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Current Status of Functional Imaging in Eating Disorders

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Abstract

Eating Disorders are complex psychiatric problems that involve biologic and psychological factors. Brain imaging studies provide insights how functionally connected brain networks may contribute to disturbed eating behavior, resulting in food refusal and altered body weight, but also body preoccupations and heightened anxiety. In this article we review the current state of brain imaging in eating disorders, and how such techniques may help identify pathways that could be important in the treatment of those often detrimental disorders.

Introduction

The conceptual framework of the pathophysiology and etiology of the eating disorders (EDs) anorexia nervosa (AN) and bulimia nervosa (BN) has undergone significant changes in the past few decades. Brain imaging techniques give us the opportunity to assess regional brain activity and neuroreceptor function *in vivo* in humans, and thus may help us understand how neuronal circuits are related to behavior and pathophysiology.

Various neuroimaging tools are now available for ED research. Functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) are used to assess brain activity thought to be associated with changes in regional cerebral blood flow, while positron emission tomography (PET) and single photon emission computed tomography (SPECT) are now mostly used to study neurotransmitter receptor function and regional cerebral glucose metabolism (rCGM). Recent advances in the field of brain research using neuroscience-based imaging paradigms have made great progress with respect to emotional and cognitive processes that may be altered in psychiatric illness. For example, a lot has been learned about brain pathways that are involved in fear provoking stimuli,[1] induction of abnormal mood states,[2] processing of food and other rewarding stimuli,[3] cognitive flexibility,[4] and numerous other areas with potentially direct relevance to eating disorders. In comparison with, for instance, psychosis or depression research, the body of neurobiologic research in EDs is relatively small, but nevertheless significant advances have been made over the past ten years to shed light on biological brain processes that may be part of the pathophysiology of AN and BN.

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Of importance when reviewing ED research are state related factors. The ill state of the EDs, particularly of AN, can be accompanied by severe metabolic, electrolyte, and endocrine disturbances.[5] As such, research in ill EDs is always potentially confounded by these effects. Even in recovered subjects, however, it has to be taken into consideration that observed differences may represent either premorbid traits contributing to the development of the illness, or a consequence of having been previously ill. In addition, there is a restricting type (AN-R) and a binge-purging type (AN-B/P) of AN and findings in one sub-type may not be representative for all AN individuals.

Functional Magnetic Resonance Imaging (fMRI) Task Activation Studies

Functional brain imaging is commonly performed in conjunction with paradigms and tasks that are meant to elicit areas of brain activation that might be specific for AN pathophysiology. Many different paradigms have been used over the past years. Most recently, functional magnet resonance imaging (fMRI) has been a primary technique to elicit brain function. The strength of fMRI is largely due to its lack of radiation, almost ubiquitous availability since most MR machines can be used to acquire fMRI images, and relatively low cost. On the contrary, while looking for “greater activation” in one subject group versus another has been a frequent goal, now this is often too simplistic and a good fMRI study is based on a good neuroscience model related to for instance ED behavior with known brain response in animals so that blood flow alterations in humans can ideally be related to known neuronal function.

Anorexia Nervosa

Visual high calorie presentation elicited high anxiety in AN together with left mesial temporal as well as left insular and bilateral anterior cingulate cortex (ACC) activity.[6] These results seem consistent with anxiety provocation and related limbic activation.[7] Uher[8] used pictures of food and non-food aversive emotional stimuli to assess ill and recovered AN subjects compared to controls. Food images stimulated medial prefrontal and ACC in both recovered and ill AN, but lateral prefrontal regions only in recovered AN; in controls food pictures were associated with occipital, basal ganglia and lateral prefrontal activation. Aversive non-food stimuli activated occipital and dorsolateral prefrontal cortex in all three subject groups. In recovered AN, prefrontal cortex, ACC and cerebellum were more highly activated compared to both controls and chronic AN after food presentation. This suggested that higher ACC and medial prefrontal cortex activity in both ill and recovered AN compared to CW may be a trait marker for AN. These are areas of executive function, decision making, error monitoring and also reward expectancy. Such alterations could suggest heightened vigilance or processing activity in response to visual food stimuli. Taken together, these studies suggest that the prefrontal cortex could be active in the capacity to appropriately or inappropriately restrict food, possibly via heightened fear related activation and anxious cognitions followed by related decision making such as food restriction.

Santel[9] compared restricting type AN (AN-R) with controls confronted by food images in both hungry and satiated states. They noted a decrease in inferior parietal lobule (IPL) activation among satiated AN, and furthermore, the magnitude of decrease correlated with illness severity. The IPL is composed of both the primary somatosensory and sensory association cortices, so this finding suggests a decrease in sensory sensitivity, or increased habituation, to food images in ill AN, which could indicate a pathogenetic mechanism that facilitates fasting or restriction. In turn, in the hungry state, AN showed decreased activation to food stimuli in the occipital cortex compared to control women (CW), which may indicate a learned or innate attentional bias away from food stimuli in the hungry state in AN, which again would facilitate fasting. Another recent study that investigated brain response in relation to feeding status indicated higher dorsal posterior cingulate in the hunger, but higher

insula activation in the satiated state, in AN versus CW.[10] The posterior cingulate is involved in monitoring one's own internal state[11] and may be particularly sensitive to food deprivation in AN, while the primary taste and sensory integration brain region insula[12] may be sensitized after feeding. Alterations in those areas therefore could be related to AN's ability to be able to restrict food, but the mechanism need further exploration.

