Laboratory of Neuroimaging

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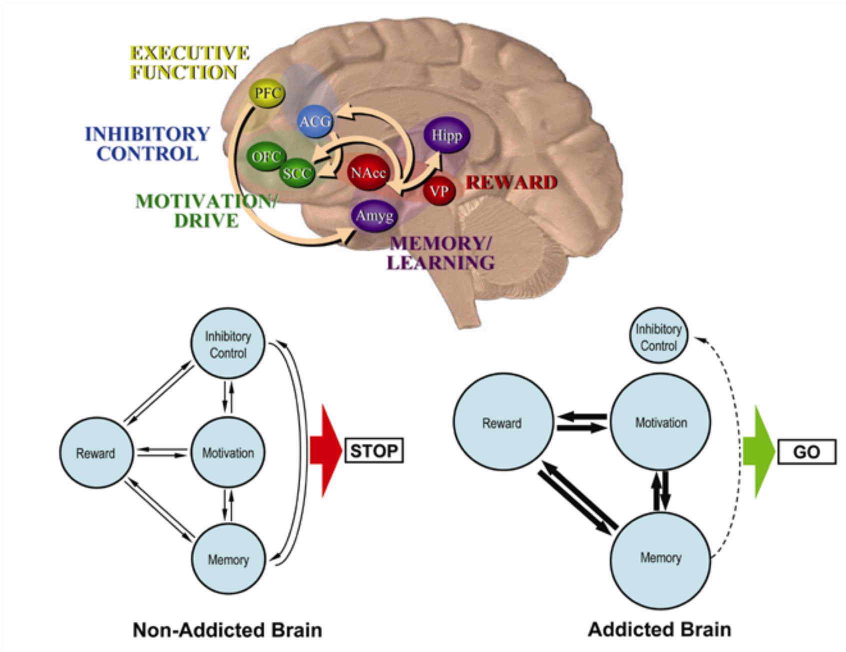
This laboratory utilizes brain imaging to investigate the neurobiology of addictive behaviors, compulsive overeating and obesity, attention deficit hyperactivity disorder (ADHD) and the effects that conditions such as sleep deprivation can have on brain function. Also being conducted are translational studies investigating the physiological and neurochemical mechanisms underlying reinforcing effects of drugs of abuse in comparison to those of non-drug reinforcers (food and money). The specific aims are:

1) To characterize the molecular changes underlying addiction and related disorders and their relationship to brain function, treatment and vulnerability.
2) To identify the neurobiological underpinnings of ADHD and the impact of its treatment on substance abuse comorbidity.
3) To explore common neural mechanisms underlying drug addiction and obesity and their implications for treatment development.



Model of brain circuits involved with addiction: reward/motivation, conditioning/memory, and executive function/inhibitory control.

Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction

The ability of drugs of abuse to increase dopamine in the nucleus accumbens underlies their reinforcing effects. However, preclinical studies have shown that with repeated drug exposure neutral stimuli paired with the drug (conditioned stimuli) start to increase dopamine by themselves, an effect that could underlie drug-seeking behavior. We tested whether dopamine increases occur to conditioned stimuli in human subjects addicted to cocaine and whether this is associated with drug craving. We tested eighteen cocaine-addicted subjects using positron emission tomography and [^{11}C]raclopride (dopamine D2 receptor radioligand sensitive to competition by endogenous dopamine). We measured changes in dopamine by comparing the specific binding of [^{11}C]raclopride when subjects watched a neutral video (nature scenes) versus when they watched a cocaine-cue video (scenes of subjects smoking cocaine).
[^{11}C]Raclopride's specific binding in dorsal (caudate and putamen) but not in ventral striatum (where nucleus accumbens is located) was significantly reduced in the cocaine-cue condition and the magnitude of this reduction correlated with self-reports of craving. Moreover, subjects with the highest scores on measures of withdrawal symptoms and of addiction severity that have been shown to predict treatment outcomes, had the largest dopamine changes in dorsal striatum. This provides evidence that dopamine in the dorsal striatum (region implicated in habit learning and in action initiation), is involved with craving and is a fundamental component of addiction. Inasmuch as craving is a key contributor to relapse, strategies aimed at inhibiting dopamine increases from conditioned responses are likely to be therapeutically beneficial in cocaine addiction.

