

**IS ANOREXIA NERVOSA AN EATING DISORDER?
How neurobiology can help us understand
the puzzling eating symptoms of anorexia nervosa**

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Introduction

How is it possible for people with anorexia nervosa (AN) to consume a few hundred calories a day and maintain an extremely low weight for many years, when most people struggle to lose even a few pounds?

People with AN exhibit a highly rigid, ritualized, and inadequate intake of food and so become severely underweight. They tend to resemble each other in other ways, too: They often become sick around the same time (early adolescence), show similar symptoms and behaviors, and are mostly females¹. They typically resist eating and engage in a powerful pursuit of weight loss, yet paradoxically are obsessed with food and eating rituals. Even when underweight, they tend to see themselves as fat and deny being underweight. They tend to resist treatment and lack insight about the seriousness of the medical consequences of AN.

These similarities support the possibility that underlying neurobiological contributions drive the behaviors seen in AN.

Two types of eating-related behaviors are seen in AN: Restricting-type anorexics (AN) lose weight purely by dieting, without binge eating or purging. Binge-eating/purging-type anorexics (AN-BN) restrict food intake to lose weight, but periodically engage in binge eating and/or purging, as do those 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}. This chapter will focus on restricting-type AN.

Eating disorder or brain disorder?

Although we call AN an eating disorder, we don't know whether it reflects a primary disturbance of the brain systems that regulate appetite, or whether changes in appetite are caused by other factors, like anxiety or obsessional preoccupation with weight gain. Starvation and weight loss have powerful effects on the brain and other organ systems, causing neurochemical disturbances that could exaggerate pre-existing traits⁴, adding symptoms that maintain or accelerate the disease process. For example, AN patients exhibit reduced brain volume⁵, altered metabolism of brain regions known to modulate emotion and thought⁶, and a return to childhood levels of female hormones⁷. The fact that such disturbances tend to normalize after weight restoration suggests that they are a consequence of AN rather than a cause.

A number of regions in the brain help regulate food and weight. In the hypothalamus, for instance, chemicals like insulin and leptin send messages about hunger and energy balance. With weight loss, the levels of these chemicals become abnormal, signaling that the body doesn't have enough fuel and that the person needs to eat. The evidence suggests that such changes are driven by starvation and serve to conserve energy or stimulate hunger and feeding⁸; they likely do not cause AN. But people with AN seem able to override or ignore signals from lower brain regions like the hypothalamus. New studies point to the ways uniquely human higher brain regions like the frontal cortex and insula are implicated in the ongoing starvation of AN. These higher brain regions play a crucial role in emotions, personality, and rewards, all of which are thought to be important in AN.

AN and personality traits

Genes play a major role in causing eating disorders^{3,9,10}, likely contributing to a range of personality traits that put people at risk for AN. People who develop AN tend to display certain characteristics in childhood, years before they become ill, including anxiety and depression, perfectionism, people-pleasing behaviors, a drive for thinness, and obsessiveness. These traits tend to persist after recovery.

In AN, as in other illnesses, we often talk about *trait* versus *state*. People are born with certain personality traits, like perfectionism or a tendency toward anxiety, that last their whole lives. States are more situation specific—say, the kind of anxiety many New Yorkers felt right after 9/11. States can be affected by environment or circumstances; traits cannot.

Obsessive personality traits include an overconcern for symmetry and exactness¹¹. For instance, people with AN may color-code the clothes in their closet; they may have specific spots for items in their room and get upset if things are moved. On the plus side, they tend to be achievement-oriented, compliant, and make exceptional students. Children who later develop AN are typically described as “the best little girl in the world.” They tend to be rule abiding, rigid, and anxious children who are high in harm avoidance, a personality trait characterized by a tendency to criticize and doubt past thoughts and behaviors, worry about the future, and struggle with uncertainty¹². Studies show these personality traits are heritable, and are often seen in unaffected family members, independent of body weight¹³, suggesting that they’re risk factors for the development of AN. Not everyone who develops AN has all these traits, of course. Some people have only one or a few. Others may not have any. Still, our experience is that most people who develop AN show at least some of these personality traits and temperament in childhood.

