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The Neurobiology of Eating Disorders

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KEYWORDS

• Anorexia nervosa • Bulimia nervosa • Eating disorder • Brain • Imaging
• Neurobiology

KEY POINTS

- An eating disorder is a severe psychiatric illnesses with a complex biopsychosocial background.
- Brain imaging now allows study of the living human brain.
- Understanding the neurobiology of eating disorders holds promise for developing more effective treatments.
- New research enables the development of models for brain function and food avoidance.

INTRODUCTION

Anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and avoidant or restrictive food intake disorder (ARFID) are severe psychiatric disorders.[1] The understanding of the brain has dramatically changed over the past century with the development of human in vivo brain imaging. Whereas earlier studies collected cerebrospinal fluid samples to study metabolites (eg, neurotransmitters), brain research now uses techniques such as MRI to study brain gray matter (GM) and white matter (WM) volumes, cortical thickness, and surface area. Also based on MRI, diffusion weighed imaging and diffusion tensor imaging measure water diffusion to test WM tract integrity and strength of WM connectivity between brain regions.[2] The most commonly used functional brain imaging technique is functional MRI, which measures changes in local blood flow as a proxy for brain activation.[3] PET and single-photon emission computed tomography (SPECT) use radioactive ligands to study glucose

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metabolism or neurotransmitter receptor distribution. Neurobiological research in eating disorders (EDs) holds promise for developing a medical model perspective to reduce stigma and help develop better treatments.[4]

METHODS

This article provides a state-of-the-art review of current neurobiological research in EDs in children, adolescents, and young adults up to 25 years of age when brain structure has generally matured to adult levels while avoiding effects from aging or illness chronicity.[5] The US National Library of Medicine database, PubMed, was searched for brain research studies done in youth or young adults. Methodologies have greatly improved over the past 5 years. Neurobiological research that highlights current knowledge of ED neurobiology, with a particular emphasis on studies from the past 5 years, is presented.[6]

NEUROCHEMICAL STUDIES

PET imaging showed higher serotonin 1A-receptor binding in AN and BN when the participants were ill and after recovery, suggesting state-independent alterations. The serotonin 2A-receptor, in contrast, was normal in ill AN participants but lower after recovery, suggesting dynamic adaptations.[7,8] BN did not show significant dopamine D2-receptor group differences versus controls, but lower striatal dopamine release was associated with higher binge eating frequency.[9]

Hormones or neuroactive peptides, such as sex hormones or gut hormones, also affect brain response.[10] Those substances that regulate body homeostasis are often altered during the ill state of EDs, which may disturb normal food reward circuits.[10] Neuroendocrines and peptides, such as fat cell-derived leptin or ghrelin from the gastric mucosa, stimulate or dampen brain dopamine response and alterations in this system, which could further alter food approach in AN and BN.[11,12] To date, however, those hypotheses rely mostly on basic research. Cytokines, markers of inflammatory processes, have been found altered, and meta-analyses indicate a pattern of elevated tumor necrosis factor-alpha in AN, whereas the data on other cytokines are somewhat mixed, with no alterations in BN.[13,14] Whether those markers are relevant for ED illness development, maintenance or recovery remains elusive. Cytokines are elevated in obesity, but no data exist for BED or ARFID.

GRAY MATTER VOLUME AND CORTICAL THICKNESS

Earlier studies suggested that brain volume is universally reduced in AN, but brain structure studies in participants with EDs have found smaller, larger, or no differing volumes across varying brain regions versus controls.[15–17] Reduced cortical volumes in AN are related to illness severity and normalize during weight recovery.[18–23] Studies that controlled for short-term malnutrition and dehydration found larger left orbitofrontal cortex, as well as right insula volumes, in adolescents and adults with AN.[24,25]

The literature on BN is scarcer, and GM structure studies in adolescents or young adults with BED or ARFID are lacking. Mixed results in BN show either larger or normal regional GM volumes,[26,27] whereas another study found lower temporoparietal GM surface area due to lower WM.[28] Binge eating or purging frequency may reduce cortical volume or thickness.[29,30] A study that controlled for acute malnutrition and binge eating or purging found larger left orbitofrontal and insula volume but smaller bilateral caudate and putamen volumes.[25]

