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Serotonin: Imaging Findings in Eating Disorders

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Abstract

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior, weight regulation, and disturbances in attitudes and perceptions toward body weight and shape. Several lines of evidence nominate disturbances of serotonin (5-HT) pathways as playing a role in the pathogenesis and pathophysiology of AN and BN. For example, 5-HT pathways are known to contribute to the modulation of a range of behaviors commonly seen in individuals with AN and BN. New technology using brain imaging with radioligands offers the potential for understanding previously inaccessible brain 5-HT neurotransmitter function and its dynamic relationship with human behaviors. Recent studies using positron emission tomography and single photon emission computed tomography with 5-HT-specific radioligands have consistently shown 5-HT_{1A} and 5-HT_{2A} receptor and 5-HT transporter alterations in AN and BN in cortical and limbic structures, which may be related to anxiety, behavioral inhibition, and body image distortions. These disturbances are present when subjects are ill and persist after recovery, suggesting that these may be traits that are independent of the state of the illness. Effective treatments for AN and BN have been elusive. A better understanding of neurobiology is likely to be important for developing specific and more powerful therapies for these often chronic and deadly disorders.

Keywords

Anorexia nervosa; Bulimia nervosa; Serotonin; Receptor; Transporter; Brain imaging; PET; SPECT

1 Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior, weight regulation, and disturbances in attitudes and perceptions

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toward body weight and shape. In AN, there is an inexplicable fear of weight gain and unrelenting obsession with fatness even in the face of increasing cachexia. BN usually emerges after a period of dieting, which may or may not have been associated with weight loss. Binge eating is followed by either self-induced vomiting or some other means of compensation for the excess of food ingested. The majority of people with BN have irregular feeding patterns and satiety may be impaired. Although abnormally low body weight is an exclusion for the diagnosis of BN, some 25–30% of individuals with BN presenting to treatment centers have a prior history of AN; however, all individuals with BN have pathological concern with weight and shape.

It has been argued that AN and BN share some risk and liability factors because these disorders are often cross-transmitted in families and share many behavioral traits (Kendler et al. 1991; Lilenfeld et al. 1998; Strober et al. 2000; Walters and Kendler 1995). Similar to AN, individuals with BN commonly have anxiety, obsessionality, depression, a seemingly relentless drive to restrain food intake, an extreme fear of weight gain, and a distorted view of their body shape. AN tend to be over-controlled, whereas BN tend to have poor impulse control, greater novelty seeking (Strober et al. 1997; Wagner et al. 2006; Lilenfeld et al. 2006), and high rates of drug and substance abuse (Hudson et al. 2007). It is important to note that both AN and BN tend to restrict their eating and lose normal meal patterns (Mitchell et al. 1998). We hypothesize that AN can maintain this inhibition continuously, whereas BN have periodic disinhibition and overconsume food.

Although psychosocial factors are hypothesized to cause AN and BN, recent studies show that genetic heritability accounts for approximately 50–80% of the risk and creates neurobiological vulnerabilities (Kendler et al. 1991; Berrettini 2000; Bulik et al. 2006; Kaye et al. 2008; Steinglass and Walsh 2004; Treasure and Campbell 1994). It is important to note that considerable evidence suggests that childhood temperament and personality traits can create a vulnerability for developing AN and BN during adolescence. Recent studies (Lilenfeld et al. 2006; Stice 2002; Anderluh et al. 2003) describe negative emotionality, harm avoidance (HA), perfectionism, inhibition, drive for thinness, altered interoceptive awareness, and obsessive-compulsive personality traits as childhood predisposing factors that precede the onset of an ED, persist after recovery, and are elevated in unaffected family members (Bulik et al. 2007).

Several lines of evidence nominate disturbances of serotonin (5-HT) pathways as playing a role in the pathogenesis and pathophysiology of AN and BN. For example, 5-HT pathways are known to contribute to the modulation of a range of behaviors commonly seen in individuals with AN and BN. That is, 5-HT has been implicated in personality or temperament traits such as HA (Cloninger 1987) and behavioral inhibition (Soubrie 1986). Moreover, 5-HT has been implicated in psychiatric symptoms such as obsessionality (Barr et al. 1992), anxiety and fear (Charney and Deutch 1996), depression (Grahame-Smith 1992), as well as physiological traits such as satiety for food consumption. Second, many studies show disturbances of 5-HT activity in individuals who were ill or recovered from AN and BN. Third, medications that act on 5-HT pathways have some degree of efficacy in individuals with ED.

It is important to emphasize that brain neurotransmitter pathways do not work in isolation. For example (Tremblay and Blier 2006), the norepinephrine, dopamine, and 5-HT systems have reciprocal interactions so that it is virtually impossible to act on a specific neuronal element without a cascade effect on the other systems. In terms of clinical research in humans, we have perhaps more tools for investigating 5-HT activity and more understanding of its function than for other neurotransmitter systems. For that reason, this chapter will focus on 5-HT.

