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REVIEW ARTICLE

Advances from neuroimaging studies in eating disorders

*Guido K. W. Frank**

Departments of Psychiatry and Neuroscience, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, Colorado, USA

Over the past decade, brain imaging has helped to better define eating disorder–related brain circuitry. Brain research on gray matter (GM) and white matter (WM) volumes had been inconsistent, possibly due to the effects of acute starvation, exercise, medication, and comorbidity, but newer studies have controlled for such effects. Those studies suggest larger left medial orbitofrontal gyrus rectus volume in ill adult and adolescent anorexia nervosa after recovery from anorexia nervosa, and in adult bulimia nervosa. The orbitofrontal cortex is important in terminating food intake, and altered function could contribute to self-starvation. The right insula, which processes taste but also interoception, was enlarged in ill adult and adolescent anorexia nervosa, as well as adults recovered from the illness. The fixed perception of being fat in anorexia nervosa could be related to altered insula function. A few studies investigated WM integrity, with the most consistent finding of reduced fornix integrity in anorexia and bulimia nervosa–a limbic pathway that is important in emotion but also food intake regulation. Functional brain imaging using basic sweet taste stimuli in eating disorders during the ill state or after recovery implicated repeatedly reward pathways, including insula and striatum. Brain imaging that targeted dopamine-related brain activity using taste-reward conditioning tasks suggested that this circuitry is hypersensitive in anorexia nervosa, but hyporesponsive in bulimia nervosa and obesity. Those results are in line with basic research and suggest adaptive reward system changes in the human brain in response to extremes of food intake–changes that could interfere with normalization of eating behavior.

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Introduction

The eating disorders (EDs) anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric disorders of unknown etiology. The complex interactions between psychosocial and neurobiological abnormalities in EDs have limited the development of neuroscience-based treatments.[1] EDs usually begin during adolescence and occur most commonly in females.[2] Individuals with AN are typically at a body weight below 85% of that expected for age and height, and they feel fat despite being underweight. This strict weight criterion was dropped though in the new edition of the *Diagnostic and Statistical Manual for Mental Disorders*, Fifth Edition (DSM-5), as was loss of regular menses as a diagnostic criterion. A restricting-type (AN-R), marked by food restriction and commonly over-exercising has been distinguished from a binge-eating/purging-type (AN-B/P), where afflicted individuals eat large amounts of food in a relatively short period of time ("binge eating"), or engage in behaviors to counteract weight gain, such as self-induced vomiting or use of laxatives or diuretics ("purging"). BN individuals are usually at normal weight, and engage in recurrent binge eating and purging behavior at least once a week for at least 3 months. A new diagnosis, "binge eating disorder" (BED), is part of the diagnostic ED categories in DSM-5 that involves episodes of excessive eating as in BN, but without compensatory behaviors.

Brain imaging provides a "window" into the living human brain and may help elucidate mechanisms that are related to ED pathophysiology. A host of neuroimaging tools has been developed that can be used in ED research.[3] To study brain gray matter (GM) and white matter (WM) volumes, magnetic resonance imaging (MRI) is commonly used. In addition, cortical thickness and surface area can also be measured using MRI, although those measures are not interchangeable, as altered thickness does not necessarily translate into altered volume for instance.[4] A relatively novel method also based on MRI technology is diffusion tensor imaging (DTI), which measures water diffusion along axons and

* Address for correspondence: Guido K. W. Frank, MD, Departments of Psychiatry and Neuroscience, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Gary Pavilion A036/B-130, 13123 East 16th Avenue, Aurora, CO 80045, USA. (Email: guido.frank@ucdenver.edu)

tests the integrity of white matter tracts, as well as whether there is damage on the level of WM cells.[5] The now most commonly used *functional* brain imaging technique is functional magnetic resonance imaging (fMRI), which measures changes in local blood flow and resulting deoxyhemoglobin levels during brain activation[6]–the so-called blood oxygen level dependent (BOLD) fMRI. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactive ligands that distribute throughout the brain. Those methods can provide information about regional cerebral glucose metabolism or distribution of neurotransmitter receptors.

