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23

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Contents

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Abstract

Medical imaging techniques like PET and SPECT have been applied for investigation of brain function in anorexia and bulimia nervosa. Regional abnormalities have been detected in cerebral blood flow, glucose metabolism, the availability of several neurotransmitter receptors (serotonin 1A and 2A, dopamine D2/D3, histamine H1, mu-opioid, GABA(A)-benzodiazepine, and cannabinoid CB1), stimulant-induced dopamine release, presynaptic FDOPA influx, and the density of serotonin transporters. Different subtypes of eating disorders appear to be associated with specific functional changes. It is hard to judge whether such changes are a consequence of chronic dietary restrictions or are caused by a putative anorexia (or bulimia) nervosa endophenotype. Many abnormalities (particularly those of glucose metabolism) appear to be reversible after restoration of weight or normal patterns of food intake and may represent consequences of purging or starvation. However, some changes of regional flow and neurotransmitter systems persist even after successful therapy which suggests that these reflect traits that are independent of the state of the illness. Changes of the serotonergic system (altered activity of 5-HT_{1A} and 5-HT_{2A} receptors and 5-HT transporters) may contribute to dysregulation of appetite, mood, and impulse control in eating disorders and may represent a trait which predisposes to the development of anxiety, obsessionality, and behavioral inhibition. Assessment of functional changes in the brain with PET or SPECT may have prognostic value and predict neuropsychological status after several years of therapy.

23.1 Introduction

Anorexia nervosa (AN, literally nervous inability to eat) is a psychiatric disorder with four important diagnostic features:

1. An unrealistic but intense fear of weight gain.
2. A conspicuous distortion of body image. Even though serious underweight is present, the patient feels fat and is obsessed with becoming thinner.
3. A body weight smaller than 85% of the value expected for the individual's height and age or—in the case of children—a failure to gain weight with increasing age. Food intake is limited so much that health is compromised—in some cases to the point of death.
4. Amenorrhea (females missing at least three subsequent menstrual periods after menstruation has been established) or a delayed puberty (the first menstruation occurring at an exceptionally advanced age) (American Psychiatric Association 2000). This last criterion was removed in DSM-5.

Two major subtypes of anorexia have been distinguished. Restrictive anorexics rigorously limit their food intake. They may also exercise excessively or abuse drugs which promote weight loss, but they never engage in binge eating. Purge-type

anorexics show repeated cycles of binge eating and purging. For short periods of time (usually less than 2 h), they eat excessively large amounts of food. Subsequently, they initiate a purging process which may involve heavy exercise, self-induced vomiting, and misuse of laxatives (or enemas) and diuretics.

Most subjects with anorexia nervosa are women (>90%). The onset of the disorder is usually either at adolescent age (13–18 years) or at midlife (age 40–50 years).

Bulimia nervosa (BN, literally nervous extreme hunger) shares many characteristics with purge-type anorexia (Russell 1979). However, bulimic individuals are typically at normal or high normal weight, in contrast to anorexics which are emaciated. In order to be characterized as bulimics, subjects should engage in cycles of binge eating and purging at least two times per week for a period of at least 3 months. During episodes of binge eating, they consume excessive amounts of calories, up to four times as much as healthy volunteers, but during non-binge meals, they eat significantly less than controls (Heaner and Walsh 2013). In DSM-5, the threshold for the diagnosis of BN has been lowered, so that once-a-week binge eating and purging is sufficient to be diagnosed as a bulimic.

Both eating disorders are considered as a serious public health problem in Western societies. Self-imposed food restriction may lead to health complications, such as growth retardation, dental problems, constipation, stomach rupture, anemia, congestive heart failure, kidney failure, electrolyte imbalance, and osteoporosis. Repeated purging can result in heartburn (a burning feeling in the chest because of acid entry in the esophagus), esophageal inflammation, damage to tooth enamel, and acid-related scarring of the fingers. Most anorexics (and bulimics) experience depression and anxiety. Anorexia has one of the highest mortality rates of any psychiatric disorder (estimated as at least 5%) (Roux et al. 2013).

Binge eating disorder (BED) resembles BN in many respects, but is not associated with purging. Thus, individuals with BED display loss of control, repetitive binge eating episodes, and marked distress concerning binge eating (de Zwaan et al. 1993). However, the definition of precise criteria to identify BED as a psychiatric syndrome has remained difficult (Williamson and Martin 1999; Cooper and Fairburn 2003; Klein et al. 2016).

Medical imaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) can provide insights into the physiological and biochemical alterations of the human brain that are associated with eating disorders. Because of the aim of this book series, the current chapter is focused on observations made with PET and SPECT. Comprehensive reviews on imaging findings in AN and BN were published in recent years (Donnelly et al. 2018; Bargiacchi 2014; Phillipou et al. 2014; Frank 2012; Frank and Kaye 2012; Jauregui-Lobera 2011; Kaye 2008).

23.2 Anorexia and Brain Perfusion

Several SPECT studies have focused on abnormalities of cerebral perfusion in anorexia nervosa. The initial study of this kind was already performed in 1989. Regional cerebral blood flow (rCBF) was measured in the resting state using a ^{133}Xe

inhalation method. The study population consisted of 12 female patients (age 16–27) and a healthy control group (age 19–37 years, 5 females and 7 males). The patients were examined both at the time of admission and after a period of treatment and weight gain. No significant differences between patients and controls (or between the two patient scans) were observed (Krieg et al. 1989). It should be noted that the average age of the control group was 10 years higher than the patient group; moreover, the control group was not sex matched.

A subsequent study measured the flow response to a food stimulus (eating of a custard cake). The hypothesis of this paradigm is that rCBF in certain cortical areas will increase after presentation of the stimulus, and the magnitude or regional extent of that increase may be different in patients and healthy controls. The study population consisted of seven female AN patients (age 19 ± 5 years) and five gender- and age-matched healthy subjects. Cerebral blood flow was measured with the tracer ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO), before and after presentation of the stimulus, both at the time of admission and after 2–3 months of therapy. Before therapy, anorexics demonstrated a significant 7–9% increase in rCBF in the inferior frontal cortex in response to the food stimulus. After therapy, the response was no longer observed, and it was also absent in the control group (Nozoe et al. 1993). The study data can be interpreted as evidence for activation of the arousal system in untreated patients (who, in contrast to normal subjects, felt discomfort while eating the cake).

A later study examined the regional pattern of cerebral perfusion (^{99m}Tc-HMPAO-SPECT) in two female anorexia patients at the time of diagnosis and after remission of symptoms, which involved more than 1 year of therapy. Diffuse, bilateral hypoperfusion was observed during the first SPECT scan in frontal, parietal, and frontotemporal areas, particularly in the left hemisphere. After symptom remission, the pattern of rCBF became normal (Kuruoglu et al. 1998). Thus, there seems to be state-related hypoperfusion in AN. A Swedish study (Rastam et al. 2001) compared ^{99m}Tc-HMPAO-SPECT scans in 21 patients with adolescent-onset AN (19 females, 2 males, mean age 22 years) to similar scans in a very young patient group without neuropsychiatric disorder who underwent SPECT for cardiovascular or oncologic indications (5 females, 4 males, age 10 years). Anorexic patients showed reduced perfusion in temporal, parietal, occipital, and orbitofrontal lobes compared to the control group. This finding was suggestive of AN-related hypoperfusion, although some of the flow changes could also be related to the age difference between the study groups. This study also showed reduced cerebral blood flow (to 66%) in temporal and associated areas, with no correlation with body mass index, residual eating disorder psychopathology, or intelligence quotient.

In a more extended activation study, ^{99m}Tc-HMPAO-SPECT was used to measure changes of rCBF in seven female patients with purely restrictive anorexia, seven female AN patients with habitual binge/purge behavior, and seven age-matched, healthy female volunteers. The stimulus consisted of visualizing a custard cake followed by imagining its eating. Binge/purge anorexics showed significant increases of flow in the inferior, superior, prefrontal, and parietal regions of the right hemisphere, in contrast to purely restrictive anorexics or healthy volunteers (Naruo et al.

2000). This observation may indicate that the perception of food is different in binge/purge anorexics, resulting in greater anxiety in this patient group. Indeed, binge/purge anorexics scored higher levels of apprehension in regard to food intake than either restrictive anorexics or healthy controls.

