# THE BRAIN AND OBESITY: THE CLINICAL PICTURE

***Rudolph Leibel***
***Division of Molecular Genetics, Naomi Berrie Diabetes Center***
***Columbia University, New York, NY***

Human body weight is regulated, and that regulation occurs primarily through the central nervous system. Many molecules and cells have been identified as components of this system that necessarily relies on communication of the status of short (gut)- and long (fat)-term aspects of fuel availability. There are clear genetic influences on susceptibility to obesity, but the full repertoire—and proportionate contributions—of relevant genes primarily responsible for these influences is not known. Obesity results from chronic, relatively small excesses of energy intake over expenditure. In obese humans, this imbalance derives primarily from excessive intake rather than reduced expenditure. However, weight reduction lowers energy expenditure and predisposes to weight regain because energy intake is not reduced proportionately. Evolutionary considerations would suggest that the defenses against gain of body fat are less strong than those against fat loss, as the latter affects immediate survival and reproductive efficiency. Oncoming technologies that enable real-time imaging and *in vivo* analysis of the relevant organs (CNS, muscle, liver, islets) in human subjects, combined with thoughtful use of model organisms to generate and vet hypotheses, will provide important information in the efforts to cure and prevent obesity. Areas in which these technologies can now be fruitfully applied include *prospective* studies of weight perturbation, responses to anorexiant and other drugs, individuals segregating for known predisposing obesity alleles, and patients undergoing intestinal exclusion procedures. Both functional and structural responses should be looked for.

# CNS PATHWAYS REGULATING BODY WEIGHT AND GLUCOSE HOMEOSTASIS

***Joel Elmquist***
***Division of Hypothalamic Research, Departments of Internal Medicine and Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX***

Metabolic cues such as leptin and insulin directly act on key collections of neurons both within and outside the hypothalamus to regulate food intake, body weight, and glucose homeostasis. In addition, it is now established that classic neurotransmitters may also act on the same neuronal groups to regulate energy balance. However, the inherent complexity of these CNS circuits has made it extremely difficult to definitively identify the key neurons that are required to maintain glucose homeostasis and energy balance. Over the past several years, the ability to manipulate gene expression in a neuron-specific fashion has become feasible. In this talk, we will describe some of our recent findings using mouse models that allow neuron-specific manipulation of receptors regulating energy balance and glucose homeostasis. We will focus much of our attention on the role of insulin and leptin to regulate melanocortin neurons. We will also describe results using a novel mouse model to investigate the role of serotonin action on hypothalamic POMC neurons to regulate food intake, body weight, and glucose homeostasis.

# MAGNETIC RESONANCE METHODS FOR FUNCTIONAL AND ANATOMICAL NEUROIMAGING

***Peter Bandettini***
***Chief, Section on Functional Imaging Methods, Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, MD***

Functional MRI continues to grow in terms of studies performed as well as range and depth of questions being asked. This steady progress is primarily due to the noninvasiveness, sensitivity, specificity, and resolution (both temporal and spatial) of fMRI and MRI. In this lecture, I will give a brief overview of MRI, DTI, VBM, and fMRI, highlighting some of the strong and weak points of each technique. A very general overview of what types of approaches have been made in the context of studying obesity will be presented as well. Lastly, I will conclude with what I think are potentially fruitful approaches to using neuroimaging for the study of obesity.

# MEG METHODS FOR FUNCTIONAL NEUROIMAGING

***David Poeppel***
***University of Maryland at College Park and New York University***
***College Park, MD***

Magnetoencephalography (MEG) is an entirely noninvasive electromagnetic technique that measures neuronal signals using sophisticated superconducting detectors placed near the scalp. Intracranial electrical sources (i.e., populations of neurons) generate coherent activity that is sufficiently large to detect at the surface. These measurements are made with high temporal resolution (1 ms) but at the expense of spatial resolving power, which is estimated to be on the order of 5-10 mm, depending on the nature of the source and the type of source model employed. MEG (like EEG) is well suited to evaluate processing models or, more generally, the temporal evolution of some aspect of perception or cognition.

