

# Translational Neuroimaging in Drug Addiction and Obesity

Michael Michaelides, Panayotis K. Thanos, Nora D. Volkow, and Gene-Jack Wang

## Abstract

The use of translational noninvasive neuroimaging has revealed that drug addiction and obesity share striking similarities in functional impairment in discrete brain regions and neurotransmitter circuits. Imaging experiments in both humans and rodents (using complementary experimental designs) show similar abnormalities in brain glucose metabolism in the prefrontal cortex (involved in inhibitory control) and hippocampus (memory) as well as impairments in dopamine signaling in the striatum (involved in food and drug reward, goal orientation, motivation, and habit formation). In both species, many of these observations have been obtained through concurrent and parallel monitoring of both brain activity and behavioral manifestations during drug administration, food sensory (visual, olfactory) stimulation, and craving. This review aims to show that noninvasive brain imaging strategies such as small animal positron emission tomography offer significant potential and promise for modeling motivational disorders such as drug addiction and obesity in humans. Rodent addiction models will prove valuable for understanding brain responses to drug cues and will help guide treatment, especially in relapse situations triggered by exposure to conditioned drug cues.

**Key Words:** addiction; dopamine; functional magnetic resonance imaging (fMRI); leptin; neuroimaging; obesity; positron emission tomography (PET); rodent model

## Introduction

In our approach to the research conducted in our laboratories and reviewed in this article, we consider *ingestive behavior* a collection of acts that involve introducing something into one's body, whether by eating, drinking,

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injecting, smoking, or snorting. We believe it is possible that behaviors associated with seeking or consuming food and drugs of abuse are influenced by similar biochemical and physiological processes.

Disorders such as obesity and drug addiction result from repeated overconsumption of food and drugs and likely originate from disturbances in ingestive behavior (reviewed by Volkow and Wise 2005). The application of such a hypothesis can facilitate the comparison of insights and constructs from obesity and drug addiction research and may thus lead to new discoveries for each disorder. Indeed, there is scientific evidence of biological similarities between drug addiction and obesity (Volkow and Wise 2005). A significant component of such evidence has derived from translational noninvasive neuroimaging experiments in humans and rodents. These studies have shown that in the context of addiction and obesity humans and rodents share similar abnormalities in both brain metabolism in discrete brain areas and brain dopamine (DA<sup>1</sup>) circuitry. We discuss comparable findings in drug-addicted individuals and rodent models of drug addiction.

This review highlights the translational approach to obesity and drug addiction research by describing imaging modalities and presenting findings related to the application of noninvasive translational neuroimaging in the two types of research in both humans and rodents.

## Neurobiology of Ingestive Behavior and Energy Regulation

The involvement of homeostatic mechanisms in ingestive behavioral regulation is well documented. In feeding and energy regulation, such mechanisms include satiety and adiposity signals (Woods and D'Alessio 2008). Satiety signals include ghrelin, cholecystokinin, glucagon-like peptide 1, and gastrin-releasing peptide, among others. These signals are phasic in nature and respond rapidly to regulate the amount of food consumed once feeding has been initiated. They are synthesized and act directly on the brain, and they are also secreted in the periphery.

<sup>1</sup>Abbreviations that appear  $\geq 3x$  throughout this article: BOLD, blood oxygen level-dependent; CPP, conditioned place preference; D<sub>2</sub>R, D<sub>2</sub> receptor; DA, dopamine; [<sup>18</sup>F]FDG, 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose; fMRI, functional magnetic resonance imaging; PET, positron emission tomography

Adiposity signals include insulin and leptin, which enter the brain by active transport and act on specific sites in key brain regions. These signals are characterized by slow (tonic) release and are generally believed to signal insulin for medium- to short-term energy stores (i.e., carbohydrates, glucose) and leptin for long-term energy stores (i.e., fat) for initiating food-seeking behaviors. Release of such phasic and tonic signals is influenced by reward and learning processes that are crucial for survival, such as environmental conditioned stimuli (cues) that have been previously associated with food reinforcement (Narayanan et al. 2010).

In drug use, homeostatic mechanisms similarly regulate consumption and initiate drug-seeking behaviors. These mechanisms may be exemplified by features of abuse and addiction such as withdrawal (i.e., drug use is required to correct brain imbalances and return the brain to “normal”) and sensitivity to conditioned drug cues, which are major factors involved in maintenance and relapse behaviors in both active drug users and patients completing rehabilitation programs (Heber and Carpenter 2011; Volkow and Wise 2005; Volkow et al. 2011). As the focus here is on imaging techniques, we refer the reader to more comprehensive reviews (Volkow et al. 2011; Woods and D’Alessio 2008) as well as an article in this issue on the neurobiology of ingestive behavior (Barson et al. 2012).

## Similarities Between Obesity and Drug Addiction

Obesity and drug addiction are major societal diseases. Aside from their direct effects on physical health, these disorders may be associated with significant and devastating mental health problems for those afflicted. They can also lead to dysfunctional relations for the affected individual both within the family and with coworkers and other members of society. In addition, sky-rocketing medical costs associated with treatment for drug addiction and obesity (especially for obesity-related complications such as type 2 diabetes and heart disease) affect all members of society. The escalating prevalence of obesity and type 2 diabetes observed in children in recent years is particularly alarming (1 in 3 children born after 2000 is expected to develop type 2 diabetes) (Narayan et al. 2003) and necessitates the use of novel methods to understand and potentially treat this disease. Annual costs related to obesity have been estimated at \$147 billion (Finkelstein et al. 2009) and for drug addiction \$181 billion (Harwood 2004).

Obesity and drug addiction likely result from disturbances in ingestive behavior (Volkow and Wise 2005). Recent studies have documented the involvement of satiety and adiposity signals in drug addiction; for example, psychostimulants (i.e., cocaine and amphetamine) affect circulating levels of ghrelin and leptin (Kobeissy et al. 2008). Accordingly, food restriction indirectly (via its changes in circulating peptide and hormone concentrations) enhances drug seeking (Carr 2007), and ghrelin antagonists attenuate

cocaine- and amphetamine-induced locomotor activity and conditioned place preference (CPP<sup>1</sup>) in rats. These behaviors are paralleled by decreases in DA release in the nucleus accumbens (ventral striatum), a brain region heavily implicated in food and drug reward (Jerlhag et al. 2010).

Aside from homeostatic mechanisms, ingestive behavior for both food and drugs of abuse is affected by nonhomeostatic mechanisms that are influenced by taste, pleasure, habits, social interactions, convenience, availability, and stress (Volkow and Wise 2005).