2 The Role of 5-HT Neurotransmitter Function in Eating Disorders

A role for biological determinants in the pathogenesis of eating disorders (EDs) has been proposed for the past 60 years (Treasure and Campbell 1994). In particular, an increased knowledge of the neurotransmitter modulation of feeding behavior has raised questions as to whether a disturbance in monoamine function may play a role in these disorders. 5-HT pathways play an important role in postprandial satiety. Treatments that increase intrasynaptic 5-HT, or directly activate 5-HT receptors, tend to reduce food consumption, whereas interventions that dampen 5-HT neurotransmission or block receptor activation reportedly increase food consumption and promote weight gain (Blundell 1984; Leibowitz and Shor-Posner 1986). Moreover, CNS 5-HT pathways have been implicated in the modulation of mood, impulse regulation and behavioral constraint, and obsessionality, and they affect a variety of neuroendocrine systems.

5-HT is synthesized from its precursor tryptophan, an essential amino acid that must be obtained through the diet. Following dietary consumption, tryptophan is taken up by the brain and hydroxylated by the enzyme tryptophan-5-hydroxylase (Petty et al. 1996). The product of this reaction, 5-hydroxytryptophan, is then decarboxylated by aromatic amino acid decarboxylase to the compound 5-hydroxytryptamine to the metabolite product known as 5-hydroxyindoleacetic (5-HIAA), which may be measured as a means of assessing 5-HT turnover or metabolism (Petty et al. 1996).

There has been considerable interest in the role that 5-HT may play in AN and BN (Jimerson et al. 1990; Kaye and Weltzin 1991; Treasure and Campbell 1994; Brewerton 1995; Kaye et al. 1998b). In part, this is related to the fact that studies, using hormonal response to 5-HT agents or other methods, have found that AN and BN have alterations in 5-HT metabolism.

When underweight, individuals with AN have a significant reduction in basal concentrations of the 5-HT metabolite 5-HIAA in the cerebral spinal fluid (CSF) compared to healthy controls (Kaye et al. 1984), as well as blunted plasma prolactin response to drugs with 5-HT activity and reduced ^{3}H-imipramine binding (Jimerson et al. 1990; Kaye and Weltzin 1991; Treasure and Campbell 1994; Brewerton 1995; Kaye et al. 1998a). Together, these findings suggest reduced serotonergic activity during the acute phase of illness, although this may arise secondarily from reductions in dietary supplies of the 5-HT synthesizing amino acid tryptophan. By contrast, CSF concentrations of 5-HIAA are reported to be elevated in long-term weight-recovered AN individuals (Kaye et al. 1991a). These contrasting findings of reduced and heightened serotonergic activity in acutely ill and long-term recovered AN

individuals, respectively, may seem counterintuitive; however, since dieting lowers plasma tryptophan levels in otherwise healthy women (Anderson et al. 1990), resumption of normal eating in individuals with AN may unmask intrinsic abnormalities in serotonergic systems that mediate certain core behavioral or temperamental underpinnings of risk and vulnerability.

Given that food restriction is not an inherently reinforcing behavior in healthy individuals, persistent dieting to the point of starvation suggests that food restriction may have some intrinsic benefit for individuals with AN. The ratio of tryptophan to other large neutral amino acids has been found to be significantly reduced in AN (Favaro et al. 2000). This reduction is likely to be a consequence of starvation since food restriction results in a decrease in dietary tryptophan consumption and thereby a decrease in the concentration of tryptophan available for 5-HT synthesis.

Premorbidly, individuals with AN report high levels of anxiety and obsessionality. Evidence suggests that individuals with AN may have an intrinsic defect in the 5-HT system. These individuals may have high levels of 5-HT in the synapse premorbidly resulting in a dysphoric state. Dieting may serve as a means of regulating this overactivity of 5-HT by decreasing the amount of tryptophan available for 5-HT synthesis, as evidence of reduced 5-HT activity is found during the acute phase. A study of acute tryptophan depletion found that a reduction of dietary tryptophan was associated with decreased anxiety and an elevation of mood in individuals with AN during the acute phase of illness and following long-term recovery (Kaye et al. 2003). Acute tryptophan depletion did not have significant anxiolytic effects for control women.

Considerable evidence also exists for a dysregulation of serotonergic processes in BN. Examples include blunted prolactin response to the 5-HT receptor agonists *m*-chlorophenylpiperazine, 5-hydroxytrytophan, and DL-fenfluramine, and enhanced migraine-like headache response to *m*-CPP challenge (Jimerson et al. 1990; Kaye and Weltzin 1991; Treasure and Campbell 1994; Brewerton 1995; Kaye et al. 1998a; Steiger et al. 2001a, b, c). Acute perturbation of serotonergic tone by dietary depletion of tryptophan has also been linked to increased food intake and mood irritability in individuals with BN compared to healthy controls. And, like AN, women with long-term recovery from BN have been shown to have elevated concentrations of 5-HIAA in the CSF, whereas CSF 5-HIAA levels are normal in ill BN (Kaye et al. 1984, 1988, 1990, 1991a, 1998b; Jimerson et al. 1992). Furthermore, Steiger and colleagues (Steiger et al. 2005b) found that individuals recovered from BN have reduced platelet [3H-] paroxetine binding, which is thought to be a marker of 5-HTT activity.

