# Neuroimaging Studies in Eating Disorders

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FOCUS POINTS

- The most studies of anorexia nervosa show gray and white matter alterations that, at least in part, remit with recovery; functional imaging studies suggest limbic, frontal, and parietal cortex as areas of disturbance; serotonin receptor alterations exist when ill and after recovery.
- Bulimia nervosa also shows serotonin receptor alterations after recovery, but very few studies exist in this disorder.
- There may be common and distinct areas of disturbance when comparing those brain imaging findings with other psychiatric disorders (eg, obsessive-compulsive disorder) but this needs to be studied further.


## ABSTRACT

*The understanding of the eating disorders (EDs) anorexia (AN) and bulimia nervosa (BN) has undergone remarkable advancements in the past decade. Most studies that have been done in AN show brain gray and white matter volume loss during the ill state that, at least in part, remit with recovery. Similar patterns occur for brain phopsholipids assessed using magnet resonance spectroscopy (MRS). Imaging studies have been used to provide functional information regarding serotonin neuroreceptor dynamics, regional cerebral blood flow, or cerebral glucose metabolism. Such studies have implicated cingulate, frontal, temporal, and parietal regions in AN. Investigators have found that challenges such as food and body image distortions may activate some of these regions, raising the possibility that such studies may shed light on puzzling AN symptoms, such as body image distortions or extremes of appetitive behaviors. Emerging data suggest these disturbances persist after recovery from AN, suggesting the possibility that these are traits that may create a vulnerability to develop an ED. While fewer studies have been done in BN or binge eating disorder, there may be disturbances of serotonin metabolism in similar brain regions. Taken together, these findings give promise for future investigations with the hope of delineating brain pathways that contribute to the etiology of EDs.*


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## INTRODUCTION

The conceptual framework of the pathophysiology and etiology of the eating disorders (EDs) has undergone significant changes in the past decades. The etiology of EDs is still unknown. Several lines of research have raised the possibility that trait disturbances of brain neurotransmitters may contribute to the pathogenesis of ED. These neurotrasmitter systems include serotonin (5-HT) and dopamine pathways and a number of neuropetides.[1] A major reason for our lack of understanding of brain and behavior is that tools for measuring neurotransmitter activity have been limited. These include indirect measures, such as concentrations of neurotransmitters in cerebrospinal fluid (CSF) or hormonal responses to drug challenges. Brain imaging techniques now give us the opportunity to assess regional brain activity and neuroreceptor function in vivo in humans and, therefore, may help us understand how neuronal circuits are related to behavior and pathophysiology.

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A range of neuroimaging tools are now available. Structural imaging techniques, such as computer tomography (CT), may provide information on gross structural abnormalities. Magnetic resonance spectroscopy (MRS) can detect brain chemicals that are involved in brain metabolism. Positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) can be used to assess brain activity thought to be associated with changes in regional cerebral blood flow (rCBF) or glucose metabolism (rCGM). Neurotransmitters-receptor and transporter function can be assessed with PET and SPECT.

Studies in a number of psychiatric disorders suggest brain structures, such as the amygdala or frontal cortical areas, are involved in emotional processing.[2,3] Patients with EDs have comorbid mood disturbances and anxiety, and it has been hypothesized that similar biological markers,[1] as in other disorders might be found. Moreover, people with EDs have poorly understood symptoms, such as body image distortions and restrictive eating. Over the past decade, brain imaging studies have begun to help us understand the brain pathways that may contribute to such symptoms.