## Functional Brain Imaging Techniques in Drug Addiction and Obesity Research

### Functional Magnetic Resonance Imaging

#### *Background*

Functional magnetic resonance imaging (fMRI<sup>1</sup>) offers anatomical and temporal specificity and enables measurement of changes in blood flow in discrete brain areas in response to stimulus presentation. Blood flow responses (ratio of oxygenated to deoxygenated hemoglobin) distort the MRI scanner’s magnetic field, a change that manifests in the contrast at the individual voxel level and is termed the blood oxygen level–dependent (BOLD<sup>1</sup>) signal (Rajagopalan et al. 1995). This contrast is co-registered to a structural brain template, which helps delineate the location of the BOLD signal response. The change in signal is then correlated with the stimulus or event presentation to determine any potential functional involvement of a specific brain region.

#### *Strengths and Weaknesses*

The use of fMRI is widespread in clinical research because it is entirely noninvasive, the effects of magnetic field exposure do not carry any identified health risks, and it offers excellent anatomical and temporal resolution of brain function in response to disease, complex behavioral tasks, stimuli, or situations. fMRI is based on the principles of neurovascular coupling, and BOLD signal measurements correlate well with neuronal local field potentials in certain brain regions (Ojemann et al. 2010), suggesting that the BOLD signal represents an indirect assessment of neuronal function.

The translational value of fMRI and details regarding its application in rodents have been described elsewhere (Benveniste and Blackband 2006). Imaging awake animals with fMRI has also been reported (Lahti et al. 1998), but this technique requires the use of specialized restraining devices for the animal and may thus require time-consuming stress minimization or training procedures to avoid introducing fear or stress-related experimental confounds to the BOLD signal measures (King et al. 2005).

To our knowledge, fMRI experiments in an animal model of obesity have not been carried out. However, fMRI

experiments focusing on drug addiction (particularly brain activation and concurrent drug administration) have been performed in anesthetized rodents, as described below in the section on Translational Neuroimaging in Drug Addiction Research.

## Positron Emission Tomography

### Background

Positron emission tomography (PET<sup>1</sup>) is a noninvasive imaging modality that involves administration of positron-emitting radiotracers and subsequent visualization and quantification of the uptake of such tracers in biological tissue over time. PET imaging is a valuable tool for both human and animal medical research because it allows for the monitoring of changes in radiotracer uptake dynamically (in a single imaging session) and longitudinally (across multiple imaging sessions) in the same subject.

As the administered radiotracer decays, it produces positrons, which eventually collide with random electrons and annihilate each other. This annihilation causes the emission of gamma rays, which project at opposite directions (180°) from the point of annihilation. The PET scanner is equipped with gamma ray detectors that are positioned in a ring around the subject. After detecting the gamma ray emissions, the point of annihilation is computed, and sophisticated algorithms are implemented that result in a 2-dimensional image of radiotracer location in the targeted tissue. The radiotracers we focus on in this review are the glucose analogue 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose ([<sup>18</sup>F]FDG<sup>1</sup>) and the DA D<sub>2</sub>/D<sub>3</sub> receptor antagonist [<sup>11</sup>C]raclopride.

### Strengths and Weaknesses

PET imaging is of high translational value. With the recent development of small animal PET scanners that enable the imaging of rats and mice, brain-disease and brain-behavior associations demonstrated in human studies can be investigated using animal models, in which genetic and environmental factors can be manipulated to uncover cause-effect relationships for specific diseases and behaviors. The findings from such experiments can be translated to human research and contribute to treatment outcomes.

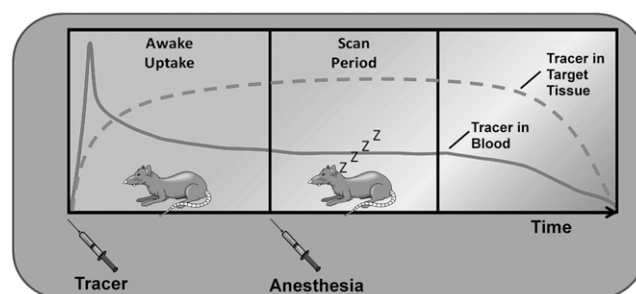
Another strength of PET imaging of laboratory animals is the fact that the same subject can be scanned repeatedly over time with minimal invasiveness (i.e., administration of anesthesia and radiotracer injection) and strong reproducibility (Alexoff et al. 2003). Compared with traditional *ex vivo* pharmacology experiments, these features make it possible to decrease costs and experimental variability, monitor disease progression, track changes in biological variables in response to treatment, assess drug and gene therapy efficacy, and establish cause-effect relations between brain function and behavior. Furthermore, recent developments in PET instrumentation technology have produced scanners that do

not require using anesthesia or immobilizing the subject (Purschke et al. 2005; Schulz et al. 2011). However, these scanners have yet to be thoroughly tested.

Advances in experimental design have partially circumvented the effects of anesthesia on radiotracer uptake. One improvement involves adapting a scanning protocol to include a radiotracer uptake period during which the animal subject is awake (Thanos et al. 2008b) (Figure 1). The major advantage of this approach is that, depending on pharmacokinetic properties of the tracer, it permits the assessment of brain activity, metabolism, and neurotransmitter function in response to stimulus (i.e., conditioned cues) and/or event presentation.

There are some important limitations to this imaging modality, however, the most significant of which is its low temporal resolution. Other limitations include the rate of radiotracer uptake or binding to receptors or enzymes, which must not be too fast (to avoid confounds from cerebral blood flow) or too slow (to avoid limiting its modeling). Another important limitation involves the nonspecific effects of radiotracer uptake (binding to targets other than the primary target; i.e., affinity for nonspecific targets), although these can be controlled by normalizing the measured radiotracer uptake in the desired region against the uptake in a brain area known to not express the desired target. This practice also allows for controlling for differences in metabolic effects of brain radiotracer uptake between subjects. Yet another important consideration is the pharmacological effect of radiotracer administration that can result from occupancy of the targeted receptor or transporter by portions of the radiotracer that are not radioactively labeled during its radiosynthesis.

Finally, depending on the tracer and study objectives, it is important when using PET to monitor certain variables (e.g., blood pressure, heart rate, body weight, and circulating



**Figure 1** Schematic representation of  $\mu$ PET imaging strategy for assessing brain metabolism (with 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose) or D<sub>2</sub>/D<sub>3</sub> receptor binding availability (with [<sup>11</sup>C]raclopride) in response to a specific cue, stimulus, or environment in awake animals. The tracer, injected and followed by an uptake period designed to expose the subject to specific cues, stimuli, or drug is sufficient to induce high and stable tracer kinetics in the tissue of interest with low levels in blood. Once the uptake period is met, animals can be anesthetized and scanned. Scanning is initiated when tracer concentrations have reached stable levels, and terminated before stability is lost but in time to ensure appropriate radioactivity counts.

glucose concentrations), especially when the experimental focus is obesity or metabolism. The implementation of voxel-based analytical approaches (e.g., statistical parametric mapping) requires the use of dedicated rodent brain atlases, which, unlike human atlases, are from a single subject, introducing a confounding element to this approach.

