Getting Beneath the Phenotype of Anorexia Nervosa: The Search for Viable Endophenotypes and Genotypes

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Treatment for anorexia nervosa has changed little from that described by Gull over a century ago. To focus merely on symptomatic relief from "not eating," as occurs with some forms of hospital care, is primitive. The evidence base to guide treatment is thin. Nevertheless, there is hope that better understanding of the causes and maintaining factors may translate into more sophisticated treatments. This review aims to look beyond the overt and startling "not eating" phenotype of anorexia nervosa and consider eating disorder endophenotypes. The first part of the review sets the eating behaviour, clinical, and psychopathological features into the context of what is now understood about the central control of appetite. The evidence base for a framework of potential eating disorder endophenotypes follows. Finally, ideas about how to translate endophenotypes into treatment are introduced.

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Clinical Implications

- New treatments for AN that are specifically tailored to address risk factors (causal or maintaining) may improve the outcome of AN.
- Cognitive remediation addressing how AN sufferers think (for example, the superiority of detail over global processing and the difficulty in changing set) rather than thought content could be used to change compulsive elements of the psychopathology.
- The vulnerability and plasticity of the reward and motivation pathways in adolescence may explain how a failure of treatment early in the course of the illness may lead to a poor outcome.

Limitations

- This is not a systematic review of risk factors for AN.
- Little to no research exists examining how genetic factors moderate or mediate some of the biological aspects of AN.
- Some aspects of the eating disorder phenotype are moderated by environmental factors, and research designs that examine interactions between fixed and fluid aspects of the psychopathology are needed.

Key Words: anorexia nervosa, bulimia nervosa, binge eating, endophenotype, neuropsychology, phenotype

Spotting possible cases of AN is a common preoccupation of the celebrity media. Images of starvation fascinate and sell copy but trivialize and stigmatize the problem. In the clinic, we see the dark side wherein quality of life for the individual and her family shrivels away and the shadow of death looms. This review aims to move away from superficial appearances and focus on the brain mechanisms that contribute to the biological understanding of AN. There are several things that this review does not aim to accomplish. It is not a broad systematic review of risk factors, because there is already a recent excellent exemplar.[1] Also, environmental factors have been omitted from its scope. Following their systematic review, Keel and Klump[2] argue that environmental activators have less relevance for AN. However, the subject of gene–endophenotype–environmental interactions will probably dominate future thinking. In the sister piece to this article, Steiger and Bruce[3] define the environmental context that allows bulimic behaviours to flourish. What this review aims to do is to focus on developing a biological framework for AN that uses endophenotypes as building blocks. The overall aim is to develop ideas for new, tailored treatments for AN as alternatives to the hand-me-down treatment protocols that have been such a poor fit.

The Phenotype

A change in eating behaviour and weight loss lies at the core of AN. In the classic form, insufficient calorie intake is the defining behaviour. However, in more than one-third of cases, episodes of extreme overeating (binges) develop. Various compulsive behaviours (such as exercise, vomiting, and laxative abuse), some of which suppress appetite or compensate for the overeating, are also part of the clinical presentation. Overexercise occurs in more than 40% of cases and is associated with other compulsive symptoms.[4,5] Links with obsessive–compulsive, harm avoidant, and inhibited personality traits are strong.[6] The verbal justification of AN behaviours is culturally embedded and has varied over time and place. In Western countries, current concerns about weight and shape dominate, but various alternative explanations were offered in the earliest large case series.[7] The biology of eating, the core behaviour, is the starting point for this review. Consideration of the compulsive behaviours such as overexercise, which uniquely mark this disorder as separate from the other clinical anorexias, follows.

Abbreviations used in this article

5-HT	serotonin
AN	anorexia nervosa

The Biology of Eating Behaviour

The central control of eating behaviour can be divided into 2 components, the homeostatic and hedonic, as illustrated in Figure 1. This figure outlines the central anatomy and neurochemistry, as well as the main peripheral signals that feed back into the system. Once leptin, the missing link in the homeostatic control of eating, was discovered,[8] the unfolding of the cascade of central mechanisms within the hypothalamus and beyond followed.[9] The biological mechanisms underpinning the hedonic aspects of eating are now the subject of active research.[10–12] There are 2 components, wanting and liking. In essence, the incentive component—the wanting, desire, or at the extreme, craving for food—involves dopaminergic pathways. The consummatory, pleasure, or "liking" network involves opiate and cannabinoid systems.[13,14] The incentive component is moderated by homeostatic factors and is shaped by experiences with the environment.[15] The hedonic system does not merely subserve appetite for food; it is also part of a global organizational unit governing behavioural choice. Decisions are made on the basis of reward and pleasure to be gained.

