New insights into symptoms and neurocircuit function of anorexia nervosa

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Abstract | Individuals with anorexia nervosa have a relentless preoccupation with dieting and weight loss that results in severe emaciation and sometimes death. It is controversial whether such symptoms are secondary to psychosocial influences, are a consequence of obsessions and anxiety or reflect a primary disturbance of brain appetitive circuits. New brain imaging technology provides insights into ventral and dorsal neural circuit dysfunction — perhaps related to altered serotonin and dopamine metabolism — that contributes to the puzzling symptoms found in people with eating disorders. For example, altered insula activity could explain interoceptive dysfunction, and altered striatal activity might shed light on altered reward modulation in people with anorexia nervosa.

Anorexia nervosa (AN), a disorder of unknown aetiology, is characterized by restricted eating and a relentless pursuit of thinness (BOX 1). AN is possibly the most homogenous of all psychiatric disorders. There is a narrow range of age of onset (early adolescence), stereotypic presentation of symptoms and course, and relative gender specificity[1]. Individuals with AN have an ego-syntonic resistance to eating and a powerful pursuit of weight loss, yet are paradoxically preoccupied with food and eating rituals to the point of obsession. Individuals have a distorted body image and, even when emaciated, tend to see themselves as 'fat', express denial of being underweight and compulsively over-exercise. They are often resistant to treatment and lack insight regarding the seriousness of the medical consequences of the disorder.

Two types of eating-related behaviour are seen in AN (BOX 1). Restricting-type anorexics lose weight purely by dieting without binge eating or purging. Binge-eating/purging-type anorexics also restrict their food intake to lose weight, but have a periodic disinhibition of restraint and engage in binge eating and/or purging as do individuals with bulimia nervosa (BN). Considering that transitions between syndromes occur in many, it has been argued that AN and BN share some risk and liability factors[2,3]. However, this Review focuses on restricting-type AN.

Although AN is characterized as an eating disorder, it remains unknown whether there is a primary disturbance of appetitive pathways, or whether disturbed appetite is secondary to other phenomena, such as anxiety or obsessional preoccupation with weight gain. There has been considerable interest in the role of the hypothalamus in food and weight regulation in AN, although it remains uncertain whether hypothalamic alterations are a cause or a consequence of the symptoms. This Review focuses on another perspective. That is, although the hypothalamus is an important regulator of food intake and body weight, there is limited evidence that hypothalamic peptides have a role in the aetiology of AN. However, studies in animals and healthy humans are leading to a new understanding of overlapping neural pathways that contribute to the modulation of reward and emotion in response to appetitive stimuli. Given the probable link between feeding behaviour and affective processes in AN, the neural substrates underlying these processes are potential candidate regions for understanding the pathophysiology of this illness. This Review integrates findings from pharmacological, behavioural and neuroimaging studies that contribute to the understanding of appetite regulation, reward, neurotransmitters and neurocircuits that are associated with AN.

State and trait

When malnourished and emaciated, individuals with AN have widespread and severe alterations of brain and peripheral-organ function; however, it is unclear whether these changes are the cause or the consequence of malnutrition and weight loss. Therefore, to understand the aetiology and course of illness of AN, it is useful to divide

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Interoception
The sensing and integrating of afferent proprioceptive and visceroceptive information, resulting in feeling the 'inner state' of the body, which is important for allocating attention, evaluating context and planning actions.

the neurobiological alterations into two categories. First, there seem to be premorbid, genetically-determined trait alterations that contribute to a vulnerability to develop AN. Second, there are state alterations secondary to malnutrition that might sustain the illness, and perhaps accelerate the out-of-control spiral that results in severe emaciation and the highest mortality rate of any psychiatric disorder.

Trait-related alterations. Large-scale community-based twin studies have shown that 50% to 80% of the variance in AN and BN can be accounted for by genetic factors[3–5]. The genetic vulnerability to eating disorders might be expressed as a diffuse phenotype of continuous behavioural traits, as suggested by evidence of significant heritability of disordered eating attitudes, weight preoccupation, dissatisfaction with weight and shape, dietary restraint, binge eating and self-induced vomiting[6–8], and of significant familiality of subthreshold forms of eating disorders[2,9].

Considerable evidence has suggested that childhood temperament and personality traits can lead to a predisposition to develop AN during adolescence. Recent studies[10–12] describe negative emotionality, harm avoidance, perfectionism, inhibition, drive for thinness, altered interoceptive awareness and obsessive-compulsive personality traits as childhood predisposing factors that precede the onset of an eating disorder (FIG. 1) and that persist after recovery (see below). Studies suggest that these traits are heritable, can be present in unaffected family members and are independent of body weight[13], providing further evidence that they confer liability to the development of AN.

State-related alterations. Starvation and emaciation have profound effects on the functioning of the brain and other organ systems. They cause neurochemical disturbances that could exaggerate premorbid traits[14], adding symptoms that maintain or accelerate the disease process (FIG. 1). For example, subjects with AN have a reduced brain volume[15], an altered metabolism in frontal, cingulate, temporal and parietal regions[16], and a regression to pre-pubertal gonadal function[17]. The fact that such disturbances tend to normalize after weight restoration suggests that they are a consequence rather than a cause of AN.

It is likely that many of the starvation-driven endocrine and metabolic changes that result from AN are compensatory and attempt to conserve energy or stimulate hunger and feeding[18]. For example, subjects with AN have altered concentrations[19] of neuropeptide Y (NPY), leptin, corticotropin-releasing hormone (CRH), cholecystokinin, beta-endorphin and pancreatic polypeptide. It is important to note that such alterations are likely to cause alterations in mood, cognitive function, impulse control and autonomic and hormonal systems[20], which indicates that they might contribute to the behavioural symptoms associated with the ill state. For example, intracerebroventricular CRH administration in experimental animals produces many of the physiological and behavioural changes associated with AN, including hypothalamic hypogonadism, altered emotionality, decreased sexual activity, hyperactivity and decreased feeding behaviour[21]. Therefore, it can be argued that some secondary changes in peptide concentrations can sustain AN behaviours (FIGS 1,2) by driving a desire for more dieting and weight loss. Moreover, malnutrition-associated alterations exaggerate emotional dysregulation, consistent with the many individuals with AN that meet DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, forth edition) criteria[1] for major depression, obsessive compulsive disorder (OCD) or other anxiety disorders[22,23].

