Neurocircuity of Eating Disorders

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Abstract *Objectives*: This chapter reviews brain imaging findings in anorexia and bulimia nervosa which characterize brain circuitry that may contribute to the pathophysiology of eating disorders (EDs).

Summary of recent findings: Recent imaging studies provide evidence of disturbed gustatory processing in EDs which involve the anterior insula as well as striatal regions. These results raise the possibility that individuals with anorexia nervosa have altered appetitive mechanism that may involve sensory, interoceptive, or reward processes. Furthermore, evidence of altered reward mechanisms is supported by studies that suggest that individuals with anorexia nervosa and bulimia nervosa share a trait toward similar anterior ventral striatal pathway dysregulation. This shared trait disturbance of the modulation of reward and emotionality may create a vulnerability for dysregulated appetitive behaviors. However, those with anorexia nervosa may be able to inhibit appetite and have extraordinary self-control because of exaggerated dorsal cognitive circuit function, whereas individuals with bulimia nervosa are vulnerable to overeating when they get hungry, because they have less ability to control their impulses.

Future directions: Current therapeutic interventions have modest success. Better understanding of neurocircuits that may be related to altered appetite, mood, impulse control, and other symptoms underlying the pathophysiology of EDs might improve psychotherapeutic and drug treatment strategies.

Keywords Anorexia nervosa · Appetite regulation · Bulimia nervosa · Brain imaging · Interoceptive awareness · Reward

1 Introduction

The pathophysiology of anorexia nervosa (AN) and bulimia nervosa (BN) is poorly understood. The primary characteristic required for a DSM IV (Diagnostic and Statistical Manual of Mental Disorders) diagnosis of AN and BN is pathological eating: AN must restrict and lose weight, and BN must binge and purge. The complex appetitive symptoms displayed by AN and BN are relatively unique and tend not to be shared with other psychiatric disorders. The stereotypic presentation and relentless expression of these feeding behaviors supports the possibility that they reflect some aberrant function of appetitive pathways. In addition, many individuals with eating disorders (ED) have (1) extremes of behavioral inhibition and dysinhibition; (2) anxiety, depression, and obsessionality; and (3) puzzling symptoms such as body image distortion, perfectionism, and anhedonia. Data support the hypothesis that these behaviors tend to express in concert because they are likely to be encoded in limbic and cognitive circuits known to modulate and integrate neuronal processes related to appetite, emotionality, and cognitive control.

1.1 Confounding Effects of Malnutrition

When malnourished and emaciated, individuals with AN, and to a lesser degree BN, have alterations of brain and peripheral organ function that are arguably more severe than in any other psychiatric disorder; for example, enlarged ventricles and sulci widening (Ellison and Fong 1998), altered brain metabolism in frontal, cingulate, temporal, and parietal regions (Kaye et al. 2006), and widespread neuropeptide, hormonal, and autonomic disturbances (Boyar et al. 1974; Jimerson and Wolfe 2006; Kaye et al. 2009). Determining whether such symptoms are a consequence or a potential cause of pathological feeding behavior or malnutrition is a major methodological problem in the field. It is difficult to study EDs prospectively because of the young age of onset and difficulty in premorbid identification of people who will develop EDs. Neurobiological studies during the acute illness are confounded by the effects of malnutrition. Thus we have used a method of identifying behavioral phenotypes that are independent of the confounding effects of malnutrition by studying women who are recovered AN and BN.

1.2 Vulnerabilities That Create a Risk for Developing AN and BN

Recent studies show that certain childhood temperament and personality traits (Lilenfeld et al. 2006; Stice 2002; Anderluh et al. 2003; Fairburn et al. 1999) such as negative emotionality, harm avoidance, perfectionism, inhibition, drive for thinness, altered interoceptive awareness, and obsessive–compulsive personality create a vulnerability for developing AN and BN. Malnutrition tends to exaggerate these premorbid behavioral traits (Pollice et al. 1997) after the onset of the illness, with the addition of other symptoms that maintain or accelerate the disease process, including exaggerated emotional dysregulation and obsessionality (Godart et al. 2007; Kaye et al. 2004).

