Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology

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Drugs and food exert their reinforcing effects in part by increasing dopamine (DA) in limbic regions, which has generated interest in understanding how drug abuse/addiction relates to obesity. Here, we integrate findings from positron emission tomography imaging studies on DA’s role in drug abuse/addiction and in obesity and propose a common model for these two conditions. Both in abuse/addiction and in obesity, there is an enhanced value of one type of reinforcer (drugs and food, respectively) at the expense of other reinforcers, which is a consequence of conditioned learning and resetting of reward thresholds secondary to repeated stimulation by drugs (abuse/addiction) and by large quantities of palatable food (obesity) in vulnerable individuals (i.e. genetic factors). In this model, during exposure to the reinforcer or to conditioned cues, the expected reward (processed by memory circuits) overactivates the reward and motivation circuits while inhibiting the cognitive control circuit, resulting in an inability to inhibit the drive to consume the drug or food despite attempts to do so. These neuronal circuits, which are modulated by DA, interact with one another so that disruption in one circuit can be buffered by another, which highlights the need of multiprong approaches in the treatment of addiction and obesity.

\textbf{Keywords:} dopamine; positron emission tomography; imaging; self-control; compulsion

1. INTRODUCTION

Drug abuse and addiction, and certain types of obesity can be understood as resulting from habits that strengthen with repetition of the behaviour and that become increasingly harder for the individual to control despite their potentially catastrophic consequences. Consumption of food, other than eating from hunger, and some drug use are initially driven by their rewarding properties, which in both instances involves activation of mesolimbic dopamine (DA) pathways. Food and drugs of abuse activate DA pathways differently (table 1). Food activates brain reward circuitry both through palatability (involves endogenous opioids and cannabino- 

oids) and through increases in glucose and insulin concentrations (involves DA increases), whereas drugs activate this same circuitry via their pharmacological effects (via direct effects on DA cells or indirectly through neurotransmitters that modulate DA cells such as opiates, nicotine, \gamma-aminobutyric acid or cannabi- 

oids; Volkow & Wise 2005).

The repeated stimulation of DA reward pathways is believed to trigger neurobiological adaptations in other neurotransmitters and in downstream circuits that may make the behaviour increasingly compulsive and lead to the loss of control over food and drug intake. In the case of drugs of abuse, repeated supraphysiological DA stimulation from chronic use is believed to induce plastic changes in brain (i.e. glutamatergic cortico-striatal pathways), which result in enhanced emotional reactivity to drugs or their cues, poor inhibitory control over drug consumption and compulsive drug intake (Volkow & Li 2004). In parallel, dopaminergic stimulation during intoxication facilitates conditioning to drugs and drug- associated stimuli (drug cues), further strengthening learned habits that then drive the behaviour to take drugs when exposed to cues or to stressors. Similarly, repeated exposure to certain foods (particularly, large quantities of energy-dense food with high-fat and sugar contents; Avena \textit{et al.} 2008) in vulnerable individuals can also result in compulsive food consumption, poor food intake control and conditioning to food stimuli. In vulnerable individuals (i.e. those with genetic or developmental predisposing factors), this can result in obesity (for food) or in addiction (for drugs).

The neurobiological regulation of feeding is much more complex than the regulation of drug abuse, since food consumption is controlled not only by reward but also by multiple peripheral, endocrinological and central factors beyond those that participate in reward (Levine \textit{et al.} 2003). In this paper, we concentrate solely on the neurocircuitry linked with the rewarding properties of food, since it is likely to be a key contributor in accounting for the massive increase in obesity that has emerged over the past three decades. Our hypothesis is that adaptation in the reward circuit and also in the motivational, memory and control circuits that occur with repeated exposure to large quantities of highly palatable food is similar to that which one observes with repeated drug exposures (table 2). We also postulate that differences between

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individuals in the function of these circuits prior to compulsive eating or drug abuse are likely to contribute to the differences in vulnerability to food or drugs as the preferred reinforcer. These include differences in sensitivity to rewarding properties of food versus that to drugs; differences in their ability to exert inhibitory control over their intention to eat appealing food in the face of its negative consequences (gain weight) or to take an illicit drug (illegal act); and differences in the propensity to develop conditioned responses when exposed to food versus drugs.

