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## The Neurobiology of Eating Disorders

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### Keywords

Anorexia nervosa; bulimia nervosa; eating disorder; brain; imaging; neurobiology

### Introduction

Anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED) and avoidant/restrictive food intake disorder (ARFID) are severe psychiatric disorders.<sup>1</sup> Our understanding of the brain has dramatically changed over the past century with the development of human in vivo brain imaging. While earlier studies collected cerebrospinal fluid samples to study for instance neurotransmitter metabolites, brain research now uses techniques such as magnetic resonance imaging (MRI) to study brain gray (GM) and white matter (WM) volumes, cortical thickness and surface area. Also based on MRI, are diffusion weighted (DWI) and diffusion tensor imaging (DTI), which measure water diffusion to test WM tract integrity and strength of WM connectivity between brain regions.<sup>2</sup> The most commonly used *functional* brain imaging technique is functional magnetic resonance imaging (fMRI), which measures changes in local blood flow as a proxy for brain activation.<sup>3</sup> Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactive ligands to study glucose metabolism or neurotransmitter receptor distribution. Neurobiological research in EDs holds promise to develop a medical model perspective to reduce stigma and help develop better treatments.<sup>4</sup>

### Methods

This article provides a state-of-the-art review of current neurobiological research in eating disorders in children, adolescents and young adults up to 25 years of age when brain

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structure has generally matured to adult levels while avoiding effects from aging or illness chronicity.<sup>5</sup> The US National Library of Medicine database PubMed was searched for brain research studies done in youth or young adults. Methodologies have much improved over the past five years, and we present neurobiological research that highlights our current knowledge of ED neurobiology with a particular emphasis on studies from the past five years.<sup>6</sup>

### Neurochemical Studies

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

Hormones or neuroactive peptides such as sex hormones or gut hormones also affect brain response.<sup>10</sup> Those substances that regulate body homeostasis are often altered during the ill state of EDs which may disturb normal food reward circuits.<sup>10</sup> 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 could furthermore alter food approach in AN and BN.<sup>11,12</sup> Those hypotheses to date, however, rely mostly on basic research to date. Cytokines, markers of inflammatory processes, have been found altered and meta-analyses indicate a pattern of elevated tumor necrosis factor-alpha in AN, while the data on other cytokines in are somewhat mixed, with no alterations in BN.<sup>13,14</sup> 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 EDs have found smaller, larger, or no differing volumes across varying brain regions versus controls.<sup>15-17</sup> Reduced cortical volumes in AN are related to illness severity and normalize during weight recovery.<sup>18-23</sup> 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.<sup>24,25</sup>

The literature on BN is smaller, 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,<sup>26,27</sup> while another study found *lower* temporo-parietal GM surface area due to lower WM.<sup>28</sup> Binge-eating/purging frequency may reduce cortical volume or thickness,<sup>29,30</sup> and a study that controlled for acute malnutrition and binge-eating/purging found larger left orbitofrontal and insula volume, but smaller bilateral caudate and putamen volumes.<sup>25</sup>

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.<sup>31</sup> Future studies will test whether ARFID is

associated with similar structural brain changes as AN and whether BED is associated with reduced brain volume as in obesity or regionally higher volume measures as in BN.<sup>32</sup>

### White Matter Volume, Integrity and Structural Connectivity

Similarly to GM studies, there has been inconsistency with higher or lower localized or overall WM volumes in EDs.<sup>24,25,33,34</sup> 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.<sup>35</sup> Water diffusion MRI can be used to calculate fractional anisotropy (FA),<sup>36</sup> thought to reflect axonal integrity. Adolescent AN showed higher, lower or no FA group differences.<sup>37–40</sup> Lower FA normalizes with weight restoration, and it is unclear whether FA has implications for ED behaviors.<sup>41,42</sup> The small 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.<sup>43–45</sup> Those regions are important for taste, reward, and energy homeostasis regulation, and altered WM connections could affect food intake regulation. Studies that estimated 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.<sup>43,46</sup> Duration of illness correlated positively with fiber connectivity in AN, suggesting that the longer ED behaviors caused WM damage (FA reduction), the more this was compensated during recovery by increasing fiber connectivity.<sup>46</sup>