Overall, rodent functional neuroimaging has enabled investigators to make significant contributions to the study of obesity and drug addiction. We describe some of these contributions in the next section.

## Translational Neuroimaging in Drug Addiction Research

### Imaging Studies of the Brain in Response to Drugs and Drug Stimuli

#### *Drug Administration*

fMRI experiments in drug-addicted human subjects are limited in providing insight into mechanisms involved in drug addiction. Although such studies have highlighted brain activation responses to cocaine (Breiter et al. 1997), heroin (Sell et al. 1999, 2000), and nicotine (Stein et al. 1998), these effects have not been investigated in normal human subjects because of the obvious ethical considerations as well as challenges in subject recruitment, variability (most subjects are polydrug abusers), and controlled substance administration.

Small animal fMRI experiments, on the other hand, offer the advantage of assessing brain activation in response to drug administration in both naïve and drug-exposed subjects, thereby providing deeper insight into the mechanisms that may produce addiction in the first place. This assessment can be done by scanning rodents before and after drug administration, and correlating brain activation before and after drug exposure with an abuse profile (measured via behavioral testing). Such studies have been undertaken, but due to the requirement of motionless scanning using fMRI and the need to scan the subject during the period of drug administration, the experiments have been limited to the pharmacological effects of drugs on the brain in the anesthetized state. The studies have nevertheless provided significant insight into how the brain responds to drugs in naïve or drug-exposed subjects.

One study reported increases in the BOLD signal in the prefrontal and cingulate cortex and decreases in the dorsal and ventral striatum, thalamus, and hypothalamus (Xi et al. 2004) in response to heroin. Interestingly, in that study rats that self-administered heroin showed less of a BOLD signal response than heroin-naïve rats, indicating decreased sensitivity to brain activation (i.e., tolerance) in response to the drug. In the same study, treatment with the  $\gamma$ -aminobutyric acid (GABA) inhibitor gamma-vinyl GABA failed to affect the BOLD signal response to heroin, suggesting that heroin pharmacological brain responses were independent of GABA metabolism. A prior study, however, showed that

blocking the mu opioid receptor was successful in altering the BOLD signal response to heroin in rats (Xu et al. 2000).

fMRI studies in rodents have also provided valuable insight into how the brain responds to other drugs. One study reported that cocaine increased brain activation in frontal cortical regions, the dorsal and ventral striatum, and the thalamus (Marota et al. 2000). A major advantage of the specific imaging technique used in that study was that the authors reported differential temporal brain responses among the activated brain regions. This feature of fMRI is unique in that it offers high temporal resolution. Finally, D<sub>1</sub> receptor (D<sub>1</sub>R<sup>1</sup>) antagonism was able to block the cocaine-induced brain responses.

Thus, incorporating a pharmacological challenge allows investigators to make generalizations to specific neurotransmitter systems and mechanisms. fMRI studies in rodents offer significant promise for modeling human drug use and its pharmacological treatment. Future studies assessing behavioral interventions coupled with imaging will shed additional light in this area.

As an alternative to fMRI, microPET ( $\mu$ PET) has been used to study the pharmacological effects of a drug on brain activity by measuring brain glucose metabolism (using FDG as radiotracer) while the animal is awake and unrestrained.

Recent  $\mu$ PET studies reported changes in *in vivo* brain activity in mice after acute psychostimulant administration (Michaelides et al. 2010; Thanos et al. 2008a). The animals stayed awake and unrestrained during the FDG uptake period and were anesthetized 5 minutes before the PET scan (Figure 1). One study showed that an intraperitoneal dose of 10 mg/kg of cocaine decreased glucose metabolism in discrete brain regions (olfactory bulb, motor cortex, striatum, hippocampus, thalamus, and cerebellum) in wild-type mice but not (except in the thalamus) in mice that lacked the dopamine transporter (Thanos et al. 2008a). These results suggest that the acute pharmacological effects of cocaine on the brain are mediated primarily by dopaminergic mechanisms but that thalamic noradrenergic and serotonergic mechanisms are also involved.

Another study using a similar imaging procedure reported that an acute intraperitoneal 10 mg/kg dose of methylphenidate increased brain metabolism in the cerebellum and decreased it in the left and right prefrontal cortices in wild-type mice, but had the opposite effects in mice lacking D<sub>4</sub> receptors. This result implies the potential regulation of methylphenidate pharmacological activity via the D<sub>4</sub>R in these brain regions (Michaelides et al. 2010).

These studies offer insight into the use of small animal functional neuroimaging techniques to assess acute and long-term pharmacological effects of addictive substance administration. The development of genetically engineered models that mimic genetic abnormalities similar to those observed in clinical experiments makes such approaches even more advantageous.

#### *Drug Cues*

fMRI studies of pharmacological effects on human brain activity have shed light on the brain mechanisms involved in

the perception of conditioned drug cues while providing testable hypotheses on potential treatments (Goldstein et al. 2007, 2009a,b; Tomasi et al. 2007; Volkow et al. 2006, 2010b). Exposing subjects to cues previously associated with drug abuse is not subject to the same regulatory constraints as pharmacological administration and therefore presents a feasible alternative to drug addiction studies in non-drug-abusing populations. We do not, however, discuss human fMRI findings here because no translational studies currently use these techniques.

In rodents, fMRI experiments that involve exposure to a cue require the subject to be awake, a state that has not yet been reported. As mentioned above, devices that allow for awake fMRI imaging do exist, but their application to drug addiction research has not been assessed.

## Brain Imaging Studies of Dopamine in Drug Addiction Research

### *Drug Administration*

Investigators who have used PET in human imaging experiments have documented that acute administration of stimulant drugs of abuse such as amphetamine, methylphenidate, nicotine, and alcohol leads to increases in DA in reward/motivation-associated brain regions (i.e., striatum) and that the magnitude of these changes is linked to the subjective experience of being “high” (Volkow et al. 2010a). PET imaging studies in humans have also shown that long-term drug exposure leads to decreases in DA release in the striatum as well as decreased sensitivity to reinforcing and dopaminergic effects (Volkow et al. 2010a) in response to drug administration in addicted individuals.

Rodent  $\mu$ PET studies on the DA system have documented changes in  $D_1$  and  $D_2$  receptor availability in response to chronic cocaine exposure (Tsukada et al. 1996) and cocaine withdrawal (Maggos et al. 1998). In particular, withdrawal from cocaine for 10 days increased  $D_1$ R binding availability to normal (precocaine) levels, but produced a further decline in  $D_2$ R binding availability (Maggos et al. 1998). Interestingly,  $D_2$ R binding levels returned to normal precocaine levels by the 21<sup>st</sup> day of withdrawal, indicating that  $D_1$  and  $D_2$  receptors exhibit different plasticity in response to withdrawal from cocaine.

