Published in final edited form as:

Psychopharmacology (Berl). 2014 May ; 231(9): 1897–1912. doi:10.1007/s00213-014-3461-1.

Addicted to Palatable Foods: Comparing the Neurobiology of Bulimia Nervosa to that of Drug Addiction

Natalie A. Hadad, M. A. and Lori A. Knackstedt, Ph.D.

Department of Psychology University of Florida P.O. Box 112250 Gainesville, FL 32611-2250

Abstract

Rationale: Bulimia Nervosa (BN) is highly comorbid with substance abuse and shares common phenotypic and genetic predispositions with drug addiction. Although treatments for the two disorders are similar, controversy remains about whether BN should be classified as addiction.

Objectives: Here we review the animal and human literature with the goal of assessing whether BN and drug addiction share a common neurobiology.

Results: Similar neurobiological features are present following administration of drugs and bingeing on palatable food, especially sugar. Specifically, both disorders involve increases in extracellular dopamine (DA), D1 binding, D3 mRNA, and FosB in the nucleus accumbens (NAc). Animal models of BN reveal increases in ventral tegmental area (VTA) DA and enzymes involved in DA synthesis that resemble changes observed after exposure to addictive drugs. Additionally, alterations in the expression of glutamate receptors and prefrontal cortex activity present in human BN or following sugar bingeing in animals are comparable to the effects of addictive drugs. The two disorders differ in regards to alterations in NAc D2 binding, VTA DAT mRNA expression, and the efficacy of drugs targeting glutamate to treat these disorders.

Conclusions: Although additional empirical studies are necessary, the synthesis of the two bodies of research presented here suggests that BN shares many neurobiological features with drug addiction. While few FDA-approved options currently exist for the treatment of drug addiction, pharmacotherapies developed in the future which target the glutamate, DA, and opioid systems may be beneficial for the treatment of both BN and drug addiction.

Keywords

Bulimia Nervosa; Addiction; Neurobiology; Dopamine; Glutamate; Opioid; Palatable Food; Bingeing; Sugar; Sucrose

Introduction

Bulimia Nervosa (BN) is an eating disorder characterized by recurrent binge eating episodes coupled with compensatory behaviors to avoid weight gain, a lack of control over eating, fear of gaining weight, and distorted body image. The DSM-V defines a binge eating

episode as the ingestion of a larger amount of food than most individuals would eat in a similar situation within 2 hours (American Psychiatric Association 2013). Binges can include a variety of foods, but typically include sweet, high-calorie foods (Broft et al. 2011; Fitzgibbon and Blackman 2000). The DSM-IV TR classifies two types of BN: 1) the purging type, which is characterized by regular engagement in self-induced vomiting or the misuse of laxatives, enemas, or diuretics, and 2) the non-purging type, which includes other inappropriate compensatory behaviors, such as fasting or excessive exercise (American Psychiatric Association 2000). However, since most BN individuals engage in both “purging” and “non-purging” compensatory behaviors, the DSM-5 has combined these two types of BN and refers to them collectively as *purge behaviors* (American Psychiatric Association 2013). BN affects between 1% and 3% of the population across American, European, and Australian cultures (Smink et al. 2012) and is highly comorbid with substance use disorders (American Psychiatric Association 2013; Conason and Sher 2006; Nøkleby 2012). Relative to the general public, individuals with eating disorders are at a five-fold increased risk of abusing alcohol or illicit drugs (The National Center on Addiction and Substance Abuse 2003).

Given the high rates of comorbidity and the phenotypic and genetic similarities between eating and substance use disorders, eating disorders have been proposed to be a form of addiction (Brisman and Siegel 1984; Carbaugh and Sias 2010; Conason and Sher 2006). Specific to BN, behavioral characteristics associated with repeated binge eating episodes, preoccupation with food and weight, difficulty abstaining from binge eating and compensatory behaviors, and eating in secrecy are analogous to characteristics of substance dependence that include repeated substance consumption, obsession with the substance, unsuccessful efforts to reduce use, and withdrawal from social activities in order to use the substance in private or with substance-using friends (American Psychiatric Association 2013). Genetically, the single nucleotide polymorphism Taq1A in the dopamine DRD2/ANKK1 gene (Berggren et al. 2006; Connor et al. 2008; Nisoli et al. 2007) and polymorphisms in the serotonin system (Di Bella et al. 2000; Gervasini et al. 2012; McHugh et al. 2010) similarly increase risk for acquiring both BN and drug addiction, further corroborating the idea that BN is a type of addiction.

Despite symptom and genetic commonalities among BN and drug addiction, and the fact that addiction models are used as a basis for treatment of BN (Trotzky 2002; Wilson 1995), there remains controversy about whether or not BN is a form of addiction. This problem results, at least in part, from difficulties associated with modeling BN in laboratory animals. Although there is no perfect animal model of BN, several animal paradigms that capture characteristics of BN have been created (for detailed review of these models, see Avena and Bocarsly 2012). These animal models have allowed for great advances in the study of BN, but the number of studies assessing the neurobiology of BN is fewer than those investigating substance abuse.

Binge eating is a critical diagnostic component of BN (American Psychiatric Association 2013) and, as discussed above, typically involves over-consumption of sweet, high calorie foods (Broft et al. 2011; Fitzgibbon and Blackman 2000). Another essential component of BN is the use of inappropriate compensatory behaviors, such as fasting and purging

(American Psychiatric Association 2013). As such, here we focus primarily on animal models that pair bingeing of sweet or high fat foods with experimenter- or self-induced restriction or purging. To date, little is known about how the neurobiology of BN maps on to current addiction models. Thus, the present review synthesizes results of animal and human studies of BN and drug addiction in order to examine whether BN shares neurobiological features with drug addiction.

Animal models of BN

Several animal paradigms that recapitulate characteristics of BN are used to study the neurobiology of BN. Given that the DSM-5 is relatively new, animal models typically mimic traits associated with one of the two types of BN described in the DSM-IV TR: non-purging and purging BN. Thus, for the remainder of this paper, we will utilize the distinction between non-purging and purging BN as outlined by the DSM-IV TR and described above.

Modeling non-purging BN

The “food restriction/deprivation” model uses rats to recapitulate the non-purging type of BN by imposing periods of food restriction or deprivation and periods of free access to chow or palatable foods (e.g., Hagan and Moss 1991; 1997). After three cycles of food deprivation to 75% of normal body weight followed by recovery to normal weight, rats display binge-like eating during the first hour of ad lib feeding of rat chow (Hagan and Moss 1991). Similarly, rats subjected to 12-weeks of 4-day food restriction periods followed by 2- to 4-day periods of free access to chow or palatable foods experience hyperphagia during free access periods (Hagan and Moss 1997). Notably, these rats exhibit long-term aberrant feeding patterns and continue to display binge-eating behaviors even after returning to a normal feeding schedule and body weight, particularly when presented with palatable food (Hagan and Moss 1997).

In the “sugar addiction” model, rats are given intermittent access to a sugar solution: 12-16 hours of food deprivation followed by 8-12 hours of access to 10% sucrose or 25% glucose plus chow and water daily (e.g., Avena et al. 2008a, b; Avena et al. 2006a; Colantuoni et al. 2002). Compared to control rats, rats given intermittent access to sucrose increase sucrose intake and display binge-like behaviors, which is defined by the amount of sucrose consumed during the first hour of each access period (Avena et al. 2008a; Avena et al. 2006a; Colantuoni et al. 2002). Notably, rats given intermittent access to a sucrose solution voluntarily eat significantly less regular chow than rats given intermittent or ad libitum access to chow (Avena et al. 2008a; Avena et al. 2006a). This hypophagia is similar to eating patterns of BN-individuals who tend to restrict food intake preceding and following binges (American Psychiatric Association 2013). Rats given intermittent access to sugar (but not regular chow) also display physical signs of withdrawal (e.g. teeth chattering, head shaking) after 24-36 hours of deprivation. This model allows for the assessment of neurobiological features during binge eating and subsequent restriction, which accurately models key characteristics of non-purging BN.

Unlike the models described above, the “limited access” model does not expose rats to food restriction or deprivation. Rather, rats are given ad libitum access to standard chow and

water, as well as intermittent access to a palatable food composed of fat, sugar, or a fat/sugar combination for 1-2 hours (e.g., Corwin and Wojnicki 2006; Wong et al. 2009). Rats given intermittent access to 100% vegetable shortening binge on fat and voluntarily decrease regular chow consumption (Corwin and Wojnicki 2006). This decrease in standard chow consumption is similar to rats given intermittent access to a 10% sucrose solution (e.g., Avena et al. 2008a) and hypophagia seen in BN-individuals (American Psychiatric Association 2013). Thus, the “limited access” model recapitulates eating patterns of non-purging BN-individuals by capturing self-imposed restriction coupled with bingeing.

Taken together, the “food restriction/deprivation” model, the “sugar addiction” model, and the “limited access” model all induce binge eating. Furthermore, they are characterized by experimenter- or self-imposed restriction. As detailed above, bingeing and restriction are two key features of non-purging BN. Thus, by interchanging periods of binge eating and restriction of chow and/or palatable food, these models serve as satisfactory animal models of non-purging BN.

Modeling purging BN

Creating an animal model of the purging type of BN has been difficult because rats lack the esophageal muscular anatomy to vomit. Thus, in order to capture both bingeing and purging behaviors in one animal model, researchers have combined the sham-feeding rat model with binge eating (e.g., Avena et al. 2006b). In the sham-feeding rat model, a gastric fistula is inserted into the rat’s stomach or esophagus, resulting in minimal contact between food and the animal’s gastric and intestinal mucosa. Because the gastric fistula causes ingested liquid to drain from the rat’s stomach, caloric absorption is limited (Casper et al. 2008). By cycling sham-fed rats through a 12-hour food restriction period followed by 12 hours of free access to food, rats binge on sweet foods and purge via the gastric fistula (Avena et al. 2006b). This procedure has been recently validated among BN-individuals (see Klein and Smith 2013). Specifically, BN women who are modified-sham-fed by sipping and spitting on liquid solutions engage in hyperphagia whereas normal controls and women with Anorexia Nervosa do not. Thus, although animal models cannot fully capture the complexity of human eating disorders (Avena and Bocarsly 2012), the sham-feeding rat model coupled with binge eating accurately captures purging BN.

Criteria for inclusion in the present review

The animal models described above recapitulate key characteristics of BN. Mimicking non-purging BN, the “food restriction/deprivation,” “sugar addiction,” and “limited access” models couple bingeing with experimenter- or self-imposed restriction. Importantly, these are two key characteristics of non-purging BN (American Psychiatric Association 2000). Capturing the two main components of purging BN (American Psychiatric Association 2000), the sham-feeding/bingeing model recapitulates bingeing coupled with purging. There are other models of BN, such as the restriction-stress model that couples food restriction with stress (e.g., Hagan et al. 2002; Inoue et al. 1998). However, these models have not been used to assess neurobiological changes addressed in this manuscript and, thus, they will not be discussed.

The present review includes animal models described above. Since restriction and bingeing are the main components of BN (American Psychiatric Association 2013), also included here are findings from studies that involve *either* fasting or bingeing in laboratory animals. We compare results from such studies to those obtained using various models of drug addiction which each capture essential components of human addiction: conditioned place preference, operant drug self-administration, oral consumption of alcohol, and the reinstatement of drug-seeking following extinction of the drug-seeking response. Importantly, unlike recent reviews that compare the neurobiological underpinnings of addiction to that of binge eating in animals that leads to obesity (e.g., DiLeone et al. 2012; Volkow et al. 2013), findings from studies using animal models of obesity are not included here because BN individuals are not typically overweight (American Psychiatric Association 2013).

The Neurobiology Underlying the Acquisition of Addiction

Addictive drugs such as cocaine, amphetamines, opiates, alcohol, and nicotine all directly or indirectly stimulate dopamine (DA) neurons in the ventral tegmental area (VTA), resulting in the release of DA into the nucleus accumbens (NAc) and prefrontal cortex (PFC) (for review see Bromberg-Martin et al. 2010). While the precise role of this DA release in directing behavior has been debated over the course of the past three decades, it is clear that DA release in these regions is an essential mediator of the acquisition of drug-seeking (for review see Wise 2004). DA release is necessary to encode environmental cues and behavioral responses associated with obtaining rewards and enables the use of learned information to execute drug-seeking behavior (for review see Schultz 2004; Wise 2004).

DA cell bodies are found in the VTA and the substantia nigra (SN). The VTA sends projections to the NAc via the mesolimbic DA pathway and to the PFC via the mesocortical pathway. The SN projects to both the ventral and dorsal striatum. Post-synaptic DA receptors are grouped into D1-like receptors, which include the D1 and D5 subtypes, and D2-like receptors, which include D2, D3, and D4 receptors. D1-like receptors are Gs-coupled and are preferentially expressed on the post-synaptic membrane while D2-like receptors are Gi-coupled and are expressed both pre- and post-synaptically. The consequences of binding at these receptor types are varied depending on the site of expression and brain region (for details, see review by El-Ghundi et al. 2007). As discussed below, both D1 and D2 receptors are implicated in addiction, as is the DA transporter (DAT) which is responsible for the removal of DA from the extracellular space. In this section we review results obtained from animal studies of BN to ascertain if the effects of BN on the mesolimbic DA system are comparable to those of addictive drugs.