Using ^{99m}Tc-HMPAO-SPECT and statistical parametric mapping (SPM) analysis, a follow-up study (Naruo et al. 2001) examined cerebral perfusion patterns during the resting state in the same three subject groups as were mentioned above. Restrictive anorexics showed a significantly reduced rCBF in frontal areas (especially the anterior cingulate cortex), which was not noticed in binge/purge anorexics or healthy volunteers. Since the anterior cingulate cortex is involved in mood regulation, attention control, and the cognitive process of selection following somatosensory stimuli, reduced blood flow in this area may be related to disturbances of perception and emotional control in patients with restrictive anorexia. Similar findings were reported in a study which employed SPM, ^{123}I-iodoamphetamine (^{123}I-IMP), and SPECT to examine rCBF in eight restrictive anorexics, six binge/purge anorexics, and eight healthy controls (all female). Anorexics showed hypoperfusion in the medial prefrontal cortex and the anterior cingulate gyrus. In addition, they demonstrated increased perfusion in the thalamus, amygdala, and hippocampus (Takano et al. 2001). In a rather recent ^{99m}Tc-HMPAO study, involving 13 restrictive anorexics, 13 binge/purge anorexics, and a healthy control group (10 women), bilaterally decreased perfusion was noted during the resting state in the patients, but no significant differences were observed between the patient groups (Yonezawa et al. 2008).

Activation studies measuring, directly or indirectly, cerebral blood flow have shown changes in certain areas of the brain. When patients with anorexia nervosa are exposed to food and examined with functional MRI, SPECT, or PET, an activation was noted in the insula, orbitofrontal cortex, prefrontal cortex, anterior cingulate, and temporal lobes (Nozoe et al. 1993; Uher et al. 2004). An activation study with the tracer ^{15}O-CO_2, positron emission tomography (PET), and SPM analysis examined rCBF during exposure to three types of visual stimuli: high-calorie foods, low-calorie foods, and nonfood items. A group of eight female patients with anorexia nervosa was compared to eight healthy female control subjects. When high-calorie foods were presented, control subjects reported a significant desire to eat, whereas patients reported anxiety. The patient group showed bilateral elevations of rCBF in the medial temporal lobe compared to the control group. In the left occipital cortex and right temporo-occipital cortex of the patient group, high-calorie food induced greater increases of rCBF than the low-calorie stimulus. These findings resemble results obtained in patients with psychotic disorders, in the sense that food phobia appears to be associated with exaggerated responses in the visual association cortex (Gordon et al. 2001).

Three studies employed ^{99m}Tc-HMPAO and SPECT to examine rCBF in anorexic children. More than half of the patients showed a left temporal lobe hypoperfusion, which did not disappear after regaining normal weight (Gordon et al. 1997). This might reflect primary functional changes related to the disorder rather than brain starvation. In the second study (Chowdhury et al. 2003), asymmetric hypoperfusion

was sometimes also noticed in the parietal lobe, frontal lobe, thalamus, and caudate nuclei. Patients with a deficit of perfusion had higher median Eating Disorders Examination subscale scores than those without. Temporal lobe asymmetry may thus reflect a neurologic abnormality that contributes to the development of anorexia. In the third study, 75% of the patients with early-onset AN were found to show a unilateral reduction of blood flow in the temporal lobe. This reduction was not associated with nutritional status, length of illness, and mood or eating disorder psychopathology, but significantly associated with impaired visuospatial ability, impaired complex visual memory, and enhanced speed of information processing in the patient group (Lask et al. 2005).

A later ^{99m}Tc-HMPAO-SPECT study examined changes in resting rCBF before and after weight gain in 12 female patients with restrictive anorexia nervosa (age 18.6 ± 3.5 years). A control group of 11 normal females (age 21.8 ± 2.1 years) was also included. At the time of the first scan, the patients had lower rCBF in the bilateral anterior lobes, right parietal lobe, insula, and occipital lobes. After weight gain, flow in the right parietal lobe was increased, but reduced flow in the anterior cingulate cortex persisted. Lower body mass index in the patient group was associated with lower rCBF in the occipital lobes. Apparently, rCBF in some brain areas of anorexic individuals normalizes after weight gain. Decreases of flow in these areas may thus be state-related. However, rCBF in the anterior cingulate cortex appears unaffected by treatment and may reflect abnormal brain function related to the clinical features of restrictive anorexia (Kojima et al. 2005). This should be considered as a tentative conclusion, since the recovery of body weight by the patients after treatment was far from complete. Another study which employed ^{123}I-IMP SPECT to assess rCBF in anorexic patients reported increases of flow after inpatient-behavioral therapy in several brain areas, including the anterior cingulate cortex (Matsumoto et al. 2006). However, this study was limited by the small size (n = 8) and heterogeneous character of the patient group, three patients being restrictive and the other five binge/purge anorexics. A third SPECT study of this kind was performed in ten young girls (average age 13 years) with anorexia nervosa. Because of the young age of the patient group, a similar group of healthy controls could not be included for ethical reasons. Relative increases of rCBF during recovery were observed in the bilateral parietal lobe and limbic lobe including the posterior cingulate cortex. Flow changes in the last area could reflect affective changes related to eating motivation after successful therapy (Komatsu et al. 2010). Another ^{99m}Tc-HMPAO-SPECT study involved nine patients with early-onset AN (at age lower than 15 years) who were scanned again after 4.2 years of treatment. Seven out of these nine patients showed reductions of cerebral blood flow which persisted even after long-term therapy, particularly in the medial temporal region. Thus, this study suggested that in a substantial number of cases, rCBF does not return to normal after weight restoration (Frampton et al. 2011).

The Stroop interference task (SIT) is a popular neuropsychological test examining the ability of a subject to correctly process information in the presence of interfering stimuli. An interesting SPECT study using ^{99m}Tc-ethyl cysteinate dimer

(ECD) compared brain perfusion in the resting state with scores in the SIT test in 16 patients with anorexia nervosa (11 restrictive, 5 binge/purge individuals). Four patients scored abnormally low in the neuropsychological test, and within the entire group, a significant correlation was observed between the SIT score and rCBF in the superior frontal gyrus of both hemispheres. These findings can be interpreted as evidence for impaired error detection and immediate correction in anorexic individuals (Ferro et al. 2005).

A final ^{99m}Tc-HMPAO-SPECT study examined whether rCBF at initial presentation predicts neuropsychological status after 4 years of therapy. The study group consisted of 15 children with early-onset anorexia nervosa and 15 healthy controls. Some patients with early-onset anorexia nervosa appeared to have no measurable perfusion abnormalities. Patients with hypoperfusion in the SPECT scan showed significantly lower scores for delayed visual recall and higher scores for verbal inhibition than healthy controls after 4 years. However, patients with normal perfusion in the SPECT scan showed similar scores as controls for delayed visual recall, visual object recognition, verbal fluency, cognitive inhibition, switching, planning, and verbal inhibition in all neuropsychological tests after 4 years, even though some of them suffered from a persistent eating disorder. Thus, rCBF at initial presentation seems to predict neuropsychological status at 4-year follow-up (Frampton et al. 2012).

An interesting arterial spin labeling MRI study investigated whether former AN patients (21 women remitted from restricting-type AN, age 24 ± 2 years) and healthy female control subjects (n = 16, age 27 ± 2 years) showed a different response of cerebral blood flow to hunger and satiety. All subjects were scanned after a 16-h period of fasting and just after eating a meal. In three brain regions (right ventral striatum, right subgenual anterior cingulate cortex, and left posterior insula), the former AN patients demonstrated a significantly different flow response to hunger than the control group. Whereas healthy subjects showed an increased flow in the hungry compared to the fed condition, former AN patients had decreased flow when hungry compared to being fed. Decreased flow in the left insula was associated with higher self-report assessments of hunger on the fasting day in the former patient group (Wierenga et al. 2017). This study indicated that even after successful treatment, women remitted from AN have aberrant blood flow changes in homeostatic neural circuits in response to hunger.

In conclusion, most studies suggest that AN is associated with hypoperfusion in several brain areas (Table 23.1). Blood flow may normalize in most regions after successful therapy but remain low in others, particularly the anterior cingulate cortex. A subgroup of patients appears to display a normal pattern of regional blood flow even prior to therapy. Reductions of flow in early-onset anorexia may be predictive of persisting neuropsychological problems at adolescent age. An extensive review of functional neuroimaging in anorexia nervosa (SPECT, PET, and fMRI) was published in 2009 (van Kuyck et al. 2009).

It should be noted that intracranial tumors may masquerade as early-onset anorexia nervosa. Such tumors can be detected using SPECT, PET, or other medical imaging techniques (O'Brien et al. 2001).