2. REWARD/SALIENCY CIRCUITY IN ADDICTION AND OBESITY

Since DA underlies the rewarding properties of food and many drugs, we postulate that differences in the reactivity of the DA system to food or to drugs could modulate the likelihood of their consumption. To test this hypothesis, we have used positron emission tomography (PET) and a multiple tracer approach to assess the DA system in the human brain in healthy controls as well as in subjects that are addicted to drugs and in those that are morbidly obese. Of the synaptic markers of DA neurotransmission, the availability of DA D₂ receptors in striatum is recognized to modulate the reinforcing responses to both drugs and food.

(a) Drug responses and vulnerability for drug abuse/addiction

In healthy non-drug abusing controls, we showed that D₂ receptor availability in the striatum modulated their subjective responses to the stimulant drug methylphenidate (MP). Subjects describing the experience as pleasant had significantly lower levels of receptors compared with those describing MP as unpleasant (Volkow et al. 1999a, 2002a). This suggests that the relationship between DA levels and reinforcing responses follows an inverted U-shaped curve: too little is not optimal for reinforcement but too much is aversive. Thus, high D₂ receptor levels could protect against drug self-administration. Support for this is given by preclinical studies showing that upregulation of D₂ receptors in nucleus accumbens (NAc; region in striatum implicated in drug and food reward) dramatically reduced alcohol intake in animals previously trained to self-administer alcohol (Thanos et al. 2001), and by clinical studies showing that subjects who despite having family histories of addiction were not addicted had higher D₂ receptors in striatum than individuals without such family histories (Mintun et al. 2003; Volkow et al. 2006a).

Using PET and the D₂ receptor radioligands, we and other researchers have shown that subjects with a wide variety of drug addictions (cocaine, heroin, alcohol and
methylphenidate) have significant reductions in D₂ receptor availability in striatum that persist months after protracted detoxification (reviewed by Volkow et al. 2004). In addition, drug abusers (cocaine and alcohol) also show decreased DA release, which is likely to reflect reduced DA cell firing (Volkow et al. 1997; Martinez et al. 2005). DA release was measured using PET and [¹¹C]raclopride, which is a D₂ receptor radioligand that competes with endogenous DA for binding to D₂ receptors and thus can be used to assess the changes in DA induced by drugs. The striatal increases in DA (seen as reductions in the specific binding of [¹¹C]raclopride) induced by the intravenous administration of stimulant drugs (MP or amphetamine) in cocaine abusers and alcoholics were markedly blunted when compared with controls (more than 50% lower; Volkow et al. 1997, 2007a; Martinez et al. 2005, 2007). Since DA increases induced by MP are dependent on DA release, a function of DA cell firing, we speculated this difference probably reflected decreased DA cell activity in the cocaine abusers and alcoholics.

These studies suggest two abnormalities in addicted subjects that would result in decreased output of DA reward circuits: decreases in DA D₂ receptors, and DA release in striatum (including NAc). Each would contribute to the decreased sensitivity in addicted subjects to natural reinforcers. Indeed, drug-addicted individuals appear to suffer from an overall reduction in the sensitivity of their reward circuits to natural reinforcers. For example, a functional magnetic resonance imaging study showed reduced brain activation in response to sexual cues in cocaine-addicted individuals (Garavan et al. 2000). Similarly, a PET study found evidence suggesting that the brains of smokers react in a different way to monetary and non-monetary rewards when compared with non-smokers (Martin-Solch et al. 2001). Since drugs are much more potent at stimulating DA-regulated reward circuits than natural reinforcers, they would still be able to activate these downregulated reward circuits. Decreased sensitivity of reward circuits would result in a decreased interest for environmental stimuli, possibly predisposing subjects to seek drug stimulation as a means to temporarily activate these reward circuits.

(b) Eating behavioural patterns and vulnerability for obesity
In healthy normal weight subjects, D₂ receptor availability in the striatum modulated eating behavioural patterns (Volkow et al. 2003a). Specifically, the tendency to eat when exposed to negative emotions was negatively correlated with D₂ receptor availability (the lower the D₂ receptors, the higher the likelihood that the subject would eat if emotionally stressed).

In morbidly obese subjects (body mass index (BMI) > 40), we showed lower than normal D₂ receptor availability and these reductions were proportional to their BMI (Wang et al. 2001). That is, subjects with the lower D₂ receptors had higher BMI. Similar results of decreased D₂ receptors in obese subjects were recently replicated (Haltia et al. 2007). These findings led us to postulate that low D₂ receptor availability could put an individual at risk for overeating. In fact, this is consistent with findings showing that blocking D₂ receptors (antipsychotic medications) increases food intake and raises the risk for obesity (Allison et al. 1999). However, the mechanisms by which low D₂ receptor availability would increase the risk of overeating (or how they increase the risk for drug abuse) are poorly understood.