Our group conducted a  $\mu$ PET study in rats showing that 2 months of oral methylphenidate administration decreased  $D_2$ R binding availability, whereas 8 months increased it (Thanos et al. 2007). Interestingly, the animals that showed the increased binding after 8 months also self-administered less cocaine (Thanos et al. 2007). Although a clear advantage of using  $\mu$ PET in this study was that we were able to scan the same animals after 2 and 8 months of methylphenidate treatment, we were not able to assess the effect of 2-month methylphenidate treatment on cocaine self-administration to confirm that the decreased  $D_2$ R was associated with increased cocaine self-administration.

Human PET imaging studies have shown that discrete cues associated with cocaine abuse (observed in a video of subjects smoking cocaine) elicited increases in striatal DA in cocaine addicts and that the magnitude of increase was positively correlated with reports of drug craving and addiction severity scores (Volkow et al. 2006, 2010a) (Figure 2). Similar findings have been observed in rat models of cocaine abuse in which  $\mu$ PET and the CPP paradigm were used jointly to assess the relation between changes in brain DA and behavioral preference for a conditioned contextual cue associated with cocaine administration (i.e., the cocaine-paired chamber) (Schiffer et al. 2009) (Figure 2). In this study, rats were exposed to a CPP procedure and, after being conditioned to associate the effects of cocaine with a contextual environment, injected with radiolabeled [<sup>11</sup>C]raclopride and exposed to both the vehicle and the cocaine-paired conditioning environment on two separate occasions. Like the human experiments, this study showed that exposure to drug cues leads to DA increases in the ventral striatum and that the magnitude of increase correlates with cocaine CPP (Schiffer et al. 2009).

## Translational Neuroimaging in Obesity Research

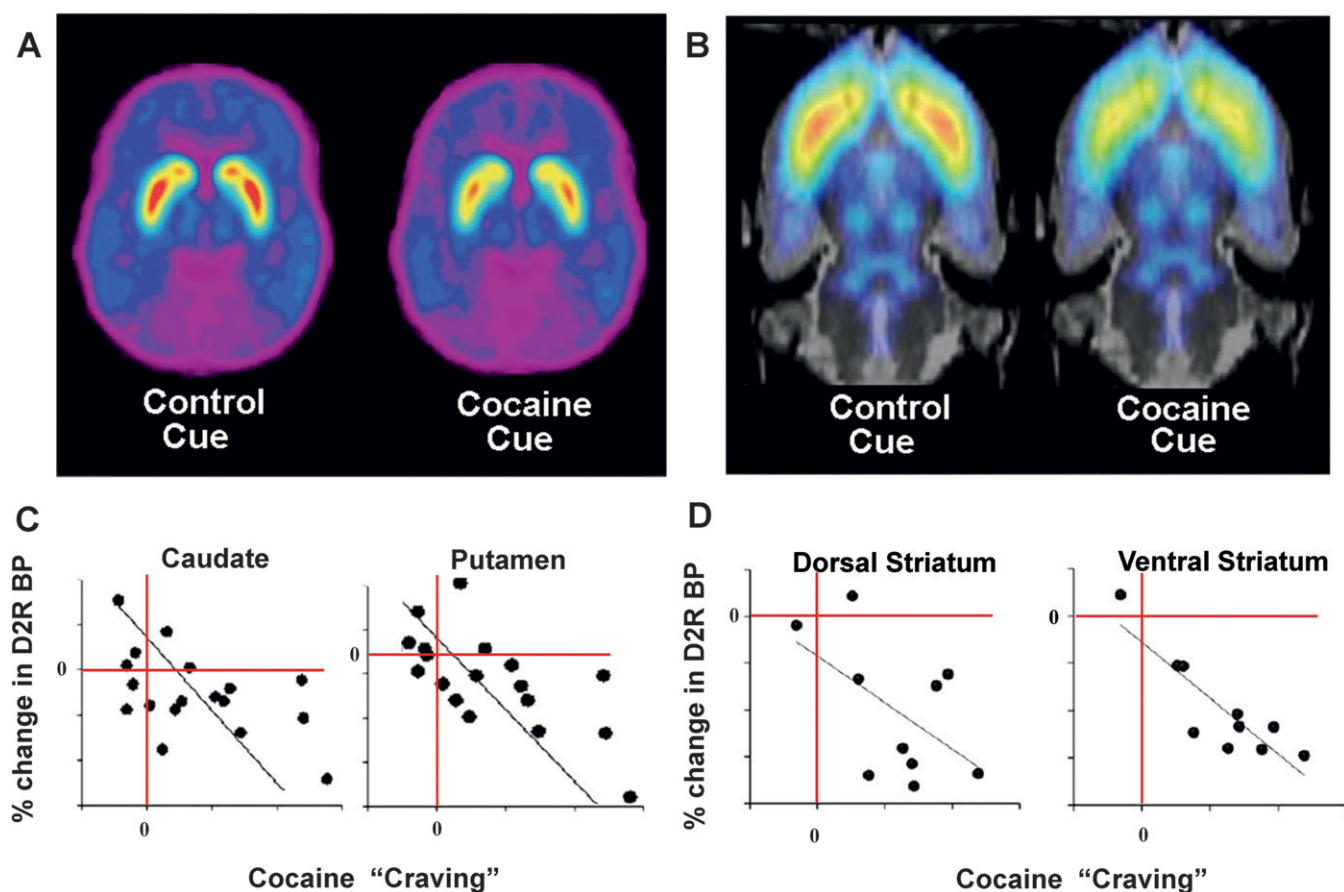
### Brain Activation in Response to Food and Food Cues

#### *Obesity and Sensory Processing*

The human brain is highly sensitive to food stimuli, probably because food is essential for survival. Brain imaging studies have shown that food presentation leads to large and significant increases in brain metabolism (Wang et al. 2004).

Using PET and [<sup>18</sup>F]FDG, we showed that, when presented with food, subjects exhibited significant increases in brain metabolism in the superior temporal, anterior insula, and orbitofrontal cortices. Increases in the latter, in particular, positively correlated with ratings of hunger and desire for consuming the food (Wang et al. 2004). Using a similar imaging approach, we showed that obese (relative to lean) individuals at baseline condition (i.e., without food presentation) exhibit greater brain metabolism in brain areas associated with sensory processing (Wang et al. 2002). We speculated that this enhanced level of brain metabolism may render obese individuals sensitive to hedonic and reward-related features of food via exteroceptive stimulation and thus contribute to overeating.