In a review on brain imaging in EDs in this journal 10 years ago,[7] the state of research was that the most common structural abnormalities found were global reductions of GM and WM in AN, with a tendency toward similar findings in ill BN–changes that tended to normalize with recovery. Further, regional cerebral blood flow and glucose metabolism were reduced in EDs in the temporal, parietal, or cingulate cortex, while limited data suggested some persistence of these findings after recovery from AN and BN. fMRI studies using visual stimuli of food or body images in AN suggested involvement of prefrontal, anterior cingulate, and parietal cortices, and a study in BN suggested altered anterior cingulate and cuneus activity in response to a sweet taste stimulus. A variety of neurotransmitter receptor studies had been done in EDs, indicating reduced serotonin (5HT) 2A receptor binding when ill and after recovery from AN. BN subjects showed increased 5HT1A receptor and reduced 5HT transporter binding when ill, but reduced 5HT2A receptor activity when recovered. Findings of 5HT disturbances after recovery especially suggested possible trait disturbances of the 5HT system that could be related to depressive symptoms or anxiety in EDs.

This article will provide a review of advancements since then in our understanding of EDs through structural and functional brain imaging. The methods described above have been more refined in the past decade, and brain circuits are now emerging that could contribute to ED development or the difficulties to recover from those often-chronic disorders. A comprehensive review would go beyond the scope of this article, however; the article is limited to advancements over the past 10 years, with a specific focus on brain taste reward processing, and each section indicates search terms used. The article further focuses on (1) brain volume, (2) white matter integrity, (3) brain neurotransmitter imaging, and (4) functional brain imaging using taste stimuli. Studies on neurocognitive brain function or cognitive-emotional processing of visual presentation of food images are not discussed in light of space limitations. The interpretation of human brain imaging data is typically complicated by the fact that the measures we take, such as brain volume or brain function measured by blood flow, are not able to identify molecular targets in the way that basic science research can by directly testing how manipulation of neurotransmitter neurons or receptors can affect illness behavior and vice versa. This review highlights in particular studies that a) investigated subjects with EDs under highly behavior-wise controlled conditions, including short term nutrition, and b) studies that used functional brain imaging models that are closely aligned with basic research. This approach will hopefully advance our understanding of a molecular neurobiology that specifically drives food avoidance, episodic overeating, or purging behavior.

Brain Volume

Research on brain structure in EDs has been inconsistent,[8–16] with early studies suggesting reduced total GM and WM volumes, and reduced or normal total brain tissue volumes after recovery.[8] For the study of regionally specific volume alterations, brain analysis methods have become available that allow automated whole brain comparison reducing bias.[8] We searched studies using the terms anorexia nervosa, bulimia nervosa, volume, and imaging. A recent systematic review[8] suggested reduced GM volume in AN in insula, frontal operculum, occipital, medial temporal, or cingulate cortex, but concluded that there is a high level of heterogeneity and inconsistency across studies. One recent study found *increased* GM volume in the dorsolateral prefrontal cortex, but in contrast others reported for instance reduced dorsolateral prefrontal cortex volume in AN which predicted body mass index.[14,17–19] After short-term recovery, AN showed reduced GM in the insula, striatum, occipital, frontal, and parietal cortex,[19] but brain tissue seems to increase with weight gain,[21] and was normal after long-term recovery in a study in adults[22] and another in adolescents.[23] A very recent study in adolescents and young adults with AN suggested widespread cortical thinning in AN in the ill state, but that was not the case in a group after long-term recovery from AN.[20]

Some studies suggested correlations between illness or environmental factors and brain volume. One study suggested that illness duration could be related to reduced cerebellum and mesencephalon volumes,[24] and another report associated obstetric complications with larger volume and functional connectivity in AN.[25] The mechanism regarding how such factors could cause altered brain structure is uncertain though.

