From Disordered Eating to Addiction: the "Food Drug" in Bulimia Nervosa

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ABSTRACT

The high prevalence of substance abuse in individuals with Bulimia Nervosa (BN) and the pervasive symptom substitution in many types of drug addiction suggest that a number of substances—including food—can impair an individual's self-control, even in the presence of negative consequences. Nonetheless, the neurobiological similarities between BN and drug addiction are not clearly established. This review explores how the specific eating patterns seen in BN (binge eating and purging, with intermittent dietary restriction) are particularly addictive and differentiate BN from other eating disorders and obesity. A number of peripheral and central biological aberrations seen in BN may result in altered reward sensitivity in these individuals, particularly through effects on the dopaminergic system. Neurobiological findings support the notion that BN is an addictive disorder, which has treatment implications.

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INTRODUCTION

Eating disorder research has generally focused on familial and environmental factors that contribute to the psychopathology in bulimia nervosa (BN). While the development of BN has been linked to past sexual abuse (Sanci, Coffey et al. 2008), weak social attachment (Lehoux and Howe 2007), low self-esteem (Meijboom, Jansen et al. 1999; Fairburn, Cooper et al. 2003), and a desire to lose weight (Haines, Kleinman et al.; Chernyak and Lowe 2010), less is known about the neurobiological factors that contribute to the *maintenance* of these maladaptive behaviors that persist despite adverse consequences.

The cardinal symptom of BN is binge eating—that is, the rapid consumption of an objectively large amount of food in a discrete period of time accompanied by a sense of lack of control or feeling that one cannot either restrain from eating, or stop once started (American_Psychiatric_Association 2000). Bingeing, in turn, is followed by a compensatory "purging" behavior such as self-induced vomiting. This cycle can occur anywhere from several times weekly to numerous times a day in what can be viewed as a psychological addiction to the binge and purge (Brisman and Siegel 1984).

Initially, the purging behavior may be motivated by a desire to lose weight. However, the purging that follows the binge in BN rarely results in significant (if any) weight loss. Studies have shown that reductions in binge eating, purging, and food restriction after treatment do not result in significant changes (i.e. weight gain) in Body Mass Index (BMI), as one might expect (Gendall, Bulik et al. 1999; Carter, McIntosh et al. 2004). On the contrary, higher frequency of purging actually predicts greater weight *loss* during treatment when the behavior is stopped (Gendall, Bulik et al. 1999). Results

from other studies support this notion that dieting behaviors do not maintain BN behaviors (Burton and Stice 2006). Thus, although sociocultural pressures to be thin may initiate bulimic behaviors, other factors must contribute to the maintenance of BN when weight loss is not accomplished. It is plausible that neurobiological substrates affected in drug addiction perpetuate the binge-purge cycle in BN.

Substance abuse disorders are commonly coincident with BN. Between 30 and 50 percent of individuals with BN abuse or are dependent on alcohol or drugs (Mitchell, Hatsukami et al. 1985; Beary, Lacey et al. 1986; Hall, Beresford et al. 1989; Holderness, Brooks-Gunn et al. 1994; Striegel-Moore, Garvin et al. 1999; von Ranson, Iacono et al. 2002; O'Brien and Vincent 2003) compared to approximately nine percent in the general population (SAMHSA 2004). Up to 35 percent of individuals who abuse or are dependent on alcohol or drugs also have an eating disorder (Beary, Lacey et al. 1986; Krahn 1991; Mitchell, Fletcher et al. 1992; Holderness, Brooks-Gunn et al. 1994), compared to about 1.6 percent in the general population (Hudson, Hiripi et al. 2007).

Bulimia Nervosa and drug addiction both exhibit mood altering effects, environmental cueing, reinforcement, craving, compulsion and loss of control (Rogers and Smit 2000). The high prevalence of substance abuse in individuals with BN and the pervasive symptom substitution in many types of addiction suggest that a number of substances—including food—have the capacity to impair an individual's inhibitory regulation and control over certain behaviors, even in the presence of negative consequences. Still, the potentially addictive properties of food in the specific eating patterns of BN are not fully understood. Behavioral and epidemiological similarities between BN and drug addiction have been described (Rogers and Smit 2000; Benjamin

and Wulfert 2005), but only one study has directly explored neurological reward substrates in persons with BN (Wagner, Aizenstein et al. 2010).

Defining Addiction

Drug "addiction" is a condition characterized by compulsive drug intake, craving and seeking, despite negative consequences associated with drug use. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR, 2000) classifies addiction in terms of substance abuse or substance dependence. Substance dependence (SD) may be considered a more severe form of addiction and as such, diagnostic criteria are more stringent.

