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The Neurobiology of Anorexia Nervosa

Ashley Higgins

Abstract

Anorexia nervosa is considered the most deadly psychological illness. Individuals with and recovered from anorexia nervosa experience numerous physical and mental health difficulties, and treatment outcomes remain unpromising. Anorexia nervosa is rare in the general population, but common among individuals with a first-degree relative with the disorder. In addition, the onset of anorexia nervosa is developmentally specific, which suggests a partly biological etiology. A better understanding of the biological and neurobiological etiology of anorexia nervosa is direly needed to inform new therapies and to identify individuals at risk for the disorder. This paper summarizes the research related to neurotransmitter abnormalities, aberrant brain activity, and genetic and epigenetic mechanisms that may contribute to the etiology of this deadly disorder.

Keywords: anorexia nervosa, neurobiology, neurotransmitters, genetics, etiology

1. Introduction

Anorexia nervosa (AN) is a serious psychological disorder characterized by low body weight, unhealthy weight loss methods, and an extreme focus on weight and body shape [1]. AN is associated with significant mortality risks due to medical complications, as well as the fact that one in five patients with AN die by suicide [2, 3]. The physical sequelae of AN, which are caused by self-starvation, affect nearly every major organ system. For instance, the gastrointestinal complications of AN include dysphagia [4], delayed gastric emptying [5], and risk of gastric dilation or even perforation [6]. Hematological and musculoskeletal complications include osteoporosis, fracture risk [7], and low red and white blood cell counts [8]. The endocrine system is impacted via elevated cortisol and growth hormones, low serum thyroid levels, and hypoglycemia [5, 9]. Dermatological complications include lanugo, acrocyanosis, and thinning hair [10]. Neurological complications, which will be discussed in depth throughout this chapter, are well-documented in terms of the effects of long-term caloric restriction on brain volume and neural activity [11]. Finally, cardiac complications, which are most often linked to mortality in AN, include bradycardia [12], prolonged QTc interval [13], and left ventricular atrophy [14].

Current medication and psychotherapies have limited success in treating AN. The prognosis is especially poor if treatment begins more than 3 years after the onset of symptoms [15]. AN currently has no viable treatment options [16], as current medications and psychotherapies provide only minor to modest effects, with especially poor outcomes among women with entrenched AN [16–18]. It is estimated that only half of individuals with AN achieve full remission of symptoms,

and even recovered patients typically maintain a low weight and experience chronic depressive symptoms [19]. Given the lack of viable treatment options for AN, leading eating disorders researchers are now recommending that future research focus on identification of risk factors and other preventive strategies [20, 21].

Many of the identified risk factors for AN are biological or genetic in nature. AN is a rare disorder, with estimated lifetime prevalence ranging from 0.1 to 3.6%, and a point prevalence rate ranging from 0.1 to 1.2% in the general population [22]. Though the overall prevalence of AN is quite low, AN represents the third most common chronic illness with adolescent onset [23]. In addition, the risk of AN is elevated among individuals with a family history of AN. It is a well-documented finding that AN tends to run in families [24, 25]. Some studies have found a 10-fold risk of AN among first-degree relatives of individuals with the disorder [26–28] or an overall heritability of 0.56 [25]. Furthermore, AN has a developmentally specific age of onset. Taken together, these findings suggest the presence of biological and/or genetic risk factors in the etiology of AN [29].

Individuals with AN often display a relentless pursuit of further weight loss and believe themselves to be overweight even when they are emaciated. In addition to pathological eating patterns, individuals with EDs also experience a host of unusual symptoms, such as “(1) extremes of behavioral inhibition and dysinhibition; (2) anxiety, depression, and obsessionality; and (3) puzzling symptoms such as body image distortion, perfectionism, and anhedonia” ([30], p. 38) as well as “intense body-focused anxiety, self-disgust, compulsive behavior and altered information processing—i.e. raised pain threshold, reduced sense of taste, anosognosia, inability to integrate thoughts and feelings, poor visuospatial memory, cognitive rigidity and weak central coherence” ([31], p. 580). Any biological mechanisms accounting for the inherent eating pathology of AN should also modulate these emotional and cognitive phenomena.

Identifying true risk factors for AN presents a complicated methodological problem. By definition, a risk factor must be present prior to the onset of illness, and identifying these factors prior to the symptom onset requires a prospective design [32]. However, given the low prevalence rate of AN, prospective studies are often too complicated to perform; thus, the research literature on AN risk factors is often limited to retrospective studies, with their inherent bias in retrospective recall [33].