3. Inhibitory control/emotional reactivity circuit in addiction and obesity

(a) Drug abuse and addiction
Drug availability markedly increases the likelihood of experimentation and abuse (Volkow & Wise 2005). Thus, the ability to inhibit prepotent responses that are likely to occur in an environment with easy access to drugs is likely to contribute to the ability of the individual to refrain from taking drugs. Similarly, adverse environmental stressors (i.e. social stressors) also facilitate drug experimentation and abuse. Since not all subjects react the same to stress, differences in emotional reactivity have also been implicated as a factor that modulates the vulnerability for drug abuse (Piazza et al. 1991).

In studies on drug abusers and those on subjects at risk for addiction, we have assessed the relationships between the availability of D₂ receptors and regional brain glucose metabolism (marker of brain function) to evaluate the brain regions that have reduced activity when D₂ receptors are decreased. We have shown that the reductions in striatal D₂ receptors in the detoxified drug-addicted subjects were associated with decreased metabolic activity in orbitofrontal cortex (OFC), anterior cingulate gyrus (CG) and dorsolateral prefrontal cortex (DLPFC; figure 1; Volkow et al. 1993, 2001, 2007a). Since OFC, CG and DLPFC are involved with inhibitory control (Goldstein & Volkow 2002) and with emotional processing (Phan et al. 2002), we had postulated that their improper regulation by DA in addicted subjects could underlie their loss of control over drug intake and their poor emotional self-regulation. Indeed, in alcoholics, reductions in D₂ receptor availability in ventral striatum are associated with craving severity and greater cue-induced activation of the medial prefrontal cortex and CG (Heinz et al. 2004). In addition, because damage to the OFC results in perseverative behaviours (Rolls 2000) and in humans impairments in OFC and CG are associated with obsessive compulsive behaviours (Insel 1992), we also postulated that DA impairment of these regions could underlie the compulsive drug intake that characterizes addiction (Volkow et al. 2005).

However, the association could also be interpreted to indicate that impaired activity in prefrontal regions could put individuals at risk for drug abuse and then the repeated drug use could result in the down-regulation of D₂ receptors. Indeed, support for the latter possibility is provided by our studies, in subjects who despite having a high risk for alcoholism (owing to a dense family history of alcoholism) were not alcoholics: in these, we showed higher D₂ receptors in striatum than in individuals without such family histories (Volkow et al. 2006a). In these subjects, the higher the D₂ receptors, the higher the metabolism in...
OFC, CG and DLPFC. In addition, OFC metabolism was also positively correlated with personality measures of positive emotionality. Thus, we postulate that high levels of D2 receptors could protect against addiction by modulating prefrontal regions involved in inhibitory control and emotional regulation.

(b) Food intake and obesity
Since food availability and variety increase the likelihood of eating (Wardle 2007), the easy access to appealing food requires the frequent need to inhibit the desire to eat it (Berthoud 2007). The extent to which individuals differ in their ability to inhibit these responses and control how much they eat is likely to modulate their risk for overeating in our current food-rich environments (Berthoud 2007).

As described above, we had previously documented a reduction in D2 receptors in morbidly obese subjects. This led us to postulate that low D2 receptors could put an individual at risk for overeating. The mechanisms by which low D2 receptors could increase the risk of overeating is unclear but we postulated that, just as for the case with drug abuse/addiction, this could be mediated by D2 receptor-mediated regulation of prefrontal regions.

To assess whether the reductions in D2 receptors in morbidly obese subjects were associated with activity in prefrontal regions (CG, DLPFC and OFC), we assessed the relationship between D2 receptor availability in striatum and brain glucose metabolism. Both SPM analysis (to assess correlations on a pixel-by-pixel basis with no pre-selection of regions) as well as independently drawn regions of interest revealed that D2 receptor availability was associated with metabolism in dorsolateral prefrontal cortex (Brodmann areas (BA) 9 and 10), medial OFC (BA 11) and CG (BA 32 and 25; figure 2). The association with prefrontal metabolism suggests that decreases in D2 receptors in obese subjects contribute to overeating in part through deregulation of prefrontal regions implicated in inhibitory control and emotional regulation.