Do symptoms in individuals with AN reflect trait or state? The difficulty in distinguishing changes that are due to trait from those that are related to state in studies of subjects with AN has been a major confound in the research of this disorder. Prospective, longitudinal studies are difficult given the young age of potential subjects, the rarity of the disorder and the many years of follow-up required. An alternative strategy is to study individuals who have recovered from AN, thus avoiding the confounding influence of malnutrition and weight loss on biological systems. There is presently no agreed-upon definition of recovery from AN, but our research defines it as having a stable and healthy body weight for months or years, with stable nutrition, relative absence of dietary abnormalities and, in females, normal menstruation. Although the process of recovery from AN is poorly understood and, in most cases, protracted, approximately 50% to 70% of affected individuals will eventually attain complete or moderate resolution of the illness, although this might not occur until their early to mid 20s[24–26]. Studies have described temperament and character traits that still persist after long-term recovery from AN, such as negative emotionality, harm avoidance, perfectionism, desire for thinness and mild dietary preoccupation. It is possible that such persistent symptoms are 'scars' caused by chronic malnutrition. However, the fact that such behaviours[24,27,28] are similar to those described for children who will develop AN[10–12] argues that they reflect underlying traits that contribute to the pathogenesis of this disorder.

Box 1 | **DSM-IV, diagnostic criteria for anorexia nervosa[1]**

- Refusal to maintain body weight at or above a minimally normal weight for age and height (for example, weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected.)
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- In postmenarcheal females, amenorrhea (that is, the absence of at least three consecutive menstrual cycles).
- There are two types of anorexia nervosa: 1. Restricting type, in which the person has not regularly engaged in binge-eating or purging behaviour; 2. Binge-eating/purging type, in which the person has regularly engaged in binge-eating or purging behaviour (that is, self-induced vomiting or the misuse of laxatives, diuretics or enemas).

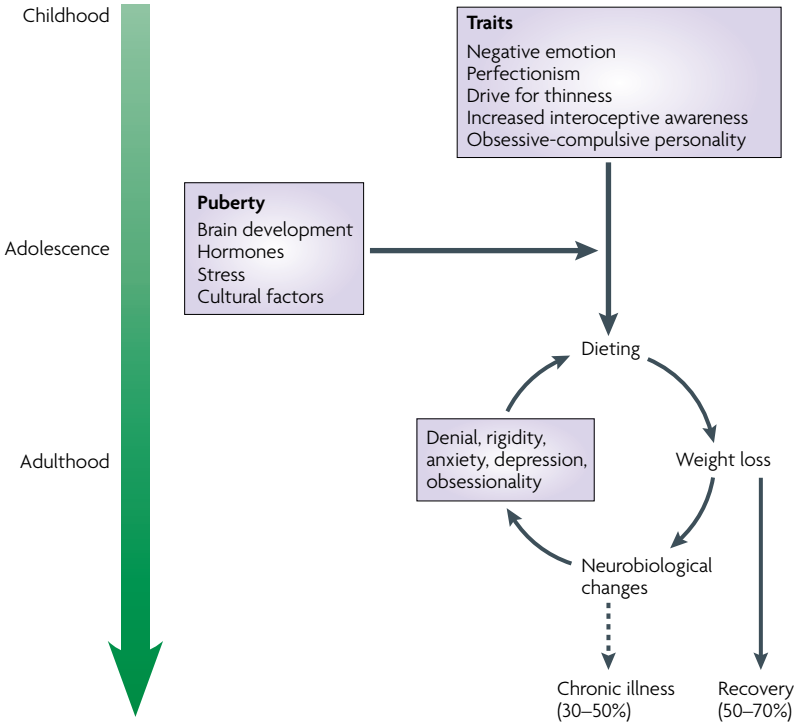

Figure 1 | **The time course and phenomenology of anorexia nervosa.** Childhood personality and temperament traits, which contribute to a vulnerability for developing anorexia nervosa (AN), become intensified during adolescence as a consequence of the effects of multiple factors, such as puberty and gonadal steroids, development, stress and culture. Individuals with AN find that dieting reduces, and eating enhances dysphoric mood. But with chronic dieting and weight loss, there are neurobiological changes which increase denial, rigidity and obsessions, as well as depression and anxiety, so that individuals often enter a downward spiral. Although 50% or more of individuals with AN recover by their early to mid-20s, a significant proportion of subjects develop a chronic illness or die.

Neurobiology and behaviour

Common comorbid behaviours typical of both recovered and ill AN individuals are often expressed in concert. These include inhibition, anxiety, depression and obsessionality, and puzzling symptoms such as body image distortion, perfectionism, and anhedonia. These behaviours could be encoded in limbic and cognitive circuits known to modulate and integrate neuronal processes that are related to appetite, emotionality and cognitive control. Two neurocircuits that have been described based on imaging, neurophysiological and lesion studies[29,30] might be of particular relevance to understanding behaviour in AN. A ventral (limbic) neurocircuit that includes the amygdala, insula, ventral striatum and ventral regions of the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) seems to be important for identifying the emotional significance of stimuli and for generating an affective response to these stimuli[29,30]. A dorsal (cognitive) neurocircuit is thought to modulate selective attention, planning and effortful regulation of affective states, and includes the hippocampus, dorsal regions of the ACC, dorsolateral prefrontal cortex (DLPFC), parietal cortex and other regions[29,30]. Indeed, earlier brain imaging studies have shown that subjects who have recovered from AN have altered activity in frontal, anterior cingulate and parietal regions[31–33] Several investigators have proposed that dysregulation of these two circuits contributes to several psychiatric disorders including major depression, anxiety disorders and OCD. It is possible that aberrant function of these circuits causes altered emotion regulation or obsessionality but that the molecular basis of these dysfunctions differs between disorders[30]. Indeed, the neurobiological disturbances in people with eating disorders may differ from those found in people with depression, anxiety or OCD. For example, the binding potential of the serotonin (5-HT) receptor 1A (5-HT_{1A}) is decreased in subjects with depression[34], as well as in people with social phobia[35] and panic disorder[36], whereas it tends to be increased in people with eating disorders[37–40].

This Review focuses on the findings derived from several imaging technologies. Studies using positron emission tomography (PET) brain imaging and related technologies have assessed 5-HT and dopamine (DA) neurotransmitter systems in subjects with AN and in those who have recovered. Second, recent functional MRI (fMRI) studies have begun to shed light on altered activity in interconnected brain regions of these individuals. Together these studies provide new insights into neurobiological disturbances that characterize this deadly disorder.