The American Psychiatric Association (DSM-IV-TR) defines "substance dependence" as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
(a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect *or*
(b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
(a) The characteristic withdrawal syndrome for the substance *or*
(b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent

physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Even using the more conservative criteria, BN meets the definition for an addiction disorder, both psychologically and neurochemically. Although only three of these criteria are required for a diagnosis of SD, BN putatively possesses all seven. Common to BN and SD is an underlying compulsion to engage in the 'drug' using activity even in the presence of injurious consequences. In BN, these consequences include (but are not limited to) gastroesophageal reflux disorder, tooth decay, renal failure, cardiac arrhythmia, and even death (Yasuhara, Naruo et al. 2005; Casiero and Frishman 2006; Mitchell and Crow 2006). Despite knowledge of the consequences of the disorder, individuals with BN persist in the binge-purge cycle, fulfilling criteria 7 for substance dependence. Although many seek treatment, more than 50% end up in relapse (Keller 1992; Field, Herzog et al. 1997), consistent with "unsuccessful efforts to cut down or control substance use" (criteria 4). Indeed, loss of control when trying to moderate eating is a key feature of BN (Fairburn 1983). During a meal, individuals with BN may try to eat smaller portions, but end up eating much larger amounts than intended (criteria 3), transitioning them into a binge (Hall and Cohn 1999). The subsequent binge-purge cycle can take up to several hours and is repeated multiple times a day for some individuals, clearly fulfilling the time requirement (criteria 5) for substance dependence (Stavrou 2008). The amount of time (and money) dedicated to bulimic behavior (obtaining binge foods, finding a secretive place to consume and purge the food, and recovering from the post-purge hypoglycemia) significantly impacts other activities, estranges social relationships, and diminishes job performance (Brisman and Siegel 1984;

Keilen, Treasure et al. 1994), pursuant to criteria 6 for substance dependence. The persistence of bulimic behaviors despite harmful consequences could be explained by the tolerance and withdrawal phenomena that develop as the disease progresses.

NEUROBIOLOGY OF BULIMIA NERVOSA AND LINKS TO ADDICTION

Reinforcement

The mesolimbic dopaminergic system is centrally involved in the acute positive effects of a number of rewarding stimuli, including drugs of abuse (Hoebel 1985; Di Chiara and Imperato 1988; Di Chiara 1999). Microdialysis and positron emission tomography (PET) studies show that illicit drugs increase extracellular DA preferentially in the ventral striatum—particularly in the nucleus accumbens (NAc) area—in rats, non-human primates, and humans (Panksepp 1998; Di Chiara 2002). As such, increased DA release could be a crucial mechanism for reinforcement of rewarding stimuli (Di Chiara and Imperato 1988; Koob and Bloom 1988; Pontieri, Tanda et al. 1995). The subjective perception of pleasure varies among individuals based on the degree of dopaminergic activity the stimulus/drug evokes, with greater DA release associated with a more euphoic "high" (Volkow, Wang et al. 1999). In their study, the intensity of the "high" induced by methylphenidate was significantly correlated with the levels of released DA (Volkow, Wang et al. 1999). Thus, the subjects who reported the most intense "high" were those who had the greatest increase of DA release.

In principle, food should have similar properties of reinforcement if bulimic behavior (i.e. binge eating) belongs within the framework of addiction. Food does release DA in the NAcc (Hernandez and Hoebel 1988; Tanda and Di Chiara 1998;

Hoebel, Rada et al. 1999; Hajnal, Smith et al. 2004; Avena, Rada et al. 2006). Palatable food (high sugar or sugar/fat) in particular causes even greater DA release (Martel and Fantino 1996). In fact, orosensory properties of sweet foods alone can invoke this reward effect. For example, rats that are fed saccharine, an artificial sweetener (Mark, Blander et al. 1991), or are 'sham fed' sucrose using gastric cannulas to empty stomach contents (Avena, Rada et al. 2006) still exhibit significant rises in accumbens DA despite the lack of postingestive effects or macronutrient absorption. Hajnal, Smith, and Norgren (2004) demonstrated the same effect of sweet taste on NAc DA when rats obtain sucrose by merely licking (Hajnal, Smith et al. 2004). These findings indicate that sweet taste alone is enough for reinforcement, which has important implications for BN in which macronutrient absorption is attenuated due to purging.

Moreover, accumbens DA increases as a function of sucrose solution concentration, with the sweetest solution evoking the greatest overflow of DA (Nissenbaum and Sclafani 1987; Hajnal, Smith et al. 2004). This suggests that "sweeter" foods are more. Individuals with BN appear to have a heightened subjective response to sweet taste (Rodin, Bartoshuk et al. 1990; Franko, Wolfe et al. 1994) and frequently claim to crave sweets (Mitchell, Pyle et al. 1981; Drewnowski, Bellisle et al. 1987; Wurtman 1988). Given the reinforcing properties of sweet taste, BN individuals might be predisposed to repetitive use (and in turn, heightened reinforcement) of high sugar binges. In fact, women with BN have reported popular binge foods to be sweet desserts, such as cake and ice cream, and have a heightened preference for sweets as compared to non-binging controls (Abraham and Beumont 1982; Drewnowski, Bellisle et al. 1987; Drewnowski 1989).

