

Does a Shared Neurobiology for Foods and Drugs of Abuse Contribute to Extremes of Food Ingestion in Anorexia and Bulimia Nervosa?

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Is starvation in anorexia nervosa (AN) or overeating in bulimia nervosa (BN) a form of addiction? Alternatively, why are individuals with BN more vulnerable and individuals with AN protected from substance abuse? Such questions have been generated by recent studies suggesting that there are overlapping neural circuits for foods and drugs of abuse. To determine whether a shared neurobiology contributes to eating disorders and substance abuse, this review focused on imaging studies that investigated response to tastes of food and tasks designed to characterize reward and behavioral inhibition in AN and BN. BN and those with substance abuse disorders may share dopamine D2 receptor-related vulnerabilities, and opposite findings may contribute to "protection" from substance abuse in AN. Moreover, imaging studies provide insights into executive corticostriatal processes related to extraordinary inhibition and self-control in AN and diminished inhibitory self-control in BN that may influence the rewarding aspect of palatable foods and likely other consummatory behaviors. AN and BN tend to have premorbid traits, such as perfectionism and anxiety that make them vulnerable to using extremes of food ingestion, which serve to reduce negative mood states. Dysregulation within and/or between limbic and executive corticostriatal circuits contributes to such symptoms. Limited data support the hypothesis that reward and inhibitory processes may contribute to symptoms in eating disorders and addictive disorders, but little is known about the molecular biology of such mechanisms in terms of shared or independent processes.

Key Words: Addictive disorders, anorexia nervosa, bulimia nervosa, eating disorders, fMRI imaging, PET

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by pathologic eating behaviors and distorted body image. They have a narrow range of age of onset (early adolescence), stereotypic presentation of symptoms and course, and tend to be female gender-specific. Although often considered to be caused by psychosocial factors, recent studies have shown that genetic heritability accounts for approximately 50% to 80% of the risk of developing AN and BN (1,2) and contributes to neurobiological factors underlying these eating disorders (EDs) (3).

Two types of consummatory behavior are seen in AN and BN. Individuals with restricting-type AN lose weight purely by restricted dieting. Individuals with BN, who tend to maintain a normal body weight, alternate restricting with episodic binge eating and/or purging. In addition, some individuals have both AN and BN (AN-BN). For AN, there is an anxiety-reducing character to dietary restraint and reduced daily caloric intake (4–6), whereas eating stimulates dysphoric mood (7). For BN, negative affect, mood lability, and stress may trigger binge-eating episodes, and the binge and purge cycle may then serve to reduce dysphoria and/or anxiety (8–13).

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It has been argued that AN and BN share some common risk and liability factors because these disorders are often cross-transmitted in families, and transitions between AN and BN occur (14–17). Importantly, AN and BN tend to share certain temperament and personality traits, which often first occur in childhood before the onset of an ED and may create a vulnerability to developing one. These traits include anxiety (18), harm avoidance (19), perfectionism (20), obsessionality (21,22), and interoceptive deficits (23). Moreover, these traits persist after recovery (24).

In contrast, AN and BN tend to have opposite extremes of inhibitory self-control. Those with pure restrictor-type AN tend to be overcontrolled and overconcerned about consequences. They have long been noted to be anhedonic and ascetic, able to sustain self-denial of food as well as most comforts and pleasures in life (25). For example, those with AN have an enhanced ability to delay reward (i.e., show less reduction in the value of a monetary reward over time) compared with healthy volunteers (26). This enhanced cognitive control and ability to delay reward may help to maintain persistent food restriction. In contrast, individuals with BN and AN-BN tend to have poor impulse control; engage in greater novelty-, pleasure-, and stimuli-seeking behavior; and are less paralyzed by concerns with future consequences (23,24,27–29).