Serotonin function in AN. The 5-HT system has been intensively studied in people with AN as considerable evidence suggests that this neurotransmitter system could play a part in symptoms such as enhanced satiety[41], impulse control[42,43] and mood[44,45]. Indeed, there is much evidence of abnormal functional activity of the 5-HT system in subjects with AN[46,47] (FIG. 2). For example, in underweight and malnourished individuals suffering from AN the cerebrospinal fluid (CSF) has reduced amounts of 5-hydroxyindoleacetic acid (5-HIAA) — which is the major brain metabolite of 5-HT and is thought to reflect extracellular 5-HT concentrations[48]. By contrast, 5-HT metabolite levels were elevated in the CSF of subjects who had recovered from AN.

It is important to note that the 5-HT system involves 14 or more receptors, and interacts with many other neurotransmitters and molecules. Only a few of these components can currently be measured *in vivo* in humans. Still, imaging studies of 5-HT functional activity are useful; although the complexity of 5-HT circuits cannot be fully elucidated in humans, such imaging studies can characterize potential state and trait differences between individuals with AN and healthy controls, be used to model relationships of 5-HT activity to behaviour and provide new insights on potentially more effective treatment targets. In fact, brain imaging studies consistently show that, when compared with healthy subjects, individuals with or having recovered from eating disorders have elevated and diminished binding potential for postsynaptic 5-HT_{1A} receptors and 5-HT_{2A} receptors, respectively[37–40,49–51]. Studies of individuals with or having recovered from AN tend to produce similar findings, supporting the notion that there are trait-related alterations of 5-HT function in AN.

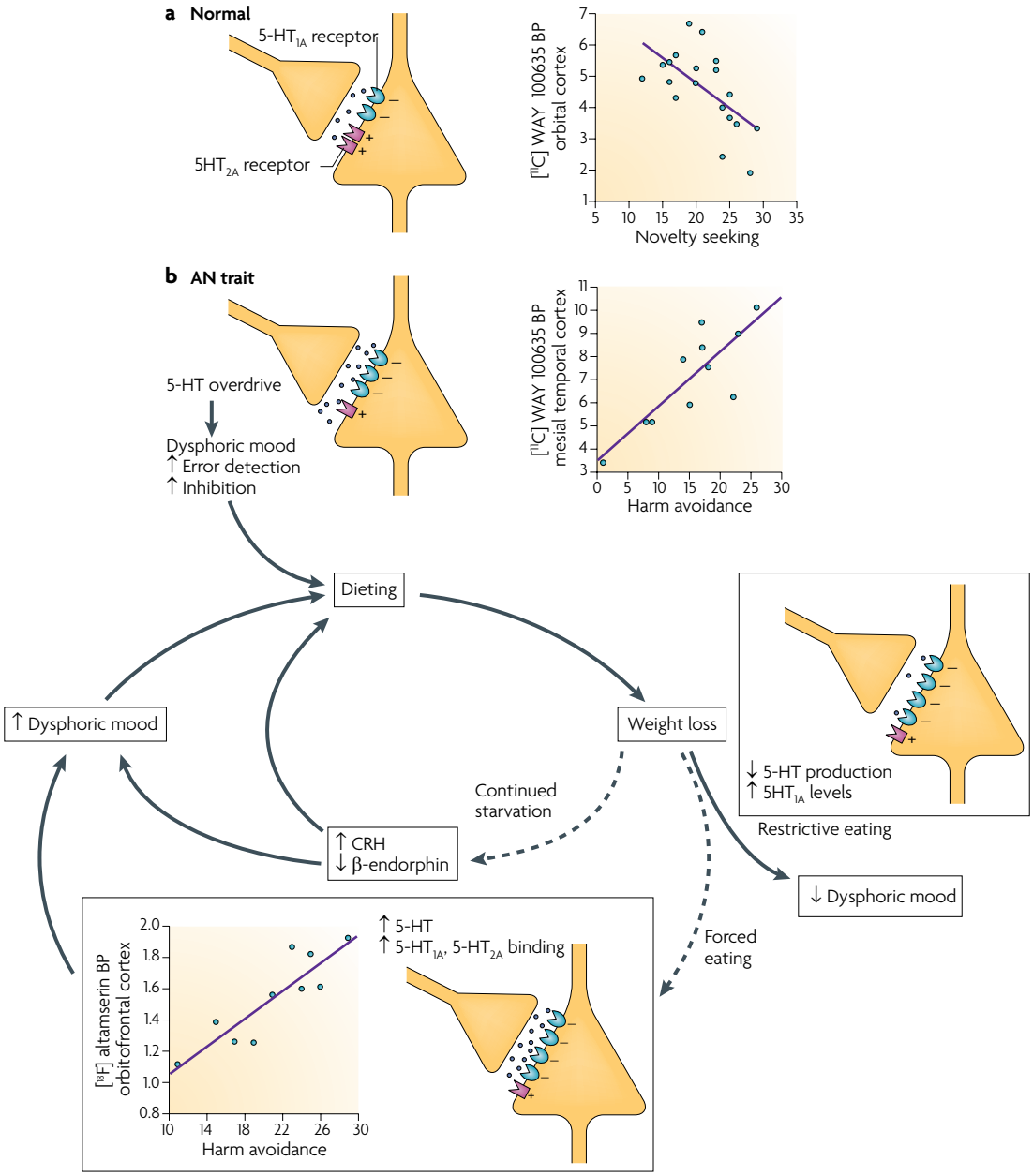

Figure 2 | **The role of serotonin neural function in anorexia nervosa.** It is well known that people with anorexia nervosa (AN) enter a vicious cycle, whereby malnutrition and weight loss drive the desire for further restricted eating and emaciation. Evidence suggests that, compared with healthy individuals (**a**), individuals who are vulnerable to developing an eating disorder might have a trait for increased extracellular serotonin (5-HT) concentrations[68] and an imbalance in postsynaptic 5-HT_{1A} and 5-HT_{2A} receptor activity[37–40,49–51] (**b**), which together might contribute to increased satiety and an anxious, harm-avoidant temperament. Gonadal steroid changes during menarche or stress related to adolescent individuation issues might further alter activity of the 5-HT system and so exacerbate this temperament, resulting in a chronic dysphoric state. It is important to note that food–mood relationships in AN are very different from those in healthy controls. That is, palatable foods in healthy subjects are associated with pleasure, and starvation is aversive. By contrast, palatable foods seem to be anxiogenic in AN, and starvation reduces dysphoric mood. In subjects with AN, starvation and weight loss result in reduced levels of 5-HIAA in the cerebrospinal fluid (CSF)[74] (and inferentially reduced extracellular 5-HT concentrations) but exaggerated 5-HT_{1A} receptor binding in limbic and cognitive cortical regions[39]. Starvation-induced reductions of extracelluar 5-HT levels might result in reduced stimulation of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors, and thus decreased dysphoric symptoms. However, when individuals with AN are forced to eat, the resulting increase in extracellular 5-HT levels, and thus stimulation of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors, increases dysphoric mood, which makes eating and weight gain aversive. Alternatively, if subjects with AN continue to starve, anorexigenic signals related to neuropeptide disturbances (for example, increased corticotropin-releasing hormone (CRH)[21] and reduced β-endorphin[166]) might drive further food restriction and changes in behaviour and cognition, which thus promotes AN symptoms. Scatterplots reproduced, with permission, from REF. 39 © (2007) American Medical Association and REF. 40 © (2005) Elsevier.