A possible difference between drugs of abuse and food is that drugs (i.e. opiates, cocaine, methamphetamine) can increase extracellular DA with every administration (Pothos, Rada et al. 1991; Wise, Newton et al. 1995), while food-induced increases in DA usually wane with additional intake of the same substance (Di Chiara and Tanda 1997; Bassareo and Di Chiara 1999). However, sweet foods can persistently increase accumbens DA in a fashion similar to addictive drugs using an intermittent eating pattern (Colantuoni, Rada et al. 2002; Rada, Avena et al. 2005). This feeding paradigm has been shown to create dependency (Colantuoni, Rada et al. 2002), as indicated by withdrawal signs such as teeth chattering and fear sensitivity. Other feeding models used as controls included: *ad libitum* feeding with chow; intermittent feeding (12-hour access/12-hour deprivation) with chow; and *ad libitum* feeding with chow and sucrose solution (Rada, Avena et al. 2005). All three control groups underwent 12-hour deprivation prior to feeding on testing days to control for any effects of energy depletion on microdialysis samples. Only the intermittent sucrose feeding group showed persistent increase in DA as demonstrated on day 21 of testing, while the control groups showed a blunting in DA response compared to day 1. This feeding schedule is consistent with the eating patterns seen in BN where individuals restrict intake early in the day and then binge later in the evening, usually on palatable foods high in sucrose (Drewnowski, Krahn et al. 1992; Gendall, Sullivan et al. 1997).

Palatable foods may also produce reinforcement through the opioid system. Like drugs of abuse (Schulz, Wuster et al. 1980; Koob and Bloom 1988; Hollt and Horn 1989; Kreek 1992), food (especially sweet/high fat) is associated with the release of endogenous opioids (Dum, Gramsch et al. 1983; Kirkham and Cooper 1988; Colantuoni,

Schwenker et al. 2001; Colantuoni, Rada et al. 2002; Kelley, Bakshi et al. 2002; Nathan and Bullmore 2009). Moreover, palatable food can activate opioid receptors in the VTA and further stimulate DA releasing cells in the NAc (Tanda and Di Chiara 1998). The effects on consumption of palatable food (Sahr, Sindelar et al. 2008), as well as food-induced dopamine release in the accumbens, were attenuated by the opioid receptor antagonists, naltrexone (Taber, Zernig et al. 1998) and LY255582 (Sahr, Sindelar et al. 2008). In tests of individual preferences in rats, high saccharin preference is associated with higher intake of intravenous morphine and alcohol, two drugs that exert direct effects on the opioid system (Gosnell and Krahn 1992; Gosnell, Lane et al. 1995).

Given the similar neural substrates of acute reward in drugs of abuse and palatable foods, such reinforcement could induce compulsive bingeing—and ultimately, 'binge dependence', in individuals with BN. In addition to the reinforcing properties of the binge, purging may also reinforce BN behavior in an addictive manner. Specifically, vomiting may acutely increase endogenous opioids in BN individuals (Abraham and Joseph 1986). Moreover, the rise in acetylcholine (ACh) in the NAc during a meal is significantly reduced in sham-feeding rats (Avena, Rada et al. 2006). Increased Ach is involved in the satiation process when DA rises during food intake (Mark, Rada et al. 1992), and a blunted Ach response may heighten sensitivity to the increases in accumbens DA released while eating. Thus, purging may strengthen the rewarding dopaminergic release from binge eating. Taken together, the intermittent dietary restriction, followed by binge eating and purging of palatable foods, may result in neurobiological changes consistent with drug addiction in individuals with BN.

Dependence, Tolerance and Withdrawal

Even though the reinforcing effects of drugs may initiate drug taking behavior, repeated drug use often continues despite negative consequences, possibly due to long-term, neuromodulatory effects that persist beyond the "high" after acute administration. Chronic administration of drugs of abuse, such as cocaine, alcohol, and heroin, alters brain substrates of reward (Wang, Volkow et al. 1997; Moore, Vinsant et al. 1998; Volkow, Wang et al. 2000). Likewise, repetitive bingeing on sucrose, interspersed with dietary restriction, can cause long-term neurobiological changes in experimental animals similar to those seen in long term drug users.

With drugs of abuse, terminal regions of the mesolimbic DA system adapt by increasing D-1 receptor binding with stimulants, decreasing D-2 receptor sensitivity with opiates, and increasing mu-opioid receptor binding with both (Imperato, Obinu et al. 1996; Vanderschuren and Kalivas 2000; Unterwald, Kreek et al. 2001). Similarly, in "sugar-dependent" rats, food restriction followed by access to palatable food increases (i.e. sensitizes) mu-opioid and D1 receptor binding and decreases D2 receptor binding in limbic regions (Colantuoni, Schwenker et al. 2001; Bello, Lucas et al. 2002; Colantuoni, Rada et al. 2002). Other neurochemical changes reminiscent of drugs of abuse, such as increases in D3 receptor mRNA (Mash and Staley 1999; Spangler, Goddard et al. 2003), also occur in sucrose bingeing rats with intermittent access (Spangler, Wittkowski et al. 2004). Moreover, rats maintained on a food deprivation/refeeding schedule are more responsive to the hyperphagic effects of the kappa opioid agonist, butorphanol, suggestng that this pattern of binge eating may modulate the endogenous opioid system (Hagan and Moss 1991; Boggiano, Chandler et al. 2005). A decrease in enkephalin gene expression

in the NAc occurs in rats given restricted access to highly palatable food for two weeks (Kelley, Will et al. 2003). Chronic treatment with morphine produces a similar down-regulation of enkephalin gene expression (Uhl, Ryan et al. 1988; Georges, Stinus et al. 1999) and ethanol also decreases enkephalin expression when given to rats chronically (Cowen and Lawrence 2001).