It has been found that *low* levels of CSF 5-HIAA are associated with impulsive and non-premeditated aggressive behaviors (Stein et al. 1993), which cut across traditional diagnostic boundaries. Thus, it is of interest that recovered AN and BN women had elevated CSF 5-HIAA concentrations. Behaviors found after recovery from AN and BN, such as obsessionality with symmetry and exactness, anxiety, and perfectionism, tend to be opposite in character to behaviors displayed by people with low 5-HIAA levels. Together, these studies contribute to a growing literature suggesting that CSF 5-HIAA concentrations may

correlate with a spectrum of behavior. Reduced CSF 5-HIAA levels appear to be related to behavioral under-control, whereas increased CSF 5-HIAA concentrations may be related to behavioral over-control.

3 Brain Imaging Studies

New technology using brain imaging with radioligands offers the potential for understanding previously inaccessible brain 5-HT neurotransmitter function and its dynamic relationship with human behaviors. Technologies that are used to date include single photon emission computed tomography (SPECT) and positron emission tomography (PET). Studies that have used these imaging techniques in EDs are summarized in Table 1.

The marriage of PET imaging with *selective* neurotransmitter *radioligands* has resulted in a technology permitting new insights into regional binding and specificity of 5-HT neurotransmission in vivo in humans and their relationship to behaviors. It is important to note that the 5-HT system involves 14 or more receptors and interacts with many other neurotransmitters and molecules. Only a few of these components can currently be measured in vivo in humans. Although the complexity of 5-HT circuits cannot be fully elucidated in humans, such imaging studies of 5-HT functional activity are useful in that they can characterize potential state and trait differences between AN and BN patients and healthy controls, be used to model relationships of 5-HT activity to behavior, and provide new insights into targets for more effective treatment.

3.1 5-HT_{2A} Receptor

Postsynaptic 5-HT_{2A} receptors are in high densities in the cerebral cortex and other brain regions of rodents and humans (Burnet et al. 1997; Saudou and Hen 1994). The 5-HT_{2A} receptor is of interest in ED because it has been implicated in the modulation of feeding and mood, as well as SSRI response (Bonhomme and Esposito 1998; De Vry and Schreiber 2000; Simansky 1996; Stockmeier 1997).

Our group has used this technology to study women ill with AN and after recovery from AN and BN (>1 year no binging or purging, normal weight, and regular menstrual cycles) to confirm 5-HT disturbances and provide new insights into the disorder. Although women ill with BN have been found to have normal 5-HT_{2A} receptor binding (Goethals et al. 2004), studies of recovered BN women (Kaye et al. 2001a), using PET with [^{18}F]altanserin, a specific 5-HT_{2A} receptor antagonist, found a significant reduction in bilateral medial orbital frontal cortex 5-HT_{2A} binding. These data lend further support to the possibility that vulnerabilities for impulse dyscontrol and mood disturbances cut across diagnostic boundaries and involve 5-HT and frontal lobe activity. REC BN women did not show the age-related decrease in 5-HT_{2A} binding found in control women. This is further evidence of persistent 5-HT alterations after recovery from this illness. Moreover, studies using PET and [^{18}F]altanserin (Frank et al. 2002) investigated women who were recovered from restricting-type AN (REC AN). REC AN had reduced 5-HT_{2A} activity, relative to CW, in mesial temporal (amygdala and hippocampus) regions, as well as cingulate, sensorimotor, and occipital/parietal cortical regions. Bailer and colleagues (Bailer et al. 2004) found that women who were recovered from binging–purging type AN (REC AN−BN) had

significantly reduced 5-HT_{2A} receptor binding in the left subgenual cingulate, left parietal cortex, and right occipital cortex compared to CW. Audenaert et al. (2003) used SPECT and 123I-5-I-R91159 and found that ILL AN subjects had reduced binding of postsynaptic 5-HT_{2A} receptors in the left frontal, bilateral parietal, and occipital cortex, while bulimic type AN had reduced 5-HT_{2A} binding in the parietal cortex in comparison to restricting-type AN (Goethals et al. 2007). However, using PET and [^{18}F]altanserin we found similar 5-HT_{2A} receptor binding in a mixed group of ILL AN and AN−BN compared to CW (Bailer et al. 2007a). However, the SPECT study did not account for possible brain volume loss in ILL AN, so that the reduced binding may be the result of partial volume averaging, leading to an underestimation of binding per unit brain volume in the ILL AN group. Different imaging techniques also vary in terms of resolution; thus it makes it difficult to directly compare studies.