Nucleus accumbens dopamine

Stimulation of DA neurons in the VTA causes DA to be released in the NAc and regulates motivated behavior and the acquisition of drug addiction. Ethanol, nicotine, opiates, amphetamine, and cocaine increase DA levels in the NAc, but drugs not abused by humans do not alter DA levels in this area (Di Chiara and Imperato 1988). Furthermore, whereas DA release is sustained following repeated drug administration, the effect of food on DA release abates over time unless food availability is novel or inconsistent (Ljungberg et al. 1992;

Mirenowicz and Schultz 1994). Here we discuss data derived from animal models of purging and non-purging BN which indicate that the NAc DA response to palatable food differs from that to regular chow.

In their study of sucrose sham-fed-sucrose-bingeing rats, Avena and colleagues (2006b) examined NAc DA release in response to sucrose. Rats in the sham-fed groups whose gastric fistulas were open during the first hour of food access displayed sucrose-bingeing behavior and consumed significantly more sucrose during the first hour of access on all testing days (days 1, 2, and 21) relative to real-fed rats whose gastric fistulas remained closed. In vivo microdialysis revealed that NAc extracellular DA significantly increased for both sham-fed and real-fed rats in response to tasting sucrose on all testing days. Importantly, although sucrose ingested during the first binge was immediately drained from sham-fed rats' stomachs, the DA response in the NAc continued to be observed on day 21. Similar results have been found using variations of the "sugar addiction" model. Exposing rats to a 12-hour food restriction period followed by a period of free access to sugar results in daily sugar bingeing and continued DA release in the NAc shell on days 1, 2, and 21 of sugar access (Rada et al. 2005). In contrast, control rats with ad libitum access to chow or sugar or ad libitum access to chow with access to sucrose for only 1-hour on two days do not binge on sugar, nor do they exhibit maintained DA release in the NAc shell. In another study, rats were deprived of food for 16 hours followed by access to chow for 8 hours with a 10% sucrose solution available for the first two hours for 21 days, resulting in sugar bingeing and significant increases in extracellular NAc DA on day 21 (Avena et al. 2008b). On day 28, after 7 days of being reduced to 85% of their original body weight, rats that drank sucrose showed an increase in NAc DA that was significantly higher than NAc DA release that resulted from drinking sucrose at normal body weight on day 21 (Avena et al. 2008b). In another study, cycling rats through 28 days of the "sugar addiction" protocol followed by 36 hours of fasting resulted in significantly lower NAc shell DA relative to rats given intermittent or ad libitum access to chow (Avena et al. 2008a).

Taken together, while restriction or sham-feeding coupled with sucrose-bingeing results in extracellular NAc DA increases which do not habituate over time (e.g., Avena et al. 2008b; Avena et al. 2006b; Colantuoni et al. 2001; Rada et al. 2005), DA levels decrease in the NAc shell during fasting periods (e.g., Avena et al. 2008a). When 2-hour access to sucrose is regained after fasting periods, extracellular NAc DA levels exceed what is observed in control animals given access to sucrose, which is indicative of a sensitized DA response (e.g., Avena et al. 2008b). Similarly, rats exposed to cocaine, morphine, nicotine, tetrahydrocannabinol, and heroin display increased extracellular NAc DA (e.g., Di Chiara and Imperato 1988; Gaddnas et al. 2002; Pothos et al. 1991; Tanda et al. 1997), whereas withdrawal from these substances decreases NAc DA (Acquas and Di Chiara 1992; Barak, Carnicella, Yowell, & Ron, 2011; Gaddnas et al. 2002; Mateo, Lack, Morgan, Roberts, & Jones, 2005; Natividad et al. 2010; Pothos et al. 1991; Rada, Jensen, & Hoebel, 2001; Weiss et al. 1992; Zhang et al. 2012). Likewise, the firing rate of VTA DA neurons decrease upon morphine (Diana et al. 1999) and cannabinoid (Diana et al. 1998) withdrawal. Similar to DA activity in response to sucrose after a period of restriction (Avena et al. 2008b), NAc DA concentrations increase when rats are re-exposed to nicotine after a 1 or 10-day period of withdrawal from 4 or 12 weeks of oral nicotine self-administration (Zhang et al. 2012). The

firing rate of VTA DA neurons significantly increase in response to morphine (Diana et al. 1999) and cannabinoid (Diana et al. 1998) administration after withdrawal. However, a cocaine challenge injection after 1 or 7 days of withdrawal from extended access self-administration fails to increase NAc DA, indicating the development of tolerance and not sensitization (Mateo et al., 2005). Following short-access intravenous nicotine self-administration, a nicotine challenge after 24 hours of withdrawal produces NAc DA elevations that are lower than those observed in drug-naïve rats, also indicating the development of tolerance (Rahman, Zhang, Engleman, & Corrigall, 2004). While extended access methamphetamine self-administration (Le Cozannet, Markou, & Kuczenski, 2013) produces results akin to Rahman et al. (2004), methamphetamine challenge injections following both non-contingent and short access to methamphetamine self-administration result in sensitized DA release relative to naïve controls (Lominac, Sacramento, Szumlinski, & Kippin, 2012).

In sum, while the reintroduction of palatable food after a period of deprivation results in sensitized DA release, the same effect is only observed following withdrawal from self-administered oral nicotine, self-administered short-access methamphetamine, and non-contingent administration of cannabinoids, morphine, and methamphetamine. DAT activity decreases after a period of fasting (Patterson et al., 1998), which may contribute to elevated DA observed in this brain region during re-feeding. A similar effect is seen during withdrawal from experimenter-administered methamphetamine (German, Hanson, & Fleckenstein, 2012).

Nucleus accumbens dopamine receptor expression

Rats exposed to a repeated restriction-refeeding cycle with access to both glucose and chow for 31 days progressively increase glucose intake, but not chow intake (Colantuoni et al. 2001). Twelve to 15 hours after bingeing, D1 receptor binding in the NAc shell and core is significantly higher in food-restricted, glucose-bingeing rats relative to controls. Within 1.5 to 2.5 hours after a sucrose binge, rats that are food restricted and given limited access to sucrose and chow for 7 days exhibit significantly lower D2 binding in the NAc relative to rats given limited access to chow alone (Bello et al. 2002). Relative to control animals given only chow, rats with intermittent access to sucrose for 21 days become sucrose dependent and exhibit decreased D2 mRNA and increased D3 mRNA in the NAc 1 hour after gaining access to sucrose and chow (Spangler et al. 2004).

Similar increases in NAc D1 receptor binding and/or mRNA levels have been found following repeated non-contingent administration of cocaine (Unterwald et al. 2001), nicotine (Bahk et al. 2002), and amphetamine (Young et al. 2011). However, Le Foll et al. (2003) found only increased D3 binding and mRNA but no change in D1 following non-contingent nicotine. Similarly, Metaxas et al. (2010) found no change in D1 expression following nicotine self-administration. Both continuous and intermittent self-administration of alcohol (Sari et al. 2006), and extended access to cocaine self-administration (Ben-Shahar et al. 2007) increase D1 mRNA as well as its surface expression (Conrad et al. 2010).

Increased D1 expression likely leads to a sensitized response to DA. The release of DA and subsequent stimulation of D1 receptors in the NAc occurring upon administration of

addictive drugs produces a signaling cascade that includes an increase in expression of transcription factors such as FosB (for review see Nestler et al. 2001). Preventing FosB transcriptional activity reduces the rewarding effects of drugs (Zachariou et al. 2006) and over-expression enhances drug reward (Colby et al. 2003; Kelz et al. 1999; Zachariou et al. 2006). Food restriction also increases FosB levels in the NAc of rats (Stamp et al. 2008; Vialou et al. 2011), which increases the motivation to obtain highly palatable food rewards, as evidenced by the finding that viral vector-mediated overexpression of FosB increases consumption of palatable food (Vialou et al. 2011). Thus, it is likely that BN increases FosB levels in the NAc in a manner similar to addictive drugs, thereby increasing the rewarding value of bingeing.

Bingeing also results in decreased D2 binding in the NAc (e.g., Bello et al. 2002; Colantuoni et al. 2001; Spangler et al. 2004). Notably, Taq1A, a common genetic polymorphism found among BN and drug-addicted individuals (Berggren et al. 2006; Connor et al. 2008; Nisoli et al. 2007), is related to reduced D2 receptor density (Neville et al. 2004). Although cocaine decreases D2 expression in the NAc (Conrad et al. 2010), repeated experimenter-administered nicotine (Bahk et al. 2002), experimenter-administered amphetamine (Mukda et al. 2009), and self-administered alcohol (Sari et al. 2006) increase D2 expression among rats. In light of the work with human drug addicts showing reductions in D2 binding (Volkow et al. 2001; Volkow et al. 1993), it is interesting that the same phenomenon is not observed following nicotine, amphetamine, or alcohol exposure in animals. However, the reduction in D2 binding seen in humans may precede drug exposure, and thus lower D2 levels would not necessarily be observed following exposure in animals. A reduction in D2 expression would likely produce increased DA efflux that could drive bingeing or drug-seeking.

In summary, sucrose bingeing in animal models of BN results in sustained elevation of NAc DA, increased D1 receptor binding and D3 mRNA, and decreased D2 receptor binding and mRNA in the NAc. While the D1 and D3 changes parallel those produced by addictive drugs (with the possible exception of nicotine for D1 changes), D2 reductions are not observed in many animal studies of drug addiction. It is possible that while D2 reductions present in humans serve to drive drug consumption, these reductions precede drug use and are not caused by it.

Dopamine in the ventral tegmental area

Dopaminergic cell bodies in the VTA project to the PFC, hippocampus, amygdala and NAc. Somatodendritic release of DA also occurs in the VTA upon cell firing (Beckstead et al. 2004) and has a significant impact on the activity of dopaminergic VTA neurons. This form of DA release activates local inhibitory D2 autoreceptors (Cragg and Greenfield 1997), thus inhibiting DA cell firing in the VTA (Bernardini et al. 1991; Wang 1981; White and Wang 1984) and DA release in the PFC and NAc terminal fields (Kalivas and Duffy 1991; Zhang et al. 1994). Therefore, somatodendritic release of DA in the VTA plays a pivotal role in the regulation of DA transmission along the mesocorticolimbic projections.

In vivo microdialysis has been used to examine concentrations of VTA DA during re-feeding. Rats were deprived of food and water for 36 hours prior to a period of re-feeding

during which microdialysis was performed (Yoshida et al. 1992). A significant increase in VTA DA concentrations was observed during re-feeding and drinking relative to baseline. VTA DA levels were sustained for 20-40 minutes after the end of the feeding and drinking sessions. Similarly, an IP injection of ethanol results in heightened extracellular VTA DA within 20 minutes, which then peaks 40 minutes after the injection and then declines to baseline (Kohl et al. 1998). Likewise, intravenous (Bradberry and Roth 1989) and IP (Reith et al. 1997; Zhang et al. 2001) cocaine administration and acute IP injections of methamphetamine (Zhang et al. 2001) increase extracellular DA in the VTA. While results of the Yoshida et al. (1992) study suggest an important role of VTA DA in feeding behaviors, rats in the study were only cycled through one period of food restriction and refeeding, and binge-eating behaviors were not assessed. Furthermore, there was no control group in the study, so it is unknown if the same effect would be seen among rats not exposed to the deprivation-refeeding paradigm. As such, conducting the same experiment using an animal model of BN is necessary.

Transmission along the mesolimbic projection is also modulated by DAT mRNA levels. DAT mRNA is synthesized in the VTA and regulates DA reuptake within the VTA. It is also transported to the NAc to regulate synaptic reuptake of DA. To date, only one study has assessed DAT adaptations in the VTA utilizing an animal model of BN (Bello et al. 2003). In the study, rats were either food-restricted or given ad libitum access to sucrose or standard chow, followed by a first meal of either sucrose or standard chow. Food-restricted rats given scheduled-access to sucrose consumed significantly more chow than any other group of rats. However, in contrast to previous research (e.g., Avena et al. 2008a; Avena et al. 2006a; Colantuoni et al. 2002; Corwin and Wojnicki 2006; Hagan and Moss 1997), group differences in sucrose intake were not found (Bello et al. 2003). Conflicting results may be due to the fact that Bello and colleagues cycled rats through the protocol only once and presented rats with only 20-minute access to sucrose. However, group differences in sucrose intake arise when rats are cycled through deprivation and access several times and are granted access to sucrose for 1 to 12 hours (e.g., Avena et al. 2008a; Avena et al. 2006a; Colantuoni et al. 2002; Corwin and Wojnicki 2006; Hagan and Moss 1997). Nonetheless, rats were found to increase their sucrose intake by threefold over the course of 7 days (Bello et al. 2003), indicating binge-like behaviors. Relative to controls and rats given free- or scheduled-access to chow, rats given restricted-access to scheduled sucrose displayed significantly higher DAT binding and mRNA levels in the VTA and DAT binding in the NAc (Bello et al. 2003). As discussed above, NAc DA increases upon presentation of palatable food, and the upregulation in DAT expression in the NAc may occur as an attempt to compensate for this increase. This suggests that non-purging BN coupled with sucrose-bingeing produces effects on VTA DA that differ from those produced by the ingestion of non-palatable foods. Repeated exposure to amphetamine (Lu and Wolf 1997; Shilling et al. 1997) and nicotine (Li et al. 2004) increases VTA DAT mRNA. In contrast, non-contingent cocaine decreases (Cerruti et al. 1994), while both limited- and extended-access to cocaine self-administration have no effect on (Ben-Shahar et al. 2006), DAT mRNA expression in the VTA.