# PET METHODS FOR FUNCTIONAL NEUROIMAGING AND PET DATA ANALYSIS

***Peter Herscovitch, M.D.***
***Director, Positron Emission Tomography Department***
***National Institutes of Health, Bethesda, MD***

Positron emission tomography (PET) is a nuclear medicine imaging technique that uses positron-emitting radiopharmaceuticals that can be detected with a specialized scanner. It provides cross-sectional images of the distribution of radioactivity in the body. From these images, *in vivo* physiological and biochemical measurements can be made. Five basic principles will be discussed, to provide an understanding of the science of PET:

(1) PET provides regional measurements of the absolute *concentration* of radioactivity in the body, in units of microCi or MBq per cc of tissue.

(2) There is a very wide variety of radiopharmaceuticals for PET. These are labeled with positron-emitting atoms such as C-11 or F-18, and are used to image biochemical processes or protein targets.

(3) PET uses the tracer principle. Because of the high sensitivity of PET, small amounts of radiopharmaceutical give useful images. The radiopharmaceuticals have high specific activity and a very small injected dose of the compound, typically < 1 microgram. Therefore, there is no physiologic or pharmacologic effect.

(4) Tracer kinetic models are required, to convert measurements of radiotracer concentration in tissue to quantitative physiological and biochemical measurements.

(5) Specialized methods of image analysis are used. These relate regional measurements of biochemistry and physiology to underlying brain anatomy, and help to detect abnormalities in disease.

# A FRANK DISCUSSION OF STUDY DESIGN

***Russell Poldrack***
***Department of Psychology, University of California at Los Angeles, Los Angeles, CA***

Neuroimaging studies can be deceptively easy to implement, analyze, and publish. In my talk, I will discuss some of the issues that complicate the interpretation of results from neuroimaging studies, and focus on how study designs can be implemented to help address some of these issues.

# SPECIAL CONSIDERATIONS FOR FUNCTIONAL NEUROIMAGING OF PEDIATRIC POPULATIONS

***BJ Casey***
***Sackler Institute for Developmental Psychobiology,***
***Weill Medical College, Cornell University, New York, NY***

Only recently have we begun to understand and appreciate the complexities of human brain development with the emergence of noninvasive imaging techniques. At the forefront of these methodological advances has been the development of functional capabilities of magnetic resonance imaging (fMRI). This methodology hinges on the precision of behavioral measures in capturing the psychological constructs and behavioral phenomenon that change with development and/or are disrupted in child and adolescent psychiatric disorders. A number of considerations arise for pediatric imaging studies in this context that include acclimating the child to the scanner environment, using age-appropriate measures and precision of assaying the behavior, and processing and analysis of the imaging data. These considerations, in addition to the important issues related to regional brain development and individual differences, will be discussed with emphasis on study designs that assess change during transitions into and out of developmental or pathological states.

## SPECIAL CONSIDERATIONS FOR ANALYSIS OF fMRI DATA

***Robert Cox***
***National Institute of Mental Health, Bethesda, MD***

In this brief talk, I will outline the standard methods for analysis of functional MRI datasets: pre-processing steps, linear and nonlinear regression of time series, and statistical analysis of data from multiple subjects (group analysis). I will also discuss some of the various inter-regional connectivity analyses that are becoming popular, both with stimulus/activation experimental designs and with resting-state data.

## DATA INTERPRETATION IN THE REAL WORLD

***David Poeppel***
***University of Maryland at College Park and New York University***
***College Park, MD***

Noninvasive functional neuroimaging has become ubiquitous; both hemodynamic (fMRI, PET) and electromagnetic (MEG, EEG) approaches to record from the human brain are now widely available for basic and clinical research. Although the data acquisition and data analysis approaches are becoming increasingly sophisticated and nuanced, the typical interpretation of brain activity remains coarse. For example, too often we operate under a "cartographic imperative"—localization of function is treated as a surrogate for explanation. However, the goal must be theoretically motivated, computationally explicit, and provide neurobiologically plausible accounts of brain activity as the basis for human behavior.