Obesity may also be associated with impaired sensory sensitivity to interoceptive (as well as exteroceptive) stimuli. Findings from our group support the notion that interoceptive signals relating to postingestive food effects may be involved in regulating food-related satiety and reward.



**Figure 2**  $D_2/D_3$  receptor ( $D_2R$ ) binding availability, assessed using the binding potential (BP) (ratio of  $B_{max}/K_d$ ;  $B_{max}$  = maximal receptor binding,  $K_d$  = receptor affinity) in (A) cocaine-addicted humans (from Volkow et al. 2006, 2010a, with permission) and (B) cocaine-exposed rats in response to cocaine cues (from Schiffer et al. 2009, with permission). In humans, the percent change in  $D_2R$  binding availability between a condition in which the subject is exposed to a cocaine cue or a neutral cue is negatively correlated with subjective craving in the caudate and putamen (C). In rats, the percent change in  $D_2R$  binding availability in the ventral and dorsal striatum is negatively correlated with preference for a contextual environment previously paired with cocaine exposure (for the purpose of this illustration this behavior has been oversimplified as “craving”) (D). See text for complete references.

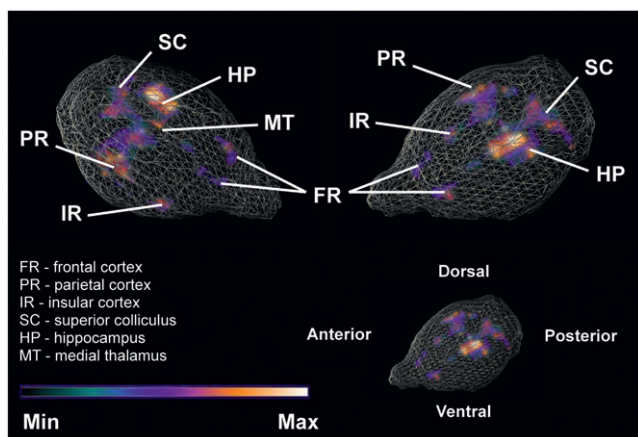
Using [ $^{18}F$ ]FDG and PET in obese humans, we evaluated the effects on brain metabolism of an implantable gastric stimulator (IGS), a device used for clinical obesity management that operates by electrically stimulating the enteric nervous system and disrupting gastric motility (this motility stimulates feelings of hunger) (Chen 2004). IGS is effective in decreasing food consumption, blood pressure, and body weight in obese humans (Cigaina 2004), and we therefore hypothesized that its therapeutic efficacy involves modulation of food satiety signals (i.e., similar to postprandial signals to the brain originating from the vagus nerve). The obese subjects had the device for 1 to 2 years and showed increased brain metabolism in brain regions associated with memory (hippocampus), reward and goal-directed behaviors (striatum), proprioception and motor function (cerebellum), and inhibitory control (orbitofrontal cortex). These increases in brain function in response to IGS paralleled decreases in “emotional eating” scores.

Interestingly, hippocampal activation has been reported in human brain imaging studies in response to food craving,

hunger, taste, and food stimulation (Haase et al. 2009). In addition, the brain regions activated by IGS are activated in response to drug craving in drug-addicted subjects, which suggests that similar brain circuits may be involved in mediating food craving in obese individuals and drug craving in drug-addicted individuals (Volkow et al. 2011).

### *Obesity and Gut Signaling*

Few rodent in vivo neuroimaging studies focus on food presentation and its effects on brain activity, and only one study has assessed brain activation in response to food stimulus presentation in awake rats. In that study, the effects of leptin receptor deficiency, genetic obesity, and food restriction were tested on brain functional activation before and after olfactory stimulation with a bacon scent in obese leptin receptor-deficient (*fa/fa*) and control rats using  $\mu$ PET and [ $^{18}F$ ]FDG (Thanos et al. 2008b) (Figure 3). The obese rats showed lower metabolism in brain regions related to



**Figure 3** Statistical parametric mapping (SPM) showing significant changes in regional brain glucose metabolism in response to awake uptake of 2- $^{18}\text{F}$ fluoro-2-deoxy-D-glucose and concurrent olfactory stimulation to a conditioned food cue in rats (from Thanos et al. 2008b, with permission; see text for complete reference).

memory (hippocampus) and greater metabolism in brain areas associated with reward and goal-directed behavior (medial thalamus) relative to the control rats with normal leptin signaling.

This study was the first and to our knowledge only study to demonstrate the efficacy of using  $\mu\text{PET}$  for the noninvasive and repeated study of food cue effects in the brain of awake rats. Previous fMRI studies in obese rats involved delivery of the food stimuli via glucose infusion or ingestion directly into the stomach and were done under anesthesia (Chen et al. 2007). It was therefore not possible to assess the cognitive effects associated with exposure to food-related cues.

The findings from the experiments described here suggest that obesity may be a state of impaired food-related reward and memory function, and that gut peptides such as leptin may be involved in reward and memory-related processes specific for the acquisition of palatable food. A role for leptin in such processes has been implicated in human neuroimaging experiments. In particular, studies using fMRI showed unique functional activation of brain areas associated with reward, emotion, and inhibitory control in response to food cue presentation in leptin-deficient obese humans (Baicy et al. 2007; Farooqi et al. 2007).

## Brain Imaging of Dopamine in Obese Subjects

### *Dopamine and Diet*

The involvement of brain dopamine in obesity has been documented using  $^{11}\text{C}$ raclopride in both human and animal studies. Findings from our group using this radioligand and PET have demonstrated decreased  $\text{D}_2\text{R}$  binding availability in the striatum in morbidly obese humans (Wang et al. 2001) and rats (Thanos et al. 2008c) (Figure 4). Because PET

allows for repeated measurements in the same subject over time, we were able to demonstrate that decreased  $\text{D}_2\text{R}$  binding availability could be prevented when obese rats had limited access to food (Thanos et al. 2008c). This effect was also coupled to positive changes in body weight, locomotor activity, and circulating insulin and leptin levels (Thanos et al. 2008c). Furthermore, the same study showed that an overnight fast increased DA signaling in the striatum (measured indirectly via  $\text{D}_2\text{R}$  binding availability at fasted and fed states).

More recently, in obese subjects, decreased  $\text{D}_2\text{R}$  binding availability in the striatum was positively correlated to glucose metabolism in the dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus, and somatosensory cortices (Volkow et al. 2008). These frontal areas are involved in regulating inhibitory control and saliency attribution, suggesting that functional interactions between frontal and mesolimbic circuitry may act to regulate overeating. The positive correlation between glucose metabolism in the somatosensory regions and striatal  $\text{D}_2\text{R}$  could also in part reflect DA regulation of the reinforcing or hedonic properties of food.