Another methodological approach samples from individuals who have recovered from AN (RECAN). While recovery from AN is a long and ill-defined process, more than half of individuals with AN are able to completely or partly achieve remission [34]. Individuals RECAN are assumed to no longer be experiencing the sequelae of the starvation state. However, the use of individuals RECAN is limited as a methodological approach in that “scar” effects from a period of illness could be misidentified as premorbid risk factors [35]. In order to circumvent the possibility of “scar” effects, studies must identify endophenotypes that are present among individuals with active AN, individuals RECAN, and among unaffected family members [36, 37]. Utilizing this approach, several potential endophenotypes have been identified, by eliminating any neurobiological findings that improve with refeeding and identifying abnormalities that are shared by individuals with AN and their unaffected family members [16].

Many of the neurobiological phenomena to be discussed in this paper are present premorbidly, exaggerated by malnutrition, and return to premorbid levels after recovery [38]. There are currently promising lines of research on dopaminergic [29], serotonergic [39], and noradrenergic pathways [31], as well as dysregulations in appetitive functioning [30], genetic and epigenetic contributions [40, 41], contributions from gonadal hormones [42], and aberrations in brain activity [43].

2. Dopamine

Dopaminergic functioning modulates reward and affect, and an aberration in dopaminergic functioning has been implicated in obsessive or ritualistic behaviors, such as the food rituals observed in individuals with AN [29]. It seems intuitive that reward functioning is impaired in AN, as individuals with AN often present as abstemious, anhedonic, and temperate in a multitude of behaviors even in childhood, long before the onset of symptoms [44]. Dopamine is central in processing reward in both primary and secondary reinforcers, including food [45–47]. Several research studies have revealed altered striatal dopamine function in individuals with and RECAN [29, 48, 49]. Ingestion of highly palatable foods, such as high-sugar foods, may trigger dopamine release in individuals without AN; this release of dopamine in response to food is similar to the release of dopamine elicited by amphetamine use, which is often associated with feelings of euphoria [50]. However, among individuals RECAN, amphetamine use triggers the expected endogenous dopamine release, but this release of dopamine is experienced as highly unpleasant and anxiogenic [51]. If similar processes take effect during exposure to highly palatable food, which would be experienced as highly anxiogenic to individuals with AN, this could partially account for the persistence that individuals with AN display in their pursuit of self-starvation; if food is anxiogenic, self-starvation downregulates this anxiety. Whereas individuals without AN experience pleasure from foods, individuals with AN find it aversive. Thus, the reinforcing aspects of food are not experienced by individuals with active AN or individuals RECAN.

Reward processing in general appears to be altered in individuals with AN, even in situations that do not involve food- or weight-related cues. In fMRI research, individuals RECAN failed to differentiate between winning and losing money in a gambling task [52]. Therefore, individuals with AN may have a diminished ability to identify the positive or negative value of a stimulus. Individuals with AN fail to show appropriate appetitive motivational system activation to a variety of cues [49]. Thus, altered dopaminergic function reflects high conditioning of reward for disease-salient stimuli, but a failure to respond appropriately to other positive and negative cues [18].

Among individuals RECAN, dopamine metabolite concentrations in the cerebral spinal fluid remain depleted years after the disorder [53]. Perhaps to correct for this depletion, dopamine 2 and 3 (D_2/D_3) receptor binding in the ventral striatum is elevated among individuals RECAN [44]. At this time there are no publications on dopamine aberrations in unaffected family members. However, animal models of anorexia strongly suggest a dopaminergic endophenotype, as administering dopamine antagonists in activity-based anorexia in rats facilitates increased food intake [54]. This hints at a dopaminergic role in promoting weight loss, which can be reversed with psychopharmacology that acts on the dopamine system.

3. Serotonin

Additionally, serotonergic (5-HT) dysfunction may be a biological marker for AN. Serotonin has seemed a likely candidate for some time, given this neurotransmitter's active influence in modulating mood and appetite [29]. A recent meta-analysis has concluded that being a carrier of the S allele of the 5-HTTLPR polymorphism of the serotonin transporter gene is predictive of eating disorders, particularly anorexia [55]. The gene coding of the serotonin transporter (5-HTT) works in the presynaptic neuron to terminate serotonin activity in the synapse and recycle serotonin back into the presynaptic neuron. 5-HTT is coded by a gene on

chromosome 17, and the 5-HTTLPR polymorphism of this gene has the greatest impact on behavior. The S allele is a short variant of this 5-HTTLPR polymorphism, which decreases the availability of 5-HTT and results in dysphoria.

