et al.*, 1989; Bardo *et al.*, 1995; Fiorino and Phillips, 1999; Avena and Hoebel, 2003b, a; Green *et al.*, 2003; Gosnell, 2005; Pitchers *et al.*, 2010a)
Psychostimulant self-administration	↑ or NC	↑	↓ (w/ concurrent availability)		↓ or NC	(Carroll *et al.*, 1989; Lett, 1989; Bardo *et al.*, 2001; Covington and Miczek, 2001; Cosgrove *et al.*, 2002; He and Grasing, 2004; Lenoir *et al.*, 2007; Smith *et al.*, 2008; Green *et al.*, 2010)
Psychostimulant conditioned place preference	↑	↑	↓	↑	↓ (exercise) ↑ (environmental enrichment)	(Shippenberg and Heidbreder, 1995; Davis *et al.*, 2008; Green *et al.*, 2010; Pitchers *et al.*, 2010a; Thanos *et al.*, 2010)
Reinstatement of drug-seeking behavior	↑	↑			↓	(Stewart, 2000; Lynch *et al.*, 2010; Zlebnik *et al.*, 2010)
Neurochemical Plasticity						
Sensitized NAc dopamine response	No	✓	No (intermittent sugar)	✓		(Robinson and Becker, 1982; Kohlert and Meisel, 1999; Leri *et al.*,

	Reinforcer Type					
	Opiates	**Psychostimulants**	**High Fat/High Sugar Food**	**Sex**	**Exercise/EE/Sensory Reinforcement**	**References**
						2003; Avena *et al.*, 2008)
Altered striatal dopamine signaling	↓D2, ↑D3	↑D1, ↓D2, ↑D3	↑D1, ↓D2, ↑D3, reduced DA turnover		↑ D2	(Packard and Knowlton, 2002; Porrino *et al.*, 2004a; Porrino *et al.*, 2004b; Davis *et al.*, 2008)
Altered striatal opioid signaling	NC enkephalin ↑ or NC μ receptors ↑ dynorphin	↑ μ receptors ↑ κ receptors ↑ dynorphin	↑ μ receptors (also in offspring) ↓ enkephalin ↑ enkephalin in offspring	↑ μ receptors	NC μ receptors ↑ dynorphin	(Hammer, 1989; Unterwald *et al.*, 1994b; Bardo *et al.*, 1997; Steiner and Gerfen, 1998; Turchan *et al*, 1999; Weme *et al.*, 2000; Colantuoni *et al.*, 2001; Kelley *et al.*, 2003; Spangler *et al.*, 2004; Bradley *et al.*, 2005; Contet *et al.*, 2008; Solecki *et al*, 2009; Vucetic *et al.*, 2010; Wee and Koob, 2010)
Elevated amygdala CRF during withdrawal	✓	✓	✓			(Maj *et al*, 2003; Teegarden and Bale, 2007; Koob and Le Moal, 2008)
Reduced NAc CREB phosphorylation	✓	✓	✓ (withdrawal)		✓	(McDaid *et al.*, 2006a; McDaid *et al.*, 2006b; Teegarden and Bale, 2007; Wallace *et al.*, 2008; Green *et al.*, 2010)
Elevated NAc delta FosB	✓	✓	✓	✓	✓	(Nestler *et al.*, 1999; Werme *et al.*, 2002; Wallace *et al.*, 2008; Solinas *et al.*, 2009; Pitchers *et al.*, 2010b)
Mesocorticolimbic Synaptic Plasticity						
Altered VTA AMPA/NMDA ratio during withdrawal	✓	✓	✓			(Saal *et al.*, 2003; Chen *et al.*, 2008a; Chen *et al*, 2010)
NAc dendrite number	↓	↑		↑		(Fiorino and Kolb, 2003; Robinson and Kolb, 2004; Meisel and

	Reinforcer Type					
	Opiates	**Psychostimulants**	**High Fat/High Sugar Food**	**Sex**	**Exercise/EE/Sensory Reinforcement**	**References**
						Mullins, 2006; Pitchers *et al.*, 2010a)
NAc spine density	↓	↑	NC (operant sucrose pellets, limited access)	↑		(Fiorino and Kolb, 2003; Robinson and Kolb, 2004; Crombag *et al*, 2005; Meisel and Mullins, 2006; Pitchers *et al.*, 2010a)

CREB: cyclic AMP response element binding protein, CRF: corticotropin releasing factor, NAc: nucleus accumbens, N/A: not applicable, NC: no change, VTA: ventral tegmental area.