Behavioral measures in these animals also indicate that palatable food has addiction potential similar to drugs of abuse. Animals sensitized to a particular drug of abuse will often show an increased locomotor response to a different drug of the same class ("cross-sensitization") (Pierce and Kalivas 1995; Itzhak and Martin 1999; Pontieri, Monnazzi et al. 2001). Importantly, drug cross-sensitization is also seen with palatable food, suggesting that both stimuli act on common neural circuitry (Bakshi and Kelley 1994; Avena and Hoebel 2003; Avena and Hoebel 2003; Avena and Hoebel 2003a; Avena and Hoebel 2003b; Avena, Carrillo et al. 2004). Amphetamine-sensitized rats showed sugar-induced hyperactivity and sugar hyperphagia, (Avena and Hoebel 2003b). Conversely, sugar-dependent rats have a heightened sensitivity to amphetamine (Avena and Hoebel 2003a). Cross-sensitization also occurs with alcohol, whereby sugar-dependent rats show enhanced intake of unsweetened ethanol (Avena, Carrillo et al. 2004).

Drug dependence is also marked by tolerance, in which the response to a drug decreases with repeated exposure such that larger doses are required to achieve the same effect (McSweeney, Murphy et al. 2005). This phenomenon may be due to decreased responsiveness of molecular mediators (Klaassen 2001). Tolerance is a key characteristic of all drug addictions (Davis and Carter 2009) and also occurs in sugar-dependent rats

(Colantuoni, Schwenker et al. 2001; Rada, Avena et al. 2005). BN individuals also report increases in binge size from onset of their disorder and tolerance may be responsible for escalating intake (Beth Persac LMFT, Leah Graves RD, Claudia Cooke LPC, personal communication, Oct 2010). These individuals use larger quantities of sweeteners and prefer more intensely sweet samples than do nonbingers (Drewnowski, Bellisle et al. 1987; Drewnowski 1990; Franko, Wolfe et al. 1994), perhaps indicating decreased sensitivity to sweet taste.

Another hallmark of drug addiction is the withdrawal phenomenon. Abstinence from drugs of abuse induces neurochemical changes, such as decreases in striatal D1 and D2 receptor mRNA (Georges, Stinus et al. 1999), decreased extracellular DA in the NAc (Acquas and Di Chiara 1992; Rossetti, Hmaidan et al. 1992), and an increase in accumbens acetylcholine (ACh) (Fiserova, Consolo et al. 1999). Similarly, sugar-dependent rats show a significant increase in extracellular ACh and a significant decrease in DA release in the NAc shell as compared to control groups during 36 h food deprivation (Avena, Bocarsly et al. 2008). This alteration in DA/ACh balance in the NAc is seen during withdrawal from drugs such as morphine, nicotine, and alcohol (Rada, Mark et al. 1996; Rada, Jensen et al. 2001; Rada, Johnson et al. 2004). It would be interesting to see if similar changes occur when only palatable food is withheld while still allowing access to regular chow during the “deprivation” period.

Acute abstinence from drugs of abuse also causes behavioral and psychological withdrawal symptoms. In murine models of addiction, these symptoms include increased fear sensitivity and anxiety (as measured by reduced time on the exposed arm of an elevated plus maze), ultrasonic vocalization, paw shakes, and teeth chattering (File,

Andrews et al. 1993; Dawson and Tricklebank 1995; London, Kimes et al. 1995; Mutschler and Miczek 1998; Salas, Main et al. 2007). When food deprived for 24 hours, intermittent sucrose feeding rats also show somatic signs of withdrawal, including teeth chattering and paw shakes, and increased anxiety (Colantuoni, Rada et al. 2002; Wideman, Nadzam et al. 2005; Avena, Rada et al. 2008b). Control rats fed chow ad libitum do not experience these symptoms upon food deprivation. Furthermore, withdrawal symptoms can be induced pharmacologically in sugar dependent animals using the opioid antagonist naloxone, indicating alterations in the opioid system in sugar dependence (Colantuoni, Rada et al. 2002). Individuals with BN also display signs of drug withdrawal, such as increased anxiety, sleep disturbance, and craving (Brower, Maddahian et al. 1988) during abstinence from bingeing. Although human evidence for "sugar withdrawal" is largely anecdotal, there are consistent reports of headaches, irritability, anxiety, and flu-like symptoms among heavy sugar consumers who become abstinent (Davis and Carter 2009; Ifland, Preuss et al. 2009). Given that relapse among drug users often occurs to avoid unpleasant withdrawal symptoms, the high relapse rate among individuals with BN suggests a role for withdrawal symptoms in precipitating relapse.

