

Neurobiology of anorexia and bulimia nervosa

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Abstract

Anorexia nervosa (AN) and bulimia nervosa (BN) are related disorders of unknown etiology that most commonly begin during adolescence in women. AN and BN have unique and puzzling symptoms, such as restricted eating or binge-purge behaviors, body image distortions, denial of emaciation, and resistance to treatment. These are often chronic and relapsing disorders, and AN has the highest death rate of any psychiatric disorder. The lack of understanding of the pathogenesis of this illness has hindered the development of effective interventions, particularly for AN. Individuals with AN and BN are consistently characterized by perfectionism, obsessive–compulsiveness, and dysphoric mood. Individuals with AN tend to have high constraint, constriction of affect and emotional expressiveness, ahedonia and asceticism, whereas individuals with BN tend to be more impulsive and sensation seeking. Such symptoms often begin in childhood, before the onset of an eating disorder, and persist after recovery, suggesting they are traits that create a vulnerability for developing an ED. There is growing acknowledgement that neurobiological vulnerabilities make a substantial contribution to the pathogenesis of AN and BN. Considerable evidence suggests that altered brain serotonin (5-HT) function contributes to dysregulation of appetite, mood, and impulse control in AN and BN. Brain imaging studies, using 5-HT specific ligands, show that disturbances of 5-HT function occur when people are ill, and persist after recovery from AN and BN. It is possible that a trait-related disturbance of 5-HT neuronal modulation predates the onset of AN and contributes to premorbid symptoms of anxiety, obsessionality, and inhibition. This dysphoric temperament may involve an inherent dysregulation of emotional and reward pathways which also mediate the hedonic aspects of feeding, thus making these individuals vulnerable to disturbed appetitive behaviors. Restricting food intake may become powerfully reinforcing because it provides a temporary respite from dysphoric mood. Several factors may act on these vulnerabilities to cause AN to start in adolescence. First, puberty-related female gonadal steroids or age-related changes may exacerbate 5-HT dysregulation. Second, stress and/or cultural and societal pressures may contribute by increasing anxious and obsessional temperament. Individuals with AN may discover that reduced dietary intake, by reducing plasma tryptophan availability, is a means by which they can modulate brain 5-HT functional activity and anxious mood. People with AN enter a vicious cycle which accounts for the chronicity of this disorder because caloric restriction results in a brief respite from dysphoric mood. However, malnutrition and weight loss, in turn, produce alterations in many neuropeptides and monoamine function, perhaps in the service of conserving energy, but which also exaggerates dysphoric mood. In summary, this article reviews findings in brain chemistry and neuroimaging that shed new light on understanding the psychopathology of these difficult and frustrating disorders.

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1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are related disorders of unknown etiology that most commonly begin during adolescence in women (DSM-IV; Table 1). They are frequently chronic and often disabling conditions that are characterized by

aberrant patterns of feeding behavior and weight regulation, and deviant attitudes and perceptions toward body weight and shape. In AN, an inexplicable fear of weight gain and unrelenting obsession with fatness, even in the face of increasing cachexia, accounts for a protracted course, extreme medical and psychological morbidity, and standardized mortality rates exceeding those of all other psychiatric disorders. BN usually emerges after a period of food restriction, which may or may not have been associated with weight loss. Binge eating is followed by either self-induced vomiting, or by some other means of compensation for the excess of food ingested. Although abnormally low body

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Table 1

DSM IV, Diagnostic criteria for anorexia nervosa

- A Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected.)
- B Intense fear of gaining weight or becoming fat, even though underweight.
- C Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- D In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)
- Specify type:
Restricting type: during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
Binge-eating/purging type: during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

DSM IV, Diagnostic Criteria for Bulimia Nervosa

- A Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following
 (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
 (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
- B Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting, or excessive exercise
- C The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months
- D Self-evaluation is unduly influenced by body shape and weight
- E The disturbance does not occur exclusively during episodes of anorexia nervosa
- Specify type:
Purging type: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
Non-purging Type: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

weight is an exclusion for the diagnosis of BN, some 25% to 30% of bulimics have a prior history of AN.

Because AN and BN present most often during adolescence in women, they are often theorized to be caused by cultural pressures for thinness [1] since dieting and the pursuit of thinness are common in industrialized countries. Still, AN and BN affect only an estimated 0.3% to 0.7% and 1.5% to 2.5%, respectively, of females in the general population [2]. This disparity between the high prevalence of pressures for thinness and the low prevalence of eating disorders (EDs), combined with clear evidence of AN occurring at least several centuries ago [3], the stereotypical presentation, substantial heritability, and developmentally specific age-of-onset distribution, underscores the possibility of contributing biological vulnerabilities.

Considering that transitions between syndromes occur in many, it has been argued that AN and BN share at least some risk and liability factors [4,5]. In fact, AN and BN are cross transmitted in families. [6,7] Moreover there is an increased prevalence of AN and BN as well as subthreshold forms of ED in relatives, consistent with the possibility of a continuum of transmitted liability in at risk families manifesting a broad spectrum of eating disorder phenotypes [7]. Twin studies can differentiate genetic from environmental effects by comparing concordance for a trait, or disorder, between identical (monozygotic; MZ) and fraternal (dizygotic; DZ) twins. Twin studies of AN and BN suggest there is approximately a 50 to 80% genetic contribution to liability [4,8–11] accounted for by additive genetic factors. These heritability estimates are similar to those found in schizophrenia and bipolar disorder, suggesting that AN and BN may be as genetically-influenced as disorders traditionally viewed as biological in nature.

2. Clinical symptoms and puzzling behaviors

The DSM-IV diagnostic criteria for AN and BN focus on eating behavior and body image distortions. Because of their unusual and prominent nature, these symptoms tend to capture much attention. The pathogenesis of the disturbed eating behaviors is poorly understood [5,12]. Individuals with AN rarely have complete suppression of appetite, but rather exhibit an ego-syntonic resistance to feeding drives while simultaneously being preoccupied with food and eating rituals to the point of obsession. Individuals with AN severely restrict food intake, particularly fats and carbohydrates, but rarely stop eating completely; rather they restrict their caloric intake to a few hundred calories a day. They tend to be vegetarians, have monotonous choices in food intake, select unusual combinations of foods and flavors, and have ritualized eating behaviors. Similarly, BN is not associated with a primary, pathological increase in appetite; rather, like individuals with AN, individuals with BN have a seemingly relentless drive to restrain their food intake, an extreme fear of weight gain, and often have a distorted view of their actual body shape. Loss of control with overeating in individuals with BN usually occurs intermittently and typically only some time after the onset of dieting behavior. Restrained eating behavior and dysfunctional cognition relating weight and shape to self-concept are shared by all types of patients with EDs.

