

Nothing tastes as good as SKINNY feels

Unmasking the Neurobiological Basis of Anorexia

By Louise Yang

Food is an unquestionable need for basic human survival. It is also present at most social events and celebrations due to the central role it plays in bringing people together. Yet for some people, every single meal and every single bite is a struggle. This isolating and life-threatening condition is anorexia nervosa (AN), a chronic illness characterized by excessively decreased caloric intake, disturbed body image, and an intense fear of weight gain (Park et al. 2014). It is a debilitating and heartbreaking disease not just for the patient but for friends and family who must watch their loved one physically waste away before their very own eyes. The lack of proper food intake caused by anorexia deprives the body of essential proteins and nutrients that give way to a domino effect of health issues (Figure 1). This puzzling, treatment-resistant disease has long been thought of as Western culture-bound syndrome

driven by toxic societal pressures to diet and be as skinny as possible. *How can it be that in countries with such abundance women are driven to starving themselves? Why are some people more susceptible to this disease? Is it their fault?*

The interplay between environment and genetics is essential

for understanding the prevention and development of anorexia. In addition, discovering the neurobiological changes made by this disease are essential for treatment and grasping why recovery is so difficult. There is no clear recovery plan for anorexia and current treatments, such as psychotherapeutic or pharmacological ones that target abnormal serotonin systems, have proven inadequate (Fitzpatrick & Lock, 2011). Researchers are shedding light on the abnormal brain circuitry displayed in anorexic patients in hopes of discovering novel pharmaceuticals and better-targeted treatment methods for this currently incurable disease.

History of Anorexia

Despite its reputation as a modern disorder, the first medical report of anorexia was made in 1689 by London physician Richard Morton.

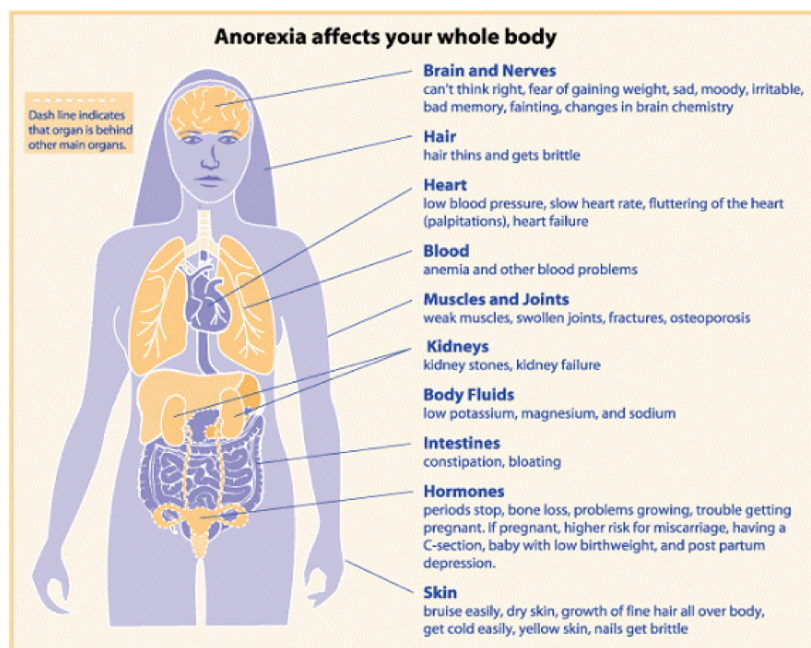
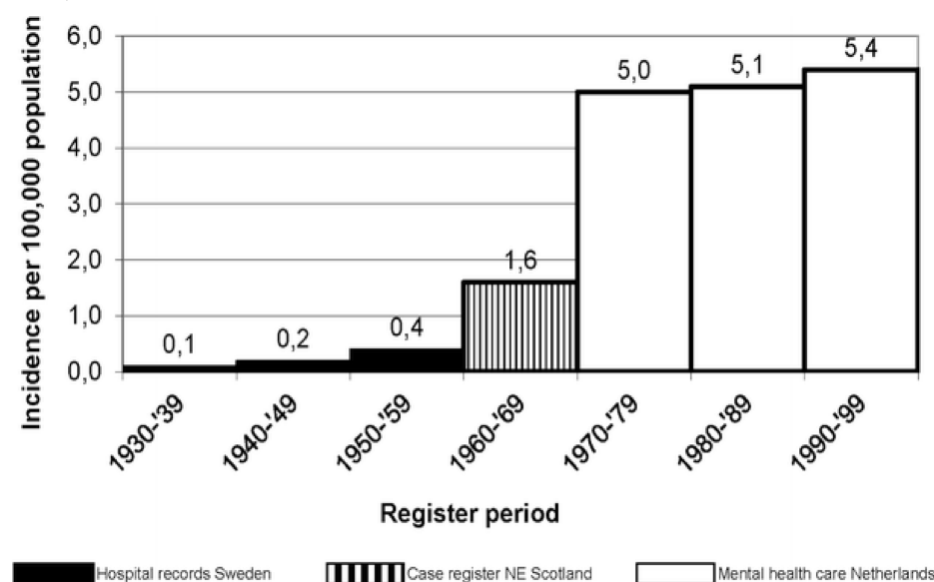


