JULS

Review Article

Genetic and neurobiological etiology of anorexia nervosa

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Abstract

Anorexia nervosa (AN) is a life-threatening eating disorder (ED) characterized by restrictive eating, the obsessive pursuit of thinness and an intense fear of weight gain. The lifetime prevalence of AN is 0.1-1% and the mortality rate of 8-15% is higher than in any other psychiatric illness. Common treatments are often based on therapies for psychiatric disorders which frequently co-occur with AN. These are generally unsuccessful with high relapse rates, up to 20% of patients show no long-term improvement and many continue to exhibit disordered eating patterns. Despite the severity and chronic nature of AN, the etiology is largely unknown. Multiple theories have been developed outlining the familial, psychological and cultural factors contributing to AN pathology. However, in order to improve recovery outcomes more specific treatments based on genetic and neurobiological evidence need to be developed. Brain imaging and gene polymorphism studies suggest that alterations in the serotonin (5-HT) and dopamine (DA) neurotransmitter systems may explain the genetic and psychiatric components of AN. 5-HT and DA mediate many clinical traits frequently elevated in AN and dysfunction in these systems has been linked to comorbid disorders. The purpose of this mini-review is to summarize the current evidence for alterations in 5-HT and DA systems in AN pathology and to suggest future research directions.

Introduction

Anorexia nervosa (AN)—first described in the medical literature in the 1870's—is a mental disorder characterized by an obsessive fear of weight gain and the relentless pursuit of thinness [1]. Currently, four criteria must be met for the clinical diagnosis of AN, which is further subdivided into restricting (AN-R) and binging-purging (AN-BP) subtypes (see Table below). When patients do not fulfill one of the criteria, a diagnosis of 'eating disorder – not otherwise specified' (ED-NOS) is given. In addition to the wide range and severity of clinical symptoms, there are also high levels of lifetime transitions between AN subtypes, most frequently from AN-R to AN-BP [2]. Furthermore, around 20-30% of patients originally diagnosed with AN later develop bulimia nervosa (BN) and a smaller proportion of BN patients develop AN [3, 4].

Although lifetime prevalence is only 0.1-1% in the general population, AN has the highest mortality rate of any other psychiatric illness, at 6% per decade, typically due to malnutrition or suicide [5-8]. Furthermore, current treatments are generally ineffective and AN remains one of the most difficult psychiatric illnesses to treat [9]. This is partly due to the lack of treatment therapies specifically designed for AN and to the ego-syntonic nature of the disorder. AN behaviors are perceived as positive and rewarding to the patient with benefits outweighing the clinical and psychological consequences. This is because the symptoms are in accordance with the patients' goals of weight gain prevention [3]. Consequently, up to 20% of patients remain chronically ill and require frequent hospitalizations, less than 50% make a full recovery and about 30% achieve partial symptom remission [10]. Furthermore, 30-50% of weight-restored patients discharged from treatment relapse within a year or less and require subsequent treatment [11]. In addition, many of the patients attaining a "full" recovery continue to exhibit elevated levels of perfectionism, anxiety and obsessional behaviours associated with AN psychopathology [12-14].

Thus, finding the genetic and neurobiological underpinnings of AN psychopathology are vital for developing science-based and effective treatment programs [15]. This review will summarize the genetic components, comorbid psychiatric disorders and current literature regarding the role of 5-HT and DA systems in AN.

Diagnostic Criteria for Anorexia Nervosa
1. Refusal to maintain body weight at or above a minimally normal weight for age and height (<85% of expected weight).
2. Intense fear of gaining weight or becoming fat, even though underweight.
3. Disturbance in the way in which one's body weight or shape is experienced, denial of the seriousness of the low body weight.
4. Amenorrhea (i.e., the absence of at least three consecutive cycles).
Subtypes
• **Restricting Type:** During the current episode of AN, the person has not regularly engaged in binge-eating or purging behavior
• **Binge-eating/purging type:** During the current episode of AN, the person has regularly engaged in binge-eating or purging behavior.