Research using animal models of food restriction suggest that dopaminergic VTA efferents may regulate this key characteristic of non-purging BN. Relative to control rats with free

access to food, rats undergoing chronic food restriction display increased VTA expression of two enzymes involved in DA synthesis: tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AAAD) (Lindblom et al. 2006). Thus, a period of fasting may prepare VTA DA neurons to release greater amounts of DA in the NAc upon presentation of palatable food. Chronic food restriction results in a significant increase in the expression of DAT in the VTA (Lindblom et al. 2006). However, it is important to note that food restriction is only one characteristic of non-purging BN. Thus, future research should examine how bingeing coupled with food restriction or purging influences VTA TH, AAAD, and DAT levels. Chronic cocaine and morphine administration significantly increase VTA TH immunoreactivity (Beitner-Johnson and Nestler 1991), but methamphetamine administration does not significantly alter TH mRNA levels in the VTA (Shishido et al. 1997).

In sum, animal models that mimic non-purging BN and other key components of BN, such as food restriction, have been used to find increased DAT mRNA, elevated expression of enzymes associated with DA synthesis (TH and AAAD), and increased DA concentrations in the VTA. These results are comparable to neuroadaptations found following repeated amphetamine, morphine, and nicotine exposure, but conflict with those produced by non-contingent and self-administered cocaine as well as methamphetamine administration. Taken together, preliminary findings reviewed in this section indicate that VTA dopaminergic alterations present in animal models of BN are similar to those present following exposure to certain addictive drugs.

The effects of dopamine antagonists on binge eating and drug-seeking

Because DA release occurs in the NAc during bingeing, a number of studies have examined the ability of systemic administration of D1 and D2 receptor antagonists to modulate this behavior. Using the limited-access protocol with fat/sucrose mixtures, Wong and colleagues (2009) found that the D2 antagonist raclopride exerts dose-dependent reductions in the binge consumption of palatable foods with specific concentrations of sucrose. In their study, rats were permitted access to a mixture of 100% shortening with either 3.2, 10, or 32 % sucrose (w/w) for one hour, with either daily or intermittent (MWF) access. Only rats given intermittent access to palatable food containing either 3.2 or 10% sucrose met the criteria for bingeing. In these animals, the 0.1 mg/kg (IP) dose of raclopride *increased* bingeing while the 0.3 mg/kg (IP) dose *decreased* consumption of the palatable food in rats consuming 3.2% sucrose. Raclopride did not have an effect on intake among rats given daily- or intermittent-access to a high (32%) sucrose concentration fat/sucrose mixture at any dose, nor did it affect consumption in rats given daily access. In a similar study by the same group, the same doses of raclopride were tested for their ability to reduce binge consumption of *either* fatty (shortening) or sucrose-containing (3.2, 10, and 32%) foods after animals were given either daily or intermittent access to these foods (Corwin and Wojnicki 2009). Similar to the results of the Wong et al. (2009) study, the 0.1 mg/kg dose of raclopride significantly increased intake of shortening among rats exposed to the limited-access protocol and given intermittent 1-hour access to 100% fat, but these effects were not observed among rats given daily access to fat (Corwin and Wojnicki 2009). The highest dose of raclopride (0.3 mg/kg) decreased sucrose consumption for *all* conditions of sucrose bingeing. In another study, rats

treated with 0.3 mg/kg (IP) raclopride and given intermittent 4-hour access to a 56% solid fat emulsion or daily 4-hour access to 18%, 32%, or 56% solid fat emulsions significantly decreased their intake (Rao et al. 2008). Raclopride does not alter regular chow intake (Corwin and Wojnicki 2009; Rao et al. 2008; Wong et al. 2009), indicating that raclopride specifically influences consumption of palatable foods and only does so in animals that binge on these foods.

Relative to drug addiction, 0.1 mg/kg raclopride attenuates context-induced cocaine reinstatement (Crombag et al. 2002) and 0.25 mg/kg raclopride attenuates heroin-induced relapse (Shaham and Stewart 1996). The administration of moderate (0.1 mg/kg) and high (0.3 mg/kg) doses of raclopride for five consecutive days prevents cannabinoid (WIN)-induced alcohol relapse (Alen et al. 2008). Intra-amygdala infusion of raclopride produces a dose-dependent effect on cue-primed reinstatement of cocaine-seeking that is akin to its effects on binge eating: a low dose stimulates reinstatement while a higher dose attenuates it (Berglind et al. 2006). Taken together, high doses of raclopride decrease, while low doses increase, fat and sucrose consumption in bingeing rats, but not in non-bingeing rats given daily access to palatable food. Relative to the reinstatement of drug-seeking, raclopride's effects on sucrose bingeing are similar to those produced by intra-amygdala infusions but not systemic injections.

The D1 antagonist SCH 23390 reduces bingeing on palatable food. Treating rats with 0.1 or 0.3 mg/kg (IP) SCH 23390 reduces intake of 3.2%, 10%, and 32% liquid sucrose solutions in rats given limited access (one hour/day) to sucrose either daily or intermittently, with effects more pronounced for rats given intermittent access (Corwin and Wojnicki 2009). Furthermore, a dose of 0.3 mg/kg SCH 23390 significantly decreases shortening intake for rats given daily and intermittent 1-hour access to fat while a 0.3 mg/kg dose has no effect. Notably, SCH 23390 does not influence regular chow intake (Corwin and Wojnicki 2009; Rao et al. 2008; Wong et al. 2009). Similarly, treating rats with SCH 23390 significantly attenuates operant responding for access to cocaine-associated stimuli, but the response to standard chow-associated stimuli are not influenced at most doses (Weissenborn et al. 1996). SCH 23390 also attenuates renewal of context-induced cocaine self-administration (Crombag et al. 2002), heroin-induced relapse (Shaham and Stewart 1996), ethanol relapse (Liu & Weiss, 2002) and food-deprived-induced heroin reinstatement (Tobin et al. 2009) in rats. SCH 23390 decreases nicotine self-administration (Sorge & Clarke, 2009; Stairs, Neugebauer, & Bardo, 2010) and cocaine self-administration (Sorge & Clarke, 2009). While SCH 23390 significantly attenuates cocaine-seeking after a period of withdrawal in both males and females given short-access to cocaine self-administration, this effect is diminished in animals given extended access (Ramos, Doyle, Lycas, Chernau, & Lynch, 2013), in line with the reduction in DA release which occurs following extended access (discussed above). In summary, the D1 antagonist SCH 23390 inhibits consumption of palatable foods and attenuates the reinstatement of drug-seeking.

Because enhanced DA release is observed in the NAc during bingeing, it is tempting to suggest that the effects of systemic D1 and D2 antagonism on bingeing are mediated by the NAc. Testing the ability of specific infusion of agonists and antagonists into the NAc to reduce bingeing is necessary. The D2 antagonist raclopride exerts a biphasic effect on binge

consumption of palatable foods; this may arise as a consequence of the different nature of the two populations of D2 receptors (pre- and post-synaptic). Low doses of agonists preferentially stimulate pre-synaptic D2 autoreceptors, thereby diminishing DA release (Henry et al. 1998). It can be hypothesized that low doses of the antagonist raclopride would also have a preferential effect on autoreceptors, thereby increasing DA efflux (e.g., See et al. 1991) and driving the consumption of palatable foods. A high dose would also block post-synaptic receptors, thereby decreasing consumption of palatable foods. These results indicate that DA release and binding to post-synaptic D1, and possibly D2, receptors stimulate binge eating. Increasing DA release through antagonism of D2 autoreceptors also increases bingeing. These results parallel findings of increased D1 binding and decreased D2 binding in the NAc in rats with a history of bingeing on palatable food. Taken together, it is likely that decreased NAc D2 expression leads to enhanced DA release during bingeing episodes while enhanced D1 expression primes post-synaptic neurons to respond more potently to DA released during a binge.

Transitioning to Addiction: The Neurobiology of Regulated and Compulsive Behaviors

Once DA signaling in the mesolimbic circuitry causes drug-seeking behavior to be “overlearned,” the execution of habitual and automatic behavior involves the glutamatergic projection from the PFC to the NAc (for review see Kalivas and O’Brien 2008; Koob and Le Moal 2001). Hypofrontality further reduces the ability to regulate behaviors, thus playing a key role in the loss of control over drug seeking (for review see Kalivas and O’Brien 2008). This section reviews findings from animal and human binge eating studies that examine glutamatergic signaling and cortical activity.

Glutamatergic neurotransmission in BN

Alterations in the expression of glutamate receptors and receptor subunits have been extensively assessed following self-administration of addictive drugs by rodents. Glutamate has multiple receptor types located both pre- and post-synaptically. Here we discuss relevant data regarding three post-synaptic receptors that are known to mediate neuroplasticity: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and metabotropic glutamate receptor 5 (mGluR5).

Following abstinence from extended access cocaine self-administration, there is an increase in NAc surface expression of the GluA1 subunit of the tetrameric AMPA receptor, but no change in the expression of the GluA2 subunit (Conrad et al. 2008). This adaptation results in increased expression of calcium-permeable, GluA2-lacking AMPA receptors (CP-AMPA), which in turn increases the excitability of post-synaptic neurons, thereby strengthening synaptic connections (Conrad et al. 2008). Increased CP-AMPA have been observed after 30, 45, and 70 days of withdrawal, but not after only one day of withdrawal (Conrad et al., 2008; Ferrario et al., 2011; Wolf & Tseng, 2012) or after only short access to cocaine self administration (Purgianto et al. 2013). Food-restricted rats show a significant increase in post-synaptic density expression of GluA1 in the NAc relative to controls while GluA2 expression does not change (Peng et al. 2011). Thus, it is feasible that the periods of

food restriction that occur during BN cause the insertion of CP-AMPA which then alter the responsivity of post-synaptic neurons in the NAc to incoming glutamate. Self-administration of addictive drugs also results in an increase in synaptically-released glutamate in the NAc, which drives relapse after a drug-free period; this increase has been shown to occur in the case of relapse to alcohol (Gass et al. 2011), cocaine (McFarland et al. 2003), and heroin (LaLumiere and Kalivas 2008). The potentiated glutamate release combined with the highly excitable post-synaptic neurons containing CP-AMPA results in a circuit that is primed to drive drug-seeking behavior (via the NAc projections to the motor output regions of the brain). To date, no studies utilizing animal models of BN or binge eating have examined glutamate levels in the NAc or other brain regions following consumption of palatable food after a period of abstinence (food restriction). However, if such an increase were to occur, it would support the hypothesis that the loss of control over consumption of palatable food and addictive drugs after a period of abstinence relies on a similar neurocircuitry.

Supporting the hypothesis that glutamate release is involved in BN, the NMDA receptor antagonist memantine decreases binge-like lard consumption in non-deprived rats and produces a concomitant increase in consumption of standard laboratory chow (Popik et al. 2011). The same study showed that MTEP (3-(2-Methyl-4-thiazolyl-ethynyl) pyridine), a negative allosteric modulator of mGluR5, resulted in a trend for reducing lard consumption. Using a baboon model of binge-eating disorder in which baboons were given intermittent access to sugar with ad libitum access to standard chow, Bisaga and colleagues (2008) found that both memantine and MTEP decrease binge-like consumption of sugar. A similar effect of memantine on the frequency of binge eating was observed in a clinical trial (Brennan et al. 2008).

While glutamate microdialysis studies have yet to be conducted using animal models of BN, the fact that glutamate receptor antagonists memantine and MTEP decrease binge eating support the hypothesis that binge eating involves glutamatergic transmission, although potentially in a brain region outside the NAc. In rodents, MTEP has reliably been shown to decrease seeking of cocaine (Bäckström and Hyytiä 2006; Knackstedt et al. 2013; Kumaresan et al. 2009; Martin-Fardon et al. 2009), alcohol (Sidhpura et al. 2010), methamphetamine (Osborne and Olive 2008), and opioids (Brown et al. 2012). Several small-scale clinical trials have found that memantine reduces the subjective effects of nicotine (Jackson et al. 2009) and heroin (Comer and Sullivan 2007) and reduces withdrawal symptoms from both alcohol (Krupitsky et al. 2007) and opioids (Bisaga et al. 2001). However, a larger, placebo-controlled study indicated that memantine does not reduce drinking in alcohol-dependent patients (Evans et al. 2007). Interestingly, in a 29-patient open label pilot study, memantine reduced time spent gambling and increased cognitive flexibility (Grant et al. 2010), indicating that memantine may be effective in patients with addictions to behaviors such as gambling and binge eating but not to addictive drugs. In sum, although there is a paucity of research utilizing animal models of BN to examine alterations in glutamate transmission, preliminary findings reviewed in this section suggest that similar adaptations in the glutamate neurotransmitter system may underlie BN and drug-seeking.

Loss of control

Drug addiction involves the transition from declarative, executive functions to habitual behaviors and a loss of control over drug-taking which results from a disruption of PFC activity (Kalivas and O'Brien 2008; Koob and Le Moal 2001). As previously mentioned, one of the key characteristics of BN is a sense of loss of control over eating, with the inability to stop eating or control what or how much one is eating (American Psychiatric Association 2013). Functional magnetic resonance imaging (fMRI) studies have found that, relative to healthy controls, BN-individuals exhibit significantly lower PFC activity during executive control cognitive tasks such as impulsivity control (Marsh et al. 2011; Marsh et al. 2009). Low levels of activity in the frontostriatal pathways, including the left inferolateral PFC, are related to impulsive responding (Marsh et al. 2009), indicating impaired executive functioning among BN-individuals. Relative to controls, BN-individuals show higher activity in the PFC when they are presented with images of food (Uher et al. 2004), cued with negative words concerning body image (Miyake et al. 2010), or shown overweight bodies (Spangler and Allen 2012).