A study in AN and BN indicated less gray matter in AN compared to controls and BN in the cerebellum, temporal, frontal, and occipital cortex, but reduced caudate volume in BN compared to AN and controls; furthermore, that study also found bilaterally increased

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somatosensory cortex volume in AN and BN groups.[26] Another study in BN suggested reduced caudate volume in the dorsal striatum but normal nucleus accumbens volume.[29] The studies in BN otherwise suggested normal or increased localized GM volume in orbitofrontal cortex and striatum.[8,27] A new study that investigated cortical thickness in BN found widespread brain surface volume reductions in frontal and temporo-parietal areas.[28]

These variable results may reflect the heterogeneity of approaches, as only some studies corrected for age or overall brain volumes, some studies distinguished restricting from binge eating/purging AN while others did not, and the effects of comorbid diagnoses or medication were often not directly taken into account. Especially important for ED research are the acute effects of dehydration and starvation,[30] as well as excessive exercise.[31] Those factors may contribute to brain volume changes that relate to the acute state of dehydration or nourishment, but may not be directly related an underlying specific ED pathophysiology. Especially the studies that show widespread alterations across more or less the entire cortex may be confounded by global effects of malnutrition, and may reveal less about brain pathology that actually drives eating disorder behavior. This hypothesis is supported by a study that found that the faster adolescents had lost weight and presumably the more they had restricted food and fluid intake, the smaller their brain gray matter volume was.[32]

In an effort to avoid the effects of acute starvation, malnutrition, and dehydration, we recently studied a sample of currently ill ED individuals who had been in highly supervised treatment including a fixed meal plan for between 1 and 2 weeks and thus were nutritionally highly controlled. In addition, we controlled for age, depression, anxiety, medication-use, and brain volume. We found that brain GM volume could identify shared abnormalities among ED groups but also distinguish AN from BN individuals.[33] This sample of individuals with restricting-type currently ill (n = 19) or recovered AN (n = 24), ill BN (n = 19), and healthy control women (n = 24) showed increased GM volume of the medial orbitofrontal cortex gyrus rectus. In addition, ill and recovered AN had increased right insula GM volumes, while BN individuals had increased left insula GM volumes compared to controls. Furthermore, dorsal striatum volumes were reduced in BN and recovered AN, and predicted sensitivity to reward in all ED groups. We also studied adolescents with AN (n = 19) and controls (n = 22), with similar methods. AN adolescents showed increased left orbitofrontal and right insular volumes similarly to AN adults compared to controls (see Figure 1).[34] A recent study in obesity from our group suggests, in contrast, reduced orbitofrontal cortex gyrus rectus volume.[35]

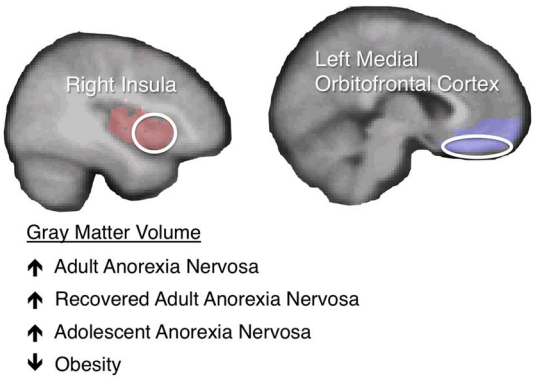

FIGURE 1. Increased left orbitofrontal gyrus rectus and right insula volume in anorexia nervosa across states of illness and age groups.

The orbitofrontal cortex is important in food intake control, telling us when to stop a certain type of food, regulating so-called sensory specific satiety.[36] It is possible that larger orbitofrontal gyrus rectus in EDs is associated with stronger sensory experience of food and maybe also other salient stimuli,[37] which could drive food avoidance. In fact, the medial orbitofrontal cortex has previously been associated with food avoidance,[38] and this region therefore could be a key structure in EDs. ED phenotypes differ with restriction in AN and episodic binge eating in bulimia on the contrary–behaviors that may be driven by insula and basal ganglia differences between the two disorders.[37,39] The left insula receives information on gastric distention[40] and self-reported fullness.[41] Thus, altered insula size could interfere with normal interoception in bulimia, which may contribute to a reduced ability to sense "fullness" or satiation, and then guilt-experienced overeating may trigger the urge to purge after excessive food intake. In healthy controls, left sided anterior and posterior insula activation was associated with gastric distension, and this was mediated by body mass index (BMI)[42]–supporting the idea that alterations in the left insula could indeed contribute to inadequately feeling full and interfering with meal termination. The right anterior insula has been associated with self-recognition, the "abstract representation of oneself,"[43] and interoceptive awareness,[44] and so a fixed perception of being fat while severely underweight in AN[45] could thus be related to right-sided, increased, abnormal anterior insula volume.