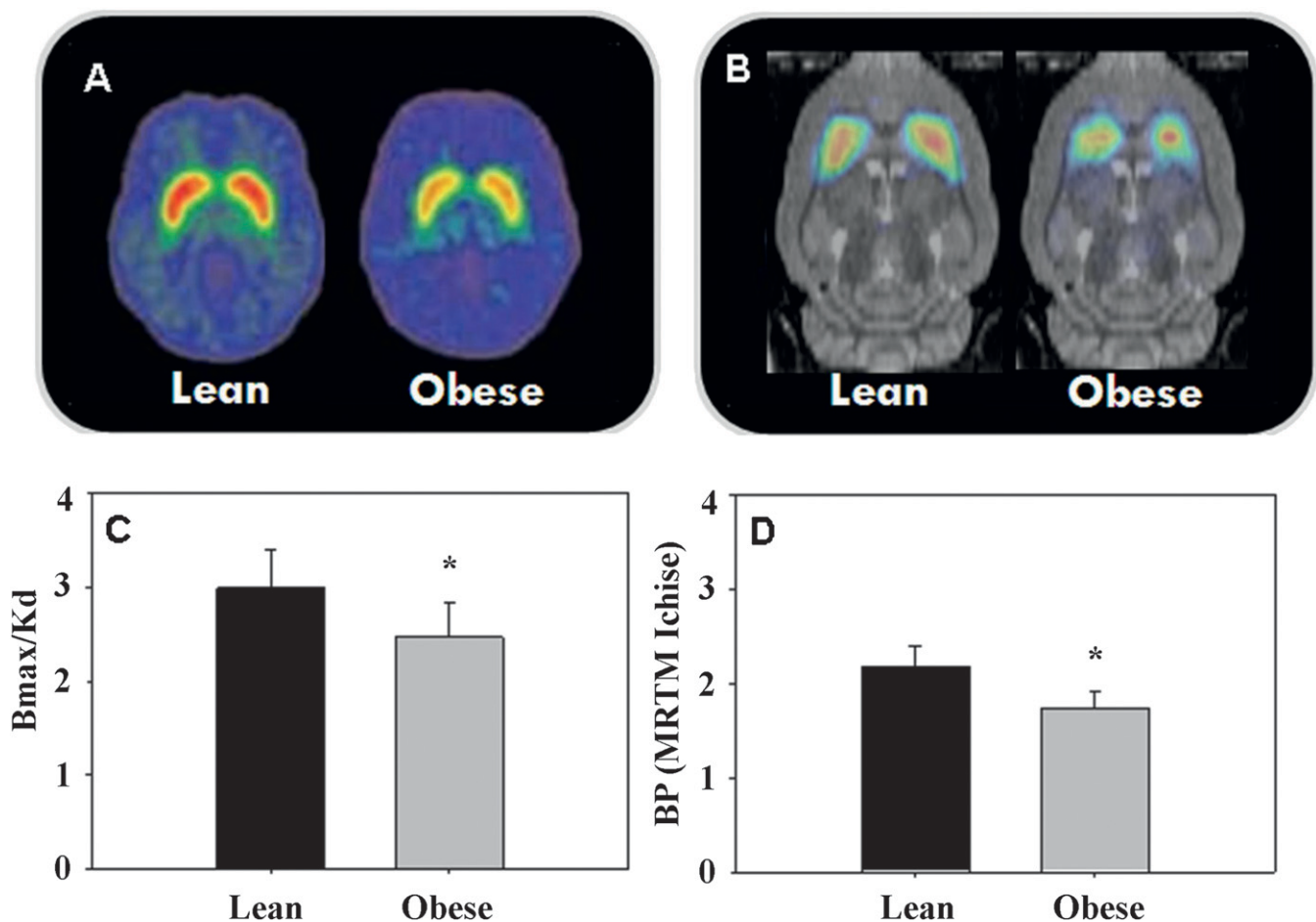
Another study from our group implicated psychosocial factors that may, in concert with imbalances in striatal DA metabolism, lead to impaired eating habits. This study showed that striatal DA responses in the dorsal striatum (measured as the change in  $\text{D}_2\text{R}$  binding availability between a baseline and stimulus condition) were positively correlated with restraint behavior (the ability to consciously inhibit craving) during food presentation (Volkow et al. 2003). In the same study, emotionality was negatively correlated with baseline  $\text{D}_2$  receptor binding availability, suggesting that individuals with low availability may be prone to emotional disturbances and that, in the context of food availability, DA changes and emotional imbalances may inhibit the individual's ability to refrain from consuming the food.

The ability to model such studies in animals using PET and combining behavioral monitoring with genetics may help elucidate some of the molecular determinants of such behaviors, which are currently not well understood.

### *Obesity and Bariatric Surgery*

Because postsurgery patients show immediate and sustained decreases in food intake, and because striatal  $\text{D}_2$  receptors are decreased in obese humans and rodents (Thanos et al. 2008c; Wang et al. 2001), recent studies have focused on assessing  $\text{D}_2\text{R}$  changes in response to bariatric surgery. Only two studies to date have documented such changes—and they reported opposite results.

Dunn and colleagues (2010) reported decreased  $\text{D}_2\text{R}$  binding availability 7 weeks after surgery, whereas Steele and colleagues (2010) reported increases in  $\text{D}_2\text{R}$  binding availability 6 weeks after surgery. Although both studies used similar surgical approaches and imaging procedures, they also reported results from a small cohort of patients



**Figure 4** Basal D<sub>2</sub>/D<sub>3</sub> receptor (D<sub>2</sub>R) binding availability in lean and obese humans (A) (Wang et al. 2001, with permission) and rats (B) (Thanos et al. 2008c, with permission). Striatal D<sub>2</sub>R binding availability is lower in obese compared with lean humans (ratio of B<sub>max</sub>/K<sub>d</sub>; B<sub>max</sub> = maximal receptor binding, K<sub>d</sub> = receptor affinity) (C) (Wang et al. 2001, with permission) and rats (assessed using the Ichise multi-linear reference tissue model; MRTM) (D) (Thanos et al. 2008c, with permission; see text for complete references).

(5 in each study), which could have contributed to low statistical power and the probability of false positives.

Further research on DA system alterations in response to bariatric surgery is needed to clarify whether the decreased feeding observed in these patients is due to DA imbalances. In addition to this approach, and because this clinical population is not prevalent, preclinical bariatric surgery models can be used to obtain insight into the effects of such surgery on brain DA.