Moreover, imaging studies provide insight into how disturbed 5-HT function is related to dysphoric mood in AN[52,53]. That is, PET imaging studies show striking and consistent positive correlations between the binding potential of both 5-HT_{1A} and 5-HT_{2A} receptors and harm avoidance — a multifaceted temperament trait[54] that contains elements of anxiety, inhibition, and inflexibility. Studies in animals and healthy humans support the possibility that 5-HT_{1A} and 5-HT_{2A} receptor activity has a role in anxiety[55–58]. It is important to note that there is high co-localization (80%) of the 5-HT_{2A} and 5-HT_{1A} postsynaptic receptors in the rodent frontal cortex[59] and other cortical regions[60]. Through interneurons, they mediate, respectively, direct hyperpolarizing and depolarizing actions of 5-HT on prefrontal neurons that project to cortical and subcortical areas[61,62]. Interactions between 5-HT_{1A} and 5-HT_{2A} receptors in the medial prefrontal cortex (mPFC) and related regions seem to modulate anxiety, attentional functioning[63], impulsivity and compulsive perseveration[62], and exploration of new environments[64]. It remains to be determined whether the imbalance between enhanced 5-HT_{1A} and diminished 5-HT_{2A} receptor binding potential contributes to such symptoms in individuals with eating disorders.

Implications for satiety and the benefit of starvation. It is thought that, in individuals with AN, dietary restraint reduces anxiety, whereas eating stimulates dysphoric mood[53,65,66]. Is altered 5-HT function the link between restricted feeding behaviour and anxiety in subjects suffering from AN? It is well-known that carbohydrate intake increases extracellular 5-HT concentrations in the brain through complex metabolic effects on tryptophan, the amino acid precursor of 5-HT[53,67]. We propose that, both premorbidly and after recovery from AN, a normal amount of food ingestion is associated with exaggerated extracellular brain 5-HT secretion[68]. This is consistent with increased CSF 5-HIAA levels in people who have recovered from AN[68]. Increased 5-HT concentrations inhibit appetite, perhaps through activation of 5-HT_{2C} receptors[69]; however, 5-HT_{2C} receptor binding has not been measured by imaging studies in individuals with AN. Increased 5-HT_{1A} binding potential is positively associated with harm avoidance in subjects who have recovered from AN[40] (FIG. 2), and enhanced anxiety and harm avoidance are traits that are present premorbidly and persist after recovery from AN. It is therefore possible that carbohydrate-induced increases in extracellular 5-HT levels drive anxiety and harm avoidance through stimulation of 5-HT_{1A} receptors (FIG. 2), offering a potential explanation for feeding-related dysphoric mood in AN. By contrast, when individuals with AN starve, extracellular 5-HT concentrations might diminish, resulting in a brief respite from dysphoric mood. Studies in animals and healthy humans show that both a restricted diet (which significantly lowers plasma tryptophan) and experimentally reduced tryptophan depletion decrease 5-HT synthesis in the brain[67,70,71]. Indeed, malnourished and emaciated individuals with AN have reduced plasma tryptophan availability[72,73] and reduced CSF 5-HIAA levels[74]. Importantly, experimental manipulations that reduce the levels of tryptophan in the brain decrease anxiety in both ill and recovered AN subjects[53]. However, starvation in AN seems to be associated with a compensatory increase in postsynaptic 5-HT_{1A} receptor binding potential[39]. Moreover, 5-HT_{2A} receptor binding is positively related to harm avoidance in subjects suffering from AN. Therefore, when individuals with AN are forced to eat (FIG. 2), it is likely that they have a relative increase in extracellular 5-HT concentrations in the brain, leading to an exaggeration of dysphoric mood. Thus, individuals with AN might pursue starvation in an attempt to avoid the dysphoric consequences of eating and consequently spiral out of control.

Dopamine and reward processing in AN. People with AN often exercise compulsively, are anhedonic and ascetic, and find little in life that is rewarding aside from the pursuit of weight loss[1]. Such temperament persists, in a more modest form, after recovery[24,75], indicating that these characteristics are traits rather than being state related. DA dysfunction, particularly in striatal circuits, might contribute to altered reward and affect, decision-making and executive control, as well as stereotypic motor movements and decreased food ingestion in subjects with AN[76]. Evidence that the DA system is involved in AN includes reduced CSF levels of DA metabolites in both ill individuals and those having recovered from AN[77], functional DA D2 receptor (DRD2) gene polymorphisms in subjects with AN[78] and impaired visual discrimination learning[79], which is thought to reflect DA-signalling function, in individuals with AN. A PET study found that subjects who recovered from AN had increased D2/D3 receptor (DRD3) binding in the ventral striatum[76], a region that modulates responses to reward stimuli[80,81]. This could indicate increased D2/D3 densities, decreased extracellular DA, or both, in individuals who recovered from AN. In addition, D2/D3 receptor binding in the dorsal caudate–dorsal putamen correlated positively with harm avoidance in subjects who had recovered from AN[76].

To determine whether individuals who have recovered from AN have fundamentally different responses to reward compared with healthy controls, an event-related fMRI study examined the blood oxygen level-dependent (BOLD) signal while participants performed a simple choice and feedback task[82]. The task was adapted from a well-characterized 'guessing-game' protocol[83] that is known to activate the ventral striatum and subgenual ACC, with control participants showing differential activity in these areas in response to positive and negative monetary feedback. In the subjects who had recovered from AN activity in the subgenual ACC and its ventral striatal target was similar during positive and negative feedback[82], suggesting that individuals with AN have a circuit-based abnormality during this simple task and might have difficulty discriminating between positive and negative feedback. Animal studies show that DA has a role in the processing of

motivational aspects to stimuli in the ventral striatum: DA modulates the influence of limbic inputs on striatal activity[30,80,81] and is thought to thereby mediate the 'binding' of hedonic evaluation of stimuli to objects or acts ('wanting' response)[84]. The ventral striatal responses in subjects who had recovered from AN[82] might reflect a failure to appropriately bind, modulate or discriminate responses to salient stimuli. These data support the possibility that individuals who have recovered from AN might have an impaired ability to identify the emotional significance of stimuli[30], which could be important in understanding why it is so difficult to motivate them to engage in treatment or appreciate the consequences of their behaviour[85].