Importantly, these and other data[32] suggest that when studying currently ill ED individuals, it is imperative to control for nutritional state as well as comorbidity and medication use in order to be able to get more consistent results, as well as identify brain alterations that are important for relevant ED behavior, as opposed to results that are mostly related to quickly changing effects of starvation. Controlling for those effects is not only important for volumetric studies, but new research also

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indicates that this factor affects studies on brain activity and function.[46]

White Matter Integrity

Brain WM axons physically connect cortical and subcortical brain structures, and thus could have critical impact on cognitive and emotional processing.[47] Brain research that targets WM function uses the magnetic resonance imaging (MRI) technique diffusion tensor imaging (DTI).[5] DTI measures water diffusion along WM tracts, which is expressed as fractional anisotropy (FA). Higher FA is thought to reflect better axonal coherence, density, and myelination.[48] Other measures, such as the apparent diffusion coefficient (ADC) or mean diffusion coefficient, provide information about the average diffusion-freedom water molecules have across cells and correlates with local cell breakdown.[49] In this section, we searched for white matter, anorexia, and bulimia nervosa as search terms.

The first study in this research area came from our group and showed in adult ill AN compared to controls reduced FA in the bilateral fimbria-fornix, fronto-occipital fasciculus, and posterior cingulum WM, and harm avoidance was predicted by bilateral fimbria-fornix FA in AN but not controls.[50] Those findings were not due to WM volume deficits and suggested alterations in limbic and association pathways, which could contribute to disturbed feeding, emotion processing, and body perception in AN. The prediction of harm avoidance in AN by fimbria-fornix WM integrity suggested that this pathway may be mechanistically involved in high anxiety in AN. Altered fornix WM diffusivity in adults with AN was most recently supported by 2 additional studies.[51,52] One of those studies[51] also found positive correlations between BMI and FA, suggesting that weight loss could be related to the changes found. A DTI study in a mixed sample of ill and recovered adult AN found FA reductions in the posterior thalamic radiation, which includes the optic radiation, and the left mediodorsal thalamus. Those alterations could be related to body image distortion, as those pathways connect the extrastriate visual cortex with other brain regions involved in body perception.[53] A small study in AN after recovery indicated no FA differences between AN and control subjects, although more severe illness history was associated with lower WM integrity, and low power may have precluded significant group differences.[54] WM integrity in adolescents with AN was lower in fornix, posterior frontal, and parietal areas, but higher in anterior frontal, orbitofrontal, and temporal lobes.[34] Those results of both increased and decreased WM integrity measures in adolescents are interesting, and could indicate an interaction of normal developmental and ED-specific changes of WM over time. That is, ED behavior could interfere with normal WM growth in adolescence, thereby leading to long-lasting or permanent WM alterations that will be part of the larger ED brain pathophysiology. In adults with BN, FA was decreased in the bilateral corona radiata extending into the posterior limb of the internal capsule, corpus callosum, right sub-insular white matter, and right fornix.[55] The fornix alterations pointed to a possibly common alteration of WM across ED subtypes. Lesions to the corona radiata and internal capsule have been found in central taste disorders,[56] and deep brain stimulation in the internal capsule leads to altered taste and smell perception, as well as anxiety, panic, and mood alterations.[57] Thus lesions in the corona radiata in BN could be related to a variety of specific or associated behaviors found in BN, such as mood disturbance or anxiety.

In summary, the number of studies on WM integrity in EDs is very small, but so far the results suggest that reduced fornix FA is common across AN and BN groups. The fornix is part of the limbic system, which is involved in reward processing[58] and emotion,[59] but also feeding regulation as well as behavior extinction.[60] The clinical significance of those findings will need further study, and whether this is a premorbid condition or an effect from the illness.