Adapted from Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

Genetic factors

Clinical observations have suggested that EDs, several psychiatric disorders and AN-associated personality traits tend to cluster in families. To investigate the genetic basis and heritability of EDs and associated traits among AN relatives, family and twin studies are conducted. Genome-wide screenings such as linkage analyses and association studies are used to find candidate genes responsible for the genetic predisposition to AN [16]. So far, a linkage to chromosome 1 in AN-R has been demonstrated, but the findings remain preliminary due to small sample size [17].

Families of AN probands have a greater prevalence of EDs than the general population, afflicting 3-12% of first-degree relatives [18-21]. Lifetime prevalence of AN in relatives of AN probands varies from 1-10%, with an average of 2.7% (based on 9 studies, total of

574 probands and 1637 relatives, compiled by [4]), almost 15 times greater than in relatives of healthy controls [18-26]. The prevalence decreases for second-degree relatives (1-2%) but remains greater than the general population (0.1-1%), suggesting genetic factors play an important role in the development of AN [27]. A twin-study comparing AN probands and ED-affected twins found that 63% of the pairs were AN-AN, 20% AN-BN and 16% AN-ED-NOS [28]. The findings that the prevalence of EDs, especially AN, is elevated among family members of AN probands is consistent with the hypothesis that different EDs have a shared but nonetheless separate etiology, which may explain the high lifetime transition rates between AN and BN [1].

Twin studies show a concordance for AN of 35-56% in monozygotic twins and 5-7% in dizygotic twins [27, 29]. Furthermore, controlled family studies consistently report high values of heritability in the narrow sense for AN (h^2=0.7, ranging between h^2=0.58-0.8 in different studies), suggesting a strong genetic predisposition [27, 29-33]. Finally, heritability for ED symptoms such as dietary restraint, self-induced vomiting, weight and body image preoccupation in the absence of an ED are also high, between 32-72% [34]. These studies suggest that ED clustering in families is predominantly due to additive genetic factors, but that the predisposition to AN (and other EDs) is mediated by many genes. These genetic factors likely contribute to the development of psychiatric disorders and personality traits comorbid with AN.

Psychiatric disorders and personality traits

AN patients have elevated rates of anxiety, depression, and obsessive-compulsive disorders and personality traits marked by rigidity, perfectionism and reduced emotional expression [19, 35-37]. Obsessive compulsive disorder (OCD), characterized by recurrent irrational obsessions and compulsions that may impair an individual's life is 15 times more common in AN patients than the general public [38]. OCPD, a less severe form of OCD, marked by perfectionism, rigidity, neatness and a preoccupation with rules is also elevated in AN patients, with 15% fitting the criteria of OCPD after recovery [39]. Major depressive disorder and anxiety spectrum disorders also occur with increased frequency among AN patients, with a lifetime prevalence of 70% and between 41-65%, respectively [23]. Furthermore, major depression occurs with increased frequency among relatives (7-25% compared to 2-3% in controls) [40], and evidence from twin studies suggests a shared transmission liability of EDs and anxiety disorders [41].

Personality traits, such as a need for order, symmetry and exactness, inflexible thinking, social introversion, low novelty seeking, harm avoidance and perfectionism typically pre-date AN onset and persist after recovery [37, 42-44]. Alexithymia, an impairment in the ability to recognize, process and describe emotions, is also highly prevalent in both ill and recovered AN patients (77% compared to 6.7% in controls) [45-47]. Finally, these disorders and personality traits also occur in greater proportions among first and second degree relatives, especially in mothers of AN probands [48]. For an extensive review on EDs, associated personality traits and psychiatric disorders see Lilenfeld et al. (2006).

Psychiatric comorbidities are inline with genetic evidence, suggesting that multiple genes are involved in predisposing individuals to a variety of psychiatric disorders and personality traits, including AN. Furthermore, the persistence of many psychiatric symptoms after recovery suggests that these behaviours may be true predisposing factors and not effects of malnutrition [49]. However, the extent to which these are pre-morbid personality traits contributing to AN development, and are not 'scar-effects', or long-term personality changes as a result of the disorder, remains unclear [48]. Nonetheless, the shared comorbidity of OCD, depression, anxiety disorders with AN provides clues to the possible genes and neurobiological mechanisms involved in AN etiology. Furthermore, dysfunction in 5-HT and DA has been implicated in these disorders. This evidence suggests that 5-HT and DA dysregulation are important contributors to AN etiology.