Taken together, BN individuals show hypofrontality when presented with non-food-related cues and excessive activity when presented with disorder-related cues. This pattern of activity is also seen among drug addicts. Specifically, hypoactivity in the PFC in response to non-drug-related cognitive tasks is evident among chronic users of cocaine (Goldstein et al. 2007), methamphetamine (Kim et al. 2011; Nestor et al. 2011; Salo et al. 2009), and alcohol (Crego et al. 2010; Muraige et al. 2012). Presenting addicts with images of drug-related stimuli increases PFC activity among alcoholics (George et al. 2001; Grusser et al. 2004; Tapert et al. 2004), cocaine (Wilcox et al. 2011), and nicotine-dependent individuals (Lee et al. 2005). Thus, BN-individuals display aberrant patterns of PFC activity similar to drug addicted individuals.

The Opioid System and Binge Eating

The opioid neuropeptide system mediates pleasure and analgesia, primarily through binding of opioid neuropeptides at the μ -opioid receptor (MOR). Many classes of addictive drugs release endogenous opioids or bind to opioid receptors, producing feelings of euphoria (for review see Goodman 2008; Koob and Le Moal 2001). Rats that chronically self-administer heroin show an increase in MOR binding in the NAc, hippocampus, VTA, and caudate putamen (Fattore et al. 2007). Similarly, non-purging BN rats cycled through the "sugar addiction" model exhibit a significant increase in MOR binding in the NAc shell, hippocampus, and cingulate cortex (Colantuoni et al. 2001). Administering the opioid receptor antagonist naloxone to sugar-bingeing rats induces somatic signs of opiate dependency, such as teeth chattering, head shakes, and signs of anxiety (Colantuoni et al. 2002). The same was not observed in rats that binged on a palatable diet composed of a sugar and fat combination (Bocarsly et al. 2011), suggesting a specific neurobiological circuitry associated with sugar-bingeing.

Naltrexone, an antagonist at μ - and kappa-opioid receptors, is used to treat addiction and shows promise for the treatment of BN (Conason and Sher 2006). Naltrexone decreases bingeing of palatable foods among binge-eating rats (Berner et al. 2011; Corwin and

Wojnicki 2009; Giuliano et al. 2012; Wong et al. 2009). However, the ability of naltrexone to reduce consumption of palatable food after binge-like access varies with the composition of the palatable food, with high sucrose levels being more resistant to the suppressive effect (Corwin and Wojnicki 2009; Wong et al. 2009). In human clinical studies of BN, naltrexone alone or in combination with the serotonin reuptake inhibitor fluoxetine decreases bulimic symptomology (e.g., Jonas and Gold 1986; Maremmani et al. 1996; Marrazzi et al. 1995; Mitchell et al. 1989). Naltrexone is beneficial in the treatment of addiction to alcohol (Conason and Sher 2006) and heroin (Krupitsky et al. 2006), but has been shown to be ineffective at reducing craving for other drugs (for review see Modesto-Lowe and Van Kirk 2002). A novel MOR antagonist, GSK1521498, has an affinity for this receptor that is three times higher than naltrexone. One study found that GSK1521498 reduced binge-like consumption of a chocolate diet and prevented the reduction in consumption of normal chow that often accompanies binge consumption of palatable food in rats (Giuliano et al. 2012). Thus, the role of MOR in mediating binge eating and alcohol addiction appears to be similar.

Treatment Implications

Applying addiction-focused treatment to BN may reduce the high rate of relapse associated with BN. However, removing addictive drugs from a drug addict's environment is plausible whereas food is necessary for life (Broft et al. 2011). Furthermore, since BN-individuals refrain from "taboo" foods during non-bingeing restriction periods (Fitzgibbon and Blackman 2000), removing palatable foods from the environment of a BN-individual may heighten guilt associated with ingestion of these foods, thus triggering inappropriate compensatory behaviors. Therefore, given similar neurobiological mechanisms underlying drug addiction and BN, pharmacotherapy used for drug addictions may reduce bingeing of palatable foods. Specifically, pharmaceutical treatment targeting DA, glutamate, or opioid neurotransmitter systems that are shown to be effective for drug addiction may similarly be beneficial for the treatment of BN. Cognitive behavioral therapy coupled with medication may be useful for transitioning habitual behaviors back to declarative, regulated behaviors, thereby increasing sense of control over eating, reducing bingeing, and decreasing the usage of compensatory behaviors. At this time, the only FDA-approved medication for addiction that also shows promise for BN is naltrexone, although future studies that assess effects of naltrexone on bulimic symptomology are warranted (Ramos et al. 2007). Upon the development of additional pharmacotherapies targeting these neurotransmitter systems for the treatment of drug addiction, the shared neurobiological features of these disorders warrant testing such pharmacotherapies in animal models of BN.

Conclusions

This review synthesized results from human and animal studies of BN and drug addiction and found more similarities than differences in their underlying neurobiological mechanisms (see Table 1). Specifically, the results reviewed here indicate that the dopaminergic system, glutamatergic signaling, the opioid system, and cortical activity play similar roles in BN and drug addiction. These similarities are especially evident for sugar bingeing. A history of sugar bingeing and deprivation results in decreased DA levels in the NAc following fasting

and enhanced release upon consumption of sweet food. Combined with an increase in post-synaptic D1 receptors, this enhanced DA release likely serves to sensitize animals to the rewarding effects of sweet food and/or the cues associated with consumption of such food, leading to an increase in the probability that animals will binge in the future. Preliminary evidence also indicates that glutamatergic adaptations in the NAc following a history of binge eating prime the post-synaptic neurons in this region to respond more strongly to cues associated with palatable food. These adaptations also occur in animals with a history of addictive drug self-administration. More research that examines VTA DA is necessary, but preliminary results highlight similarities between BN and addiction to some drugs. Differences between the two disorders include changes in NAc DA response following extended access to drug self-administration, NAc D2 binding, VTA DAT mRNA levels, and the efficacy of memantine to reduce symptoms. Although more empirical studies on the topic are necessary, the results presented here indicate that bingeing on palatable foods, mainly sugar, coupled with food restriction or purging influences neurobiology in a manner similar to that of addictive drugs.

References

- Acquas E, Di Chiara G. Depression of mesolimbic dopamine transmission and sensitization to morphine during opiate abstinence. *J Neurochem.* 1992; 58:1620–1625. [PubMed: 1313849]
- Alen F, Moreno-Sanz G, Isabel de Tena A, Brooks RD, Lopez-Jimenez A, Navarro M, Lopez-Moreno JA. Pharmacological activation of CB1 and D2 receptors in rats: predominant role of CB1 in the increase of alcohol relapse. *Eur J Neurosci.* 2008; 27:3292–3298. [PubMed: 18554293]
- American Psychiatric Association. 4th. American Psychiatric Association; Washington, DC: 2000. Diagnostic and statistical manual of mental disorders. Text Revision
- American Psychiatric Association. 5th. Washington, DC: 2013. Diagnostic and statistical manual of mental disorders.
- Avena NM, Bocarsly ME. Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology.* 2012; 63:87–96. [PubMed: 22138162]
- Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. *Physiol Behav.* 2008a; 94:309–315. [PubMed: 18325546]
- Avena NM, Rada P, Hoebel BG. Sugar bingeing in rats. *Curr Protoc Neurosci.* 2006a Chapter 9: Unit9.23C.
- Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience.* 2008b; 156:865–871. [PubMed: 18790017]
- Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. *Neuroscience.* 2006b; 139:813–820. [PubMed: 16460879]
- Bahk JY, Li S, Park MS, Kim MO. Dopamine D1 and D2 receptor mRNA up-regulation in the caudate-putamen and nucleus accumbens of rat brains by smoking. *Prog Neuropsychopharmacol Biol Psychiatry.* 2002; 26:1095–1104. [PubMed: 12452531]
- Barak S, Carnicella S, Yowell QV, Ron D. Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for alcohol reward and seeking. *J neurosci.* 2011; 31:9885–9894. [PubMed: 21734280]
- Beckstead MJ, Grandy DK, Wickman K, Williams JT. Vesicular dopamine release elicits an inhibitory postsynaptic current in midbrain dopamine neurons. *Neuron.* 2004; 42:939–946. [PubMed: 15207238]

- Beitner-Johnson D, Nestler EJ. Morphine and cocaine exert common chronic actions on tyrosine hydroxylase in dopaminergic brain reward regions. *J Neurochem.* 1991; 57:344–347. [PubMed: 1675665]
- Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. *Neuroreport.* 2002; 13:1575–1578. [PubMed: 12218708]
- Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A. Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. *Am J Physiol.* 2003; 284:R1260–8.
- Ben-Shahar O, Keeley P, Cook M, Brake W, Joyce M, Nyffeler M, Heston R, Ettenberg A. Changes in levels of D1, D2, or NMDA receptors during withdrawal from brief or extended daily access to IV cocaine. *Brain Res.* 2007; 1131:220–228. [PubMed: 17161392]
- Ben-Shahar O, Moscarello JM, Ettenberg A. One hour, but not six hours, of daily access to self-administered cocaine results in elevated levels of the dopamine transporter. *Brain Res.* 2006; 1095:148–153. [PubMed: 16712814]
- Berggren U, Fahlke C, Aronsson E, Karanti A, Eriksson M, Blennow K, Thelle D, Zetterberg H, Balldin J. The TAQI DRD2 A1 allele is associated with alcohol-dependence although its effect size is small. *Alcohol Alcohol.* 2006; 41:479–485. [PubMed: 16751215]
- Berglind WJ, Case JM, Parker MP, Fuchs RA, See RE. Dopamine D1 or D2 receptor antagonism within the basolateral amygdala differentially alters the acquisition of cocaine-cue associations necessary for cue-induced reinstatement of cocaine-seeking. *Neuroscience.* 2006; 137:699–706. [PubMed: 16289883]
- Bernardini GL, Gu X, Viscardi E, German DC. Amphetamine-induced and spontaneous release of dopamine from A9 and A10 cell dendrites: an in vitro electrophysiological study in the mouse. *J Neural Transm Gen Sect.* 1991; 84:183–193. [PubMed: 1679335]
- Berner LA, Bocarsly ME, Hoebel BG, Avena NM. Pharmacological interventions for binge eating: lessons from animal models, current treatments, and future directions. *Curr Pharm Des.* 2011; 17:1180–1187. [PubMed: 21492094]
- Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW. The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. *Psychopharmacology.* 2001; 157:1–10. [PubMed: 11512037]
- Bisaga A, Danysz W, Foltin RW. Antagonism of glutamatergic NMDA and mGluR5 receptors decreases consumption of food in baboon model of binge-eating disorder. *Eur Neuropsychopharmacol.* 2008; 18:794–802. [PubMed: 18573641]
- Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. *Physiol Behav.* 2011; 104:865–872. [PubMed: 21635910]
- Bradberry CW, Roth RH. Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. *Neurosci Lett.* 1989; 103:97–102. [PubMed: 2779859]
- Brennan BP, Roberts JL, Fogarty KV, Reynolds KA, Jonas JM, Hudson JL. Memantine in the treatment of binge eating disorder: an open-label, prospective trial. *Int J Eat Disord.* 2008; 41:520–526. [PubMed: 18433015]
- Brisman J, Siegel M. Bulimia and alcoholism: two sides of the same coin? *J Subst Abuse Treat.* 1984; 1:113–118. [PubMed: 6598815]
- Broft AI, Berner LA, Martinez D, Walsh BT. Bulimia nervosa and evidence for striatal dopamine dysregulation: a conceptual review. *Physiol Behav.* 2011; 104:122–127. [PubMed: 21549135]
- Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron.* 2010; 68:815–834. [PubMed: 21144997]
- Brown RM, Stagnitti MR, Duncan JR, Lawrence AJ. The mGlu5 receptor antagonist MTEP attenuates opiate self-administration and cue-induced opiate-seeking behaviour in mice. *Drug Alcohol Depend.* 2012; 123:264–268. [PubMed: 22129842]
- Bäckström P, Hyttiä P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology.* 2006; 31:778–786. [PubMed: 16123768]