Table 23.1 Studies of rCBF in the resting state

Study groups	Study moment	Tracer	Findings	After therapy	Reference
AN, control	Pre-/post-therapy	^{133}Xe	No difference	No difference	Krieg et al. (1989)
AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ fro, par, frotem (bilateral)	Normalization	Kuruoglu et al. (1998)
AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ tem, par, occ, orbfro	–	Rastam et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ fro (acc) in R-AN only	–	Naruo et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{123}I-IMP	↓ acc, mpc ↑ th, am, hip	–	Takano et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ bilaterally (R-AN, BP-AN)	–	Yonezawa et al. (2008)
AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ left tem	Persisting	Gordon et al. (1997)
AN	Only 1 session	^{99m}Tc-HMPAO	↓ left tem a.o.	–	Chowdhury et al. (2003)
AN	Only 1 session	^{99m}Tc-HMPAO	↓ left tem lobe	–	Lask et al. (2005)
R-AN, control	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ ant, right par, ins, occ	Persisting in acc	Kojima et al. (2005)
AN	Pre-/post-therapy	^{123}I-IMP	↓ many brain areas	Normalization	Matsumoto et al. (2006)
AN	Pre-/post-therapy	^{123}I-IMP	↓ many brain areas	Normalization	Komatsu et al. (2010)
Early-onset AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ many brain areas	Persisting (med tem)	Frampton et al. (2011)
R-AN, BP-AN	SIT test	^{99m}Tc-ECD	↓ sup fro gyrus = ↓ test score	–	Ferro et al. (2005)
Early-onset AN, control	Only 1 scan session	^{99m}Tc-HMPAO	↓ only in some patients	Lower test scores	Frampton et al. (2012)
R-AN, control	Post-therapy, hungry vs fed	None (MRI)	↓ when hungry, controls ↑ when hungry (compared to fed)	–	Wierenga et al. (2017)
BN, AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ AN left par, ↑ BN left tem a.o.	–	Nozoe et al. (1995)
BN (1 subject)	No therapy	^{123}I-IMP	↑ in binge than in purge phase; asymmetry only in purge phase	–	Hirano et al. (1999)

Table 23.1 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
BN, control	Post-therapy	^{15}O-Water	No differences any more	Normalization (from ↑ in ctx and left th)	Frank et al. (2000)
BN, BP-AN, R-AN, control	Post-therapy	^{15}O-Water	No differences any more	Normalization (from ↑ in BN and ↓ in AN)	Frank et al. (2007)
BN, BP-AN, R-AN	Only 1 session	^{99m}Tc-ECD	Perfusion covaries only with body dissatisfaction/ ineffectiveness	–	Goethals et al. (2007a)

acc anterior cingulate cortex, *am* amygdala, *AN* anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *ctx* cortex, *ECD* ethyl cysteinate dimer, *fro* frontal, *frotem* frontotemporal, *gyr* gyrus, *hip* hippocampus, *HMPAO* hexamethylpropylene amine oxime, *IMP* iodoamphetamine, *ins* insula, *med* medial, *mpc* medial parietal cortex, *occ* occipital, *orbfro* orbitofrontal, *par* parietal, *R-AN* restrictive type of anorexia nervosa, *sup* superior, *tem* temporal, *th* thalamus

23.3 Bulimia and Brain Perfusion

An initial ^{99m}Tc-HMPAO-SPECT study in bulimia nervosa compared rCBF in five patients with bulimia (age 21.0 ± 2.9 years), eight patients with anorexia (age 24.1 ± 7.8 years), and nine healthy controls (age 20.3 ± 1.0 years). Blood flow was measured before and after eating a custard cake. Flow was expressed as ratio units, by comparing tracer uptake in a brain region to uptake in the cerebellum. Differences between the groups were observed only during the first scan. Whereas anorexics showed *reduced* flow in the left parietal region, bulimics demonstrated significantly *increased* flow in the bilateral inferior frontal and left temporal regions compared to the control group. Flow increases were noted in anorexics, and flow decreases in bulimics after eating; thus, any differences between the groups were abolished by the food stimulus (Nozoe et al. 1995). Since the frontal cortical area of the brain controls feeding together with the hypothalamus, flow differences in frontal regions may reflect disease-related differences in cortical function. Frontal lobe damage can result in hyperphagia; thus, dysfunction of this brain area could be related to binge eating in bulimics.

A case report examined rCBF in a male patient with bulimia nervosa (age 27 years), first during a period of purging and, 22 days later, during binge eating, using ^{123}I-IMP and SPECT. Global CBF was higher during the binge eating phase than during the purge phase. In the purge phase, an asymmetric pattern was noted, with lower values for rCBF in the right temporal, parietal, and occipital lobe. This asymmetry disappeared during binge eating. Thus, rCBF differs between the two phases of bulimia nervosa, and flow asymmetry is dependent on the eating state (Hirano et al. 1999).

A subsequent study examined rCBF in nine women with bulimia nervosa who had recovered from their disorder by showing stable food intake, normal weight, and regular menses for a period of more than 1 year. rCBF was measured with the tracer [^{15}O]water and PET, and flow patterns were compared to those of an age-matched healthy control group (13 females). Significant differences between the groups were not observed, but rCBF in several cortical areas and the left thalamus was significantly and inversely related to length of recovery in the patient group (Frank et al. 2000). Apparently, differences in rCBF between bulimics and controls are state-related and disappear during recovery.

A later [^{15}O] water PET study compared rCBF in 10 women who had recovered from restrictive anorexia, 8 women who had recovered from binge/purge anorexia, 9 women who had recovered from bulimia, and 18 healthy control subjects. Partial volume-corrected rCBF values in the four groups were not significantly different in any brain region. Thus, rCBF appears to normalize after recovery not only in bulimics but also in subjects with anorexia nervosa (Frank et al. 2007).

An interesting PET study with ^{15}O-water has suggested a vagal pathophysiology for bulimia nervosa and the accompanying depressive symptoms. Mechanical distention of the stomach with a balloon in female healthy volunteers and the associated vagal stimulation was shown to result in activation of several brain areas, including areas which are involved in the emotional aspects of eating (lateral inferior frontal and orbitofrontal cortex) and in the symptoms of depression (anterior cingulate cortex). The hypothesis that vagal afferent activity is involved in the cycles of binge eating and vomiting in bulimia nervosa with their associated symptoms of depression was subsequently tested in two ways: first, pain detection thresholds were examined in patients with BN and were found to fluctuate in association with bulimic episodes, suggesting fluctuation of vagal activity. A double-blind treatment protocol of bulimic individuals was then carried out with the serotonin 5-HT$_3$ antagonist ondansetron. This treatment significantly decreased binge eating and vomiting in BN patients, abolished the fluctuation in pain thresholds, and reduced the depressive symptoms. These findings were interpreted as evidence for the hypothesis that cyclic increases in vagal activity drive the urge to binge eat and vomit (Faris et al. 2006).

A large ^{99m}Tc-ECD SPECT study examined rCBF in 67 female patients with eating disorders (31 restrictive anorexics, 16 binge/purge anorexics, and 20 bulimics). SPM analysis was applied to the SPECT data, and brain areas were identified in which perfusion covaried with symptoms measured by the Eating Disorder Inventory. The only significant correlation observed was a positive correlation between scores on body dissatisfaction and ineffectiveness and rCBF in the prefrontal and parietal cortex (Goethals et al. 2007a). Based on this finding, the authors argued that neurobiological findings in eating disorders, such as changes in the serotonergic system, may reflect not only emotional and behavioral factors (e.g., decreased impulse control) but also cognitive-evaluative features: attention, memory, and judgment being continuously affected by an overconcern with eating, body size, and shape.

This hypothesis was explored in a later study in which rCBF was measured with ^{99m}Tc-HMPAO and SPECT in 34 subjects (9 restrictive anorexics, 13 bulimics, and 12 healthy controls) under three different conditions: at rest, after viewing a neutral stimulus (landscape video), and after viewing their own-filmed body image (positive stimulus). Anorexics showed a hyperactivation of the left parietal and right superior frontal cortex by the positive as compared to the neutral stimulus. Bulimics showed a hyperactivation of the right temporal and right occipital areas. Activation of the right temporal lobe may reflect an aversive response and abnormal activation of the left parietal lobe the storage of a distorted prototypical image of the body (Beato-Fernandez et al. 2009). In a follow-up study performed in the same subjects, the right temporal lobe activation in bulimics was shown to persist even after 1 year of participation in a treatment program for eating disorders (Rodriguez-Cano et al. 2009). Thus, although progress was made in the control of purging symptoms, mood (depression), and self-esteem, the aversive response of the patients toward their own body shape was still present after 1 year, and more specific long-term therapies are needed for the treatment of body dissatisfaction.

In summary, using either SPECT or PET, abnormal activation of certain brain areas has been detected both in BN and AN after presentation of various stimuli, related either to food intake or body shape (Table 23.2). These responses have been interpreted as symptoms of anxiety or phobia. Most abnormalities disappear after successful treatment, but abnormal activation of the right temporal lobe may persist in BN and reflect persistence of body dissatisfaction.

