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Advances in the diagnosis of anorexia nervosa and bulimia nervosa using brain imaging

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Abstract

Introduction—Anorexia and bulimia nervosa are severe psychiatric disorders and the availability of brain imaging techniques hold promise that those techniques will be useful in clinical practice.

Areas covered—In this review I describe currently available brain imaging techniques and focus on the brain imaging methods functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Those techniques have helped describe alterations in brain circuitry in AN and BN that related to anxiety and reward processing. Novel computational models help further define brain function in relation to particular neurotransmitters.

Expert opinion—Brain imaging techniques are exciting methods to learn about brain function and progress has been made to identify in healthy populations brain circuits that code behaviors. These techniques have been used in AN and BN over the past decade and have improved our understanding of brain function in those disorders. Still, human brain imaging is not at a point yet where it could be used diagnostically. However, with the refinement of imaging hardware as well as improved models that describe brain function we will get closer to our aims to not only better understand the neurobiology of those disorders, but predict illness development, treatment response and long term prognosis.

1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are severe eating disorders (EDs) that usually begin during adolescence, occur most commonly in females, and are associated with an intense fear of gaining weight [1]. The diagnostic criteria for AN are low weight, defined as a body weight below 85% of that expected for age and height, AN individuals feeling fat despite being underweight, and a loss of regular menses. 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 engage in eating 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, use of laxatives or diuretics, or excessive exercise (“purging”). BN individuals are at normal or high normal weight, but the disorder is characterized by recurrent binge eating and purging behavior at least two times per week for at least three months. Comorbid depressive and anxiety disorders are common in both disorders and altered cognitive function has also been identified in AN and BN [1–4].

The conceptual framework of the pathophysiology and etiology of AN and BN has undergone significant changes in the past few decades. Brain imaging techniques now give us the opportunity to better understand how brain circuits may be implicated in pathologic ED states and behaviors. Furthermore, brain research in eating disorders has become more

refined with respect to for instance the psychological models tested [5]. Specifically, those techniques could become important clinical tools for 1. early detection of risk whether someone is likely to develop AN or BN – which would guide the use of primary prevention measures, 2. providing information what prognosis a patient with AN or BN may have – which would guide intensity of treatment and long term follow up, and 3. disentangling biologic from more psychological factors that drive the illness - which would also help personalize treatment with respect to psychotherapeutic versus biological interventions.

This review will describe the methodologies that novel brain imaging techniques use and how they may be helpful in answering the above questions. We will then describe important brain circuits that may be involved in AN and BN, and what evidence research studies have provided in the effort to relate brain function to ED specific behaviors. Brain imaging research in eating disorders has been small compared to research in mood or psychotic disorders, but brain reward system and anxiety pathways related studies are among the most promising and we will focus on those two systems. Lastly we will propose future studies that take advantage of new imaging methods and analyses in order to use this technology as hopefully diagnostic-predictive tools, useful in clinical practice.

2. Brain imaging technology

A host of neuroimaging tools is now available for ED research [6]. Structural imaging techniques such as computer tomography (CT) and radiation-free magnetic resonance imaging (MRI) provide information on gross structural abnormalities, and a recent meta analysis has reviewed the available studies [7]. A relatively novel method that also uses MRI technology is diffusion tensor imaging (DTI) which has recently been applied in AN [8]. That technique uses water diffusion measures to test the functionality of white matter tracts along their axons as well whether there is damage on the level of white matter cells. Magnetic resonance spectroscopy (MRS) can detect brain chemicals containing choline, aspartate and others, which are involved in brain neurotransmission.

Electroencephalography (EEG) and evoked potentials (EPs) record neuronal electrical activity, and quantitative electroencephalography (qEEG) employs spectral analysis of EEG data from multiple-electrode, whole-head recordings and provides better spatial resolution compared to the traditional EEG. Magnetoencephalography (MEG) records and maps magnetic fields allowing studying neuron function via the electrical currents that brain activation produces.