Neurophysiologic responses to taste stimuli are in the early stages of investigation. Wagner[13] used a 10% sucrose solution and water in recovered AN-R and found decreased ACC, insula, and striatal activation to both taste stimuli. Furthermore, self-report of pleasantness of the taste stimulus and activation in these brain regions were only correlated in controls. A confirmation study (unpublished data) similarly found reduced brain response to sucrose in recovered AN-R compared to controls, and a lack of a correlation of pleasantness rating for sucrose with insula activation. This suggests a possible difference in the processing of tastes between AN-R and controls. The insula is implicated both in early processing of sensory stimuli as well as reward associations.[14] The ACC, as above, is implicated in reward anticipation and executive function.[15] It is an interesting contrast that ACC is activated by visual food stimuli in AN in Uher's study above, whereas its activation is decreased by gustatory stimuli in this study; this may represent a difference in stimulus saliency and anticipation versus actual stimulus-receipt processing. ACC activation was also found to be decreased in response to sweet stimuli among BN subjects[16] (see below), despite the very different behavioral approaches to food seen in the phenotypes of AN-R versus BN. The response of AN-B/P to similar stimuli remains to be seen. However, a major problem with those studies is that since the taste stimuli were readily distinguishable, it is not clear what the impact of cognitive restraint may have been with respect to reward activation control. A recent study that investigated brain response to randomly applied pleasant and aversive taste stimuli in recovered AN suggested heightened brain response to both taste qualities in the insula and striatum suggesting an overly sensitive brain taste reward system.[17]

Body image distortion is an integral part of AN pathophysiology and is part of its diagnostic criteria.[5] In a small pilot study confronting three AN subjects and three CW with their own digitally distorted body images using a computer-based video technique and fMRI,[18] AN had greater activation in the brainstem, right sided amygdala and fusiform gyrus, again suggesting anxiety related to the body experience that is reflected by amygdala activity. However, in a follow up study in a larger and more homogeneous sample using the same paradigm, another study[19] found no amygdala activation but a hyper-responsiveness in brain areas belonging to the frontal visual system and the attention network (Brodmann area [BA] 9) as well as intraparietal lobule (IPL, BA 40), including the anterior part of the intraparietal sulcus. The latter areas are specifically involved in visuo-spatial processing. More broadly, the parietal lobes are implicated in body schema integration and body ownership.[20] This finding makes the involvement of the brain anxiety circuit less clear but suggests that perceptual alterations may be related directly to the mechanisms of body image construction. Another study that used line drawings of body shapes found reduced occipito-temporal (lateral fusiform gyrus) and parietal cortex activation in AN subjects compared to controls and BN subjects.[21] Interestingly, the AN subjects rated both underweight as well as overweight pictures as highly aversive and the reduced activation in those face and body recognition regions[22] may indicate a general aversion to body related topics and a probably cognitively driven reduced brain response. The amount of research in body image related issues in AN is sparse; studies in controls may help develop new paradigms. In a study in a group of CW only found left amygdala activation in relation to unpleasant body-related words, as well as contra-lateral parahippocampal activation that was negatively related to the Eating Disorders Inventory-2 (EDI-2) score.[23] The same group compared healthy control women with matched males in the same body-related word paradigm, and again found

increased left amygdala activation among only the women, whereas the men showed increased activity in medial prefrontal cortex and hippocampus.[23, 24] Thus young women, with or without AN, may have somewhat similar—probably learned—anxiety reactions to stimuli related to body image, which may help to explain in neurobiological terms why women are so much more susceptible to AN than men.

Related to body image distortion, Sachdev[25] studied brain response to images of self versus non-self in ill AN-R and AN-B/P versus CW. This study found decreased activation in frontal, insula, precuneus and occipital regions for AN subjects compared to CW when faced with self-images; responses to other-images were similar. This suggests a potential variation in attention to or interpretation of self-images in AN. One might have expected a greater activation for AN subjects given their extreme sensitivity to their own appearance, however a conflation of self/other processing in AN patients might help maintain unrealistic ideas and expectations about their own bodies, and the unduly influence of appearances of others and media imagery.[26] A study of 18 CW ages 18-35 examined activations as women actively compared images of themselves to slim fashion models; this revealed activity in both body shape-related areas including lateral fusiform gyri, right IPL, right lateral prefrontal and left ACC. Furthermore, activations in basal ganglia and amygdala were correlated with a self-report of anxiety generated by the task.[27] Thus even in healthy women both body image and anxiety mechanisms are implicated in the emotionally laden task of comparison to social ideals.

Interestingly, AN individuals showed greater brain response after body image targeted psychotherapy compared to before when looking at pictures of their own body in the prefrontal and temporal cortex.[28] An AN waitlist control showed decreases in brain response. The implication of this finding is unclear but could indicate that the therapy resulted in a greater willingness to focus on their own body.