## Conclusions

The use of functional imaging to map food-associated homeostatic and reward brain pathways in humans is arduous and time consuming because these pathways are densely clustered in higher cognitive areas (i.e., cortex). Furthermore, the reward or hedonic value associated with food is tied to memories, emotions, events, and specific individuals, making it difficult to assess the effects of food perception at the group level. Nevertheless, functional brain imaging studies have begun to shed light on the pathways associated with

food and drug presentation and on the encoding of food and drug cues in the human brain. At the same time, new imaging techniques enable measurement of the rodent brain's encoding of food and drug presentation.

Although these techniques are in their infancy, they hold significant promise for elucidating the networks and mechanisms involved in the brain's encoding of food and drug reward and the cues that signal food or drugs. With rodent models, it is possible to manipulate experimental settings and variables (behavior, genetics, and diet) in efforts to enhance understanding and eventually treatment of drug addiction and compulsive overeating and obesity.

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## References

- Alexoff DL, Vaska P, Marsteller D, Gerasimov T, Li J, Logan J, Fowler JS, Taintor NB, Thanos PK, Volkow ND. 2003. Reproducibility of 11C-raclopride binding in the rat brain measured with the micropet R4: Effects of scatter correction and tracer specific activity. *J Nucl Med* 44:815-822.
- Baicy K, London ED, Monterosso J, Wong ML, Delibasi T, Sharma A, Licinio J. 2007. Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. *Proc Natl Acad Sci U S A* 104:18276-18279.
- Barson J, Morganstern I, Leibowitz SF. 2012. Neurobiology of consummatory behavior: Mechanisms underlying overeating and drug use. *ILAR J* 53:35-58.
- Benveniste H, Blackband SJ. 2006. Translational neuroscience and magnetic-resonance microscopy. *Lancet Neurol* 5:536-544.
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE. 1997. Acute effects of cocaine on human brain activity and emotion. *Neuron* 19:591-611.
- Carr KD. 2007. Chronic food restriction: Enhancing effects on drug reward and striatal cell signaling. *Physiol Behav* 91:459-472.
- Chen J. 2004. Mechanisms of action of the implantable gastric stimulator for obesity. *Obes Surg* 14(Suppl 1):S28-S32.
- Chen M, Zhang TM, Luo SL, Zhou C, Wu XM, Zhou NN, Cai K, Yang ZH, Wang WC, Zhao WF, Li SY, Wang Z, Zhang YT, Li GZ. 2007. Functional magnetic resonance imaging and immunohistochemical study of hypothalamic function following oral glucose ingestion in rats. *Chin Med J (Engl)* 120:1232-1235.
- Cigaina V. 2004. Long-term follow-up of gastric stimulation for obesity: The Mestre 8-year experience. *Obes Surg* 14(Suppl 1):S14-S22.
- Dunn JP, Cowan RL, Volkow ND, Feurer ID, Li R, Williams DB, Kessler RM, Abumrad NN. 2010. Decreased dopamine type 2 receptor availability after bariatric surgery: Preliminary findings. *Brain Res* 1350:123-130.
- Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. 2007. Leptin regulates striatal regions and human eating behavior. *Science* 317:1355.
- Finkelstein EA, Trogon JG, Cohen JW, Dietz W. 2009. Annual medical spending attributable to obesity: Payer- and service-specific estimates. *Health Aff (Millwood)* 28:W822-W831.
- Goldstein RZ, Tomasi D, Rajaram S, Cottone LA, Zhang L, Maloney T, Telang F, Alia-Klein N, Volkow ND. 2007. Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience* 144:1153-1159.
- Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. 2009a. Anterior cingulate cortex hypo-activations to an emotionally salient task in cocaine addiction. *Proc Natl Acad Sci U S A* 106:9453-9458.
- Goldstein RZ, Tomasi D, Alia-Klein N, Honorio Carrillo J, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. 2009b. Dopaminergic response to drug words in cocaine addiction. *J Neurosci* 29:6001-6006.
- Haase L, Cerf-Ducastel B, Murphy C. 2009. Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage* 44:1008-1021.
- Harwood H. 2004. *The Economic Costs of Drug Abuse in the United States: 1992-2002*. Bethesda: Office of National Drug Control Policy (ONDCP).
- Heber D, Carpenter CL. 2011. Addictive genes and the relationship to obesity and inflammation. *Mol Neurobiol* 44:160-165.
- Jerlhag E, Egencioglu E, Dickson SL, Engel JA. 2010. Ghrelin receptor antagonism attenuates cocaine- and amphetamine-induced locomotor stimulation, accumbal dopamine release, and conditioned place preference. *Psychopharmacology (Berl)* 211:415-422.
- King JA, Garelick TS, Brevard ME, Chen W, Messenger TL, Duong TQ, Ferris CF. 2005. Procedure for minimizing stress for fMRI studies in conscious rats. *J Neurosci Methods* 148:154-160.
- Kobeissy FH, Jeung JA, Warren MW, Geier JE, Gold MS. 2008. Changes in leptin, ghrelin, growth hormone and neuropeptide-Y after an acute model of MDMA and methamphetamine exposure in rats. *Addict Biol* 13:15-25.
- Lahti KM, Ferris CF, Li F, Sotak CH, King JA. 1998. Imaging brain activity in conscious animals using functional MRI. *J Neurosci Methods* 82:75-83.
- Maggos CE, Tsukada H, Kakiuchi T, Nishiyama S, Myers JE, Kreuter J, Schlussman SD, Unterwald Em, Ho A, Kreek MJ. 1998. Sustained withdrawal allows normalization of in vivo [<sup>11</sup>C]N-methylspiperone dopamine D2 receptor binding after chronic binge cocaine: A positron emission tomography study in rats. *Neuropsychopharmacology* 19:146-153.
- Marota JJ, Mandeville JB, Weisskoff RM, Moskowitz MA, Rosen BR, Kosofsky BE. 2000. Cocaine activation discriminates dopaminergic projections by temporal response: An fMRI study in rat. *Neuroimage* 11:13-23.
- Michaelides M, Pascau J, Gispert JD, Delis F, Grandy DK, Wang GJ, Desco M, Rubinstein M, Volkow ND, Thanos PK. 2010. Dopamine D4 receptors modulate brain metabolic activity in the prefrontal cortex and cerebellum at rest and in response to methylphenidate. *Eur J Neurosci* 32:668-676.
- Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. 2003. Lifetime risk for diabetes mellitus in the United States. *JAMA* 290:1884-1890.
- Narayanan NS, Guarnieri DJ, Dileone RJ. 2010. Metabolic hormones, dopamine circuits, and feeding. *Front Neuroendocrinol* 31:104-112.
- Ojemann GA, Corina DP, Corrigan N, Schoenfield-McNeill J, Poliakov A, Zamora L, Zanos S. 2010. Neuronal correlates of functional magnetic resonance imaging in human temporal cortex. *Brain* 133:46-59.
- Purschke M, Kandasamy A, Kriplani A, Lecomte R, O'Connor P, Pratte J, Radeka V, Schlyer D, Southekal S, Stoll S, Vaska P, Villanueva A, Woody C, Junnaker S, Krishnamoorthy S, Shokouhi S, Fontaine R, Dzhordzhadze V. 2005. The ratcap conscious small animal pet tomograph. In 14th IEEE-NPSS Real Time Conference, p 63.
- Rajagopalan P, Krishnan KR, Passe TJ, Macfall JR. 1995. Magnetic resonance imaging using deoxyhemoglobin contrast versus positron emission tomography in the assessment of brain function. *Prog Neuropsychopharmacol Biol Psychiatry* 19:351-366.
- Rusch MD, Andris D. 2007. Maladaptive eating patterns after weight-loss surgery. *Nutr Clin Pract* 22:41-49.
- Schiffer WK, Liebling CN, Reiszal C, Hooker JM, Brodie JD, Dewey SL. 2009. Cue-induced dopamine release predicts cocaine preference: Positron emission tomography studies in freely moving rodents. *J Neurosci* 29:6176-6185.
- Schulz D, Southekal S, Junnaker SS, Pratte JF, Purschke ML, Stoll SP, Ravindranath B, Maramraju SH, Krishnamoorthy S, Henn FA, O'Connor P, Woody CL, Schlyer DJ, Vaska P. 2011. Simultaneous assessment of rodent behavior and neurochemistry using a miniature positron emission tomograph. *Nat Methods* 8:347-352.
- Sell LA, Morris J, Bearn J, Frackowiak RS, Friston KJ, Dolan RJ. 1999. Activation of reward circuitry in human opiate addicts. *Eur J Neurosci* 11:1042-1048.
- Sell LA, Morris JS, Bearn J, Frackowiak RS, Friston KJ, Dolan RJ. 2000. Neural responses associated with cue evoked emotional states and heroin in opiate addicts. *Drug Alcohol Depend* 60:207-216.
- Steele KE, Prokopowicz GP, Schweitzer MA, Magunson TH, Lidor AO, Kuwabara H, Kumar A, Brasic J, Wong DF. 2010. Alterations of central dopamine receptors before and after gastric bypass surgery. *Obes Surg* 20:369-374.
- Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS. 1998. Nicotine-induced limbic cortical activation in the human brain: A functional MRI study. *Am J Psychiatry* 155:1009-1015.
- Thanos PK, Michaelides M, Benveniste H, Wang GJ, Volkow ND. 2007. Effects of chronic oral methylphenidate on cocaine self-administration and striatal dopamine D2 receptors in rodents. *Pharmacol Biochem Behav* 87:426-433.
- Thanos PK, Michaelides M, Benveniste H, Wang GJ, Volkow ND. 2008a. The effects of cocaine on regional brain glucose metabolism is attenuated in dopamine transporter knockout mice. *Synapse* 62:319-324.
- Thanos PK, Michaelides M, Gispert JD, Pascau J, Soto-Montenegro ML, Desco M, Wang R, Wang GJ, Volkow ND. 2008b. Differences in

