Neurobiological Underpinnings of Obesity and Addiction: A Focus on Binge Eating Disorder and Implications for Treatment

July 20, 2015 | CME [1]
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This CME is intended to help differentiate binge eating disorder (BED) from other eating disorders and understand the mechanisms that may put BED into the realm of addiction disorders.

Premiere Date: July 20, 2015
Expiration Date: January 20, 2017

This activity offers CE credits for:
1. Physicians (CME)
2. Other

ACTIVITY GOAL
To differentiate binge eating disorder (BED) from other eating disorders and understand the mechanisms that may put BED into the realm of addiction disorders.

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
1. Recognize the differences between BED and other eating disorders
2. Understand how BED relates to addiction disorders
3. Recognize treatment approaches—pharmacological and psychotherapeutic

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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Iris M. Balodis, PhD, has no disclosures to report.
Carlos M. Grilo, PhD, reports that he has received grants and research support from the National Institutes of Health, he is on the speakers bureau of Shire, and he is a consultant for Shire and Sunovion.
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Obesity has been considered within an addiction framework with the term “food addiction” debated as a potential clinical entity. Certain core addiction characteristics, such as diminished control or loss of control while eating, food cravings, and continued behaviors despite negative consequences, appear pertinent to some patterns of disordered eating. Systematic investigations into neurobiological mechanisms underlying these features are ongoing in an effort to understand potential contributions to different patterns of overeating. It is likely that obesity is the result of multiple factors. Genetics, environment, various overeating behaviors (from excess snacking to overeating of nutrition-poor but calorie-dense foods to binge eating), insufficient lifestyle physical activity, and various metabolic conditions may all contribute in complex ways to obesity.

A central research goal is to define how different etiologies and pathways contribute to the many manifestations of overeating and obesity. Discussing obesity as a unitary disorder may obfuscate research findings that pertain to this complex problem; therefore, our focus is on binge eating disorder (BED).

The notion of food addiction has recently been applied to BED, which is defined by recurrent episodes of consuming unusually large amounts of food. It is important to note that persons with BED experience a subjective sense of loss of control during these episodes, but they do not perform the extreme weight compensatory behaviors that characterize bulimia nervosa. BED is the most prevalent eating disorder; it affects approximately 4% of the US population, occurs across all weight categories, and is strongly associated with severe obesity. It is linked with increased risk of psychiatric and medical comorbidities. Moreover, BED exhibits behavioral and psychological dimensions that are distinct from other eating disorders.

Although BED is currently categorized as an eating disorder in DSM-5, distinct parallels are noted in phenomenological/behavioral features between BED and addiction. Recurrent binging episodes, a lack of control, and personal distress/negative social consequences appear as core characteristics across both disorders. Understanding the neural systems underlying these features is particularly important because they contribute significantly to appetite regulation, weight, and treatment response.

Despite the prevalence and clinical impact of BED, functional and structural neuroanatomical studies specifically examining BED are only beginning to emerge. These neuroimaging studies are fundamental for demonstrating structural and functional brain characteristics supporting BED as a condition distinct from other forms of obesity or other forms of disordered eating (eg, anorexia nervosa, bulimia nervosa). In addition, these studies clarify the clinical relevance of specific features.

Reward processing in BED
Given the frequent consumption of highly palatable foods during binge eating episodes, reward processing needs to be considered in BED. Several neuroimaging studies in BED demonstrate increased activity in prefrontal areas while viewing food stimuli. Specifically, food cues produce greater activity increases in the ventromedial prefrontal cortex/orbitofrontal cortex in individuals with BED than in healthy, overweight, or bulimic cohorts. This region not only processes multimodal information and encompasses the secondary taste cortex, but it also signals the motivational properties of food and other reinforcers, including drugs. Greater activity in the orbitofrontal cortex during food cue exposure relates to higher reward sensitivity, which supports the idea that individuals with BED are hypersensitive to the motivational and rewarding properties of food.

Structural differences are also observed in persons with BED: gray matter volume differences have been identified in the medial prefrontal regions in these individuals; this is similar to gray matter volume differences detected in substance-dependent populations. Palatable flavors (as compared with water) also stimulate greater responses in reward neurocircuitry, including the orbitofrontal cortex, insula, and striatum, in compulsive overeaters. Specifically, high-calorie foods (eg, chocolate milk) produce stronger connectivity between the ventral striatum and other reward regions, relative to water. Higher binge eating scores relate to stronger ventral striatal connections and provide mechanistic information on how BED features might relate to
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reward-related learning mechanisms. A reward system that is hyperresponsive to food/taste cues is consistent with the incentive-sensitization hypothesis in addiction that posits that addiction-related cues stimulate and eventually hijack reward neurocircuitry. A large body of research demonstrates that the striatum (particularly the ventral component including the nucleus accumbens) signals reward anticipation. In persons with addictions, the striatum is involved with craving. Understanding whether similar parallels in craving occur in BED and how these may be altered across the course of the disorder is important for future directions.