Dopamine transporter levels in treatment and drug naïve adults with and without ADHD

Attention deficit hyperactivity disorder (ADHD) is the most frequent psychiatric disorder in children, yet data are sparse on its pathophysiology. Great interest has been generated by imaging studies showing increases in dopamine transporter (DAT) levels in subjects with ADHD. However, not all studies confirmed this and the role of DAT on the neurobiology of ADHD remains unclear. The purpose of this study was to investigate the levels of DAT in the brain of ADHD subjects with control of potentially confounding factors (previous medication and/or drug histories, co-morbidity) and to investigate the significance of the variability in transporters levels on clinical measures of inattention and hyperactivity.

Positron emission tomography and [^{11}C]cocaine were used to measure DAT in 20 never medicated adults with ADHD and 25 controls. Images were analyzed using regions of interest and statistical parametric mapping (SPM). Symptoms of inattention and hyperactivity were quantified using the Conners Adult Attention Rating Scale (CAARS). DAT levels were lower in left caudate (13%, $p < 0.05$) and in left nucleus accumbens ($p < 0.005$) in ADHD subjects than in controls. However, DAT levels in putamen, which did not differ between groups, were positively associated with inattention (CAARS A and E) both in ADHD and control subjects. Thus, for a given transporter level, the scores for inattention were on average five times greater in ADHD subjects than in controls. These results do not support increases in DAT in ADHD but instead document decreases in left caudate and nucleus accumbens/ventral cingulate. The data also provide evidence that DAT levels modulate attention, but suggest that additional pathology (e.g prefrontal or cingulostriatal pathways, noradrenergic neurotransmission) is necessary to account for the large differences in inattention observed between controls and ADHD subjects.

Depressed dopamine activity in caudate and limbic regions in adults with ADHD

Attention deficit hyperactivity disorder (ADHD) is the most frequent psychiatric disorder of childhood. There is considerable evidence that brain dopamine is involved in ADHD but it is unclear whether dopamine activity is enhanced or depressed. The purpose of this study was to test the hypotheses that striatal dopamine activity is depressed in ADHD and that this contributes to symptoms of inattention. Subjects were 19 with ADHD that had never been medicated and 24 healthy controls. They were scanned with positron emission tomography and [^{11}C]raclopride (D2/D3 receptor radioligand sensitive to competition with endogenous dopamine) after placebo and after intravenous methylphenidate, a stimulant that increases extracellular dopamine by blocking dopamine transporters. The difference in [^{11}C]raclopride binding (estimated as Bmax/Kd) between placebo and methylphenidate was used as marker of dopamine release. Symptoms were quantified using the Conners Adult Attention Rating Scale.

On Placebo, dopamine D2/D3 receptor availability in left caudate was lower ($p < 0.05$) in ADHD subjects than controls. Methylphenidate induced smaller decrements in [^{11}C]raclopride binding in caudate (blunted DA increases)($p < 0.05$) and higher scores on self-reports of “drug liking” in ADHD than in control subjects. The blunted response to methylphenidate in caudate was associated with symptoms of inattention ($p < 0.005$) and with higher self-reports of “drug liking” ($p < 0.01$). Exploratory analysis using statistical parametric mapping (SPM) revealed that methylphenidate also decreased [^{11}C]raclopride binding in hippocampus and amygdala and that these decrements were smaller in ADHD subjects ($p < 0.001$).

This study provides evidence that dopamine activity is depressed in caudate and limbic regions in adults with ADHD and that in caudate it is associated with inattention. The enhanced reinforcing effects of intravenous methylphenidate in ADHD subjects, which were associated with depressed dopamine responses, suggest that dopamine dysfunction may contribute to substance abuse comorbidity in ADHD.

Mechanisms of action of methylphenidate as cognitive enhancer in healthy controls