Figure 1 Diagram of the physical effects of Anorexia Nervosa. <http://www.myedin.org/understanding-anorexia.html>

Figure 2 Meta-analysis of yearly incidences of AN cases in northern Europe. (Makino, 2004)



However, even up to the 1970s, cases of anorexia were seen as clinical oddities that doctors rarely saw, let alone knew how to treat (Arnold, 2016). While rates of anorexia had been steadily climbing since the 1950s (Figure 2), it was not until the death of singer Karen Carpenter in 1983 that anorexia hit mainstream awareness. The young singer's death from anorexia-induced organ failure led to sensationalization of the disease as the media speculated on why teenage girls were suddenly "dying to be thin." Psychologists blamed the cause of the disease on a troubled home life and pushy parents, coupled with unrealistic standards of beauty propagated by the media and supermodels. Anorexia was seen as a willful choice made by selfish young teenage girls who simply had to choose to get better (Arnold, 2016). The answer to anorexia is simply to eat, right? Unfortunately, this backward approach was often recommended to those who suffer anorexia, to no

avail. However, growing evidence of the genetic and neurobiological basis behind this debilitating disease have begun dismantling these dangerous preconceptions and brought about a new understanding of the cause and possible treatment of this currently incurable disease.

Who is affected?

Anorexia affects around 1% of the population, with 95% of anorexics being females. The average age of onset is between 14 to 19 years (Hudson et al., 2007). In addition, anorexia has the highest mortality rate among all psychiatric illnesses with one in five deaths being caused by suicide. Patients with AN show high comorbidity with mood disorders such as depression (35-50%), and around half have comorbid anxiety disorders including social phobias and obsessive-compulsiveness (Ulfvebrand et al., 2015). Anorexia is considered a chronic illness because

even though weight restoration is manageable, relapse is a prevalent issue (Zanadian et al., 2007). For example, patients discharged from the hospital will slowly but surely return to their old unhealthy eating habits and continue the cycle of hospitalization.

A study found the following five personality traits increased the risk of developing an eating disorder: perfectionism, inflexibility, rule following, excessive doubt and caution, and a drive for order and symmetry (Anderluh et al., 2003). Patients with anorexia also have trouble zooming out and seeing the big picture and, instead, get stuck on the little details, which can cause difficulties with decision making. In addition, patients with anorexia show difficulty mentally switching from one task to another (Arnold, 2016). This strangely similar cluster of characteristics shared by patients with anorexia hints at the underlying biological factors behind this disease because, in addition to pre-dating disease, these traits often persist after recovery.

Is Anorexia a Western Disorder?

Anorexia has long been thought of as a western issue that primarily affects white women. Since the late 20th century there have been many reports of eating disorders in Western countries, and few cases had been seen in non-western countries other than Japan. However, a study in 2004 found that while the prevalence of anorexia in non-western countries is lower than in western countries, it has

been slowly increasing. Population and patient-based estimates of AN in non-western countries ranged from .002% to 0.7% and was associated with an increase in abnormal eating attitudes (Makino, 2004). This is, perhaps, an effect of globalization and the spread of Western beauty ideals through the media. For example, before the 1990s there had only ever been one reported case of anorexia on the island of Fiji. However, after the introduction of television to the island in the mid-1990s, there was a sudden influx of cases. In addition, in Japan the increase in anorexia between 1985 and 1992 paralleled modernization. It is argued that anorexia is more prevalent during times of cultural change and confusion for immigrants and individuals who are part of rapidly developing countries (Pke et al., 2015). Even with this rise in anorexia, the numbers still remain relatively low in comparison to the general population. Therefore, the question must be asked, why are some people more vulnerable to developing the disease than others? Most people are exposed daily to unhealthy beauty ideals, yet never spiral into illness.