One reason we’re not sure is because it’s challenging to design the kind of long-term studies that could look for these traits, given the young age of potential subjects, the rarity of the disorder, and the need to follow subjects for many years. An alternative strategy is to study people who have recovered from AN, avoiding the confounding influences of malnutrition and weight loss. There is no single agreed-upon definition of recovery from AN; in our research we use a definition that includes stable and healthy body weight for months or years, with stable nutrition, the relative absence of dietary abnormalities, and normal menstruation.

The process of recovery in AN is poorly understood and, in most cases, protracted. But we do know that between 50 and 70 percent of affected individuals will eventually have complete or moderate resolution of the illness, though this might not occur until their mid 20s¹⁴⁻¹⁶. Studies describe temperament and character traits that persist after long-term recovery, including negative emotionality, harm avoidance and perfectionism, desire for thinness, and mild dietary preoccupation. Such persistent symptoms may be “scars” caused by chronic malnutrition. But the fact that such behaviors^{14, 17, 18} are similar to those described in children who go on to develop AN¹⁹⁻²¹ argues that they reflect underlying traits rather than consequences of AN.

Some of the common behaviors seen in both recovered and acute AN are often found together. Our research group has been exploring how these behaviors are coded in the brain. It would be an oversimplification to think these traits are somehow contained in neurotransmitters or brain regions; the human brain is far too complex. But these behaviors might be encoded in the neural pathways that modulate emotion, reward, and the human ability to think about consequences and the future.

Two neural pathways—the limbic and the cognitive—affect appetite, emotionality, and cognitive control and seem to be particularly relevant to behavior in AN. The *limbic* neurocircuit includes the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate cortex (ACC) and orbitalfrontal cortex (OFC); it seems to help people identify the emotional significance of events and stimuli and respond appropriately^{22, 23}. The *cognitive* neurocircuit affects selective attention, planning, inhibition, and emotional self-control, and includes the hippocampus, dorsal regions of the ACC, dorsolateral prefrontal cortex (DLPFC), and parietal cortex^{22, 23}. Earlier brain imaging studies have demonstrated that people recovered from AN show altered activity in frontal, ACC, and parietal regions²⁴⁻²⁶—elements in both the limbic and cognitive pathways.

Neurobiology and appetite

Appetite is a complex phenomenon, a function of signals coming from nerves and hormones in the brain, the gut, and fat and sugar stores throughout the body (Figure 1). Higher brain

structures may be particularly involved in the kind of disturbed eating that characterizes AN. Recent studies suggest that the motivation to eat (or not eat) is related to the palatability of food, the level of a person's energy stores, and the cognitive ability to control or restrain eating²⁷⁻²⁹.

Appetite is clearly disturbed in AN. People with AN dislike high-fat foods^{30, 31} and react differently to hunger and satiety cues than people without AN^{32, 33}. For people with AN, eating less *reduces* anxiety, while that eating makes them feel *more* anxious and/or depressed³⁴⁻³⁶. These responses to food are shared by most people with AN, supporting the possibility that they reflect some unusual function of the neural circuits involved in regulating eating behavior. They also tend to remain even after weight restoration.

In imaging studies, we often use a sweet-taste perception ([Figure 2](#)) task to activate brain areas involved in regulating appetite. Receptors on the tongue respond to a sweet taste³⁷, then send a signal through the brain stem and lower brain regions to the primary taste center in the anterior insula³⁸⁻⁴², an area deep in the brain, near the frontal and temporal lobes, which is important in the perception and interpretation of physical sensations. The insula is the first area in the cortex to recognize when we've tasted something sweet, salty, or sour. Along with a related network including the amygdala, the ventral ACC and the OFC, the insula helps determine whether we find a taste pleasant or unpleasant.

