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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 disinhibition; (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.

Author details

Ashley Higgins
Immaculata University, Malvern, PA, United States of America

*Address all correspondence to: ahiggins@immaculata.edu

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References

- [1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013
- [2] Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: A meta-analysis of 36 studies. *Archives of General Psychiatry*. 2011;**68**:724-731. DOI: 10.1001/archgenpsychiatry.2011.74
- [3] Franko DL, Keshaviah A, Eddy KT, Krishna M, Davis MC, Keel PK, et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *American Journal of Psychiatry*. 2013;**170**:917-925. DOI: 10.1176/appi.ajp.2013.12070868
- [4] Holmes SR, Gudridge TA, Gaudiani JL, Mehler PS. Dysphagia in severe anorexia nervosa: A case report. *International Journal of Eating Disorders*. 2012;**45**:463-466. DOI: 10.1002/eat.20971
- [5] Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. *The American Journal of Medicine*. 2016;**129**:30-37. DOI: 10.1016/j.amjmed.2015.06.031
- [6] Mascolo M, Dee E, Townsend R, Brinton JT, Mehler PS. Severe gastric dilatation due to superior mesenteric artery syndrome in anorexia nervosa. *International Journal of Eating Disorders*. 2015;**48**:532-534. DOI: 10.1002/eat.22385
- [7] Faje AT, Fazeli PK, Miller KK, Katzman DK, Ebrahimi S, Lee H, et al. Fracture risk and areal bone mineral density in adolescent females with anorexia nervosa. *International Journal of Eating Disorders*. 2014;**47**:458-466. DOI: 10.1002/eat.22248
- [8] Hutter G, Ganepola S, Hofmann WK. The hematology of anorexia nervosa. *International Journal of Eating Disorders*. 2009;**42**:293-300. DOI: 10.1002/eat.20610
- [9] Lo Sauro C, Ravaldi C, Cabras PL, Faravelli C, Ricca V. Stress, hypothalamicpituitary-adrenal axis and eating disorders. *Neuropsychobiology*. 2008;**57**:95-100. DOI: 10.1159/000138912
- [10] Strumia R. *Eating Disorders and the Skin*. New York, NY: Springer; 2012
- [11] Fuglset TS, Endestad T, Hilland E, Bang L, Tamnes CK, Landrø NI, et al. Brain volumes and regional cortical thickness in young females with anorexia nervosa. *BMC Psychiatry*. 2016;**16**:404-412. DOI: 10.1186/s12888-016-1126-9
- [12] Yahalom M, Spitz M, Sandler L, Heno N, Roguin N, Turgeman Y. The significance of bradycardia in anorexia nervosa. *The International Journal of Angiology*. 2013;**22**:83-94. DOI: 10.1055/s-0033-1334138
- [13] Krantz MJ, Sabel AL, Sagar U, Long CS, Barbey JT, White KV, et al. Factors influencing QT prolongation in patients hospitalized with severe anorexia nervosa. *General Hospital Psychiatry*. 2012;**34**:173-177. DOI: 10.1016/j.genhosppsych.2011.08.003
- [14] Lamzabi I, Syed S, Reddy VB, Jain R, Harbhajanka A, Arunkumar P. Myocardial changes in a patient with anorexia nervosa: A case report and review of literature. *American Journal of Clinical Pathology*. 2015;**143**:734-737. DOI: 10.1309/AJCP4PLFF1TTKENT
- [15] Treasure J, Russell G. The case for early intervention in anorexia nervosa: Theoretical explanation of maintaining factors. *British Journal of Psychiatry*.

2011;**199**:5-7. DOI: 10.1192/bjp.bp.110.087585

- [16] Bulik C, Berkman ND, Brownley KA, Sedway JA, Lohr KN. Anorexia nervosa treatment: A systematic review of randomized control trials. *International Journal of Eating Disorders*. 2007;**40**:310-320. DOI: 10.1002/eat
- [17] Holtkamp K, Konrad K, Kaiser N, Ploenes Y, Heussen N, Grzella I, et al. A retrospective study of SSRI treatment in adolescent anorexia nervosa: Insufficient evidence for efficacy. *Journal of Psychiatric Research*. 2005;**39**:303-310. DOI: 10.1016/j.jpsychires.2004.08.001