While REC AN showed significantly negative relationships between age and 5-HT_{2A} receptor binding for most cortical regions (Frank et al. 2002), REC AN−BN (Bailer et al. 2004) and REC BN (Kaye et al. 2001a) did not show any significant relations to age. These data raise the question of whether 5-HT activity in BN is dissociated from normal age-associated changes, a finding that may offer new clues into the pathophysiologic mechanisms contributing to EDs. Whether the 5-HT system becomes free-running and insensitive to normal developmental mechanisms remains to be explored.

In summary, when 5-HT_{2A} receptor binding is compared between subgroups, both REC AN and AN−BN have reductions in the subgenual cingulate, parietal, and occipital cortex. In comparison, only REC AN have reduced 5-HT_{2A} receptor binding of the mesial temporal region and pregenual cingulate (Frank et al. 2002).

The PET imaging studies in ill and REC AN subjects described above found significant correlations between HA and binding for the 5-HT_{2A} receptors in mesial temporal and other limbic regions. Bailer and colleagues (Bailer et al. 2004) found that REC AN−BN subjects showed a positive relationship between [^{18}F]altanserin binding in the left subgenual cingulate and mesial temporal cortex and HA. For ill AN subjects, [^{18}F]altanserin binding was positively related to HA in the suprapragenual cingulate, frontal, and parietal regions (Bailer et al. 2007a).

The anterior cingulate cortex has an executive function (Devinsky et al. 1995). The subcaudal cingulate regions play a role in emotion (affect component) and have extensive connections with the amygdala, periaqueductal gray, frontal lobes, ventral striatum, etc. It is involved in conditioned emotional learning, vocalizations associated with expressing internal states, and assigning emotional valence to internal and external stimuli (Devinsky et al. 1995; Takenouchi et al. 1999; Bush et al. 1999). Mesial temporal regions include the amygdala and related regions which play a pivotal role in anxiety and fear (Charney and Deutch 1996) as well the modulation and integration of cognition and mood. The amygdala may enable the individual to initiate adaptive behaviors to threat based on the nature of the threat and prior experience (Charney and Deutch 1996). Most other brain imaging studies also show that ill and REC AN have cingulate and temporal alterations.

Do people with AN have symptoms that might be related to cingulate–temporal dysfunction? HA is common in AN (Brewerton et al. 1993; Kleifield et al. 1993; Bulik et al. 1995; O'Dwyer et al. 1996; Ward et al. 1998; Klump et al. 2000). Most ED subjects have one or more anxiety disorder diagnosis, who usually have an onset *before* the onset of their ED. Moreover, AN have an obsessive, perseverative, and rigid personality style and have difficulty shifting sets. While AN do well on goal-directed behavior, they have difficulties incorporating feedback and modifying their behavior. For example, they often feel that they should be able to do things perfectly and not make mistakes, and have little appreciation for the fact that mistakes are a normal learning experience. Moreover, they often fail to accurately recognize and incorporate affective and social stimuli in the environment, as confirmed by laboratory tests (Strupp et al. 1986; Kingston et al. 1996). We hypothesize that people with AN do not seem to be able to access and use conventional strategies for problem solving, such as learning from making mistakes. Rather, they obsessively repeat the same strategies despite the fact that such strategies are maladaptive and are not productive. These characteristic styles raise the question of whether there is some physiologic disturbance of executive brain mechanisms that detect errors or plan and verify actions. Perhaps a disturbance in cingulate–temporal pathways results in an obsessive focus on certain events and excludes the comprehension and incorporation of other stimuli.

Moreover, a most puzzling symptom in AN is their severe and intense body image distortion in which emaciated subjects perceive themselves as fat. We have previously shown that REC AN−BN had a negative relationship between the Eating Disorder Inventory – 2 Drive for Thinness (Garner 1991) (EDI-DT) subscale and [^{18}F]altanserin binding in the right subgenual cingulate, right pregenual cingulate, the lateral temporal cortex, the left parietal cortex, and the prefrontal cortex (Bailer et al. 2004). Furthermore, the AN studies described above (Frank et al. 2002; Bailer et al. 2004; Audenaert et al. 2003) all found alterations in 5-HT_{2A} activity in the left parietal region. These findings raise the speculation that left parietal alterations in REC AN and AN−BN might contribute to body image distortions. It is well known that lesions in the right parietal cortex may not only result in denial of illness, but may also produce experiences of disorientation of body parts and body image distortion (Critchley 1953). Theoretically, body image distortion might be related to the syndrome of neglect (Mesulam 1981), which may be coded in parietal, frontal, and cingulate regions that assign motivational relevance to sensory events. The refractory body image distortion in patients suffering from AN is a central feature of the illness. Other studies, using functional magnetic resonance imaging, support the speculation that left parietal disturbances may contribute to body image distortion (Wagner et al. 2003).