AN and BN individuals commonly have clusters of other puzzling symptoms. Excessive exercise and motor restlessness are common in AN [13]. While not well studied, excessive exercise is thought to be associated particularly with the purging subtype of AN, as well as with a constellation of anxious/obsessional temperament. Individuals with AN often have resistance to treatment [14]. In part this is due to the ego syntonic nature of the disorder, which is demonstrated by the patient's denial of being underweight and refusal to accept the seriousness of the medical consequences of the disorder. Consequently, few control trials of any therapy have been performed, in part, because it has been difficult to enlist cooperation of individuals with AN, and in part because psychological and pharmacological strategies that have been successful in other disorders appear to be less effective in this illness.

3. Mood and impulse control

Individuals with AN and BN have elevated rates of lifetime diagnoses of anxiety and depressive disorders, and obsessive-compulsive disorder [6,15–17]. In addition, individuals with AN and BN are both consistently characterized by perfectionism, obsessive-compulsiveness, neuroticism, negative emotionality, harm avoidance, low self-directedness, low cooperativeness, and traits associated with avoidant personality disorder (PD). Consistent differences that emerge between ED groups are high constraint and persistence, low novelty seeking, constriction of affect and emotional expressiveness, ahedonia and asceticism, and reduced social spontaneity in restrictor-type AN. Individuals with BN are more likely to have high impulsivity, sensation seeking, novelty seeking, and traits associated with borderline PD in BN, and substance abuse [18].

In summary, individuals with restricting type AN are more likely to have restricted eating, constricted affect and emotional mood expression, and impulse over control, as well as personality traits of marked rigidity, conformity, and reduced social spontaneity. Individuals with BN may show similar traits, but in addition, may exhibit histories of episodic overeating, extremes of intense affect, and impulse dysregulation. Thus several domains (eating, affect, impulse control) are involved in systematic ways, specifically, over control in AN, and switches between over control and under control in BN, which raises the question of whether there is a disturbance of modulation of multiple systems.

4. Neurocognition

Individuals with AN have an obsessive, perseverative, and rigid personality style and have difficulty shifting sets. While those with AN do well on goal directed behavior, they have difficulties incorporating feedback and modifying their behavior. For example, they often feel that they should be able to do things perfectly without making mistakes, and they have little appreciation for the fact that mistakes are a normal learning experience. Moreover, they often fail to accurately recognize and incorporate affective and social stimuli in the environment, as confirmed by laboratory tests [19,20]. Those ill with and REC from (REC) AN tend [21] to have delayed setshifting, which allows for the adaptation of behavior in line with changing demands of the environment. Furthermore, individuals with AN have enhanced ability to pay attention to detail or use a logical/analytic approach but exhibit worse performance with global strategies [19,22].

5. State and trait

It has long been debated whether symptoms in individuals with AN and BN are cause or consequence of malnutrition. Confounding this understanding is the issue that most studies of symptoms have been done when individuals are ill with an ED. Recent studies have shown that the majority of people with AN and BN exhibit childhood perfectionism, obsessive-compulsive personality patterns, and anxiety that *predate the onset of AN and BN* [16,23,24]. Moreover, studies done on 3 continents (Table 2)

have shown that in AN and BN individuals with a lifetime history of an anxiety disorder diagnosis, the anxiety disorder most often began in childhood before the onset of the ED [25–28]. The most common [15] premorbid childhood disorders were OCD and social phobia. In summary, such symptoms may be susceptibility factors that make people vulnerable to developing an ED. Malnutrition tends to exaggerate premorbid behavioral traits, [29], not cause them.

It is important to note that such temperament and personality traits persist after recovery from an ED. While a definition of recovery has not been formalized, investigators tend to include people after they were at a stable and healthy body weight for months or years, were not malnourished and had not engaged in pathological eating behavior during that period of recovery. Some investigators include a criterion of normal menstrual cycles and a minimal duration of recovery, such as one year. Investigators [30–33] have found that women who were long-term REC from AN and BN have a persistence of anxiety, perfectionism, and obsessional behaviors (particularly symmetry, exactness, and order).

6. Gender, age, and puberty

AN and BN most commonly develop during adolescence or young adulthood [34] in proximity to puberty. Adolescence [35] 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 may challenge the rigidity of those at risk for AN and BN, and thus open a window of vulnerability [35]. Importantly, biological changes may significantly enhance the risk of onset of an ED, particularly in women. This latter possibility is supported by twin studies which found essentially no genetic influence on overall levels of ED symptoms in 11 year-old twins, but significant genetic effects (>50%) in 17 year old twins [36]. These findings collectively imply that puberty may play a role in the genetic diathesis for ED symptoms. The changes associated with adolescence differ in males and females and may therefore contribute to the sexual dimorphism of AN. Menarche is associated [35] with a rapid change in body composition and neuropeptides modulating metabolism. Little is known about whether the rise in estrogen levels associated with puberty in females is contributory. Estrogens modulates serotonergic function [37] as well as stress-related neuropeptides such as cortisol releasing hormone (CRH) [38] via a variety of mechanisms. Moreover, a major phase of synaptogenesis, pruning and

Table 2
Lifetime and premorbid rates of anxiety disorders (AD)

Study	ED	N	Lifetime AD (%)	AD before ED (%)
Deep [25]	AN	24	68	58
Godart [26]	AN	29	83	62
Godart [26]	BN	34	71	62
Bulik [27]	AN	68	60	54
Bulik [28]	BN	116	57	54
Kaye [15]	AN, BN	672	64	61
				23 OCD
				13 social phobia

myelination of predominantly frontal and limbic areas occurs around the time of puberty and adolescence and is thought to have a functional role in the integration of emotional processing with cognition [39].