From another perspective, there have been efforts to characterize behavioral domains that represent these symptoms. A considerable literature shows that harm avoidance, a temperament trait (30) that contains elements of anxiety, inhibition, and inflexibility, is elevated in individuals who are ill and recovered from AN and BN (27). In addition, individuals with AN and BN have increased sensitivity to punishment (31), but those with AN have reduced sensitivity and BN have increased sensitivity to reward. Individuals with ED with bingeing and/or purging behavior also endorse greater sensation seeking than AN and control subjects, whereas those with AN tend to score lower on novelty seeking than BN subjects, providing further evidence that differences in reward sensitivity and/or behavioral inhibition may differentiate AN from BN, although what distinguishes shared and independent traits remains unclear (27).

Relationship of ED Traits to Substance Use

This issue explores the relationship between food and addiction and overlapping neural circuits of reward and self-control. AN and BN show patterns of extremes of self-control and food consumption that appear to extend to their use of alcohol and illicit drugs. That is, meta-analyses (32,33) show increased rates of drug and alcohol abuse in BN and decreased rates in AN. Because of space limitations, this review focuses on two areas of research in ED. First, we discuss dopamine (DA) positron emission tomography (PET) studies, because DA is considered a key to the rewarding effects of natural and drug rewards (34). Second, to characterize the role of reward, interoception, and executive control in AN and BN, this review focuses on functional magnetic resonance imaging (fMRI) studies that have used taste of foods, reward, or inhibition tasks.

Difficulties Untangling Cause from Consequence in EDs

Studies of EDs must consider the impact of malnutrition on brain function. For example, malnutrition in AN (3) is associated with changes in brain structure (e.g., reduction in gray matter, greater cerebrospinal fluid [CSF] volume, altered white matter integrity) and profound metabolic, electrolyte, and endocrine disturbances. Furthermore, studies in animals suggest that diet and weight can influence DA metabolism (35,36). One method of avoiding the confounding effects of abnormal nutritional status is to study those who have recovered (REC) from AN and BN, although it remains conjectural whether abnormal findings reflect traits or scars. Thus, cause and consequence of pathologic eating and the impact of malnutrition on neural processes in AN and BN remain a major methodological question.

DA Function in AN and BN

Several lines of evidence suggest that individuals with ED have altered striatal DA function. PET studies with the radioligand [¹¹C]raclopride find that REC AN patients have increased binding of DA D2/D3 receptors at baseline in the anterior ventral striatum (AVS) relative to control subjects (25,37). Because PET measures of [¹¹C]raclopride binding are sensitive to endogenous DA concentrations (38), this difference could be due to either a reduction in the intrasynaptic DA concentration or an elevation of the density and/or affinity of the D2/D3 receptors in this region. The former is supported by data showing that REC AN have a reduction of the DA metabolite homovanillic acid (HVA) in CSF. To our knowledge, no PET DA studies have been reported in ill AN.

Dorsal caudate and dorsal putamen DA D2/D3 binding potential (BP_{ND}) was positively and significantly associated with harm avoidance in REC AN/AN-BN patients (25) and in REC AN/AN-BN/BN patients (37). Importantly, rats characterized as risk averse (39) showed greater D2 mRNA expression in the dorsal caudate, supporting human studies suggesting that DA signaling in executive cortical striatal circuitry is related to risk of adverse consequences or inhibitory control (40,41) or anxiety (42). A study using PET [¹¹C]raclopride binding with amphetamine to assess endogenous DA production (43) found that DA release in the precommissural dorsal caudate (preDCA) was associated with increased anxiety in REC AN subjects. In contrast, control subjects showed euphoria associated with AVS DA release, consistent with many, but not all, control responses to amphetamine (44–46). Ingestion of palatable food is associated with striatal endogenous

DA release (47). If individuals with AN experience endogenous DA release as anxiogenic rather than hedonic, it may explain their pursuit of starvation, because food refusal may be an effective means of diminishing such anxious feelings in AN individuals.