The use of stimulants (methylphenidate and amphetamine) as cognitive enhancers by the general public is increasing and is controversial. It is still unclear how they work or why they improve performance in some individuals but impair it in others. In this study we tested the hypothesis that stimulants enhance signal to noise ratio of neuronal activity and thereby increase neuronal efficiency. We measured the effects of methylphenidate (MP) on brain glucose metabolism using PET and FDG in 23 healthy adults. We predicted that by decreasing noise MP would reduce the glucose needed to perform the task. Brain metabolism was measured four times: when subjects performed a mathematical task after administration of placebo and after administration of MP (20 mg p.o.), and when subjects were exposed to a control condition (viewing nature cards with no task) after being given a placebo and after being given MP. The cognitive task significantly increased whole brain metabolism when compared with the control condition both when given with placebo and with MP. Whole brain metabolism differed significantly for the conditions ($P<0.0005$) and was lower for the control (36.6±6 μmol/100g/min) and the neutral non-task condition preceded by MP (35.8±5 μmol/100g/min) than for the cognitive task with placebo (43.2±7 μmol/100g/min) or the cognitive task preceded by MP (40.3±7 μmol/100g/min). The increase in whole brain metabolism was significantly smaller when the cognitive task was preceded by MP, than when preceded by placebo (11±22% versus 21±26 %; $p < 0.01$). In contrast, when MP was given with the neutral non-task condition whole brain metabolism did not differ from the control condition (< -2% change). The smaller task-related increase in brain glucose consumption following MP was related to focusing of brain activity. This was revealed by the statistical parametric (SPM) analysis, which indictaed that the area of significant activation ($P<0.001$) with the cognitive task was larger with placebo (67,985 pixels) than with MP (22,632 pixels). Inasmuch as the brain required about 50% less increase in glucose for the same level of performance, this provides evidence that MP may increase the brain's efficiency to a single task in healthy controls. While beneficial when neuronal resources are diverted by distracting stimuli this could be detrimental when brain resources are already optimally focused.

Involvement of dopamine and prefrontal regions in obesity

The role of dopamine (DA) in inhibitory control is being increasingly recognized and its disruption may contribute to behavioral disorders of dyscontrol such as obesity. However, the mechanism by which impaired dopamine neurotransmission interferes with inhibitory control is poorly understood. We had previously documented a reduction in dopamine D2 receptors (D2R) in morbidly obese subjects. To assess if the reductions in D2R were associated with activity in brain regions implicated in inhibitory control (cingulate gyrus, dorsolateral prefrontal and orbitofrontal cortex), PET was used with [^{11}C]raclopride to assess D2R, with [^{11}C] d-threo methylphenidate to assess dopamine transporters (DAT) and with [^{18}F]FDG to assess regional brain glucose metabolism in ten morbidly obese subjects (BMI > 40 kg/m2). Correlation analyses were done to assess the relationship between brain glucose metabolism and D2R and DAT availability. D2R availability was associated with metabolism in dorsolateral prefrontal ($P<0.003$), medial orbitofrontal ($P<0.01$) and anterior cingulate gyrus ($P<0.01$). In addition, D2R were associated with metabolism in somatosensory cortices ($P<0.01$). The correlations with DAT and regional metabolism were not significant, which suggests that the association of synaptic dopamine markers with prefrontal metabolism was specific to D2R receptors. This study shows a significant association between D2R in striatum and the activity in dorsolateral prefrontal cortex, medial orbitofrontal and cingulate gyrus, brain regions implicated in inhibitory control and in compulsive behaviors, which suggests that this may be one of the mechanisms by which low D2R in obesity could lead to poor behavioral control and overeating. In addition we have also documented a significant association between D2R availability and metabolism in somatosensory cortex, which process palatability and that may modulate the incentive salience of food.

Effects of sleep deprivation on brain dopamine activity and cognitive function

Sleep deprivation (SD) is associated with disruption in cognitive performance and changes in mood and energy. The mechanisms through which sleep deprivation deteriorates human performance are poorly understood but medications that increase dopamine (DA) reverse some of the changes. Here we assess the effects of SD on brain DA neurotransmission in healthy controls and its relationship to brain function during a cognitive task. We measured changes in DA using PET and [^{11}C]raclopride during rested wakefulness (RW) and after 24 hours of SD in 15 healthy controls. We also measured DA transporters (DAT) using PET and [^{11}C]cocaine as a DAT radioligand. We measured DAT since they are the main synaptic mechanism that regulates extracellular concentration of DA and are also the pharmacological targets of stimulant medications used to promote wakefulness. To quantify D2/D3 receptor availability as well as DAT availability we quantified Bmax/Kd (distribution volume ratio in striatum to that in cerebellum V 1). We also measured cognitive performance using visual attention and working memory tasks and assessed self-reports of sleepiness and tiredness. SD did not change the specific binding of [^{11}C]cocaine in striatum (Bmax/Kd measures in caudate, putamen and thalamus), which indicated that it did not change DAT availability. In contrast, SD significantly decreased the specific binding of [^{11}C]raclopride (Bmax/Kd measures in caudate, putamen and thalamus) when compared with RW. The differences in ventral striatum were not significant. The correlation between changes in D2 receptor availability (measure of DA changes) with SD and the behavioral reports were significant for a positive correlation with fatigue (Caudate: $r = 0.83$, $P<0.0001$) and with desire for sleep (Caudate: $r=0.72$, $P<0.003$). The correlation between DA changes and performance in the visual attention task was significant in putamen ($r=0.79$, $P<0.001$), thalamus ($r=0.80$, $P<0.001$) and caudate ($r=0.56$, $P<0.05$) and for working memory in putamen ($r=0.71$, $P<0.004$), and thalamus ($r=0.57$, $P<0.03$). Here we show that one night of SD increases DA in striatum and thalamus. Inasmuch as DA enhancing drugs help to maintain wakefulness we postulate that the DA increases serve to maintain arousal as the drive to sleep increases but one that is insufficient to counteract behavioral and cognitive impairment.