One of the most commonly used functional brain imaging technique is functional magnetic resonance imaging (fMRI), which is used to tie behavior to specific brain activation and thus identify circuits that code cognitive and emotional processes. Human brain imaging is limited in as far as we have to use indirect measures to investigate neuron response. Regional brain activation is associated with increased blood flow in that particular area [9] and thus an increase of incoming oxygenated hemoglobin. fMRI takes advantage of the magnetic properties of oxygenated versus deoxygenated hemoglobin. Deoxyhemoglobin is paramagnetic and fMRI can measure the changes in local deoxyhemoglobin levels during brain activation and resulting blood flow, the so called blood oxygen level dependent (BOLD) fMRI. There is a dynamic interplay between brain activation and increased blood flow, which is directly related to the BOLD response, and oxygen extraction by the brain cells, the so called neurovascular coupling [10], but the exact dynamics are still investigated. Furthermore, it is yet unclear whether an increase in BOLD response in a brain region indicates activation due to incoming or outgoing neuron activation [11, 12]. During fMRI, study subjects typically perform certain tasks that are designed to be specific to normal or pathologic states such as disordered eating or depression.

Other common and important functional brain imaging techniques are positron emission tomography (PET) and single photon emission computed tomography (SPECT). They use radioactive substances that are injected into and distribute throughout the body including the brain. Brain radioactivity is measured over time, which provides information about the metabolic or neuroreceptor system studied. For instance, the dynamics of regional cerebral glucose metabolism (rCGM) can be calculated using fluorodeoxyglucose (^{18}F), and neurotransmitter receptor specific ligands such as (^{18}F)altanserin can be used to study serotonin 2A receptor distribution. Neurotransmitter release, such as dopamine, may also be studied using (^{11}C)raclopride together with challenge drugs [13, 14]. PET is superior to SPECT due to a better spatial quantitative localization of the signal and is now the dominant technique for neuroreceptor studies.

3. Relevance of brain imaging for eating disorder research

Recent advances in the field of brain research using neuroscience-based imaging paradigms have made great progress with respect to linking altered brain response to emotional and cognitive processes in healthy populations as well as psychiatric illnesses including AN and BN. For example, a lot has been learned about brain pathways that are involved in fear provoking stimuli [15], induction of abnormal mood states [16], processing of food and other rewarding stimuli [17], cognitive flexibility [18], and numerous other areas with potentially direct relevance to eating disorders. The body of neurobiological research in EDs to date is still relatively small, but nevertheless significant advances have been made over the past ten years to shed light on biological brain processes that may be part of the pathophysiology of AN or BN.

Of importance when reviewing ED brain research are state related factors. The ill state of the EDs, particularly of AN, can be accompanied by severe metabolic, electrolyte, and endocrine disturbances [19]. As such these effects always potentially confound research in ill EDs. We have taken care to indicate where studies have examined the ill state versus recovered state of these illnesses, as this may help to somewhat disentangle findings related to starvation versus traits related to the underlying pathophysiology of the illness. Even in recovered subjects, however, it has to be taken into consideration that observed differences compared to controls may represent either premorbid traits contributing to the development of the illness, or a consequence of having been previously ill.

4. Neurocircuits important to eating disorders

AN and BN show a complex interplay between neurobiological, psychological and environmental factors [20]. That is, severe emaciation from self driven food refusal, motivation for weight-loss, and a perception of being overweight in spite of a very low body weight in AN, and the frequent binge/purge episodes with intermittent food restriction in BN [1] suggest strong psychological factors that perpetuate illness behavior. Little is known about the pathophysiology or biomarkers that characterize AN and BN brain function [21], although there have been recent advances with respect to describing brain neuro-circuitry in AN [22, 23], implicating the insular cortex, cingulate cortex and basal ganglia and pointing toward anxiety and reward related brain pathways. The exact impact of abnormal brain response on behavior is largely unknown though. Very few imaging studies have been done in BN, which limits the information about larger neuronal pathways contributing to illness behavior. Please see Figure 1. for a schematic outline of brain circuits involved in anxiety and reward processing.