Only REC BN have reductions of the medial orbital frontal cortex (Kaye et al. 2001a). It is well recognized that BN subjects have extremes of self-control, such as alternating between undereating and overeating. Both 5-HT activity and frontal lobe function have been associated with behavioral disinhibition and extremes of self-control, such as obsessionality and impulsive aggressive behaviors (Tucker et al. 1995). We postulate that inherent disturbance of orbital frontal 5-HT circuits in BN contributes to a vulnerability for imprecise and poorly modulated behavioral control, which is reflected in reduced 5-HT_{2A} receptor binding.

3.2 5-HT_{1A} Receptor

Our group used PET imaging with the radioligand [^{11}C]WAY100635 to assess the BP of the 5-HT_{1A} receptor. The 5-HT_{1A} autoreceptor is located presynaptically on serotonergic somatodendritic cells in the raphe nucleus, where it functions to decrease 5-HT neurotransmission (Staley et al. 1998). High densities of postsynaptic 5-HT_{1A} exist in the hippocampus, septum, amygdala, and entorhinal and frontal cortex, where they serve to mediate the effects of released 5-HT. Although the molecular organization for the receptor transduction seems to be identical in all of the areas where 5-HT_{1A} receptors are expressed, some differences in both functional and regulatory properties have been reported from area to area (Lanfumey and Hamon 2000). Studies in animals and humans implicate the 5-HT_{1A} receptor in anxiety (Cervo et al. 2000; File et al. 2000; Olivier et al. 2001) and depression and/or suicide (Matsubara et al. 1991; Arango et al. 1995; Mann 1999).

Bailer et al. (2007a) have reported that ill AN individuals have a 50–70% increase in [^{11}C]WAY100635 BP in subgenual, mesial temporal, orbital frontal, and raphe brain regions as well as prefrontal, lateral temporal, anterior cingulate, and parietal regions. Similarly, REC AN−BN and REC BN subjects (Bailer et al. 2005, 2010) have a significant 20–40% increase in [^{11}C]WAY100635 BP in these same regions, compared to CW. While women recovered from restrictive-type AN had normal [^{11}C]WAY 100635 BP (Bailer et al. 2005), [^{11}C]WAY 100635 BP values were markedly elevated in some subjects and were recently found to be significantly increased in lean and recovered restricting-type AN individuals (using the radioligand [^{18}F]MPPF) (Galusca et al. 2008). Increased 5-HT_{1A} BP was positively associated with HA in REC restricting-type AN individuals (Bailer et al. 2005). Increased 5-HT_{1A} postsynaptic activity has also been reported in ill BN subjects (Tiihonen et al. 2004). Several interpretations are possible, which will require further testing to confirm. First, in recovered state, increased binding of the 5-HT_{1A} receptor may be associated specifically with REC BN, whether they have had a history of AN. Second, elevated 5-HT_{1A} receptor binding may be further exaggerated in the ill state of both AN and BN individuals, suggesting a possible trait phenomenon that is exacerbated by nutritional abnormalities. These data also may provide insight into possible new pharmaceutical treatments for AN and BN. Although numerous controlled trials have shown some efficacy for a variety of antidepressant medications in BN, relatively few individuals achieve abstinence on medication, as most continue to binge and purge. For example, a large-scale controlled trial of fluoxetine, which showed that a relatively high dose of 60 mg/day was superior to 20 mg/day for BN (Romano et al. 2002), had a 1-year remission rate of only 17.7%. Many subjects remained symptomatic on medication, and there was a worsening on all measures of efficacy over time. This result is consistent with other clinical observations (Walsh et al. 1991) that suggest limited improvement and considerable relapse with long-term antidepressant treatment in BN. The efficacy of SSRIs is dependent on neuronal release of 5-HT (Tollefson 1995), and 5-HT release in turn results in desensitization of the 5-HT_{1A} receptor (Blier and de Montigny 1999). Highly elevated 5-HT_{1A} receptor activity in BN raises the question of whether BN individuals have difficulty in achieving SSRI-induced 5-HT_{1A} autoreceptor desensitization. Such a difficulty could explain the need for higher doses of fluoxetine as well as partial response to drugs. Perhaps, higher doses of SSRIs or the addition of 5-HT_{1A} specific agents may prove useful in BN. With regard to AN, despite

considerable evidence of 5-HT abnormalities, ill AN patients show little response to SSRI administration (Attia and Schroeder 2005), in terms of improvement of mood or reduction of core ED symptoms. It is possible that elevated activity of 5-HT_{1A} receptors in the raphe nucleus in ill AN patients results in reduced 5-HT neuronal firing, and thus decreased extracellular 5-HT levels (Kaye et al. 1988), consistent with the reduced CSF 5-HIAA levels found in these patients. Thus, it is possible that SSRIs are not effective in ill AN patients because SSRIs would not have much effect if synaptic 5-HT levels are depleted by malnutrition.