Mechanism underlying reinforcing and therapeutic effects of alcohol and stimulant drugs

Several studies have focused on the role of various genes in the mechanism(s) of action of stimulant drugs and alcohol. Receptors/genes examined were: D2R, D4R, DAT and CB1. A transgenic breeding facility for D2 and D4 mice as well as new breeding colonies for CB1 and DAT has facilitated this research. Finally we were able to set up and master microdialysis in the rat, and plan on extending this to simultaneous operant alcohol, cocaine and food self-administration (SA) studies. We are interested in this so to further examine the role of dopamine and other neurotransmitters and their receptors/genes using inbred and outbred rats and transgenic mice.

Studies were conducted measuring the effects of acute administration of methylphenidate (MP) and amphetamine in D4R transgenic mice on locomotor activity and on conditioned place preference (CPP). Results indicated that D4R-deficient and WT mice displayed CPP and increased locomotor activity in response to each of the 3 psychostimulants tested. However, significant differences were observed with respect to each genotype's overall behavioral responses. D4R-deficient mice displayed significantly enhanced CPP only at the highest dose of MP (3 mg/kg, i.p.) and cocaine (4 mg/kg, i.p.) and the lowest dose of AMPH (1 mg/kg, i.p.). In the locomotor test D4R knockout (KO) mice only displayed significantly increased locomotor activity when exposed to the highest dose of each drug. Locomotor responses of WT and D4R KO mice to cocaine and MP were not significantly different. These results suggest distinct mechanisms for D4R modulation of the rewarding (perhaps via attenuating dopaminergic signaling) and locomotor (perhaps by enhancing serotonergic stimulation) properties of these stimulant drugs. Thus individuals with D4R polymorphisms might show enhanced reinforcing responses to stimulant medications and attenuated sensitivity to the locomotor stimulatory effects of AMPH. We also utilized $DAT^{-/-}$ mice to study the brain metabolic effects of cocaine, as described below in the section on the role of D2R and DAT in the actions of cocaine.

Neurobiology of addictive behaviors

The phenomenology of obesity has many similarities to the compulsive behaviors observed in addiction. DA is involved in reinforcing the effects of drugs of abuse and food. The involvement of DA in pathological eating and obesity is poorly understood and has not been directly assessed. DA is involved in the regulation of food intake and Wang et al (2004) found that obese persons have decreased D2R availability in the striatum. We used adolescent male Zucker obese (leptin deficiency that makes them more prone to obesity) and lean rats, divided into unrestricted (U) and restricted (R) (70% of unrestricted food intake/day) diet groups. We examined the developmental and diet effects on D2R levels in these rats by both autoradiography (ARG) and μPET at 1 and 4 months of age. Results showed lower D2R binding in Ob U than Le U rats observed with ARG, which most likely reflects decreases in striatal D2 receptor levels whereas the increased receptor availability observed with μPET is likely to reflect reduced DA release (resulting in decreased competition with endogenous DA). Lack of a significant difference between Ob R and Le R suggests that the differences in dopamine activity and D2R levels between Ob and Le Zucker rats are modulated by access to food. The ARG finding of an attenuation of the age-related loss of D2R binding corroborates previous studies of the salutary effects of food restriction in the aging process. Because [^{11}C]raclopride is sensitive to competition with endogenous DA, the higher D2R binding in obese rats with raclopride despite the lower D2R levels shown with spiperone could reflect lower extracellular DA in the Ob rats and merits further investigation.