- Carbaugh RJ, Sias SM. Comorbidity of bulimia nervosa and substance abuse: Etiologies, treatment issues, and treatment approaches. *J Ment Health Counsel.* 2010; 32(2):125–138.
- Casper RC, Sullivan EL, Tecott L. Relevance of animal models to human eating disorders and obesity. *Psychopharmacology.* 2008; 199:313–329. [PubMed: 18317734]
- Cerruti C, Pilotte NS, Uhl G, Kuhar MJ. Reduction in dopamine transporter mRNA after cessation of repeated cocaine. *Brain Res.* 1994; 22:132–138.
- Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, Hoebel BG. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res.* 2002; 10:478–488. [PubMed: 12055324]
- Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport.* 2001; 12:3549–3552. [PubMed: 11733709]
- Colby CR, Whisler K, Steffen C, Nestler EJ, Self DW. Striatal cell type-specific overexpression of DeltaFosB enhances incentive for cocaine. *J Neurosci.* 2003; 23:2488–2493. [PubMed: 12657709]
- Comer SD, Sullivan MA. Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. *Psychopharmacology.* 2007; 193:235–245. [PubMed: 17406858]
- Conason AH, Sher L. Alcohol use in adolescents with eating disorders. *Int J Adolesc Med Health.* 2006; 18:31–36. [PubMed: 16639856]
- Connor JP, Young RM, Saunders JB, Lawford BR, Ho R, Ritchie TL, Noble EP. The A1 allele of the D2 dopamine receptor gene region, alcohol expectancies and drinking refusal self-efficacy are associated with alcohol dependence severity. *Psychiatry Res.* 2008; 160:94–105. [PubMed: 18514919]
- Conrad KL, Ford K, Marinelli M, Wolf ME. Dopamine receptor expression and distribution dynamically change in the rat nucleus accumbens after withdrawal from cocaine self-administration. *Neuroscience.* 2010; 169:182–194. [PubMed: 20435100]
- Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature.* 2008; 454:118–121. [PubMed: 18500330]
- Corwin RL, Wojnicki FH. Binge eating in rats with limited access to vegetable shortening. *Curr Protoc Neurosci.* 2006 Chapter 9: Unit9.23B.
- Corwin RL, Wojnicki FH. Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. *Behav Pharmacol.* 2009; 20:537–548. [PubMed: 19724193]
- Cragg SJ, Greenfield SA. Differential autoreceptor control of somatodendritic and axon terminal dopamine release in substantia nigra, ventral tegmental area, and striatum. *J Neurosci.* 1997; 17:5738–5746. [PubMed: 9221772]
- Crego A, Rodriguez-Holguin S, Parada M, Mota N, Corral M, Cadaveira F. Reduced anterior prefrontal cortex activation in young binge drinkers during a visual working memory task. *Drug Alcohol Depend.* 2010; 109:45–56. [PubMed: 20079980]
- Crombag HS, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. *Neuropsychopharmacology.* 2002; 27:1006–1015. [PubMed: 12464457]
- Di Bella D, Catalano M, Cavallini MC, Riboldi C, Bellodi L. Serotonin transporter linked polymorphic region in anorexia nervosa and bulimia nervosa. *Mol Psychiatry.* 2000; 5:233–234. [PubMed: 10889521]
- Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A.* 1988; 85:5274–5278. [PubMed: 2899326]
- Diana M, Melis M, Muntoni AL, Gessa GL. Mesolimbic dopaminergic decline after cannabinoid withdrawal. *Proc Natl Acad Sci U S A.* 1998; 95:10269–10273. [PubMed: 9707636]
- Diana M, Muntoni AL, Pistis M, Melis M, Gessa GL. Lasting reduction in mesolimbic dopamine neuronal activity after morphine withdrawal. *Eur J Neurosci.* 1999; 11:1037–1041. [PubMed: 10103095]

- DiLeone RJ, Taylor JR, Picciotto MR. The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. *Nat Neurosci.* 2012; 15:1330–1335. [PubMed: 23007187]
- El-Ghundi M, O'Dowd BF, George SR. Insights into the role of dopamine receptor systems in learning and memory. *Rev Neurosci.* 2007; 18:37–66. [PubMed: 17405450]
- Evans SM, Levin FR, Brooks DJ, Garawi F. A pilot double-blind treatment trial of memantine for alcohol dependence. *Alcohol Clin Exp Res.* 2007; 31:775–782. [PubMed: 17378918]
- Fattore L, Vigano D, Fadda P, Rubino T, Fratta W, Parolaro D. Bidirectional regulation of mu-opioid and CB1-cannabinoid receptor in rats self-administering heroin or WIN 55,212-2. *Eur J Neurosci.* 2007; 25:2191–2200. [PubMed: 17419755]
- Ferrari R, Le Novere N, Picciotto MR, Changeux JP, Zoli M. Acute and long-term changes in the mesolimbic dopamine pathway after systemic or local single nicotine injections. *Eur J Neurosci.* 2002; 15:1810–1818. [PubMed: 12081661]
- Ferrario CR, Loweth JA, Milovanovic M, Ford KA, Galinanes GL, Heng LJ, Tseng KY, Wolf ME. Alterations in AMPA receptor subunits and TARPs in the rat nucleus accumbens related to the formation of Ca(2+)-permeable AMPA receptors during the incubation of cocaine craving. *Neuropharmacology.* 2011; 61:1141–1151. [PubMed: 21276808]
- Fitzgibbon ML, Blackman LR. Binge eating disorder and bulimia nervosa: Differences in the quality and quantity of binge eating episodes. *Int J Eat Disord.* 2000; 27:238–243. [PubMed: 10657897]
- Gaddnas H, Piepponen TP, Ahtee L. Mecamylamine decreases accumbal dopamine output in mice treated chronically with nicotine. *Neurosci Lett.* 2002; 330:219–222. [PubMed: 12270632]
- Gass JT, Sinclair CM, Cleva RM, Widholm JJ, Olive MF. Alcohol-seeking behavior is associated with increased glutamate transmission in basolateral amygdala and nucleus accumbens as measured by glutamate-oxidase-coated biosensors. *Addict Biol.* 2011; 16:215–228. [PubMed: 21054692]
- Gearhardt AN, White MA, Potenza MN. Binge eating disorder and food addiction. *Curr Drug Abuse Rev.* 2011; 4:201–207. [PubMed: 21999695]
- George MS, Anton RF, Bloomer C, Teneback C, Drobos DJ, Lorberbaum JP, Nahas Z, Vincent DJ. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry.* 2001; 58:345–352. [PubMed: 11296095]
- German CL, Hanson GR, Fleckenstein AE. Amphetamine and methamphetamine reduce striatal dopamine transporter function without concurrent dopamine transporter relocation. *J Neurochem.* 2012; 123:288–297. [PubMed: 22804716]
- Gervasini G, Gordillo I, Garcia-Herraiz A, Flores I, Jimenez M, Monge M, Carrillo JA. Polymorphisms in serotonergic genes and psychopathological traits in eating disorders. *J Clin Psychopharmacol.* 2012; 32:426–428. [PubMed: 22561477]
- Giuliano C, Robbins TW, Nathan PJ, Bullmore ET, Everitt BJ. Inhibition of opioid transmission at the mu-opioid receptor prevents both food seeking and binge-like eating. *Neuropsychopharmacology.* 2012; 37:2643–2652. [PubMed: 22805601]
- Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry.* 2007; 164:43–51. [PubMed: 17202543]
- Goodman A. Neurobiology of addiction. An integrative review. *Biochem Pharmacol.* 2008; 75:266–322.
- Grant JE, Chamberlain SR, Odlaug BL, Potenza MN, Kim SW. Memantine shows promise in reducing gambling severity and cognitive inflexibility in pathological gambling: a pilot study. *Psychopharmacology.* 2010; 212:603–612. [PubMed: 20721537]
- Grusser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, Heinz A. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology.* 2004; 175:296–302. [PubMed: 15127179]
- Hagan MM, Moss DE. An animal model of bulimia nervosa: opioid sensitivity to fasting episodes. *Pharmacol Biochem Behav.* 1991; 39:421–422. [PubMed: 1946582]

- Hagan MM, Moss DE. Persistence of binge-eating patterns after a history of restriction with intermittent bouts of refeeding on palatable food in rats: implications for bulimia nervosa. *Int J Eat Disord.* 1997; 22:411–420. [PubMed: 9356889]
- Hagan MM, Wauford PK, Chandler PC, Jarrett LA, Rybak RJ, Blackburn K. A new animal model of binge eating: key synergistic role of past caloric restriction and stress. *Physiol Behav.* 2002; 77:45–54. [PubMed: 12213501]
- Henry DJ, Hu XT, White FJ. Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D1 and D2 receptor-selective agonists: relevance to cocaine sensitization. *Psychopharmacology.* 1998; 140:233–242. [PubMed: 9860115]
- Inoue K, Kiriike N, Okuno M, Fujisaki Y, Kurioka M, Iwasaki S, Yamagami S. Prefrontal and striatal dopamine metabolism during enhanced rebound hyperphagia induced by space restriction--a rat model of binge eating. *Biol Psychiatry.* 1998; 44:1329–1336. [PubMed: 9861476]
- Jackson A, Nesic J, Groombridge C, Clowry O, Rusted J, Duka T. Differential involvement of glutamatergic mechanisms in the cognitive and subjective effects of smoking. *Neuropsychopharmacology.* 2009; 34:257–265. [PubMed: 18418361]
- Jonas JM, Gold MS. Treatment of antidepressant-resistant bulimia with naltrexone. *Int J Psychiatry Med.* 1986; 16:305–309. [PubMed: 3557806]
- Kalivas PW, Duffy P. A comparison of axonal and somatodendritic dopamine release using in vivo dialysis. *J Neurochem.* 1991; 56:961–967. [PubMed: 1993900]
- Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology.* 2008; 33:166–180. [PubMed: 17805308]
- Kelz MB, Chen J, Carlezon WA Jr. Whisler K, Gilden L, Beckmann AM, Steffen C, Zhang YJ, Marotti L, Self DW, Tkatch T, Baranaukas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR, Nestler EJ. Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine. *Nature.* 1999; 401:272–276. [PubMed: 10499584]
- Kim YT, Song HJ, Seo JH, Lee JJ, Lee J, Kwon DH, Yoo DS, Lee HJ, Suh KJ, Chang Y. The differences in neural network activity between methamphetamine abusers and healthy subjects performing an emotion-matching task: functional MRI study. *NMR Biomed.* 2011; 24:1392–1400. [PubMed: 21472808]
- Klein, DA.; Smith, GP.; Avena, NM. *Animal Models of Eating Disorders (Neuromethods)*. Humana Press; New York, NY, US: 2013. Sham Feeding in Rats Translates into Modified Sham Feeding in Women with Bulimia Nervosa and Purging; p. 155-177.
- Knackstedt LA, Trantham-Davidson HL, Schwendt M. The role of ventral and dorsal striatum mGluR5 in relapse to cocaine-seeking and extinction learning. *Addict Biol.* 2013
- Kohl RR, Katner JS, Chernet E, McBride WJ. Ethanol and negative feedback regulation of mesolimbic dopamine release in rats. *Psychopharmacology.* 1998; 139:79–85. [PubMed: 9768545]
- Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology.* 2001; 24:97–129. [PubMed: 11120394]
- Krupitsky EM, Rudenko AA, Burakov AM, Slavina TY, Grinenko AA, Pittman B, Gueorguieva R, Petrakis IL, Zvartau EE, Krystal JH. Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. *Alcohol Clin Exp Res.* 2007; 31:604–611. [PubMed: 17374039]
- Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Beshpalov AY, Verbitskaya EV, Neznakov NG, Grinenko AY, O'Brien CP, Woody GE. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *J Subst Abuse Treat.* 2006; 31:319–328. [PubMed: 17084785]
- Kumaresan V, Yuan M, Yee J, Famous KR, Anderson SM, Schmidt HD, Pierce RC. Metabotropic glutamate receptor 5 (mGluR5) antagonists attenuate cocaine priming- and cue-induced reinstatement of cocaine seeking. *Behavioural Brain Res.* 2009; 202:238–244.
- LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J Neurosci.* 2008; 28:3170–3177. [PubMed: 18354020]
- Le Cozannet R, Markou A, Kuczenski R. Extended-access, but not limited-access, methamphetamine self-administration induces behavioral and nucleus accumbens dopamine response changes in rats. *Eur J Neurosci.* 2013; 38:3487–3495. [PubMed: 24112125]

- Le Foll B, Diaz J, Sokoloff P. Increased dopamine D3 receptor expression accompanying behavioral sensitization to nicotine in rats. *Synapse*. 2003; 47:176–183. [PubMed: 12494400]
- Lee JH, Lim Y, Wiederhold BK, Graham SJ. A functional magnetic resonance imaging (fMRI) study of cue-induced smoking craving in virtual environments. *Appl Psychophysiol Biofeedback*. 2005; 30:195–204. [PubMed: 16167185]
- Li S, Kim KY, Kim JH, Park MS, Bahk JY, Kim MO. Chronic nicotine and smoking treatment increases dopamine transporter mRNA expression in the rat midbrain. *Neurosci Lett*. 2004; 363:29–32. [PubMed: 15157990]
- Lindblom J, Johansson A, Holmgren A, Grandin E, Nedergard C, Fredriksson R, Schioth HB. Increased mRNA levels of tyrosine hydroxylase and dopamine transporter in the VTA of male rats after chronic food restriction. *Eur J Neurosci*. 2006; 23:180–186. [PubMed: 16420427]
- Liu X, Weiss F. Reversal of ethanol-seeking behavior by D1 and D2 antagonists in an animal model of relapse: differences in antagonist potency in previously ethanol-dependent versus nondependent rats. *J Pharmacol Exp Ther*. 2002; 300:882–889. [PubMed: 11861794]
- Ljungberg T, Apicella P, Schultz W. Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol*. 1992; 67:145–163. [PubMed: 1552316]
- Lominac KD, Sacramento AD, Szumlanski KK, Kippin TE. Distinct neurochemical adaptations within the nucleus accumbens produced by a history of self-administered vs non-contingently administered intravenous methamphetamine. *Neuropsychopharmacology*. 2012; 37:707–722. [PubMed: 22030712]
- Lu W, Wolf ME. Expression of dopamine transporter and vesicular monoamine transporter 2 mRNAs in rat midbrain after repeated amphetamine administration. *Brain Res*. 1997; 49:137–148.
- Maremmani I, Marini G, Castrogiovanni P, Deltito J. The effectiveness of the combination fluoxetine-naltrexone in bulimia nervosa. *Eur Psychiatry*. 1996; 11:322–324. [PubMed: 19698474]
- Marrazzi MA, Bacon JP, Kinzie J, Luby ED. Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. *Int Clin Psychopharmacol*. 1995; 10:163–172. [PubMed: 8675969]
- Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, Walsh BT, Peterson BS. An fMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. *Am J Psychiatry*. 2011; 168:1210–1220. [PubMed: 21676991]
- Marsh R, Steinglass JE, Gerber AJ, Graziano O'Leary K, Wang Z, Murphy D, Walsh BT, Peterson BS. Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry*. 2009; 66:51–63. [PubMed: 19124688]
- Martin-Fardon R, Baptista MA, Dayas CV, Weiss F. Dissociation of the effects of MTEP [3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]piperidine] on conditioned reinstatement and reinforcement: comparison between cocaine and a conventional reinforcer. *J Pharmacol Exp Ther*. 2009; 329:1084–1090. [PubMed: 19258516]
- Mateo Y, Lack CM, Morgan D, Roberts DC, Jones SR. Reduced dopamine terminal function and insensitivity to cocaine following cocaine binge self-administration and deprivation. *Neuropsychopharmacology*. 2005; 30:1455–1463. [PubMed: 15702135]
- Maurage P, Joassin F, Philippot P, Heeren A, Vermeulen N, Mahau P, Delperdange C, Corneille O, Luminet O, de Timary P. Disrupted regulation of social exclusion in alcohol-dependence: an fMRI study. *Neuropsychopharmacology*. 2012; 37:2067–2075. [PubMed: 22510722]
- McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci*. 2003; 23:3531–3537. [PubMed: 12716962]
- McHugh RK, Hofmann SG, Asnaani A, Sawyer AT, Otto MW. The serotonin transporter gene and risk for alcohol dependence: a meta-analytic review. *Drug Alcohol Depend*. 2010; 108:1–6. [PubMed: 20060655]
- Metaxas A, Bailey A, Barbano MF, Galeote L, Maldonado R, Kitchen I. Differential region-specific regulation of $\alpha 4\beta 2^*$ nAChRs by self-administered and non-contingent nicotine in C57BL/6J mice. *Addict Biol*. 2010; 15:464–479. [PubMed: 20731631]
- Mirenowicz J, Schultz W. Importance of unpredictability for reward responses in primate dopamine neurons. *J Neurophysiol*. 1994; 72:1024–1027. [PubMed: 7983508]