In terms of appetite, any treatment that increases intrasynaptic 5-HT or activates 5-HT receptors will reduce appetite and food consumption, while any treatment that reduces transmission or blocks receptors will promote weight gain [56]. Caloric restriction has an enormous impact on the available serotonin in the brain [29]. Tryptophan is one of 20 essential amino acids and can be absorbed only through caloric intake, especially carbohydrate intake [57]. Tryptophan, through a series of chemical processes, becomes serotonin. A restricted diet limits the amount of tryptophan (and, therefore, the amount of serotonin) that is available to the brain [58]. In addition, a restricted diet decreases the rate of synthesis in serotonin receptors and the density of serotonin transporters, which results in oversensitivity to serotonin in postsynaptic receptors [59]. Not surprisingly, individuals in the acutely ill state have lowered concentrations of the 5-HT metabolite 5-HIAA in the cerebral spinal fluid [56]. However, elevated levels of 5-HIAA were likely present premorbidly. Individuals with AN premorbidly report high levels of anxiety, dysphoria, and obsessionality, which are associated with high levels of 5-HT in the synapse [42]. Dieting actually serves to regulate the 5-HT in the synapse. This reduction of serotonin, in the short term, results in anxiolytic effects for people who restrict calories [29]. These anxiolytic effects could explain why individuals with AN cling so desperately to their restrictive behaviors: these behaviors are inadvertently medicating underlying anxiety.

The serotonin system includes at least 14 different receptors. The 5-HT_{1A} and 5-HT_{2A} receptors appear most influential in the pathogenesis of AN. The 5-HT_{1A} autoreceptor serves to decrease 5-HT transmission [56]. Individuals with AN have 50–70% more binding at these receptors, and retain 20–40% more binding after recovery. In addition, the 5-HT_{1A} receptor may play a role in the efficacy of selective serotonin reuptake inhibitors (SSRIs), which are potentially effective at treating depression and anxiety [60, 61]. While starvation decreases 5-HT across the brain, the overactive 5-HT_{1A} receptor continues to inhibit 5-HT transmission. The combination of these forces is so powerful that SSRIs exert minimal impact in increasing intrasynaptic 5-HT, which fails to provide symptom relief for individuals with AN [56]. In AN, SSRIs fail to desensitize 5-HT_{1A} receptors, which inhibits presynaptic 5-HT.

Newer imaging technologies, such as PET imaging with selective neurotransmitter radioligands, allow for viewing in vivo neurotransmitter activity in the brain. Postsynaptic 5-HT_{2A} receptors have been studied in this way. The 5-HT_{2A} receptor has been afforded special attention because activity at this receptor is influential in two of the central, yet most perplexing, symptoms of AN: poor problem-solving abilities and distorted body image [62, 63]. 5-HT_{2A} receptor binding is reduced in several brain areas, especially in the cingulate and temporal regions. The cingulate-temporal dysfunction could be related to inefficient problem-solving behaviors among individuals with AN, who struggle with incorporating affective and social stimuli into tasks [64]. Individuals with AN do not seem to learn from mistakes, but stubbornly and obsessively use the same strategies, despite poor results. This could indicate dysfunction in executive functioning and planning. In terms of distorted body image, which is characterological for individuals with AN, 5-HT_{2A} disturbances in the left parietal region of the brain are thought to be responsible [62]. Lesions in the right parietal region have been associated with neglect, which could be theoretically related to body image distortion, especially if this information is coded in the parietal regions of each hemisphere [56]. The activity at 5-HT_{2A} receptors remains dysregulated even after a year of maintaining normal weight, regular menstruation, and no binge/purging/restricting. Prolonged dysregulation at these receptors may partially account for the inefficacy of SSRIs in treating AN, regardless of the phase of the disorder [17, 18].

Additionally, serotonergic dysfunction is common to other psychiatric concerns, especially those that are likely to be comorbid with AN, such as major depression [65] and anxiety disorders [66]. While abnormalities in serotonergic functioning are common to all of these disorders, different patterns of serotonergic functioning emerge on a molecular level [67]. While 5-HT_{1A} receptor binding is often decreased in individuals with or recovered from depression [68, 69] and panic disorder [70], 5-HT_{1A} receptor binding is increased in individuals with AN [29]. This could indicate that serotonergic dysfunction is a common vulnerability for a variety of disorders, with disorder-specific patterns at the neuronal level. This also accounts for higher rates of psychiatric concerns among family members of individuals with AN.