Those results highlight that food restriction, binge eating, and purging change brain structure. Insula and orbitofrontal cortex are important for taste perception and (food) reward valuation, and alterations could interfere with the drive to eat. Whether brain volume alterations drive ED behaviors remains unclear.[31] Future studies will test whether ARFID is associated with similar structural brain changes, as in AN, and whether BED is associated with reduced brain volume, as in obesity, or with regionally higher volume, measures as in BN.[32]

WHITE MATTER VOLUME, INTEGRITY, AND STRUCTURAL CONNECTIVITY

Similar to GM studies, there has been inconsistency with higher or lower localized or overall WM volumes in EDs.[24,25,33,34] Altered astrocyte density exhibited in an animal model of AN could be a mechanism for low WM volume in EDs due to malnutrition and dehydration.[35]

Water-diffusion MRI can be used to calculate fractional anisotropy (FA),[36] which is thought to reflect axonal integrity. Adolescent AN showed higher, lower, or no FA group differences.[37–40] Lower FA normalizes with weight restoration, and it is unclear whether FA has implications for ED behaviors.[41,42] The scarce literature on WM integrity and FA in BN indicates lower FA across widespread WM pathways across the whole brain, including lower FA between insula, orbitofrontal cortex, striatum, and hypothalamus.[43–45] Those regions are important for taste, reward, and energy homeostasis regulation, and altered WM connections could affect food intake regulation. Studies that estimated the number of WM connections found in AN and BN greater structural WM connectivity between insula, orbitofrontal cortex, and ventral striatum, consistent with AN after recovery.[43,46] Duration of illness correlated positively with fiber connectivity in AN, suggesting that the longer ED behaviors caused WM damage (FA reduction), which was compensated for during recovery by increasing fiber connectivity.[46]

FUNCTIONAL AND EFFECTIVE CONNECTIVITY

The posterior cingulate, medial prefrontal, medial temporal, and inferior parietal cortices, the so-called default mode network (DMN), is involved in interoception and self-relevant mentalizing (ie, making sense of self and other). Studies found elevated DMN connectivity in AN,[47–49] possibly driven by lower blood glucose.[50] The anterior cingulate, insula, and orbitofrontal cortex, the so-called salience network (SN), orients the organism to support food approach.[51] AN showed higher connectivity between the dorsal anterior and posterior cingulate gyrus, and BN showed stronger connectivity between the dorsal anterior cingulate and medial orbitofrontal cortex.[52,53] Higher dorsal anterior cingulate to precuneus connectivity in AN and BN correlated positively with body shape questionnaire scores, implicating brain regions at the interface of executive function and vision.[52] Other studies found greater resting functional connectivity in AN between ventral striatum and frontal cortex, implicating reward-processing and decision-making circuits.[37] Functional connectivity during food and nonfood passive picture viewing was higher in AN and BN in the insula, and in BN in the orbitofrontal cortex,[54] whereas young adults with AN showed lower SN connectivity during sugar tasting.[55] These patterns suggest dysfunctional SN functioning and maybe predisposing to food restriction. The prefrontal cortex, the so-called executive control network, showed lower connectivity and lower and higher connectivity in AN between the insula and frontal regions, suggesting imbalances between networks.[56,57]

All in all, higher and lower functional resting-state connectivity has been observed in participants with EDs compared with controls, implicating networks associated with

executive function, reward processing, and perception, which supports the notion of those circuits being altered in EDs. SN alterations during the resting state could perturb a readiness to approach food, whereas elevated DMN activity could indicate an inability to come to an internal restful state.[58] Studies in ARFID and BED are lacking.[59]

Effective connectivity, the hierarchical or directional activation between brain regions, was higher in AN from the medial orbitofrontal cortex and insula to the inferior frontal gyrus,[57] and from the orbitofrontal cortex to the nucleus accumbens,[37] implicating taste-reward circuits. Two studies found that effective connectivity during sugar tasting was directed from the ventral striatum to the hypothalamus in AN and BN, whereas in controls the hypothalamus drove ventral striatal activity.[43,60] This was interpreted as a possible mechanism for top-down control in EDs to control homeostatic information and override hunger signals.