- Mitchell JE, Christenson G, Jennings J, Huber M, Thomas B, Pomeroy C, Morley J. A placebo-controlled, double-blind crossover study of naltrexone hydrochloride in outpatients with normal weight bulimia. *J Clin Psychopharmacol.* 1989; 9:94–97. [PubMed: 2656781]
- Miyake Y, Okamoto Y, Onoda K, Shirao N, Otagaki Y, Yamawaki S. Neural processing of negative word stimuli concerning body image in patients with eating disorders: an fMRI study. *NeuroImage.* 2010; 50:1333–1339. [PubMed: 20045473]
- Modesto-Lowe V, Van Kirk J. Clinical uses of naltrexone: a review of the evidence. *Exp Clin Psychopharmacol.* 2002; 10:213–227. [PubMed: 12233982]
- Mukda S, Kaewsuk S, Ebadi M, Govitrapong P. Amphetamine-induced changes in dopamine receptors in early postnatal rat brain. *Dev Neurosci.* 2009; 31:193–201. [PubMed: 19145071]
- Nakagawa T, Suzuki Y, Nagayasu K, Kitaichi M, Shirakawa H, Kaneko S. Repeated exposure to methamphetamine, cocaine or morphine induces augmentation of dopamine release in rat mesocorticolimbic slice co-cultures. *PLoS One.* 2011; 6:e24865. [PubMed: 21980362]
- Natividad LA, Tejeda HA, Torres OV, O'Dell LE. Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. *Synapse.* 2010; 64:136–145. [PubMed: 19771590]
- Nestler EJ, Barrot M, Self DW. DeltaFosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci U S A.* 2001; 98:11042–11046. [PubMed: 11572966]
- Nestor LJ, Ghahremani DG, Monterosso J, London ED. Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. *Psychiatry Res.* 2011; 194:287–295. [PubMed: 22047731]
- Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Hum Mutat.* 2004; 23:540–545. [PubMed: 15146457]
- Nisoli E, Brunani A, Borgomainerio E, Tonello C, Dioni L, Briscini L, Redaelli G, Molinari E, Cavagnini F, Carruba MO. D2 dopamine receptor (DRD2) gene Taq1A polymorphism and the eating-related psychological traits in eating disorders (anorexia nervosa and bulimia) and obesity. *Eat Weight Disord.* 2007; 12:91–96.
- Nøkleby H. Comorbid drug use disorders and eating disorders - a review of prevalence studies. *Nordic Studies on Alcohol and Drugs.* 2012; 29:303–314.
- Osborne MP, Olive MF. A role for mGluR5 receptors in intravenous methamphetamine self-administration. *Ann N Y Acad Sci.* 2008; 1139:206–211. [PubMed: 18991866]
- Patterson TA, Brot MD, Zavosh A, Schenk JO, Szot P, Figlewicz DP. Food deprivation decreases mRNA and activity of the rat dopamine transporter. *Neuroendocrinology.* 1998; 68:11–20. [PubMed: 9695934]
- Peng XX, Ziff EB, Carr KD. Effects of food restriction and sucrose intake on synaptic delivery of AMPA receptors in nucleus accumbens. *Synapse.* 2011; 65:1024–1031. [PubMed: 21425350]
- Popik P, Kos T, Zhang Y, Bisaga A. Memantine reduces consumption of highly palatable food in a rat model of binge eating. *Amino Acids.* 2011; 40:477–485. [PubMed: 20571841]
- Pothos E, Rada P, Mark GP, Hoebel BG. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. *Brain Res.* 1991; 566:348–350. [PubMed: 1814554]
- Purgianto A, Scheyer AF, Loweth JA, Ford KA, Tseng KY, Wolf ME. Different adaptations in AMPA receptor transmission in the nucleus accumbens after short vs long access cocaine self-administration regimens. *Neuropsychopharmacology.* 2013; 38:1789–1797. [PubMed: 23546386]
- Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience.* 2005; 134:737–744. [PubMed: 15987666]
- Rada P, Jensen K, Hoebel BG. Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. *Psychopharmacology.* 2001; 157:105–110. [PubMed: 11512050]
- Rahman S, Zhang J, Engleman EA, Corrigan WA. Neuroadaptive changes in the mesoaccumbens dopamine system after chronic nicotine self-administration: a microdialysis study. *Neuroscience.* 2004; 129:415–424. [PubMed: 15501598]

- Ramoa CP, Doyle SE, Lycas MD, Chernau AK, Lynch WJ. Diminished Role of Dopamine D1-Receptor Signaling with the Development of an Addicted Phenotype in Rats. *Biol Psychiatry*. 2013
- Ramos N, Versini A, Gorwood P. Eating disorders: an overview of treatment responses and the potential impact of vulnerability genes and endophenotypes. *Expert Opin Pharmacother*. 2007; 8:2029–2044. [PubMed: 17714058]
- Rao RE, Wojnicki FH, Coupland J, Ghosh S, Corwin RL. Baclofen, raclopride, and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. *Pharmacol Biochem Behav*. 2008; 89:581–590. [PubMed: 18353432]
- Reith ME, Li MY, Yan QS. Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. *Psychopharmacology*. 1997; 134:309–317. [PubMed: 9438681]
- Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2009; 65:706–709. [PubMed: 19136097]
- Sari Y, Bell RL, Zhou FC. Effects of chronic alcohol and repeated deprivations on dopamine D1 and D2 receptor levels in the extended amygdala of inbred alcohol-preferring rats. *Alcohol Clin Exp Res*. 2006; 30:46–56. [PubMed: 16433731]
- Schultz W. Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Curr Opin Neurobiol*. 2004; 14:139–147. [PubMed: 15082317]
- See RE, Sorg BA, Chapman MA, Kalivas PW. In vivo assessment of release and metabolism of dopamine in the ventrolateral striatum of awake rats following administration of dopamine D1 and D2 receptor agonists and antagonists. *Neuropharmacology*. 1991; 30:1269–1274. [PubMed: 1686300]
- Shaham Y, Stewart J. Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology*. 1996; 125:385–391. [PubMed: 8826544]
- Shilling PD, Kelsoe JR, Segal DS. Dopamine transporter mRNA is up-regulated in the substantia nigra and the ventral. *Neurosci Lett*. 1997; 236:131–134. [PubMed: 9406754]
- Shishido T, Watanabe Y, Matsuoka I, Nakanishi H, Niwa S. Acute methamphetamine administration increases tyrosine hydroxylase mRNA levels in the rat locus coeruleus. *Brain Res*. 1997; 52:146–150.
- Sidhpura N, Weiss F, Martin-Fardon R. Effects of the mGlu2/3 agonist LY379268 and the mGlu5 antagonist MTEP on ethanol seeking and reinforcement are differentially altered in rats with a history of ethanol dependence. *Biol Psychiatry*. 2010; 67:804–811. [PubMed: 20189165]
- Smink FR, van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. *Curr Psychiatry Rep*. 2012; 14:406–414. [PubMed: 22644309]
- Sorge RE, Clarke PB. Rats self-administer intravenous nicotine delivered in a novel smoking-relevant procedure: effects of dopamine antagonists. *J Pharmacol Exp Ther*. 2009; 330:633–640. [PubMed: 19448141]
- Spangler DL, Allen MD. An fMRI investigation of emotional processing of body shape in bulimia nervosa. *Int J Eat Disord*. 2012; 45:17–25. [PubMed: 21312206]
- Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Mol Brain Res*. 2004; 124:134–142. [PubMed: 15135221]
- Stairs DJ, Neugebauer NM, Bardo MT. Nicotine and cocaine self-administration using a multiple schedule of intravenous drug and sucrose reinforcement in rats. *Behav Pharmacol*. 2010; 21:182–193. [PubMed: 20440201]
- Stamp JA, Mashoodh R, van Kampen JM, Robertson HA. Food restriction enhances peak corticosterone levels, cocaine-induced locomotor activity, and DeltaFosB expression in the nucleus accumbens of the rat. *Brain Res*. 2008; 1204:94–101. [PubMed: 18342839]

- Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science*. 1997; 276:2048–2050. [PubMed: 9197269]
- Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. *Addict Behav*. 2004; 29:33–50. [PubMed: 14667419]
- The National Center on Addiction and Substance Abuse. The National Center on Addiction and Substance Abuse (CASA) at Columbia University; New York: 2003. Food for Thought: Substance Abuse and Eating Disorders.
- Tobin S, Newman AH, Quinn T, Shalev U. A role for dopamine D1-like receptors in acute food deprivation-induced reinstatement of heroin seeking in rats. *Int J Neuropsychopharmacol*. 2009; 12:217–226. [PubMed: 18405418]
- Trotzky A. The treatment of eating disorders as addiction among adolescent females. *Int J Adolesc Med Health*. 2002; 14:269–274. [PubMed: 12613109]
- Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, Andrew CM, Williams SC, Campbell IC, Treasure J. Medial prefrontal cortex activity associated with symptom provocation in eating disorders. *Am J Psychiatry*. 2004; 161:1238–1246. [PubMed: 15229057]
- Unterwald EM, Kreek MJ, Cuntapay M. The frequency of cocaine administration impacts cocaine-induced receptor alterations. *Brain Res*. 2001; 900:103–109. [PubMed: 11325352]
- Vialou V, Cui H, Perello M, Mahgoub M, Yu HG, Rush AJ, Pranav H, Jung S, Yangisawa M, Zigman JM, Elmquist JK, Nestler EJ, Lutter M. A role for DeltaFosB in calorie restriction-induced metabolic changes. *Biol Psychiatry*. 2011; 70:204–207. [PubMed: 21215388]
- Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry*. 2001; 158:2015–2021. [PubMed: 11729018]
- Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse*. 1993; 14:169–177. [PubMed: 8101394]
- Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev*. 2013; 14:2–18. [PubMed: 23016694]
- Wang RY. Dopaminergic neurons in the rat ventral tegmental area. III. Effects of d- and l-amphetamine. *Brain Res Reviews*. 1981; 3:153–165.
- Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res*. 1992; 593:314–318. [PubMed: 1450939]
- Weissenborn R, Deroche V, Koob GF, Weiss F. Effects of dopamine agonists and antagonists on cocaine-induced operant responding for a cocaine-associated stimulus. *Psychopharmacology*. 1996; 126:311–322. [PubMed: 8878347]
- White FJ, Wang RY. A10 dopamine neurons: role of autoreceptors in determining firing rate and sensitivity to dopamine agonists. *Life Sci*. 1984; 34:1161–1170. [PubMed: 6708722]
- Wilcox CE, Teshiba TM, Merideth F, Ling J, Mayer AR. Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. *Drug Alcohol Depend*. 2011; 115:137–144. [PubMed: 21466926]
- Wilson GT. Psychological treatment of binge eating and bulimia nervosa. *J Ment Health*. 1995; 4:451–457.
- Wise RA. Dopamine, learning and motivation. *Nature reviews Neuroscience*. 2004; 5:483–494.
- Wolf ME, Tseng KY. Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? *Front Mol Neurosci*. 2012; 5:72. [PubMed: 22754497]
- Wong KJ, Wojnicki FH, Corwin RL. Baclofen, raclopride, and naltrexone differentially affect intake of fat/sucrose mixtures under limited access conditions. *Pharmacol Biochem Behav*. 2009; 92:528–536. [PubMed: 19217918]
- Yoshida M, Yokoo H, Mizoguchi K, Kawahara H, Tsuda A, Nishikawa T, Tanaka M. Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area

in the rat: measurement by in vivo microdialysis. *Neurosci Lett*. 1992; 139:73–76. [PubMed: 1407684]

Young KA, Liu Y, Gobrogge KL, Dietz DM, Wang H, Kabbaj M, Wang Z. Amphetamine alters behavior and mesocorticolimbic dopamine receptor expression in the monogamous female prairie vole. *Brain Res*. 2011; 1367:213–222. [PubMed: 20933511]