## NEUROIMAGING OF INTRINSIC CONNECTIVITY

***Michael Greicius***
***Assistant Professor, Department of Neurology, Stanford University, Stanford, CA***

Resting-state functional connectivity MRI is a (relatively) novel approach to functional brain imaging that allows for the detection of several canonical resting-state networks (RSNs). As interest in RSNs has grown, so too have the potential applications of this new modality to pressing clinical research questions. This talk will review some of the basics behind RSN connectivity analysis. We will begin by exploring the differences between RSN analyses and more standard task-activation fMRI studies. We will then consider the two main approaches to detecting RSNs (region-of-interest [ROI] analyses and independent component analysis [ICA]). Next, we will focus on how cognitive and emotional attributes may be reflected in the connectivity strength of these networks and on how these networks adapt and interact in the setting of a task. The bulk of the talk will be devoted to the numerous clinical RSN studies that have come out in the last 5 years. While highlighting some of the more plausible applications (in Alzheimer's disease, for example), we will consider both the strengths and weaknesses of this approach in studying neuropsychiatric disorders. The talk will conclude with a discussion of how we might enhance the clinical utility of RSN analyses to allow for a better understanding of pathogenesis, earlier and more accurate diagnoses, and early objective markers of treatment effect.

## NEUROIMAGING OF DRUG ABUSE

***Elliot Stein***
***Chief, Neuroimaging Research Branch, National Institute on Drug Abuse, Baltimore, MD***

Considerable preclinical data suggest important overlaps between the central nervous system sites and neurobiological mechanisms underlying ingestion of addicting drugs (e.g., cocaine) and food intake. The American Association of Addiction Medicine proposed adding food as an addiction to that of drug dependence in humans more than 15 years ago. Although there have been considerable inroads in understanding human drug addiction mechanisms using both MRI and PET, few studies have applied imaging to understand obesity. This talk will briefly review the literature supporting common mechanisms between feeding behavior and drug abuse and then provide an overview of cognitive and pharmacological imaging studies on drug abuse and how this research model may be applied to better inform the neurobiology of obesity.

## THE SENSES AND EMOTION—TASTE AND SMELL

***Dana Small***
***Associate Professor, Department of Psychiatry and The John B. Pierce Laboratory, Yale University School of Medicine, New Haven, CT***

The word "taste" is often used to describe the sensation of food in the mouth. However, what we colloquially refer to as "taste" is more accurately labeled "flavor", which is the unitary perception that results from the integration of multiple distinct sensory inputs, including taste, smell, and oral somatosensation. Taste and flavor are both proximal sensations, in that the stimulus must come into contact with the body for sensation to occur. Information about food, in particular its availability, is also obtained through the distal senses of olfaction and vision. We have described evidence for separable circuits encoding the sensation of food aromas compared to the sensation of these same aromas when they are experienced as flavors and suggest that these distinct responses reflect differential engagement of anticipatory (aroma) and consummatory (flavor) food reward circuits. In more recent work, we found selective quantitative and qualitative differences in brain response to food aromas and food receipt in overweight and obese individuals. An example of a selective quantitative change occurs in the dorsal striatum (caudate and putamen), in which response to ingestion of a milkshake, but not to the smell of the aroma predicting the delivery of the milkshake, is inversely related to body mass and predicts future weight gain. These relationships depend upon the taq1 A1 polymorphism, which has been linked with lower dopamine signaling and higher body mass. In the amygdale, both quantitative and qualitative changes are observed. In lean subjects, the amygdala selectively encodes food aromas (i.e., cues). In overweight subjects, the cue response is enhanced and abnormal response to receipt is observed. This abnormal response to receipt is associated with stable behavioral traits whose persistence has been shown to lead to obesity. Taken together, these and other emerging findings support the hypothesis that individual differences in anticipatory and consummatory food reward render some individuals at risk for overconsuming in the presence of a surplus of palatable, calorie-dense foods.

**Acknowledgements:** This work was performed in collaboration with Jennifer Felsted, Sonja Spoor, Cara Bohon, Eric Stice, Elissa Epel and David Kessler. It was supported by NIH R03 DA022292-01 and a private donation awarded to Dana Small and by NIH/NIDDK R01 MH064560 Supplement NOT-RM-05-007 awarded to Eric Stice.