Table 23.2 Studies of rCBF (activation paradigm)

Study groups	Study moment	Stimulus	Tracer	Findings	After therapy	Reference
AN, control	Pre-/post-therapy	Cake eating	^{99m}Tc-HMPAO	↑ inf fro ctx in AN	Normalization	Nozoe et al. (1993)
R-AN, BP-AN, control	Only 1 session	Imagined eating	^{99m}Tc-HMPAO	↑ right hs in BP-AN	–	Naruo et al. (2000)
AN, control	Only 1 session	Visual (food)	$^{15}O–CO_2$	↑ med temp	–	Gordon et al. (2001)
BN, R-AN, control	Pre-therapy	Visual (body)	^{99m}Tc-HMPAO	↑ fro ctx (AN), ↑ ri tem occ (BN)	–	Beato-Fernandez et al. (2009)
BN, R-AN, control	Post-therapy	Visual (body)	^{99m}Tc-HMPAO	↑ ri tem (BN only)	Normalization AN, persisting BN	Rodriguez-Cano et al. (2009)

AN anorexia nervosa, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *Ctx* cortex, *HMPAO* hexamethylpropylene amine oxime, *hs* hemisphere, *Inf* inferior, *med* medial, *occ* occipital, *R-AN* restrictive type of anorexia nervosa, *ri* right, *tem* temporal

23.4 Anorexia and Cerebral Metabolism of Glucose

The first study of cerebral glucose metabolism in anorexia nervosa was published in 1987. Five female anorectic patients were scanned with PET and the tracer FDG, both during the anorectic state and after behavioral therapy. Scans were made in the resting state, with eyes closed and ears unplugged. Significant bilateral hypermetabolism in the caudate nucleus was observed in the anorectic state in comparison with results obtained after weight gain (Herholz et al. 1987). A subsequent study included nine patients with bulimia and seven patients with anorexia. Relative glucose metabolism in the caudate, compared to the rest of the brain, was significantly higher in anorexia than in bulimia (Krieg et al. 1991). These findings could be interpreted as high motor activity in the anorexic patients resulting in increased dopamine turnover in the caudate nucleus and metabolic hyperactivity.

A more extensive study appeared in 1995. FDG-PET scans were made during rest, with eyes closed and with low ambient noise, in 20 underweight anorectic girls and 10 age-matched healthy female volunteers. Compared to controls, the patients showed a global hypometabolism, the most striking difference being present in the frontal and parietal cortex (Delvenne et al. 1995). The observed hypometabolism might reflect a primary cortical dysfunction underlying anorexia nervosa, but it could also be related to physiological or morphological changes as a consequence of starvation or to depression in the patient group. A subsequent study examined cerebral glucose metabolism in ten anorectic girls, both at the onset of therapy and after weight gain. Ten age-matched healthy females were used as controls. In the underweight state, patients showed the same hypometabolism as was observed previously, but after weight gain, cerebral glucose metabolism normalized, and patient data were no longer significantly different from those acquired in controls although a trend toward inferior metabolism in some brain areas was still apparent (Delvenne et al. 1996). For this reason, glucose hypometabolism appears to be state- rather than trait-related. A third FDG-PET study included ten underweight females with anorexia nervosa, ten underweight depressed patients, and ten depressed patients with normal weight (all age- and sex-matched). Absolute values for glucose metabolic rate were significantly correlated with body mass index in all subjects; the lowest values were observed in the anorexic group. Thus, glucose hypometabolism seems to be a consequence of low weight (Delvenne et al. 1997a). The hypothesis that cerebral hypometabolism of glucose is a consequence of starvation was confirmed in a further study which compared FDG-PET scans of ten young depressed patients with low weight without anorexia nervosa with those of ten age- and sex-matched healthy volunteers. Absolute global and regional metabolic rates of glucose were significantly lower in the patient group than in the control group (Delvenne et al. 1997b). One factor that could partially explain the described findings is the downregulation of glucose transporters under nutrient starvation (Merrall et al. 1993), since these proteins are involved in uptake of FDG from the blood.

A more recent PET study involved 14 women with anorexia nervosa, 20 aged-matched healthy control subjects, and the same group of anorexics after randomization to 3 weeks of low-dose replacement testosterone therapy or placebo. The study

confirmed that cerebral glucose metabolism is significantly reduced in several cortical areas of anorexics as compared to controls. Testosterone therapy resulted in increases of metabolism in many areas including one region (posterior cingulate) which had previously shown hypometabolism (Miller et al. 2004). The clinical significance of this finding should be further examined.

In several PET studies (Delvenne et al. 1997a, 1999), relative glucose metabolism in the parietal cortex of anorexics was shown to be significantly decreased compared to controls and significantly increased in the caudate nucleus. Similar decreases of relative glucose metabolism were also noted in the parietal cortex of patients with bulimia; thus, it appears to be a common feature in both eating disorders (Delvenne et al. 1999).

Two PET studies have examined changes of cerebral glucose metabolism in an animal model of anorexia nervosa. In the first study, female Wistar rats received either free access to food or were severely restricted in their food intake until a 30% weight loss occurred. Body weight was then maintained at 70% of the control value by adjusting daily food intake and by providing free access to a running wheel. The tracer ^{18}F-FDG was administered intraperitoneally and was allowed to be distributed in the body of the awake animals for 50 min before the rats were anesthetized and scanned. Absolute values for glucose metabolic rate could not be determined by this protocol (since an arterial input function was missing), but relative glucose metabolism was found to be significantly altered in the food-deprived animals, decreases being noted in the hippocampus and striatum and increases in the cerebellum (Barbarich-Marsteller et al. 2005). The second study used a somewhat different approach. Here, food restriction (1.5 h instead of 24 h/day) and running wheel access were combined from the beginning. Animals were scanned after 9 days, when body weight in the food-restricted/exercised group had declined by 20%. FDG was not allowed to be distributed in awake but in pentobarbital-anesthetized rats, and the study used male animals rather than females. Decreases of glucose metabolic rate were observed in cortical areas and striatum, whereas increases occurred in the mediodorsal thalamus, ventral pontine nuclei, and cerebellum. Brain metabolism in the cingulate and the surrounding motor and somatosensory cortex was positively correlated to weight loss (van Kuyck et al. 2007). Both studies suggested that changes of cerebral metabolism can be detected with PET in animal models of anorexia nervosa and that these changes are related to loss of body weight.

A Chinese study used ^{18}F-FDG-PET and SPM to detect regional differences of glucose metabolism in the brain of AN patients ($n = 6$, all female, age 17 ± 1 years) compared to healthy controls ($n = 12$, all female, age 24 ± 3 years). The patients demonstrated increased metabolism in the frontal lobe, bilateral hippocampus, amygdala, and lentiform nucleus, left insula, and left subcallosal gyrus. Decreased metabolism was observed in the parietal lobe (on both sides of the brain). Four patients were subsequently treated with deep brain stimulation (DBS) in the nucleus accumbens, for a period of 3–6 months. DBS reduced the hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus in this patient group (Zhang et al. 2013). The observed metabolic differences between AN patients and controls may be related to AN symptoms such as a distorted perception of body image, lack of

recognition of the symptoms of malnutrition, distorted emotions associated with food-related stimuli, and aberrant responses to these stimuli.

A Canadian pilot study evaluated how cerebral glucose metabolism correlates with clinical improvement after DBS of the subcallosal cingulate in patients with anorexia nervosa. The authors showed that reversal of abnormalities seen in the anterior cingulate, insula, and parietal lobe at baseline (i.e., before DBS) is strongly correlated with the clinical benefits caused by this kind of therapy besides some adverse effects associated with DBS (Lipsman et al. 2013). A follow-up study from the same group monitored the impact of DBS of the subcallosal cingulate after a treatment period of 1 year in 16 patients with treatment-refractory AN. Although adverse events occurred in a substantial number of patients ($n = 7$), mean body mass index was significantly increased (from 13.8 ± 1.5 to 17.3 ± 3.4), and measures of depression, anxiety, and affective regulation were significantly improved. These beneficial consequences of treatment were associated with decreases of cerebral glucose metabolism (^{18}F-FDG-PET) in several brain areas (frontal gyri, caudate/putamen, thalamus, globus pallidus, cerebellum) and increases in some posterior cortical regions (Lipsman et al. 2017). The authors concluded that in patients with chronic (avg 18 years) treatment-refractory AN, DBS is well tolerated and associated with significant improvement of many disease symptoms.

Various studies, both in experimental animals and humans, have indicated that both DBS and electroacupuncture at acupoints result in changes of cerebral glucose metabolism and may be beneficial in the treatment of refractory AN. Thus, Chinese authors hypothesized that changes of regional ^{18}F-FDG uptake after electroacupuncture may serve as a biomarker to predict the therapeutic effect of DBS (Liu et al. 2015). Since DBS is an invasive form of therapy with associated risks, it seems important to apply DBS only in subjects which may benefit from this approach. However, the Chinese hypothesis has not yet been tested.