1.3 Recovered (REC) AN and BN Subjects

The process of recovery in AN is poorly understood and, in most cases, protracted. Still, approximately 50–70% of affected individuals will eventually have complete or moderate resolution of the illness, often in the early to mid-20s (Wagner et al. 2006a; Steinhausen 2002; Strober et al. 1997). It is important to emphasize that temperament and personality traits such as negative emotionality, harm avoidance and perfectionism, and obsessional behaviors persist after recovery from both AN and BN (Casper 1990; Srinivasagam et al. 1995; Wagner et al. 2006a;

Steinhausen 2002) and are similar to the symptoms described premorbidly in childhood. Compared to the ill state, symptoms in REC AN and BN tend to be mild to moderate, including elevated scores on core ED measures. Interestingly, REC AN and BN tend to be more alike than different on many of these measures, although there are some differences on factors related to impulse control or stimuli seeking, such as novelty seeking (Strober et al. 1997; Wagner et al. 2006a; Lilenfeld et al. 2006).

1.4 Persistent Alterations in ED Found in Brain Imaging Studies After Recovery

Studies from our group found that AN and BN after recovery show normalization of gray and white matter volume (Wagner et al. 2006b) and cerebral blood flow (Frank et al. 2007) and tend to have normal neuropeptide function (Kaye et al. 2009), suggesting that these factors are not the cause of persistent neurobiological disturbances. However, several studies in REC AN showed hypoperfusion of frontal, temporal, parietal, and occipital regions (Rastam et al. 2001; Gordon et al. 1997) as well as of frontal and anterior cingulate cortex (ACC) activation, in response to pictures of food (Uher et al. 2003), suggesting disturbances of limbic and cognitive neural circuits. Many studies suggest that disturbances of limbic and cognitive neural networks occur in a range of psychiatric disorders, such as major depression (Drevets 2001; Tremblay et al. 2005), anxiety disorders (Protopopescu et al. 2005; Stein et al. 2007; Wright et al. 2003), and obsessive–compulsive disorder (OCD) (Insel 1992; Saxena 2003). Specifically, a ventral neurocircuit (Phillips et al. 2003), which includes the amygdala, insula, ventral striatum, and ventral regions of the ACC and the prefrontal cortex (PFC), is necessary for identifying emotional significance of stimuli and for generating affective responses to these stimuli. These regions are also important for automatic regulation and mediation of autonomic responses to emotional stimuli and contexts accompanying the production of affective states. In comparison, a dorsal executive function neurocircuit, which includes the hippocampus, 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. It is possible that the altered emotional regulation or cognition found in all of these syndromes involves aberrant function of these circuits, but perhaps with different patterns on a molecular level (Phillips et al. 2003). In fact, neurobiological disturbances in EDs are different from those found in depression, anxiety, or OCD. For example, decreased 5-HT_{1A} receptor binding has been reported in ill (Drevets et al. 1999; Sargent et al. 2000) and recovered (Bhagwagar et al. 2004) depressed subjects, as well as those with social phobia (Lanzenberger et al. 2007) and panic disorder (Neumeister et al. 2004). However, increased 5-HT_{1A} receptor binding has been found in EDs (Kaye 2008).

1.5 Implications

We hypothesize that behaviors and abnormal physiology that persist after REC are a re-emergence of the vulnerabilities that created a risk for developing an ED. While it is possible that these findings could be "scars" caused by chronic malnutrition, several studies (Bulik et al. 2007) show that these factors are heritable, occur in unaffected family members, and are independent of body weight, which strongly support the argument that they are traits, not scars. Because no agreed-upon definition of recovery from AN or BN presently exists, our research studies employ a definition that emphasizes stable and healthy body weight for more than 1 year, with stable nutrition, relative absence of dietary abnormalities, normal menstruation, and free of medication. Because many individuals with AN and BN cross from one subtype to another over the course of their illness, it is not possible to investigate "pure" subtypes in the ill state. However, we can ascertain whether they had pure or mixed subtypes over the course of their illness once they have recovered. Thus we have studied pure subtypes of AN (REC AN; e.g., restricting- type who never binged or purged) or BN (REC BN; e.g., no history of AN).