7. Neurobiology

There is growing acknowledgement that neurobiological vulnerabilities make a substantial contribution to the pathogenesis of AN and BN [3]. But we have little understanding of how such vulnerabilities result in disturbances of brain pathways or what systems are primarily involved. For example, are there disturbances of pathways related to the modulation of feeding behaviors, or mood, or temperament, or obsessiveness, or impulse control? Are there primary disturbances of pathways that may modulate some factors related to body proprioception, and thus result in body image distortions? In the past, answering these questions has been thwarted by the inaccessibility of the brain. Technology capable of characterizing the complexity of brain circuits in humans, such as imaging or genetics, have only recently become available. Still, past studies have been useful in terms of grossly identifying systems that may be involved in ED. Because these technologies tend to only be able to characterize one molecule at a time, they cannot answer questions about complex interactions and function.

8. Neuropeptides

Central nervous system (CNS) neuropeptide dysregulation could contribute to abnormal function of gonadal hormones, cortisol, thyroid hormones and growth hormone in ED [40,41]. Moreover, mechanisms for controlling food intake involve a complicated interplay [42] between peripheral systems (including gustatory stimulation, gastrointestinal peptide secretion, and vagal afferent nerve responses) and CNS neuropeptides and/or monoamines. Studies in animals show that neuropeptides, such as CRH, leptin, the endogenous opioids (such as beta-endorphin), and neuropeptide-Y (NPY) modulate feeding behaviors and energy metabolism [43,44]. One of the few strategies capable of assessment of neuropeptides *in vivo* in humans is to measure their concentrations in cerebrospinal fluid (CSF). In fact, when malnourished and underweight, AN individuals have altered concentrations of CRH, NPY, beta-endorphin, and leptin (Fig. 1). However, these disturbances tend to normalize after recovery [45]. This observation can be interpreted to suggest that such disturbances are consequences rather than causes of malnutrition, weight loss and/or altered meal patterns. It should be noted that many systems known to modulate feeding and related functions remain to be explored in ED. For example, genotype studies raise the possibility that altered melanocortin [46] or cannabinoid [47] systems could play a role in ED.

9. Serotonin

Much technology has focused on characterizing monoamine function. In part, this is because many of the medications used to treat psychiatric disorders act on these systems. The

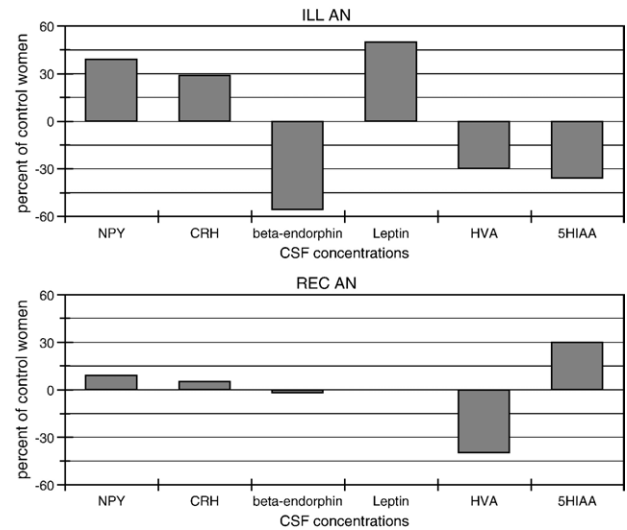


Fig. 1. Comparison of CSF concentrations of neuropeptide and monoamine metabolites in individuals who were ill (underweight) and long-term recovered from AN. CSF values in AN are compared to healthy control women, where control mean values are set to 0.

monoamine systems, serotonin (5-HT), dopamine (DA), and norepinephrine (NE), are complex pathways with multiple receptors, transporters, enzymes, and intracellular cascades, etc. Consequently, our understanding of the pathophysiology of these systems in psychiatric disorders is limited. The cell bodies of monoamine neurons are located in the brainstem and project to cortical and striatal limbic regions [48]. Each has multiple receptors, grouped on the basis of shared genetic sequences and second messengers.

Theoretically, 5-HT disturbances could contribute to appetite dysregulation [49,50], anxious and obsessional behaviors and extremes of impulse control [51–55]. Considerable evidence suggest that disturbances of the monoamine function occur when people are ill with ED, and persist after recovery from AN and BN. [45,56–59]. For example, ill AN subjects have a significant reduction in CSF 5-hydroxyindoleacetic acid (5-HIAA) compared to healthy control women (CW) whereas CSF 5-HIAA levels are normal in ill BN subjects (Fig. 1; ([33,60–64] Kaye, unpublished data). In comparison, REC AN and BN subjects have higher than normal concentrations of CSF 5-HIAA, that is about 50% greater than CSF 5-HIAA levels found in the ill state (Fig. 1). In addition, REC AN and BN show altered behavioral responses to 5-HT challenges [65–68] or other measures, such as platelet binding of paroxetine [69]. As noted above, determining cause and effect is a major methodological confound in this illness. Thus this review will focus on studies that have been done in people who have REC from AN and BN.

10. Diet and brain 5-HT neurotransmission

Tryptophan (TRP), an essential amino acid only available in the diet, is the precursor of 5-HT. Meal consumption, depending on the proportion of carbohydrate and protein, can enhance brain 5-HT release [70,71]; thereby affecting appetite regulation. In brief, carbohydrate consumption causes an insulin-

mediated fall in plasma levels of the large neutral amino acids (LNAA; tyrosine; phenylalanine; valine; leucine; isoleucine) which compete with TRP for uptake into the brain. This elevates the plasma TRP/large neutral amino acid ratio (TRP/LNAA), and thus brain TRP, which rapidly accelerates brain 5-HT synthesis and release. Dietary proteins tend to block these effects by contributing large amounts of LNAA to the blood stream. Considerable amounts of evidence in animals and healthy humans [70–76] show that a restricted diet significantly lowers plasma TRP, resulting in a decreased plasma ratio of TRP to neutral amino acids, and, in turn, a reduction in the availability of TRP to the brain. Thus, restricted diet (and experimentally reduced TRP) decreases brain 5-HT synthesis, down-regulates the density of 5-HT transporters [77], and produces a compensatory supersensitivity of postsynaptic receptors in response to reduced 5-HT turnover [78,79]. Limited data show that malnourished and emaciated AN women have a reduction of plasma TRP availability [80]. In addition, these alterations in postmeal amino acid metabolism are only partly reversed by nutritional rehabilitation [80]. It has been speculated [1,12] that there is an anxiety-reducing character to dietary restraint in people with AN. In fact, we have found that the anxiolytic effects of dieting in AN were related to a reduction in 5-HT neurotransmission. [66]. Moreover administration of meta-chlorophenylpiperazine (m-CPP), a relatively selective 5-HT drug [81–85] is associated with a significant reduction in dysphoric mood states in one study [68] but not in another [86].