## *ANOREXIA NERVOSA*

AN is a disorder that usually begins during adolescence in females, and is associated with an intense fear of gaining weight, feeling fat, emaciation, and amenorrhea. A restricting type (AN-R) has been distinguished from a binge eating/purging type (AN-B/P).[4] Comorbid obsessive-compulsive disorder (OCD), depression, and anxiety are common.[5]

### *Computed Tomography and Magnetic Resonance Imaging Studies*

It is well known from CT and MRI studies that underweight AN patients tend to have enlarged sulci and ventricles and decreased brain mass.[6-8] While these alterations shift towards normal with weight restoration, it is not certain whether they normalize.[9,10] It is not clear whether these changes during the ill state are related to changes in gray or white matter, or the extracellular space. Moreover, it remains uncertain whether these are generalized brain changes or are specific to particular brain regions. The most extensive structural studies have been done by Katzman and colleagues.[11] They found, in 13 adolescent AN women, reduced total gray matter and white matter as well as increased CSF volume during the ill state. By contrast, in a cohort of ill AN, BN, and controls, Husain and colleagues[12] assessed the midsagital plane acquired by MRI, finding reduced midbrain and thalamic size in AN but no gray matter alterations. Lambe and colleagues[13] studied recovered AN and found that they had reduced gray matter and increased CSF volume compared with controls, but greater gray matter and smaller CSF volume compared with subjects with AN. Furthermore, a longitudinal study of six women during the ill state and after weight recovery (mean: 16 months)[14] showed that white matter volume was remitted after weight recovery, but a gray matter deficit and CSF volume persisted.

The reason for changes in brain volume is also unknown. Some data suggest that cortisol may contribute to brain alterations. Katzman and colleagues[11] found that urinary free cortisol was positively correlated with CSF, but inversely with gray matter volume. AN patients have increased CSF cortisol.[15] Therefore, it is possible that hypercortisolemia may play a role in reduced brain mass in AN. Recently, mesial temporal (amgdalo-hippocampal complex) size[16] was found to be reduced in AN, but there was no relationship with hormonal levels, including urinary free cortisol. It is unclear if this finding was confined to the mesial temporal cortex or ubiquitous, making its interpretation difficult.

The question of whether alterations in brain mass contribute to cognitive or mood changes in AN has not been well studied. Kingston and colleagues[17] combined structural imaging with psychological assessments, including anxiety, depression, attention, and memory, in 46 AN inpatients before and after weight gain, compared with controls. No significant correlations were found, suggesting either no specificity of disturbance that can be related to specific behavior or simply inefficient analysis methods.

In summary, these studies tend to indicate that during the ill state a gray matter and probably white matter volume loss occurs that at least partially recovers with weight restoration. Those structural alterations are relatively non-specific, and behavioral correlates have not been discovered.

### *Magnetic Resonance Spectroscopy Studies*

MRS can give information on nerve cell damage by assessing brain metabolites such as choline, *N*-acetylaspartate (NAA), phosphorus, and myo-inositol. MRS studies in juvenile AN patients found higher choline containing compounds relative to total creatine and lower ratios of NAA relative to choline in white matter.[18,19] Those changes were interpreted to be altered cell membrane turnover, as they were reversible with recovery.[20] Two studies[21,22] showed reduced brain phospholipids that positively correlated with body mass

index, also suggesting a state dependent phenomenon. The latter study also found body mass index positively correlated with frontal cortex myo-inositol, which is a part of the 5-HT second messenger neurotransmission system[23] and could be consistent with reduced 5-HT activity in AN.[1]

### *Positron Emission Tomography and Single Photon Emission Computed Tomography Studies: Resting Condition*

Most studies that have assessed "resting" brain activity in AN have used SPECT (Table). Gordon and colleagues[24] found that 13 of 15 individuals with AN had unilateral temporal lobe hypoperfusion that persisted in the subjects studied after weight restoration. Kuruoglu and colleagues[25] studied two patients with AN with bilateral hypoperfusion in frontal, temporal, and parietal regions which normalized after 3 months of remission. Takano and colleagues[26] found hypoperfusion in the medial prefrontal cortex and anterior cingulate and hyperperfusion in the thalamus and amygdalohippocampal complex. In a study by Chowdhury and colleagues,[27] adolescent subjects with AN had unilateral temporo-parietal and frontal lobe hypoperfusion, and Rastam and colleagues[28] found temporo-parietal and orbitofrontal hypoperfusion in ill and recovered AN subjects. Fewer studies have assessed glucose metabolism using PET. Delvenne and colleagues[29-32] studied individuals with AN with frontal and parietal hypometabolism compared with controls, who normalized with weight gain.