2 Appetitive Regulation and AN and BN

Due to the puzzling nature of many ED symptoms, the ED field lags behind other psychiatric disorders in terms of progress in understanding responsible brain circuits and pathophysiology. Although AN and BN are characterized (APA 2000) as EDs, it remains unknown as to whether there is a primary disturbance of appetitive function. The regulation of appetite and feeding are complex phenomena, integrating peripheral signals (gastrointestinal (GI) tract, adipose tissue, hormonal secretion, etc.), hypothalamic factors (neuropeptides), cortical and subcortical processes (reward, emotionality, cognition), and external influences (Rolls 1997; Schwartz et al. 2000; Elman et al. 2006). While it is possible that a disturbance could occur anywhere in this axis in AN and BN, limbic and cortical brain circuits that contribute to appetite are of particular interest because these circuits (1) show persistent altered function after recovery and (2) code for rewarding and emotionality properties of food, homeostatic needs, and cognitive modulation (Elman et al. 2006; Hinton et al. 2004; Kelley 2004).

2.1 Studies of Altered Feeding Behavior in AN and BN

Relatively little data exist on appetite regulation in ED despite the prominent nature of these symptoms. Laboratory studies support clinical observations that individuals with AN dislike high-fat foods (Fernstrom et al. 1994; Drewnowski et al. 1988)

and BN tend to binge on sweet and high-fat foods (Kaye et al. 1992; Weltzin et al. 1991). These patterns of responses did not change following weight regain. Other studies (Garfinkel et al. 1978, 1979) reported altered interoceptive disturbances in AN in terms of the absence of satiety aversion to sucrose, and that these disturbances persisted after normalization of weight or failure to rate food as positive when hungry (Santel et al. 2006). In addition, there is evidence (Kaye et al. 2003; Strober 1995; Vitousek and Manke 1994) that there is an anxiety-reducing character to dietary restraint in AN. For BN, negative mood states and hunger may precipitate a binge (Hilbert and Tuschen-Caffier 2007; Smyth et al. 2007; Waters et al. 2001) and overeating may relieve dysphoria and anxiety (Abraham and Beaumont 1982; Kaye et al. 1986; Johnson and Larson 1982). Taken together, these studies support the possibility of an altered response to palatable foods and a dysphoria-reducing aspect to pathological eating.

2.2 *Brain Imaging Studies of Feeding Behavior in AN and BN Confirm Alterations in Limbic and Cognitive Circuits*

Neuroimaging studies using different techniques in emaciated and malnourished individuals with AN found consistently altered activity in the insula and orbitofrontal cortex (OFC), as well as in mesial temporal, parietal, and the ACC regions as compared to control women (CW) (Ellison et al. 1998; Gordon et al. 2001; Naruo et al. 2000; Santel et al. 2006; Uher et al. 2004). One functional magnetic resonance imaging (fMRI) study (Uher et al. 2003) found that pictures of food stimulated ACC and medial prefrontal cortex (mPFC) activity in both ill and REC AN individuals, but not CW. These findings suggest that hyperactivity of these regions may be a trait marker of AN.

2.3 *Neurocircuitry of Appetite Regulation*

Sweet taste perception (Fig. 1) is peripherally mediated by tongue receptors (Chandraskekar et al. 2006) through cranial nerves, the nucleus tractus solitarius, and thalamic ventroposterior medial nucleus, to the primary gustatory cortex, which in humans comprise the frontal operculum and the anterior insula (AI) (Ogawa 1994; Scott et al. 1986; Yaxley et al. 1990; Faurion et al. 1999; Schoenfeld et al. 2004). Projections from the primary taste cortex reach the central nucleus of the amygdala and, from there, the lateral hypothalamus and midbrain dopaminergic regions (Simon et al. 2006). The primary taste cortex also projects heavily to the striatum (Chikama et al. 1997; Fudge et al. 2005). The AI is contiguous with the posterior OFC at the operculum. This region is reciprocally connected with the mPFC and