# HYPOTHALAMIC RESPONSE TO HORMONES AND NUTRIENT INGESTION

***Jeroen van der Grond***
***Associate Professor, Department of Radiology,***
***Leiden University Medical Center, Leiden, The Netherlands***

Overweight or obesity is a fast growing social and economic burden in the western world. A large number of medical conditions have been associated with obesity. It is well recognized that, in most cases, the combination of excessive caloric consumption and an inactive lifestyle are the primary causes of obesity.

The brain plays a crucial role in the decision to eat, integrating multiple hormonal and neuronal signals. The link between food or eating and the brain is not only about the effect of nutrition on behaviour, brain development, and performance. It is also about the mechanisms of the brain behind eating behavior, such as satiety, hunger, addiction, or even buying behaviour. The purpose of the current line of research is to find central biomarkers reflecting the human brain response to hunger, taste, and satiation.

Although the perception of food is multifactorial, the role of the hypothalamus in the regulation of energy homeostasis is well established, and there has been a remarkable progress in our understanding of the neurobiological complexity of the hypothalamic pathways involved in the regulation of satiation and body weight.

In previous studies, we have shown that the decrease in BOLD signal after the administration of a glucose load points at a decrease in neuronal activity in the hypothalamus. It is possible that the administration of glucose directly inhibits hypothalamic neuronal activity, which may be elevated in a state of hunger. Alternatively, the administration of glucose may activate inhibitory pathways (prefrontocortical hypothalamic pathways), which in turn suppress the neuronal activity of the hypothalamus. On the other hand, we have shown that caloric intake only or sweet taste only does not provoke inhibition of the hypothalamic neuronal activity. In this respect, the central research question is focused on the aim to investigate physiological processes or physiological responses (insulin, gut hormones, autonomic nervous system afferent signals) that are related to the intake of glucose, which mediates the observed hypothalamic response.

It is to be expected that, in the next decade, the hypothalamus will become a target of interest because both fMRI and PET studies have also shown that in obese individuals, the decrease in hypothalamic activity following a meal is significantly reduced compared with lean. This may point a central role for the hypothalamus as a biomarker for satiation, indicating a new target for investigating the neurofunctional features of normal and abnormal eating behavior. Current research lines include the hypothalamic response on/in dieting, ageing, DM2, and anorexia nervosa.

# PYY AND HYPOTHALAMUS TO CORTICOLIMBIC SWITCHING

***Rachel Batterham***
***Department of Medicine, University College London, United Kingdom***

In response to meal ingestion, several hormones are released from the gastrointestinal tract, which play a role in the regulation of energy homeostasis. Peptide YY (PYY), synthesised by gut-endocrine cells, predominantly as an N-terminally truncated form $PYY_{3–36}$, is one such hormone. The first evidence for a role of PYY3-36 in the regulation of body weight resulted from the findings that peripheral PYY3-36 administration dose dependently decreased feeding in rodents. Subsequently, in humans, intravenous infusion of PYY3-36 was found to reduce hunger and decrease 24 h caloric intake in lean, normal-weight, and obese subjects. In addition, fasting and postprandial circulating PYY3-36 levels were found to be reduced in obese subjects suggesting that PYY-deficiency might contribute to the pathogenesis of obesity. To further understand the physiological role of PYY, mice lacking *Pyy* were generated. These animals were hyperphagic, developed marked obesity, but displayed increased sensitivity to exogenous PYY3-36, which reversed their obese phenotype.

Studies in rodents suggested that the hypothalamus and brainstem were key target sites mediating the anorectic effects of PYY3-36. To investigate in humans the brain circuits upon which PYY3-36 acts, a double-blind placebo controlled study was undertaken, combining PYY3-36 infusion with continuous functional magnetic resonance imaging and behavioural measures. PYY3-36 modulated neural activity within brainstem and hypothalamic regions consistent with rodent studies. However, the greatest effect of PYY3-36 on brain activity was seen within the left caudolateral orbital frontal cortex (OFC), a polymodal brain region implicated in reward processing. Critically under high PYY3-36 plasma conditions, mimicking the fed state, changes in neural activity within the OFC predicted subsequent feeding behaviour. In contrast, in low PYY3-36 conditions, hypothalamic activation predicted subsequent food intake. Thus, the presence of postprandial plasma concentrations of PYY3-36 switched food intake regulation from a homeostatic to a hedonic, corticolimbic area. Further evidence for a hedonic role for PYY3-36 is supported by rodent studies showing that PYY3-36 decreases the motivation to seek high-fat food.