Given etiological research on the separate roles of dopamine and serotonin, it is not surprising that the most recent research suggests that interactions between serotonin and dopamine activity truly elicit and maintain the eating pathology of AN [56]. This interaction is not well understood, but could hold promise for future pharmacological interventions for AN.

4. Norepinephrine

Based on previous research on dopaminergic and serotonergic dysfunction in individuals with active AN, individuals RECAN, and unaffected family members, it is safe to conclude that neurotransmitter activity is aberrant both during the premorbid, active, and recovery periods of AN. Dopaminergic and serotonergic pathways could account for some, though not all, of the core symptoms of AN [29, 42]. While these pathways (particularly the serotonergic pathway) partly account for rigidity and perfectionism among individuals with AN, individuals with AN display a variety of perplexing symptoms that seem unrelated to both the starvation state itself or serotonin dysfunction alone; individuals with AN report difficulty with pain perceptual, alexithymia, reduced sense of taste, as well as numerous other perplexing symptoms [31]. Aberrant activity in the noradrenergic pathway could better account for this vast range of deficits.

Norepinephrine is a neurotransmitter which serves multiple functions in the body and brain, including regulation of sympathetic arousal/anxiety and cerebral blood flow [71]. Norepinephrine levels are elevated premorbidly in AN [72], but appear to be decreased in plasma and cerebrospinal fluid during active AN and RECAN [72–74]. Premorbidly high levels of norepinephrine lead to high sympathetic arousal and anxiety [31]. Among individuals with AN, this anxiety is often focused on food- and weight-related issues, though the inherently high trait levels of perfectionism and neuroticism can manifest in other achievement domains such as schoolwork or sports [75]. Since this anxiety is linked to an abundance of norepinephrine, dieting in the early stages of AN counteracts this by depleting the brain of the precursors to norepinephrine that are normally ingested through food [31]. Dieting is then maintained through negative reinforcement, leading to a reduction in body weight and entrenchment of AN symptoms. Furthermore, aberrant activity in the noradrenergic system has been linked to irregular patterns of activation in the insula, which will be discussed in the next section.

5. Brain volume, blood flow, and neural activity

Various neuroimaging studies show substantial structural abnormalities in the brain among individuals with active AN [30, 76, 77]. However, significant questions remain as to:

whether such anomalies reflect regionally specific disturbances that might help explain disorder-defining psychopathology or merely generic, global consequences of malnutrition. Similarly, it remains unclear whether structural alterations in AN constitute premorbid traits or persisting “scars,” as might be the case if they would still be evident following weight restoration ([76], p. 214).

Decreased volumes of white and gray brain matter have been documented throughout the brain during the acute phases of illness [77, 78]. More specifically, gray matter atrophy has been noted in the cerebellum, hypothalamus, caudate nucleus and frontal, parietal and temporal areas [77, 79, 80], as well as in the cingulate cortex [81] and the precuneus [82]. The rate of gray matter atrophy is not uniform across the brain during active AN; atrophy in the hypothalamus may appear early in AN, whereas atrophy in the cerebellum is a late consequence of AN among patients with longer durations of illness [77].

However, these gray and white matter findings appear to be specific to the acute phase of illness and caused by malnutrition and cerebral dehydration [77]. A meta-analysis revealed that gray matter is reduced by 5.6% during the acute phases of AN, whereas white matter is reduced by 3.8% [83]. A few months of treatment and results in approximately 50% of gray matter regain and nearly all of the white matter being regained. A few years following remission of AN, gray matter and white matter depletions are no longer statistically significant. It is possible that hormone levels impact how much gray matter is recovered, as high levels of cortisol at the time of hospitalization are negatively correlated with gray matter restoration following weight gain [84]. All told, the decreased volume of white and gray matter in individuals with AN normalizes with proper nutrition [38, 85]. Thus, these gray and white matter findings are not likely to be a contributing factor to the neurobiological etiology of AN.

In contrast, abnormal patterns of blood flow to the brain and brain activity persist after recovery. For instance, individuals who have recovered from AN often have hypoperfusion in the frontal, parietal, temporal and occipital areas of the brain [86]. In addition, overactivation of the frontal and anterior cingulate cortex (ACC) and insula following exposure to pictures of food or the taste of food is present both during active AN and after recovery [87, 88]. Hyperactivity in these regions could be an endophenotype for AN and be related to more global difficulties with appetitive mechanisms.