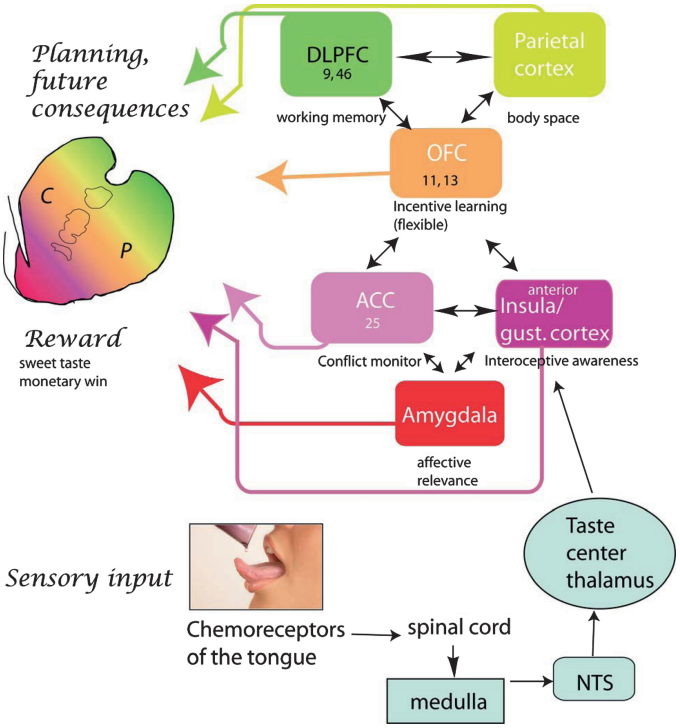

Fig. 1 *Schematic of cortical–striatal pathways with a focus on taste*. Chemoreceptors on the tongue detect a sweet taste. The signal is then transmitted through brainstem and thalamic taste centers to the primary gustatory cortex, which lies adjacent to and is densely interconnected with the anterior insula (AI). The AI is an integral part of the "ventral (limbic) neurocircuit" through its connections with the amygdala, the anterior cingulate cortex, and the orbitofrontal cortex. Afferents from the cortical structures involved in the ventral neurocircuit (AI and interconnected limbic cortices) are directed to the ventral striatum, whereas cortical structures involved in cognitive strategies (the dorsal neurocircuits) send inputs to the dorsolateral striatum. Thus, the sensory aspects of taste are primarily an insula phenomenon, whereas higher cortical areas modulate pleasure, motivation, and cognitive aspects of taste. These aspects are then integrated, resulting in an "eat" or "don't eat" decision. Coding the awareness of pleasant sensation from the taste experience via the AI might be altered in AN patients, tipping the balance of striatal processes away from normal, automatic reward responses mediated by the ventral striatum and toward a more "strategic" approach mediated by the dorsal striatum. The figure links each cortical structure with similarly colored arrows, indicating all cortical structures project to striatum in topographic manner. *ACC* anterior cingulate cortex; *DLPFC* dorsolateral prefrontal cortex; *NTS* nucleus tractus solitarius; *OFC* orbitofrontal cortex

ACC (Carmichael and Price 1996). The ventral striatum receives input from the AI and ACC (Carmichael and Price 1996; Fudge et al. 2005; Haber et al. 1995).

The AI and associated gustatory cortex respond not only to the taste and physical properties of food, but also to its rewarding properties (O'Doherty et al. 2001; Schultz et al. 2000; Small 2002). Some studies argue that the AI provides a