**The Genetics Behind
Developing AN**

While many people diet and express sentiments to lose weight, only a small percentage actually develop an eating disorder. This is due to the highly genetic component of anorexia. Genetic heritability accounts for approximately 50 to 80% of the risk of develop-

ing anorexia, while also contributing to the neurobiological factors that underlie the disease (Kaye et al., 2009).
A recent transgenic mouse model demonstrates the interplay of genetics, biology, and sociocultural variables that contribute to

the onset of anorexia. Researchers transgenically created mice with the BDNF gene, which is a gene that has been associated with anorexia in humans. Adolescent mice with the BDNF gene variant placed under environmental stressors of social stress and on a

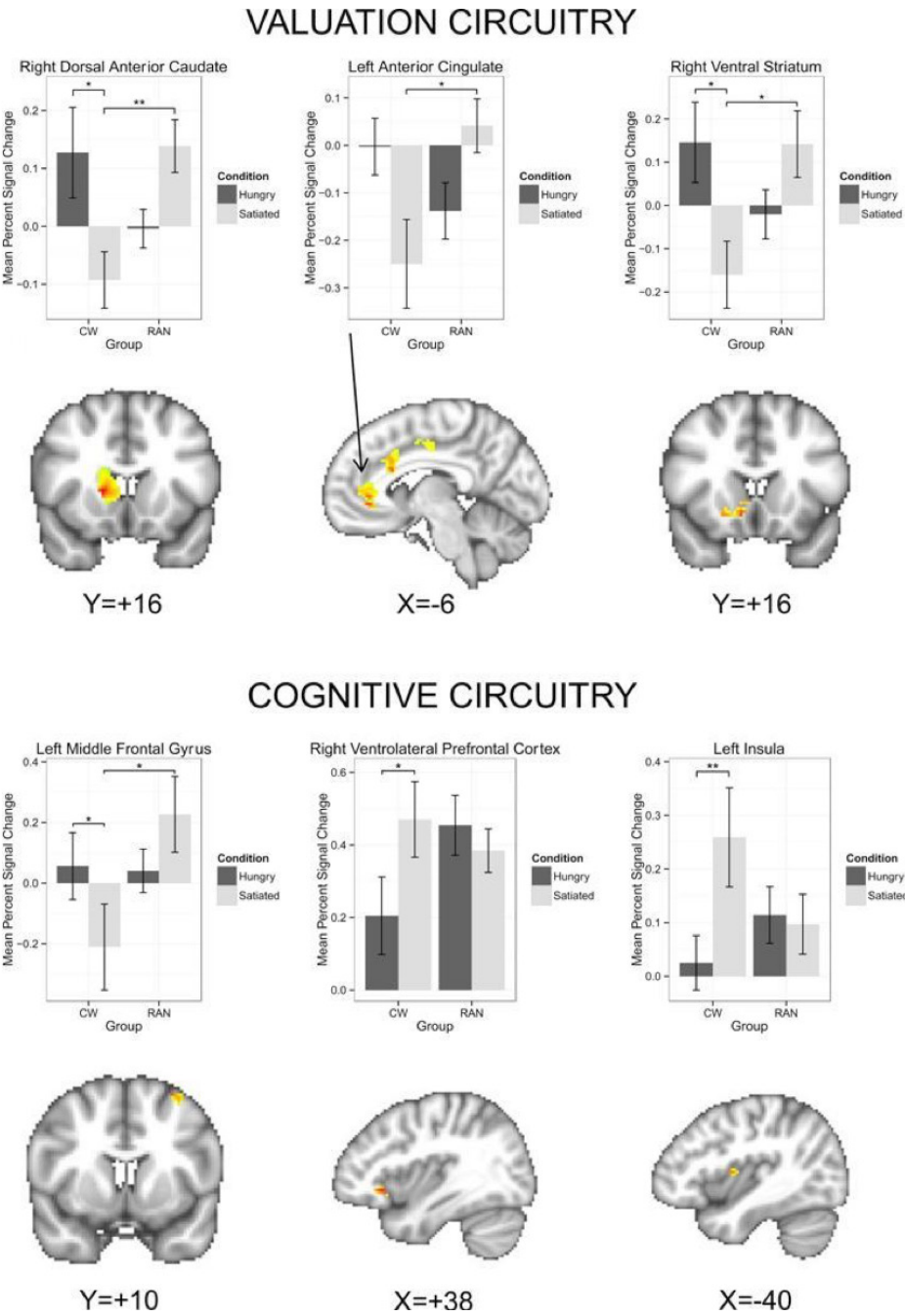


Figure 3 fMRI of the activation of the reward versus the cognitive circuitry of patients with AN versus controls when hungry versus satiased. (Wierenga et al. 2015)

calorie-restricted diet were much more likely than controls to begin avoiding food (Madra & Zeltser, 2016). This change was not seen in adult mice, and was also not induced when mice were subjected to only one stressor and not the other. This demonstrates that having an at-risk genotype in itself is not sufficient for developing anorexia-like behavior, but that disease development is the combination of stress, dieting, and age that work together with a genetic predisposition. This can help explain the increase in rates of anorexia in non-western countries due to the introduction of unhealthy socio-cultural standards of weight loss and beauty which then triggers disease development in youths who are already genetically susceptible. Researchers hope to use this new mouse model to study the change and disruptions in neuronal circuits that cause

the metabolic, neuroendocrine, and behavioral disease symptoms (Madra & Zeltser, 2016). This leads to the question, what are the neuronal disruptions in AN?

Dysregulation of the Reward System in AN