[18] Kaye WH, Frank GK, Bailer UF, Henry SE. Neurobiology of anorexia nervosa: Clinical implications of alternations of the function of serotonin and other neuronal systems. *International Journal of Eating Disorders*. 2005;**37**:S15-S19. DOI: 10.1002/eat.20109

[19] Novotney A. New solutions: Psychologists are developing promising new treatments and conducting novel research to combat eating disorders. *Monitor on Psychology*. 2009;**40**:46. Available from: <http://www.apa.org/monitor/2009/04/treatments.aspx>

[20] DeSocio JE, O'Toole JK, Nemirow SJ, Lukack ME, Magee MJ. Screening for childhood eating disorders in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*. 2007;**9**:16-20. DOI: 10.4088/PCC.v09n0103

[21] Fleming M, Towey K, editors. *Educational Forum on Adolescent Health: Adolescent Obesity, Nutrition, and Physical Activity*. Chicago, IL: American Medical Association; 2003

[22] Dahlgren CL, Wisting L, Rø Ø. Feeding and eating disorders in the

DSM-5 era: A systematic review of prevalence rates in non-clinical male and female samples. *Journal of Eating Disorders*. 2017;**5**:56-65. DOI: 10.1186/s40337-017-0186-7

[23] Nicholls D, Viner R. ABC of adolescence: Eating disorders and weight problems. *British Medical Journal*. 2005;**330**:950-953. DOI: 10.1136/bmj.330.7497.950

[24] Bulik CM, Sullivan PF, Wade TD, Kendler KS. Twin studies of eating disorders: A review. *International Journal of Eating Disorders*. 2000;**27**:1-20. DOI: 10.1002/(SICI)1098-108X(200001)27:1<1::AID-EAT1>3.3.CO;2-H

[25] Bulik C, Sullivan PF, Tozzi F, Furberg H, Lichtenstein P, Pedersen NL. Prevalence, heritability, and prospective risk factors for anorexia nervosa. *Archives of General Psychiatry*. 2006;**63**:305-312. DOI: 10.1001/archpsyc.63.3.305

[26] Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KP, Plotnicov K, Pollice C, et al. A controlled family study of anorexia nervosa and bulimia nervosa: Psychiatric disorders in first-degree relatives and effects of proband comorbidity. *Archives of General Psychiatry*. 1998;**55**:603-610. DOI: 10.1001/archpsyc.55.7.603

[27] Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Controlled family study of anorexia and bulimia nervosa: Evidence of shared liability and transmission of partial syndromes. *American Journal of Psychiatry*. 2000;**157**:393-401. DOI: 10.1176/appi.ajp.157.3.393

[28] Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Males with anorexia nervosa: A controlled study of eating disorders in first-degree relatives. *International Journal of Eating Disorders*. 2001;**29**:263-269. DOI: 10.1002/eat.1017