representation of food in the mouth which is independent of hunger and, thus, of reward value (Rolls 2005), whereas the OFC computes the hedonic value of food (O'Doherty et al. 2000; Kringelbach et al. 2003; Rolls 2005). Other studies (Small et al. 2001) suggest that the AI and OFC have overlapping representations of sensory and reward/affective processing of taste. The AI is centrally placed to receive information about the salience (both appetitive and aversive) and relative value of the stimulus environment and integrate this information with the effect that these stimuli may have on the body state. The AI has bidirectional connections to the amygdala, nucleus accumbens (Reynolds and Zahm 2005), and OFC (Ongur and Price 2000). The striatum (Kelley 2004) receives inputs from brain regions involved in reward, incentive learning, and emotional regulation, including the ACC, the ventromedial PFC, the OFC, and AI (Fudge et al. 2004, 2005; Haber et al. 2006; Chikama et al. 1997). The OFC is associated with flexible responses to changing stimuli (Izquierdo et al. 2004; Kazama and Bachevalier 2006) such as the incentive value, e.g., whether the animal is hungry (Critchley and Rolls 1996; Hikosaka and Watanabe 2000; Gottfried et al. 2003). Of note, the OFC is highly dependent on 5-HT innervation for flexible reversal learning (Clarke et al. 2007), so that 5-HT abnormalities in ED may contribute to the disturbed inhibitory control (inability to incorporate changing incentive value of stimuli). The information about the interoceptive state processed in the AI is relayed to the ACC, which, as part of the central executive system, can generate an error signal that is critical for conflict monitoring and the allocation of attentional resources (Carter et al. 1999). Thus, interoception involves monitoring the sensations that are important for the integrity of the internal body state and connecting to systems that are important for allocating attention, evaluating context, and planning actions (Paulus and Stein 2006). The role of the AI is thus focused on how the value of stimuli might affect the body state. Thus, these regions play an important role in determining homeostatic appetitive needs when hungry or satiated. In addition, interoceptive sensations are often associated with intense affective and motivational components (Paulus and Stein 2006), and the evaluative component of the signal is highly dependent on the homeostatic state of the individual.

2.4 Gustatory fMRI Studies

Our group (Wagner et al. 2008) administered tastes of 10% sucrose and water in a blind, controlled manner to individuals with REC AN and healthy CW. There were two main findings: (1) Compared to CW, the individuals with REC AN had a significantly reduced blood-oxygen-level dependent (BOLD) response to the blind administration of sucrose or water in the AI (Fig. 1, left insula $p = 0.003$), ACC, and striatal regions; (2) CW, but not individuals with REC AN, showed a positive relationship between self-ratings of pleasantness and the intensity of the signal for sugar in the AI, ventral, and dorsal putamen as well as ACC.

2.5 Implication

Appetitive dysregulation in AN and BN is poorly understood. Appetite regulation is a complex process that involves the integration of a wide variety of signals such as energy needs in the body, hedonic attraction to palatable foods, and long-term cognitive concerns about weight. The data reviewed above are the first to localize potential pathology of appetite disturbances in individuals with AN. We hypothesize that REC AN individuals have altered incentive processing in the AI and related regions. AN individuals fail to become appropriately hungry when starved, and thus are able to become emaciated.

3 Does the Anterior Insula Contribute to Altered Interoceptive Awareness in AN?

Do AN individuals have an AI disturbance specifically related to gustatory modulation or a more generalized disturbance related to the integration of interoceptive stimuli? Interoception has long been thought to be critical for self-awareness because it provides the link between cognitive and affective processes and the current body state (Craig 2002; Paulus and Stein 2006). This lack of recognition of the symptoms of malnutrition, diminished insight and motivation to change, and altered central coherence could be related to disturbed AI function.

It is thought that altered interoceptive awareness might be a precipitating and reinforcing factor in AN (Bruch 1962; Fassino et al. 2004; Garner et al. 1983; Lilenfeld et al. 2006). Indeed, many of the symptoms of AN, such as distorted body image, lack of recognition of the symptoms of malnutrition (e.g., a failure to appropriately respond to hunger), and diminished motivation to change, could be related to disturbed interoceptive awareness. In particular, there might be a qualitative change in the way that specific interoceptive information is processed. For example, individuals with AN might experience an aversive visceral sensation when exposed to food or food-related stimuli. This experience might fundamentally alter the reward-related properties of food and result in a bias towards negative emotionality. Moreover, the aversive interoceptive experience associated with food might trigger top-down modulatory processes aimed at anticipating and minimizing the exposure to food stimuli ("harm avoidance"), leading to increased anticipatory processing aimed to reduce the exposure to the aversively valued stimulus. Therefore, individuals with AN might exhibit attenuated responses to the immediate reward-related signal of food (reducing hunger) but show increased responses to the long-term reward signal associated with the goal of weight reduction or other "ideal" cognitive constructs. Finally, the AI has been implicated in risk-prediction errors (Preuschoff and Quartz 2008), suggesting that impairments in insula functioning might lead to anomalous attitudes in a context of uncertainty and thus contribute to harm avoidance. Thus, given the prominent alterations in insula

activity in AN patients, one might speculate that these individuals experience an altered sensitivity to or integration of internal body signals. Specifically, the projection of the AI to the anterior cingulate may serve to modulate the degree to which cognitive control is engaged to alter behavior toward poor decision making that does not subserve the homeostatic weight balance but instead results in progressive weight loss.