4.1. Reward Circuitry

Food consumption is intimately connected to the brain reward system, and highly related to taste [24], driving the motivation to eat [25–27]. The brain reward system is therefore an important research target for AN and BN [28, 29].

Gustatory inputs from the tongue, immediately after food contact and prior to gut involvement, project via brain stem and thalamus to the primary taste cortex comprised by insula and frontal operculum, and project from there to the ventral striatum and amygdala, and subsequently to hypothalamus, midbrain, and frontal cortex [30]. Hence, a highly complex network is involved in taste processing and food reward. In addition to the transmission of taste quality, there are learned associations between food and pleasant or unpleasant experiences, and those internal representations of food stimuli get activated when we see, smell or think of food [24]. This cephalic phase that includes desire and craving for food stimuli involves prefrontal and subcortical structures and activation of dopamine circuits which stimulate motivation to act and approach food rewards (“wanting”). The pleasurable experience of food (“liking”) has been related to opioid release in the brain [25, 31, 32]. Those pathways could be disturbed in altered eating behavior states.

Animal studies have suggested heightened brain reward response including brain dopamine activation due to food restriction and weight loss [33–35]. Malnutrition also affects reward circuitry in animal studies via other neurotransmitters and hormones, including leptin [36], ghrelin [37], glutamate [38], and opioids [39], but the dopamine system is particularly well characterized and can be studied empirically [26, 31]. AN and BN are associated with reduced dopamine metabolites in cerebrospinal fluid [40–42] and women recovered from AN showed in PET studies increased dopamine D2/3 receptor availability in the ventral striatum [43]. The presentation of body images during fMRI brain imaging found that AN individuals were more responsive in the striatum than controls to images of thin bodies using fMRI [44]. Recovered AN (fMRI) showed reduced functional brain response to a repeated application of taste in the insula and ventral and dorsal striatum [45], but increased response in the caudate to randomly given monetary reward stimuli and AN did not distinguish between win and loss in the ventral striatum [46]. Those results in opposite directions suggest that unpredictable versus predictable stimulus presentation may be important when studying AN. It is uncertain whether findings in recovered AN were predating the disorder or are effects of the illness. Furthermore, various genetic studies implicated dopamine D2 and D4 receptor function in AN [47–49]. In summary, it appears that AN is associated with profound effects on brain dopamine and reward functioning, but the impact of those alterations is not yet clear. Altered brain dopamine function could be related to abnormal reward pathways in AN [22] but such hypotheses need further study [50].

BN has commonly been associated with addiction disorders [51] due to the episodic and often compulsive nature of bingeing on highly palatable foods. The motivation to approach food and other rewards, called ‘wanting’, has been associated with the neurotransmitter DA [28], and the same neural pathways that reinforce those natural appetitive behaviors are also activated in response to addictive drugs [52]. This has led to the hypothesis that prone individuals could get “addicted” to food, including increased preference and tolerance as well as reduction of dysphoria, behaviors that are common in substance using individuals [53, 54]. A recent study used fMRI and a dopamine related reward paradigm that delivers or omits unpredictably taste reward stimuli, and brain response was modeled based on known dopamine neuron response patterns [55]. That study indicated that BN is associated with reduced responsiveness to unexpected receipt or omission of taste reward stimuli in the ventral putamen. Further, the dopamine model related brain response was reduced in the BN group in the insula, ventral putamen and prefrontal cortex, and brain response in BN was

predicted by binge/purge frequency. These results suggest reduced DA reactivity in BN that is related to illness severity.