As noted above, EDs are frequently comorbid with depression and anxiety disorders. However, while individuals with EDs tend to have elevated [^{11}C]WAY 100635 BP, reduced binding of 5-HT_{1A} receptor ligands was found in most [for review, see (Drevets et al. 2007; Savitz et al. 2009)], but not all, studies of major depression (Miller et al. 2009). In addition, reduced binding of 5-HT_{1A} receptor ligands was found in social phobia (Lanzenberger et al. 2007) and panic disorder (Neumeister et al. 2004; Nash et al. 2008). Thus, it can be argued that these disorders may be etiologically different.

3.3 Brain Regions/Pathways Enervated by $5HT_{1A/2A}$ Receptors

In REC subjects, altered 5-HT_{1A} and 5-HT_{2A} receptor BP shows persistent alterations in frontal, subgenual cingulate, and mesial temporal regions that are part of the ventral limbic system.

Several lines of evidence show that 5-HT_{1A} and 5-HT_{2A} receptors interact in the brain. In rats, 5-HT_{1A} and 5-HT_{2A} receptors interact robustly to regulate the inhibition of exploration of novel environments produced by either 5-HT_{1A} or 5-HT_{2A} receptor agonists (Krebs-Thomson and Geyer 1998). 5-HT_{2A} and 5-HT_{1A} receptors are highly co-localized in rodent frontal cortex (Amargos-Bosch et al. 2004). Postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors mediate, respectively, the direct hyperpolarizing and depolarizing actions of 5-HT on prefrontal neurons (Santana et al. 2004), which in turn project to numerous cortical and subcortical areas. Thus, a balance between postsynaptic 5-HT_{1A} and 5-HT_{2A} receptor activity on neurons may modulate the descending excitatory input into limbic and motor structures. These data raise the speculation that postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors fine-tune cortical systems that modulate behavioral inhibition and self-control. Mixed 5-$HT_{2A/1A}$ agonists, e.g., psilocybin, seem to disrupt the 5-$HT_{1A/2A}$ balance (Vollenweider et al. 1999) by driving 5-HT_{2A} activity, resulting in excessive neuronal output contributing to extremes of disinhibition, disorganization, and loss of self-control. In our studies, REC ED subjects had a relative increase in 5-HT_{1A} receptor activity compared to 5-HT_{2A} receptor binding. While speculative, this possible imbalance could contribute to behavioral inhibition and over-control commonly seen in ED. As discussed before, we found considerable correlations between binding of these two receptors and HA. Taken together, these findings raise the possibility that mesial temporal (amygdala)–cingulate $5HT_{1A/2A}$ imbalance may also be a trait shared by AN subgroups related to behavioral inhibition, anticipatory anxiety, or integration of cognition and mood.

3.4 5-HT Transporter

Studies with SPECT and [123I] beta-CIT showed that ill BN subjects had a 17% reduced 5-HT transporter (5-HTT) availability in the hypothalamus and thalamus (Tauscher et al. 2001). Two of those individuals had a history of AN, but specific imaging data for those two individuals were not identified. Our group (Bailer et al. 2007b) used PET imaging with [^{11}C]McN5652 comparing 11 subjects recovered (>1 year normal weight, regular menstrual cycles, no binging or purging) REC AN, 7 REC AN−BN, 9 REC BN, and 10 healthy CW. After correcting for multiple comparisons, we found that the REC AN had significantly increased [^{11}C] McN5652 BP compared to REC AN−BN for the dorsal raphe and antero-ventral striatum. However, neither group was different from healthy CW. In addition, REC BN were similar to CW and REC AN. No other studies have been done in AN. However, other imaging and peripheral platelet studies have found evidence of reduced 5-HTT in BN (Tauscher et al. 2001; Steiger et al. 2005b) and binge eating disorder individuals (Kuikka et al. 2001). A SPECT study compared 5-HTT availability in the midbrain and thalamus in 13 female twins with BN (nine with purging and four with nonpurging) versus 25 CW using a different radioligand for 5-HTT, [123I]ADAM (Koskela et al. 2007). They found that purging type BN had increased midbrain [123I]ADAM binding compared to CW, supporting a 5-HT-based distinction between those with purging and nonpurging behaviors, across both studies. While BN individuals show a response to higher doses of fluoxetine (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992), the efficacy of such medication has been questioned, as relatively few individuals abstain from binge and purge behaviors, and relapse during treatment is common (Walsh 1991). It remains controversial whether SSRIs are effective in AN individuals. Our clinical experience and data (Kaye et al. 1991b, 2001b; Walsh et al. 2006) suggest that individuals with AN respond better to fluoxetine than do those with AN−BN. While highly speculative, our findings raise the provocative possibility that decreased 5-HTT function may be related to poor response to SSRI medication, whereas individuals with increased 5-HTT activity may respond to higher SSRI doses. In general, REC AN individuals had elevated 5-HTT binding, suggesting they have relatively greater 5-HT uptake, and reduced extracellular 5-HT, compared to REC AN−BN. In support of this possibility, the REC AN−BN individuals tend to have higher binding of 5-HT$_{1A}$ postsynaptic receptors and autoreceptors (Bailer et al. 2005), which may be a compensatory means of downregulating raphe activity (Cooper 1996; Hajos et al. 2003). Moreover, reduced 5-HTT activity, resulting from functional polymorphisms (Steiger et al. 2005a), has been associated with affect dysregulation, which tends to be more common in the BN subgroups. Traits such as sensation seeking and insecure attachment are elevated in BN syndromes carrying low function alleles of the 5-HTT promoter polymorphism, who report prior physical or sexual maltreatment (Steiger et al. 2007). Furthermore, in people with impulsive aggression, reduced 5-HTT binding was found in the anterior cingulate cortex, a region involved in affecting regulation (Frankle et al. 2005).