Moreover, the women who had recovered from AN had exaggerated activation in the caudate–dorsal striatum and in the 'cognitive' cortical regions that project to this area, specifically the DLPFC and the parietal cortex[82]. The caudate nucleus is activated by tasks in which there is both a perceived connection between action and outcome, and some uncertainty about whether the action will lead to the desired outcome[86]. Many of these women indicated an attempt at 'strategic' (as opposed to hedonic) responses to improve the ratio of wins to losses, which perhaps contributed to the greater activation of this region. In the absence of appropriate reward processing through ventral-striatal/DA paths, individuals who have recovered from AN might focus on a detailed strategy rather than the overall situation[87]. From another perspective, control women appropriately 'lived in the moment'. That is, they realized they had to make a guess and then moved on to the next task. By contrast, subjects with AN tend to exaggeratedly and obsessively worry about the consequences of their behaviours — looking for 'rules' when there are none — and are overly concerned about making mistakes. A recent fMRI imaging study, using a set shifting task, showed relatively similar findings in individuals with AN[88], namely hypoactivation in the ventral anterior cingulate-striato-thalamic loop, with predominant activation of frontoparietal networks. Together these data suggest that individuals with AN might be less able to precisely modulate affective response to immediately salient stimuli but have increased activity in neurocircuits concerned with planning and consequences.

Serotonin–dopamine interactions. Do interactions between 5-HT and DA systems contribute to symptoms in AN? It has been speculated that 5-HT is the crucial substrate of an aversive motivational system which might oppose a DA-related appetitive system[89,90]. Indeed, studies of animals show that 5-HT_{2C} receptors tonically inhibit DA neurons[91,92]. A PET study in subjects that had recovered from eating disorders found positive correlations between 5-HT transporter and D2/D3 receptor binding in the ventral striatum and dorsal caudate (U. F. Bailer and W.H.K., unpublished observations). From another perspective, studies suggest that 5-HT has a role in action choice by controlling the timescale of delayed rewards through differential effects on ventral and dorsal striatal circuits[93,94]. This is consistent with evidence that reduced and increased 5-HT activity are associated with impulsive, aggressive behaviours and behavioural inhibition, respectively[43,93,95]. Considered together, individuals with AN might have a trait towards an imbalance between 5-HT and DA pathways, which could have a role in an altered interaction between ventral and dorsal neurocircuits.

Despite considerable evidence of 5-HT abnormalities, individuals with AN show little response, in terms of improvement of mood or reduction of core eating disorder symptoms, when treated with selective serotonin re-uptake inhibitors (SSRIs)[96]. The efficacy of SSRIs is dependent on neuronal release of 5-HT[97], and 5-HT release in turn results in desensitization of the 5-HT_{1A} receptor[98]. It is possible that elevated activity of 5-HT_{1A} receptors in the raphe nucleus of subjects with AN (FIG. 2) results in reduced 5-HT neuronal firing, and thus decreased extracellular 5-HT levels[74], consistent with the reduced CSF 5-HIAA levels found in these individuals. Therefore, it is possible that SSRIs are not effective in individuals with AN because SSRIs would not have much effect if synaptic 5-HT levels are depleted by malnutrition. Preliminary data raise the possibility that olanzapine (Zyprexa; Eli Lilly) — which has effects on both DA and 5-HT receptors — and possibly other atypical antipsychotics might be useful for increasing weight gain and reducing anxiety and obsessionality in AN[99].

Neurocircuitry of appetite

How can individuals with AN restrict their food intake every day, maintain a low weight for many years and sometimes die of starvation, when most people struggle to lose a few pounds? Appetite is a complex incentive motivational drive and is thought to depend on interrelated psychobiological factors including food's rewarding properties, an individual's homeostatic needs and the cognitive ability to favour alternative (to eating) behaviours[100–102]. Appetite is clearly disturbed in subjects with AN: they dislike high-fat foods[103,104], do not find sucrose aversive when satiated and fail to rate food as positive when hungry[105,106]. These responses tend not to change following weight regain and, as noted above, there is evidence that dietary restraint reduces anxiety and that eating results in dysphoric mood in individuals with AN[53,65,66]. The complex food consummatory symptoms of eating disorders are relatively unique and have a stereotypic and relentless expression, supporting the possibility that they reflect some aberrant function of neural circuits involved in regulating eating behaviour.

Although a sweet-taste perception task does not test the complexity of food choices[107], it can be used in brain imaging studies to activate brain areas involved in appetite regulation. Sweet-taste perception (FIG. 3) is peripherally mediated by tongue receptors[108] through a neural system consisting of cranial nerves, the nucleus tractus solitarii, and thalamic ventroposterior medial nucleus, to the primary gustatory cortex, which in humans comprises the frontal operculum and the anterior insula[109–113]. The anterior insula and associated gustatory cortex

Hedonic
A sensation related to or characterized by pleasure

Visceroception
A sensation originating from the internal organs.

Proprioception
A sensation originating from the joints and the subcutaneous tissues.

respond to the taste and physical properties of food, and may also respond to its rewarding properties[114–117].

Other regions comprising the ventral neurocircuit mentioned above are interconnected with the insula (FIG. 3), including the amygdala, the ventral ACC and the OFC. The ACC is linked to hypothalamic and brainstem pathways that mediate autonomic and visceral control[118,119]. The pregenual ACC is implicated in 'conflict monitoring' and detecting unpredicted outcomes to guide subsequent behaviour[80,120–122]. The OFC is associated with flexible responses to changing stimuli: it responds to the anticipated negative (or positive) value of external stimuli and flexibly alters responses based on changing incentive values of a stimulus[123–126]. The anterior insula, ACC and OFC all innervate a broad region of the rostral ventral striatum, in which behavioural repertoires are computed based on these inputs. These interconnected regions of the ventral neurocircuit play an important part in determining homeostatic appetitive needs (FIG. 3). Indeed, brain imaging studies have consistently shown that food deprivation (compared to having been fed) in healthy individuals activates the insula and the OFC[117,127–130]. Cortical regions included in the dorsal neurocircuit — such as the DLPFC, the parietal cortex and the posterior insular region — mediate cognitive functions such as planning and sequencing. These regions send inputs to more dorsolateral parts of the striatum, but also might interface and overlap with ventral striatal areas[131,132]. Together, these inputs are thought to modulate the striatal activity that underlies the approach or avoidance of food.