The retained responsiveness of obese subjects to the anorectic effects of PYY3-36 coupled with its newly identified hedonic effects suggest that targeting the PYY system may offer a therapeutic strategy for obesity.

## LEPTIN, HYPOTHALAMUS, AND CORTICAL REGULATION

***Joy Hirsch***
***Professor of Functional NeuroRadiology, Neuroscience, and Psychology***
***Director, Program for Imaging and Cognitive Sciences (PICS)***
***Columbia University Medical Center, New York, NY***

Why is it so hard to sustain voluntary weight loss? Increased hunger and food intake during attempts to maintain weight loss are not understood, and pose a critical problem in the treatment of obesity. We employed functional magnetic resonance imaging (fMRI) and a double-blind, within subject, clinical trial to reveal food-specific brain activity during three conditions: 1) initial obese weight, 2) 10 percent weight-reduced (with placebo injections), and 3) 10 percent weight-reduced (with replacement injections). Hypothalamus responses were evident during initial weight and leptin-restored weight loss conditions, consistent with a model of leptin hormone levels as a signal for food-related responsiveness (Rosenbaum, M., et al. *J Clin Invest*, 2008).

Comparisons of cortical responses elicited by food stimuli during weight-reduced conditions with and without leptin replacement also reveal distinct patterns of cortical responses, and extend current models of food-intake regulation to include hormonal influences on specific cortical systems that mediate cognitive and emotional control of eating behavior. Thus, these and similar recent findings enrich current models of obesity and eating disorders with the discovery of inter-related hormonal and specific cognitive systems and guide future investigations of therapeutic interventions for the cure of obesity.

# LESSONS ABOUT OBESITY FROM NEUROIMAGING

***Angelo Del Parigi***
***Pfizer Inc., New York, NY***

In the last 10 years, neuroimaging has been generating, at increasing pace, vast amounts of data on human eating behavior and its aberrations leading to weight gain and obesity. Several obesity centers today consider neuroimaging as one of the most promising tools for studying the pathophysiology of obesity in humans.

One of the advantages of neuroimaging is the opportunity to explore the whole brain at once: this allows appreciating the complexity of the central control of eating behavior beyond predetermined regions of interest. In fact, neuroimaging biomarkers of obesity have been identified in several cortical and subcortical regions of the brain, such as the prefrontal cortex, hypothalamus, striatum, and other limbic/paralimbic regions. However, single center studies have many limitations and often fail to obtain the statistical power necessary to reach generalizable conclusions. Conversely, intercenter meta-analyses are limited by the heterogeneity of populations/phenotypes, experimental designs, scanning protocols, equipment, and data analysis procedures. Furthermore, technical and experimental constraints combined with the heterogeneity of behavioral phenotypes associated with weight gain limit the ability to test fundamental hypotheses on the pathophysiology of obesity.

Is it then time for an "Obesity Neuroimaging Consortium," that is, a consortium among scientific institutions technically and scientifically equipped to use neuroimaging for the study of the pathophysiology of human obesity? A steering committee would have the task of designing a protocol that could be implemented in multiple centers and set the rules for data analysis procedures and the writing of reports. This initiative should attract funding from federal agencies as well as from private sponsors, including biotechnology and pharmaceutical industries. From a scientific standpoint, a multicenter study would have a sufficiently large sample size to answer basic questions on the central control of eating behavior in humans and provide the foundation for the identification of novel biomarkers and targets for the pharmacotherapy of obesity, which are acutely needed.

## DIET, WEIGHT LOSS, AND MAINTENANCE

***Cary Savage***
***Department of Psychiatry and Behavioral Sciences,***
***University of Kansas Medical Center, Kansas City, KS***

Obesity rates are on the rise and associated with serious public health consequences and rising health care costs. Eating behavior is influenced by a convergence of processes in the brain, including homeostatic factors, motivational and reward processing, and cognitive control. Motivational and reward processing are especially important contributors to overeating in humans. Food is a highly salient reinforcer and its presentation is associated with increased activity in limbic and paralimbic networks in the brain. Increased activity in these networks may contribute to increased eating behavior. Initial functional magnetic resonance imaging (fMRI) studies from our group and others have identified brain regions that respond differently to visual food cues in obese and healthy weight (HW) individuals, and are positively correlated with reports of hunger in obese participants. Although these early studies shed some light on neural contributions to overeating, many important questions remain. For instance, it is not yet known whether brain activation patterns change after dieting, or if they change differentially in successful and unsuccessful dieters. In addition, little is currently understood regarding neurobiological processes that contribute to long-term maintenance of healthy weight.

