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Various psychological and family dynamics contribute to anorexia nervosa (AN). From a biological standpoint, why would someone intentionally starve herself or himself to the brink of death? Research is now making progress in understanding what happens before and during the illness and how this behavior can be explained.

About once a month I meet with parents of patients in our eating disorder treatment program at Children’s Hospital Colorado to talk about how brain changes may contribute to their children’s difficulties to recover. Most of these parents have a child in whom AN has been diagnosed. My first question is whether the behavior they see in their children “makes any sense” to them. The uniform answer is no.

AN is characterized by restriction of energy intake relative to requirements, leading to a significantly low body weight for age, sex, developmental trajectory, and physical health; intense fear of gaining weight or becoming fat, even though underweight; and disturbance in the way one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of current low body weight.

Previous research has shown that AN is associated with high premorbid and comorbid anxiety disorders. Anxious traits may make some individuals more prone to respond to environmental cues to be conscious of their weight, and they may feel a need to lose weight to be more socially accepted. High comorbid depression may also aid in this dynamic.

Recent research in animals and humans suggests that the brain dopamine system could also be an important part of the pathophysiology of AN. This is important because brain dopamine circuits provide important signals regarding the presence and amplitude of food and other rewards as well as code the value of salient stimuli.

Animal studies suggest that food restriction may sensitize, while excessive food intake may desensitize, brain reward pathways. Food restriction and weight loss seem to go along with heightened brain dopamine-related reward response in rodents, and over-consumption of food on the contrary showed addiction-like dopamine D2 receptor down-regulation.

Previous research in AN indicated dopamine alterations, including altered levels of dopamine metabolites in the brain and number of dopamine receptors in specific brain regions, such as the ventral striatum, but we know little about how such alterations may be clinically important.

Functional brain imaging helps bridge this gap. For instance, striatal brain response to images of thin bodies was stronger in individuals with AN than in controls. Individuals who recovered from AN showed reduced insular and striatal brain response to repeated sweet taste, but increased caudate response to randomly given monetary or taste stimuli.

A study from our group in patients with AN and obese individuals applied a reward-learning paradigm that had been associated with brain dopamine function. We found that patients with AN had higher and obese individuals had lower brain response to unexpected taste stimulus receipt or omission in the insula, basal ganglia, and frontal cortex. These findings suggest hypersensitive dopamine-related brain activation in AN, but the opposite in obesity, consistent with basic research described above. Thus, when a person with AN starves herself, the dopamine system may get overly sensitized. This may lead to overstimulation of reward pathways and eventually to a reduced drive to approach food through negative feedback, creating a vicious circle of more and more food restriction.

Other recent research suggests that specific alterations in brain volume could contribute to behavior in AN. For the most part, studies that have investigated brain volume in the disorder have been
We believe that this is because of fast-occurring volume changes resulting from times of food or fluid restriction or times with more normalized or periodic excessive eating. We have studied women with AN under highly nutritionally controlled circumstances and found that when ill and after long-term recovery, there were larger right insula and left medial orbitofrontal cortex volumes. In addition, we found similar results in a cohort of adolescent girls with AN. The orbitofrontal cortex tells us when to stop eating a certain food, a mechanism also called sensory-specific satiety. If there is enlargement of that structure in persons with AN, it could be that they get the signal to stop eating faster than they "should" in order to maintain a normal bodyweight. The right insula has been associated with integration of body cues, and an enlarged volume may exaggerate body perception and fears of fatness, and thus fuel body image distortion.

**Conclusion**

AN continues to be an incredibly difficult-to-treat disorder with high mortality and limited treatment options. However, emerging research helps us describe a model of brain disturbance in the disorder, which is much appreciated by patients and their parents, as well as by treating clinicians. While we are not yet able to translate those research findings into more effective treatments, they help conceptualize the disorder from a neuroscience level and take it out of the realm of obscurity into a much better-defined and -described brain disorder that we can research and develop treatments for based on hypotheses and empirical data.

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**Disclosures:**

Dr Frank is Assistant Professor in the department of psychiatry at the University of Colorado School of Medicine, Denver; Associate Director, Children’s Hospital Colorado Eating Disorders Program; and Director, Developmental Brain Research Program at the University of Colorado Anschutz Medical Campus, Aurora. He reports no conflicts of interest regarding the subject matter of this article.

**References:**


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