To summarize the findings in humans, most PET studies have reported cerebral hypometabolism in patients with AN as compared to controls, particularly in the frontal and parietal cortex (Table 23.3). Such hypometabolism appears to be a consequence of starvation rather than a trait leading to the development of anorexia. The ratio of metabolism in caudate nucleus to the rest of the brain is increased in anorexia. This may be a symptom of excessive motor activity in anorexics.

23.5 Anorexia and Brown Fat Activity

For a long time, brown adipose tissue was considered to exist only in young children. However, whole-body ^{18}F-FDG-PET scans revealed that brown fat also exists in some human adults where it may play a significant role in total body metabolism. For this reason, Italian researchers examined several groups of young females in underweight condition: seven subjects with constitutional leanness (CL), seven subjects with AN, seven subjects with AN after stable refeeding, and an aged-matched control group with normal weight ($n = 24$). In CL subjects, the body does not store significant amounts of fat, even in overfeeding conditions. The PET scans revealed the presence of brown fat in all subjects with CL and in

Table 23.3 Studies of CMR glucose in the resting state

Study groups	Study moment	Tracer	Findings	After therapy	Reference
AN	Pre-/post-therapy	^{18}F-FDG	Rel ↑ cau nuc	Normalization	Herholz et al. (1987)
AN, BN	Only 1 session	^{18}F-FDG	Rel ↑ cau nuc in AN	–	Krieg et al. (1991)
AN, control	Only 1 session	^{18}F-FDG	↓ globally in AN	–	Delvenne et al. (1995)
AN, control	Pre-/post-therapy	^{18}F-FDG	↓ globally in AN	Normalization	Delvenne et al. (1996)
AN, dep uw, dep nw	Only 1 session	^{18}F-FDG	CMRglucose correlates with BMI	–	Delvenne et al. (1997a)
Dep uw, control	Only 1 session	^{18}F-FDG	↓ in uw group	–	Delvenne et al. (1997b)
AN, control	Pre-/post-therapy	^{18}F-FDG	↓ in AN ctx areas	Normalization	Miller et al. (2004)
AN, control	Pre/post DBS	^{18}F-FDG	↑ fro lobe, hip, amy, lentiform nuc, left ins, left sc ↓ par lobe	Normalization (fro lobe, hip, lentiform nuc)	Zhang et al. (2013)
AN, BN, control	Only 1 session	^{18}F-FDG	Rel ↓ par ctx, rel ↑ cau nuc AN, BN	–	Delvenne et al. (1997a, 1999)
BN, control	Only 1 session	^{18}F-FDG	Not different, ant prefro correlated to depression	–	Andreason et al. (1992)
BN, control	Only 1 session	^{18}F-FDG	↓ globally in BN, rel ↓ in par ctx. CMRglucose *not* correlated with BMI or depression	–	Delvenne et al. (1997c)

AN anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *cau* caudate, *dep* depressive individuals, *nw* normal weight, *nuc* nucleus, *ob* obese, *occ* occipital, *par* parietal, *prefro* prefrontal, *uw* underweight

3 out of 24 normal subjects, but brown fat was completely absent in the AN or refed AN groups. Thus, brown adipose tissue may play a role in resistance of the human body against lipid storage and may be lacking in subjects with AN (Pasanisi et al. 2013).

23.6 Bulimia and Cerebral Metabolism of Glucose

In an early FDG-PET study, cerebral metabolic rate of glucose was examined in eight women with bulimia and eight normal healthy females during the performance of a visual vigilance task. Healthy subjects showed asymmetry with higher glucose

metabolism in the right than in the left hemisphere, but this asymmetry was absent in the patient group suggesting absence of the normal right activation and impaired processing of the visual task (Wu et al. 1990). In a subsequent publication, an additional group of eight women with major affective disorder was included. In contrast to the bulimics, depressed subjects showed normal activation in the right hemisphere during processing of the visual task, but they had decreased metabolism in the basal ganglia. Thus, although bulimics frequently suffer from symptoms of depression, their regional pattern of brain activation differs from that observed in major affective disorder (Hagman et al. 1990).

A later FDG-PET study examined the cerebral metabolic rate of glucose in 11 women with bulimia nervosa and 18 healthy age- and sex-matched control subjects. The bulimics were also tested for symptoms of major depression and obsessive-compulsive disorder. No group differences in orbitofrontal glucose metabolism were detected, but lower metabolism in the left anterolateral prefrontal cortex was correlated to greater depressive symptoms in the patient group (Andreason et al. 1992).

Another imaging study with PET and FDG examined cerebral glucose metabolism at rest (eyes closed, ears unplugged) in 11 normal-weight bulimic girls and 11 age- and sex-matched healthy volunteers. In contrast to the previous study, both global and regional levels of glucose metabolism were significantly lower in bulimics than in healthy controls. Relative levels of metabolism (compared to the rest of the brain) were reduced only in the parietal cortex. No correlations were found between absolute or relative glucose metabolic rates, body mass index, anxiety scores, or scores of depression (Delvenne et al. 1997c). The observed reductions in glucose metabolism could either be a consequence of nutritional deficiencies or a brain dysfunction underlying eating disorders.

In summary, most PET studies have reported that cerebral glucose metabolism in bulimics is either decreased or not significantly different from that in healthy controls (Table 23.3). However, data from FDG studies using an activation paradigm suggest that the processing of visual tasks may be impaired in BN (Table 23.4).

Table 23.4 Studies of CMR glucose (activation paradigm)

Study groups	Study moment	Stimulus	Tracer	Findings	After therapy	Reference
BN, control	Only 1 session	Visual task	^{18}F-FDG	Asymmetry in controls No right activation in BN	–	Wu et al. (1990)
BN, MAD, control	Only 1 session	Visual task	^{18}F-FDG	As above (BN, controls) Normal asymmetry in MAD, plus ↓ in bas gan	–	Hagman et al. (1990)

bas gan basal ganglia, *BN* bulimia nervosa, *MAD* major affective disorder

23.7 Alterations of the Serotonergic System in Eating Disorders

Several observations suggest that eating disorders may be associated with altered serotonergic neurotransmission in the brain. Serotonergic signaling in the hypothalamus is known to be involved in the control of food intake and body weight, serotonin acting as an eating-inhibitory substance (Leibowitz 1986). Serotonin (5-HT) uptake in platelets of bulimia nervosa patients is increased compared to healthy controls (Goldbloom et al. 1990), and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine can suppress bulimic symptoms (Freeman and Hampson 1987). Such observations (and many others, including the role of serotonin in regulation of mood and impulse control) have prompted imaging studies of 5-HT receptors and transporters in the brain of patients with eating disorders (Table 23.5; reviewed in (Bailer and Kaye 2011; Barbarich et al. 2003; Kasper et al. 2002; Kaye et al. 2005a, 2005b).

An initial study used the tracer [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) and SPECT to quantify 5-HT transporter binding in the thalamus and hypothalamus and dopamine (DA) transporter binding in the striatum of ten medication-free, female bulimic patients and ten age-matched healthy controls. A significant (17%) reduction of both 5-HT and DA transporter binding was noted in patients compared to controls, and 5-HT transporter availability was negatively correlated to the duration of illness (Tauscher et al. 2001). Similar findings were

Table 23.5 Studies of the serotonergic system

Study groups	Study moment	Tracer	Findings	After therapy	Reference
5-HT transporter binding					
BN, control	Only 1 session	^{123}I-β-CIT	↓	–	Tauscher et al. (2001)
ob BN, ob control	Only 1 session	^{123}I-β-CIT	↓ midbr	–	Kuikka et al. (2001)
ob BN, ob control	Pre-/post-therapy	^{123}I-β-CIT	↓ midbr	Normalization	Tammela et al. (2003)
BN, BP-AN, R-AN, control	Post-therapy	^{11}C-McN5652	Differences between groups	Persisting	Bailer et al. (2007a)
BN, control	Post-therapy	^{11}C-DASB	↓ midbr, cin ↑ acc, sup tem gyr	Persisting	Pichika et al. (2012)
BED, control	Only 1 session	^{11}C-MADAM	↓ n ac, inf tem gyr, orbfro ctx ↑ par-occ ctx	–	Majuri et al. (2017a)

(continued)