11. Implications for medication

While BN individuals show a response to higher doses of fluoxetine [87], the efficacy of such medication has been questioned since relatively few individuals abstain from binge and purge behaviors, and relapse during treatment is common [88]. Despite the abundance of data implicating 5-HT dysregulation in AN, it remains controversial whether SSRIs are effective in restricting type AN (RAN) individuals [89,90]. Our clinical experience [91] suggests that RAN respond better to fluoxetine than do binge eating-purging type AN (BAN) and that some BN individuals can be relatively insensitive to high doses of SSRIs. Few control trials of any therapy have been performed, in part, because it has been difficult to enlist cooperation of individuals with AN, and in part because psychological and pharmacological strategies that have been successful in other disorders appear to be less effective in this illness. For severely emaciated patients, hospitalization for supportive medical care and weight restoration may be useful or necessary. Still, relapse is common after discharge.

12. Dopamine

Altered striatal DA function may contribute to symptoms in AN. Reduced CSF DA metabolites occur in malnourished individuals with AN [60] and persist after recovery [92]. Individuals with AN have altered frequency of functional polymorphisms of DA D2 receptor genes that might affect

receptor transcription and translation efficiency [93]. The anteroventral striatum (AVS) and dorsal caudate are components of limbic and executive-associative pathways [94–96]. Thus striatal DA dysfunction might contribute to altered reward and affect, decision-making, and executive control, as well as to stereotypic motor activity [95] and decreased food ingestion [97] in AN.

13. Brain imaging

The past decade has seen the introduction of tools, such as brain imaging, which hold the promise of being better able to characterize complex neurocircuits and their relationship to behavior in living humans. In fact, these tools have rapidly advanced knowledge to the point where we can begin to make educated guesses about the pathophysiology of AN and BN and start to model mechanisms that may be used to test hypotheses.

Brain imaging studies in AN and BN can be divided into several categories. First, there has been substantial literature, using computerized tomograph (CT) and more recently magnetic resonance imaging (MRI) that seeks to determine whether there are brain structural alterations in individuals with ED. Second, are imaging studies, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT, that employ a radioligand. These studies, which may use flurodeoxyglucose (FDG) to study glucose metabolism, or a ligand that is specific for a serotonin receptor, provide information that is specific for the system being studied, such as the 5-HT_{2A} receptor. Third, more recent studies have used fMRI or other technologies to assess blood flow responses to some stimuli, such as pictures of food. Overall, imaging studies have been relatively consistent, in that many studies show differences in ill and REC ED individuals in frontal, cingulate, temporal, and/or parietal regions compared to controls. However, it should be noted that these studies have not consistently identified regions, pathways, or behavioral correlates. Sample sizes have been small, and imaging technologies and methods vary widely. Moreover, investigations have tended to assess relatively large regions of brain that vary widely between studies. Papers to date indicate gross alterations of brain function. Because brain pathways are highly complex, the neuroanatomy of AN and BN have only begun to be characterized.

14. Brain structure

Neuroimaging studies with CT reported cerebral atrophy and enlarged ventricles in ill AN [98–106]. In BN similar but less pronounced structural brain abnormalities were reported [107] and may have been related to a chronic dietary restriction. Similarly, MRI studies in AN showed larger CSF volumes in association with deficits in both total grey matter (GM) and total white matter (WM) volumes [108] as well as enlarged ventricles [109–111]. Fewer neuroimaging studies have been conducted in BN, and those have found decreased cortical mass [112–114]. Whether these abnormalities persist to a lesser degree after weight restoration is less certain, since some studies show persistent alterations [108] but other studies show normalization of grey and white matter after recovery in AN and BN {Wagner, 2006 #2829}. As noted above, in order to avoid the confounding

effects of malnutrition, extremes of food ingestion and/or weight loss, the review of other imaging studies will focus mostly on studies of individuals after recovery from an ED.

15. Body image distortion

A most puzzling symptom of AN is the severe and intense body image distortion in which emaciated individuals perceive themselves as fat. Theoretically, body image distortion might be related to the syndrome of neglect, [217] which may be coded in parietal, frontal, and cingulate regions that assign motivational relevance to sensory events. It is well known that lesions in the right parietal cortex may not only result in denial of illness or anosognosia, somatoparaphrenia, the numerous misidentification syndromes, but may also produce experiences of disorientation of body parts and body image distortion. Wagner and colleagues confronted AN patients and age-matched healthy controls with their own digitally distorted body images as well as images of a different person using a computer-based video-technique [115]. These studies reported a hyper-responsiveness in brain areas belonging to the frontal visual system and the attention network (BA 9) as well as inferior parietal lobule (BA 40), including the anterior part of the intraparietal (IPL) sulcus. Bailer [116] reported negative relationships between 5-HT_{2A} receptor activity and the Eating Disorder Inventory Drive for Thinness scale in the left parietal cortex and other regions. It is intriguing to raise the possibility that left hemisphere disturbances of this pathway may contribute to body image distortion. It has long been recognized that parietal cortex mediates perceptions of the body and its activity in physical space [117]. Recent work extends this concept to suggest that the parietal lobe contributes to the experience of being an ‘agent’ of one’s own actions [118]. The well-known distortion of body image in individuals with AN may suggest abnormalities of circuits through the postulated ‘self’ networks. In line with this, left parietal cortical activation has previously been linked to AN womens’ evaluation of body image [115,116].