Dr. Savage will briefly review previous fMRI studies of food motivation in obese and healthy weight groups. He will then describe ongoing efforts to use fMRI to measure functional outcome of initial weight loss in diet-based interventions and to identify predictors of successful weight loss and longer term weight loss maintenance.

# NEUROIMAGING OF FOOD ADDICTION

***Nora Volkow***
***Director, National Institute on Drug Abuse and***
***Chief, Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD***

Food intake is regulated by multiple factors that include metabolic and nutritional needs as well as the reinforcing properties of food. Similarly, obesity is likely to result from the complex interplay of these factors as well as genetic, developmental, and environmental factors. The reinforcing component of food is particularly relevant as it motivates food consumption. The reinforcing effects of food are mediated in part by its ability to increase dopamine in brain reward and motivation circuits, and imaging studies in humans have shown that the increases in dopamine induced by the display of food are associated with the desire and the motivation to consume the food. Because the reinforcing effects of drugs of abuse are also mediated by their ability to increase dopamine in the same circuits as food, a question that arises is: Why does food not produce addiction? This is likely to reflect the fact that the increases in DA induced by food when compared with those of drugs of abuse are smaller, of shorter duration, and habituate with repeated administration. Despite these differences, in some obese individuals, the loss of control and compulsive food-taking behavior shares characteristics to the compulsive drug intake observed in drug-addicted subjects. We have used imaging to investigate in these obese individuals both the brain DA system as well as regional brain metabolism, and to compare it with the changes seen in drug-addicted individuals. These studies have shown that morbidly obese subjects have significant reductions in striatal DA D2 receptor availability, which are equivalent to those we have previously reported in drug-addicted subjects. However, obese subjects showed enhanced activity of somatosensory cortical regions involved with processing palatability, which is a variable that contributes to the hedonic properties of food. We hypothesize that decreased levels of D2 receptors would make addicted subjects less sensitive to natural reinforcers at the expense of more powerful reinforcers; in the case of obese individuals, the enhanced sensitivity to palatability would make food a stronger reinforcer, driving its preference over that of other reinforcers.

## EATING DISORDERS

***Walter Kaye***
***Professor, Department of Psychiatry, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, University of California at San Diego, Pittsburgh, PA***

**Introduction:** Individuals with anorexia nervosa (AN) restrict food and lose weight, and individuals with bulimia nervosa (BN) binge and purge. The stereotypic presentation and relentless expression of these feeding behaviors support the possibility that they reflect some aberrant function of appetitive pathways. In addition, food ingestion in AN and BN is strongly associated with modulation of emotionality and reward. For AN, palatable food is anxiogenic whereas starvation is "rewarding." In contrast, in BN, binge episodes are often provoked by negative mood states and stress whereas binge behavior is "comforting."

**Methods:** We characterized response to palatable food in AN and BN using functional magnetic resonance imaging (fMRI) and tastes of sucrose as a simple probe of sensory and hedonic pathways. To avoid the possible confounding effects of aberrant nutrition on appetitive function, we studied individuals who were recovered from AN (RAN) and BN (RBN) (greater than 1 year of normal weight, normal nutrition, normal menses, and not on medication) compared to healthy control women (CW). fMRI measured neural activation while subjects received 10 percent sucrose compared to either water, or tastes of artificial sweetener matched so sweet tastes could not be consciously distinguished. Analysis of Functional NeuroImages (AFNI) software was used to assess main effect activation ($p = 0.005$), condition ($p = 0.05$), and group comparisons ($p = 0.05$) in brain regions known to process the sensory and hedonic aspects of taste.