Zachariou V, Bolanos CA, Selley DE, Theobald D, Cassidy MP, Kelz MB, Shaw-Lutchman T, Berton O, Sim-Selley LJ, Dileone RJ, Kumar A, Nestler EJ. An essential role for DeltaFosB in the nucleus accumbens in morphine action. *Nat Neurosci*. 2006; 9:205–211. [PubMed: 16415864]

Zhang H, Kiyatkin EA, Stein EA. Behavioral and pharmacological modulation of ventral tegmental dendritic dopamine release. *Brain Res*. 1994; 656:59–70. [PubMed: 7804846]

Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. *Biol Psychiatry*. 2012; 71:184–191. [PubMed: 21872847]

Zhang Y, Loonam TM, Noailles PA, Angulo JA. Comparison of cocaine- and methamphetamine-evoked dopamine and glutamate overflow in somatodendritic and terminal field regions of the rat brain during acute, chronic, and early withdrawal conditions. *Ann N Y Acad Sci*. 2001; 937:93–120. [PubMed: 11458542]

Table 1

Major findings of the neurobiology of Bulimia Nervosa as it compares to drug addiction

	Bulimia Nervosa	Drug Addiction
NAC Extracellular DA	Increases during bingeing ^[1-5] Decreases during fasting ^[10] Increases during re-exposure ^[5]	Increases with exposure to drug ^[6-9] Decreases during withdrawal ^[7, 8, 11-17] Increases or no change during re-exposure depending on schedule of access ^[14, 15, 18-21]
D1 binding in NAC	Increases ^[2]	Increases or no change depending on method of administration ^[21-28]
D2 binding in NAC	Decreases ^[2, 29, 30]	Decreases for Coc, but increases for other drugs ^[21, 24, 26, 31]
D3 mRNA in the NAC	Increases ^[30]	Increases ^[21-27]
FosB in NAC	Increases ^[32, 33]	Increases ^[34-37]
DA in VTA	Increases ^{*,[4]}	Increases ^[38-42]
VTA DAT binding/mRNA	Increases ^{*,[43, 44]}	Increases for Amph and Nic, but not Coc ^[45-49]
VTA TH	Increases ^{*,[44]}	Increases for Coc and Mor, but not Meth ^[50, 51]
Raclopride (IP)	High doses decrease bingeing ^[52-54] Low doses increase bingeing ^[52, 53]	High doses attenuate relapse ^[55-58] Low doses stimulate reinstatement ^[58]
SCH 23390 (IP)	Reduces sucrose and fat intake ^[53]	Attenuates reinstatement ^[55, 56, 59-63]
GluA1 in the NAC	Increases following restriction ^[64]	Increases following 30-70 d abstinence ^[65-68]
GluA2 in the NAC	No changes following restriction ^[64]	No changes following abstinence ^[65]
Glutamate release in NAC	Unknown [*]	Increases ^[69-71]
Memantine	Decreases bingeing ^[72-74]	No effect ^[75-79]
MTEP	Decreases bingeing ^[72-73]	Decreases drug-seeking ^[80-86]
PFC activity	Hypofrontality with non-disorder-related cues ^[87, 88] Hyperfrontality with disorder-related cues ^[95-97]	Hypofrontality with non-drug-related cues ^[89-94] Hyperfrontality with drug-related cues ^[98-102]
μ-opioid receptor binding	Increases ^[2]	Increases ^[103]
Naltrexone treatment	Beneficial for bingeing of some foods ^{*,[52, 53, 104-110]}	Beneficial for Alc and Hern use, but not other drugs ^[111-113]

Note. DA = dopamine; VTA = ventral tegmental area; NAC = nucleus accumbens; PFC = prefrontal cortex; Amph = amphetamine; Nic = nicotine; Coc = cocaine; Mor = morphine; Meth = methamphetamine; Alc = alcohol; Hem = heroin.

* More research is necessary

¹ Avena NM, Rada P, Moise N, Hoebel BG (2006b) Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. *Neuroscience* 139: 813-820.

² Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG (2001) Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* 12: 3549-3552.

³ Rada P, Avena NM, Hoebel BG (2005) Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience* 134: 737-744.

- ⁴Yoshida M, Yokoo H, Mizoguchi K, Kawahara H, Tsuda A, Nishikawa T, Tanaka M (1992) Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area in the rat: measurement by in vivo microdialysis. *Neurosci Lett* 139: 73-76.
- ⁵Avena NM, Rada P, Hoebel BG (2008b) Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing on sucrose. *Neuroscience* 156: 865-871.
- ⁶Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A* 85: 5274-5278.
- ⁷Gaddnas H, Piepponen TP, Ahtee L (2002) Mecamylamine decreases accumbal dopamine output in mice treated chronically with nicotine. *Neurosci Lett* 330: 219-222.
- ⁸Pothos E, Rada P, Mark GP, Hoebel BG (1991) Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. *Brain Res* 566: 348-350.
- ⁹Tanda G, Pontieri FE, Di Chiara G (1997) Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science* 276: 2048-2050.
- ¹⁰Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG (2008a) After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. *Physiol Behav* 94: 309-315.
- ¹¹Acquas E, Di Chiara G (1992) Depression of mesolimbic dopamine transmission and sensitization to morphine during opiate abstinence. *J Neurochem* 58: 1620-1625.
- ¹²Natividad LA, Tejeda HA, Torres OV, O'Dell LE (2010) Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. *Synapse* 64: 136-145.
- ¹³Weiss F, Markou A, Lorang MT, Koob GF (1992) Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res* 593: 314-318.
- ¹⁴Zhang L, Dong Y, Doyon WM, Dani JA (2012) Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. *Biol Psychiatry* 71: 184-191.
- ¹⁵Mateo Y, Lack CM, Morgan D, Roberts DC, Jones SR (2005) Reduced dopamine terminal function and insensitivity to cocaine following cocaine binge self-administration and deprivation. *Neuropsychopharmacology* 30: 1455-1463.
- ¹⁶Rada P, Jensen K, Hoebel BG (2001) Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. *Psychopharmacology* 157: 105-110.
- ¹⁷Barak S, Carnicella S, Yowell QV, Ron D (2011) Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for alcohol reward and seeking. *J neurosci* 31: 9885-9894.
- ¹⁸Rahman S, Zhang J, Engleman EA, Corrigan WA (2004) Neuroadaptive changes in the mesoaccumbens dopamine system after chronic nicotine self-administration: a microdialysis study. *Neuroscience* 129: 415-424.
- ¹⁹Le Cozannet R, Markou A, Kuczenski R (2013) Extended-access, but not limited-access, methamphetamine self-administration induces behavioral and nucleus accumbens dopamine response changes in rats. *Eur J Neurosci* 38: 3487-3495.
- ²⁰Lominac KD, Sacramento AD, Szumlinski KK, Kippin TE (2012) Distinct neurochemical adaptations within the nucleus accumbens produced by a history of self-administered vs non-contingently administered intravenous methamphetamine. *Neuropsychopharmacology* 37: 707-722.
- ²¹Bahk JY, Li S, Park MS, Kim MO (2002) Dopamine D1 and D2 receptor mRNA up-regulation in the caudate-putamen and nucleus accumbens of rat brains by smoking. *Prog Neuropsychopharmacol Biol Psychiatry* 26: 1095-1104.
- ²²Le Foll B, Diaz J, Sokoloff P (2003) Increased dopamine D3 receptor expression accompanying behavioral sensitization to nicotine in rats. *Synapse* 47: 176-183.
- ²³Young KA, Liu Y, Gobrogge KL, Dietz DM, Wang H, Kabbaj M, Wang Z (2011) Amphetamine alters behavior and mesocorticolimbic dopamine receptor expression in the monogamous female prairie vole. *Brain Res* 1367: 213-222.
- ²⁴Sari Y, Bell RL, Zhou FC (2006) Effects of chronic alcohol and repeated deprivations on dopamine D1 and D2 receptor levels in the extended amygdala of inbred alcohol-preferring rats. *Alcohol Clin Exp Res* 30: 46-56.
- ²⁵Ben-Shahar O, Keeley P, Cook M, Brake W, Joyce M, Nyffeler M, Heston R, Ettenberg A (2007) Changes in levels of D1, D2, or NMDA receptors during withdrawal from brief or extended daily access to IV cocaine. *Brain Res* 1131: 220-228.

- ²⁶ Conrad KL, Ford K, Marinelli M, Wolf ME (2010) Dopamine receptor expression and distribution dynamically change in the rat nucleus accumbens after withdrawal from cocaine self-administration. *Neuroscience* 169: 182-94.
- ²⁷ Unterwald EM, Kreek MJ, Cuntapay M. (2001) The frequency of cocaine administration impacts cocaine-induced receptor alterations. *Brain Res* 900: 103-09.
- ²⁸ Metaxas A, Bailey A, Barbano MF, Galeote L, Maldonado R, Kitchen I (2010) Differential region-specific regulation of $\alpha 4\beta 2^*$ nAChRs by self-administered and non-contingent nicotine in C57BL/6J mice. *Addict Biol* 15: 464-479.
- ²⁹ Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum (2002) *Neuroreport* 13: 1575-78.
- ³⁰ Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF (2004) Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Molecular Brain Res* 124: 134-42.
- ³¹ Mukda S, Kaewsuk S, Ebadi M, Govitrapong P. (2009) Amphetamine-induced changes in dopamine receptors in early postnatal rat brain. *Dev Neurosci* 31: 193-201.
- ³² Stamp JA, Mashoodh R, van Kampen JM, Robertson HA. (2008) Food restriction enhances peak corticosterone levels, cocaine-induced locomotor activity, and DeltaFosB expression in the nucleus accumbens of the rat. *Brain Res* 1204: 94-101.
- ³³ Vialou V, Cui H, Perello M, Mahgoub M, Yu HG, Rush AJ, Pranav H, Jung S, Yangisawa M, Zigman JM, Elmquist JK, Nestler EJ, Lutter M (2011) A role for DeltaFosB in calorie restriction-induced metabolic changes. *Biol Psychiatry* 70: 204-207.
- ³⁴ Nestler EJ, Barrot M, Self DW (2001) DeltaFosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci U S A* 98: 11042-11046.
- ³⁵ Zachariou V, Bolanos CA, Selley DE, Theobald D, Cassidy MP, Kelz MB, Shaw-Lutchman T, Berton O, Sim-Selley LJ, Dileone RJ, Kumar A, Nestler EJ (2006) An essential role for DeltaFosB in the nucleus accumbens in morphine action. *Nat Neurosci* 9: 205-211.
- ³⁶ Colby CR, Whisler K, Steffen C, Nestler EJ, Self DW (2003) Striatal cell type-specific overexpression of DeltaFosB enhances incentive for cocaine. *J Neurosci* 23: 2488-2493.
- ³⁷ Kelz MB, Chen J, Carlezon WA, Jr., Whisler K, Gilden L, Beckmann AM, Steffen C, Zhang YJ, Marotti L, Self DW, Tkatch T, Baranaukas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR,
- ³⁸ Bradberry CW, Roth RH (1989) Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. *Neurosci Lett* 103: 97-102.
- ³⁹ Nakagawa T, Suzuki Y, Nagayasu K, Kitaichi M, Shirakawa H, Kaneko S (2011) Repeated exposure to methamphetamine, cocaine or morphine induces augmentation of dopamine release in rat mesocorticolimbic slice co-cultures. *PLoS One* 6: e24865.
- ⁴⁰ Kohl RR, Katner JS, Chernet E, McBride WJ (1998) Ethanol and negative feedback regulation of mesolimbic dopamine release in rats. *Psychopharmacology* 139: 79-85.
- ⁴¹ Reith ME, Li MY, Yan QS (1997) Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. *Psychopharmacology* 134: 309-317.
- ⁴² Zhang Y, Loonam TM, Noailles PA, Angulo JA (2001) Comparison of cocaine- and methamphetamine-evoked dopamine and glutamate overflow in somatodendritic and terminal field regions of the rat brain during acute, chronic, and early withdrawal conditions. *Ann N Y Acad Sci* 937: 93-120.
- ⁴³ Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A (2003) Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. *Am J Physiol Regul Integr Comp Physiol* 284: R1260-8.
- ⁴⁴ Lindblom J, Johansson A, Holmgren A, Grandin E, Nedergard C, Fredriksson R, Schioth HB (2006) Increased mRNA levels of tyrosine hydroxylase and dopamine transporter in the VTA of male rats after chronic food restriction. *Eur J Neurosci* 23: 180-186.
- ⁴⁵ Lu W, Wolf ME (1997) Expression of dopamine transporter and vesicular monoamine transporter 2 mRNAs in rat midbrain after repeated amphetamine administration. *Brain Res* 49: 137-148.
- ⁴⁶ Shilling PD, Kelsoe JR, Segal DS (1997) Dopamine transporter mRNA is up-regulated in the substantia nigra and the ventral. *Neurosci Lett* 236: 131-134.