4. MOTIVATION/DRIVE IN DRUG ABUSE/ADDICTION AND OBESITY
(a) Drug abuse and addiction
In contrast to the decreases in metabolic activity in prefrontal regions in detoxified cocaine abusers, these regions are hypermetabolic in active cocaine abusers (Volkow et al. 1991). Thus, we postulate that during cocaine intoxication or as the intoxication subsides, the drug-induced DA increases in striatum activate OFC and CG, which result in craving and compulsive drug intake. Indeed, we have shown that intravenous MP increased metabolism in OFC only in the cocaine abusers in whom it induced intense craving (Volkow et al. 1999b). Activation of the OFC and the CG in drug abusers has also been reported to occur during craving elicited by viewing a cocaine-cue video (Grant et al. 1996) and by recalling previous drug experiences (Wang et al. 1999).

(b) Obesity
Imaging studies in obese subjects have documented increased activation of prefrontal regions upon exposure to a meal, which is greater in obese than lean subjects (Gautier et al. 2000). When food-related stimuli are given to obese subjects (as when drug-related stimuli are given to addicts; Volkow & Fowler 2000), medial...
Prefrontal cortex is activated and cravings are reported (Gautier et al. 2000; Wang et al. 2004; Miller et al. 2007). Several areas of the prefrontal cortex (including OFC and CG) have been implicated in motivation to feed (Rolls 2004). These prefrontal regions could reflect a neurobiological substrate common to the drive to eat or the drive to take drugs. Abnormalities of these regions could enhance either drug- or food-oriented behaviour, depending on the sensitivity to the reward and/or established habits of the subject.

5. MEMORY, CONDITIONING AND HABITS TO DRUGS AND FOOD

(a) Drug abuse and addiction

Circuits underlying memory and learning, including conditioned incentive learning, habit learning and declarative memory (reviewed by Vanderschuren & Everitt 2005), have been proposed to be involved in drug addiction. The effects of drugs on memory systems suggest ways that neutral stimuli can acquire reinforcing properties and motivational salience, i.e. through conditioned incentive learning. In research on relapse, it is important to understand why drug-addicted subjects experience an intense desire for the drug when exposed to places where they have taken the drug, to people with whom prior drug use occurred and to paraphernalia used to administer the drug. This is clinically relevant since exposure to conditioned cues (stimuli associated with the drug) is a key contributor to relapse. Since DA is involved with the prediction of reward (reviewed by Schultz 2002), we hypothesized that DA might underlie conditioned responses that trigger craving. Studies in laboratory animals support this hypothesis: when neutral stimuli are paired with a drug they will, with repeated associations, acquire the ability to increase DA in NAc and dorsal striatum (becoming conditioned cues). Furthermore, these neurochemical responses are associated with drug-seeking behaviour (reviewed by Vanderschuren & Everitt 2005).

In humans, PET studies with $[^{11}C]$raclopride recently confirmed this hypothesis by showing that in cocaine abusers drug cues (cocaine-cue video of scenes of subjects taking cocaine) significantly increased DA in dorsal striatum and these increases were associated with cocaine craving (figure 3; Volkow et al. 2006b; Wong et al. 2006). Because the dorsal striatum is implicated in habit learning, this association is likely to reflect the strengthening of habits as chronicity of addiction progresses. This suggests that a basic neurobiological disruption in addiction might be DA-triggered conditioned responses that result in habits leading to compulsive drug consumption. It is likely that these conditioned responses involve adaptations in cortico-striatal glutamatergic pathways that regulate DA release (reviewed Kalivas et al. 2005). Thus, while drugs (as well as food) may initially lead to DA release in ventral striatum (signalling reward), with repeated administration and as habits develop there appears to be a shift in the DA increases occurring into the dorsal striatum.

(b) Food and obesity

DA regulates food consumption not only through modulation of its rewarding properties (Martel & Fantino 1996) but also by facilitating conditioning to food stimuli that then drive the motivation to consume the food (Kiyatkin & Gratton 1994; Mark et al. 1994). One of the first descriptions of a conditioned response was by Pavlov who showed that when dogs were...
exposed to repeated pairing of a tone with a piece of meat the tone by itself would elicit salivation in these animals. Since then, voltammetry studies have shown that the presentation of a neutral stimulus that has been conditioned to food results in increases in striatal DA and that the DA increases are linked to the motoric behaviour required to procure the food (lever pressing; Roitman et al. 2004).