In terms of DA studies in ill BN individuals, although CSF HVA levels were normal, two studies found reduced CSF HVA (48,49) was associated with increased frequency of binge behaviors in ill BN. A stimulant PET [¹¹C]raclopride paradigm (50) in ill BN subjects found a trend toward decreased mean D2/D3 receptor BP_{ND} in the posterior putamen and caudate and a significantly reduced/blunted DA release to the psychostimulant challenge in the anterior and posterior putamen. Similar to the CSF HVA studies, there was a statistically significant negative association between the frequencies of binge eating and vomiting and the striatal DA response. Studies overfeeding animals with a palatable high-energy diet have shown progressively worsening reward deficit with lower basal and evoked DA levels in the nucleus accumbens and reduced D2 striatal levels (for review see Kenny) (51). Thus, studies showing that binge behavior in ill BN is associated with reduced CSF HVA and DA release are consistent with these rodent studies. Importantly, REC BN and AN-BN have normal DA D2/D3 striatal binding (37) and CSF HVA levels, supporting the notion of being “addicted” to food (52). However, a study using a catecholamine-depletion design, points to reduced reward learning in REC BN (53). Whether this is a trait vulnerability or a scar creating a persistent dysregulation of the central catecholaminergic neurotransmitter systems is unknown.

There have been relatively consistent findings (54,55) of reduced PET [¹¹C]raclopride binding potential in the striatum, including the ventral striatum in those with substance abuse disorders. It is of potential relevance that decreased D2/D3 receptor binding has been found in obese subjects (51,56). There is some indication that ill BN individuals may have reduced striatal [¹¹C]raclopride binding, which raises the intriguing possibility that BN and substance abuse or obesity share DA D2 receptor-related vulnerabilities. As noted earlier, three studies have found correlations between reduced DA activity and increased binge and vomit frequency, although the cause and consequence between consummatory patterns and DA function remain conjectural. REC restricting-type AN subjects have increased AVS [¹¹C]raclopride binding, although data are also limited in this regard. This raises the provocative question of whether such opposite findings contribute to “protection” from substance abuse in AN. The reasons for possible striatal regional differences between AN and BN are not known. DA D2/D3 receptors are just one small part of a complex DA system that involves the interaction of a number of DA receptors and other molecules. There are differences within striatal regions in terms of the relative balance of D2 and D3 receptors (57), expression of the DA transporter (58), and DA D1 receptor density (59). Moreover, there are not homogenous regions in terms of function. For example, DA D2/D3 receptors show opposite roles in subregions of the nucleus accumbens (60). Finally, there is uncertainty regarding state effects of illness and whether these are secondary to extremes of dietary intake, premonitory and persistent traits, or scars. Considerable data show that AN individuals also have disturbances of serotonin systems. For a brief review, please see Supplement 1.

Higher-order Neural Processes Modulating Reward, Emotionality, and Inhibition

Data support the hypothesis (3) that AN and BN individuals have an imbalance within and/or between ventral limbic and

dorsal cognitive circuits. Specifically, a ventral limbic neural circuit, which includes the amygdala, anterior insula (AI), AVS, ventral regions of the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC), is involved in identifying rewarding and emotionally significant stimuli and for generating affective responses to these stimuli (61,62). A dorsal executive function neural circuit, which includes dorsal regions of the caudate, dorsolateral prefrontal cortex (DLPFC), parietal cortex, and other regions, is thought to modulate selective attention, planning, and effortful regulation of affective states (61,62). The ventral limbic and dorsal cognitive neural circuits are critically involved in inhibitory decision-making processes, especially involving reward-related behaviors. Together they process the reward value and/or affective valence of environmental stimuli, assess the future consequences of one's own actions (response selection), and inhibit inappropriate behaviors (response inhibition). Dysfunction within these regions has been proposed to be a key neural mechanism underlying altered behavioral regulation, reward regulation, or cognition found in addiction (63,64).

Reward and Interoceptive Function in Regard to Tasting Food in AN and BN

fMRI studies of appetitive behaviors in ED have used designs that either administer a taste of some food or present images of food. This review focuses on studies of taste because much is known about how tastes of food activate reward and interoceptive circuitry in healthy subjects (34,65). In brief, the AI is the primary gustatory taste cortex and thus responds to tastes of food (3). The AI, as well as the ACC and OFC, code the sensory-hedonic response to taste and innervate a broad region of the rostral ventral-central striatum (66–68), where behavioral repertoires are then computed. Thus, this network may play a crucial role in linking sensory-hedonic experiences to the motivational components of reward (66) as well as emotionality, providing conscious awareness of these urges (34,62).