4 Reward Function in AN and BN

It is also possible that food has little rewarding value to AN and thus may be associated with corresponding responses in the OFC or the striatum. Clinical observations suggest that AN individuals have disturbed reward modulation that affects a wide range of appetitive behaviors – not just food. Individuals with AN have long been noted to be anhedonic and ascetic, and are able to sustain self-denial of food as well as most comforts and pleasures in life (Frank et al. 2005). Reward is one characteristic that differentiates AN and BN, since BN individuals tend to be more impulsive, pleasure and stimuli seeking, and less paralyzed by concerns with future consequences (Cassin and von Ranson 2005). Positive reinforcers or rewards promote selected behaviors, induce subjective feelings of pleasure and other positive emotions, and maintain stimulus–response associations (Thut et al. 1997). Negative reinforcement also plays an essential role by encouraging avoidance or withdrawal behavior, as well as production of negative emotions.

4.1 Altered DA Function in AN and BN

Animal studies indicate that dopamine (DA) in the striatum plays a key role in the optimal response to reward stimuli (Delgado et al. 2000; Montague et al. 2004; Schultz 2004). In fact, genetic, pharmacologic, and physiologic data (Kaye 2008; Bergen et al. 2005; Lawrence 2003; Friederich et al. 2006) show that ill and REC individuals with AN have altered striatal DA function. DA disturbances could contribute to an altered modulation of appetitive behaviors, as well as symptoms of anhedonia, dysphoric mood, and increased motor activity (Halford et al. 2004; Volkow et al. 2002). Because fewer DA studies have been done in BN individuals, it remains uncertain whether they have trait-related DA disturbances (Jimerson et al. 1992; Kaye et al. 1990). In terms of positron emission tomography (PET) studies, our group found that REC AN had increased [^{11}C]raclopride BP_{ND} in the anterior ventral striatum (AVS) (Frank et al. 2005). Because PET measures of [^{11}C] raclopride binding are sensitive to endogenous DA concentrations (Drevets et al. 2001), elevated [^{11}C]raclopride BP_{ND} could indicate either a reduction in intrasynaptic DA concentrations or an elevation of the density and/or affinity of the D2/D3 receptors.

4.2 BOLD Response to Reward and Punishment Is Altered in AN

Human neuroimaging studies show that a highly interconnected network of brain areas including OFC, mPFC, amygdala, striatum and DA mid-brain is involved in reward processing of both primary (i.e., pleasurable tastes) (Berns et al. 2001; McClure et al. 2003) and secondary (i.e., money) reinforcers (O'Doherty 2004; Breiter et al. 2001; Delgado et al. 2000; Gehring and Willoughby 2002; Montague et al. 2004). These regions code stimulus–reward value, maintain representations of predicted future reward and future behavioral choice, and may play a role in integrating and evaluating reward prediction to guide decisions. In animals, DA modulates the influence of limbic inputs on striatal activity (Goto and Grace 2005; Montague et al. 2004; Schultz 2004; Yin and Knowlton 2006) and mediates the "binding" of hedonic evaluation of stimuli to objects or acts ("wanting" response) (Berridge and Robinson 1998). It has been postulated that dorsal striatum is engaged by real or perceived stimulus–response outcomes, with DA projections modulating this behavior (Tricomi et al. 2004; O'Doherty et al. 2004).