- [29] Kaye WH. Neurobiology of anorexia and bulimia nervosa. *Physiology and Behavior*. 2008;**94**:121-135. DOI: 10.1016/j.physbeh.2007.11.037
- [30] Kaye W, Wagner A, Fudge JL, Paulus M. Neurocircuitry of eating disorders. In: Adan RA, Kaye WH, editors. *Behavioral Neurobiology of Eating Disorders*. New York, NY: Springer; 2011. pp. 37-57
- [31] Nunn K, Frampton I, Lask B. Anorexia nervosa—A noradrenergic dysregulation hypothesis. *Medical Hypotheses*. 2012;**78**:580-584. DOI: 10.1016/j.mehy.2012.01.033
- [32] Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Coming to terms with risk factors for eating disorders: Application of risk terminology and suggestions for a general taxonomy. *Psychological Bulletin*. 2004;**130**:19-65. DOI: 10.1037/0033-2909.130.1.19
- [33] Anderlueh MB, Tchanturia K, Rabe-Hesketh S, Collier D, Treasure J. Lifetime course of eating disorders: Design and validity testing of a new strategy to define the eating disorders phenotype. *Psychological Medicine*. 2009;**39**:105-114. DOI: 10.1017/S0033291708003292
- [34] Franko DL, Tabri N, Keshaviah A, Murray HB, Herzog DB, Thomas JJ, et al. Predictors of long-term recovery in anorexia nervosa and bulimia nervosa: Data from a 22-year longitudinal study. *Journal of Psychiatric Research*. 2018;**96**:183-188. DOI: 10.1016/j.jpsychires.2017.10.008
- [35] Kaye WH, Greeno CG, Moss H, Fernstrom J, Fernstrom M, Lilenfeld LR, et al. Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa. *Archives of General Psychiatry*. 1998;**55**:927-935. DOI: 10.1001/archpsyc.55.10.927
- [36] Lilenfeld LR. Personality and temperament. In: Adan RA, Kaye WH, editors. *Behavioral Neurobiology of Eating Disorders*. New York, NY: Springer; 2011. pp. 3-16
- [37] Lilenfeld LR, Stein D, Bulik CM, Strober M, Plotnicov K, Pollice C, et al. Personality traits among currently eating disordered, recovered and never ill first-degree female relatives of bulimic and control women. *Psychological Medicine*. 2000;**30**:1399-1410. DOI: 10.1017/S0033291799002792
- [38] Wagner A, Greer P, Bailer UF, Frank GK, Henry SE, Putnam K, et al. Normal brain tissue volumes after long-term recovery in anorexia and bulimia nervosa. *Biological Psychiatry*. 2006;**59**:291-293. DOI: 10.1016/j.biopsych.2005.06.014
- [39] Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, Treasure JT, et al. Evidence for a susceptibility gene for anorexia nervosa on chromosome 1. *American Journal of Human Genetics*. 2002;**70**:787-792. DOI: 10.1086/339250
- [40] Tenconi E, Santonastaso P, Monaco F, Favaro A. Obstetric complications and eating disorders: A replication study. *International Journal of Eating Disorders*. 2015;**48**:424-430. DOI: 10.1002/eat.22304
- [41] Urwin R, Nunn K. Epistatic interaction between the monoamine oxidase A and serotonin transporter genes in anorexia nervosa. *European Journal of Human Genetics*. 2005;**13**:370-375. DOI: 10.1038/sj.ejhg.5201328
- [42] Kaye W, Fudge J, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. *Nature Reviews Neuroscience*. 2009;**10**:573-584. DOI: 10.1038/nrn2682
- [43] Nunn K, Frampton I, Fugslet T, Torzsok-Sonnevand M, Lask B. The

insula hypothesis of anorexia nervosa. *Medical Hypotheses*. 2011;**76**:353-357. DOI: 10.1016/j.mehy.2010.10.038

[44] Frank G, Bailer UF, Henry S, Drevets W, Meltzer CC, Price JC, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]ralopride. *Biological Psychiatry*. 2005;**58**:908-912. DOI: 10.1016/j.biopsych.2005.05.003

[45] Schultz W. Neural coding of basic reward terms of animal learning theory, game theory, microeconomics, and behavioural ecology. *Current Opinion in Neurobiology*. 2004;**14**:139-147. DOI: 10.1016/j.conb.2004.03.017

[46] McClure S, Berns G, Montague P. Temporal prediction errors in a passive learning task activate human striatum. *Neuron*. 2003;**38**:339-346. DOI: 10.1016/S0896-6273(03)00154-5

[47] O'Doherty J. Reward representations and reward-related learning in the human brain: Insights from neuroimaging. *Current Opinion in Neurobiology*. 2004;**14**:769-776. DOI: 10.1016/j.conb.2004.10.016

[48] Bergen A, Yeager M, Welch R, Haque K, Ganjei JK, Mazzanti C, et al. Association of multiple DRD2-141 polymorphisms with anorexia nervosa. *Neuropsychopharmacology*. 2005;**30**:1703-1710. DOI: 10.1038/sj.npp.1300719

[49] Friederich HC, Kumari V, Uher R, Riga M, Schmidt U, Campbell IC, et al. Differential motivational responses to food and pleasurable cues in anorexia and bulimia nervosa: A startle reflex paradigm. *Psychological Medicine*. 2006;**36**:1327-1335. DOI: 10.1017/S0033291706008129

[50] Avena NM, Bocarsly ME. Dysregulation of brain reward systems in eating disorders: Neurochemical

information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology*. 2012;**63**:87-96. DOI: 10.1016/j.neuropharm.2011.11.010

[51] Bailer UF, Narendran R, Frankle WG, Himes ML, Duvvuri V, Mathis CA, et al. Amphetamine induced dopamine release increases anxiety in individuals recovered from anorexia nervosa. *International Journal of Eating Disorders*. 2012;**45**:263-271. DOI: 10.1002/eat.2093