Many of us resolve to avoid fatty foods and unhealthy desserts, yet our self-control often vanishes when tempted by a piece of cake after a long day. This normal behavior makes sense considering the role of hunger as our body's cue to seek out and approach food. In addition, hunger actually increases the intensity of food rewards, and this enhanced sensitivity to reward is a motivational cue to eat, mediated through increased activation of reward salience circuitry in the ventral striatum, dorsal caudate, anterior cingulate cortex (Wierenga et al. 2015). How are patients with anorexia able to ignore these urges? Unlike healthy controls, who show an increased activation of reward circuitry when hungry, patients with remitted AN do not show this increased activation, lessening their sensitivity to the motivational drive of hunger (Figure 3).

Furthermore, patients with remitted AN showed increased activation in the ventrolateral prefrontal cortex (Figure 3). This increased activity in cognitive control circuitry perhaps allows them to better resist the temptations of food. This can, perhaps, explain the puzzling question of how individuals with AN are able to restrict food intake (Wierenga

et al. 2015). In addition, these differences in activation might possibly occur before the development of the disorder, demonstrating the strong biological factors that predispose certain individuals to developing AN. Frank (2013) proposed a model of structural and functional alterations in the insula and frontal cortex, areas that contribute to both reward and anxiety processing, that can occur prior to AN development along with additional changes in these circuits from malnutrition that can further hinder recovery by promoting illness behavior and relapse (Frank, 2013).

The neurotransmitter dopamine plays a vital role in regulating the reward system, and alterations in mesolimbic dopamine levels have been shown in activity-based anorexia mouse models (Avena & Bocarsly, 2012). Although current dopamine-targeting drug treatments have proven ineffective in treating the disease, there is promising research into atypical antipsychotics that may modulate the irregular dopamine systems seen in anorexia (McKnight & Park, 2010).