Although there are relatively few neuroimaging studies of taste and interoceptive function in ED, the literature to date is relatively consistent between the ill and REC states, supporting the possibility that reward and interoceptive processing are trait characteristics. A study (69) that administered tastes of sucrose or water found that REC AN subjects showed lower neural activation of the insula, including the primary cortical taste region, and ventral and dorsal striatum to both sucrose and water compared with control subjects. Insular neural activity correlated with pleasantness ratings for sucrose in control women (CW), but not in AN subjects. A study (70) that used response to chocolate milk when hungry and satiated found that ill AN subjects had minimal insula response to the tastes of food when hungry. Administration of boluses of cream, water, and a noncaloric viscous taste (71) found that REC BN showed an exaggerated AVS response for the cream/water contrast compared with REC AN or CW. Considered together, these findings raise the intriguing possibility that individuals who undereat or overeat have an altered set point, and/or altered sensitivity for sensory-interoceptive-reward processes, when consuming palatable foods (65). Thus, the set point for under eaters may mimic a continuous state of satiety that limits interoceptive and reward processing, whereas over eaters may experience a more tonic state of subjective hunger and thus hyperactivate related brain circuits.

Recent studies in the field of obesity have highlighted the importance of anticipation in the neural response to food stimuli. For example, animal studies (72) show that following stimulus conditioning, DA neurons shift firing from the consumption of food to the anticipated consumption of food or to cues associated with food consumption. There are a number of studies using tastants in ED in which the design might elicit anticipatory responses. An associative learning task between conditioned visual stimuli and unconditioned sucrose taste stimuli (73) found that reward learning signals were greater in the ill AN and less in the obese participants compared with the control participants in the AVS, insula, and OFC, suggesting that brain reward circuits were more responsive in AN and less responsive in obese participants. In a complex design viewing and tasting alone/together pleasant/unpleasant stimuli that appeared to mix anticipatory and consummatory response (74), REC AN subjects had increased ventral striatal activity in response to sights and flavors of a pleasant stimuli (chocolate) and increased insula and posterior dorsal caudate response to flavors and sights of aversive foods when compared to control subjects. Taken together, these studies suggest AN may be highly responsive to stimulus cues, perhaps as a mechanism to predict and control the anxiety produced by stimuli that may be associated with subjective unpleasantness, similar to anticipatory sensitivity connected with stimulus avoidance found in highly anxious individuals (75).

Interestingly, a reciprocal processing pattern has been observed in BN individuals. Using a response to anticipated or tastes of chocolate milkshake (vs. tasteless solution) (76), ill BN women, in contrast to healthy control subjects, showed trends for hypoactivation in the right anterior insula in response to anticipated and in the left middle frontal gyrus, right posterior insula, right precentral gyrus, and right mid dorsal insula in response to consumption. A conditioned visual stimuli and unconditioned sucrose taste stimuli paradigm (77) found that ill BN individuals showed reduced brain response compared with control subjects for unexpected receipt and omission of taste stimuli, as well as reduced brain regression response to the temporal difference learning computer model generated reward values in insula, ventral putamen, amygdala, and OFC. These studies suggest that in contrast to AN, BN may be less sensitive to food cues, which may contribute to their tendency to overeat during binge episodes.

The imbalance of stimulus consumption and anticipation in AN and BN may suggest dysfunctional stimulus integration that could relate to the clinically observed disconnect between reported and actual interoceptive states. Key in this process is the insula, which is thought to code interoceptive prediction error and signaling mismatch between actual and anticipated bodily arousal, which in turn elicits subjective anxiety and avoidance behavior (78). A study of response to pain confirms a mismatch between anticipation and objective responses in REC AN subjects (79). That is, REC AN subjects, compared with control subjects, showed greater activation within right AI, DLPFC, and cingulate cortex during pain anticipation, and greater activation within DLPFC and decreased activation within posterior insula during painful stimulation. Greater anticipatory AI activation correlated positively with alexithymia (difficulty identifying emotions) in REC AN subjects, suggesting an altered ability to accurately perceive bodily signals persists after recovery. Such disturbances could be tied to the preponderance of alexithymia in AN (80), which also is related to increased insula activation and is thought to be tied to deficits in emotional processing (81).