The role of neurotransmitters: linking genetics and psychiatry

Advances in brain imaging technology combined with gene polymorphism analyses are providing new insights into the pathobiology of AN. Positron emission tomography (PET) scans allows researchers to investigate receptor densities and binding properties as well as the effects of different gene polymorphisms in AN subjects. Functional magnetic resonance imaging (fMRI) enable scientists to study the brain areas and general pathways involved in specific cognitive tasks [50].The serotonergic system, involved in the regulation of appetite and mood, and the dopaminergic system, primarily implicated with modulating reward and motor activity, have been the main focus of AN research [51].

Serotonin

Mounting evidence suggests that alterations in the serotonergic system play an important role in AN pathogenesis. 5-HT (5-hydroxytryptamine) regulates many traits frequently elevated in AN, such as harm avoidance, behavioral inhibition, obsessive behaviours and satiety [52, 53]. 5-HT dysfunction has also been associated with obsessive-compulsive, anxiety and depression disorders [38, 54-56]. Furthermore, altered serotonergic activity occurs during the ill state and persists after recovery [55, 57, 58].

Plasma tryptophan levels, a food-derived amino acid precursor to serotonin, can be depleted via dietary restriction, resulting in a decrease in 5-HT synthesis, reduction in 5-HT turnover and down-regulation of 5-HT transporters [59]. As expected, AN patients have low tryptophan availability and reduced 5-HT turnover rates [60]. However, long-term weight recovered patients demonstrate elevated central serotonin activity, indicated by higher than normal concentrations of 5-HT metabolites in the cerebrospinal fluid, and high 5-HT turnover rates [55]. Intriguingly, studies have found that depletion of tryptophan reduces dysphoric and anxious mood, suggesting that AN individuals may restrict dietary intake in order to diminish unpleasant emotions [61].

Much of the literature has focused on alterations of 5-HT1A and 5-HT2A receptors and the 5-HT transporter (5-HTT). Alterations in 5-HT receptor binding activity using PET in specific brain regions, namely the subgenual cingulate, mesial temporal, lateral temporal and parietal regions have been shown using PET [62, 63]. Furthermore, studies utilizing PET have revealed alterations in both the 5-HT1A and 5-HT2A receptor binding activity in recovered AN groups [64-70]. It has been suggested that decreased 5-HT receptor binding activity in subgenual cingulate and mesial temporal cortex, including the amygdala and hippocampus, reflects a compensatory mechanism for the increased 5-HT activity and high turnover rate present after recovery [63].

Although there is evidence from brain imaging studies and psychiatric comorbidities that altered 5-HT neurotransmission is important in AN psychopathology, evidence pointing to specific gene polymorphisms has been contradictory. Certain alleles may result in altered 5-HT activity and may also underlie the high heritability of AN. Most attention has been given to the 1438A/G promoter polymorphism in the 5-HT2A receptor and so far out of 14 studies, six found an increased incidence of the -1438A polymorphism in AN patients [71-76], but eight others did not confirm the result [77-84]. Gene polymorphism studies of 5-HTT have yielded similar contradictory results, with some positive studies suggesting an association [85-88], and others showing no difference between AN and controls [76, 77]. While the role of the 5-HT system in AN pathology is suggested by clinical symptoms in AN patients and supported by PET studies, finding the culprit alleles has been more difficult, as the gene polymorphism studies, do not suggest a strong association between a particular allele and AN.

Dopamine

DA, an important neurotransmitter involved in reward [89], feeding behaviors [90], motor activity [91] and harm avoidance has also been implicated in AN pathobiology [3]. The DA system may mediate rewarding feelings and contribute to the 'drive for activity' present in AN [92]. Alterations in intrasynaptic DA concentration, receptor activity and receptor density in AN patients may alter DA functioning and consequently alter behaviour [93]. Specifically, alterations in DA D2/D3 receptors have been shown in studies using PET. The D2/D3 receptor system is overactive in recovered AN patients in several brain regions, namely the anteroventral striatum and receptor activity in the several other regions, such as caudate and dorsal putamen, was positively correlated with harm avoidance [93].