[52] Wagner A, Aizenstein H, Venkatraman M, Fudge J, May J, Mazurkewicz L, et al. Altered reward processing in women recovered from anorexia nervosa. *American Journal of Psychiatry*. 2007;**164**:1842-1849. DOI: 10.1176/appi.ajp.2007.07040575

[53] Kaye WH, Frank GK, McConaha C. Altered dopamine activity after recovery from restricting-type anorexia nervosa. *Neuropsychopharmacology*. 1999;**21**:503-506. DOI: 10.1016/S0893-133X(99)00053-6

[54] Verhagen LA, Luijendijk MC, Hillebrand JJ, Adan RA. Dopamine antagonism inhibits anorectic behavior in an animal model for anorexia nervosa. *European Neuropsychopharmacology*. 2009;**19**:153-160. DOI: 10.1016/j.euroneuro.2008.09.005

[55] Calati R, De Ronchi D, Bellini M, Serretti A. The 5-HTTLPR polymorphism and eating disorders: A meta-analysis. *International Journal of Eating Disorders*. 2011;**44**:191-199. DOI: 10.1002/eat.20811

[56] Bailer UF, Kaye WH. Serotonin: Imaging findings in eating disorders. *Current Topics in Behavioral Neurosciences*. 2011;**6**:59-79. DOI: 10.1007/7854_2010_78

[57] Markus CM. Dietary amino acids and brain serotonin function:

Implications for stress-related affective changes. *Neuromolecular Medicine*. 2008;**10**:247-258. DOI: 10.1007/s12017-008-8039-9

[58] Kiezebrink K, Mann ET, Bujac SR, Stubbins MJ, Campbell DA, Blundell JE. Evidence of complex involvement of serotonergic genes with restrictive and binge/purge subtypes of anorexia nervosa. *World Journal of Biological Psychiatry*. 2010;**11**:824-833. DOI: 10.3109/15622975.2010.484550

[59] Haleem DJ. Exaggerated feedback control decreases brain serotonin concentration and elicits hyperactivity in a rat model of diet-restriction-induced anorexia nervosa. *Appetite*. 2008;**52**:44-50. DOI: 10.1016/j.appet.2008.07.009

[60] Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. *The Lancet*. 2010;**373**:746-758. DOI: 10.1016/S0140-6736(09)60046-5

[61] Cuijpers P, Straten A, Warmerdam EH, Andersson G. Psychological treatment versus combined treatment of depression: A meta-analysis. *Depression & Anxiety*. 2009;**26**:279-288. Available from: <http://dSPACE.ubvu.vu.nl/handle/1871/16593>

[62] Bailer UF, Price JC, Meltzer CC, Mathis CA, Frank GK, Weissfeld L, et al. Altered 5-HT_{2A} receptor binding after recovery from bulimia-type anorexia nervosa: Relationships to harm avoidance and drive for thinness. *Neuropsychopharmacology*. 2004;**29**:1143-1155. DOI: 10.1038/sj.npp.1300430

[63] Frank G, Kaye WH, Meltzer CC, Price JC, Greer P, McConaha C, et al. Reduced 5-HT_{2A} receptor binding after recovery from anorexia nervosa.

Biological Psychiatry. 2002;**52**:896-906. DOI: 10.1016/S0006-3223(02)01378

[64] Klump KL, Bulik CM, Pollice C, Halmi KA, Fichter MM, Berrettini WH, et al. Temperament and character in women with anorexia nervosa. *Journal of Nervous and Mental Disorders*. 2000;**188**:559-567. DOI: 10.1097/00005053-200009000-00001

[65] Tremblay LK, Naranjo CA, Graham SJ, Hermann N, Mayberg HS, Hevenor SJ, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Archives of General Psychiatry*. 2005;**62**:1228-1236. DOI: 10.1001/archpsyc.62.11.1228

[66] Stein M, Simmons A, Feinstein J, Paulus M. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*. 2007;**164**:318-327. DOI: 10.1176/appi.ajp.164.2.318

[67] Phillips M, Drevets WR, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*. 2003;**54**:504-514. DOI: 10.1016/S0006-3223(03)00168-9

[68] Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, et al. Brain serotonin_{1A} receptor binding measure by positron emission tomography with [¹¹C]WAY-100635: Effects of depression and antidepressant treatment. *Archives of General Psychiatry*. 2000;**57**:174-180. DOI: 10.1001/archpsyc.57.2.174