Taken together, studies in the resting condition most frequently suggest alterations of the temporal, parietal or cingulate cortex during the ill state, and a few studies suggest persistent alterations in those areas after weight gain. This could be a potentially important finding given that the mesial temporal cortex is implicated in emotional processing and increased anxiety in AN could be related to altered amygdala function. However, studies have been generally small and need replication in AN subgroups, stratified by restricting and binge eating/purging type, in order to clarify the results.

### *Positron Emission Tomography, Single Photon Emission Computed Tomography, and Functional Magnetic Resonance Imaging Task-Activation Studies*

Functional imaging has been done in conjunction with paradigms and tasks that are meant to elicit areas of brain activation that might be specific for AN pathophysiology. Several different paradigms have been used. Eating custard cake showed increased brain activity in AN compared to controls using SPECT in frontal, occipital, parietal, and temporal areas.[33,34] Food imagination on SPECT showed that AN-B/P had greater right-sided parietal and prefrontal activation compared with controls and AN-R,[35] and Gordon and colleagues[36] found in AN that high calorie foods provoked anxiety and led to greater temporo-occipital activation when compared with low-calorie foods using PET. Ellison and colleagues,[37] using fMRI, also found that visual high calorie presentation elicited high anxiety in AN together with left mesial temporal as well as left insular and bilateral anterior cinculate cortex (ACC) activity. Those results could be consistent with anxiety provocation and related amygdala activation, which has been found in the past, and the notion that the emotional value of an experience is stored in the amygdala.[38]

Uher and colleagues[39] used pictures of food and non-food aversive emotional stimuli to assess ill and recovered AN subjects Food-stimulated medial prefrontal and ACC in both recovered and ill AN, but lateral prefrontal regions only in recovered AN. In controls, food was associated with occipital, basal ganglia, and lateral prefrontal activation. Aversive non-food stimuli activated occipital and dorsolateral prefrontal cortex in all three subject groups. In recovered AN patients, prefrontal cortex, ACC, and cerebellum were more highly activated compared with both controls and chronic AN after food. This suggested that higher ACC and medial prefrontal cortex activity in both ill and recovered AN subjects compared with controls may be a trait marker for AN. These are areas of executive function, decision-making, error monitoring, and reward expectancy. Such alterations could suggest heightened vigilance or processing activity in response to visual food stimuli.

Body image distortion is an integral part of AN pathophysiology. Studies[40] have been done confronting three AN subjects and three controls with their own digitally distorted body images using a computer-based video technique and fMRI. AN patients had greater activation in the brain stem, right amygdala, and fusiform gyrus, again suggesting anxiety related to the body experience that is reflected by amygdala activity. In a follow-up study in a larger and more homogenous sample using the same paradigm, Wagner and colleagues[41] found no amygdala activation but a hyper-responsiveness in brain areas belonging to the frontal visual system and the attention network (Brodman area 9)

as well as inferior parietal lobule (Brodman area 40), including the anterior part of the intraparietal sulcus. The latter areas are specifically involved in visuospatial processing. This finding makes the involvement of the brain anxiety circuit less clear but may suggest that perceptual alterations may be related to the neglect phenomenon.[42] In comparison, a study of a group of control women,[43] found left amygdala activation in relation to unpleasant body-related words, as well as contralateral parahippocampal activation that was negatively related to the Eating Disorders Inventory score. Thus, in young women, both controls and AN subjects may have somewhat similar anxiety reactions to their body images being distorted.

It is difficult to compare these studies, as the imaging modalities and tasks are not consistent and the groups of subjects are small. Still, it appears that temporal and cingulate activity are frequently different between AN and controls. Those regions are part of the emotion/anxiety processing network. Anxiety is a premorbid trait in AN, and a disturbance in those areas could reflect a biological trait related correlate. Parietal cortical areas also seem to repeatedly distinguish AN from controls. In comparison, OCD also showed ACC and temporo-parietal activation in different studies.[44] Future studies will need to determine whether there is a common neuronal network alteration in AN and OCD.