Animal models of BN have limitations. First, the time course for "chronic" binge eating in rodents is 2-3 weeks, while the duration of illness in humans is usually years. Second, the psychological component of BN is impossible to mimic in animals. Although some stress-induced models of binge eating have addressed some of the environmental precipitants of BN, they do not incorporate long term comorbidities such as depression and anxiety and complex interactions with factors in social history. Thus,

the translational nature of findings from rodent models is limited and must be interpreted with caution.

Dopamine and Reward sensitivity in BN

A number of clinical and genetic studies indicate that individuals with BN may have aberrant dopamine activity. Frequently-bingeing (14 times/week) BN patients have reduced levels of the dopamine metabolite homovanillic acid (HVA) in cerebrospinal fluid and decreased plasma HVA concentrations (Jimerson, Lesem et al. 1992). Studies of peripheral dopamine metabolites support these findings for frequently (1x/day) binging patients (Kaplan, Garfinke et al. 1989; Kaye, Ballenger et al. 1990). However, after treatment and normalization of eating behaviors, HVA concentrations in recovered bulimics are similar to healthy controls with no eating disorder history (Jimerson, Lesem et al. 1992). Therefore, these lower levels could be a state-dependent phenomenon, possibly resulting from down-regulation of an overstimulated dopamine system during binge eating.

Aberrations in the dopamine transporter (DAT) have been described in individuals with BN. The disorder is associated with the short s allele of the DAT gene (Shinohara, Mizushima et al. 2004), confering lower transporter binding (Heinz, Goldman et al. 2000). This short *s* allele polymorphism is also significantly associated with substance abuse disorders (Sander, Harms et al. 1997; Jorm, Henderson et al. 2000). Based on single photon emission computed tomography (SPECT), subjects with BN have reduced striatal DAT availability compared to healthy controls, and this difference is more pronounced with longer duration of illness (Tauscher, Pirker et al. 2001). However,

peripheral levels of DAT are significantly higher in individuals with BN compared to healthy controls (Frieling, Romer et al. 2010). This could reflect a difference in central versus peripheral DA signaling. Alternatively, levels of DAT may upregulate as the illness progresses to compensate for repeated DA surges during years of bingeing.

Peripherally, individuals with BN have been shown to have reduced D2 receptor gene subscript which may be indicative of central receptor levels (Frieling, Romer et al. 2010). Individuals with lower levels of D2 receptors may be hyporesponsive to reward, consistent with the "reward deficiency syndrome" (Blum, Braverman et al. 2000; Wang, Volkow et al. 2004). On the other hand, lower receptor density could result in excessive dopamine release in response to reward in susceptible individuals. Along these lines, individuals with BN could putatively have heightened sensitivity to food reward. Wagner and colleagues have demonstrated altered striatal response to reward in BN using fMRI (Wagner, Aizenstein et al. 2010). Interestingly, reward sensitivity in BN significantly correlates with the average weekly frequency of purge, with individuals purging more often having heightened sensitivity (Farmer, Nash et al. 2001).

Peripheral hormones

Dopaminergic function and reward sensitivty in patients with BN may be indirectly altered through systemic signals, such as ghrelin and insulin, in individuals with BN. These homeostatic regulators of food intake may also be implicated in hedonic eating and reward functioning. Insulin receptors are present in reward centers of the brain (i.e. VTA) (Unger, Livingston et al. 1991) and insulin increases mRNA levels and synaptic activity of DAT both in vivo and in vitro (Figlewicz, Szot et al. 1994; Patterson,

Brot et al. 1998). This suggests that increased insulin may decrease DA signaling, and an attenuated insulin response could enhance DA transmission, perhaps augmenting reward sensitivity to DA releasing agents such as palatable food and drugs. BN patients who binge/purge frequently have a blunted insulin response to an oral glucose challenge (Russell, Hooper et al. 1996) and decreased insulin sensitivity (Kiriik, 1990) similar to heroine addicted subjects (Ceriello, Giugliano et al. 1987). With a diminished insulin response, food intake in BN may result in greater acute DA release, thereby enhancing reward sensitivity to food and strengthening the reinforcing properties of binge eating. BN subjects also have diminished insulin production after purging (Johnson, 1994), which may further reinforce the maladaptive behaviors.

On the other hand, some investigators have described an exaggerated insulin response to a glucose challenge in purging BN individuals (Russell, Hooper et al. 1996; Yasuhara, Tatebe et al. 2004) similar to that seen in alcoholics (Leggio, Ferrulli et al. 2008). If increased insulin results in diminished DA activity, this supports the "reward deficiency" hypothesis whereby reward seeking behaviors (i.e. binge eating) compensate for low DA (Blum, Braverman et al. 2000; Comings and Blum 2000). These two theories may be reconciled by recognizing that both ends of the reward sensitivity spectrum could predispose an individual to addiction.