These regions of the brain seem to become more active when we're hungry and less active when we're full⁴³⁻⁴⁷. When we're very hungry, food tastes better, and we feel more motivated to eat. When we're full, food may still taste good, but it tends to be less rewarding. And even delicious food can become unpleasant: Eating a small piece of chocolate cake at dessert may be pleasing, but being forced to eat the whole cake might be a bad experience, thanks to a phenomenon called sensory-specific satiety, which explains why we grow "tired" of eating one food during a meal and switch to another.

The insula and related regions connect to a subcortical area, the ventral striatum, which is important for carrying out motivated behavior. Together, these regions help us sense the pleasurable, motivating value of food, and how this value may change, depending on whether we're hungry or full.

Inside the AN brain

Imaging studies show some intriguing differences between the brains of people who have had AN and the brains of healthy control subjects. Many of these differences may be seen in the insula. For instance, when people without AN are given sugar during a sweet-perception task, the more they say they enjoy the sugar, the more activity they showed in their insula, ACC and striatum⁴⁸, supporting the idea that these regions are important for sensing reward. People who are recovered from AN show less activity in these areas ([Figure 3](#)) when tasting sugar⁴⁸.

When looking at pictures of food, both recovered and underweight people with AN show altered activity in the insula, the OFC, the mesial temporal and parietal cortex, and the ACC^{26, 49-53}. People recovered from AN showed less activity in the insula and other parts of the neural network, suggesting that the ability to perceive a palatable taste is fundamentally altered in AN, even after recovery, and that people with AN have a reduced incentive and/or motivation to approach food ([Figure 4](#)).

Overall, the results of these brain imaging studies suggest that people with AN have lower-than-usual drive in a number of the systems that respond to hunger and appetite, which may explain how it's possible for them to pursue emaciation to the point of death. Normally when people become hungry, neural networks around the brain become more active, making food taste more rewarding and driving the motivation to eat. People with AN may get mixed messages from various parts of the brain, which may explain why they often have obsessions with food and cooking yet don't have enough motivation to eat.

In addition to playing a role in taste, the insula is critically involved in *interoceptive processing*⁵⁴⁻⁵⁶, making us aware of physical sensations of pain, heat or cold, itch, tickle, muscle tension, air hunger, and other bodily processes⁵⁷. The insula is responsible for registering a change in any of these physiological processes and telling the body to do something about it; for instance, the insula becomes more active when hungry, signaling the need to eat.

Some clinicians have theorized that altered interoceptive awareness might help trigger and reinforce AN^{19, 58-60}. Recent studies from our group suggest that people with AN may exhibit a generalized alteration of insula activity involving other interoceptive signals besides taste. This raises the question of whether altered insula function contributes to a fundamentally and physiologically altered sense of self in AN⁶¹. Many of the most puzzling symptoms of AN, like distorted body image, a failure to appropriately respond to hunger, and diminished motivation to change could be related to disturbed interoceptive awareness.

Reward processing in AN

Many people with AN exercise compulsively and find little in life rewarding aside from the pursuit of weight loss¹. Like other traits, these too persist, in a more modest form, after recovery^{14, 62}. These particular traits all involve the neurotransmitter dopamine, which contributes to altered reward and affect, decision-making, and executive control. There is considerable evidence that altered function of dopamine occurs in AN⁶³, possibly contributing to overexercise and decreased food intake⁶⁴.

Our group did a brain imaging study where we asked both healthy controls and people recovered from AN to perform a simple choice and feedback task⁶⁵. The task was adapted from a well-characterized “guessing-game” protocol⁶⁶ known to activate the ventral striatum and ACC. In controls, the neural activity for winning money was very different from the activity for losing money. But in people recovered from AN, brain activity in the ACC and its ventral striatal target was similar whether they won or lost⁶⁵. This suggests that people with AN might have trouble discriminating between positive and negative feedback and identifying the emotional significance of stimuli²³, which in turn could help explain why it is so tough to motivate them to go into treatment or appreciate the consequences of their behaviors⁶⁷.