### *Receptor Imaging Studies*

Neurotransmitters, such as 5-HT and dopamine, are distributed throughout the brain via specific neuronal pathways. Their influence on behavior is believed to be via action on specific receptors that are located mostly post-synaptically but also for some receptor types pre-synaptically in, for example, the midbrain. Radioligands exist for several of the serotonin receptor types. One of the most commonly assessed receptor type is the 5-HT 2A ($5\text{-HT}_{2A}$) receptor, which is involved in the regulation of feeding, mood, and anxiety, and in antidepressant action.[45] Three studies[46-48] have assessed $5\text{-HT}_{2A}$ receptor binding in ill and recovered AN women. Ill subjects[46] showed reduced binding in the left frontal, bilateral parietal, and occipital cortex. Recovered AN-R[47] also had reduced $5\text{-HT}_{2A}$ binding, most strongly in mesial temporal and parietal cortical areas as well as in the cingulate cortex. In another study, women recovered from AN-B/P had reduced $5HT_{2A}$ binding relative to controls in the left subgenual cingulate, left parietal, and right occipital cortex.[48] In that study, $5HT_{2A}$ binding was positively related to harm avoidance and negatively to novelty seeking in cingulate and temporal regions, with negative relationships between $5HT_{2A}$ binding and drive for thinness.

Those findings further highlight the possibility of disturbances of the ACC and mesial temporal cortex in AN. Since these disturbances persist after recovery, it is possible they are trait disturbances. The ACC receives afferents from the amygdala and has direct projections to the premotor frontal cortex and other limbic regions. It plays a crucial role in initiation, motivation, and goal-directed behaviors[49] as well as reward.[50] The amygdala mediate the interpretation of fear and the representation of emotional stimuli values.[38] One could state the hypothesis that AN patients have disturbed processing of emotional stimuli valence, resulting in poor flexibility in reevaluating actual danger of those stimuli and reduced adaptation to new situations. Future studies will need to determine whether relationships between $5HT_{2A}$ receptor activity and measures for anxiety, such as harm avoidance, can be replicated. This could be an exciting avenue for the link of neurochemistry and behavior.

## *BULIMIA NERVOSA*

BN is characterized by recurrent binge eating followed by behaviors to counteract weight gain, such as self-induced vomiting. Individuals with BN, usually at normal weight, present with a fear of gaining weight and food and body weight-related preoccupations. BN is usually associated with increased depressive and anxious feelings. Impulsive behaviors as well as cluster B behaviors are frequent.[4]

### *Computed Tomography and Magnetic Resonance Imaging Studies*

Only a few structural studies have been performed in BN. Pituitary abnormalities have been suggested,[51] as well as cerebral atrophy[52,53] and ventricular enlargement.[54-56] No conclusions on etiology or impact of those structural lesions could have been drawn yet[52] since those measures may be short-term dependent on nutritional intake.[57]

### *Magnetic Resonance Spectroscopy Studies*

A mixed group of AN and BN subjects had reduced prefrontal myo-inositol and lipid compounds[22,58] compared with controls. However, it is unclear whether those findings were specific to either AN or BN or were related to both.

### *Positron Emission Tomography and Single Photon Emission Computed Tomography Studies: Resting Condition*

Similar to findings in AN, rCGM in the resting state was reduced globally in BN compared with controls, with significantly reduced rCGM in the parietal cortex using PET.[59] Interestingly, depressive symptoms in a bulimic group correlated with rCGM in the left anterolateral prefrontal cortex in one study.[60] This finding has not been replicated. Another study[61] investigated brain activity in BN versus depressed subjects and found that BN patients had reduced right frontal activation compared with controls and depressed subjects, but depressed subjects had reduced basal ganglia activity supporting different pathophysiology for BN and depression. In nine recovered (mean: 57 months) BN subjects[62] rCBF was similar compared with 12 controls but correlated negatively with length of recovery, which could reflect either a scarring effect or possibly a return to permorbid lower rCBF. A follow up study will need to clarify this finding.