TASK-BASED FUNCTIONAL MRI STUDIES

Reward System

Food is a salient stimulus or natural reward, and reward pathways similar to substances of abuse are activated when people desire, approach, or eat food.[61] Important regions in this circuitry include the ventral striatum (receives midbrain dopaminergic input, drives motivation and reward approach), the orbitofrontal cortex (reward valuation), and the anterior cingulate (error monitoring, reward expectation).[61] Several but not all studies in the past in adolescents or young adults found altered reward system response in AN to food-related or body-related visual stimuli.[62–66] In a recent study in which participants saw positively valenced (nonfood and nonbody) pictures and were asked to regulate their emotions, ventral striatal activity correlated with body-related ruminations and negative affect in AN, suggesting that emotion regulation interacts with both ED thoughts and depressive feelings.[67] In a delay-discounting task (choosing between immediate smaller or delayed larger rewards), the AN group responded faster, and lower activation in AN in the cingulate and frontal regions indicated a more efficient control circuitry.[68] In another study, youth with AN learned better in response to punishment but associated brain-activation was similar versus controls.[69–71] Receiving stimuli unexpectedly has been associated with brain dopamine response and early evidence indicated heightened response to unexpected pleasant or unpleasant stimuli in AN.[72,73] A paradigm that has been closely associated with brain dopamine response is the prediction error model, a learning paradigm in which individuals learn to associate unconditioned taste with conditioned visual stimuli.[74] In 2 studies using monetary or taste stimuli, unexpected receipt or omission was reflected in higher insula and striatal brain response in adolescents with AN versus controls. Brain activation predicted weight gain during treatment, but short-term weight restoration was not associated with normalization of brain response.[75,76] Those studies suggested heightened dopamine-related brain response that does not easily normalize with weight recovery.[76] In summary, altered reward circuits in AN may be associated with altered learning and brain dopamine function, and traits such as sensitivity to punishment could be predisposing.[60]

In BN, negative affect positively correlated with striatal and pallidum brain response during milkshake receipt.[77] Low mood may, therefore, enhance the reward value of food stimuli in BN and trigger binge eating. Other studies showed less frontal cortical, ventral striatal, and hippocampus activation in BN, which correlated with binge or purge frequency in a task that provided monetary reward when navigating through a maze.[78,79] Therefore, altered learning, executive control, and reward brain response could be effects of both abnormal brain development and BN illness behavior.

Perception and Interoception

Self-perception of being fat while being underweight could be due to abnormal central interoception neurocircuitry or primarily driven by cognitive-emotional processes. Some studies in AN implicated the parietal and occipital cortices when viewing self or others.[80,81] Neuropsychological studies implicated altered nonvisual perception, such as haptic (tactile) perception, proprioception (sense of one's position in space), or interoception (sense of internal organs) in AN, showing altered insula response in AN.[82] This suggested that the insula may have an essential function in the intersection between interoception and cognitive-emotional processing in AN. Some studies implicated taste perception in EDs. In AN, the insula (primary taste cortex) poorly distinguished between taste stimuli.[83] In studies on binge eating, bitter taste led to higher medial prefrontal electroencephalography signal, or umami taste, more strongly activated the insula in BN, whereas hedonic ratings were lower.[84,85]

Cognition

During a reversal learning task involving positive and negative feedback, participants with AN changed behavior strategy more frequently after negative feedback, related to cingulate activation.[86] During the Wisconsin Card Sorting Test for cognitive flexibility, participants with AN had higher activation during behavior change in the frontal, parietal, and occipital regions but lower activation during learning or maintaining rule-based behavior.[87] Visual attention in participants with BN led to higher activation in parietooccipital regions but lower response in the DMN versus controls, and behavior control was associated with lower activation in the anterior cingulate.[88] Behaviorally, groups performed similarly in the studies, and the meaning of altered brain function in the context of normal behavioral response needs further study. Individuals with BN showed worse cognitive performance when food images were intermixed with the task procedures, whereas premotor cortex and dorsal striatum were more strongly activated compared with controls, suggesting a distressing effect.[84] In another study, BN showed that positive emotions improved performance on response inhibition.[89] Therefore, mood may be an important factor for recovery.