4 Conclusion

SPECT and PET-radioligand studies confirm that altered 5-HT neuronal pathway activity persists after recovery from AN and BN and support the possibility that these psychobiological alterations might contribute to traits, such as increased anxiety, that may

contribute to a vulnerability to develop an ED. Clinical and epidemiological studies have consistently shown that one or more anxiety disorders occur in the majority of people with AN or BN (Godart et al. 2002; Walters and Kendler 1995; Kendler et al. 1995; Kaye et al. 2004). Silberg and Bulik (2005), using twins, found a unique genetic effect that influences liability to early anxiety and ED symptoms. When a lifetime anxiety disorder is present, the anxiety most commonly occurs first in childhood, preceding the onset of AN or BN (Deep et al. 1995; Bulik et al. 1997; Godart et al. 2000). Anxiety and HA remain elevated after recovery from AN, AN−BN, and BN (Wagner et al. 2006), even if individuals never had a lifetime anxiety disorder diagnosis (Kaye et al. 2004). The PET imaging data suggest that such behaviors are related to disturbances of 5-HT neurotransmitter function in limbic and executive pathways (Kaye et al. 2009). It is thought that in individuals with AN, dietary restraint reduces anxiety, whereas eating stimulates dysphoric mood (Kaye et al. 2003; Strober 1995; Vitousek and Manke 1994). Is altered 5-HT function the link between restricted feeding behavior and anxiety in AN patients? It is well known that carbohydrate intake increases extracellular 5-HT concentrations in the brain through complex metabolic effects on tryptophan, the amino acid precursor of 5-HT (Fernstrom and Wurtman 1972; Kaye et al. 2003). We hypothesize that both premorbidly and after recovery from AN, a normal level of food ingestion is associated with exaggerated extracellular brain 5-HT secretion (Kaye et al. 1991a). This is consistent with increased CSF 5-HIAA levels in recovered AN individuals (Kaye et al. 1991a). Increased 5-HT concentrations inhibit appetite, perhaps through activation of the 5-HT_{2C} receptor (Simansky et al. 2004); however, 5-HT_{2C} receptor binding has not been measured by imaging studies in individuals with AN. Increased 5-HT_{1A} BP is positively associated with HA in REC AN individuals (Bailer et al. 2005), and enhanced anxiety and HA are traits that are present premorbidly and persist after recovery from AN (Wagner et al. 2006). Thus, it is possible that carbohydrate-induced increases in extracellular 5-HT levels drive anxiety and HA through stimulation of the 5-HT_{1A} receptor, offering a potential explanation for feeding-related dysphoric mood in AN. By contrast, when individuals with AN starve, extracellular 5-HT concentrations might reduce, resulting in a brief respite from dysphoric mood. Studies in animals and healthy humans show that both a restricted diet (which significantly lowers plasma tryptophan) and experimentally reduced tryptophan depletion decrease brain 5-HT synthesis (Fernstrom and Wurtman 1972; Young and Gauthier 1981; Anderson et al. 1990). Indeed, malnourished and emaciated AN patients have reduced plasma tryptophan availability (Schweiger et al. 1986; Attia et al. 2005) and reduced CSF 5-HIAA (Kaye et al. 1988). Importantly, experimental manipulations that reduce brain tryptophan levels decrease anxiety in both ill and REC AN subjects (Kaye et al. 2003). However, starvation in AN seems to be associated with a compensatory increase in postsynaptic 5-HT_{1A} receptor BP (Bailer et al. 2007a). Moreover, 5-HT_{2A} receptor binding is also positively related to HA in ill AN patients (Bailer et al. 2007a). Thus, when AN patients are forced to eat, it is likely that they have a relative increase in extracellular 5-HT concentrations in the brain, leading to an exaggeration of dysphoric mood. Thus, AN patients might pursue starvation in an attempt to avoid the dysphoric consequences of eating and spiral out of control.