Another peripheral hormone altered in individuals with BN is ghrelin. This molecule enhances appetite and increases food intake (Wren, Seal et al. 2001a; Wren, Small et al. 2001b) and is negatively associated with BMI, with obese individuals having lower circulating levels (Gautier, Chen et al. 2000; Shiiya, Nakazato et al. 2002). Ghrelin levels generally increase before meals and decrease afterwards, but in individuals with

acute BN, basal ghrelin levels are higher (Tanaka, Naruo et al. 2002; Tanaka, Naruo et al. 2003; Kojima, Nakahara et al. 2005) and postprandial ghrelin suppression is attenuated (Kojima, Nakahara et al. 2005; Monteleone, Martiadis et al. 2005). These differences are not confounded by differences in body weight. Furthermore, the ghrelin response at the onset of a meal is significantly greater in BN subjects, and positively correlates with the severity of patients' illness (Monteleone, Serritella et al. 2010). Individuals with BED (even without comorbid obesity) have lower than normal circulating levels of ghrelin (Geliebter, Yahav et al. 2004; Monteleone, Fabrazzo et al. 2005), highlighting that the binge eating in BN may be marked by distinct biological patterns.

The increased ghrelin response in BN may be linked to the mesolimbic reward circuitry crucial to addiction. Ghrelin can increase NAc dopamine levels (Jerlhag, Egecioglu et al. 2006; Jiang, Betancourt et al. 2006) and increase dopamine neuronal activity in the VTA (Abizaid, Liu et al. 2006). Enhanced ghrelin activity during food intake could therefore heighten the rewarding effect of binge eating in BN.

Opioids and Serotonin

Individuals with BN have lower levels of β-endorphin, the endogenous opioid (Brewerton, Lydiard et al. 1992), and μ-opioid receptor binding in the insular cortex is decreased in BN subjects (Bencherif, Guarda et al. 2005). The insular cortex is repeatedly implicated in other reward-driven behaviors, including drug abuse (Garavan, Pankiewicz et al. 2000) and gambling (Elliott, Friston et al. 2000). This downregulation could be a compensatory response to repeated bingeing. In cocaine-dependent (Zubieta, Gorelick et al. 1996) and alcohol-dependent subjects (Heinz, Reimold et al. 2005), drug

abstinence is associated with an upregulation of μ-opioid receptor binding that is proportional to drug craving. BN individuals could experience a similar phenomenon while abstaining from the binge-purge cycle for periods of time.

Opioid antagonists (i.e. naloxone, naltrexone) reduce binge eating in this population (Jonas and Gold 1986a; Jonas and Gold 1986b; Jonas and Gold 1987; Drewnowski, Krahn et al. 1995; Marrazzi, Kinzie et al. 1995a; Marrazzi, Bacon et al. 1995b), with apparently selective suppression of ingestion of highly palatable foods (i.e. common "binge" foods) (Fantino, Hosotte et al. 1986; Drewnowski, Krahn et al. 1995; Yeomans and Gray 2002). In one study, the difference was only significant in BN subjects as compared to non-binging controls, whether lean or obese (Drewnowski, Krahn et al. 1995). Opioid antagonists are also effective in treating other addiction disorders such as alcohol dependence (Volpicelli, Alterman et al. 1992; Mason, Ritvo et al. 1994; Swift, Whelihan et al. 1994; Davidson, Palfai et al. 1999; Monti, Rohsenow et al. 1999), nicotine/tobacco dependence (Wewers, Dhatt et al. 1998; Hutchison, Monti et al. 1999), and heroine withdrawal (Hulse, Ngo et al.; Krupitsky, Zvartau et al.; Grinenko, Krupitskii et al. 2003). Nevertheless, as with substance abuse disorders, naltrexone is not effective for all individuals with BN (Mitchell, Christenson et al. 1989).

BN is also marked by serotonergic dysfunction in ill patients, as manifested by a blunted neuroendocrine response to a single administration of a serotoninergic agonist (Brewerton, Mueller et al. 1992; Goldbloom, Garfinkel et al. 1996; Jimerson, Wolfe et al. 1997; Levitan, Kaplan et al. 1997; Monteleone, Brambilla et al. 1998). Levels of 5-hydroxyindoleacetic acid (5-HIAA), a major serotonin metabolite, are reduced in the CSF of bulimic individuals, but only for frequently binging (i.e. twice daily) patients,

indicating that disease severity may be a factor in altered neurobiology (Jimerson, Lesem et al. 1992).

Imaging studies indicate increased 5-HT1A receptor binding in patients with active BN (Tiihonen, Keski-Rahkonen et al. 2004). Repeated amphetamine administration also increases 5-HT1A binding affinity in rodents (Bonhomme, Cador et al. 1995), possibly because of functional interactions between the dopaminergic and serotonergic systems. Serotonin may facilitate DA release, particularly in reward centers, such as the NAc and striatum (Benloucif and Galloway 1991; Parsons and Justice 1993; Yadid, Pacak et al. 1994; De Deurwaerdere, Bonhomme et al. 1996; Yoshimoto, Yayama et al. 1996; Hallbus, Magnusson et al. 1997). Therefore, serotonin disturbances seen in BN may alter reward sensitivity through their effects on mesolimbic dopamine pathways. As such, selective serotonin-reuptake inhibitors (SSRIs), the first line drug therapy for BN (Walsh and Devlin 1995), may act by modulating DA. If SSRIs enhance DA neurotransmission, they may augment hyporesponsiveness to reward.