16. Appetitive regulation

Individuals with AN and those who have had lifetime diagnoses of both AN and BN (AN-BN) tend to have negative mood states and dysphoric temperament. There is evidence that there is a dysphoria reducing character to dietary restraint [1,12,66] and binge-purge behaviors [119–121]. This would suggest some interaction between pathways regulating appetitive behaviors and emotions. In fact, functional magnetic resonance imaging (fMRI) studies support this hypothesis. When emaciated and malnourished AN individuals are shown pictures of food, they display abnormal activity in the insula and orbitofrontal cortex (OFC) as well as in mesial temporal, parietal, and the anterior cingulate cortex [122–127]. Studies using SPECT, PET-O15, or fMRI, found that when subjects ill with AN ate food, or were exposed to food, they had activated temporal regions, and often increased anxiety [122,124–126]. Those results could be consistent with anxiety provocation and related amygdala activation, and the notion that the emotional value of an

experience is stored in the amygdale [128]. Uher [129] used pictures of food and non-food aversive emotional stimuli and fMRI to assess ill and REC AN subjects. Food stimulated medial prefrontal and anterior cingulate cortex in both REC and ill AN subjects but lateral prefrontal regions only in the REC group. In REC AN subjects, prefrontal cortex, ACC and cerebellum were more highly activated after food compared to both control subjects and those chronically ill with AN. This finding suggested that higher ACC and medial prefrontal cortex activity in both ill and REC AN women compared to CW may be a trait marker for AN.

17. Imaging studies of 5-HT and DA function

The development of selective tracers for the 5-HT system has made in vivo study of 5-HT receptor function possible using PET brain imaging. In turn, this offers the possibility of better understanding of 5-HT neurotransmitter activity and dynamic relationships to behavior.

18. 5-HT_{1A} receptor

Our group used PET imaging with the radioligand [¹¹C]WAY100635 to assess the binding potential (BP) of the 5-HT_{1A} receptor. The 5-HT_{1A} autoreceptor is located presynaptically on 5-HT somatodendritic cell bodies in the raphe nucleus, where it functions to decrease 5-HT neurotransmission [130]. High densities of postsynaptic 5-HT_{1A} exist in the hippocampus, septum, amygdala, and entorhinal and frontal cortex, where they serve to mediate the effects of released 5-HT. Although the molecular organization for the receptor transduction seems to be identical in all of the areas where 5-HT_{1A} receptors are expressed, some differences in both functional and regulatory properties have been reported from area to area [131]. Studies in animals and humans implicate the 5-HT_{1A} receptor in anxiety [132–134] and depression and/or suicide [55,135,136].

Bailer [137] reported that ill AN individuals had a 50 to 70% increase in [¹¹C]WAY100635 BP in subgenual, mesial temporal, orbital frontal, and raphe brain regions as well as prefrontal, lateral temporal, anterior cingulate, and parietal regions. Similarly, REC BAN and BN subjects [138] (Kaye unpublished data) (Fig. 2) had a significant 20 to 40% increase in [¹¹C]WAY100635 BP in these same regions compared to CW [138]. In contrast, REC RAN women showed no difference in [¹¹C]WAY100635 BP compared to controls [138]. Increased 5-HT_{1A} postsynaptic activity has been reported in ill BN subjects [139].

The role of the 5-HT_{1A} receptor in behavior is not certain. 5-HT_{1A} receptor activity has been reported to play a role in anxiety [133]. For example, some, but not all studies, show that 5-HT_{1A} knockout mice have increased anxiety [140]. REC RAN subjects showed positive relationships between harm avoidance, a trait characterized by anticipatory worry and fear of uncertainty, and postsynaptic [¹¹C]WAY100635 BP in subgenual cingulate, mesial temporal, lateral temporal, medial orbital frontal, and parietal cortex. It is not clear why this animal model and human phenomena appear to be opposite.

As noted above, EDs are frequently comorbid with depression and anxiety disorders. Reduced [¹¹C]WAY100635

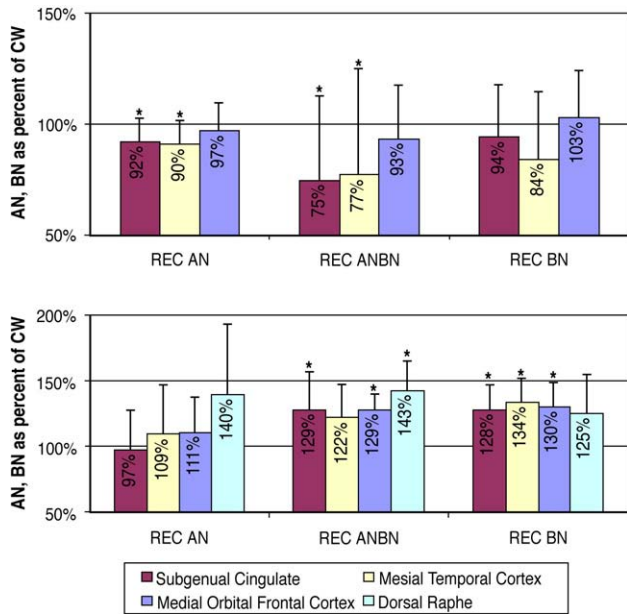


Fig. 2. Compared to CW, values for recovered anorexia and bulimia subjects expressed as a percent of the control woman values. * indicate difference at $P < .05$.

BP has been found in ill [141,142] and REC [143] depressed subjects, as well as in a primate model for depression [144]. Parsey [145] found no difference in carbonyl- ^{11}C]WAY100635 BP in MDD, although a subgroup of never medicated subjects had elevated carbonyl- ^{11}C]WAY100635 BP. Recent studies have found reduced [^{11}C]WAY100635 BP in social phobia [146] and panic disorder [147]. These findings suggest ED, mood, and depression share disturbances of common systems but are etiologically different.

There is an extensive literature associating the serotonergic systems and fundamental aspects of behavioral inhibition [51,148]. Reduced CSF 5-HIAA levels are associated with increased impulsivity and aggression in humans and non-human primates, whereas increased CSF 5-HIAA levels are related to behavioral inhibition [149,150]. Brainstem 5-HT $_{1A}$ receptors inhibit stress-induced sympathetic activity and inhibit fight-or-flight behavioral responses, supporting a role for this receptor in behavioral inhibition and self-control [151]. Furthermore, recent animal studies also support 5-HT $_{1A}$ receptors' modulation of impulse control through effects on catecholamine systems [152]. Other studies have shown that blunted 5-HT $_{1A}$ receptor number or function is associated with increased aggression [153,154]. A recent study [155] found a significant inverse relationship between dorsal raphe 5-HT $_{1A}$ autoreceptor BP and bilateral amygdala reactivity. 5-HT $_{1A}$ receptor function could contribute to behavioral inhibition in BN, although there is no direct evidence for this conjecture. Still other studies show that various measures of 5-HT activity are related to measures of affective instability and impulsivity in ill BN subjects [59,156,157].