Brain Function with Focus on Taste-Reward Processing

Food intake is driven by a complex interplay between cognitive, emotional, and energy homeostasis–maintaining mechanisms between brain and body.[61] There is a cognitive or cephalic phase that involves desire or craving, as well as a consummatory phase involving the hedonic experience. These mechanisms were then further described as dopamine function–associated "wanting," or the drive to approach a reward, and "liking," or the hedonic experience during food consumption associated with opioid system activity.[62,63] Those processes are regulated by the brain reward system, which integrates more basic metabolic hunger signals with higher order processing of taste and cognitive-emotional factors that drive whether we approach or do not approach food stimuli.[64] Important brain regions that regulate those processes are the insula, as the primary taste cortex and central gateway to the dopaminergic basal ganglia and midbrain, to higher order brain centers, including the prefrontal and cingulate cortex, which integrates cognition and emotions; the orbitofrontal cortex, which determines when to stop eating a type of food; and the amygdala, which associates stimuli with emotional experience and which is thought to modulate dopamine circuitry in the midbrain and striatum.[65–67]

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Several studies have investigated brain taste-reward circuits in eating disorders, and in this section, we review functional imaging studies using the search terms anorexia, bulimia, imaging, and taste. The primary focus in this review is on simple sweet taste stimuli, such as sucrose. Individuals who were recovered from AN showed reduced functional brain response to *repeated* but increased response to *randomly given* sweet taste stimuli,[68–70] and those results in opposite directions suggest that unpredictable and predictable stimulus presentation activate differently circuits or neurotransmitter systems, when studying AN. Whether there are stimulus impendent reward system alterations remains to be seen. Studies using monetary reward stimuli indicated that subjects who had recovered from AN or BN showed, with respect to brain activation, less of a distinction in brain response to gain versus loss,[71,72] suggesting that there could be distinct reward circuit alterations depending on the saliency of the stimulus. Another approach is to pair unconditioned taste stimuli with conditioned visual or auditory stimuli and then randomly omit an expected taste delivery or deliver a taste stimulus when none was expected. This leads to a discrepancy between reward anticipated or predicted and the reward actually received, the so called "prediction error," which is reflected in dopamine neuronal response.[73] We have previously applied a prediction error taste-reward task using the sugar solution and visual conditioned cues in AN, and compared this group with obese individuals; the rationale is that we might detect neurobiological alterations that lie on opposite ends,[37] as basic research has suggested.[74,75] We found that insula and ventral striatum prediction error response were greater or more sensitive in AN compared to controls, while obese individuals showed reduced response, supporting the notion that BMI and extremes of food intake may lead to adaptations of brain prediction error and thus dopamine brain response in humans. A similar study in BN found prediction error response reduced compared to controls,[39] but not as much as in OB (see Figure 2). BN subjects' BMI typically lies between controls and OB subjects and BMI may therefore directly be predictive of dopamine related prediction error brain response. Those results of altered prediction error response across ED groups are potentially mechanistically important, as specific dopamine receptors have been implicated, such as the dopamine D1 and D2 receptor,[76] making those receptors potential treatment targets. Otherwise, the literature on taste-reward in BN is small. After a small pilot study found lower anterior cingulate activation after sucrose stimulation in individuals who had bulimic symptoms in the past,[77] 2 studies in BN after recovery indicated increased brain response in that group compared to controls. One of those studies applied repeated fat and high viscous stimuli and reported increased activation in the anteroventral striatum.[78] The other study, which used a task with recurrent sweet taste solution delivery, reported heightened anterior insula activation.[69]

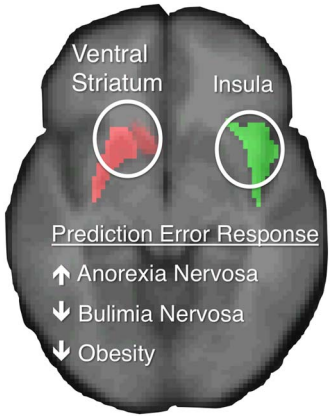

FIGURE 2. Taste-reward prediction error response across groups with disordered eating patterns.