- response to food stimuli in a rat model of obesity: In-vivo assessment of brain glucose metabolism. *Int J Obes (Lond)* 32:1171-1179.
- Thanos PK, Michaelides M, Piyis YK, Wang GJ, Volkow ND. 2008c. Food restriction markedly increases dopamine D2 receptor (D2R) in a rat model of obesity as assessed with in-vivo muPET imaging ([11C] raclopride) and in-vitro ([3H] spiperone) autoradiography. *Synapse* 62:50-61.
- Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, Volkow ND. 2007. Thalamo-cortical dysfunction in cocaine abusers: Implications in attention and perception. *Psychiatry Res* 155:189-201.
- Tsukada H, Kreuter J, Maggos CE, Unterwald EM, Kakiuchi T, Nishiyama S, Futatsubashi M, Kreek MJ. 1996. Effects of binge pattern cocaine administration on dopamine D1 and D2 receptors in the rat brain: An in vivo study using positron emission tomography. *J Neurosci* 16:7670-7677.
- Volkow ND, Wise RA. 2005. How can drug addiction help us understand obesity? *Nat Neurosci* 8:555-560.
- Volkow ND, Wang GJ, Maynard L, Jayne M, Fowler JS, Zhu W, Logan J, Gatley SJ, Ding YS, Wong C, Pappas N. 2003. Brain dopamine is associated with eating behaviors in humans. *Int J Eat Disord* 33:136-142.
- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. 2006. Cocaine cues and dopamine in dorsal striatum: Mechanism of craving in cocaine addiction. *J Neurosci* 26:6583-6588.
- Volkow ND, Wang GJ, Telang F, Fowler JS, Thanos PK, Logan J, Alexoff D, Ding YS, Wong C, Ma Y, Pradhan K. 2008. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. *Neuroimage* 42:1537-1543.
- Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. 2010a. Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays* 32:748-755.
- Volkow ND, Wang GJ, Tomasi D, Telang F, Fowler JS, Pradhan K, Jayne M, Logan J, Goldstein RZ, Alia-Klein N, Wong C. 2010b. Methylphenidate attenuates limbic brain inhibition after cocaine-cues exposure in cocaine abusers. *PLoS One* 5:E11509.
- Volkow ND, Wang GJ, Baler RD. 2011. Reward, dopamine and the control of food intake: Implications for obesity. *Trends Cogn Sci* 15:37-46.
- Wadden TA, Sarwer DB, Fabricatore AN, Jones L, Stack R, Williams NS. 2007. Psychosocial and behavioral status of patients undergoing bariatric surgery: What to expect before and after surgery. *Med Clin North Am* 91:451-469, xi-xii.
- Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. 2001. Brain dopamine and obesity. *Lancet* 357:354-357.
- Wang GJ, Volkow ND, Felder C, Fowler JS, Levy AV, Pappas NR, Wong CT, Zhu W, Netusil N. 2002. Enhanced resting activity of the oral somatosensory cortex in obese subjects. *Neuroreport* 13:1151-1155.
- Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, Fowler JS. 2004. Exposure to appetitive food stimuli markedly activates the human brain. *Neuroimage* 21:1790-1797.
- Woods SC, D'Alessio DA. 2008. Central control of body weight and appetite. *J Clin Endocrinol Metab* 93:S37-S50.
- Xi ZX, Wu G, Stein EA, Li SJ. 2004. Opiate tolerance by heroin self-administration: An FMRI study in rat. *Magn Reson Med* 52:108-114.
- Xu H, Li SJ, Bodurka J, Zhao X, Xi ZX, Stein EA. 2000. Heroin-induced neuronal activation in rat brain assessed by functional MRI. *Neuroreport* 11:1085-1092.