### Functional and Effective Connectivity

The so-called default mode network (DMN, posterior cingulate, medial prefrontal, medial temporal, and inferior parietal cortices) is involved in interoception and “self-relevant mentalizing” (making sense of each other and ourselves). Studies found elevated DMN connectivity in AN,<sup>47–49</sup> possibly driven by lower blood glucose.<sup>50</sup> The salience network (SN, anterior cingulate, insula and orbitofrontal cortex) orients the organism to support food approach.<sup>51</sup> AN showed higher connectivity between dorsal anterior and posterior cingulate gyrus, and BN stronger connectivity between dorsal anterior cingulate and medial orbitofrontal cortex.<sup>52,53</sup> 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.<sup>52</sup> Others found greater resting functional connectivity in AN between ventral striatum and frontal cortex, implicating reward processing and decision-making circuits.<sup>37</sup> Functional connectivity during food and non-food passive picture viewing was higher in AN and BN in insula, and in BN in orbitofrontal cortex,<sup>54</sup> while young adults with AN showed *lower* SN connectivity during sugar tasting.<sup>55</sup> Those patterns suggest dysfunctional SN functioning and maybe predisposing to food restriction. The executive control network (ECN, prefrontal cortex) showed lower connectivity and lower and higher connectivity in AN between insula and frontal regions suggesting imbalances between networks.<sup>56,57</sup>

All in all, higher and lower functional resting-state connectivity has been observed in EDs compared to controls, implicating networks associated with executive function, reward processing, and perception, supporting the notion of those circuits being altered in EDs. SN alterations during resting state could perturb a “readiness” to approach food while elevated

DMN activity could indicate an inability to come to an internal restful state.<sup>58</sup> Studies in ARFID and BED are lacking.<sup>59</sup>

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

### Task-Based fMRI Studies

**Reward System**—Food is a salient stimulus or “natural reward”, and reward pathways similar to substances of abuse are activated when we desire, approach or eat food.<sup>61</sup> Important regions in this circuitry include ventral striatum (receives midbrain dopaminergic input, drives motivation and reward approach), orbitofrontal cortex (reward valuation), and anterior cingulate (error monitoring, reward expectation).<sup>61</sup> Several but not all studies in the past in adolescents or young adults found altered reward system response in AN to food or body related visual stimuli.<sup>62–66</sup> In a recent study where participants saw positively valenced (non-food and non-body) 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.<sup>67</sup> In a delay discounting task (choosing between immediate smaller or delayed larger rewards) the AN group responded faster, and lower activation in AN in cingulate and frontal regions indicated a more efficient control circuitry.<sup>68</sup> In another study, youth with AN learned better in response to punishment, but associated brain-activation was similar versus controls.<sup>69–71</sup> Receiving stimuli unexpectedly has been associated with brain dopamine response and early evidence indicated heightened response to unexpected pleasant or unpleasant stimuli in AN.<sup>72,73</sup> A paradigm that has been closely associated with brain dopamine response is the prediction error model, a learning paradigm where individuals learn to associate unconditioned taste with conditioned visual stimuli.<sup>74</sup> In two 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.<sup>75,76</sup> Those studies suggested heightened dopamine-related brain response that does not easily normalize with weight recovery.<sup>76</sup> 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.<sup>60</sup>

In BN, negative affect positively correlated with striatal and pallidum brain response during milkshake receipt.<sup>77</sup> Low mood may, therefore, enhance reward value of food stimuli in BN and trigger binge-eating. Others showed in BN less frontal cortical, ventral striatal and hippocampus activation that correlated with binge/purge frequency in a task that provided monetary reward when navigating through a maze.<sup>78,79</sup> 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 parietal and occipital cortices when viewing self or others.<sup>80,81</sup>

Neuropsychological studies implicated altered non-visual 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.<sup>82</sup> 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,<sup>83</sup> and in studies on binge-eating, bitter taste led to higher medial prefrontal electroencephalography, or umami taste more strongly activated the insula in BN, while hedonic ratings were lower.<sup>84,85</sup>

**Cognition**—During a reversal learning task involving positive and negative feedback, AN changed behavior strategy more frequently after negative feedback, related to cingulate activation.<sup>86</sup> During the Wisconsin Card Sorting Test for cognitive flexibility testing, AN had higher activation during behavior change in frontal, parietal and occipital regions, but lower activation during learning or *maintaining* rule-based behavior.<sup>87</sup> Visual attention in BN led to higher activation in parieto-occipital regions but lower response in the DMN versus controls and behavior control was associated with lower activation in the anterior cingulate.<sup>88</sup> Behaviorally, groups performed similarly in those 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 while premotor cortex and dorsal striatum were more strongly activated compared to controls, suggesting a distressing effect.<sup>84</sup> In another study, BN showed that positive emotions improved performance on response inhibition.<sup>89</sup> 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 AN and controls with prefrontal and cingulate brain response, implicating those regions.<sup>90</sup> Gentle touch or intimate visual stimuli were rated less pleasant in AN compared to controls, and associated with lower caudate or parietal activity, suggesting reduced reward experience.<sup>91,92</sup>

### Microbiota and Microbiome

The human microbiota, up to 100 trillion symbiotic microbial cells are primarily bacteria in the gut.<sup>93</sup> Their collective genomes are called microbiome.<sup>94</sup> There are well known neural connections between gut and brain, and those organisms may affect psychiatric disorders including EDs.<sup>95</sup> Various studies in AN have found alterations compared to controls in microbial composition, and microbe diversity in AN may correlate with BMI and also, for

instance, blood insulin levels.<sup>96–98</sup> Healthy competitive athletes had the highest number of microbiota species compared to ED and control groups, significantly higher versus both AN and obese individuals, and dietary fiber, vitamin D and magnesium intake correlated positively with microbiota species.<sup>99</sup> 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.<sup>97,98,100</sup> 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, microbiota and the microbiome are an emerging field that could provide an important aspect of illness pathophysiology in EDs.