Women who were recovered from AN also showed exaggerated activity in certain areas of the brain, specifically the DLPFC and the parietal cortex⁶⁵. These regions are activated by tasks where there's a perceived connection between action and outcome, *and* some uncertainty about whether the action will lead to the desired outcome⁶⁸. Healthy control subjects were able to “live in the moment”: they realized they had to make a guess, they made a guess, and they moved on to the next task without undue concern. By contrast, people recovered from AN tended to worry about the consequences of their behaviors, looking for “rules” when there were none, and feeling overly concerned about making mistakes. A recent fMRI imaging study, using a set-shifting task, showed similar findings in ill AN patients⁶⁹. Together these findings suggest that people with AN might be both unsure how they feel in the moment and overly concerned about tasks involving planning and consequences ([Figure 5](#)).

One explanation for these findings may lie in the way neurocircuits overlap in the brain. For instance, the cortical regions included in the dorsal neurocircuit affect both cognitive and executive functions like planning and sequencing, and at the same time overlap with ventral striatal areas^{70, 71} that modulate the approach to or avoidance of food. If the parts of this cognitive circuit that inhibit the drive to eat are overactive, that might let people with AN suppress and override signals about bodily needs like hunger.

Conclusions and future directions

Like other eating disorders, AN typically comes on during adolescence, a time of profound biological, psychological, and sociocultural change. A considerable degree of flexibility is required to successfully manage the transition into adulthood⁷². Teenagers leave the security of their home environment and must learn to balance immediate and long-term needs and goals to achieve independence⁷².

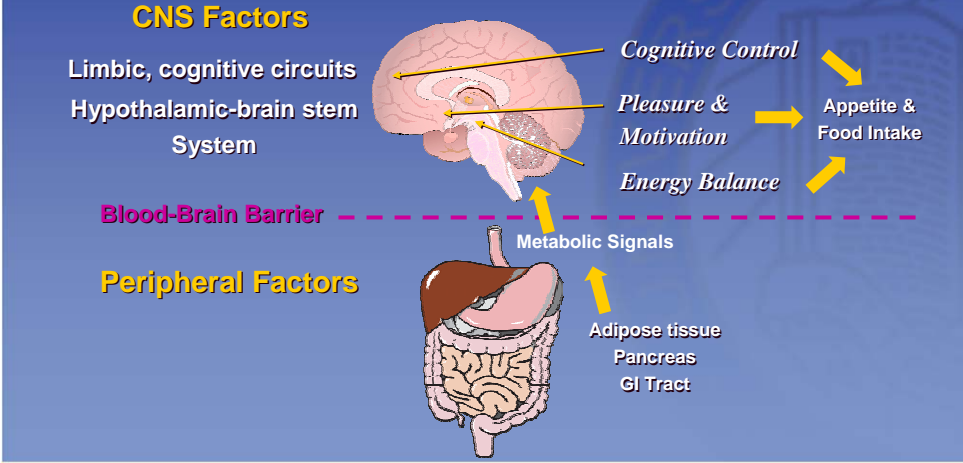
Neurobiology may offer some answers as to why AN typically develops during adolescence. AN is thought to be a disorder of complex etiology, in which genetic, biological, psychological, and sociocultural factors, and interactions between them, create susceptibility^{19, 20, 72, 73}. No single factor has been shown to be either necessary or sufficient for causing AN.

AN often begins with a restrictive diet and weight loss during adolescence, which progresses to an out-of-control spiral. People who develop AN might cross a threshold where temperament interacts with stress and/or psychosocial factors, leading to an illness with impaired insight and a powerful, obsessive preoccupation with dieting and weight loss. Psychologically, the changes of adolescence might challenge the perfectionism, harm avoidance, and rigidity of those at risk for AN and thus fuel an underlying vulnerability. The biological changes of puberty may also help trigger the onset of AN⁷⁴. Those at risk for AN may feel overwhelmed by the difficulties of learning to interact flexibly and master complex and mixed cultural and societal messages—a set of tasks made more difficult for them because of their underlying neurobiology.