4.2. Anxiety Circuitry

Anxiety has been suggested to be a key vulnerability factor for the development of AN [56], and both AN and BN have been found to have emotion regulation difficulties [57, 58]. Clinicians frequently observe a strong need for control in ED populations, while heightened anxious avoidant traits may predispose individuals to develop EDs [2, 3]. ED individuals appear to control their eating, weight and shape as a way to address their perceived lack of control over interpersonal and overall life stressors, and these behaviors could be an attempt at establishing control and to manage internal uncertainty around life events. This need for control seems to be reflected by highly elevated scores of intolerance of uncertainty in both AN and BN [59].

A neurotransmitter that is commonly associated with anxiety is serotonin, which acts on at least 14 different serotonin receptors and that is distributed throughout the brain [60]. One of the most commonly assessed receptor types is the 5HT2A receptor, which is involved in the regulation of feeding, mood, and anxiety, and in antidepressant action [60]. AN subjects showed in PET studies reduced 5HT2A binding in frontal, parietal and occipital cortex in one study but no differences compared to controls in another [61]. 5HT2A binding was reduced in recovered AN-R in the insula and cingulate cortex, as well as mesial temporal and parietal cortical areas, and in women recovered from AN-B/P in the cingulate, parietal, and occipital cortex [61]. In both studies 5HT2A binding was positively related to harm avoidance, an anxious trait that is commonly elevated in EDs. The cingulate cortex receives afferents from the amygdala and has direct projections to the frontal cortex and limbic regions, and plays an important role in initiation of and motivation for goal-directed behaviors as well as computation of the value of potentially rewarding stimuli. The amygdala mediates vigilance to potentially threatening stimuli and the interpretation and the representation of emotional stimuli values [62], and the parietal cortex is involved in body perception. It could therefore be that there is a disconnect between cognitive and emotional pathways in AN, that promote illness behavior. In BN, reduced orbitofrontal 5HT2A receptor binding was found after recovery. Orbitofrontal alterations could reflect behavioral disturbances in BN that include impulsiveness and altered emotional processing [61].

Another major serotonin receptor type is the 5HT1A receptor found throughout the forebrain as well as in the midbrain raphe nuclei. AN-R and AN-B/P had increased 5HT1A activity (PET) [63] across frontal, temporal and parietal cortex regions as well as the dorsal raphe, and after recovery AN may also have increased 5HT1A availability [64–66], raising the possibility of alternate pathogenic pathways for bingeing/purging versus restricting behavior. Importantly in the recovered AN 5HT1A binding was positively correlated with harm avoidance. Most recently, another group [66] found in both ill and recovered restricting type AN increased 5HT1A availability in similar regions supporting increased 5HT1A in the disorder across various illness stages and brain regions. BN individuals also showed increased 5HT1A receptor binding [61] in all studied brain regions, but most prominently in prefrontal, cingulate and parietal cortex. The 5HT1A receptor takes part in regulating brain serotonin release and the diffuse increases of this receptor type in AN and BN could indicate serotonin trait disturbances in EDs that drive high anxiety as reflected in excessive harm avoidance.

A study in AN that examined the serotonin transporter (5HT-T) among recovered AN found that 5HT-T availability was greater in AN-R compared to AN-B/P in the dorsal raphe and anteroventral striatum but there were no differences between the AN groups and controls [61]. No such studies have been done in currently ill AN. Ill BN individuals showed in a

SPECT study reduced 5HT transporter binding in thalamus and hypothalamus versus controls, and BN after recovery showed in one study lower 5HT-T binding in the midbrain and superior and inferior cingulate cortex, but higher transporter availability in the anterior cingulate and superior temporal gyrus [67]. The 5HT-T regulates serotonin levels in the synapse and previously found increased 5HT brain metabolites in BN after recovery could be related to 5HT-T alterations. BN also need higher dosages of serotonin reuptake inhibitors and altered 5HT-T levels may help explain less responsiveness to lower dosages.