## Conclusions

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

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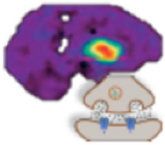

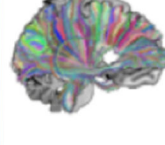
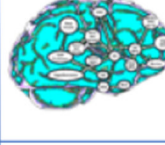
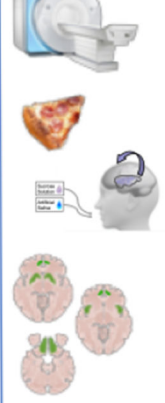

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### SYNOPSIS

Eating disorders are severe psychiatric illnesses with a typical age of onset in adolescence. Brain research in youth and young adults may help us identify specific neurobiology that contributes to the onset and maintenance of those disorders. This article provides a state-of-the-art review of our current understanding of the neurobiology of anorexia nervosa and bulimia nervosa. This includes brain structure and function studies to understand food restriction, binge-eating or purging behaviors, cognitive and emotional factors contributing to eating disorders, as well as interoception. Binge-eating disorder and avoidant restrictive food intake disorder are also discussed, but the literature is still small for the latter two disorders.

**KEY POINTS**

- Eating disorders are severe psychiatric illnesses with complex biopsychosocial background.
- Brain imaging now allows us to study the living human brain.
- Understanding the neurobiology of eating disorders holds promise to develop more effective treatments.
- New research allows us to start develop models for brain function and food avoidance.

	<p><b>Neurochemistry</b></p> <ul style="list-style-type: none"> <li>○ Serotonin 1A receptor ↑ in ill AN, BN</li> <li>○ Serotonin 2A receptor normal in ill AN, ↓ in rec AN</li> <li>○ Hormones, Neuropeptides altered in ill EDs, often normalize with recovery; may interfere with appetite regulation and reward system</li> <li>○ Cytokines ↑ in ill AN, BN, normalize with recovery</li> </ul>
	<p><b>Gray Matter Volume and Cortical Thickness</b></p> <ul style="list-style-type: none"> <li>○ Cortical volume and thickness vary among studies in EDs probably due to the confounding factors malnutrition, dehydration, comorbidity, medication use, etc.</li> <li>○ Lower volume or thickness in AN frequently normalize with weight restoration</li> </ul>
	<p><b>White Matter Volume, Integrity and Structural Connectivity</b></p> <ul style="list-style-type: none"> <li>○ WM volume varies similarly to GM studies</li> <li>○ Fractional anisotropy (FA) thought to reflect fiber integrity, tends to be lower in AN and BN</li> <li>○ Lower FA may be compensated for in AN and BN with increased fiber development between insula and orbitofrontal cortex</li> </ul>
	<p><b>Functional and Effective Connectivity</b></p> <ul style="list-style-type: none"> <li>○ ↑ and ↓ functional connectivity in DMN (interoception), SN (orientation to food stimuli) and ECN (decision making) in AN, BN</li> <li>○ Effective connectivity to the hypothalamus in AN, BN may override hunger signals</li> </ul>
	<p><b>Task-Based fMRI Studies</b></p> <ul style="list-style-type: none"> <li>○ <b>Reward circuits</b> are consistently altered to food stimuli in insula, striatum, orbitofrontal cortex</li> <li>○ Altered prediction error response to food and monetary stimuli suggest altered dopamine circuit response in AN, BN, BED</li> <li>○ <b>Perception</b>, ↑ and ↓ in insula, parietal and visual cortex to interoception or visual perception tasks</li> <li>○ AN is associated with reduced insula neural taste discrimination</li> <li>○ <b>Cognition</b> tasks often ↑ and ↓ brain response in AN although behavior response mostly normal</li> <li>○ BN had ↑ striatal and worse behavior response when distracted by food images</li> <li>○ <b>Social interaction</b>, Gentle touch and visual intimate stimuli were associated with ↓ brain response and ↓ pleasantness ratings</li> </ul>
	<p><b>Microbiota and Microbiome</b></p> <ul style="list-style-type: none"> <li>○ ↓ Diversity of gut microbial cells (microbiota) in AN, may normalize with weight restoration</li> </ul>

**Figure 1.**  
Summary of neurobiological findings in eating disorders.  
rec, recovered; AN, anorexia nervosa; BN, bulimia nervosa