Understanding responsiveness to non-food reward is also important because generalized reward processing disturbances may play a role in the etiology and maintenance of BED. In contrast to food cues, non-food reward cues (eg, monetary) produce relatively reduced frontostriatal responses in persons who have BED relative to those who do not have BED. Differences in insula activity are also seen in persons with BED. Given the importance of this area in interoceptive processing and homeostatic signaling, individuals who have BED may have difficulties integrating reward information with their bodily state. In persons with BED, anticipation of monetary reward also generates a diminished response in the ventral striatum, relative to non-BED obese individuals. This finding is particularly noteworthy because it parallels reduced anticipatory striatal processing reported in pathological gambling and alcohol-dependent populations, thereby supporting the idea of similar neural alterations underlying reward processing across the disorders. Longitudinal studies will help clarify whether reduced anticipatory processing represents a precursor for BED development. Nonetheless, these neuroimaging findings are consistent with the idea of a reward deficiency syndrome in persons with BED similar to that proposed in individuals with drug addictions. These findings suggest that blunted reward responsivity may promote the stimulation of the system through behaviors such as drug use, or in the case of BED, eating. In addition, these studies highlight important differences between obese subgroups. Obese individuals with BED and non-BED obese individuals demonstrate significantly different neural responses; therefore, collapsing across obesity subtypes risks obscuring important differences.

Another recent neuroimaging study used brain activation patterns to discriminate various disordered eating groups. Persons with BED had differential activation of insular, striatal, anterior cingulate cortex, and orbitofrontal cortex regions compared with obese non-BED persons, lean controls, and bulimic patients. In this way, increasing evidence supports distinct neurofunctional patterns that discriminate between diagnostic conditions and clinical features.

**Cognitive control in BED**

A reduced ability or willingness to control the amount of consumption and the frequency of substance intake is a cardinal feature of both addiction and BED. Substance-dependent populations demonstrate reduced recruitment of prefrontal areas during cognitive-control tasks. However, few studies have examined the neurobiological underpinnings of cognitive-control characteristics in BED.

One pilot study of generalized inhibitory processing found diminished activity in frontal areas, such as the orbitofrontal cortex and the inferior frontal gyrus—which subserve self-regulation and inhibitory control—in persons with BED relative to non-BED obese and lean cohorts. Group differences observed here appear driven by the BED group, supporting the idea for distinct cognitive-control differences in BED compared with other forms of obesity. The levels of eating restraint reported in the BED group were related to diminished orbitofrontal cortex and inferior frontal gyrus activity; in contrast, the non-BED obese and lean cohorts demonstrated positive relationships between eating restraint and recruitment of these brain areas. These results demonstrate that within the BED group, there is reduced recruitment of brain areas important for inhibitory control.

Further research is necessary, but these findings nonetheless demonstrate parallel findings with both substance-based and non–substance-based addictive disorders (eg, gambling). And, they support the idea that the ventromedial prefrontal cortex/orbitofrontal cortex areas may contribute to inhibitory-control problems across BED and addictions.

**BED treatments and early neuroimaging findings**

Emerging evidence suggests that effective addiction treatments might have relevance and may also prove therapeutic for BED. Naltrexone, an opioid antagonist, has been found to reduce cravings and prevent relapse in alcohol dependence. There is some evidence that naloxone, an opioid antagonist, curtails the duration and magnitude of binge eating episodes. In lean and obese binge eaters, the drug suppresses consumption of high-fat and sugary foods. Similarly, another opioid antagonist—GSK1521498—selectively reduces attentional bias for food cues as well as hedonic...
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In one of the first pharmacological imaging studies, Cambridge and colleagues examined the effects of an opioid antagonist on food-cue response in obese individuals with moderate binge eating symptoms and found reduced striatal (pallidum/putamen) response to highly palatable food-cue images. This study highlights this area as a hedonic hot spot whereby the opioid antagonist disrupts motivational response to food while leaving the hedonic (subjective ratings) unaffected. These converging lines of evidence suggest the potential utility of testing naltrexone and other opioid antagonists as BED treatment. It must be noted, however, that one randomized clinical trial failed to show that naltrexone had a specific effect relative to placebo for improving eating disorder pathology in women with alcohol dependence. Collectively, however, these early studies suggest that distinct neural systems may underlie motivational versus consumptive aspects of food, and this may prove important for developing treatments targeting core BED characteristics.