Food and related weight gain are still the primary fear inducing stimuli for ED individuals. Various studies have applied pictures of high and low calorie foods during brain imaging to elicit brain response in relation to behavioral measures such as anxiety ratings. In AN, those visual food presentations lead to increased brain activation. For instance, in AN high-calorie food pictures provoked anxiety and led to greater temporo-occipital activation and mesial temporal as well as left insular and bilateral anterior cingulate activity, and these results could be consistent with anxiety provocation and related limbic activation [68]. In another study [69] food images stimulated medial prefrontal and anterior cingulate cortex in recovered and ill AN, but lateral prefrontal regions only in recovered AN. In recovered AN, prefrontal cortex, anterior cingulate cortex and cerebellum were more highly activated compared to both controls and chronic AN after food presentation. This suggested that higher anterior cingulate cortex and medial prefrontal cortex activity in both ill and recovered AN compared to controls may be a trait marker for AN. These are areas of executive function, decision-making, error monitoring and also reward expectancy. Such alterations could suggest heightened vigilance or processing activity in response to visual food stimuli. Taken together, these studies suggest that the prefrontal cortex is active in the capacity to appropriately or inappropriately restrict food, possibly via heightened fear related activation and anxious cognitions that drive food restriction. Just recently, DTI has been applied in AN in a study from our group [8]. That study indicated there are white matter alterations in AN in particular in the bilateral fimbria fornix regions, outflux pathways from the hippocampus and connecting to frontal cortical regions and subcortical reward processing areas such as the ventral striatum. Furthermore, fimbria fornix white matter alterations in AN predicted harm avoidance. This study thus suggests that alterations in white matter, the connecting neurons, could be directly involved in AN pathophysiology.

In BN, presentation of food images was associated with increased response in frontal, cingulate, occipital and insula cortex, and suggesting anxious response as in the AN group [69].

In summary, integrating those brain regions together with known AN behavior, one could hypothesize the following model of a functional disconnect between the amygdala and frontal brain regions. The AN individual is initially learning to overvalue extreme ideals of thinness, and the amygdala get sensitized to food and body related stimuli as threatening. However, AN is associated with altered white matter connectivity [70] and with illness progression there is an increasing lack of connectivity between frontal cortex and amygdala. This may lead to an inability of prefrontal brain regions to control excessive amygdala activity, which continues to drive weight related fears, even if an AN individual tries to reverse course. This continuous fear response could be a reinforcing mechanism that further worsens poor flexibility in reevaluating actual danger of shape and weight related stimuli, and an inability to test and adapt to new behaviors such as re-feeding and weight gain. This process could lead to altered reward prediction of for instance food stimuli and reduced drive to approach food rewards. Additionally, a pathologic integration of signals from the body periphery may disturb normal body image and drive the perception of being fat despite being thin. It is unclear how exactly the described neurotransmitter abnormalities develop,

but since they persist after recovery, it is possible they are trait disturbances, contributing as risk factors for AN development.

5. New directions in the use of brain imaging

Each one of the above-mentioned brain imaging techniques, fMRI, PET and SPECT, has by itself important advantages and disadvantages. For instance fMRI can easily be applied together with disorder related tasks that may help elicit activation in specific brain pathways, but a downside of fMRI is the slow response time, for instance peak brain activation may take 5 seconds while our thought processes are obviously much faster. Furthermore the neurons involved in the BOLD signal most likely represent various neurotransmitter systems including glutamate, gamma-aminobutyric acid, neuropeptides as well as neurotransmitters such as serotonin, dopamine and acetylcholine [71–76]. That means that the fMRI BOLD signal reflects the activation of a number of diverse neurons, and in fact the synaptic activity between those neurons [77]. Thus used by itself, fMRI has significant limits in identifying neurotransmitter systems involved in pathologic brain response. MEG can measure fast neuronal activation that in fact resembles closer electrical brain activity. This measure is mainly confined to the brain cortex although attempts are made to advance this technique and be able to study deeper, subcortical brain structures [78]. This method also does not inform about specific neurotransmitters. PET imaging in contrast is able to measure actual molecular correlates of brain function, the availability of neurotransmitter receptors in the living human brain. However, PET does not reflect altered sensitivity of receptors, and most studies do not include a functional component, or specific task performance of the scanned subject during scanning, limiting the information how those receptors relate to actual behavior.