Because of the DA findings in REC AN individuals (Bergen et al. 2005; Frank et al. 2005; Kaye et al. 1999), our group (Wagner et al. 2007, 2009) performed an event-related fMRI study using a variation of a well-characterized "guessing-game" protocol (Delgado et al. 2000), which is known to activate the AVS with a differential response to positive and negative feedback in healthy volunteers. Importantly, REC AN (Wagner et al. 2007) and REC BN individuals (Wagner et al. 2009) failed to show a differential AVS response to positive and negative monetary feedback when compared to CW, suggesting that both groups have an impaired ability to identify the rewarding/emotional significance of a stimulus. This shared-trait disturbance of the modulation of reward and emotionality may create a vulnerability for dysregulated appetitive behaviors. In contrast, fMRI studies consistently show that ill and REC AN individuals have increased activity in cognitive neural circuits (Zastrow et al. 2009; Wagner et al. 2007), whereas ill and REC BN individuals have diminished or impaired activity in these regions (Marsh et al. 2009; Schienle et al. 2008; Wagner et al. 2009), consistent with enhanced higher order inhibitory function in AN and reduced inhibition in BN. We hypothesize that AN individuals are able to inhibit appetite and have extraordinary self-control, because they have exaggerated dorsal cognitive circuit function, whereas BN individuals are vulnerable to overeating when they get hungry, because they have less ability to control their impulses.

4.3 Implications

In summary, AN individuals may have both an impaired ability to identify the emotional significance of a stimulus and an enhanced ability to plan or foresee consequences. Because of AVS pathway dysregulation, REC AN individuals may

focus on long-term consequences rather than an immediate response to salient stimuli. In fact, AN individuals tend to have an enhanced ability to pay attention to detail or use a logical/analytic approach, but exhibit worse performance for global strategies in the here and now (Lopez et al. 2008; Strupp et al. 1986). In particular, the most anxious AN individuals may respond in an overly "cognitive" manner to both negative and positive stimuli. Consequently, they may not be able to process information about rewarding outcomes of an action and may have impaired ability to identify emotional significance of the stimuli (Phillips et al. 2003). This may provide an important, new understanding of why it is so difficult to motivate AN individuals to engage in treatment since they may not be able to appreciate rewarding stimuli (Halmi et al. 2005).

5 The Neurocircuitry of AN

Based on the above processes and associated brain areas, our group (Kaye et al. 2009) has begun to assemble a neural systems processing model of AN. Specifically, top-down (cortical) amplification of anticipatory signals related to food such as ghrelin, or stimuli associated with satiety signals (integrated within the insula), could trigger behavioral strategies for avoiding exposure to food. These anticipatory interoceptive stimuli are associated with an aversive body state that resembles some aspects of the physiological state of the body after feeding. This abnormal response to food anticipation might function as a learning signal to further increase avoidance behavior, i.e., to engage in activities aimed at minimizing exposure to food. Specifically, stimuli that predict food intake, such as displays of food or food smells, could generate a "body prediction error," resulting from comparing the current body state with the anticipated body state (e.g., feeling satiated) after feeding. This prediction error would generate a motivational or approach signal in healthy individuals but might lead to an avoidance signal in AN individuals. The dorsal and ventral neurocircuits described earlier might be involved in these processes: The ACC, one of the projection areas of the insular cortex, is important in processing the conflict between available behaviors and outcomes, e.g., "shall I eat this cake and satisfy my hunger now or shall I not eat this cake and stay thin?" (Carter et al. 2000). The OFC, another projection area of the anterior insular cortex (Ongur and Price 2000), can dynamically adjust reward valuation based on the current body state of the individual (Rolls 1996). The DPLFC can switch between competing behavioral programs based on the error signal it receives from the ACC (Kerns et al. 2004).

Although we do not propose that AN is an insula-specific disorder, we speculate that an altered insula response in response to food-related stimuli is an important component of this disease. If this is indeed the case, one would need to determine whether insula-specific interventions, such as sensitization or habituation of interoceptive sensitivity via real-time monitoring of the insular cortex activation, might help. Moreover, computational models such as those that have been proposed for

addiction (Redish 2004) might provide a theoretical approach to better understand the complex pathology of this disorder.