The Biology of Reward

The incentive system evaluates the motivational and emotional significance of events and adapts behaviour to best fit the context.[16] The system is highly plastic, with long-lasting imprints from learning about the environment. A judgment is made from past experience about the quality of the reinforcer, and this affects current behavioural choice and decision making. The core processes of this system include novelty seeking; impulsivity; sensitivity to, and conditionability of, reward and punishment; and the ability to modulate emotion. Perversities in the reward system can arise from experiences that have shaped this system, particularly in adolescence, the critical period of risk during which this system matures.[17,18] During this time, the brain is particularly vulnerable to disruption by rewards (including drugs) and stress.[19] Drugs of abuse are thought to corrupt the basic systems that control reward. Addiction research therefore has implications for the field of eating disorders. Several competing explanatory models have been developed to describe the irreversible nature of addiction. These include the allostasic, or "dark side" model[20] and the supersensitivity model.[21–26] It is possible that these theories may help explain why and how eating disorders become chronic and treatment-resistant.

Food as Reward

Foods differ in the level of reward they evoke; however, high-fat and high-sugar foodstuffs appear to be innately appealing across many species. Personality traits are linked to the response to food. The trait of sensitivity to reward is associated with overeating highly palatable food and with

Figure 1 A diagram illustrating the central control of appetite
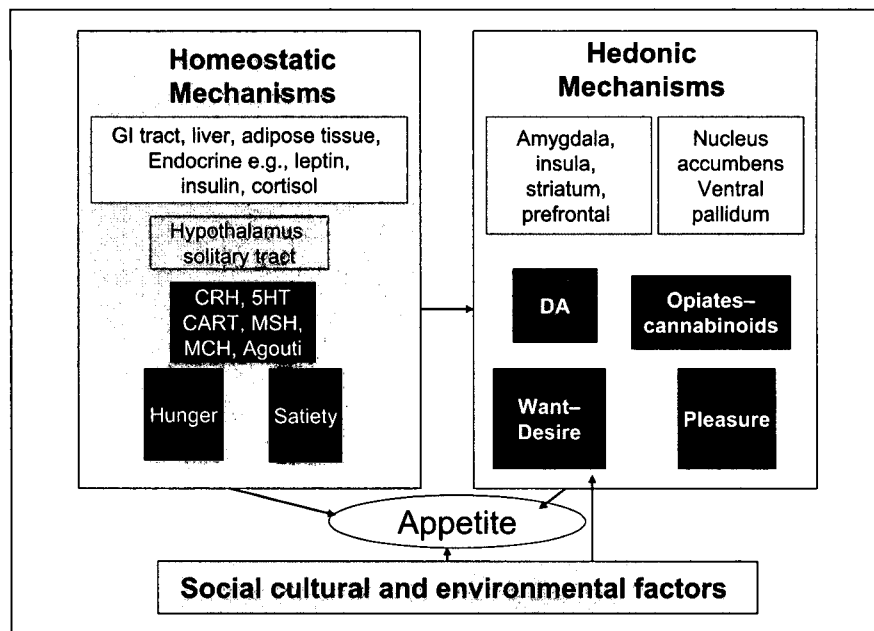
CART = cocaine- and amphetamine-regulated transcript; CRH = corticotropin-releasing hormone;
DA = dopamine; GI = gastrointestinal; MCH = melanin-concentrating hormone;
MSH = melanocyte-stimulating hormone

increased body weight.[27] Also, differences in reward sensitivity are linked to levels of activation in the incentive system in response to food cues.[28]

The Biology of Abnormal Eating Behaviours

Extreme Undereating

Several animal models of undereating exist.[29] Social stress produces weight loss in subordinate animals.[30,31] Lean sow syndrome develops in specific strains of pigs and is associated with overactivity and other parallels with AN.[32] The running rat paradigm is produced when access to food is limited and the cage is fitted with a running wheel.[33] In this model, the reward of running overrides that of food to the extent that life is endangered.[34,35] Anomalies in the neurochemistry associated with this pattern of behaviour include changes in the opiate and 5-HT systems.[36] Female animals appear to be most susceptible to develop undereating.