The complex eating pathology inherent in AN may indicate atypical functioning in appetitive mechanisms. Despite the unique and stereotypic presentation of altered eating patterns in the eating disorder diagnoses, it is still unknown whether individuals with AN have disordered appetitive functioning. The neural and limbic circuits are more likely candidates for deregulating appetitive functioning in AN than peripheral signs (such as hormonal imbalances or abnormalities in the gastrointestinal tract), because these neural and limbic circuits also regulate reward processing and emotionality, which are known to be disordered in AN [89]. Individuals with AN display an almost phobic avoidance of high-fat foods, which persists after recovery. Individuals who have recovered from AN fail to connect hunger cues with positive ratings of food [88]. Particularly promising research has focused specifically on the anterior insula, which is positioned in the primary gustatory cortex [90]. While this is still debated, researchers posit that the anterior insula codes a representation of food and its hedonic value, and projects to other parts of the brain [91, 92]. The anterior insula resides next to the orbito-frontal cortex, which interprets information from the anterior insula and is responsible for flexible decision-making with ever-changing stimuli [93]. Put another way, the anterior insula represents the food and its hedonic value, while the orbito-frontal cortex weighs those representation against hunger and other variables. Critically, the

orbito-frontal cortex is very sensitive to changes in serotonin, which could account for the inflexibility in eating pathology in individuals with AN [94]. Even though research in this area is still in its infancy, the aforementioned processing abnormalities in the anterior insula and orbito-frontal cortex shed some light as to how “AN individuals fail to become appropriately hungry when starved, and thus are able to become emaciated” ([30], p. 45).

Though disturbances related to the gustatory modulation of the anterior insula certainly appear to be a key part of a biological risk factor in AN, the anterior insula influences many processes unrelated to gustatory mechanisms [30]. Disturbances in the anterior insula could be related to a more general deficit in interoceptive awareness [95, 96]. Altered activity in the insula “supports the idea that they might suffer from a fundamentally and physiologically altered sense of self” ([97], p. 111). Some of the more mysterious symptoms of AN, such as a denial of signs of malnutrition and lack of motivation to change pathological eating behaviors, could be linked to abnormal patterns of activity in the insula [98].

6. Genetics

There is clear and compelling evidence that having a first-degree relative with AN significantly elevates one’s risk for developing AN; in fact, relatives of individuals with AN are 11.3 times more likely to develop AN [27]. There is likely some genetic contribution to the etiology of AN. Current heritability estimates range between 50 and 80% [99, 100], though specific genetic mechanisms have been difficult to identify. A noteworthy paradox was pointed out regarding the high heritability of AN and the likelihood of reduced reproductive fitness from prolonged periods of malnutrition [101]. Thus, one can conclude that genes that contribute to the etiology of AN must be rare and of recent origin. In addition, high rates of diagnostic crossover between eating disorder categories (see [102]) and high rates of comorbidity with mood and anxiety disorders (see [103]) also complicate the genetic etiology of AN, since any genetic predispositions for AN should be non-specific and shared with these other conditions.

One method of identifying genes relevant to the pathophysiology of AN is the candidate gene approach. The candidate gene approach is defined as an examination of genes that could be involved in a particular disease or syndrome because the function of those genes is related to the sequelae of the illness [104]. The candidate gene approach could be likened to finding “a needle in the haystack” of 27,000 human genes. Thus, it is not surprising that candidate gene studies for AN are controversial and many fail to replicate genetic association.

Family-based linkage analyses, or the process of detecting the location of disease genes on the chromosome, have identified three chromosomal regions of interest for AN; one resides on chromosome 13 (specifically, 13q13.3) and is related to drive-for-thinness, another resides on chromosome 2 (2p11.2) and is related to obsessionality, and a third on chromosome 1 (specifically, 1q1.3) which is related to both obsessionality and drive-for-thinness [105].

Genes related to dopamine transfer (DAT1) and dopamine receptors (DRD2) have been examined among patients with AN. Individuals with AN show elevated expression of DAT1 and reduced expression of DRD2 [106]; while the implications of these expression are not fully understood, a genetic contribution to the etiology of AN related to dopamine expression is consistent with previously mentioned research on altered reward processing in AN. Other genetic research has also identified an interaction of three genes that clear serotonin and norepinephrine from the synapse; these genes (a serotonin transporter gene, a norepinephrine

transporter gene, and a monoamine oxidase A gene) appear to contribute to the risk of restricting AN [41]. While the presence of each gene variant alone is associated with a somewhat increased risk of restricting AN, the combination of all three gene variants leads to a risk that is up to eight times greater than the risk associated with one gene variant alone.