In a separate experiment we have done FDG microPET assessment of brain metabolic activity of the above groups of animals in a) baseline and b) food challenge state. We compared brain regional activity in each group. These results showed that conditioned food stimuli generate robust activation responses in the rodent brain that are influenced by access to food and leptin receptor function. The differences were most prominent in the hippocampus, a brain region increasingly recognized as playing a central role in food behaviors, and the superior colliculus, which appears to modulate the saliency value of reinforcers and is therefore likely to mediate the enhanced value of food reinforcers as a function of deprivation. These findings have therapeutic implications since they suggest that interventions to restrict food access are likely to have different responses as a function of genetic diversity, and that a better understanding of this interaction is likely to lead to tailored interventions that maximize success in weight loss regimes.

Mechanisms underlying vulnerability to drug abuse and addiction

The present study utilized a rodent chronic oral methylphenidate (MP) paradigm. Four-week old male Sprague Dawley rats were divided into three treatment groups: 2 mg/kg MP; 1mg/kg MP; and Vehicle (water). At this point, all animals were microsurgically implanted with a jugular vein catheter and placed in operant test chambers for daily 1h sessions. In each session, rats had the opportunity to press an active lever that would result in an intravenous infusion of cocaine (1 mg/kg). Results showed that eight-month treatment with oral MP beginning in adolescence decreased cocaine-self administration (1 mg/kg) during adulthood, which could reflect increased D2R availability observed at this life stage, since D2R increases are associated with reduced propensity for cocaine self administration. In contrast, two-month treatment with MP started also at adolescence decreased D2R availability, which could raise concern that at this life stage short treatments could possibly increase vulnerability to drug abuse during adulthood. These findings indicate that MP effects in D2R expression in striatum are sensitive not only to length of treatment but also to the developmental stage at which treatment is given. Future studies that evaluate the effects of different lengths of MP treatment on drug self-administration are required to assess optimal duration of treatment regimes to minimize adverse effects on the propensity for drug self-administration.

In a parallel study, we looked at the kinetics of MP blood plasma levels using various oral drinking procedures, so that we can begin the oral MP treatment segment of the experiment with clinically comparable plasma levels. The brains of the rats above were perfused and scanned with 17T MRI microscopy to assess structural and volumetric differences in various brain regions, between the MP-treated and vehicle groups.

In a further study we are looking at the effects of D2R genotype on chronic ethanol-induced effects on cerebral and CSF volume using 9.4T MRI; as well as CB1, D3, D4 receptor and DAT levels using beta-imager autoradiography.

Effects of stimulant exposure during adolescence on D2 receptors and reinforcing responses to drugs during adulthood

Methylphenidate (MP) and amphetamine, which are the mainstay for treatment of ADHD, have raised concerns that their use during childhood or adolescence could facilitate drug abuse in adulthood. Here we measured the effects of chronic treatment (8 months) with oral MP (1 or 2 mg/kg), initiated in periadolescent rats (p 30). Following this treatment, rats were tested on cocaine self-administration and assessed for D2R availability in striatum using [^{11}C]raclopride μPET. Animals treated for 8 months with MP showed reduced rates of cocaine self-administration at adulthood. D2R availability was significantly lower in rats after 2 months of treatment with MP but significantly higher after 8 months of treatment. In vehicle-treated rats, D2R decreased with age whereas it increased in rats treated with MP. Chronic oral MP treatment beginning in adolescence decreased cocaine-self administration during adulthood. D2R availability was decreased at 2 months of treatment with MP, which could raise a concern that shorter treatment in adolescence could possibly increase vulnerability to drug abuse during adulthood.

Involvement of dopamine D2 receptors and transporters in the responses to cocaine

Prior studies had shown that D2R upregulation in the nucleus accumbens (NAc) in rodents trained to self-administer alcohol markedly attenuated alcohol intake. Here we assess the effects of D2R upregulation on cocaine intake in rats. Following 2 weeks of intravenous cocaine self-administration, rats were stereotaxically treated with an adenovirus that carried the D2R gene to upregulate D2R in the NAc. D2R vector treatment resulted in a significant decrease (75%) in cocaine infusions. This effect lasted 6 days corresponding to the time required for D2R to return to baseline levels. These findings suggest that strategies aimed at increasing D2R expression in NAc may be beneficial in treating cocaine addiction.