Given that food is an inherently emotional stimulus in AN and BN, a mismatch between limbic hyperarousal and cognitive control may be tied to both interoceptive and emotional processing deficits in this population. For a discussion of anticipatory and consummatory mismatches in obesity and addictive disorders, please see [Supplement 1](#).

Reward and Inhibition Studies

A recent series of fMRI studies based on reward and inhibition tasks has explored the response of ventral and dorsal corticostriatal systems in AN and BN compared with control subjects to better understand the modulation of reward, emotionality, and behavioral inhibition. Using a monetary choice task to investigate response to positive and negative feedback, REC AN (82) and REC BN (83) subjects had a similar abnormal AVS response in that they failed to differentiate wins and losses compared with control subjects who distinguished positive and negative feedback. Animal studies show that the AVS processes motivational aspects toward stimuli by modulating the influence of limbic inputs on striatal activity (84,85) so that even abstract rewards (money) activate the AVS in proportion to the reward amount or the deviation from an expected payoff (86). This may indicate a failure in REC AN and REC BN individuals to appropriately bind, scale, or discriminate responses to salient stimuli, suggesting an impaired ability to identify the emotional significance of stimuli (83).

In addition REC AN also exhibited (82) an exaggerated response to positive and negative feedback in the dorsal caudate relative to CW as well as elevated activity in executive cortical regions (dorsal lateral prefrontal and parietal), which project to the dorsal caudate (67) and which were positively associated with baseline trait anxiety for both wins and losses. Using a set-shifting fMRI paradigm (87), ill AN subjects showed predominant activation of frontoparietal networks indicative of excessive effortful and supervisory cognitive control during task performance, but hypoactivation in the ventral anterior cingulate-striato-thalamic loop involved in motivation related behavior. Similarly, an increase in brain response in posterior visual and inferior parietal cortex regions was found in ill restricting type AN that correlated with correctly inhibited no-go trials (88). Using a stop signal task (89), REC AN subjects had altered task-related activation in the medial prefrontal cortex, a critical node of the inhibitory control network.

Together, these results support the possibility that individuals with AN have an imbalance in information processing, with impaired ability to identify the emotional significance of a stimulus but increased traffic in neurocircuits concerned with planning and consequences, which is associated with anxiety. This overreliance on cognitive brain circuits involved in linking action to outcome may constitute an attempt at “strategic” (as opposed to hedonic) means of responding to reward stimuli. Does this protect AN against substance abuse disorders? It is noteworthy that cognitive strategies that have been shown to effectively regulate craving are associated with increased brain response in dorsal-frontal-striatal regions associated with cognitive control and decreased brain response in ventral limbic striatal regions (90).

In contrast to the possibility that excessive inhibitory control may characterize AN, inhibitory control processes may be impaired in women with BN, likely because of their failure to engage frontostriatal circuits appropriately. For example, during correct responding on incongruent trials of the Simon Spatial

Incompatibility task (29,91), ill BN adolescents and adults failed to activate the left inferolateral prefrontal cortex, bilateral inferior frontal gyrus, lenticular and caudate nuclei, and ACC. They also demonstrated aberrant function of the dorsal ACC, activating it more when making errors than when responding correctly. In support of such a possibility, REC BN subjects (83) had abnormal responses to positive and negative feedback in the dorsal caudate. In comparison, ill AN-BN subjects (88) had increased activation of the right DLPFC using a Go-NoGo task, so it remains to be determined whether AN-BN and BN individuals have discrepant findings in terms of dorsal circuit activity. In summary, these findings provide evidence of functional abnormalities in BN within the neural system that subserves self-regulatory control, which may contribute to binge eating and other impulsive behaviors.

