2010; Urs *et al*, 2012). The combined efforts of molecular pharmacologists, biochemists, and behavioral pharmacologists to decipher these complex relationships between the molecular signatures of GPCRs and how various GPCR conformations ultimately transduce cellular responses into behavioral output are an active area of study for both Academia and Industry. These new discoveries are likely to provide novel therapeutic strategies for treating psychiatric diseases.

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Obesity, Food, and Addiction: Emerging Neuroscience and Clinical and Public Health Implications

Obesity is considered among the top three leading causes of preventable death and illness in the United States (Danaei *et al,* 2009). In the United States and elsewhere, obesity's prevalence has risen considerably since the 1980s, with one-third of US adults now obese (http://www.win.niddk.nih.gov/statistics/). How health care approaches obesity is changing, with the American Medical Association recently defining obesity as a disease (http://www.bostonglobe.com/editorials/2013/06/28/ama-obesity-declaration-makes-third-america-ill/02nZ0a90RtlKE3hOWy59KK/story.html). Although the reasons why rates have risen are not entirely known and remain debated, the individual and societal costs necessitate an improved understanding. In this context, examining food and eating behaviors from interdisciplinary perspectives seems important in addressing an obesity epidemic.

Historically, obesity has been viewed from a metabolic perspective, with a focus on energy balance (Ziauddeen *et al,* 2012). More recently, it has been questioned whether obesity might be conceptualized within an addiction framework and whether certain foods may be addictive (Gearhardt *et al,* 2011a). Over time, a motivating factor for food consumption has shifted from sustenance and energy balance to pleasurable/hedonic purposes. Thus, motivational factors (positive-reinforcement-related anticipatory pleasure or negative-reinforcement-related stress reduction) might link to obesity similarly as in drug addictions. Additionally, metabolic factors implicated in homeostatic regulation may relate differently to these constructs in obese as compared with lean individuals.

To examine directly, we studied 25 obese and 25 matched lean individuals using a guided-imagery fMRI task that included individualized cues relating to personal stressors, favorite foods, or neutral-relaxing situations (Jastreboff *et al,* 2013). Obese as compared with lean individuals showed increased activation in cortico-striato-limbic structures (striatum, insula, inferior frontal gyrus and amygdala) to favorite-food cues, and activations of thalamus and striatum correlated with subjective craving in obese but not lean individuals. Similarly, stress-related

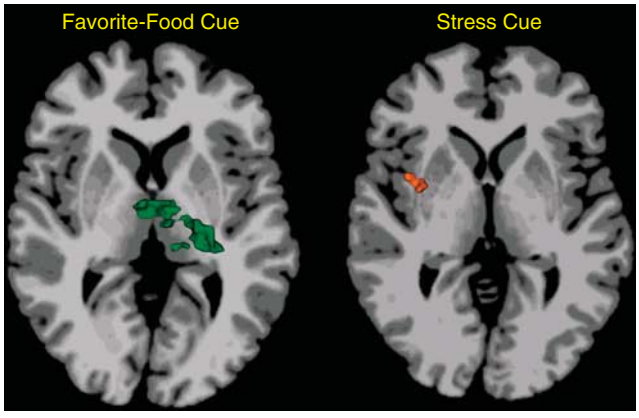

Figure 1. Overlaps in the relationships in obese individuals between brain activations and insulin resistance (HOMA-IR) and brain activations and food craving. During favorite-food cue exposure, individuals with obesity show thalamic activations that correlate both with HOMA-IR and food craving (left, green color). During stress cue exposure, individuals with obesity show insular and striatal (in putamen) activations that correlate both with HOMA-IR and food craving (right, orange color). Brain slices are located at Talaraich levels of $z = 6$ (left) and $z = 4$ (right), respectively. Right side of the brain is displayed on the left. Additional details of the original research can be found in Jastreboff *et al* (2013).

activations in the striatum and insula correlated with food craving in obese but not lean individuals. Together, these findings suggest important differences in obese and lean individuals with respect to activation patterns in motivational neurocircuitry that may promote eating behaviors.

Importantly, metabolic measures were also collected. Brain activations during all three conditions correlated with a homeostatic measure of insulin resistance (HOMA-IR) in obese but not lean individuals in regions including the insula, inferior frontal gyrus, striatum, and thalamus. Furthermore, regional brain activations (eg, in the thalamus during the favorite-food cue condition and striatum and insula during the stress condition—Figure 1) were found to mediate the relationship between HOMA-IR and food craving in obese (but not lean) individuals. These findings suggest that interventions that target motivations rather than energy balance *per se* may be particularly relevant to combating obesity in the current environment.

The current study helps integrate findings from multiple disciplines. Such integrative research may help address current debates about how best to conceptualize and treat obesity and ultimately lead to improved treatment strategies. Additionally, identifying clinically relevant subgroups with obesity (eg, those with binge-eating disorder, a condition hypothesized to show particular similarities with addictions (Gearhardt *et al*, 2011b), including in brain activations relating to reward processing (Balodis *et al*, 2013)), may help resolve current debates and target interventions.

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Targeting Emotion Circuits with Deep Brain Stimulation in Refractory Anorexia Nervosa

There is an urgent need to develop novel therapies for patients with anorexia nervosa (AN). A condition that is heterogeneous, highly resistant to treatment, and associated with striking rates of morbidity and mortality, few therapeutic advances specifically for AN have been made in the past 150 years. A re-orientation in the last two decades toward neuroscientific explanations for AN offers hope that an increased understanding of the illness' neural roots will lead to better treatments (Kaye *et al*, 2009).

Deep brain stimulation (DBS) is a neurosurgical procedure that targets critical nodes in dysfunctional neural circuits driving pathological behaviors (Lozano and Lipsman, 2013; Mayberg *et al*, 2005). DBS' efficacy in disorders like Parkinson's Disease has driven its investigation in other circuit-based conditions, including major depression (Lozano and Lipsman, 2013). Several factors led us to consider DBS in refractory AN. First, the primarily limbic structures implicated in the disorder, largely by functional neuroimaging, are consistent with the clinical observations that AN is predominantly a disorder of emotional processing. Further, the ability of DBS to safely and effectively access limbic nodes in mood- and anxiety-related circuits suggested that it could be applied to AN, a disorder marked by high rates of depressed mood and affective dysregulation.

The subcallosal cingulate (SCC) has a key role in modulating emotional states and projects cortically, to medial- and orbitofrontal cortex, as well as subcortically to nucleus accumbens. Our group has also shown that SCC neurons participate directly in emotion processing, responding preferentially to affective-laden stimuli and decisions (Lipsman *et al*, 2013a). The SCC is thus both structurally and