We know little about reward processing in youth with ED, and only one small study tested this system in adolescents with AN.[79] In that study, AN adolescents exhibited an exaggerated response to losses compared to wins in posterior executive and sensorimotor striatal regions, which supports the notion that AN is associated with heightened sensitivity to salient stimuli.[80]

In contrast to studying taste stimuli that are limited to basic nutrients such as sugars, others have investigated complex taste and food stimuli. This may have the benefit to reflect more real life situations. On the other hand, those stimuli may be more difficult to model with respect to the underlying neurobiology of taste pathways. The emotional or pleasantness value that ED subjects assign to a simple sugar solution tends to be similar to controls, while complex tastes such as highly palatable sugar/fat combinations could be associated with for instance higher fear in the ED groups, which might confound the more basic taste pathway signal. One study, for instance, applied chocolate milk and found greater activation in the right amygdala and left medial temporal gyrus in restricting-type AN compared to controls when hungry, contrasted against the satiety state.[81] This could be a sign of heightened vigilance and anxiety in that group, as having the chocolate milk indicates breaking the fasting and promoting weight gain by drinking the caloric beverage. Another study that applied a chocolate milkshake found that women with BN had a positive correlation between negative affect and activity in the putamen, caudate, and pallidum during milkshake anticipation.[82] It was hypothesized that negative affect may increase the reward value of food in BN, but it may be more likely that negative affect became a conditioned response to palatable food, as it is associated with weight gain.

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In summary, repeated and thus predictable application of basic sweet taste stimuli has been associated with reduced activation of taste-reward important regions, such as the insula and ventral striatum in AN, but increased activation in BN. The opposite, though, is the case for random application of those stimuli. This may suggest that there may be an interaction between conscious cognitive-emotional and more unconscious biological mechanisms that drive food approach and eating. A potential explanation here may be that during repeated taste application, the AN subjects "prepare" themselves and control brain response in order to avoid too high stimulation; however, during the random application, this control is not possible and an enhanced responsiveness in AN is coming to light. In BN, a reduced biological responsiveness to taste stimulation becomes obvious during random application, while the repeated taste stimulation could kindle and enhance the low baseline response, maybe through the repeated hedonic experience.

Networks

A variety of functionally connected brain networks has been identified that drive behavior, including the default mode network (DMN), salience network (SN), and executive networks for "higher-order" processing, as well as sensory and sensorimotor (SMN) networks for "lower-order" function.[83] We used the search terms anorexia, bulimia nervosa, network, and connectivity, but few studies have investigated those networks in EDs. Importantly, the methods vary: some studies investigated connectivity during resting state, others during performance of a task; some studies adhere to more strict observation of distinctly described networks, while others investigated connectivity or synchronicity of various brain regions and then speculated on functional networks involved. One study found decreased activity within the ventral visual network in ill and recovered AN patients compared to controls, but also found increased somatosensory network activity in AN.[84] This could be in line with a recent study that found altered connectivity in visual pathways when viewing human bodies,[85] suggesting overall visual network disturbances that could be related to altered body/self perception. One study in recovered AN showed increased DMN activity,[86] and in a study that contrasted AN, BN, and controls, patterns of connectivity between insula and frontal brain regions distinguished groups during a visual food cue task.[87] A recent study found alterations in connectivity patterns within the cerebellum in AN and BN compared to controls,[88] but the meaning and/or functional implications are uncertain. Similarly, a study in a small sample of AN indicated reduced resting state connectivity in AN in the frontal cortex in regions that contribute to cognitive control.[89] That study further indicated an interesting distinction, that is, from the inferior frontal gyrus to the cingulum connectivity decreased, but to the orbitofrontal cortex connectivity increased in the AN group. A study from our group found reduced SN activity during taste stimuli delivery in ill and recovered AN compared to controls, which could be a trait-related biomarker or illness remnant altering the drive to approach food.[90] We also found reduced DMN and SMN activity but in ill AN only, suggesting state-dependent abnormalities, possibly related to altered interoception and body image in AN when underweight, but remitting following recovery.

Taken together, this literature is still very small, but it seems that visual and salience network alterations could be involved in the pathophysiology of EDs, as state-dependent factors or even as biological traits.