Summary

It remains conjectural whether years of pathological eating is the sole cause of aberrant neurobiology in AN. Whereas most people find starvation to be unpleasant and recidivism after dieting is high, AN individuals find that food is anxiety provoking and starvation comforting. If AN were merely a consequence of an out-of-control diet, the rate of AN in this society would probably be much higher. Alternatively, underlying traits may be contributory. For example, many of the characteristic temperament and personality behaviors typical of AN and BN are expressed in childhood, years before the onset of an ED, suggesting the importance of certain vulnerabilities. It is also possible that altered brain function results from both underlying neurobiological traits as well as years of pathologic behavior. There have been relatively few imaging studies published in ED, so there is a limited body of data regarding neural processes in ED. Limited data suggest that some abnormal brain processes are relatively similar in the ill and REC state, suggesting little influence of illness state. However, the prospective and longitudinal studies necessary to answer these questions definitively have not been done.

Although review studies raise the possibility that individuals with AN might be protected from, and BN vulnerable to, substance abuse, it is not known whether this is related to a shared biology with appetite regulation. Although few studies have been done, individuals with restricting-type AN have increased AVS [¹¹C]raclopride binding, whereas there are suggestions that individuals with BN have reduced striatal [¹¹C]raclopride binding. This raises the intriguing possibility that BN and substance abuse share DA D2 receptor-related vulnerabilities to the rewarding aspect of palatable foods or substance use, whereas opposite findings may contribute to “protection” from substance abuse in AN. In addition, individuals with AN have extraordinary inhibition and self-control, whereas BN have diminished inhibitory self-control. fMRI studies consistently show that AN and BN have altered activity of dorsal executive/cognitive circuitry, that tends to be consistent with the possibility that individuals with AN have enhanced higher-order inhibitory function and BN have reduced inhibition. We hypothesize that individuals with AN are able to inhibit consummatory drives and have extraordinary self-control because they have exaggerated dorsal cognitive circuit function, whereas BN individuals are vulnerable to overeating when hungry and use substances because they have less ability to self-regulate and control their impulses.

Despite these advances in the neurocircuitry of appetite, reward, and cognitive control, several questions remain regarding implications for EDs in the ill and recovered state. For example, what is the cause and effect between reward and inhibition? Studies of food tastes and negative and positive feedback consistently show altered ventral limbic circuitry in AN and BN. It is possible that individuals with both AN and BN have an inability to precisely identify and/or modulate emotionality and reward in response to salient stimuli. Poor context separation may make them vulnerable to inappropriately responding to the rewarding aspects of consummatory stimuli. Do individuals with AN have “normal” cognitive association networks in the dorsal neurocircuit (e.g., DLPFC to dorsal striatum) that directs motivated actions in the face of impaired ability of the ventral striatal pathways to direct more “automatic” or intuitive motivated responses? Alternatively, is otherwise adequate ventral limbic-striatal circuitry too strongly inhibited by “hyperactive” inputs from cognitive domains such as the DLPFC and the parietal cortex? For BN, is there hypoactivity of frontal cognitive pathways that is not sufficient to inhibit “normal” hedonic/incentive motivation impulses in “reward” neural circuits, or are there exaggerated hedonic/incentive motivation impulses in “reward” neural circuits that overwhelm normal cognitive inhibition? Discovering answers to some of these questions will bring us closer to developing effective pharmacologic and behavioral treatments for these deadly disorders.

Finally, the future of ED may well be in taking a dimensional approach using the research domains (92). ED research has shown functional brain deficits in all five of the primary research domains: negative valence systems (i.e., increased anxiety), positive valence systems (i.e., increased habit formation and decreased reward processing), cognitive systems (i.e., increased behavioral inhibition), systems for social processes (i.e., increased self and social evaluations), and arousal/regulatory systems (i.e., interoceptive deficits). Future research should take into account the changing landscape of how psychiatric disorders are conceptualized, for both the DSM-V and beyond, and should aim to measure the behavioral aspects of ED in a dimensional way such that these conceptual models can be better quantified and understood.

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Supplementary material cited in this article is available online.

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