It therefore appears that rCBF and rCGM alterations during the ill state remit with recovery, although pre- or post-illness alterations cannot be excluded based on the available data. Furthermore, BN and depression may be distinguished by different patterns of brain activity, which is important considering the frequent overlap in depressive symptoms.

### *Task-Activation Studies*

Nozoe and colleagues[34] found that BN patients had greater right inferior frontal and left temporal blood flow compared with controls before, but similar activity after a meal. BN subjects have increased liking for sweet stimuli compared with controls[63] and, therefore, may have altered processing of taste stimuli. A fMRI study by Frank and colleagues[64] using a glucose challenge, found in recovered BN subjects (seven BN, three AN-B/P) reduced ACC activity compared with six controls. The ACC is an cuneus area that is involved in error monitoring but also in the anticipation of reward.[50] In this paradigm, where subjects knew which taste stimulus to expect, higher activity in controls could suggest higher reward expectation by controls than anticipated by BN-type subjects.

### *Receptor Imaging Studies*

5-HT receptor alterations may have specific implications on behavior. Kaye and colleagues[65] found reduced orbitofrontal 5-$HT_{2A}$ receptor binding in recovered BN subjects. Orbitofrontal alterations could reflect behavioral disturbances in BN that include impulsiveness and altered emotional processing[66] Altered orbitofrontal activity as found in borderline personality disorder[67] could indicate a common area for impulse control disturbance. In addition, women with BN failed to show common correlations of age and 5-$HT_{2A}$ binding. This finding raises the possibility that women with BN may have alterations of developmental mechanisms of the 5-HT system. Another study[68] reported on reduced 5-HT transporter binding in thalamus and hypothalamus in ill BN subjects. The 5-HT system has consistently been shown to be disturbed in EDs, and reduced 5-HT transporter when ill may be related to altered brain 5HT function, such as reduced 5-HT activity during the ill state.[69] Reduced 5-$HT_{2A}$ activity after recovery could reflect a trait disturbance involved in alterations of mood, anxiety, and impulse control. Most recently, increased 5-$HT_{1A}$ recptor binding was found by Tiihonen and colleagues[70] using PET in BN subjects in all studied brain regions, but most prominently in prefrontal, cingulate and a parietal cortex area. Central 5-HT function is reduced in BN and increased 5-$HT_{1A}$ receptor binding could be a negative-feedback up-regulation. Higher 5-$HT_{1A}$ binding could also be related to the well-known phenomenon that BN patients require higher doses of selective serotonin reuptake inhibitors compared with, for example, to patients being treated for depression. Those 5-HT receptor alterations and their implications on treatment will have to be further studied and the findings replicated.

## *BINGE EATING DISORDER*

BED is a proposed diagnostic category.[4] BED is characterized by BN-like symptoms, except that no compensatory measures are used. Very little is known about brain activity in BED. Karhunen and colleagues[71] found that there may be a lateralization of blood flow in BED, with higher activity in the left hemisphere compared with the right in response to visual food presentation. Also, there was a linear correlation of hunger with left frontal/prefrontal cortical activity. The same group found reduced 5-HT transporter binding[72] in the midbrain, that improved with fluoxetine and group psychotherapy,[73] suggesting, at least in part, state-dependent serotonergic alterations.

## *CONCLUSION*

Until recently, the assessment of psychiatric disorders has relied on subjective reports from patients, and biologic research has been limited