One question about AN is why so many more females develop it than males. The answer may lie in the biological changes associated with adolescence, which differ in males and females. For example, menarche is associated⁷² with a rapid change in body composition and the neuropeptides modulating metabolism. The rise in estrogen levels associated with puberty in females might affect the serotonin system⁷⁵ or levels of neuropeptides⁷⁶ that influence feeding, emotionality, and other behaviors. The brain changes associated with puberty might exacerbate these processes; for example, orbital and dorsolateral prefrontal cortex regions develop greatly during and after puberty⁷⁷, and increased activity in these cortical areas might trigger the excessive worry, perfectionism, and strategizing common to those with AN. Stress and/or cultural and societal pressures might also contribute by amplifying anxious and obsessional temperament. People at risk for AN find that restricting food intake makes them feel less anxious, and so they enter a vicious cycle where eating exaggerates anxiety and food refusal reduces it—a fact that may account for the chronicity of the disorder.

It's important to remember that the temperament and personality traits that might create a vulnerability for developing AN aren't all bad. Traits like attention to detail, concern about consequences, and a drive to accomplish and succeed can all be positive. It's 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 (e.g., worry in July about food supplies in January). But it's our clinical experience that many people who recover from AN go on to do well in life.

Systems Determining Food and Weight Regulation



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Figure 1: Overview of the many systems that contribute to food and weight regulation.

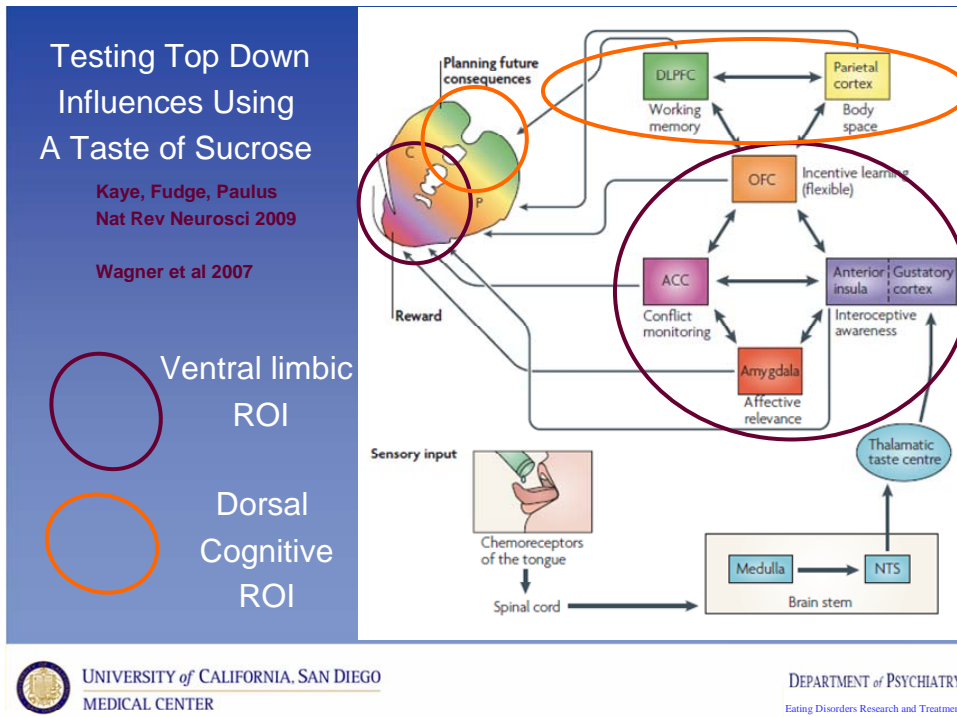
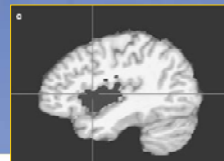
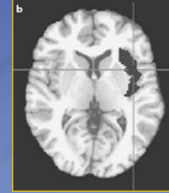
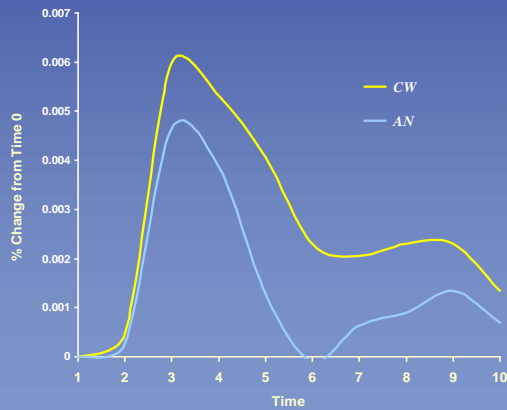