There is an extensive literature associating the serotonergic systems and fundamental aspects of behavioral inhibition (Geyer 1996; Soubrie 1986). Reduced CSF 5-HIAA levels are

associated with increased impulsivity and aggression in humans and nonhuman primates, whereas increased CSF 5-HIAA levels are related to behavioral inhibition (Fairbanks et al. 2001; Westergaard et al. 2003). Brainstem 5-HT_{1A} receptors inhibit stress-induced sympathetic activity and inhibit fight-or-flight behavioral responses, supporting a role for this receptor in behavioral inhibition and self-control (Johnson et al. 2004). Furthermore, recent animal studies also support modulation of impulse control via 5-HT_{1A} receptors through effects on catecholamine systems (Winstanley et al. 2005). Other studies have shown that blunted 5-HT_{1A} receptor number or function is associated with increased aggression (Cleare and Bond 2000; Coccaro et al. 1990). A recent study (Fischer et al. 2007) found a significant inverse relationship between dorsal raphe 5-HT_{1A} autoreceptor BP and bilateral amygdala reactivity. 5-HT_{1A} receptor function could contribute to behavioral inhibition in BN. In support of this, we found that for CW [^{11}C]WAY 100635 binding was related negatively to novelty seeking, whereas for REC BN [^{11}C]WAY 100635 binding was related positively to HA and negatively to sensation seeking. Moreover, novelty seeking and HA accounted for approximately 30% of the variance for [^{11}C]WAY 100635 binding in CW and REC BN, respectively (Bailer et al. 2010). The instruments used to assess behavior in humans tend to assess complex phenomena that are likely to be a composite of many traits, therefore confounding the understanding of how behaviors might be associated with a 5-HT receptor. For example, HA measures anxiety and behavioral inhibition, whereas novelty seeking measures exploration and impulsivity (Cloninger et al. 1994). Similarly, assessment of behavior in animals is complex. Thus, while considerable studies in animals associate 5-HT_{1A} receptor function with anxiety, most tests of anxiety in rodents are based in part on the approach/avoidance conflict between the innate tendency of an animal to explore a novel place and the tendency to avoid novel stimuli or environments (Groenink et al. 2003). Still, other studies show that various measures of 5-HT activity are related to measures of affective instability and impulsivity in ill BN subjects (Steiger et al. 2001a, b, c). Taken together, these data raise the possibility that 5-HT_{1A} receptor may contribute to the emergent ability to inhibit or self-control the expression of a number of behaviors related to stimulus seeking, anxiety, aggression, and impulsivity in BN.

A better understanding of how 5-HT contributes to symptoms in ED may help us advance beyond the trial and error system and develop new methods for identifying effective medications and psychological treatments in these often chronic and devastating disorders.

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Table 1

SPECT and PET studies assessing 5-HT function in anorexia and bulimia nervosa compared to healthy controls [modified from (Kaye et al. 2005)]

Year	Author	Method	ILL	REC	*N*	Frontal cortex	Temporal/ amygdala	Cingulate cortex	Parietal cortex
5-HT_{2A} receptor									
2001	Kaye	PET5HT_{2A}		BN	9	↓	nl	nl	nl
2002	Frank	PET 5-HT_{2A}		AN	16	nl	↓	↓	nl
2003	Audenaert	SPECT 5-HT_{2A}	AN*		15	↓	nl		
2004	Bailer	PET 5-HT_{2A}		AN−BN	10	nl	↓	↓	↓
2004	Goethals	SPECT 5-HT_{2A}	BN		10	nl	nl	nl	nl
2007	Bailer	PET 5-HT_{2A}	AN + AN−BN		15	nl	nl	nl	nl
5-HT_{1A} receptor									
2004	Tiihonen	PET 5HT_{1A}	BN		8	↑	nl	↑	
2005	Bailer	PET 5HT_{1A}		AN	13	nl	nl	nl	nl
2005	Bailer	PET 5HT_{1A}		AN−BN	12	↑	↑	↑	↑
2007	Bailer	PET 5HT_{1A}	AN + AN−BN		15	↑	↑	↑	↑
2008	Galusca	PET 5HT_{1A}	AN		8	↑	↑		↑
2008	Galusca	PET 5HT_{1A}		AN	9	↑	↑		↑
In press	Bailer	PET 5HT_{1A}		BN	13		↑	↑	↑
5-HT transporter									
2001	Tauscher	SPECT 5-HTT	BN		10	Decreased subcortical			
2007	Bailer	PET 5-HTT		AN	11			nl	
2007	Bailer	PET 5-HTT		AN−BN	7			nl	
2007	Bailer	PET 5-HTT		BN	9			nl	
2007	Koskela	SPECT 5-HTT	BN		13	Increased in midbrain in purging type only			

nl normal, ↓ decreased compared to controls, ↑ increased compared to controls, *AN* anorexia nervosa, restricting type, *AN−BN* anorexia nervosa, binging−purging type, *AN** diagnostic subgroup not specified, *BN* bulimia nervosa, *REC* recovered, *PET* positron emission tomography, *SPECT* single photon emission computed tomography, *5-HT* serotonin, *5-HTT* 5-HT transporter