19. 5-HT $_{2A}$ receptor

Our group used PET imaging with the radioligand [^{18}F]altanserin to assess BP of 5-HT $_{2A}$ receptors. (Fig. 2) Post-synaptic

5-HT $_{2A}$ receptors are in high densities in the cerebral cortex and other regions of rodents and humans [158,159]. The 5-HT $_{2A}$ receptor is of interest in ED because it has been implicated in the modulation of feeding and mood, as well as SSRI response [116,160–163].

Ill AN subjects had normal [^{18}F]altanserin BP values [137]. In comparison, REC RAN individuals [164] had reduced [^{18}F]altanserin BP in mesial temporal and parietal cortical areas as well as in subgenual and pregenual cingulate cortex. Similarly, REC BAN [116] women had reduced [^{18}F]altanserin BP relative to controls in left subgenual cingulate, left parietal, and right occipital cortex. And REC BN women only had reduced [^{18}F]altanserin BP relative to controls in the orbital frontal region. Audenaert et al. [165] used SPECT and 123I-5-I-R91159 and found that ill AN subjects had reduced binding of postsynaptic 5-HT $_{2A}$ receptors in the left frontal, bilateral parietal and occipital cortex.

20. Brain regions/pathways enervated by 5HT $_{1A/2A}$ receptors

In REC subjects, altered 5-HT $_{1A}$ and 5-HT $_{2A}$ receptor BP shows persistent alterations in frontal, subgenual cingulate and mesial temporal regions that are part of the ventral limbic system. The subcaudal cingulate regions play a role in emotion ('affect component') and have extensive connections with the amygdala, periaqueductal grey, frontal lobes, ventral striatum, etc. They are involved in conditioned emotional learning, vocalizations associated with expressing internal states and assigning emotional valence to internal and external stimuli [166]. Mesial temporal regions include the amygdala and related regions that play a pivotal role in anxiety and fear [167] as well in the modulation and integration of cognition and mood. The amygdala may enable the individual to initiate adaptive behaviors to threat based upon the nature of the threat and prior experience. Together these findings raise the possibility that mesial temporal (amygdala)-cingulate 5-HT $_{2A}$ receptor alterations may be a trait shared by AN subgroups related to anticipatory anxiety and integration of cognition and mood.

Several lines of evidence show that 5-HT $_{1A}$ and 5-HT $_{2A}$ receptors interact in the brain. In rats, 5-HT $_{1A}$ and 5-HT $_{2A}$ receptors interact robustly to regulate the inhibition of exploration of novel environments produced by either 5-HT $_{1A}$ or 5-HT $_{2A}$ receptor agonists [168]. 5-HT $_{2A}$ and 5-HT $_{1A}$ receptors are highly co-localized in rodent frontal cortex [169]. Postsynaptic 5-HT $_{1A}$ and 5-HT $_{2A}$ receptors mediate, respectively, the direct hyperpolarizing and depolarizing actions of 5-HT on prefrontal neurons [170], which in turn project to numerous cortical and subcortical areas. Thus a balance between postsynaptic 5-HT $_{1A}$ and 5-HT $_{2A}$ receptor activity on neurons may modulate the descending excitatory input into limbic and motor structures. These data raise the speculation that postsynaptic 5-HT $_{1A}$ and 5-HT $_{2A}$ receptors fine tune cortical systems that modulate behavioral inhibition and self-control. Mixed 5-HT $_{2A/1A}$ agonists, e.g. psilocybin, seem to disrupt the 5-HT $_{1A/2A}$ balance [171] by driving 5-HT $_{2A}$ activity, thus resulting in excessive neuronal output that contributes to extremes of disinhibition, disorganization, and loss of self-control. In our studies, REC ED

subjects had a relative increase in 5-HT_{1A} receptor activity compared to 5-HT_{2A} receptor binding. While speculative, this possible imbalance could contribute to behavioral inhibition and over control commonly seen in ED. As discussed below, we found considerable correlations between binding of these 2 receptors and harm avoidance. Together these findings raise the possibility that mesial temporal (amygdala)-cingulate 5HT_{1A/2A} imbalance may also be a trait shared by AN subgroups related to behavioral inhibition, anticipatory anxiety, or integration of cognition and mood.

21. 5-HT transporter (5-HTT)

Our group [172] used PET imaging with [¹¹C]McN5652 to determine if alterations of 5-HTT persist after recovery from AN and BN. We compared 11 subjects recovered (>1 year normal weight, regular menstrual cycles, no bingeing or purging) from restricting type AN (REC RAN), 7 REC from bulimia-type AN (REC BAN), and 10 healthy CW. After correction for multiple comparisons, we found that the REC RAN had significantly increased [¹¹C]McN5652 BP compared to REC BAN for the dorsal raphe and antero-ventral striatum. It remains controversial whether SSRIs are effective in RAN individuals. Our clinical experience and data [89–91] suggest that individuals with RAN respond better to fluoxetine than do those with BAN. While highly speculative, our findings raise the provocative possibility that decreased 5-HTT function may be related to poor response to SSRI medication whereas individuals with increased 5-HTT activity may respond to higher SSRI doses. In general, the REC RAN individuals had elevated 5-HTT binding, suggesting they have relatively greater 5-HT uptake, and reduced extracellular 5-HT, compared to REC BAN. In support of this possibility, the REC BAN individuals tend to have higher binding of 5-HT_{1A} post-synaptic receptors and autoreceptors [138], which may be a compensatory means of downregulating raphe activity [48,173]. Moreover, reduced 5-HTT activity, in terms of genotypes [174], has been associated with affect dysregulation, which tends to be more common in the bulimic subgroups. Furthermore, in people with impulsive aggressivity reduced 5-HTT binding was found in the anterior cingulate cortex, a region involved in affect regulation [175].