Extreme Overeating

The undereating of AN can evolve into binge eating. Several animal models of binge eating have been developed[37–44] that involve some, or all, of the following: a period of undernutrition, disjunction from homeostatic mechanisms caused by diverting food from the gastrointestinal tract, intermittent availability of palatable food, and stress. These models are associated with a disruption in the chemistry of reward, with excess, dysregulated release of dopamine and (or) endogenous opiates and cannabinoids. Further, the persistent

priming of the reward circuits that has been found in the addictions also occurs. A taste of a palatable food a month after a pattern of bingeing has been established can trigger a later recurrence of binge eating.[39] Also, there is cross-reaction between drugs of abuse and palatable foods; that is, if an animal has learned to binge eat, then it is sensitized to alcohol and (or) amphetamine.[45,46] The relevance of these models to the binge–purge subtype of AN, in which all the setting conditions are present for persistent extreme eating patterns, is obvious.

The Central Anatomy and Psychophysiology in Response to Food

In healthy women, the incentive system is activated by food cues; however, in women with AN, an anomalous pattern of activation occurs in the prefrontal cortex.[47,48] This remains present even after recovery.[47] As well, exposure to food cues elicits an exaggerated startle response, suggesting that food primes an automatic defensive reaction. Conversely, a soothing effect is found in healthy control subjects.[49] Individuals with AN show various unusual responses to food. They salivate less to food cues,[50] have lower preferences for fat–sweet substances,[51,52] eat more slowly,[53] and, when eating, have an autonomic arousal response with increased skin conductance.[54] All these findings suggest that central control of eating, particularly that involving the hedonic system, is disrupted in AN.

Brain Neurochemistry in AN

Anomalies in the central neurochemistry involved in the control of eating behaviour have been found in AN, but most of the work has used indirect measures.[55] The specific localization offered by scanning technologies is an area of active research.

Imaging work into the neurochemistry of eating disorders shows evidence consistent with the concept of a permanent disruption in the dopamine systems. For example, when subjects are at normal weight after recovery from AN, raclopride binding is increased, indicating more available D_2 receptors in the anterior striatum.[56] This has parallels with the demonstration that body mass index (in the obese end of the spectrum) correlates negatively with striatal D_2 receptors.[57] Thus lower tonic dopamine release in the striatum in AN may mean that the drive to eat is lower. This might explain the link to leanness that is associated with AN.[58]

The 5-HT system is also involved in eating behaviour and is part of the punishment (or harm avoidant) system—the system that works in opposition to reward. Individuals with AN have anomalies in the 5-HT system that persist after recovery. In a single photon emission computed tomography study,[59] reduced 5-HT_{2A} binding was found in individuals in the acute phase of the bulimic subtype of AN. Also, after recovery, this binge–purge subgroup had reduced 5-HT_{2A} binding in the subgenuate cingulate region[60] and increased 5-HT_{1A} binding in the incentive areas of the brain.[61]

Conclusions About the Central Control of Appetite in AN

In summary, the clinical and neuroscience findings summarized above suggest that individuals suffering from AN have anomalies in the systems that control motivated behaviour in relation to eating. Further, these anomalies remain after recovery and differentiate between the binge–purge and restrictive subgroups.

The Biology of the High-Risk Disposition

The following section considers the wider aspect of the clinical phenotype—the links with persistent traits such as the obsessive–compulsive, anxious, and avoidant personality dispositions.

The Genotype

Eating disorders aggregate in families, with the risk increased by a factor of 10.[62] The variance in heritability lies between 33% and 84% in twin studies.[63] Linkage to chromosome 1 has been found in the restricting subtype,[64] and anomalies in the genes controlling 5-HT function predominate in this form.[65] Obsessive traits are also linked within these families to regions on chromosome 1.[66] However, the effect size found in genetic studies is small, and so many genes of small effect may

be involved. Moreover, most studies are poorly powered, and few are replicated.

Intermediate Phenotypes and Endophenotypes in Eating Disorders

Obsessive–compulsive traits (including perfectionism and concern about mistakes) may be an intermediate phenotype, particularly for AN, because they are present in childhood,[67] remain after recovery,[68–71] and are shared with family members.[72,73] Twin studies suggest that these constructs are moderately heritable.[74] Anomalies in information processing, such as weakness in set shifting and central coherence, may underpin these traits.