Striatal and prefrontal areas emerging as distinguishing BED characteristics also suggest potential dopaminergic mechanisms, since these brain areas represent projection sites of this neurotransmitter. Indeed, dopamine transmission alterations in this reward neurocircuitry are implicated in the transition from substance use to addiction and potentially the shift from overeating to binging in BED. A positron emission tomography (PET) study that compared obese individuals with and without BED during food-cue presentations found increased striatal dopamine release following a methylphenidate challenge in the BED group. Interestingly, a higher binge eating score, but not BMI, was related to greater extracellular dopamine release in the caudate during the food stimulation task. This suggests a role for dopamine transmission in binge eating symptomatology rather than weight per se. Thus, striatal dopamine neurotransmission appears important in motivated food behavior, with altered signaling during incentive processing potentially contributing to BED symptomatology.

Controlled treatment studies have found that several pharmacotherapies appear to be effective in BED for reducing binge eating over the short term. However, the longer-term effects of medications for BED are largely unknown or have not yet been shown. Of the various medications tested for BED, some have not been effective and most have not produced significant weight losses (obesity is not a required feature of the BED diagnosis but is often a comorbid physical problem and weight loss is often considered as a secondary outcome). Two notable exceptions, topiramate and lisdexamfetamine, showed significant and substantial reductions in both binge eating and weight. This year, the FDA approved lisdexamfetamine, a dopamine-norepinephrine reuptake inhibitor originally used in the treatment of ADHD, for BED; this is the only FDA-approved medication for BED (fluoxetine is FDA-approved for bulimia nervosa). However, the efficacy and safety of lisdexamfetamine for obesity have not been established, and the product labeling states that lisdexamfetamine is not indicated for weight loss.

Specific psychotherapies for BED have been shown to have durable effects for up to several years. Cognitive-behavioral therapy is the best established treatment for BED. Strong support also exists for interpersonal psychotherapy and certain forms of behavioral weight loss interventions. However, minimal weight losses have been reported despite robust improvements in core binge eating psychopathology. Combining medication and psychological approaches has generally not enhanced treatment outcomes. Collectively, although treatment research has identified effective approaches, improved interventions are needed because a sizeable minority of patients do not benefit sufficiently, and most patients fail to lose clinically meaningful weight. Few studies to date have applied neuroimaging to BED treatment; however, these already provide some information on potential treatment targets and mechanisms of treatments. For example, a recent pilot study showed how reward neurocircuitry recruitment relates to treatment outcomes: diminished activity in ventral striatal areas at the beginning of treatment related to persistent bingeing at the end of treatment. Individuals with BED who reported bingeing at the end of a treatment trial demonstrated significantly less activation within reward neurocircuitry (including the inferior frontal gyrus) to non-food reward cues at treatment onset. A study by McCaffery and colleagues also found a link between increased inferior frontal gyrus recruitment during food-cue exposure and sustained weight loss.

Future directions

One obvious difference between BED and addictive disorders is the role of the substance in the addictive cycle. Humans are dependent on food for survival. While substantial addiction research is devoted to examining molecular mechanisms of drugs on reward neurocircuitry, the effect of food on these brain regions is less clear. It has been posited that high-fat, -salt and -sugar combinations found in many processed foods may more closely resemble a drug and hijack reward
neurocircuitry. Food-drug boundaries may be blurry, since multiple addictive products are derived from natural products; for example, alcohol, an addictive substance, is a natural product from ripe and fermenting grapes that also contains nutrients and calories. More research is necessary for understanding how the hyperpalatability of certain foods may contribute to BED development. Given the general availability of hyperpalatable foods, some researchers suggest that intermittent access rather than the specific nutritional content of food may be a key factor in the development of bingeing behavior. Nonetheless, animal models suggest an interaction between the access schedule and particularly palatable substances (e.g., sugar), since repeated intermittent access to standard food does not necessarily develop into binge eating.

The escalation of binge eating episodes in BED is another behavioral trait that parallels addictive behaviors. In humans, the shift from overeating to BED may result from dopaminergic alterations similar to those seen in addiction. It is noteworthy that PET studies of persons with BED reported dopamine transmission alterations in the dorsal rather than ventral striatum. While the ventral striatum has been implicated in food-cue reward as well as drug-cue reward, the dorsal striatum has been implicated in habit formation and reinforcement of action. However, data also link the dorsal striatum to reward processing in addictions. Given the different patterns of connectivity of dorsal and ventral striatum, it will be important to understand how ventral and dorsal striatum contribute to BED and how dopaminergic processes may be involved. A challenging but important future direction will be understanding the neurobiology of intermittent access to hyperpalatable foods and how eating restraint may lead to bingeing.

To date, the handful of imaging studies conducted in persons with BED already demonstrate divergent neural substrates of this condition relative to other forms of disordered eating and obesity, substantiating the diagnostic autonomy of BED. This research is also beginning to demonstrate how specific subgroups of obese individuals show neurocircuitry alterations similar to those in other populations characterized by problems with impulse control. Understanding the neurobiological underpinnings of core BED features may clarify distinct and/or overlapping mechanisms with addictive disorders and guide treatment development efforts.

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