Neurotransmitters

Neurotransmitter receptor imaging studies assess the "functional availability" of neurotransmitter receptors in the brain. Several studies have advanced our knowledge over the past decade, although there has also been a limitation in available receptor ligands that can be used in humans, which thus limits our ability to characterize comprehensively neurotransmitter receptor systems. Serotonin (5-HT) 1A receptor binding was found to be elevated across most brain regions in a mixed group of symptomatic restricting and binge eating/purging-type AN subjects compared to controls, as well as in binge eating/purging type AN after recovery.[91] In contrast, recovered restricting-type AN individuals showed normal brain 5-HT1A binding.[91] In addition, reduced 5-HT2A binding in frontal, parietal, and occipital cortices in ill and recovered AN individuals was found.[92] In summary, after recovery, 5-HT1A receptor binding seems to differentiate AN subtypes, whereas 5-HT2A receptor binding is reduced in both restricting and binge eating/purging AN in various brain regions. Since these disturbances occur after recovery, they may reflect either trait disturbances or scars from the illness.

Various studies could correlate 5HT receptor availability or the interaction between 5HT and DA receptors with harm avoidance, which is a behavioral correlate of anxiety,[93] but the exact mechanisms or functional relationships need further study. In BN, 5-HT transporter binding was reduced in the thalamus and hypothalamus,[94] but 5-HT1A receptor binding was increased[95] in the medial prefrontal cortex, posterior cingulate, and parietal cortex. After recovery, BN had increased 5-HT1A binding compared to controls,[96] and 5-HT1A binding in BN predicted inhibition. The dynamics between 5-HT receptor expression and synaptic 5-HT are not well understood, but reduced 5-HT2A binding in recovered BN subjects may be related to a higher level of

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endogenous 5-HT in the synaptic cleft, or a down-regulation of the receptor.

A mixed group of recovered restricting-type and recovered binge-eating/purging-type AN women showed increased DA D2/D3 receptor binding in the antero-ventral striatum,[97] while decreased DA D2/D3 receptor binding was found in obesity.[98] Those findings support the possibility that D2/D3 receptor binding may be inversely related to weight and eating, with restricting-type AN on one end and obesity on the other end of the spectrum. It is possible that increased DA D2/D3 receptor binding in AN is part of underlying mechanisms that may explain why individuals with AN are able to resist eating. It is worth noting that food restriction sensitizes D2/D3 receptors, while excessive food intake downregulates DA D2 receptors in rats; similar mechanisms in AN or obesity could complicate recovery.[75] A very recent study found that BN individuals had a trend to lower DA D2/3 receptor binding in the striatum as well as less DA release compared to controls in response to methylphenidate application.[99] While overall this body of research is small, it suggests that food restriction in AN may increase and episodic binge eating in BN or chronic overeating in obesity could reduce DA receptor activity.

Conclusion

Brain imaging will continue to be an important tool for brain research in EDs, although it is not ready to be used yet as a diagnostic tool or for directing intervention.[100] The studies conducted over the past decade have furthered our understanding of the pathophysiology of EDs in various ways. First, studies show that it is highly important to carefully select study subjects and control for nutritional status and comorbid conditions in order to identify brain regions that have functional importance and are not only a reflection of dehydration and malnutrition. From the aggregate of studies, there is now strong evidence that reward pathways may have a central role in ED pathophysiology. The orbitofrontal cortex and connecting fibers are altered across EDs, and a larger volume of the orbitofrontal cortex could contribute to being able to stop eating before the physiological need is met. Another key region is the insula, which is altered across a variety of structural and functional studies. Those regions are part of the taste-reward system, which supports the evidence that reward pathways are implicated in EDs. Within that network, it is possible that AN is associated with heightened and BN and obesity with reduced dopamine related circuit responsiveness. Importantly, those results could point toward future pharmacological interventions, as specific DA receptors are associated with brain reward function. This is supported by the reviewed brain neurotransmitters studies that indicate higher DA D2/D3 receptor availability in AN. Future research will have to combine PET neurotransmitter as well as fMRI studies in order to better integrate behavior, molecular targets, and neuronal activity and function. Results from network connectivity studies are few and variable, but there seems to be also at least some convergence pointing to altered reward circuit function. Specifically those studies indicate differences in salience network activity compared to controls, which may interfere with a normal orientation toward food-related stimuli, as opposed to, for instance, focus on academic study and achievement and overriding such basic needs.

Disclosures

Guido Frank does not have anything to disclose.

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