Set Shifting as a Possible Endophenotype in AN

Weak set shifting has been postulated to be a core component of recent causal models of AN.[75,76] A systematic review of the neurocognitive literature on eating disorders confirmed that weak set shifting was a consistent finding across the numerous tests used to examine this construct.[77] Further, set shifting fulfils several criteria of an eating disorder endophenotype. First, the effect size of the set shifting difficulty was similar in individuals in the acute and recovered states. Second, these traits were also present in unaffected family members.[78]

However, impaired set shifting is not a specific eating disorder endophenotype, since it is present in individuals with bipolar disorder tested when euthymic[79,80] and also in their first-degree relatives.[81] It is also seen within the families of individuals with schizophrenia.[82] Set shifting anomalies have been linked to variations in reward sensitivity and to dopaminergic systems.[83,84] A difficulty in set shifting is therefore a possible endophenotype that broadly increases the risk for many forms of psychiatric illnesses.

A Bias to Detail Over Global Processing (Weak Central Coherence) as a Possible Endophenotype in AN

Individuals with AN excel in tasks that require analytical and detailed strategies, such as the Matching Familiar Figures Test[85] and the Embedded Figures Task.[86] The poor visual memory so commonly seen in AN in the Rey-Osterrieth Complex Figure Test results from poor organizational strategies[87] and weak central coherence, whereby the bias to detail over the gestalt of the figure overloads the memory system. Central coherence is a term used to describe the bias of global over local overprocessing. Individuals with autism or Asperger disorder have weak central coherence,[88,89] and this trait may be an autism spectrum disorder endophenotype because it is also present in first-degree relatives.[90] Our group has employed a battery of tests used to measure central coherence in autistic spectrum disorders and found similar patterns of function in individuals with eating disorders. Thus weak central coherence may be another, nonspecific endophenotype that increases the risk of developing AN.

Learning and Conditioning

Strober proposed a model of AN in which abnormalities in fear conditioning form a core component[91] (a trait also seen in anxiety disorders[92]). Other learning tasks are also impaired; for example, individuals with AN had more errors in the early learning phase in a learning task driven by reward and error (which is thought to depend on dopaminergic mechanisms).[93] Also individuals with AN perform well on effortful learning but less well on incidental learning.[94] Anomalies in learning may account for the failure, common in AN sufferers, to adapt to environmental demands.

The Emotional Endophenotype

The anomalies in the "seeking" incentive (reward) systems as well as in the fear–anxiety (punishment) systems, described above, may be markers of the emotional endophenotype[95] of eating disorders.

In eating disorders, the response of the autonomic nervous and stress system is atypical. For example, in response to a standard stress test, individuals with AN display no objective signs of arousal in terms of changes in heart rate or cortisol release.[96] In the Iowa Gambling Task, individuals with AN also show no increase in skin conductance when making high-risk choices.[97] In a study by Friederich et al,[49] the baseline startle response in subjects with AN did not differ from that of control subjects; however, positive valenced stimuli paradoxically engaged the defensive system. Anomalies in the responsiveness of the hypothalamic–pituitary–adrenal stress system persist after recovery,[98] and this has been developed into a model explaining AN.[99]

The registration of emotion in others may be disrupted in AN, but the findings have been inconsistent.[100–103] On a cognitive developmental measure of emotion processing, individuals with AN have deficits in recognizing emotions in others.[104] A subgroup also have deficits in theory of mind tasks.[105] More work is needed to define the emotional phenotype in individuals with eating disorders.

Model Fitting

A triadic model with approach, avoidance, and regulatory components has been developed to explain some of the behavioural problems of adolescence.[106] If we apply such a model to eating disorders, then heightened sensitivity to punishment, demonstrated by avoidance behaviour, is a transdiagnostic characteristic of individuals with eating disorders, whereas sensitivity to reward may distinguish between the restricting and bingeing subgroups. Individuals displaying the restrictive subtype have reduced reward sensitivity with fewer approach behaviours, and individuals who binge eat have the opposite tendency.[107] Information-processing deficits such as weak set

shifting, an overly analytical focus, and learning anomalies may reduce the efficiency of the regulatory system.

Translating Biology into Treatment

Translation from animal models leaves many questions unanswered. Does an episode of prolonged starvation lead to persistent changes in the incentive or hedonic systems? The plasticity and resetting of the reward system according to experience may explain why recovery from AN becomes more difficult with longer duration of starvation.[108,109] Do developmental factors such as strict control over, and intermittent availability of, highly palatable food increase the risk of binge eating in AN? Is the incentive system permanently changed once binge behaviour breaks through into AN, as is postulated to occur in the addictions?