[69] Bhagwagar Z, Rabiner E, Sargent P, Grasby P, Cowen P. Persistent reduction in brain serotonin 1_A receptor binding in recovered depressed men measured by positron emission tomography with [¹¹C]WAY-100635. *Molecular Psychiatry*. 2004;**9**:386-392. DOI: 10.1038/sj.mp.4001401

- [70] Neumeister A, Brain E, Nugent A, Carson R, Bonne O, Lucnebaugh D, et al. Reduced serotonin type 1_A receptor binding in panic disorder. *Journal of Neuroscience*. 2004;**24**:589-591. DOI: 10.1523/JNEUROSCI.4921-03.2004
- [71] Isingrini E, Perret L, Rainer Q, Amilhon B, Guma E, Tanti A, et al. Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. *Nature Neuroscience*. 2016;**19**:560-563. DOI: 10.1038/nn.4245
- [72] Kaye W, Jimerson D, Lake C, Ebert M. Altered norepinephrine metabolism following long-term weight recovery in patients with anorexia nervosa. *Psychiatry Research*. 1985;**14**:333-342. DOI: 10.1016/0165-1781(85)90101-5
- [73] Kaye WH, Ebert MH, Raleigh M, Lake CR. Abnormalities in CNS monoamine metabolism in anorexia nervosa. *Archives of General Psychiatry*. 1984;**41**:350-355. DOI: 10.1001/archpsyc.1984.01790150040007
- [74] Urwin RE, Bennetts B, Wilcken B, Lampropoulos B, Beumont P, Clarke S, et al. Anorexia nervosa (restrictive subtype) is associated with a polymorphism in the novel norepinephrine transporter gene promoter polymorphic region. *Molecular Psychiatry*. 2002;**7**:652-657. DOI: 10.1038/sj.mp.4001080
- [75] Zucker NL, Herzog D, Moskovich A, Merwin R, Lin T. Incorporating dispositional traits into the treatment of anorexia nervosa. In: Adan RA, Kaye WH, editors. *Behavioral Neurobiology of Eating Disorders*. New York, NY: Springer; 2011. pp. 289-314
- [76] Bernardoni F, King JA, Geisler D, Stein E, Jaite C, Nätsch D, et al. Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: A longitudinal study. *NeuroImage*. 2016;**130**:214-222. DOI: 10.1016/j.neuroimage.2016.02.003
- [77] Boghi A, Sterpone S, Sales S, D'Agata F, Bradac GB, Zullo G, et al. In vivo evidence of global and focal brain alterations in anorexia nervosa. *Psychiatry Research: Neuroimaging*. 2011;**192**:154-159. DOI: 10.1016/j.psychresns.2010.12.008
- [78] Kerem NC, Katzman DK. Brain structure and function in adolescents with anorexia nervosa. *Adolescent Medicine Clinics*. 2003;**14**:109-118
- [79] Castro-Fornieles J, Bargalló N, Lazaro L, Andres S, Falcon C, Plana MT, et al. A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. *Journal of Psychiatric Research*. 2009;**43**:331-340. DOI: 10.1016/j.jpsychires.2008.03.013
- [80] Joos A, Klöppel S, Hartmann A, Glauche V, Tüscher O, Perlov E, et al. Voxel-based morphometry in eating disorders: Correlation of psychopathology with grey matter volume. *Psychiatry Research: Neuroimaging*. 2010;**182**:146-151. DOI: 10.1016/j.psychresns.2010.02.004
- [81] Friederich HC, Walther S, Bendszus M, Biller A, Thomann P, Zeigermann S, et al. Grey matter abnormalities within cortico-limbic-striatal circuits in acute and weight-restored anorexia nervosa patients. *NeuroImage*. 2012;**59**:1106-1113. DOI: 10.1016/j.neuroimage.2011.09.042
- [82] Gaudio S, Nocchi F, Franchin T, Genovese E, Cannatà V, Longo D, et al. Gray matter decrease distribution in the early stages of anorexia nervosa restrictive type in adolescents. *Psychiatry Research: Neuroimaging*. 2011;**191**:24-30. DOI: 10.1016/j.psychresns.2010.06.007
- [83] Seitz J, Bühren K, von Polier GG, Heussen N, Herpertz-Dahlmann B,