22. DA D2/D3 receptor

A recent study from our group, [176] found that REC AN had increased binding of D2/D3 receptors in the antero-ventral striatum (AVS), a region that contributes to optimal responses to reward stimuli [177–179]. In addition, there were positive correlations between DA D2/D3 binding in the dorsal caudate/dorsal putamen and anxiety measures in REC AN [176]. The AVS and dorsal caudate are components of limbic and executive-associative pathways [94–96]. Thus striatal DA dysfunction might contribute to altered reward and affect, decision-making, and executive control, as well as stereotypic motor activity [95] and decreased food ingestion [97] in AN.

23. 5-HT, DA, and harm avoidance

The PET imaging studies in ill and REC AN and BN subjects described above have found significant correlations between harm avoidance and binding for the 5-HT_{1A}, 5-HT_{2A}, DA D2/D3 receptors in mesial temporal and other limbic regions. Bailer [116] found that REC AN-BN subjects showed a positive relationship between [¹⁸F]altanserin BP in the left subgenual cingulate and mesial temporal cortex and harm avoidance. For ill AN subjects, [¹⁸F]altanserin BP was positively related to harm avoidance in the suprapragenual cingulate, frontal, and parietal regions. 5-HT_{2A} receptor binding and harm avoidance were shown to be negatively correlated in the frontal cortex in healthy subjects [180] and in the prefrontal cortex in patients that attempted suicide [181].

Clinical and epidemiological studies have consistently shown that one or more anxiety disorders occur in the majority of people with AN or BN [15,16,182,183]. Silberg and Bulik [184], using twins, found a unique genetic effect that influences liability to early anxiety and eating disorder symptoms. When a lifetime anxiety disorder is present, the anxiety most commonly occurs first in childhood, preceding the onset of AN or BN [25,26,28]. Anxiety and harm avoidance remain elevated after recovery from AN, AN-BN, and BN [185], even if individuals never had a lifetime anxiety disorder diagnosis. [15] Finally, anxiety [186] and Harm Avoidance from the Cloninger (TCI) [187] Temperament and Character Inventory have been a robust signal in our (WK PI) genetic studies [188]. In summary, the premorbid onset and the persistence of anxiety and harm avoidance symptoms after recovery suggest these are traits that contribute to the pathogenesis of AN and BN. The PET imaging data suggest that such behaviors are related to disturbances of 5-HT and DA neurotransmitter function in limbic and executive pathways.

24. Implications

Phillips [94] has described a ventral limbic system, which includes the amygdale, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex, which identifies the emotional significance of a stimulus and the production of an affective state in response to that stimulus. In addition, these regions are important for automatic regulation and mediation of autonomic responses to emotional stimuli and contexts accompanying the production of affective states.

The findings described above offer evidence that individuals with ED have 5-HT and DA dysregulation within brain regions that constitute limbic circuits. In general, such alterations tend to be present in the ill state and persist after recovery. Patterns of 5-HT receptor binding vary by subtype in the REC subjects, raising the possibility that each ED subtype has a unique pathophysiology. (Table 3) Similar patterns of binding (elevated 5-HT_{1A} and reduced 5-HT_{2A}) were also found in other temporal, cingulate, and parietal regions suggesting a widespread distribution involving more than just limbic function. We also found that REC AN had increased binding of the DA D2/D3 receptors in the AVS.

Table 3
Compared to normal control values of receptor and transport binding potential in subjects recovered from anorexia and bulimia nervosa

	AN	AN-BN	BN
ROI	Medial orbital frontal, subgenual cingulate, mesial temporal		
5-HT1A BP	–	↑	↑
5-HT2A BP	↓	↓	–
ROI	Anterio ventral striatum		
5-HTT BP	↑	↓	–
DA D2/D3 BP	↑	↑	–

Drawing inferences about behavior from these 5-HT and DA findings is speculative. Moreover, no receptor works in isolation in the brain. Monoamine enervation of limbic pathways is complex, and involves many pathways, receptors, enzymes, intracellular transcription messengers, other neurotransmitters and molecules. It can be hypothesized that these receptor findings might reflect the “health” of the 5-HT and DA function within limbic circuits, but not necessarily be the specific cause of these disorders. The genetic literature suggests that behavioral disorders are complex, and consist of multiple factors, each of small effect. Finally, altered 5-HT and DA receptor binding is often found in depression and anxiety, although patterns of binding tend to be different. Disturbances of affect and impulse regulation may involve similar pathways, but with very different patterns of molecular disturbances.

25. Feeding behavior

Within the limbic system are brain regions that contribute to rewarding and sensory aspects of feeding behavior. That is, a primary taste cortex resides in the rostral insula and adjoining frontal operculum [189–192]. Some studies argue that these regions provide a representation of food in the mouth that is independent of hunger, and thus is of reward value [193]. The responsiveness of taste neurons in secondary regions, such as the OFC, computes the hedonic value of food [193–195]. Other studies [196] raise the possibility that the insula and OFC contribute to feeding behavior by encoding changes in the value of food reward in addition to sensory processing, suggesting overlapping representations of sensory and affective processing of taste. As described above, previous brain imaging studies have shown pictures of food to emaciated and malnourished AN individuals. These studies found altered activity not only in the insula and OFC, but in broad regions including mesial temporal, parietal, and the anterior cingulate cortex when ill AN subjects were compared to controls [122,125–127,129,197].

Our group [198] is the first to use fMRI to investigate the effect of administration of nutrients to REC RAN individuals. Compared to CW, the remitted AN subjects had a significantly reduced fMRI signal response to the blind administration of sucrose or water in the insula, anterior cingulate and striatal regions (Fig. 3). Importantly, REC AN and CW also showed differences in correlations between experience of pleasant taste and brain activation. For CW, self-ratings of pleasantness of the sugar taste were positively correlated to the signal response in

the insula, anterior cingulate, and ventral and dorsal putamen. In comparison, REC AN individuals failed to show any relationship in these regions to self-ratings of pleasant response to a sucrose taste.