- ⁴⁷ Li S, Kim KY, Kim JH, Park MS, Bahk JY, Kim MO (2004) Chronic nicotine and smoking treatment increases dopamine transporter mRNA expression in the rat midbrain. *Neurosci Lett* 363: 29-32.
- ⁴⁸ Cerruti C, Pilotte NS, Uhl G, Kuhar MJ (1994) Reduction in dopamine transporter mRNA after cessation of repeated cocaine. *Brain Res* 22: 132-138.
- ⁴⁹ Ben-Shahar O, Moscarello JM, Ettenberg A (2006) One hour, but not six hours, of daily access to self-administered cocaine results in elevated levels of the dopamine transporter. *Brain Res* 1095: 148-153.
- ⁵⁰ Beitner-Johnson D, Nestler EJ (1991) Morphine and cocaine exert common chronic actions on tyrosine hydroxylase in dopaminergic brain reward regions. *J Neurochem* 57: 344-347.
- ⁵¹ Shishido T, Watanabe Y, Matsuoka I, Nakanishi H, Niwa S (1997) Acute methamphetamine administration increases tyrosine hydroxylase mRNA levels in the rat locus coeruleus. *Brain Res* 52: 146-150.
- ⁵² Wong KJ, Wojnicki FH, Corwin RL (2009) Baclofen, raclopride, and naltrexone differentially affect intake of fat/sucrose mixtures under limited access conditions. *Pharmacol Biochem Behav* 92: 528-536.
- ⁵³ Corwin RL, Wojnicki FH (2009) Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. *Behav Pharmacol* 20: 537-548.
- ⁵⁴ Rao RE, Wojnicki FH, Coupland J, Ghosh S, Corwin RL (2008) Baclofen, raclopride, and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. *Pharmacol Biochem Behav* 89: 581-590.
- ⁵⁵ Crombag HS, Grimm JW, Shaham Y (2002) Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. *Neuropsychopharmacology* 27: 1006-1015.
- ⁵⁶ Shaham Y, Stewart J (1996) Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology* 125: 385-391.
- ⁵⁷ Alen F, Moreno-Sanz G, Isabel de Tena A, Brooks RD, Lopez-Jimenez A, Navarro M, Lopez-Moreno JA (2008) Pharmacological activation of CB1 and D2 receptors in rats: predominant role of CB1 in the increase of alcohol relapse. *Eur J Neurosci* 27: 3292-3298.
- ⁵⁸ Berglind WJ, Case JM, Parker MP, Fuchs RA, See RE (2006) Dopamine D1 or D2 receptor antagonism within the basolateral amygdala differentially alters the acquisition of cocaine-cue associations necessary for cue-induced reinstatement of cocaine-seeking. *Neuroscience* 137: 699-706.
- ⁵⁹ Weissenborn R, Deroche V, Koob GF, Weiss F (1996) Effects of dopamine agonists and antagonists on cocaine-induced operant responding for a cocaine-associated stimulus. *Psychopharmacology* 126: 311-322.
- ⁶⁰ Tobin S, Newman AH, Quinn T, Shalev U (2009) A role for dopamine D1-like receptors in acute food deprivation-induced reinstatement of heroin seeking in rats. *Int J Neuropsychopharmacol* 12: 217-226.
- ⁶¹ Stairs DJ, Neugebauer NM, Bardo MT (2010) Nicotine and cocaine self-administration using a multiple schedule of intravenous drug and sucrose reinforcement in rats. *Behav Pharmacol* 21: 182-193.
- ⁶² Sorge RE, Clarke PB (2009) Rats self-administer intravenous nicotine delivered in a novel smoking-relevant procedure: effects of dopamine antagonists. *J Pharmacol Exp Ther* 330: 633-640.
- ⁶³ Ramoa CP, Doyle SE, Lycas MD, Chernau AK, Lynch WJ (2013) Diminished Role of Dopamine D1-Receptor Signaling with the Development of an Addicted Phenotype in Rats. *Biol Psychiatry*.
- ⁶⁴ Peng XX, Ziff EB, Carr KD (2011) Effects of food restriction and sucrose intake on synaptic delivery of AMPA receptors in nucleus accumbens. *Synapse* 65: 1024-1031.
- ⁶⁵ Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME (2008) Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 454: 118-121.
- ⁶⁶ Ferrario CR, Loweth JA, Milovanovic M, Ford KA, Galinanes GL, Heng LJ, Tseng KY, Wolf ME (2011) Alterations in AMPA receptor subunits and TARPs in the rat nucleus accumbens related to the formation of Ca(2+)-permeable AMPA receptors during the incubation of cocaine craving. *Neuropharmacology* 61: 1141-1151.
- ⁶⁷ Wolf ME, Tseng KY (2012) Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? *Front Mol Neurosci* 5: 72.

- ⁶⁸ Purgianto A, Scheyer AF, Loweth JA, Ford KA, Tseng KY, Wolf ME (2013) Different adaptations in AMPA receptor transmission in the nucleus accumbens after short vs long access cocaine self-administration regimens. *Neuropsychopharmacology* 38: 1789-1797.
- ⁶⁹ Gass JT, Sinclair CM, Cleva RM, Widholm JJ, Olive MF (2011) Alcohol-seeking behavior is associated with increased glutamate transmission in basolateral amygdala and nucleus accumbens as measured by glutamate-oxidase-coated biosensors. *Addict Biol* 16: 215-228.
- ⁷⁰ McFarland K, Lapish CC, Kalivas PW (2003) Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 23: 3531-3537.
- ⁷¹ LaLumiere RT, Kalivas PW (2008) Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J Neurosci* 28: 3170-3177.
- ⁷² Popik P, Kos T, Zhang Y, Bisaga A (2011) Memantine reduces consumption of highly palatable food in a rat model of binge eating. *Amino Acids* 40: 477-485.
- ⁷³ Bisaga A, Danysz W, Foltin RW (2008) Antagonism of glutamatergic NMDA and mGluR5 receptors decreases consumption of food in baboon model of binge-eating disorder. *Eur Neuropsychopharmacol* 18: 794-802.
- ⁷⁴ Brennan BP, Roberts JL, Fogarty KV, Reynolds KA, Jonas JM, Hudson JI (2008) Memantine in the treatment of binge eating disorder: an open-label, prospective trial. *Int J Eat Disord* 41: 520-526.
- ⁷⁵ Jackson A, Nesic J, Groombridge C, Clowry O, Rusted J, Duka T (2009) Differential involvement of glutamatergic mechanisms in the cognitive and subjective effects of smoking. *Neuropsychopharmacology* 34: 257-265.
- ⁷⁶ Comer SD, Sullivan MA (2007) Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. *Psychopharmacology* 193: 235-245.
- ⁷⁷ Krupitsky EM, Rudenko AA, Burakov AM, Slavina TY, Grinenko AA, Pittman B, Gueorguieva R, Petrakis IL, Zvartau EE, Krystal JH (2007) Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. *Alcohol Clin Exp Res* 31: 604-611.
- ⁷⁸ Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW (2001) The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. *Psychopharmacology* 157: 1-10.
- ⁷⁹ Evans SM, Levin FR, Brooks DJ, Garawi F (2007) A pilot double-blind treatment trial of memantine for alcohol dependence. *Alcohol Clin Exp Res* 31: 775-782.
- ⁸⁰ Bäckström P, Hyytiä P (2006) Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* 31: 778-786.
- ⁸¹ Knackstedt LA, Trantham-Davidson HL, Schwendt M (2013) The role of ventral and dorsal striatum mGluR5 in relapse to cocaine-seeking and extinction learning. *Addict Biol*.
- ⁸² Kumaresan V, Yuan M, Yee J, Famous KR, Anderson SM, Schmidt HD, Pierce RC (2009) Metabotropic glutamate receptor 5 (mGluR5) antagonists attenuate cocaine priming- and cue-induced reinstatement of cocaine seeking. *Behavioural Brain Res* 202: 238-244.
- ⁸³ Martin-Fardon R, Baptista MA, Dayas CV, Weiss F (2009) Dissociation of the effects of MTEP [3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]piperidine] on conditioned reinstatement and reinforcement: comparison between cocaine and a conventional reinforcer. *J Pharmacol Exp Ther* 329: 1084-1090.
- ⁸⁴ Sidhpura N, Weiss F, Martin-Fardon R (2010) Effects of the mGlu2/3 agonist LY379268 and the mGlu5 antagonist MTEP on ethanol seeking and reinforcement are differentially altered in rats with a history of ethanol dependence. *Biol Psychiatry* 67: 804-811.
- ⁸⁵ Osborne MP, Olive MF (2008) A role for mGluR5 receptors in intravenous methamphetamine self-administration. *Ann N Y Acad Sci* 1139: 206-211.
- ⁸⁶ Brown RM, Stagnitti MR, Duncan JR, Lawrence AJ (2012) The mGlu5 receptor antagonist MTEP attenuates opiate self-administration and cue-induced opiate-seeking behaviour in mice. *Drug Alcohol Depend* 123: 264-268.
- ⁸⁷ Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, Walsh BT, Peterson BS (2011) An FMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. *Am J Psychiatry* 168: 1210-1220.
- ⁸⁸ Marsh R, Steinglass JE, Gerber AJ, Graziano O'Leary K, Wang Z, Murphy D, Walsh BT, Peterson BS (2009) Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry* 66: 51-63.

- ⁸⁹Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND (2007) Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry* 164: 43-51.
- ⁹⁰Kim YT, Song HJ, Seo JH, Lee JJ, Lee J, Kwon DH, Yoo DS, Lee HJ, Suh KJ, Chang Y (2011) The differences in neural network activity between methamphetamine abusers and healthy subjects performing an emotion-matching task: functional MRI study. *NMR Biomed* 24: 1392-1400.
- ⁹¹Nestor LJ, Ghahremani DG, Monterosso J, London ED (2011) Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. *Psychiatry Res* 194: 287-295.
- ⁹²Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C (2009) Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biol Psychiatry* 65: 706-709.
- ⁹³Crego A, Rodriguez-Holguin S, Parada M, Mota N, Corral M, Cadaveira F (2010) Reduced anterior prefrontal cortex activation in young binge drinkers during a visual working memory task. *Drug Alcohol Depend* 109: 45-56.
- ⁹⁴Maurage P, Joassin F, Philippot P, Heeren A, Vermeulen N, Mahau P, Delpèrdange C, Corneille O, Luminet O, de Timary P (2012) Disrupted regulation of social exclusion in alcohol-dependence: an fMRI study. *Neuropsychopharmacology* 37: 2067-2075.
- ⁹⁵Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, Andrew CM, Williams SC, Campbell IC, Treasure J (2004) Medial prefrontal cortex activity associated with symptom provocation in eating disorders. *Am J Psychiatry* 161: 1238-1246.
- ⁹⁶Miyake Y, Okamoto Y, Onoda K, Shirao N, Otagaki Y, Yamawaki S (2010) Neural processing of negative word stimuli concerning body image in patients with eating disorders: an fMRI study. *Neuroimage* 50: 1333-1339.
- ⁹⁷Spangler DL, Allen MD (2012) An fMRI investigation of emotional processing of body shape in bulimia nervosa. *Int J Eat Disord* 45: 17-25.
- ⁹⁸George MS, Anton RF, Bloomer C, Teneback C, Drobos DJ, Lorberbaum JP, Nahas Z, Vincent DJ (2001) Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry* 58: 345-352.
- ⁹⁹Grusser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, Heinz A (2004) Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology* 175: 296-302.
- ¹⁰⁰Tapert SF, Brown GG, Baratta MV, Brown SA (2004) fMRI BOLD response to alcohol stimuli in alcohol dependent young women. *Addict Behav* 29: 33-50.
- ¹⁰¹Wilcox CE, Teshiba TM, Merideth F, Ling J, Mayer AR (2011) Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. *Drug Alcohol Depend* 115: 137-144.
- ¹⁰²Lee JH, Lim Y, Wiederhold BK, Graham SJ (2005) A functional magnetic resonance imaging (fMRI) study of cue-induced smoking craving in virtual environments. *Appl Psychophysiol Biofeedback* 30: 195-204.
- ¹⁰³Fattore L, Vigano D, Fadda P, Rubino T, Fratta W, Parolaro D (2007) Bidirectional regulation of mu-opioid and CB1-cannabinoid receptor in rats self-administering heroin or WIN 55,212-2. *Eur J Neurosci* 25: 2191-2200.
- ¹⁰⁴Berner LA, Bocarsly ME, Hoebel BG, Avena NM (2011) Pharmacological interventions for binge eating: lessons from animal models, current treatments, and future directions. *Curr Pharm Des* 17: 1180-1187.
- ¹⁰⁵Giuliano C, Robbins TW, Nathan PJ, Bullmore ET, Everitt BJ (2012) Inhibition of opioid transmission at the mu-opioid receptor prevents both food seeking and binge-like eating. *Neuropsychopharmacology* 37: 2643-2652.
- ¹⁰⁶Jonas JM, Gold MS (1986) Treatment of antidepressant-resistant bulimia with naltrexone. *Int J Psychiatry Med* 16: 305-309.
- ¹⁰⁷Maremmani I, Marini G, Castrogiovanni P, Deltito J (1996) The effectiveness of the combination fluoxetine-naltrexone in bulimia nervosa. *Eur Psychiatry* 11: 322-324.
- ¹⁰⁸Marrazzi MA, Bacon JP, Kinzie J, Luby ED (1995) Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. *Int Clin Psychopharmacol* 10: 163-172.
- ¹⁰⁹Mitchell JE, Christenson G, Jennings J, Huber M, Thomas B, Pomeroy C, Morley J (1989) A placebo-controlled, double-blind crossover study of naltrexone hydrochloride in outpatients with normal weight bulimia. *J Clin Psychopharmacol* 9: 94-97.

- ¹¹⁰ Ramoz N, Versini A, Gorwood P (2007) Eating disorders: an overview of treatment responses and the potential impact of vulnerability genes and endophenotypes. *Expert Opin Pharmacother* 8: 2029-2044.
- ¹¹¹ Conason AH, Sher L (2006) Alcohol use in adolescents with eating disorders. *Int J Adolesc Med Health* 18: 31-36.
- ¹¹² Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE (2006) Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *J Subst Abuse Treat* 31: 319-328.
- ¹¹³ Modesto-Lowe V, Van Kirk J (2002) Clinical uses of naltrexone: a review of the evidence. *Exp Clin Psychopharmacol* 10: 213-227.