Abnormal Amygdala Activation

Patients with AN often display an abnormal preoccupation with food-related items, in addition to a fear of eating high calories items. Functional magnetic resonance imaging (fMRI) was used to study the response of patients with AN when they imagined drinking high versus low calorie

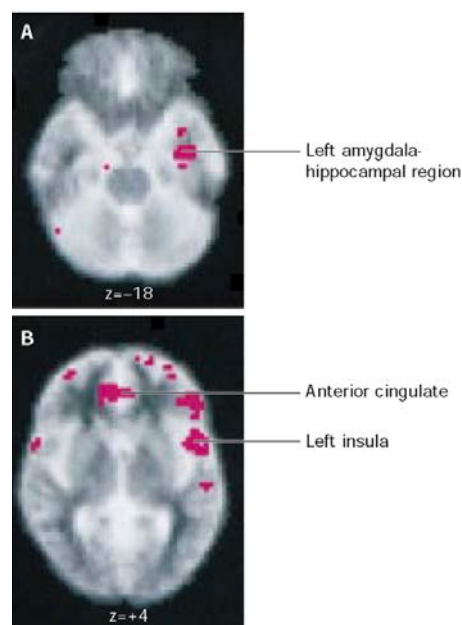
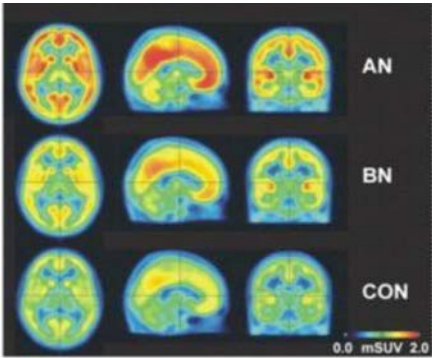


Figure 4 fMRI of increased activity in the left amygdala-hippocampal region, anterior cingulate, and left insula in the anorexic group (Ellison et al., 1998).

Figure 5 AN patients display elevated global CB1R expression in both cortical and subcortical regions (Monteleon et al., 2005).



food. Increased activation in the limbic and paralimbic network was associated with high calorie foods, suggesting a conditioned fear to high calorie foods (Figure 4). In addition, abnormal activity in the limbic and paralimbic areas has been associated with depressive and obsessive-compulsive symptoms, perhaps further contributing to the prevalence of these traits in patients with AN (Ellison et al., 1998). Even after weight restoration, patients recovering from AN continue to choose low calorie food over more nutrient dense, higher calorie food that would help them maintain a healthy body weight (Berridge, 2003). This calorie fear highlights how a better understanding of the neurobiological changes caused by AN can help the development of better-targeted strategies to improve existing treatment plans.

Anorexia is also frequently characterized by a preoccupation with body size and body dysmorphia, an obsessive focus on a perceived flaw in appearance. Concerned parents might look at their daughter and see an alarmingly skinny body with protruding

bones, yet the girl herself would perceive her body as fat. fMRI was used to study changes in the brain when patients with AN and controls were stimulated with digital pictures of their own body image. In patients with AN, stimulation with their own body image caused activation in the right amygdala, the right gyrus fusiformis, and the brainstem region (Seeger, 2002). Studies have linked activation of the right amygdala to aversive, anxiety-producing stimulus. Understanding this activation of the “fear network” in response to one’s own body can be used to help explain why, during mirror confrontation therapy, patients with AN display fear and avoidance when looking at their own body, especially during weight gain (Smeets, 1999). This knowledge can then possibly be used during recovery to learn how to combat this conditioned fear of one’s own body.

A Potential New Treatment Site- the Endocannabinoid

System

The endocannabinoid system is a new and relatively understudied potential treatment site for anorexia due to increased information about the critical role it plays in body homeostasis. CB1-receptors (CB1R) are densely located in key brain regions involved in appetite, food intake, and energy expenditure (Marco et al., 2012). Studies have shown a deregulation of the endocannabinoid system in anorexia. For example, fMRI research has demonstrated that AN patients display elevated global CB1R expression in both cortical and subcortical regions that is believed to be a long-term compensation mechanism for hypofunctioning of the endocannabinoid system (Figure 5) (Monteleon et al., 2005). Meanwhile, cannabinoids have been shown to be a safe and effective tool for treating anorexia associated with weight loss in patients with AIDS through activation of CB1 receptors ex-