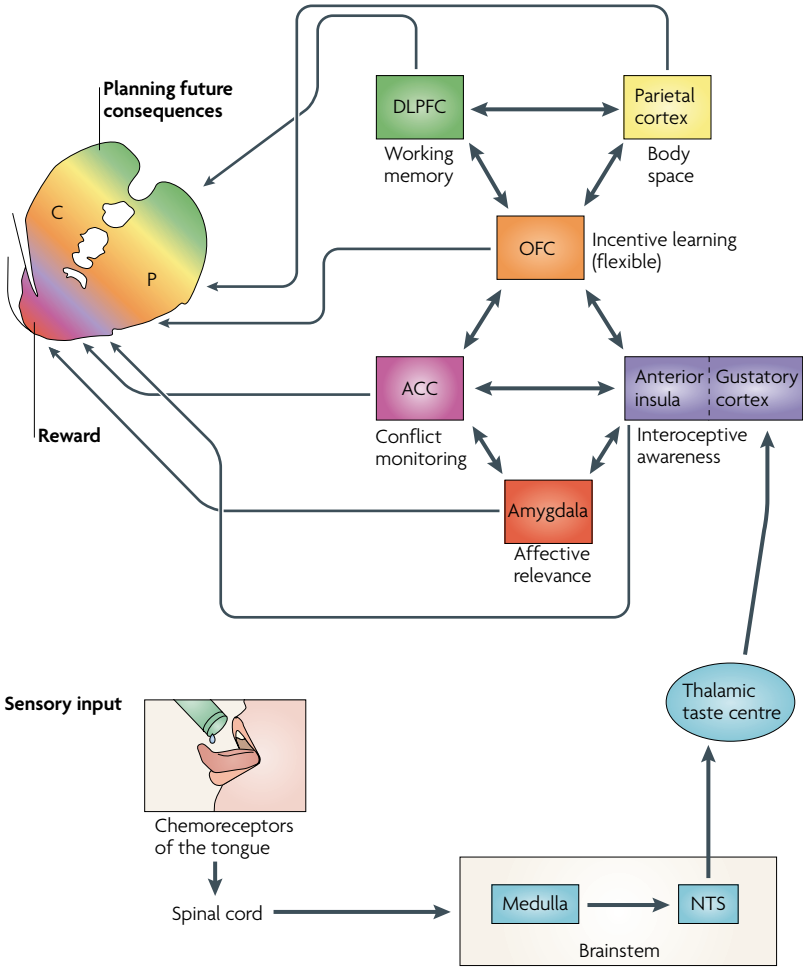

Figure 3 | **Cortical-striatal pathways with a focus on taste.** Chemoreceptors on the tongue detect a sweet taste. The signal is then transmitted through brainstem and thalamic taste centres to the primary gustatory cortex, which lies adjacent to and is densely interconnected with the anterior insula. The anterior insula is an integral part of a 'ventral (limbic) neurocircuit' through its connections with the amygdala, the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). Afferents from the cortical structures involved in the ventral neurocircuit (anterior insula and interconnected limbic cortices) are directed to the ventral striatum, whereas cortical structures involved in cognitive strategies (forming a dorsal neurocircuit) send inputs to the dorsolateral striatum. Therefore, the sensory aspects of taste are primarily an insula phenomenon, whereas higher cortical areas modulate pleasure, motivation and cognitive aspects of taste. These aspects are then integrated, resulting in an 'eat' or 'do not eat' decision. Coding the awareness of pleasant sensation from the taste experience via the anterior insula might be altered in subjects with anorexia nervosa, tipping the balance of striatal processes away from normal, automatic reward responses mediated by the ventral striatum and towards a more 'strategic' approach mediated by the dorsal striatum. The figure links each cortical structure with arrows, indicating that all cortical structures project to striatum in a topographic manner. DLPFC, dorsolateral prefrontal cortex; NTS, nucleus tractus solitarii.

A central role for the anterior insula? The anterior insula is crucially involved in interoceptive processing[140–142]. Interoception includes a range of sensations beyond taste, including the perception of pain, temperature, itch, tickle, sensual touch, muscle tension, air hunger, stomach pH and intestinal tension. Integration of these internal feelings provides an integrated sense of the physiological condition of the entire body[143] and is crucial for the instantiation of the 'self' because it provides the link between cognitive and affective processes and the current body state[140–142,144,145].

It is thought that altered interoceptive awareness might be a precipitating and reinforcing factor in AN[10,146–148].

Administering sucrose or water to subjects who have recovered from AN results in a reduced BOLD response in the insula, ACC and striatum as compared with control subjects[133]. In healthy controls, self-ratings of pleasantness of the sugar taste correlated positively with the BOLD response in the insula, the ACC and the ventral and dorsal putamen[133]. Consistent with the idea that the ability to perceive a palatable taste is fundamentally altered in AN, individuals who had recovered from AN failed to show any relationship between activity in these regions and self-ratings of the pleasantness of the sucrose taste. These findings are supported by other brain imaging studies in which the observation of food pictures by underweight subjects with AN led to altered activity in the insula, the OFC, the mesial temporal and parietal cortex and the ACC[134–138]. Moreover, the altered activity in the supergenual ACC and medial prefrontal cortex persisted after recovery[33]. Altered activity in the anterior insula, its viscerceptive and proprioceptive afferents, and its efferents to the OFC, the ACC, the amygdala and the ventral striatum might underlie the alterations found in subjects with AN in linking sensory-hedonic experiences to the motivational components of reward[139].