We have used PET to evaluate these conditioned responses in healthy controls. We hypothesize that food cues would increase extracellular DA in striatum and that these increases would predict the desire for food. Food-deprived subjects were studied while stimulated with a neutral or food-related stimulus (conditioned cues). To amplify the DA changes, we pretreated the subjects with MP (20 mg orally), a stimulant drug that blocks DA transporters (the main mechanism for the removal of extracellular DA; Giros et al. 1996). Food stimulation significantly increased DA in striatum and these increases correlated with the increases in self-reports of hunger and desire for food (Volkow et al. 2002b; figure 4). Similar findings were reported when food cues were presented to healthy controls without pretreatment with MP. These findings corroborate the involvement of striatal DA signalling in conditioned responses to food and the participation of this pathway in food motivation in humans. Since these responses were obtained when subjects did not consume the food, this identifies these responses as distinct from the role of DA in regulating reward through NAc.

We are currently evaluating these conditioned responses in obese subjects in whom we hypothesize an accentuated increase in DA when exposed to cues compared with those of normal weight individuals.

6. A SYSTEMS MODEL OF ABUSE/ADDICTION AND OF OBESITY
As summarized previously, several common brain circuits have been identified by imaging studies as being relevant in the neurobiology of drug abuse/addiction and obesity. Here, we highlight four of these circuits: (i) reward/saliency, (ii) motivation/drive, (iii) learning/conditioning, and (iv) inhibitory control/emotional regulation/executive function. Note that the two other circuits (emotion/mood regulation and interoception) also participate in modulating the propensity to eat or take drugs but for simplicity are not incorporated into the model. We propose that a consequence of the disruption of these four circuits is an enhanced value of one type of reinforcer (drugs for the drug abuser and high-density food for the obese individual) at the expense of other reinforcers, which is a consequence of conditioned learning and resetting of reward thresholds secondary to repeated stimulation by drugs (drug abuser/addict) and by large quantities of high-density food (obese individual) in vulnerable individuals. A consequence of the impairment in the reward/saliency circuit (processes mediated in part through NAc, ventral pallidum, medial OFC and hypothalamus),
which modulates our response to both positive and negative reinforcers, is a decreased value to stimuli that otherwise would motivate behaviours likely to result in beneficial outcomes while avoiding behaviours that could result in punishment. For the case of drug abuse/addiction, one can predict that as a result of dysfunction in this neurocircuit the person would be less likely to be motivated to abstain from drug use because alternative reinforcers (natural stimuli) are much less exciting and negative consequences (e.g. incarceration, divorce) are less salient. For the case of obesity, one can predict that as a result of dysfunction in this neurocircuit the person would be less likely to be motivated to abstain from eating because alternative reinforcers (physical activity and social interactions) are less exciting and negative consequences (e.g. gaining weight, diabetes) are less salient.

A consequence of disruption of the inhibitory control/emotional regulation circuit is the impairment of the individual to exert inhibitory control and emotional regulation (processes mediated in part through the DLPFC, CG and lateral OFC), which are critical components of the substrates necessary to inhibit prepotent responses such as the intense desire to take the drug in an addicted subject or to eat high-density food in an obese individual. As a result, the person is less likely to succeed in inhibiting the intentional actions and to regulate the emotional reactions associated with the strong desires (either to take the drug or to eat the food).

The consequences of the involvement of memory/conditioning/habits circuit (mediated in part through hippocampus, amygdala and dorsal striatum) are that repeated use of drugs (drug abuser/addict) or repeated consumption of large quantities of high-density food (obese individual) results in the formation of new linked memories (processes mediated in part through hippocampus and amygdala), which condition the individual to expect pleasurable responses, not only when exposed to the drug (drug abuser/addict) or to the food (obese individual) but also from exposure to stimuli conditioned to the drug (i.e. smell of cigarettes) or conditioned to the food (i.e. watching TV). These stimuli trigger automatic responses that frequently drive relapse in the drug abuser/addict and food bingeing, even in those who are motivated to stop taking drugs or to lose weight.

The motivation/drive and action circuit (mediated in part through OFC, dorsal striatum and supplementary motor cortices) is involved both in executing the act...
7. CLINICAL SIGNIFICANCE

This model has therapeutic implications for it suggests a multi-prong approach that targets strategies to: decrease the rewarding properties of the problem reinforcer (drug or food); enhance the rewarding properties of alternative reinforcers (i.e. social interactions, physical activity); interfere with conditioned-learned associations (i.e. promoting new habits to substitute for old ones); and strengthen inhibitory control (i.e. biofeedback), in the treatment of drug abuse/addiction and obesity Volkow et al. (2003b).

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