Table 23.5 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
5-HT $_{2A}$ receptor binding					
BN, control	Post-therapy	^{18}F-altanserin	↓ med fro ctx	Persisting	Kaye et al. (2001)
BP-AN, control	Post-therapy	^{18}F-altanserin	↓ cin amy hip occ, par ctx	Persisting	Frank et al. (2002)
BP-AN, control	Post-therapy	^{18}F-altanserin	↓ cin, le par, ri occ ctx	Persisting	Bailer et al. (2004)
AN, control	Only 1 session	^{18}F-altanserin	No significant differences	–	Bailer et al. (2007b)
AN, control	Only 1 session	^{123}I-5-I-R91150	↓ le fro ctx, par, occ ctx	–	Audenaert et al. (2003)
BN, control	Only 1 session	^{123}I-5-I-R91150	No significant differences	–	Goethals et al. (2004)
R-AN, BP-AN	Only 1 session	^{123}I-5-I-R91150	↓ par ctx (BP-AN)	–	Goethals et al. (2007b)
5-HT $_{1A}$ receptor binding					
BN, control	Only 1 session	^{11}C-WAY100635	↑ ang gyr, med prefro, pos cin	–	Tiihonen et al. (2004)
BP-AN, R-AN, control	Post-therapy	^{11}C-WAY100635	↑ many regions in BP-AN only	Persisting in BP-AN	Bailer et al. (2005)
AN, control	Only 1 session	^{11}C-WAY100635	↑ many ctx regions, dorsal raphe	–	Bailer et al. (2007b)
BN, control	Post-therapy	^{11}C-WAY100635	↑ many ctx regions	Persisting	Bailer et al. (2011)
R-AN	Pre-/post-therapy	^{18}F-MPPF	↑ right ctx both pre/post	Persisting	Galusca et al. (2008)

acc anterior cingulate cortex, *AN* anorexia nervosa, *ang* angular, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *cin* cingulate, *CIT* carbomethoxy-3β-(4-iodophenyl)tropane, *ctx* cortex, *fro* frontal, *gyr* gyrus, *hip* hippocampus, *inf* inferior, *le* left, *med* medial, *midbr* midbrain, *mpc* medial parietal cortex, MPPF 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p-fluorobenzamidoethyipiperazine*, *n ac* nucleus accumbens, *ob* obese, *occ* occipital, *orbfro* orbitofrontal, *par* parietal, *pos* posterior, *prefro* prefrontal, *R-AN* restrictive type of anorexia nervosa, *ri* right, *sup* superior, *tem* temporal, *WAY100635* *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide

reported in a Finnish study using the same approach. Obese binge eating women showed a significantly (28%) reduced β-CIT binding in the midbrain compared to obese controls (Kuikka et al. 2001). In a subsequent study from the same group, seven obese women with binge eating disorder were scanned with β-CIT before and after successful treatment which consisted of psychotherapy and fluoxetine medication. A repeated scan was also made in a group of six obese control subjects. After treatment, the symptoms of binge eating in the patient group had completely

disappeared, and 5-HT transporter density was significantly (24%) increased. In the control group, the binding of β-CIT was unchanged during the study period (Tammela et al. 2003).

Although 5-HT transporter density in the brain of bulimic women seems to increase after successful therapy, a PET study with the 5-HT transporter ligand [^{11}C]McN5652 indicated that altered transporter function may persist in some brain regions after recovery from eating disorders. The study involved 11 females who had recovered from restrictive anorexia, 7 who had recovered from binge/purge anorexia, 9 who had recovered from bulimia, and 10 healthy control women. Differences in transporter expression were noted between the three patient groups. The group which had recovered from restrictive anorexia showed a greater binding potential in the dorsal raphe and anteroventral striatum than the one which had recovered from binge/purge anorexia. Moreover, individuals who had recovered from binge/purge anorexia had a lower binding potential of [^{11}C]McN5652 in the anteroventral striatum than individuals who had recovered from bulimia nervosa (Bailer et al. 2007a). Apparently, patients with different eating disorders show differences in transporter function even after a recovery period of more than 1 year, and these differences could be related to differences in affective regulation and impulse control. A PET study with another 5-HT transporter ligand, [^{11}C]DASB, provided evidence for reductions of transporter availability in the brain of bulimic individuals even after complete recovery. When [^{11}C]DASB scans of eight females who had recovered from bulimia nervosa were compared to scans of eight healthy control women, the patient group had lower binding potential in the midbrain (containing the dorsal raphe) and superior and inferior cingulate and higher binding potential in the anterior cingulate and superior temporal gyrus (Pichika et al. 2012).

Another interesting study evaluated serotonin transporter binding in six patients with night eating syndrome (NES). NES is manifested by evening hyperphagia (consuming > 25% of the total daily food intake after the evening meal). Significantly higher binding of the serotonin transporter ligand ^{123}I-ADAM was observed in patients with NES as compared to six normal volunteers (Lundgren et al. 2008). A more recent PET study examined serotonin transporter density in 7 subjects with BED, 13 subjects with pathological gambling, and 16 healthy controls. Subjects with BED showed increased binding of the 5-HT transporter ligand ^{11}C-MADAM in the parieto-occipital cortex, but decreased binding in the nucleus accumbens, inferior temporal gyrus, and lateral orbitofrontal cortex compared to controls. In subjects with a pathological addiction to gambling, the regional density of the 5-HT transporter was not significantly different from healthy controls (Majuri et al. 2017a).

An early PET study examined ^{18}F-altanserin (5-HT$_{2A}$ receptor) binding in the brain of ten healthy volunteers and nine women who had recovered from bulimia nervosa. Former patients had reduced tracer binding in the medial frontal cortex. An age-related decline of 5-HT$_{2A}$ binding was noted in the brain of healthy controls but not in subjects who had recovered from bulimia (Kaye et al. 2001). Reduced binding in the frontal lobe of patient brains could be related to disturbed self-control (impulsive/obsessive behavior) and dysphoric mood states in individuals vulnerable for eating disorders. A more extensive study using the same approach was published

in the following year. That study involved 23 female healthy volunteers and 16 women who had recovered from the binge/purge type of anorexia nervosa by showing normal weight, regular menses, and stable food intake for at least 1 year. Reduced binding of [^{18}F]altanserin was observed in several areas of the patient brains (cingulate cortex, amygdala, and hippocampus). SPM analysis revealed additional reductions of 5-HT$_{2A}$ binding in the occipital and parietal cortex (Frank et al. 2002). A later [^{18}F]altanserin-PET study from the same group confirmed that 10 women who had recovered from the binge/purge type of anorexia had a significantly reduced binding potential of the tracer in several brain areas (left subgenual cingulate, left parietal cortex, and right occipital cortex) compared to 16 healthy controls. In the former patients but not in the healthy control group, 5-HT$_{2A}$ binding potential in cingulate and parietal regions was positively related to harm avoidance and negatively to novelty seeking. Moreover, 5-HT$_{2A}$ binding potential in several cortical regions was negatively correlated to drive for thinness in the patient group (Bailer et al. 2004). Since robust decreases of 5-HT$_{2A}$ binding were observed even after long-term recovery in several studies, such decreases may reflect a trait-related disturbance that contributes to the pathophysiology of anorexia nervosa. However, some of the observed differences (e.g., those in subgenual cingulate) could also be related to depressive disorder in the patient group.

A SPECT study with the 5-HT$_{2A}$ receptor antagonist 4-amino-*N*-[1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidinyl]-5-^{123}I-iodo-2-methoxybenzamide (^{123}I-5-I-R91150) examined tracer binding in the brain of 15 patients with anorexia nervosa and 11 age-matched healthy volunteers. Reduced availability of 5-HT$_{2A}$ receptors was observed in the left frontal cortex, the left and right parietal cortex, and the left and right occipital cortex of the patients as compared to controls. The frontal cortex in the patient brains showed a significant left-right asymmetry, lower levels of tracer binding occurring in the left hemisphere (Audenaert et al. 2003). However, when similar SPECT scans were made in ten patients with bulimia nervosa, 5-HT$_{2A}$ binding in such patients was found to be not significantly different from that in the healthy control group (Goethals et al. 2004). In a later study with the same tracer, SPECT scans of nine subjects with restrictive anorexia were compared to scans of seven individuals with binge/purge anorexia. Relationships between binding index and temperament scores were also explored. Patients with binge/purge anorexia showed a significantly lower 5-HT$_{2A}$ binding index in the parietal cortex than patients with restrictive anorexia. A positive correlation was noted between parietal 5-HT$_{2A}$ binding and reward dependence, suggesting that these variables could be associated with the patient groups (Goethals et al. 2007b).

Since SSRIs are potential tools for the treatment of bulimia nervosa, and the serotonin 5-HT$_{1A}$ receptor is involved in the action of these compounds by causing negative feedback inhibition of serotonin release, a Finnish group examined cerebral 5-HT$_{1A}$ receptor binding of the PET tracer [^{11}C]WAY-100635 in eight unmedicated patients with bulimia and ten healthy control subjects. The patients showed greater binding potential values in all studied brain regions, particularly the angular gyrus, the medial prefrontal cortex, and the posterior cingulate cortex. Increased 5-HT$_{1A}$ expression in patients as compared to controls could be associated with reduced serotonin release and impaired control of food intake during binge eating.