Even after treatment and remission of symptoms, a number of serotonin alterations persist in the absence of medication. The increased 5-HT1A receptor binding seen in active BN also persists in patients recovered from BN (Kaye, Bailer et al. 2005; Bailer, Bloss et al. 2010). PET imaging with [18F] altanserin shows significant differences in 5-HT2A receptor binding, most pronounced in the medial orbital frontal cortex (OFC), between women recovered from BN and controls with no eating disorder history (Kaye, Frank et al. 2001). Orbitofrontal alterations have also been linked to drug addiction (Volkow, Fowler et al. 1999). Furthermore, recovered BN subjects have elevated CSF concentrations of 5-HIAA (Kaye, Greeno et al. 1998) and evidence of

reduced 5-HT transporter function (Steiger, Richardson et al. 2005). However, other studies suggest that serotonin aberrations may normalize after bulimic behaviors remit (Wolfe, Metzger et al. 2000).

IMPLICATIONS FOR TREATMENT

Redefining BN within the framework of addiction has implications for treatment approaches and insurance coverage. Currently, Cognitive Behavioral Therapy (CBT), in conjunction with antidepressant (SSRI) medication, is the customary treatment approach, but it is not uniformly effective. Programs targeted at addiction models, or pharmacological treatments with dopaminergic effects, might prove more beneficial. Case reports suggest that dopaminergic agonists, such as methylphenidate, attenuate bulimic symptoms without impacting body weight (Schweickert, Strober et al. 1997; Sokol, Gray et al. 1999; Drimmer 2003; Dukarm 2005), but controlled clinical trials are not available.

Davis and colleagues have suggested that BN individuals may benefit from a behavioral strategy—adopted from drug abuse therapy—known as "cue exposure with response Prevention" (CERP) (Jansen 1998; Davis and Carter 2009). This approach aims to extinguish the association between conditioned food stimuli (i.e. pleasant sight or smell of food) and the unconditioned stimuli (eating). Patients are exposed to food cues, but the response (eating) is prevented. This treatment has been shown successful in reducing cravings in small scale studies with binge eaters (Jansen 1998) and with substance abusers (Havermans, Mulkens et al. 2007). Other variations involve exposure to small amounts of "binge" foods, but subsequent binging and purging is prevented

(Jansen, Broekmate et al. 1992). However, this ERP paradigm does not seem to enhance CBT (Wilson, Eldredge et al. 1991), and some studies suggest that it may even have a deleterious effect on treatment outcome (Agras, Schneider et al. 1989). This may reflect the notion of "priming", in which the initial ingestion of a drug actually increases craving for the drug (Ludwig, Wikler et al. 1974; Jaffe, Cascella et al. 1989). Likewise, binges can be triggered by small amounts of palatable (high sugar/fat) foods (Wardle and Beinart 1981; Volkow and Wise 2005). Thus, from an addiction perspective, avoiding "trigger" foods altogether may be a more favorable approach (Davis and Carter 2009).

Insurance coverage may also be impacted by classifying BN as a form of substance dependence. Inpatient coverage is routinely granted for chemical dependency, but not for BN. Those plans that do offer some coverage put a cap on the length of stay at 15-30 days, while recommended treatment stays are longer. Furthermore, the percentage covered for BN is much less than that for drug dependency. The average out-of-pocket cost for residential treatment programs for eating disorders was $6692 per week in 1996 (Frisch, Herzog et al. 2006), while costs for residential chemical dependency treatment averaged only $370 per week in 2008 (Kaskutas, Zavala et al. 2008). Thus, recognizing BN as an addiction disorder may result in more affordable treatment coverage.

IS ALL DISORDERED EATING "ADDICTIVE"?

Recently, there has been a surge in research papers and media reports arguing that obesity may be a form of addiction (Liu, von Deneen et al.; Taylor, Curtis et al.; Riva, Bacchetta et al. 2006; Acosta, Manubay et al. 2008; Rapaka, Schnur et al. 2008;

Thornley, McRobbie et al. 2008; Volkow, Wang et al. 2008). The support for this argument largely comes from animal models of binge eating. However, most obese individuals are not classic binge eaters. Among obese individuals seeking weight loss treatment, only 1.3-30.1% of them have BED (Spitzer, Devlin et al. 1992; Basdevant, Pouillon et al. 1995; Vamado, Williamson et al. 1997; Hay 1998; Ramacciotti, Coli et al. 2000; Ricca, Mannucci et al. 2000). Obesity is usually associated with overconsumption, but intake may increase chronically throughout the day in the absence of marked binging. Although eating in general stimulates reward pathways, so does music (Blood and Zatorre 2001), humor (Mobbs, Greicius et al. 2003), attractive faces (Mobbs, Greicius et al. 2003), being in love (Noriuchi, Kikuchi et al. 2008), winning a prize (Breiter, Aharon et al. 2001), and other "pleasant" stimuli. Therefore, the general statement that "food is addictive" is erroneous. It is the compulsive binging pattern seen in BN that has the ability to confer addictive potential to food substances.