Social Function and Stress

During a self-and-other social evaluation task, anxiety and body shape concerns correlated inversely in participants with AN compared with controls, with prefrontal and cingulate brain response, implicating those regions.[90] Gentle touch or intimate visual stimuli were rated less pleasant in participants with AN compared with controls, and were associated with lower caudate or parietal activity, suggesting reduced reward experience.[91,92]

MICROBIOTA AND MICROBIOME

The human microbiota, up to 100 trillion symbiotic microbial cells, is primarily bacteria in the gut.[93] Their collective genomes are called microbiome.[94] There are well-known neural connections between gut and brain, and those organisms may affect psychiatric disorders, including EDs.[95] Various studies in participants with AN have found alterations compared with controls in microbial composition, and microbe diversity in AN may correlate with body mass index and also, for instance, blood insulin levels.[96–98] Healthy competitive athletes had the highest number of microbiota species compared with ED and control groups, significantly higher versus both AN and obese individuals. Also, dietary fiber, vitamin D, and magnesium intake correlated positively with microbiota species.[99] However, microbiota diversity also normalizes

with weight recovery, and it is unclear whether microbiota could be causal for illness behavior aside from ED behaviors altering gut microbiota.[97,98,100] No studies exist in other EDs. However, BN and BED were associated with antimicrobial medication use, suggesting a role for the immune system. In summary, study of microbiota and the microbiome is an emerging field that could provide an important aspect of illness pathophysiology in EDs.

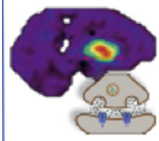
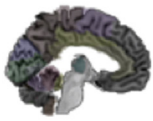
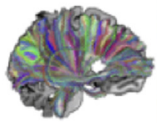
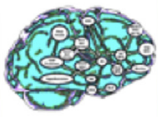
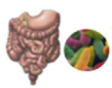
 **Neurochemistry**	○ Serotonin 1A receptor ↑ in ill AN, BN ○ Serotonin 2A receptor normall in ill AN, ↓ in rec AN ○ Hormones, Neuropeptides altered in ill EDs, often normalize with recovery; may interfere with appetite regulation and reward system ○ Cytokines ↑ in ill AN, BN, normalize with recovery
 **Gray Matter Volume and Cortical Thickness**	○ Cortical volume and thickness vary among studies in EDs probably due to the confounding factors malnutrition, dehydration, comorbidity, medication use, etc. ○ Lower volume or thickness in AN frequently normalize with weight restoration
 **White Matter Volume, Integrity and Structural Connectivity**	○ WM volume varies similarly to GM studies ○ Fractional anisotropy (FA) thought to reflect fiber integrity, tends to be lower in AN and BN ○ Lower FA may be compensated for in AN and BN with increased fiber development between insula and orbitofrontal cortex
 **Functional and Effective Connectivity**	○ ↑ and ↓ functional connectivity in DMN (interoception), SN (orientation to food stimuli) and ECN (decision-making) in AN, BN ○ Effective connectivity to the hypothalamus in AN, BN may override hunger signals
 **Task-Based fMRI Studies**	○ Reward circuits are consistently altered to food stimuli in insula, striatum, orbitofrontal cortex ○ Altered prediction error response to food and monetary stimuli suggest altered dopamine circuit response in AN, BN, BED ○ Perception, ↑ and ↓ in insula, parietal and visual cortex to interoception or visual perception tasks ○ AN is associated with reduced insula neural taste discrimination ○ Cognition tasks often ↑ and ↓ brain response in AN although behavior response mostly normal ○ BN had ↑ striatal and worse behavior response when distracted by food images ○ Social interaction, Gentle touch and visual intimate stimuli were associated with ↓ brain response and ↓ pleasantness ratings
 **Microbiota and Microbiome**	○ ↓ Diversity of gut microbial cells (microbiota) in AN, may normalize with weight restoration

Fig. 1. Summary of neurobiological findings in eating disorders. ↓, decreased; ↑, increased; ECN, executive control network; fMRI, functional MRI; rec, recovered.

SUMMARY

This article summarizes current knowledge on the neurobiology of eating disorders (Fig. 1). Although this field has grown significantly over the past decade, it is still small overall and the studies available often have low participant numbers, limiting power and study reliability, and many results have not been replicated. The authors argue for rigorous well-powered studies to find consensus across research laboratories to identify treatment targets for EDs.[101] Another critical issue is that BED, especially ARFID, is mostly an unexplored area of neurobiological research. Nevertheless, the body of research in EDs identified the importance of the short-term impact of ED behaviors, especially on brain structure, and brain reward pathways are most consistently implicated in altered brain activity across EDs. The latter is a promising target for treatment development.

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