In addition, such increases could be related to anxiety in the patient group (Tiihonen et al. 2004). A later study from the USA examined the binding of [^{11}C]WAY-100635 in the brain of 13 women who had recovered from restrictive anorexia, 12 women who had recovered from binge/purge anorexia, and 18 healthy control women. All patients had shown normal weight, regular menstrual cycles, and absence of binge/purge behavior for more than 1 year. Women who had recovered from binge/purge anorexia showed increased [^{11}C]WAY-100635 binding potential in many cortical regions (cingulate, lateral and mesial temporal, lateral and medial orbital frontal, parietal, and prefrontal) and in the dorsal raphe as compared to healthy controls. However, no significant differences were detected between the brain of women who had recovered from restrictive anorexia and the brain of healthy subjects, although 5-HT$_{1A}$ receptor binding after recovery from restrictive anorexia was positively correlated with harm avoidance and with a measure of anxiety (Bailer et al. 2005). A subsequent study applied three different PET tracers ([^{11}C]WAY-100635 for imaging of 5-HT$_{1A}$ receptors, [^{18}F]altanserin for imaging of 5-HT$_{2A}$ receptors, [^{15}O]water for measurement of cerebral blood flow) in 15 women with anorexia nervosa and 29 healthy controls. Compared to controls, the patients showed strong (30–70%) increases of 5-HT$_{1A}$ binding potential in various cortical regions and dorsal raphe nuclei. 5-HT$_{2A}$ binding potential and cerebral blood flow in the patient group were normal, but the binding potential of [^{18}F]altanserin in the supragenual cingulate and frontal and parietal cortex was positively related to harm avoidance in this group (Bailer et al. 2007b). Another study from the same group examined [^{11}C]WAY-100635 binding in the brain of 13 women who had recovered from bulimia nervosa and 21 healthy control subjects. The patient group showed significant elevations (23–34%) of 5-HT$_{1A}$ binding potential in the subgenual cingulate, mesial temporal, and parietal cortex. Binding potential values were positively related to harm avoidance and negatively to sensation seeking. In the healthy control group, 5-HT$_{1A}$ binding potential was also related negatively to novelty seeking (Bailer et al. 2011). The increased activity of 5-HT$_{1A}$ receptors in bulimic and anorexic individuals, which was detected in several PET studies, may explain why such patients show a rather poor response to serotonergic medication.

A PET study with another 5-HT$_{1A}$ receptor ligand, [^{18}F]MPPF, detected increases of tracer binding in a selective area of the right cortex both in lean and recovered patients with restrictive anorexia. Elevated perfectionism and interpersonal distrust scores were noted even in the recovered patient group (Galusca et al. 2008). The findings of this PET study indicate that anxiety symptoms and serotonergic alterations persist after recovery from eating disorders and may reflect a personality trait that contributes to their pathogenesis.

23.8 Alterations of Other Neurotransmitter Systems in Eating Disorders

Various PET studies have examined dopamine receptor binding in the brain of patients with eating disorders (Table 23.6). An early study included 10 women who had recovered from anorexia nervosa and 12 healthy control subjects. The patient

Table 23.6 Studies of other neurotransmitter systems

Study groups	Study moment	Tracer	Findings	After therapy	Reference
D_2/D_3 receptor binding					
AN, control	Post-therapy	^{11}C-raclopride	↑ ant ven str	Persisting	Frank et al. (2005)
BN, control	1 session, methylphenidate challenge	^{11}C-raclopride	↓ str, ↓ response to challenge	–	Broft et al. (2012)
AN, control	Post-therapy, amphetamine challenge	^{11}C-raclopride	Tracer binding same but mood changes different	Persisting mood differences	Bailer et al. (2012)
BP-AN, R-AN, BN, control	Post-therapy	^{11}C-raclopride	dor cau, put BP related to harm avoidance	Character-trait-related differences	Bailer et al. (2013)
AN, control	Before and after weight restoration	^{11}C-raclopride	No differences between AN and controls	Still no differences	Broft et al. (2015)
AN (treated, recovered)	Only 1 session	^{11}C-raclopride, fMRI	Increased BP in dor cau related to enhanced response to loss in a game	–	Bailer et al. (2017)
Dopamine release					
BED, control	During neutral and food stimuli, with and without oral methylphenidate	^{11}C-raclopride	Food stimuli combined with methylphenidate increase dopamine release in binge eaters but not in nonbinge eating obese subjects	–	Wang et al. (2011)
Fluoro-DOPA influx					
BED, control	Only 1 session	^{18}F-DOPA	Striatal influx reduced (by 20% in nuc accumbens)	–	Majuri et al. (2017b)
μ-Opioid binding					
BN, control	Only 1 session	^{11}C-carfentanil	↓ le ins ctx	–	Bencherif et al. (2005)
BED, control	Only 1 session	^{11}C-carfentanil	↓ many cortical and subcortical regions	–	Majuri et al. (2017b); Joutsa et al. (2018)

Table 23.6 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
Histamine H_1 binding					
AN, control	Only 1 session	^{11}C-doxepin	↑ am, len nuc control ♀ ↑ than ♂	–	Yoshizawa et al. (2009)
Cannabinoid CB_1 binding					
BN, AN. control	Only 1 session	^{18}F-MK9470	↑ globally in AN	–	Gerard et al. (2011)
			Relative ↑ ins AN, BN		
AN animal model	During model and upon recovery	^{18}F-MK9470	↑ in all cortical and subcortical areas, in ♀ also relative increases in hip, inf col, ent ctx	Normalization	Casteels et al. (2014)
AN, BN, control	Only 1 session	^{18}F-MK9470	Binding in hyp, bs inversely associated with BMI. In AN, BN groups also inverse association of binding in mb, str, ins, am, orb fro ctx, and BMI		Ceccarini et al. (2016)
GABA(A)-benzodiazepine binding					
AN	At onset of therapy and after 4 months	^{123}I-iomazenil	↓ in cin, le fro, par ctx correlated with EAT-26 and mood scores	↑ in pos cin ctx, occ gyr	Nagamitsu et al. (2016)

am amygdala, *AN* anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *BMI* body mass index, *BP-AN* binge/purge type of anorexia nervosa, *bs* brainstem, *cau* caudate, *cin* cingulate, *CIT* carbomethoxy-3β-(4-iodophenyl)tropane, *col* colliculus, *ctx* cortex, *dor* dorsal, *ent* entorhinal, *fro* frontal, *gyr* gyrus, *hip* hippocampus, *hyp* hypothalamus, *inf* inferior, *ins* insula, *le* left, *mb* midbrain, *nuc* nucleus, *occ* occipital, *orb* orbito, *pos* posterior, *R-AN* restrictive type of anorexia nervosa, *str* striatum, *ven* ventral

group had significantly higher binding potential of [^{11}C]raclopride in the anterior-ventral striatum than the control group. In women who had recovered from anorexia nervosa, [^{11}C]raclopride binding potential in the dorsal caudate and dorsal putamen was positively related to behavioral scores for harm avoidance (Frank et al. 2005). These findings could be interpreted as evidence for disturbed dopamine-related reward mechanisms in subjects with anorexia nervosa which may contribute to altered feeding behavior.

In a more recent PET study, 15 women with bulimia nervosa and 15 healthy control subjects were scanned with [^{11}C]raclopride before and after administration of methylphenidate, a drug which inhibits dopamine reuptake and stimulates dopamine release from dopaminergic terminals. Bulimic individuals tended to have lower values than healthy controls for dopamine D_2 receptor binding in two subregions of the striatum in the first scan. The reduction of [^{11}C]raclopride binding after administration of methylphenidate was significantly smaller in patients compared to controls, and a smaller response to the psychostimulant challenge was associated with a higher frequency of binge eating in the patient group (Broft et al. 2012). These data were interpreted as evidence for reduced release of dopamine in bulimia nervosa. Reduced dopamine release has also been observed in substance abuse, e.g., cocaine or alcohol dependence. However, in contrast to the findings in substance abuse, impaired dopamine release in bulimic individuals was observed only in the putamen and not in the caudate (Broft et al. 2012). This study indicates disturbances of dopamine-related reward mechanisms in bulimia which differ both from those observed in anorexia and in substance abuse.

Another PET study examined amphetamine-induced dopamine release in ten women who had recovered from anorexia and nine healthy control women. Binding potential of the PET tracer [^{11}C]raclopride was identical in the two study groups, both before and after the amphetamine challenge. However, mood changes in the groups associated with amphetamine-induced dopamine release were strikingly different. In the healthy control group, the amphetamine-induced change of [^{11}C]raclopride binding potential in the ventral striatum was significantly associated with amphetamine-induced euphoria. In the patient group, the change of [^{11}C]raclopride binding potential in the precommissural dorsal caudate was significantly associated with amphetamine-induced anxiety (Bailer et al. 2012). Apparently, food-related dopamine release produces anxiety in patients with AN, whereas feeding is pleasurable in healthy subjects. An extensive PET study examined striatal dopamine D_2/D_3 receptor availability in 25 women with AN before and after weight restoration, in comparison to an age-matched control group of 25 healthy female subjects. Binding potential values in the patient group were again found to be identical to those in the control group, both in the underweight and weight-restored condition (Broft et al. 2015).