**Results:** For RAN, fMRI response was attenuated in response to caloric and non-caloric sweet stimuli in the frontal operculum/anterior insula (FO/AI), striatum, dorsal anterior cingulate, prefrontal cortex, and thalamic pulvinar when compared to CW. In contrast, RBN had greater right anterior insula activation in response to sucrose, but not Splenda conditions when compared to CW. RBN also showed greater left posterior insula activation than CW in both sucrose and Splenda conditions. A positive relationship between FO/AI activation and taste pleasantness was found in CW, but not in recovered subjects. In comparison, RAN showed positive and RBN negative relationships between measures of anxiety and response to sucrose in the insula and other regions.

**Conclusions:** Recovered AN and BN have persistent alterations of response to palatable foods in brain regions modulating the sensory and rewarding aspects of taste. RAN had diminished, but RBN had exaggerated anterior insula hemodynamic response to tastes of sucrose. Imaging studies have consistently shown that food deprivation activates the insula and orbitofrontal cortex when compared to a fed state. It is possible that AN individuals have a reduced drive to eat, perhaps related to diminished reward. In comparison, for BN individuals, an enhanced sensory-hedonic signal in response to palatable food may drive overeating. Alternatively, the anterior insula may compute that BN individuals are underfed and thus drive food consumption. Finally, the anterior insula correlates homeostatic processing of hunger and the physiological condition of all tissues of the body with emotional awareness. For AN and BN, processing of aversive signals, such as anxious affect, may either interfere with or drive hunger.

## FOOD CRAVING

***Marcia Levin Pelchat, Ph.D.***
***Associate Member, Monell Chemical Senses Center, Philadelphia, PA***

In recent years, it has become clear that food craving (commonly defined as an intense desire to eat a particular food) is related to obesity. Food cravings, like drug cravings, can be learned and are readily triggered by cues in the environment. We have recently found that foods can be craved, but not liked (although craving and liking usually go hand-in-hand). It is of great importance that food craving usually occurs in the absence of hunger. Thus, a working hypothesis is that food craving is related to obesity because, in obesity-prone individuals, there is a heightened cue reactivity that leads to non-homeostatic eating. There are many potential confounds in food-craving research, but these can be avoided by developing a clear understanding of the distinctions among craving, hunger, and liking. It is likely that eating disorders will prove to be easier to prevent than to treat. Therefore, future research efforts should be directed toward the discovery of biomarkers indicative of risk in not-yet affected individuals.

# NEUROIMAGING OF GUT DISTENTION

***Allan Geliebter***
***Obesity Research Center, St. Luke's-Roosevelt Hospital,***
***Columbia University College of Physicians, New York, NY***

The stomach is a key storage and digestive organ and is involved in generating signals of hunger and satiety via neural and hormonal mechanisms. Gastric distension sends neural satiety signals via the vagus to the brainstem. Graded gastric balloon distension in humans reduced spontaneous liquid meal intake by about 40 percent of the balloon volume. With larger balloon volumes, it was found that obese individuals have a greater stomach capacity than lean individuals. Among the obese, those with binge eating disorder (BED), who consume large meals with loss of control, had a greater capacity than those without, and lean individuals with bulimia nervosa (binge and purge) had the largest capacity. Stomach capacity is positively correlated with meal volume. The stomach may also signal hunger through release of ghrelin, which is elevated before meals and falls afterwards. In a study of BED patients, instead of higher ghrelin levels that might promote excess food intake, lower fasting ghrelin was found with a smaller decline post meal. This could be related to binge eating episodes often occurring when the person is not hungry. It was also found that ghrelin levels were inversely related to stomach capacity, suggesting a mechanism for the lower ghrelin. Another trigger for overeating may be potent stimuli of highly palatable foods. In an fMRI study, comparing lean and obese women with and without binge eating behavior, the greatest brain responsivity was in the obese binge eaters in response to highly palatable binge-type foods. The area of greatest activation was in the premotor cortex, in the oral region, possibly related to motor planning of ingestion of such foods. In another fMRI study, the effects of graded gastric balloon distension were examined in normal weight participants. The areas most responsive were the amygdala and insula, suggesting roles for fullness perception and control of food intake. The brain imaging studies may help better elucidate the underpinnings of appetite mechanisms and disordered eating.