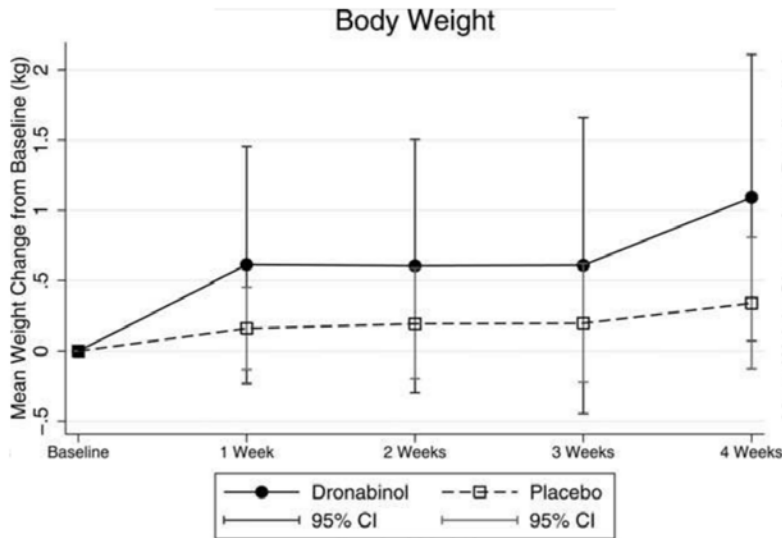


Figure 6 Dronabinol induced increase in weight gain of AN patients (Andries, 2013)

pressed in brain regions such as the hypothalamus and mesocorticolimbic system that are involved in energy modulation by promoting food intake and reinforcing the hedonic value of food (Gross, 1983).

Women with severe and long-lasting anorexia (AN) were treated with dronabinol, a synthetic cannabinoid agonist, to study its effects on body weight and eating disorder related psychopathological personality traits (Andries, 2013). Participants gained a significantly greater amount of weight during dronabinol treatment than during placebo treatment with no change in leptin levels. Dronabinol was believed to facilitate weight gain through an anabolic mechanism (Figure 6) (Andries, 2013). This result was supported by a study on the effects of CB1R agonist tetrahydrocannabinol (THC) on activity-based anorexia (ABA) modeling rats. ABA is the most widely used rodent model used to study the underlying changes in neural circuits behind anorexia. It models two key symptoms of anorexia: reduction in food intake and increase in exercise. Rats that experience food restriction while having unrestricted access to running wheel time exhibit hyperactivity by voluntarily spending more time on the running wheel than those with unrestricted access to food. These ABA also exhibit paradoxical reductions in food intake which leads to weight loss and even death without experimenter intervention. THC treatment was able to induce maintenance of a healthy

weight in ABA modeling rats due to a decrease in energy expenditure through decreased thermogenesis (Verte et al., 2011). Studying the effects of THC on the endocannabinoid system is one step closer to a promising novel pharmacological treatment for anorexia.

Early detection and Prevention

Early detection is vital for treating AN because the longer the duration of the disease, the greater the harmful effects on the body, and the greater the changes in neural circuits. A fMRI study showed that even when recovered from anorexia, subjects showed irreversible grey matter volume deficits (Katzman et al., 1997).

Policies can be made to improve school-based health curricula starting at a younger age, with content aimed at preventing eating disorders. In a longitudinal study, adolescents who engaged in dieting and unhealthy weight-control behaviors had higher rates of obesity and eating disorders five years later. Dieting is a stressor that can trigger the development of illness, and parents and schools should create prevention programs that shift away from drastic weight-control measures such as dieting in favor of measures to implement long-term healthful eating and physical activity behaviors (Neumark et al., 2006). In addition, there needs to be better and increased training of educators and health providers with respect to identifying eating disorders.

Last of all, advertising and social media policies should be

created to counter the negative self-image promoted by unrealistic and unhealthy body ideals on television, print, and social media. For example, several social media sites have paved the way by creating anti-anorexia promoting policies that have had varying levels of success. It is suggested that the media can actually be a positive influence on young, impressionable women through presenting a greater variety of body shapes and discouragement of dieting.

Conclusion

Overall, the etiology of anorexia is unknown, and much can be learned from studying the neurobiological basis of the disease. Not only can current treatment plans be altered to better fit the needs of patients in recovery, but promising new pharmacological drugs may also better target the abnormal neural circuitry in AN. Furthermore, understanding the interplay of genetics and environment in the development and maintenance of this disorder can help patients feel less guilty and isolated when battling this terrible disease.

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