For individuals with BED, patterns of food consumption may more closely resemble an addictive disorder than that in obese individuals in general. However, the binge eating seen in BED is not typically followed by dietary restriction as it is in BN (Walsh, Kissileff et al. 1989; Nunez-Navarro, Jimenez-Murcia et al. 2010). Rada and colleagues (2005) have demonstrated that this pattern of binge eating (with rats given ad libitum access to sugar or chow) results in a blunted DA response that is typical of food and other natural rewards, but not of drugs of abuse (Rada, Avena et al. 2005). Only the sucrose bingeing rats with intermittent access displayed recurrent DA release, even after several weeks of sucrose exposure (Rada, Avena et al. 2005). Furthermore, greater DA release is seen when larger quantities of food are ingested (Martel and Fantino 1996) and

individuals with BN report significantly greater binge sizes than those with BED (Mitchell, Crow et al. 1998; Guertin 1999). Binges in BN and BED do not only differ in quantifiable calories ingested, but also differ in patterns of food selection, with bulimics prioritizing dessert foods first, while BED subjects consume more meat (Cooke, Guss et al. 1997). In rodents, the presence of sweet taste in binge foods may be crucial to developing dependence, as fat-bingeing rats do not develop opiate-like withdrawal after naloxone administration (Avena, Bocarsly et al. 2008; Avena, Rada et al. 2009).

Individuals with BN demonstrate more severe psychopathology than those with BED (van Hanswijck de Jonge, Van Furth et al. 2003; Nunez-Navarro, Jimenez-Murcia et al. 2010) and thus, the binging in these disorders may represent a continuum of clinical severity. This distinction may be analogous to differences in those who abuse alcohol versus those who are alcohol-dependent. Furthermore, the significant link between comorbid drug/alcohol addiction and BN does not seem to be present for BED (Wilson 1999; Dunn, Larimer et al. 2002). It is plausible that individuals with BN have distinct neurobiological permutations that put them at a greater risk for addiction than individuals with BED. This increased risk in BN may explain why non-drug rewards, such as palatable foods, have the capacity to highjack reward circuitry and transform disordered eating into addiction in these individuals.

FUTURE DIRECTIONS

Most of the aforementioned clinical studies are cross-sectional and thus, do not address the question of whether biological differences in BN patients preceded or developed subsequent to the onset of the subjects' disorders. More longitudinal studies

are needed. Furthermore, grouping purging versus non-purging bulimics into one cohort may mask the emergence of distinct subtypes of BN. Because some evidence suggests that individuals with BN are *hypo*-responsive to reward while other lines of research implicate a hypersensitive reward circuitry, it is plausible that BN may reflect two distinct disease states. Future studies could address this distinction by analyzing neurobiological findings as a function of reward sensitivity and determine whether the presence of purging predicts these differences. BN individuals who purge may have significantly larger binge sizes (Guertin 1999) and this could be manifested in differences in neurobiology.

Although PET studies looking at DA receptor binding have been performed in individuals with AN and obesity, none exist for individuals with BN. Plausibly, differences in reward functioning and hedonic evaluation of food would be reflected in either higher or lower receptor densities. Along these lines, fMRI of BN individuals during a palatable food challenge (where the food is actually ingested) would likely result in differential activation of limbic structures as compared to healthy, weight-matched controls. Degree of activation could also be correlated with subjective ratings of food pleasantness and individual scores on the reward sensitivity scale to better delineate between hypo- versus hyper- reward functioning.

CONCLUSIONS

BN individuals clearly possess propensities for addiction as demonstrated by the significant association between bulimia and substance abuse (Mitchell, Hatsukami et al. 1985; Beary, Lacey et al. 1986; Mitchell, Hatsukami et al. 1988; Hall, Beresford et al.

1989; Wilson 1992; Holderness, Brooks-Gunn et al. 1994; Striegel-Moore, Garvin et al. 1999; von Ranson 2002; O'Brien and Vincent 2003). Evidence of a common mechanism mediating the reinforcing properties of drugs and natural rewards supports the notion that certain eating patterns can impact behavioral and neurobiological substrates in a manner similar to addictive substances. These eating patterns are seen in BN (intermittent restriction, bingeing, purging). Although substance abuse is associated with a number of eating disorders, this association is greatest for BN and AN-BP (Bulik 1987; Walfish, Stenmark et al. 1992; Holderness, Brooks-Gunn et al. 1994; Kaye, Lilenfeld et al. 1996; Welch and Fairburn 1996), highlighting the importance of the binge-purge pattern. Moreover, severe bingeing is consistently linked to alcohol use (Krahn 1991; Piran and Robinson 2006a; Piran and Robinson 2006b), while purging behaviors predict the use of many substances including alcohol, cocaine, cigarettes, stimulants, and amphetamines (Wiederman and Pryor 1996; Ross and Ivis 1999; Franko, Dorer et al. 2005; Krahn, Kurth et al. 2005; Piran and Robinson 2006a; Piran and Robinson 2006b). Taken together, it is plausible that individuals with BN suffer from a form of food addiction. Recognizing BN as an addictive disorder has important ramifications for understanding of the disease process and development of new therapeutic treatment targets.

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