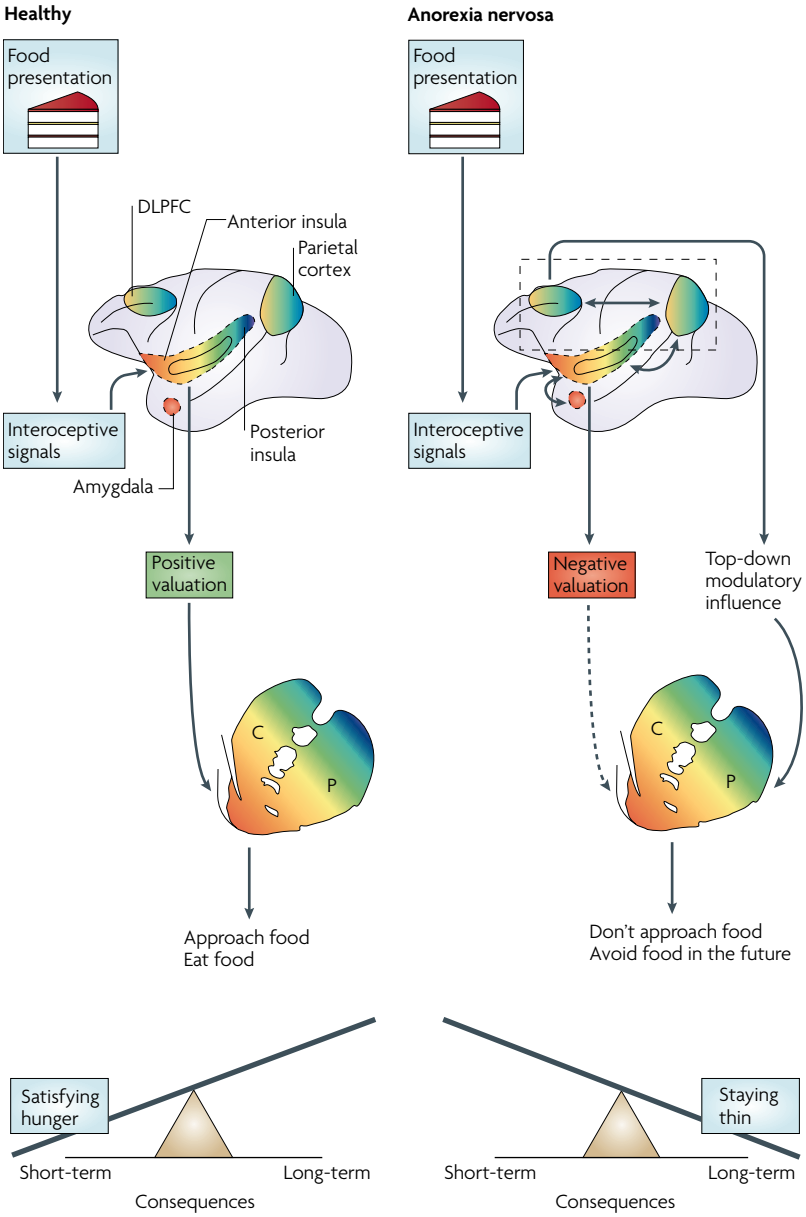

Figure 4 | **Impaired balance between interoceptive and reward processing.** We propose that subjects with anorexia nervosa (AN) experience a strong conflict between the biological need for food and the acquired aversive association with food. In healthy individuals, the presentation of food-related stimuli is associated with ascending interoceptive afferents that converge on the anterior insula, which processes state-related positive or negative valuation of these signals. In individuals with AN this interoceptive information is biased towards the negative or aversive properties of food. As a consequence, top-down, cortical circuits (dotted box) are engaged to resolve the conflict between the need for food and the aversive interoceptive evaluation, processed in the anterior insula. Thus, top-down modulatory circuits are over-engaged in people with AN, which emerges on a symptomatic level as high anticipatory reactivity, behavioural rigidity and excessive worry about future events. On a biological level, these dysfunctions are implemented in a neural system consisting of the ascending interoceptive pathways, the insular cortex, the amygdala and the anterior cingulate cortex (not shown). This information converges in the striatum, which receives inputs from the anterior insula (for the integrated bottom-up information) and the prefrontal cortex (for the top-down modulation relating to cognitive control circuits). The excessive top-down cognitive control in subjects with AN in response to interoceptive stimuli alters the striatal responses, shifting the behavioural event horizon towards satisfying long-term goals (avoiding food, getting thin) rather than short-term goals (eating food).

The role of the anterior insula in integrating interoceptive information and the altered insula activity that has been found in individuals with AN (see earlier) supports the idea that they might suffer from a fundamentally and physiologically altered sense of self[149]. Indeed, many of the symptoms of AN, such as distorted body image, lack of recognition of the symptoms of malnutrition (for example, a failure to appropriately respond to hunger) and diminished motivation to change, could be related to disturbed interoceptive awareness. In particular, there might be a qualitative change in the way that specific interoceptive information is processed. For example, individuals with AN might experience an aversive visceral sensation when exposed to food or food-related stimuli. This experience might fundamentally alter the reward-related properties of food and result in a bias towards negative emotionality. Moreover, the aversive interoceptive experience associated with food might trigger top-down modulatory processes aimed at anticipating and minimizing the exposure to food stimuli ('harm avoidance'), which leads to increased anticipatory processing aimed to reduce the exposure to the aversively valued stimulus. Therefore, individuals with AN might exhibit attenuated responses to the immediate reward-related signal of food (reducing hunger) but show increased responses to the long-term reward-signal associated with the goal of weight reduction or other 'ideal' cognitive constructs. Finally, the anterior insula has been implicated in risk prediction errors[150], suggesting that impairments in insula function might lead to anomalous attitudes in a context of uncertainty and thus contribute to harm avoidance.

Therefore, given the prominent alterations in insula activity in individuals with AN, one might speculate that they experience an altered sensitivity to or integration of internal body signals. Specifically, the projection of the anterior insula to the anterior cingulate may modulate the degree to which cognitive control is engaged to alter behaviour towards poor decision making that does not subserve the homeostatic weight balance but instead results in progressive weight loss.

A neurocircuitry of appetite regulation in AN. Based on the above processes and associated brain areas, we can begin to assemble a neural systems processing model of AN (FIG. 4). Specifically, top-down (cortical) amplification of anticipatory signals related to food or stimuli associated with satiety signals (integrated within the insula) could trigger behavioural strategies for avoiding exposure to food. These anticipatory interoceptive stimuli are associated with an aversive body state that resembles some aspects of the physiological state of the body after feeding. This abnormal response to food anticipation might function as a learning signal to further increase avoidance behaviour, that is, to engage in activities aimed at minimizing exposure to food. Specifically, stimuli that predict food intake, such as displays of food or food smells, could generate a 'body prediction error', resulting from comparing the current body state with the anticipated body state (for example, feeling satiated) after feeding. This prediction error would generate a motivational or approach signal

in healthy individuals but might lead to an avoidance signal in AN.

The dorsal and ventral neurocircuits described earlier might be involved in these processes: The ACC, one of the projection areas of the insular cortex, is important in processing the conflict between available behaviours and outcomes, for example, "shall I eat this cake and satisfy my hunger now or shall I not eat this cake and stay thin?"[151]. The OFC, another projection area of the anterior insular cortex[152], can dynamically adjust reward valuation based on the current body state of the individual[153]. The DPLFC can switch between competing behavioural programmes based on the error signal it receives from the ACC[154].

Although we do not propose here that AN is an insula-specific disorder, we speculate that an altered insula response to food-related stimuli is an important component of this disorder. If this is indeed the case, one would need to determine whether insula-specific interventions, such as sensitization or habituation of interoceptive sensitivity through real-time monitoring of the insular cortex activation, might help. Moreover, computational models such as those that have been proposed for addiction[155] might provide a theoretical approach to better understand the complex pathology of this disorder.