Cocaine's ability to block the dopamine transporter (DAT) is crucial for its reinforcing effects but its ability to block norepinephrine and serotonin transporters may also be relevant to its pharmacology. To separate the dopaminergic from the non-dopaminergic effects of cocaine on brain function we compared the regional brain glucose metabolic responses to cocaine between DAT deficient ($DAT^{-/-}$) mice with that of their $DAT^{+/+}$ littermates. We measured regional brain metabolism (marker of brain function) with 2-[^{18}F]FDG and μPET before and after cocaine (10 mg/kg i.p.). At baseline, DAT$^{-/-}$ mice had significantly greater metabolism in thalamus and cerebellum than DAT$^{+/+}$. Acute cocaine decreased whole brain metabolism and this effect was greater in DAT$^{+/+}$(15%) than in DAT$^{-/-}$mice (5%). DAT $^{+/+}$ mice showed regional decreases in multiple limbic regions whereas DAT$^{-/-}$ mice showed decreases only in thalamus. Cocaine-induced decreases in metabolism in thalamus in DAT$^{-/-}$suggest that these were mediated by cocaine's ability to block norepinephrine transporters. The greater baseline metabolism in DAT$^{-/-}$ than DAT$^{+/+}$ mice in cerebellum (brain region mostly devoid of DAT) suggests that DA indirectly regulates activity of this region.

Brain molecular targets in obesity

Improper function of leptin receptors results in overeating and obesity in obese (Ob) Zucker rats. Leptin deficiency results in hyperphagia but the downstream mechanisms underlying overeating are poorly understood. Here we evaluate the role that CB1 receptors play in obese Zucker rats. One month old Zucker rats were divided into unrestricted and restricted (70% of unrestricted rats) groups and maintained until adulthood (4 months). Brain CB1R levels were assessed (in-vitro autoradiography with [^{3}H]SR141716A). (1) CB1R levels were significantly higher at 4 months than at 1 month in all animals; (2) at 1 month CB1R levels did not differ between Ob and Lean (Le) animals (except in frontal regions); (3) at 4 months Ob rats had higher CB1R levels; and (4) diet restriction resulted in higher CB1R levels in Ob but not in Le. The high levels of CB1R in obese rats suggest that leptins inhibition of food-intake is in part mediated by downregulation of CB1R and that leptin interferes with CB1R upregulation under food deprivations conditions.

Dopamine (DA) is one of the neurotransmitters that modulates the motivation to eat and leptin may modulate eating behavior in part by its effects on DA. Here we assess the interaction between leptin and DA by monitoring D2R in Zucker Obese rats (deficient in leptin receptor function). We compared D2R levels between Zucker Obese (Ob) and Lean (Le) rats at one and four months of age with restricted (R) and unrestricted (U) food access using PET and [^{11}C]raclopride (radiotracer sensitive to competition with endogenous DA) and with ARG [^{3}H] spiperone. D2R were higher at 1 month than at 4 months of age and R animals had higher D2R than U animals. ARG showed that at 1 month and at 4 months Le U had significantly higher D2R than Ob U and that decrease in D2R binding between 1 and 4 months of age was significantly attenuated in R rats obese and lean. In contrast PET showed that at 4 months of age, Ob U showed greater D2R availability than Le U rats. The lower D2R in Ob U than Le U rats observed with ARG most likely reflects decreases in D2R levels whereas the increased availability observed with PET is likely to reflect reduced DA release. Lack of a significant difference between OB R and Le R suggests that the differences in DA between OB and Le are modulated by access to food.

The mechanisms resulting in the enhanced motivation to eat in leptin's absence are poorly understood. Here we evaluate the role of leptin on the response to conditioned food stimuli. We measured brain glucose utilization before and after conditioning to an olfactory stimulus (bacon scent) as a function of food restriction and of leptin genotype (using the Ob rats). Rats were scanned with PET using [^{18}F]FDG under two conditions: a) preconditioning and b) post conditioning. Results showed that: (1) Conditioning resulted in deactivation of hippocampus. (2) Ob rats showed greater changes with conditioning than Le rats and Ob but not Le animals deactivated the frontal cortex. (3) Access to food resulted in an opposite pattern of changes to the conditioned stimuli in olfactory nucleus (deactivated in U and activated in R) and in right insular/parietal cortex (activated in U and deactivated in R). Leptin-receptor deficiency resulted in an enhanced response to conditioned cues that included deactivation of the frontal cortex. Inasmuch as the frontal cortex enables inhibitory control to intentional action this may be one of the mechanisms that results in compulsive overeating in the Ob rats.

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