In general the anterior, less differentiated half of the insula [199–202] receives the majority of projections from the amygdala and thalamic taste centers, making it an ideal site for the formulation of hedonic representations of taste. Consistent with this, anterior portions of the insula have been shown to be differentially activated to the intensity and valence of pleasant and unpleasant tastes [196], and are thus important to examine in the eating disordered population. A large literature shows that the anterior insula and associated gustatory cortex responds not only to the taste and physical properties of food, but also to its rewarding properties [196,203,204]. Animal models show that fine-tuning of feeding responses to salient food items is lost after insula lesions. For example, the natural devaluation of food after feeding to satiety is attenuated in lesioned animals, suggesting that the insula encodes representations of the incentive value of taste under specific conditions [205]. Similarly, appropriate avoidance of foods previously associated to sickening agents is lost after insula lesions, providing further evidence that the insula encodes the incentive value of taste in particular circumstances [206].

Our results in the insula are reinforced by parallel findings in basal ganglia subregions that receive insular inputs. While the entire striatum receives inputs from the insula as a whole, the ventral putamen is a specific recipient of inputs from anterior insular regions encompassing the gustatory cortex [207]. The ventral putamen in turn projects to the globus pallidus, another region with significant alterations in signal. The pattern of relatively decreased signal in these interconnected structures suggests a circuit-wide disturbance in REC AN. Insular inputs to the striatum are hypothesized to mediate behaviors involving eating, particularly of highly palatable, high energy foods. The ventrolateral striatal subregions, including the ventral putamen, have been especially implicated [208]. AN subjects tend to avoid high calorie, palatable food. In theory, this is consistent

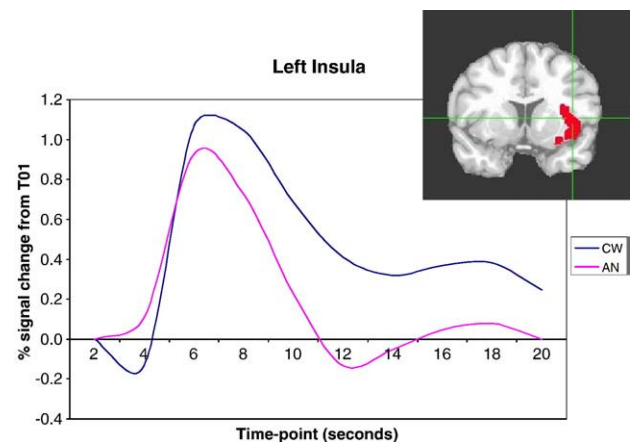


Fig. 3. Coronal view of left insula ROI ($x=-41$, $y=5$, $z=5$). Time course of BOLD signal as a mean of all 16 recovered restricting-type anorexia nervosa and 16 control women for taste-related (sucrose and water) response in the left insula.

with abnormal responses of insula-striatal circuits that are hypothesized to mediate behavioral responses to the incentive value of food.

26. The insula and interoceptive awareness

Do individuals with AN have an insular disturbance specifically related to gustatory modulation, or a more generalized disturbance related to the integration of interoceptive stimuli? The insula is thought to play an important role in processing interoceptive information, which can be defined as the sense of the physiological condition of the entire body [209]. Aside from taste, interoceptive information includes sensations such as temperature, touch, muscular and visceral sensations, vasomotor flush, air hunger and others [210]. The role of the insula is thus focused on how the value of stimuli might affect the body state. 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. The insula has bidirectional connections to limbic regions, including the amygdala, nucleus accumbens [211] and OFC [212]. Thus the insular cortex 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 insula plays a key role in interoceptive monitoring of the sensations that are important for the integrity of the internal body state and connecting to systems, through dorsolateral striatal pathways that are important for allocating attention, evaluating context, and planning actions [209,210,213].

Individuals with ED have a complex of puzzling symptoms, for which there has been no neurobiological explanation. Many of the symptoms commonly found in AN, such as distorted body image, lack of recognition of the symptoms of malnutrition, could be related to disturbed interoceptive awareness. In support of this possibility, only the controls, but not the REC RAN, showed a positive relationship between self-ratings of pleasantness and the intensity of the signal for sugar in the insula, ventral and dorsal putamen as well as anterior cingulate cortex. In addition, for example, studies have consistently found that AN and BN individuals have elevated pain thresholds [214], which persists after recovery [215], and is potentially a marker of altered interoceptive awareness. While more speculative, it is possible that other symptoms, such as diminished insight and motivation to change, and altered central coherence, could be related to disturbed interoceptive awareness. Those with AN fail to accurately recognize and incorporate affective and social stimuli in the environment, as confirmed by laboratory tests [19,20]. Furthermore, individuals with AN have enhanced ability to pay attention to detail or use a logical/analytic approach, but exhibit worse performance with global strategies [19,22].

27. Conclusion

We hypothesize that a trait-related disturbance of 5-HT neuronal modulation predates the onset of AN and contributes to premorbid symptoms of anxiety and inhibition. This dysphoric

temperament may involve an inherent dysregulation of emotional and reward pathways [216] which also mediate the hedonic aspects of feeding, thus making these individuals vulnerable to disturbed appetitive behaviors. This 5-HT disturbance contributes to a vulnerability for restricted eating and dysphoric mood states such as increased harm avoidance. Most importantly, we think that restricting food intake is powerfully reinforcing because it provides a temporary respite from dysphoric mood. Several factors may act on these vulnerabilities to cause AN to start in adolescence. First, puberty-related female gonadal steroids or age-related changes may exacerbate 5-HT dysregulation. Second, stress and/or cultural and societal pressures may contribute by increasing anxious and obsessional temperament. We hypothesize that people with AN may discover that reduced dietary intake, by reducing plasma TRP availability [80], is a means by which they can crudely modulate brain 5-HT functional activity and anxious mood. [66] People with AN enter a vicious cycle which accounts for the chronicity of this disorder because caloric restriction results in a brief respite from dysphoric mood. However, malnutrition and weight loss, in turn, produce alterations in many neuropeptides and monoamine function, perhaps in the service of conserving energy, but which also exaggerates dysphoric mood. Thus those with AN pursue starvation in an attempt to avoid the dysphoric consequences of eating. SSRI administration does not appear to be effective in counteracting 5-HT disturbances in patients with AN, perhaps because of the extreme changes induced by malnutrition in the 5-HT_{1A} receptor and extracellular 5-HT concentrations.

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