Finally, there are epigenetic factors to consider. Perhaps the most important epigenetic mechanism to consider is the role of estradiol in triggering genetic risk for AN, which is discussed below. All told, the genetic and epigenetic contributions to AN remain largely unknown. Genetic studies are limited by previously mentioned methodological issues, such as the low prevalence of AN and the near impossibility of recruiting individuals with AN during the premorbid period for genetic research. However, progress in identifying genes or patterns of gene expression could lead to pharmacological advances that are direly needed for this population given the poor response to common psychotropics such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotics [17, 18].

7. Pubertal hormones

The vast majority of individuals with AN are biologically female and begin experiencing symptoms of AN during the pubertal and pre-pubertal periods of development [1]. These findings suggest that gonadal hormones specific to females may play a role in the epigenesis of AN. It is possible that genetic factors may be more impactful for females than males with regards to drive for thinness and body dissatisfaction [107] as well as for concerns about body shape and weight [108]. In addition to gender differences in genetic factors, genetic risk for eating disorders appears to be moderated by age, as there is almost no genetic effect (5% or less on disordered eating among preadolescent female twins, but by late adolescence there is evidence of substantial genetic effects [109]. Upon closer examination, the genetic effect appears to be due to pubertal status and not age, as 11-year-old twins who had begun puberty showed a higher magnitude of genetic effects compared to same-age twins who had not begun puberty [110]. Pubertal hormones, such as estradiol, which steadily increases during puberty among females, may trigger the genetic risk for disordered eating, as high levels of estradiol are associated with magnitude of genetic effects in a manner independent of age and physical signs of puberty development, such as body hair or breast development [111].

In addition to triggering the genetic risk for AN, low estradiol levels are associated with a number of negative effects during the active phases of AN. Not surprisingly, malnourished individuals show a variety of hormonal imbalances, most of which return to baseline after recovery [42]. Pubertal hormones appear to follow this same pattern of alteration during active illness but return to baseline upon weight regain. In a typically developing adolescent, an increase in pubertal hormones aids in brain maturation, most notably in the limbic system [112, 113]. These hormone levels are altered among individuals diagnosed with AN, who may experience amenorrhea due to low body weight and/or body fat [114]. When individuals achieve weight regain and recommence with menstruation, cognitive functioning improves, suggesting that increasing levels of estradiol during weight regain may assist with neural recovery [115].

8. Conclusions and future directions

The etiology of AN is multifaceted, with contributions from genetic factors, biological factors, family dynamics, personality characteristics, and sociocultural

influences. The development of this disorder and its maintenance remain poorly understood despite a significant increase in rigorous scientific study into risk factors and shared vulnerabilities with other eating disorders and psychological disorders.

In recent years, the neurobiological etiology of AN has been examined through a wide variety of imaging studies, genetic studies, and hormonal/biological studies (see [97]). A number of key findings are summarized in this paper. Across these studies, it is clear that the brains of individuals with AN show evidence of altered reward processing and appetitive mechanisms, which are linked to a number of dopaminergic findings (perhaps, most importantly, how the brains of individuals with AN process cues of palatable foods as highly anxiogenic and aversive [50, 51]. Serotonergic functioning has been long-thought to account for behavioral rigidity and trait obsessiveness in AN [56], and recent genetic research has identified a number of potential serotonergic genetic candidates or interactions of genetic candidates that represent significant risk factors for AN [44, 74, 104, 107]. Finally, altered noradrenergic functioning and aberrant activity in the insula represent a unique but comprehensive view of the global difficulties individuals with AN have with emotions, insight, and interoceptive awareness [31, 71]. These findings, taken together, can illuminate future pathways for pharmacotherapies that will be more effective for individuals with AN. Other brain-based findings discussed in this paper, such as gray and white matter atrophy, are unlikely to represent true risk factors, because the vast majority improve with proper nutrition.

In conclusion, the neurobiological etiology of AN in-and-of-itself is complex and complicated by factors such as the low prevalence rate of AN [1], lack of prospective research [32], and the at-times catastrophic impact of malnutrition on the brain and body [38]. AN continues to be considered the most deadly psychological illness, and individuals with AN may face a lifetime of physical and emotional challenges [1]. Given the ego-syntonic nature of this disorder and that current treatment outcomes are suboptimal for this population, a better understanding of the biological vulnerabilities of this illness and the development of new therapies are direly needed.

Conflict of interest

There are no conflicts of interest to report.

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