Altered DA functioning raises the possibility that individuals with AN might have a general disturbance in the reward pathways of the brain, which may contribute to the ego-syntonic nature of AN [67, 93]. In particular, an overactive DA system provides a possible explanation for the inability of AN patients to respond appropriately to salient stimuli and be able to sustain self-denial of food as well as many other pleasurable activities. Furthermore, overactivity in the DA system is consistent with the characteristic and paradoxical correlation of increased physical activity with progressive weight-loss and increased symptom prevalence in AN [93]. Disturbances in dopamine metabolism may contribute to an increased vulnerability to develop AN [94].

Similar to gene polymorphism studies involving the 5-HT system, evidence linking a particular allele to AN vulnerability in the DA system has been inconsistent. One study found transmission disequilibrium among AN probands, parents and affected relatives in a specific D2 receptor polymorphism [95]. This study suggests an association between a D2 allele and AN, which may affect the receptor expression by changing transcription and translation efficiency and have subsequent downstream effects on the DA system. One gene polymorphism of the D4 receptor was found to be significantly associated with AN as well as high perfectionism scores [96], but another did not confirm this result [97].

Overall, these results suggest that altered 5-HT and DA functioning is involved in AN. However, a specific allele for genes involved in the 5-HT or DA systems has not been consistently associated with AN. This is surprising, since AN symptoms, psychiatric comorbidities, genetic studies and brain imaging studies suggest disturbances in 5-HT and DA systems. This lack of consistent evidence may be due to several factors, addressed in the following section, that need to be considered in the design of future studies.

Conclusions and future research directions

The understanding of neurobiological and genetic components of AN has greatly improved in the last few decades. The high heritability of AN and comorbidity with other psychiatric disorders is well established. While progress has been made in establishing the role of the 5-HT and DA system in AN pathology, the specific gene polymorphisms and receptor function changes underlying the clustering of EDs, comorbid disorders and high heritability of AN in families have been harder to resolve.

A significant limiting factor in AN research is the low prevalence rate, which has impaired the ability to conduct family and twin studies and has severely limited genome-wide associate studies [98]. Sample sizes also vary substantially among studies, for example, the number of AN probands to affected relatives can vary from 2/99 [20] to 152/290 [18], making the ability to draw conclusions on prevalence rates difficult.

However, there are more significant problems, involving the diagnostic criteria for EDs, high ED transition rates and the definition of "recovery". The criteria for AN diagnosis may result in an artificial demarcation of individuals (AN and ED-NOS) who may share the same etiology. The later group may be erroneously excluded from studies on the basis of enrollment criteria. The same problem may occur between AN and BN groups since the high lifetime transition rates between EDs and the twin study comparing AN probands with ED-affected pairs suggests these disorders share common etiology. Conversely, AN subtypes (AN-R and AN-BP) most likely have similar but nonetheless slightly distinct neurobiological and genetic etiologies that may not be evident until studies focus only on specific subgroups of AN patients.

Finally, "recovery" is often taken to be at weight-restoration and resumption of menstrual cycles, but this can occur in the presence of core psychopathology [99]. Furthermore, there is no universal agreement as to what constitutes "recovery", as such, the length and criteria for "recovery" varies widely among studies. This has significant implications on the interpretation of psychiatric and neurobiological studies of "recovered" AN patients. For example, does the persistence of several AN-associated traits suggest pre-morbid risk factors or the presence AN psychopathology despite weight-gain?

In order to address the aforementioned problems in AN (and ED research), it is necessary to conduct a wide range of studies, some of which may include patients with any ED and others which are highly selective, limiting enrollment to very strict psychiatric and clinical criteria, such as focusing on AN-R patients with no prior history of AN-BP and vice-versa. In order to address pre-morbid risk factors it is necessary to follow a large group of healthy individuals and compare those that go on to develop AN, with those that develop other EDs and ED-free individuals. This has been difficult due to the typically early-onset of AN and low prevalence rates. However, with the advent of large-scale genetic databases and worldwide collaboration among researchers resulting in larger sample sizes, the future of AN research is hopeful. These studies are important in order to develop a comprehensive understanding of AN etiology and develop targeted, specific and effective treatment programs.

Please see online supplementary material for References.

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