Figure 2: Pathways contributing to processing sweet taste. Receptors on the tongue detect a sweet taste. The signal is then transmitted through brainstem and thalamic taste centers to the primary taste cortex, which lies adjacent to and is densely interconnected with the anterior insula. The anterior 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) and the ventral striatum. Cortical structures involved in cognitive strategies (forming a dorsal neurocircuit) send inputs to the dorsolateral striatum. 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 (From Kaye, Fudge, Paulus⁶³).

Left Insula/OFC Response to Sucrose

Wagner 2008 Neuropsychopharm
CW vs. AN $p = .003$



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Figure 3: (a) Coronal, (b) axial, and (c) sagittal view of left insula. The graph shows the time course of BOLD signal as a mean of all 16 recovered restricting-type anorexia nervosa and 16 control women for taste-related (sucrose and water) response in the left insula⁴⁸.

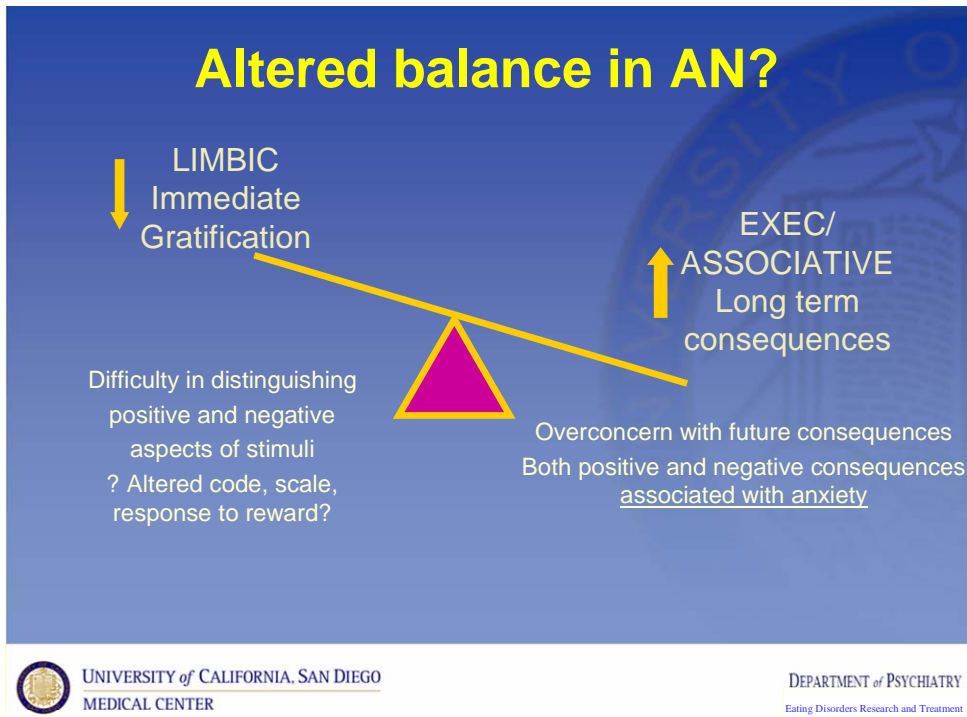


Figure 4: Data⁶⁵ suggests that individuals who have recovered from AN have an imbalance between pathways that identify the emotional significance of environmental stimuli and pathways responsible for the performance of planning and effortful functions. People with anorexia nervosa do not live in the moment. They tend to have exaggerated and obsessive worry about the consequences of their behaviors, looking for rules when there are none, and they are overly concerned