There is a variety of novel and exciting imaging methods that are increasingly available to overcome the shortcomings of each technique and make human functional brain imaging hopefully eventually relevant for clinical use. One of those methods is so called “multimodal imaging”, that is the combination of a variety of imaging techniques in order to get a more in depth information of brain function [79]. For instance, the combination of fMRI and PET imaging is now easily possible with a combined PET-MR scanner, allowing a research subject perform a specific task during scanning, the MRI scanner measures functional brain activity and the PET imaging during the same time allows information on number and for some ligands function of neurotransmitter receptors. This information is very useful in order to identify specific neurotransmitters that could be targeted pharmacologically.

Another method is to add pharmacologic challenge drugs that are known to stimulate specific neurotransmitter release, which then further would increase knowledge about the functionality of a neural system. Such brain response can be modeled in animals and tested against human brain imaging results. That is the response pattern known from direct neuron recordings can be compared with the human – yet indirect - response. The brain dopamine system has received probably the most attention in this context. Within brain reward circuits, dopamine is critically associated with providing signals regarding the presence and amplitude of rewards [26, 80]. Such signals facilitate reinforcement-learning [81], and have been found to code the value of a stimulus [82, 83], which may even include the metabolic value of food [84]. Second, computer models for dopamine neuron reward activation exist that can be related to human in vivo brain function. Such a model is the temporal difference (TD) model [85]. This model is a theoretical framework for computational reward learning-models that predict neuronal brain dopamine response. This model has been previously tested for unexpected reward receipt and omission in animal studies [86] and later validated for human brain imaging [87, 88]. In brief, dopamine neurons exhibit a phasic burst of activation in response to the presentation of an unexpected rewarding stimulus (the primary,

unconditioned reward stimulus US). After repeated presentation of an additional arbitrary stimulus (the conditioned stimulus CS) preceding the US, the phasic activation of dopamine neurons transfers in time to the presentation of the CS. Thus, the CS elicits a conditioned dopamine response. The advantage of using models like that is that we have a good knowledge what happens in the animal and results in humans are then easier to be interpreted in terms of underlying biologic mechanisms.

Another method, imaging genetics, uses genetic information of for instance neurotransmitter receptor genes and tests whether genotype can predict brain response [89]. This is an exciting new field complementary to brain imaging, but brings also challenges such as the need for very large sample sizes for sufficiently powered studies.

6. Expert Opinion

The conceptual framework of the pathophysiology and etiology of the eating disorders (EDs) anorexia nervosa (AN), bulimia nervosa (BN) is increasingly moving toward biologic models that help identify altered brain pathways in those disorders. Brain imaging techniques now give us the opportunity to assess regional brain activity and neuroreceptor function *in vivo* in humans, and thus may help us understand how neuronal circuits are related to behavior and pathophysiology. Psychiatry lacks test that would aid in making accurate diagnoses, predict disorder risk, treatment response, or relapse. Developing those methods in eating disorders as suggested for instance in the anxiety disorder field [90], is appealing since these techniques could help improve treatment outcome and reduce treatment cost.

Many studies in psychotic, anxiety, mood or substance use disorders have found alterations in brain pathways compared to healthy controls [91]. The eating disorders literature on brain imaging is much smaller but there are several key findings that seem to reliably describe alterations in those disorders. First, AN and BN are associated with serotonin receptor alterations. In particular in AN there are alterations both during the ill state of the illness as well as after recover. Furthermore, measures for serotonin receptors in AN were related to harm avoidance, a trait that describes anxious temperament. Various brain imaging studies in ill and recovered AN have indicated alterations in brain regions that are important for reward processing, brain circuits that drive our motivation to eat. Brain dopamine function has been found to be altered in AN in the past, and this raises the possibility that AN is associated with abnormal dopamine related brain reward processing which could be part of AN's food avoidance. The brain imaging literature in BN is smaller, but a recent study using a dopamine related reward task indicates altered reward processing in BN that was predicted by illness severity. This suggested that the illness has direct effects on brain function.