We have developed a model of AN[110] that integrates some of these biological features,[111] and we have further developed this into a maintenance model[110] that can be translated into new approaches into treatment.[111] The components of this treatment approach are shown in Figure 2. Treatment includes:

• A module with an emphasis on relearning healthy eating, that is, sufficiency, variety, and social eating.

• A remediation module to correct informational processing biases.

• A reward–emotion module to attain balance in the approach–avoidance systems.

• A carer module that gives the family skills to moderate the environment by reducing expressed emotion, especially overprotection and accommodation to the symptoms.[112]

It is possible that such treatment may be improved by drugs targeting sites within the hedonic network, such as dopamine, opiates, or cannabinoids, or by psychological treatments, for example, contingency management to reset the incentive system.

Conclusions

Research into understanding the biological framework of the brain in AN suggests that anomalies may exist in emotional and informational processing. The deficit in set shifting is a reliable but nonspecific risk factor. Weak central coherence is a new factor in information processing that needs further exploration. Several studies suggest that there may be anomalies in the approach–avoidance or regulation domains that control motivated behaviour. The links between the biology of addiction and the binge eating form of AN are worthy of more study. Persistent changes in the reward system, with possible upregulation to food or activity (or even downregulation to food in restricting AN), may explain why

Figure 2 Translating the endophenotype and maintaining factors into treatment
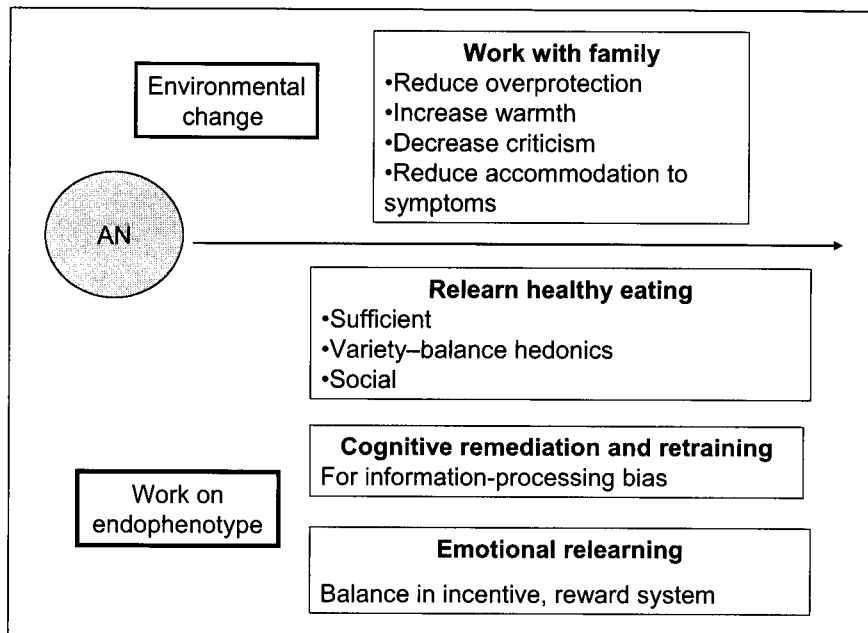
these disorders can have such a prolonged time course and how such problems can be transmitted to the next generation.

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Résumé : Les dessous du phénotype de l'anorexie mentale : la recherche d'endophénotypes et de génotypes viables

Le traitement de l'anorexie mentale a peu changé depuis la description qu'en a donnée Gull, il y a plus d'un siècle. Se concentrer seulement sur le soulagement symptomatique de « ne pas manger », comme cela se fait dans certaines formes de soins hospitaliers, est primitif. Les données probantes pour guider le traitement sont rares. Néanmoins, il y a de l'espoir qu'une meilleure compréhension des causes et des facteurs de maintien puisse se traduire par des traitements plus évolués. Cet article vise à aller plus loin que le phénotype « ne pas manger » évident et renversant de l'anorexie mentale, et à examiner les endophénotypes du trouble alimentaire. La première partie de l'article met le comportement alimentaire, les traits cliniques et psychopathologiques en contexte des connaissances actuelles sur le contrôle central de l'appétit. Les données probantes d'un cadre des endophénotypes possibles du trouble alimentaire suivent. Finalement, des idées sur la façon de traduire les endophénotypes en traitement sont présentées.