about making mistakes. Individuals who have recovered from anorexia nervosa may be less able to precisely modulate affective response to stimuli and live in the here and now. They do appear to have increased traffic in neurocircuits concerned with planning and consequences

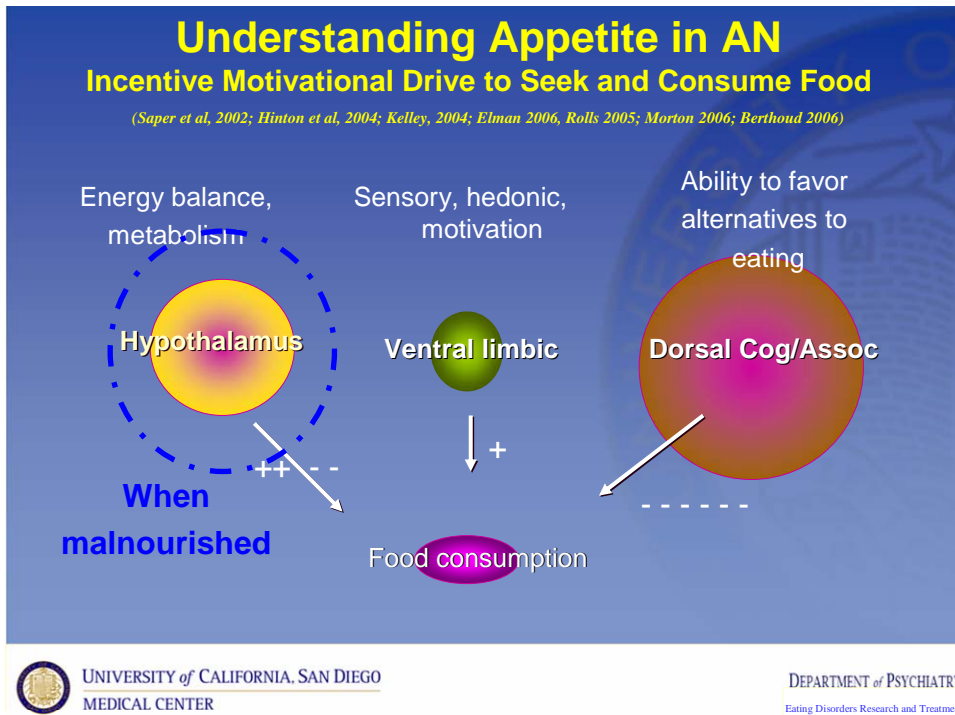


Figure 5: Multiple systems contribute to decisions about food consumption. We hypothesize that individuals with AN have a trait for altered ventral limbic system function, so thus have a diminished sensory-hedonic-motivational “drive” to consume food. In contrast, they have a trait for exaggerated dorsal cognitive function, so that they have enhanced inhibitory abilities and thus can “favor” alternatives to eating. These traits persist after recovery, but individuals with AN learn to compensate by choosing to eat the same amounts of the same foods everyday, so that they are able to maintain their weight and have adequate nutrition. Thus hypothalamic systems, which are important for responding to deficits in energy balance, are normal. However, when malnourished and underweight, the hypothalamus senses a deficit in energy balance and responds with altered levels of neuropeptides and hormones that serve to drive appetite and conserve energy. We suspect that the puzzling appetitive behaviors that ill AN show (restricted eating, yet obsessed with food, afraid to eat but scared that they cannot stop, etc) are due to these mixed signals.

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