Within the framework of the ventral and dorsal neurocircuits described above, there are also potential explanations for other core components of clinical dysfunction in AN. Negative affect – such as anxiety and harm avoidance – and anhedonia could be related to difficulties in accurately coding or integrating positive and negative emotions within ventral striatal circuits. There is considerable overlap between circuits that modulate emotionality and the rewarding aspects of food consumption (Volkow and Wise 2005). Food is pleasurable in healthy individuals but feeding is anxiogenic in AN patients, and starvation might serve to reduce dysphoric mood states. The neurobiologic mechanisms responsible for such behaviors remain to be elucidated, but it is possible that an enhancement of 5-HT-related aversive motivation and/or diminished DA-related appetitive drives (Daw et al. 2002; Cools et al. 2008) contribute to these behaviors.

Finally, it is possible that perfectionism and obsessional personality traits are related to exaggerated cognitive control by the DLPFC. The DLPFC might develop excessive inhibitory activity to dampen information processing through reward pathways (Chambers et al. 2003). Alternatively, increased activation of cognitive pathways might compensate for primary deficits in limbic function: when there are deficits in emotional regulation, overdependence upon cognitive rules is a reasonable strategy of self-management (Connan et al. 2003).

6 Conclusions and Future Directions

AN is thought to be a disorder of complex etiology, in which the genetic, biological, psychological, and sociocultural factors, and interactions between them, seem to contribute significantly to susceptibility (Connan et al. 2003; Jacobi et al. 2004; Lilenfeld et al. 2006; Stice 2002). Because no single factor has been shown to be either necessary or sufficient for causing AN, a multifactorial threshold model might be the most appropriate model (Connan et al. 2003). Typically, AN begins with a restrictive diet and weight loss during teenage years, which progresses to an out-of-control spiral. Thus, individuals might cross a threshold in which a premorbid temperament, interacting with stress and/or psychosocial factors, progresses to an illness with impaired insight and a powerful, obsessive preoccupation with dieting and weight loss. Adolescence is a time of profound biological, psychological, and sociocultural change, and it demands a considerable degree of flexibility to successfully manage the transition into adulthood. Psychologically, change might challenge the perfectionism, harm avoidance, and rigidity of those at risk for AN and thus fuel an underlying vulnerability.

We propose that somatic, autonomic, and visceral information is aberrantly processed in people who are vulnerable to developing AN. Brain changes associated with puberty might further challenge these processes. For example, orbital and DLPFC regions develop greatly during and after puberty (Huttenlocher and

Dabholkar 1997), and increased activity of these cortical areas might be a cause of the excessive worry, perfectionism, and strategizing in AN patients. It is possible that, in AN patients, hyperactivity of cognitive networks in the dorsal neurocircuit (e.g., DLPFC to dorsal striatum) directs motivated actions when the ability of the ventral striatal pathways to direct more "automatic" or intuitive motivated responses is impaired. Another possibility is that in AN patients (otherwise adequate) limbic–striatal information processing in the ventral circuit is too strongly inhibited by converging inputs from cognitive domains such as the DLPFC and the parietal cortex.

It is possible that such trait-related disturbances are related to altered monoamine neuronal modulation that predates the onset of AN and contributes to premorbid temperament and personality symptoms. Specifically, disturbances in the 5-HT system contribute to a vulnerability for restricted eating, behavioral inhibition, and a bias toward anxiety and error prediction, whereas disturbances in the DA system contribute to an altered response to reward. Several factors might act on these vulnerabilities to cause the onset of AN in adolescence. First, puberty-related female gonadal steroids or age-related changes might exacerbate 5-HT and DA system dysregulation. Second, stress and/or cultural and societal pressures might contribute by increasing anxious and obsessional temperament. Individuals find that restricting food intake is powerfully reinforcing because it provides a temporary respite from dysphoric mood. People with AN enter a vicious cycle – which could account for the chronicity of this disorder – because eating exaggerates, and food refusal reduces, an anxious mood.

AN has the highest mortality rate of any psychiatric disorder. It is expensive to treat and we have inadequate therapies. It is crucial to understand the neurobiologic contributions and their interactions with the environment, in order to develop more effective therapies. Thus, future imaging studies should focus on characterizing neural circuits, their functions, and their relationship to behavior in AN patients. Genetic studies might shed light on the complex interactions of molecules within these neural circuits. Finally, prospective and longitudinal studies should focus on identifying the neurobiologic traits and external factors that create a susceptibility for developing AN.

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