Interesting data were acquired in a PET study concerning dopamine release in patients with BED. Ten obese subjects with BED and eight obese control subjects without BED were included in this investigation. Neutral and food stimuli were presented to the subjects which were treated either with oral methylphenidate (in order to amplify dopamine release) or with placebo, and subjects were scanned with the D_2/D_3 receptor ligand ^{11}C-raclopride which is sensitive to dopamine competition. Neutral stimuli (with or without methylphenidate) and food stimuli (with placebo) were found to not increase extracellular dopamine. However, food stimuli combined with methylphenidate increased striatal dopamine release in the binge eaters, but not in the obese control subjects. The authors concluded that dopamine release alone does not predict obesity, but it may predict binge eating (Wang et al. 2011).

Another PET study examined both dopamine D_2/D_3 receptor ([^{11}C]raclopride) and serotonin transporter ([^{11}C]McN5652) binding in 7 individuals who had recovered from binge/purge anorexia, 11 individuals who had recovered from restrictive anorexia, 9 individuals who had recovered from bulimia, and 9 control women. This tracer combination was chosen because the dopaminergic system is believed to be involved in appetite and the serotonergic system in aversion; thus, these neurotransmitter systems could have opposed actions. In patients but not in healthy controls, a significant positive correlation was observed between the binding potential values of both tracers in various regions of the striatum. Scores for harm avoidance were significantly related to dopamine D_2/D_3 but not 5-HT transporter binding potential in the dorsal caudate and putamen. The interaction between 5-HT transporter and D_2/D_3 receptor binding in the dorsal putamen was a significant predictor of harm avoidance. These data suggest that serotonin/dopamine interactions contribute to harm avoidance behavior in eating disorders (Bailer et al. 2013). In a later study of the same group, blood flow responses in the striatum to wins and losses in a game (assessed by blood-oxygen-level-dependent fMRI) were compared to dopamine D_2/D_3 receptor binding potential (measured with PET and ^{11}C-raclopride). Increased D_2/D_3 binding in the dorsal striatum was found to be associated with an enhanced blood flow response to loss. This finding was tentatively interpreted as evidence for a relationship between increased dopamine receptor availability and anxious anticipation of consequences in the subject group, who consisted of individuals recovered from AN (Bailer et al. 2017).

In an interesting study from Finland, 7 subjects with BED, 15 subjects with pathological gambling, and 17 healthy control subjects were scanned with the false neurotransmitter ^{18}F-DOPA. The striatal influx of this tracer (K_1) was significantly decreased in BED with respect to controls (by 20% in the nucleus accumbens), but was not altered in the morbid gamblers. Thus, BED patients show marked presynaptic dopaminergic defects (Majuri et al. 2017b).

In comparison to healthy volunteers, bulimic individuals show significantly decreased mu-opioid receptor binding in the left insular cortex, a brain area involved in taste discrimination and eating reward (Bencherif et al. 2005). This decrease may reflect downregulation of μOR in the bulimic state as a consequence of chronically increased release of opioid peptides or a personality trait that increases the reward value of dieting. In the abovementioned ^{18}F-DOPA study from Finland, subjects were also scanned with the μ-opioid ligand ^{11}C-carfentanil. BED patients showed reductions of binding potential in many cortical and subcortical areas of the brain, whereas pathological gamblers displayed a 30–34% reduction of binding in the anterior cingulate. Thus, these two forms of addiction were associated with distinct neurobiological changes (Majuri et al. 2017b). A later study from the same group compared μ-opioid binding in the brains of BED patients, subjects with morbid obesity, and healthy controls. Both BED and morbid obesity were found to be associated with widespread reductions of μ-opioid receptor binding potential, and there were no significant differences between these two patient groups (Joutsa et al. 2018).

An interesting PET study compared binding potential of the histamine H1-receptor ligand [^{11}C]doxepin in 12 women with anorexia nervosa, 11 healthy

male volunteers, and a control group of 12 healthy females. Females showed significantly higher binding potential than males in the amygdala, hippocampus, medial prefrontal cortex, orbitofrontal cortex, and temporal cortex. Anorexia patients showed even higher binding potential in the amygdala and lentiform nucleus than the healthy control group. Correlations were observed between [^{11}C]doxepin binding in several brain areas and scores for abnormal eating behavior, depression, and anxiety. Thus, women appear to have higher histamine H1-receptor densities in the limbic system than men, and anorexia is associated with increases of H1-receptor density, particularly in the amygdala (Yoshizawa et al. 2009).

The endocannabinoid system which is located in many areas of the body is involved in the maintenance of body homeostasis via regulation of food intake and energy expenditure (Marco et al. 2012). One interesting PET study employed the tracer [^{18}F]MK9470 to assess regional cannabinoid CB_1 receptor density in the brain of 16 female patients with BN, 14 female patients with AN, and 19 age-matched healthy female volunteers. Global increases of CB_1 receptor availability were detected in anorexics as compared to healthy controls. Regional (relative) increases of CB1 receptors were detected in the insula of both patient groups and in the inferior frontal and temporal cortex in AN patients only (Gerard et al. 2011). These findings were interpreted as upregulation of CB1 receptors compensating for underactivity of the endocannabinoid system in anorectic conditions. Very similar findings were reported in an activity-based rat model of AN. This model offers the advantage that the impact of several variables (gender, diet, exercise) on the scan results can be independently assessed. In the animal model of AN (diet restriction combined with wheel exercise), strong increases of CB1 receptor binding were noted in all cortical and subcortical brain regions (+67% in males, >51% in females). Females showed in addition relative increases of CB1 receptor availability in the hippocampus, inferior colliculus, and entorhinal cortex. Diet restriction had a greater impact on the CB1 receptor population than physical exercise (wheel running), and the combination of diet restriction and exercise had the greatest effect. The observed changes of [^{18}F]ML9470 binding were normalized during recovery, when animals returned to their normal weight (Casteels et al. 2014). These PET data suggested that the rat model mimics many aspects of the human disease, and gender affects the response of the endocannabinoid system. A later, extensive PET study in humans examined CB1 receptor availability in 54 patients with various eating disorders (AN, BN, functional dyspepsia with weight loss, obesity) and an age- and gender-matched control group ($n = 26$). In all subjects, including the healthy control group, the binding of [^{18}F]ML9470 in the hypothalamus and brainstem was found to be inversely correlated with body mass index (BMI). However, in the subjects with eating disorders but not in the control group, an additional negative correlation was observed between BMI and tracer binding in the midbrain, striatum, insula, amygdala, and orbitofrontal cortex (Ceccarini et al. 2016). These findings were interpreted as evidence for a link between BMI and the cerebral endocannabinoid system in brain regions involved in the maintenance of body homeostasis, with additional involvement of the endocannabinoid system in reward areas in the patient groups.

A Japanese study examined GABA(A)-benzodiazepine receptor binding in subjects with AN, since anxiety plays an important role in the development of this disorder. Sixteen female patients were scanned with the SPECT tracer ^{123}I-iomazenil, both at the onset and after 4 months of therapy. The scan data could be compared with behavioral scores (that were acquired at the onset of therapy) and with therapeutic outcome (that was evaluated after 1 year). Higher scores in the Eating Attitudes Test with 26 items (EAT-26) corresponded with lower tracer binding in the anterior and posterior cingulate cortex. Higher scores in a Profile of Mood States (POMS) short form were associated with reduced binding in the left frontal, parietal, and posterior cingulate cortex. Decreased tracer binding in the anterior cingulate and left parietal cortex corresponded with poor therapeutic outcome. Subjects with weight gain demonstrated increases of tracer binding in the posterior cingulate cortex and occipital gyrus. These findings were interpreted as evidence for decreased GABA(A)-benzodiazepine binding in AN, related to anxiety, which normalizes after successful treatment (Nagamitsu et al. 2016).

23.9 Conclusion

PET and SPECT imaging findings provide evidence that individuals with eating disorders have altered brain function in regions that constitute limbic circuits. Fear-related responses to food and body-related stimuli have been detected, a changed reward response and sensory taste response (Frank et al. 2006) have been noted, and the availability of 5-HT transporters, serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D_2/D_3, histamine H_1, cannabinoid CB_1, GABA(A)-benzodiazepine, and mu-opioid receptors is altered. Many of these alterations persist after long-term therapy and behavioral or weight recovery. Hopefully, some of the biochemical changes detected with PET may lead to the identification of targets for pharmacological intervention. Recent functional neuroimaging studies have helped to indicate that a few experimental treatments show promise, such as ondansetron in BN and deep brain stimulation in AN.

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