TABLE. **FUNCTIONAL BRAIN IMAGING STUDIES IN ANOREXIA NERVOSA AND BULIMIA NERVOSA**

| Authors | Year | Method | Activation | ILL | REC | N | Frontal cortex | left | right |
|---|---|---|---|---|---|---|---|---|---|
| | AN "resting"studies | | | | | | | | |
| Delvenne et al[29] | 1995 | PET FDG | | AN-R, AN-B/P | | 20 | ▼ | | |
| Nozoe et al[34] | 1995 | SPECT | | AN* | | 8 | nl | | |
| Gordon et al[24] | 1997 | SPECT | | AN* | | 15 | | | |
| Kuruoglu et al[25] | 1998 | SPECT | | AN-B/P | | 2 | | ▼ | ▼ |
| Takano et al[26] | 2001 | SPECT | | AN-R, AN-B/P | | 14 | | ▼ | ▼ |
| Rastam et al[28] | 2001 | SPECT | | AN-R, AN-B/P | AN-R, AN-B/P | 21 | | ▼ | ▼ |
| Chowdhury et al[27] | 2003 | SPECT | | AN* | | 15 | | ▼ (2 of 3) | ▼ (1 of 3) |
| Audenaert et al[46] | 2003 | SPECT 5-$HT_{2A}$ | | AN* | | 15 | | ▼ | nl |
| Frank et al[47] | 2002 | PET 5-$HT_{2A}$ | | | AN-R | 16 | nl | | |
| Bailer et al[64] | 2004 | PET 5-$HT_{2A}$ | | | AN-B/P | 10 | nl | | |
| | AN "activation" studies | | | | | | | | |
| Nozoe et al[34] | 1995 | SPECT | Eating food | AN* | | 8 | nl | | |
| Naruo et al[35] | 2000 | SPECT | Food images | AN-R | | 7 | nl | | |
| Naruo et al[35] | 2000 | SPECT | Food images | AN-B/P | | 7 | | nl | ▲ |
| Gordon et al[36] | 2001 | PET rCBF | Food images | AN* | | 8 | nl | | |
| Ellison et al[37] | 1998 | fMRI | Food images | AN* | | 6 | nl | | |
| Seeger et al[40] | 2002 | fMRI | Body image | AN* | | 3 | nl | | |
| Wagner et al[41] | 2003 | fMRI | Body image | AN-R | | 15 | | ▲ | ▲ |
| Uher et al[39] | 2003 | fMRI | Food images | AN-R | AN-R | | ▲ | | |
| | BN "resting" studies | | | | | | | | |
| Hagman et al[61] | 1990 | PET FDG | | BN | | 8 | | ▲ | ▼ |
| Andreason et al[60] | 1992 | PET FDG | | BN | | 11 | | nl | ▼ |
| Delvenne et al[31] | 1997 | PET FDG | | BN | | 11 | nl | | |
| Nozoe et al[34] | 1995 | SPECT | | BN | | 5 | | nl | ▲ |
| Frank et al[62] | 2000 | PET | | | BN | 9 | nl | | |
| Tauscher et al[68] | 2001 | SPECT 5-HTT | | BN | | 10 | | | |
| Kaye et al[65] | 2001 | PET 5-$HT_{2A}$ | | | BN | 9 | ▼ | | |
| Tiihonen et al | 2004 | PET 5-$HT_{1A}$ | | BN | | 8 | ▲ | | |
| | BN "activation" studies | | | | | | | | |
| Frank et al[64] | 2004 | fMRI | Sweet taste | | BN | | | | |

ILL=illness; REC=recovered; AN=anoxeria nervosa; PET=positron emission tomography; FDG=fluoro-deoxyglucose; AN-R=anorexia nervosa, bingeing/purging type; SPECT=single photon emission computed tomography; ▲=increased compared with controls; $5HT_{2A}$=serotonin transporter; 5-$HT_{1A}$= serotonin receptor 1A.