There is overall consensus though that brain imaging is not yet rife to be used as a diagnostic tool for those disorders [91, 92]. On the other hand, brain imaging research is steadily progressing and by far not used to its extent possible. For instance, while several years ago MR scanners with 1.5T magnet strength were still common in fMRI research studies, 3T magnet strength is now common and there are scanners increasingly used that have 7T magnets which greatly improves signal to noise ratio. A significant weakness of fMRI is that the BOLD response is an indirect measure of neuronal activity, and it is also relatively slow compared to actual brain activation. However, with the constantly improving ability to model brain response related to neurotransmitter function as well as circuitry between specific brain regions, it can be expected that those models will help establish signatures that may be relatively specific for mood or anxiety states and possibly also disordered eating behavior. A problem here is that psychiatric disorders are commonly co-occurring with other disorders and large size study groups will be needed to establish reliable brain circuit

“signatures”. PET imaging has always had the benefit that it can image molecular targets, since it uses radioactive receptor ligands. This is both a great strength as well as a weakness, since there are limitations how much radioactive exposure a research subject can be subjected to. I believe that with the increasing availability of PET-MR devices there will be a combination of fMRI and PET studies that will greatly enhance our knowledge on the dynamics between brain circuit activity and underlying involved neurotransmitter receptor systems. This may then help test specific drugs’ or therapies’ effects on brain function, and may help identify predictors of treatment response, and thus help apply more effective treatment to patients in a personalized medicine approach.

A main challenge is the generalizability of brain imaging findings since sample sizes of studies tend to be small, often driven by limited resources, because of the usually high costs associated with brain imaging studies. Thus well thought through and neuroscience model based studies are necessary that target AN and BN specific brain circuits and that recruit large numbers of subjects across various sites, in order to establish standards of normal versus disordered brain response. Such studies then can help answer our questions for treatment outcome and prognosis. A novel direction of research in that direction is the study of cognitive concepts of self-regulation and thus behavior control using tasks that require subjects to attend to certain cues but suppress attention to others for a correct response in the paradigm [93–95]. Altered self-regulation could directly be involved in the control versus loss of control over eating, and contribute to illness behavior even if a patient is willing to engage in treatment.

The fields of neuroscience and psychology will continue to refine brain function models and psychiatric research will be able to integrate and test those models on patient populations including AN and BN. This will eventually help elucidate specific brain pathologies, and make those tools useful for the clinician.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ED	Eating Disorder
AN	Anorexia Nervosa
BN	Bulimia Nervosa
AN-R	Restricting type AN
AN-B/P	Binge eating/purging type AN
MR	Magnetic Resonance Imaging
fMRI	functional MRI
PET	Positron Emission Tomography
CT	Computer Tomography
SPECT	Single Photon Emission Computed Tomography
CS	Conditioned Stimulus
US	Unconditioned Stimulus

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Article Highlights

- The eating disorders anorexia and bulimia nervosa are severe eating disorders and research indicates that they are associated with complex brain alterations.
- Novel brain imaging technologies are now available that allow us to test in vivo brain function in those psychiatric disorders.
- The majority of imaging modalities used are functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) that allow studying brain function in relation to specific tasks, as well as molecular targets such as neurotransmitter receptors.
- Brain imaging has started to identify brain circuits that may be integral to brain pathology in anorexia and bulimia nervosa, such as anxiety and reward pathways.
- Human functional brain imaging is not ready yet to be used as a diagnostic tool, but the combination of brain imaging technologies and novel models of brain function hold promise that those tools will become clinically relevant.

Figure 1.