- Konrad K. Morphological changes in the brain of acutely ill and weight-recovered patients with anorexia nervosa. A meta-analysis and qualitative review. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*. 2014;**42**:7-17. DOI: 10.1024/1422-4917/a000265
- [84] Mainz V, Schulte-Rüther M, Fink GR, Herpertz-Dahlmann B, Konrad K. Structural brain abnormalities in adolescent anorexia nervosa before and after weight recovery and associated hormonal changes. *Psychosomatic Medicine*. 2012;**74**:574-582. DOI: 10.1097/PSY.0b013e31824ef10e
- [85] Roberto CA, Mayer LE, Brickman AM, Barnes A, Muraskin J, Yeung LK, et al. Brain tissue volume changes following weight gain in adults with anorexia nervosa. *International Journal of Eating Disorders*. 2011;**44**:406-411. DOI: 10.1002/eat.20840
- [86] Rastam M, Bjure J, Vestergrén E, Uvebrant P, Gillberg IC, Wentz E, et al. Regional cerebral blood flow in weight-restored anorexia nervosa: A preliminary study. *Developmental Medicine & Child Neurology*. 2001;**43**:239-242. DOI: 10.1111/j.1469-8749.2001.tb00196.x
- [87] Cowdrey FA, Park RJ, Harmer CJ, McCabe C. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. *Biological Psychiatry*. 2011;**70**:736-743. DOI: 10.1016/j.biopsych.2011.05.028
- [88] Santel S, Baving L, Krauel K, Munte T, Rotte M. Hunger and satiety in anorexia nervosa: fMRI during cognitive processing of food pictures. *Brain Research*. 2006;**1114**:138-148. DOI: 10.1016/j.brainres.2006.07.045
- [89] Hinton E, Parkinson JA, Holland A, Arana F, Roberts A, Owen A. Neural contributions to the motivational control of appetite in humans. *European Journal of Neuroscience*. 2004;**20**:1411-1418. DOI: 10.1111/j.1460-9568.2004.03589.x
- [90] Schoenfeld M, Neuer G, Tempelmann C, Schussler K, Noesselt T, Hopf J, et al. Functional magnetic resonance tomography correlates of taste perception in the human primary taste cortex. *Neuroscience*. 2004;**127**:347-353. DOI: 10.1016/j.neuroscience.2004.05.024
- [91] Rolls ET. Taste, olfactory, and food texture processing in the brain, and the control of food intake. *Physiology & Behavior*. 2005;**85**:45-56. DOI: 10.1016/j.physbeh.2005.04.012
- [92] Small D. Toward an understanding of the brain substrates of reward in humans. *Neuron*. 2002;**22**:668-671. DOI: 10.1016/S0896-6273(02)00620-7
- [93] Kazama A, Bachevalier J. Selection aspiration of neurotoxic lesions of the orbitofrontal areas 11 and 13 spared monkey's performance on the object reversal discrimination task. *Journal of Neuroscience*. 2006;**29**:2794-2804. DOI: 10.1523/JNEUROSCI.4655-08.2009
- [94] Clarke H, Walker SD, Robbins T, Roberts A. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. *Cerebral Cortex*. 2007;**17**:18-27. DOI: 10.1093/cercor/bhj120
- [95] Fassino S, Pierò A, Gramaglia C, Abbate-Daga G. Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology*. 2004;**37**:168-174. DOI: 10.1159/000079420
- [96] Lilenfeld LR, Wonderlich S, Riso LP, Crosby R, Mitchell J. Eating disorders and personality: A methodological and empirical review. *Clinical Psychology Review*. 2006;**26**:299-320. DOI: 10.1016/j.cpr.2005.10.003