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| Temporal/ amygdala | left | right | Cingulate cortex | left | right | Parietal cortex | left | right | Occipital cortex | left | right |
|---|---|---|---|---|---|---|---|---|---|---|---|
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| ▼ | | | | | | ▼ | | | | | |
| nl | | | | | | | ▼ | nl | nl | | |
| | ▼ (8 of 13 ) | ▼ (5 of 13) | | | | nl | | | | | |
| | ▼ | ▼ | | | | | ▼ | ▼ | | | |
| | ▲ | ▲ | | ▼ | ▼ | nl | | | nl | | |
| | ▼ | ▼ | | | | | ▼ | ▼ | | ▼ | ▼ |
| | ▼ (7 of 9) | ▼ (2 of 9) | | | | | ▼ (4 of 5) | ▼ (1 of 5) | | | |
| nl | | | | | | | ▼ | ▼ | | ▼ | ▼ |
| | ▼ | ▼ | | ▼ | ▼ | nl | | | | ▼ | ▼ |
| nl | | | | ▼ | nl | | ▼ | nl | | nl | ▼ |
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restricting type; ▼=decreased compared with controls; AN*=diagnostic subgroup not specified; nl=normal; AN-B/P=anorexia nervosa, receptor 2A; BN=bulimia nervosa; rCBF=regional cerebral blood flow. fMRI=functional magnetic resonance imaging; 5-HTT=serotonin

by the inaccessibility of the living human brain. The emergence of brain imaging techniques raises the possibility to assess brain function in vivo and assess human behavior in conjunction with biological correlates. The eating disorders AN and BN are relatively homogeneous disorders. The new imaging methods give hope to the prospect of identifying biologic markers that will help categorize those disorders and, in turn, identify more effective treatments that could reduce morbidity associated with these frequently debilitating and deadly illnesses.

Studying EDs is complicated due to a relatively small prevalence and the many state related (eg, hormonal) disturbances associated with these illnesses. Thus, it is difficult to assess factors that may be trait related and possibly pre-morbid. Studying subjects after long-term recovery may be our closest approximation to studying subjects premorbidly.

The most common structural abnormalities found in ill AN woman are global reduction of gray matter and white matter in ill AN patients, which remit at least in part with recovery. Ill BN patients may have similar changes. Studies[74] in depression found more specific regional volume changes but we are not aware of similar changes with recovery in other disorders. It is possible that the explanation for reduction in brain mass when ill may be brain protein, fat, or fluid loss secondary to emaciation and dehydration. However, since some ED studies found relationships of brain volume with cortisol levels and cortisol related to brain cell death,[75] it has to be assessed if hypercortisolism in ill AN patients is truly contributing to those findings.

Resting rCBF and rCGM showed mostly a general reduced cortical activity in the ill state that is most pronounced in temporal, parietal, or cingulate cortex. Very limited data suggest some persistence of these finding after recovery in both AN and BN. Whether these findings indicate involvement of the limbic system or are state- or trait-related or some complex combination of both remains unknown. Relatively few subjects have been studied, and there is a fair amount of inconsistencies among studies in terms of subject subgroups, state of illness, and other factors.

fMRI studies using visual stimuli of food or body image in AN suggested involvement of prefrontal, ACC, and parietal cortex. The only study in BN suggests altered ACC and cuneus activity in response to a sweet taste stimulus. This finding suggests that the decision-making network and that reward pathways may be differently activated in those tasks in BN. However, those studies have to be replicated. It is still unclear if ED subjects react differently to visual compared with oral high calorie stimuli, and if there are distinct alterations in the processing of taste stimuli, for example, for sweets compared with fats.

The receptor imaging studies that are available at this point show that reduced 5-$HT_{2A}$ receptor binding occurs in the ill state and persists after recovery from AN. BN subjects showed reduced 5-$HT_{2A}$ receptor activity when recovered and reduced 5-HT transporter binding when ill. They may have increased 5-$HT_{1A}$ receptor binding during the ill state. Such findings of 5-HT disturbances in ill and recovered subjects with EDs, may suggest a trait disturbance of the 5-HT system. Altered 5-HT receptor activity could be related to emotional disturbances such as increased depressive symptoms or anxiety.

Few studies have been done in EDs in comparison with depressive disorders or OCD. The overlap and comorbidity of both major depression and OCD with EDs require studies that will directly compare those disorders. EDs and, in particular, AN, are frequently debilitating with a high mortality. Studies comparing psychiatric disorders will help to find common pathways and distinct areas of disturbance that may identify targets for successful drug interventions. CNS

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