Within the framework of the ventral and dorsal neurocircuits described earlier, there are also potential explanations for other core components of clinical dysfunction in AN. Negative affect — such as anxiety and harm avoidance — and anhedonia could be related to difficulties in accurately coding or integrating positive and negative emotions within ventral striatal circuits. There is considerable overlap between circuits that modulate emotionality and the rewarding aspects of food consumption[156]. Food is pleasurable in healthy individuals but feeding is anxiogenic in individuals with AN, and starvation might serve to reduce dysphoric mood states. The neurobiologic mechanisms responsible for such behaviours remain to be elucidated, but it is possible that an enhancement of 5-HT-related aversive motivation, and/or diminished DA-related appetitive drives[89,90] contribute to these behaviours.

Finally, it is possible that perfectionism and obsessional personality traits are related to exaggerated cognitive control by the DLPFC. The DLPFC might develop excessive inhibitory activity to dampen information processing through reward pathways[157]. Alternatively, increased activation of cognitive pathways might compensate for primary deficits in limbic function: when there are deficits in emotional regulation, overdependence upon cognitive rules is a reasonable strategy of self-management[158]. The inability to 'follow one's gut (or heart)' — that is, make effective use of interoceptive information — is impaired in individuals with AN. Moreover, there is a clear shift away from valuing immediate outcomes to those associated with delayed or long-term outcomes. This behaviour is almost completely opposite to that observed in individuals with alcohol or substance abuse[159] and is consistent with the observation that individuals with AN have low comorbidity with drug and alcohol use disorders[160].

Conclusions and future directions

We propose that somatic, autonomic and visceral information is aberrantly processed in people who are vulnerable to developing AN. Brain changes associated with puberty might further challenge these processes. For example, orbital and dorsolateral prefrontal cortex regions develop greatly during and after puberty[161], and increased activity of these cortical areas might be a cause of the excessive worry, perfectionism and strategizing in people with AN. It is possible that in subjects with AN, hyperactivity of cognitive networks in the dorsal neurocircuit (for example, DLPFC to dorsal striatum) directs motivated actions when the ability of the ventral striatal pathways to direct more 'automatic' or intuitive motivated responses is impaired. Another possibility is that in individuals with AN (otherwise adequate) limbic-striatal information processing in the ventral circuit is too strongly inhibited by converging inputs from cognitive domains such as the DLPFC and the parietal cortex.

It is possible that such trait-related disturbances are related to altered monoamine neuronal modulation that predates the onset of AN and contributes to premorbid temperament and personality symptoms. Specifically, disturbances in the 5-HT system contribute to a vulnerability for restricted eating, behavioural inhibition and a bias towards anxiety and error prediction, whereas disturbances in the DA system contribute to an altered response to reward. Several factors might act on these vulnerabilities to cause the onset of AN in adolescence. First, puberty-related female gonadal steroids or age-related changes might exacerbate 5-HT and DA system dysregulation. Second, stress and/or cultural and societal pressures might contribute by increasing anxious and obsessional temperament. Individuals find that restricting food intake is powerfully reinforcing because it provides a temporary respite from dysphoric mood. People with AN enter a vicious cycle — which could account for the chronicity of this disorder — because eating exaggerates, whereas food refusal reduces, an anxious mood.

The temperament and personality traits that might create a vulnerability to develop AN might also have a positive aspect. These traits include attention to detail, concern about consequences and a drive to accomplish and succeed. It is our clinical experience that many individuals who recover from AN do well in life. It is tempting to speculate that the ability to plan ahead, control impulses, and avoid harm might have had highly adaptive value for ancestors who lived in environments where food supplies were constrained by long periods of cold weather (for example, worry in July about food supplies in January). Adolescence is a time of transition: individuals leave the security of their home environment and must learn to balance immediate and long-term needs and goals to achieve independence[158]. For such individuals, learning to flexibly interact with and master complex and mixed cultural and societal messages and pressures and cope with stress, might be difficult and overwhelming, which could exacerbate possible underlying traits of harm avoidance and a desire to achieve perfection.

Box 2 | **From vulnerability to illness — the complex aetiology of anorexia nervosa**

Anorexia nervosa (AN) is thought to be a disorder of complex aetiology, in which genetic, biological, psychological and sociocultural factors, and interactions between them, seem to contribute significantly to susceptibility[10,11,158,162]. Because no single factor has been shown to be either necessary or sufficient for causing anorexia nervosa, a multifactorial threshold model might be most appropriate (for a review see REF. 158). Typically, AN begins with a restrictive diet and weight loss during teenage years, which progresses to an out-of-control spiral (FIG. 1). Therefore, individuals might cross a threshold in which a premorbid temperament, interacting with stress and/or psychosocial factors, progresses to an illness with impaired insight and a powerful, obsessive preoccupation with dieting and weight loss. Adolescence is a time of profound biological, psychological and sociocultural change, and it demands a considerable degree of flexibility to successfully manage the transition into adulthood. Psychologically, change might challenge the perfectionism, harm avoidance and rigidity of those at risk of AN and thus fuel an underlying vulnerability. The biological changes of adolescence or puberty might also increase the risk of onset of eating disorders. This possibility is supported by twin studies[163] which implied that puberty might have a role in activating the genetic predisposition for eating disorder symptoms. Moreover, the biological changes associated with adolescence differ between males and females, which could explain the sexual dimorphism of AN. For example, menarche is associated[158] with a rapid change in body composition and neuropeptides modulating metabolism. Little is known about whether the rise in oestrogen levels associated with puberty in females is contributory to AN, but it could affect neuromodulatory systems such as serotonin[164] or neuropeptides[165] that affect feeding, emotionality and other behaviours.

AN has the highest mortality rate of any psychiatric disorder. It is expensive to treat and we have inadequate therapies. It is crucial to understand the neurobiologic contributions and their interactions with the environment, in order to develop more effective therapies. Therefore, future imaging studies should focus on characterizing neural circuits, their functions and their relationship to behaviour in individuals with AN. Genetic studies might shed light on the complex interactions of molecules within these neural circuits. Finally, prospective and longitudinal studies should focus on identifying the neurobiologic traits and external factors (BOX 2) that create a susceptibility for developing AN.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
5-HT$_{1A}$ | 5-HT$_{2A}$ | DRD2 | DRD3

FURTHER INFORMATION

Walter H. Kaye's homepage: http://eatingdisorders.ucsd.edu/

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