- [97] Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: The neurobiology of anorexia nervosa. *Trends in Neuroscience*. 2013;**36**:110-120. DOI: 10.1016/j.tins.2013.01.003
- [98] Nunn K, Frampton I, Gordon I, Lask B. The fault is not in her parents but in her insula—A neurobiological hypothesis of anorexia nervosa. *European Eating Disorders Review*. 2008;**16**:355-360. DOI: 10.1002/erv.890
- [99] Bulik CM, Thornton LM, Root TL, Pisetsky EM, Lichtenstein P, Pedersen NL. Understanding the relation between anorexia nervosa and bulimia nervosa in a Swedish national twin sample. *Biological Psychiatry*. 2010;**67**:71-77. DOI: 10.1016/j.biopsych.2009.08.010
- [100] Thornton LM, Mazzeo SE, Bulik CM. The heritability of eating disorders: Methods and current findings. In: Adan RA, Kaye WH, editors. *Behavioral Neurobiology of Eating Disorders*. New York, NY: Springer; 2011. pp. 141-156
- [101] Uher R. The role of genetic variation in the causation of mental illness: An evolution-informed framework. *Molecular Psychiatry*. 2009;**14**:1072-1082. DOI: 10.1038/mp.2009.85
- [102] Schaumberg K, Jangmo A, Thornton LM, Birgegård A, Almqvist C, Norring C, et al. Patterns of diagnostic transition in eating disorders: A longitudinal population study in Sweden. *Psychological Medicine*. 2018;1-9. DOI: 10.1017/S0033291718001472
- [103] Bühren K, Schwarte R, Fluck F, Timmesfeld N, Krei M, Egberts K, et al. Comorbid psychiatric disorders in female adolescents with first-onset anorexia nervosa. *European Eating Disorders Review*. 2014;**22**:39-44. DOI: 10.1002/erv.2254
- [104] Helder SG, Collier DA. The genetics of eating disorders. In: Adan RA, Kaye WH, editors. *Behavioral Neurobiology of Eating Disorders*. New York, NY: Springer; 2011. pp. 157-175
- [105] Devlin B, Bacanu SA, Klump KL, Bulik CM, Fichter MM, Halmi KA, et al. Linkage analysis of anorexia nervosa incorporating behavioral covariates. *Human Molecular Genetics*. 2002;**11**: 689-696. DOI: 10.1093/hmg/11.6.689
- [106] Frieling H, Römer KD, Scholz S, Mittelbach F, Wilhelm J, De Zwaan M, et al. Epigenetic dysregulation of dopaminergic genes in eating disorders. *International Journal of Eating Disorders*. 2010;**43**:577-583. DOI: 10.1002/eat.20745
- [107] Baker JH, Maes HH, Lissner L, Aggen SH, Lichtenstein P, Kendler KS. Genetic risk factors for disordered eating in adolescent males and females. *Journal of Abnormal Psychology*. 2009;**118**:576-586. DOI: 10.1037/a0016314
- [108] Sloft-Op 't Landt MCT, Bartels M, Van Furth EF, Van Beijsterveldt CEM, Meulenbelt I, Slagboom PE, et al. Genetic influences on disordered eating behaviour are largely independent of body mass index. *Acta Psychiatrica Scandinavica*. 2008;**117**:348-356. DOI: 10.1111/j.1600-0447.2007.01132.x
- [109] Klump KL, Burt SA, McGue M, Iacono WG. Changes in genetic and environmental influences on disordered eating across adolescence: A longitudinal twin study. *Archives of General Psychiatry*. 2007;**64**:1409-1415. DOI: 10.1001/archpsyc.64.12.1409
- [110] Klump KL, Perkins PS, Burt SA, McGue MATT, Iacono WG. Puberty moderates genetic influences on disordered eating. *Psychological Medicine*. 2007;**37**:627-634. DOI: 10.1017/S0033291707000189

[111] Klump KL, Keel PK, Sisk C, Burt SA. Preliminary evidence that estradiol moderates genetic influences on disordered eating attitudes and behaviors during puberty. *Psychological Medicine*. 2010;**40**:1745-1753. DOI: 10.1017/S0033291709992236

[112] Bramen JE, Hranilovich JA, Dahl RE, Forbes EE, Chen J, Toga AW, et al. Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cerebral Cortex*. 2011;**21**:636-646. DOI: 10.1093/cercor/bhq137

[113] Peper JS, Hulshoff Pol HE, Crone EA, van Honk J. Sex steroids and brain structure in pubertal boys and girls: A mini-review of neuroimaging studies. *Neuroscience*. 2011;**191**:28-37. DOI: 10.1016/j.neuroscience.2011.02.014

[114] Golden N, Carlson J. The pathophysiology of amenorrhea in the adolescent. *Annals of the New York Academy of Sciences*. 2008;**1135**: 163-178. DOI: 10.1196/annals.1429.014

[115] Chui HT, Christensen BK, Zipursky RB, Richards BA, Hanratty MK, Kabani NJ, et al. Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. *Pediatrics*. 2008;**122**:426-437. DOI: 10.1542/peds.2008-0170