Rather than image stimuli, a recent small study on mostly AN-B/P versus CW presented words that were either neutral or associated with fatness or thinness. This study found in AN a behavioral attention bias toward the fat/thin valence words, as well as unique activation patterns for each valence condition, with increases in left frontal and left insula-temporo-parietal junction activation with the thin valence, and decreases in left frontal and right parietal activation in the fat valence.[29] Notably absent was a variation in amygdala response, which might have been expected from other studies. This pattern calls further into question the significance of the emotional response to body-image-related issues, while suggesting greater significance in mechanisms of body image construction and self-perception. Further study into these mechanisms will be crucial to understanding this important part of AN pathophysiology.

A developing area of AN imaging attempts to look directly at the neurophysiology of psychological trait markers. Heightened anxious traits are well-established in AN, and dopamine-mediated reward pathways have been implicated. Wagner[30] used a monetary win/loss paradigm and found among recovered AN women a relationship between trait anxiety and response to wins and losses in the caudate. Furthermore, AN women had similar responses to positive and negative feedback in the anteroventral striatum, whereas controls' responses differed between positive and negative conditions. The overall striatal response was greater in the recovered AN women compared to controls. These findings suggest a variation in reward processing, and potentially a conflation between positive and negative stimuli that may help to explain AN's ability to effectively restrict food and maintain anhedonia, while anxiety in AN may control reward response.

It is difficult to compare these studies as the tasks are not consistent and the groups of subjects are small. Still, it appears that cingulate and prefrontal activity is frequently different between AN and CW. Those regions may be over-activated when confronted with anxiety-provoking food related stimuli. Such a heightened vigilance is probably related to anxious body and fear-of-fatness cognitions, followed by actions in order to avoid weight gain. On the other hand, AN subjects may respond less to taste and other reward stimuli, which may help to be able to restrict food intake, especially neurobiologically "rewarding" foods. It further appears that AN do have altered self-perception related brain activation and this may suggest incorrect processing of, and maybe abnormal feedback from the body periphery, which in turn may allow over-valued ideas of thinness to control the self image.

Bulimia Nervosa

An fMRI study using a glucose taste paradigm versus a control solution found in recovered subjects with bulimic symptoms (seven BN and three AN-B/P) reduced ACC activity compared to six CW.[31] The ACC is an area that is involved in error monitoring but also in the anticipation of reward.[32] In this paradigm, where subjects knew which taste stimulus to expect, higher activity in controls could suggest higher reward expectation by controls than anticipated by BN type subjects. On the other hand, Schienle[33] compared 14 BN and BED subjects, finding a relative increase in activation of the ACC in BN confronted with images of food, as well as an increase in insula signal. It is possible that the insula activation represents emotional arousal by the image, whereas the ACC activation acts as a counterbalance to that response, as the ACC is implicated in selection of emotional attention and control of sympathetic autonomic arousal.[34, 35]

Two recent studies that investigated brain response to expectation and receipt of taste stimuli indicated that BN is associated with reduced response compared to controls in brain taste reward circuitry, which may indicate reward pathway desensitization in those regions in response to excessive food, possibly similar to models of substance use.[36, 37]

One study has explored body image perception in BN.[21] In a small sample (n=9) BN subjects were compared to AN and CW and presented with line drawings of body shapes (underweight, normal and overweight). Similarly to AN, BN had reduced lateral fusiform gyrus activation, and comparably to AN high aversion ratings to any body shape. Thus, reduced brain activation may have been an aversion-driven restraint in brain response in that group. However, this area of research needs more sophisticated approaches to disentangle the various cognitive-emotional versus biologic aspects of brain response when studying body image perception and distortion.

Faris has suggested a theory for the pathogenesis of BN, based on dysfunction/hyperactivity of the afferents of the vagus nerve. They have previously demonstrated reductions in binging/purging in BN by blocking vagal nerve transmission from the viscera with the drug ondansetron.[38] More recently, they studied PET scans in 18 healthy CW undergoing artificial gastric distention, notably finding activity in left inferior frontal, bilateral opercula (frontal), left insula, and right ACC.[39] The authors suggest that given these regions of activity, most notably ACC, the subjective experience of gastric distention might have a profound emotional component that could in turn contribute to the pathophysiology of binging and purging.

Positron Emission Tomography (PET) Studies of Monoamine Function in AN and BN

PET with radioligands characterize specific aspects of neurotranmitters, such as the binding of ligands to monoamine receptors or transporters. This is a complex and costly technology, that requires a dedicated equipment, such as a cyclotron, and chemists and physicists, and

other highly trained staff. The ligands, which are chemicals that bind to the target, are tagged with a small, safe dose of radioactivity. It offers relatively direct and specific understanding of the target, such as a monoamine receptor.

PET and radioligand imaging studies frequently use the binding potential (BP or BPND) or distribution volume ratios (DVRs) as outcome parameters (see Innis et al., 2007 for a concise explanation of neuroreceptor PET imaging outcome parameters).[40] As per Willeit and Praschak[40] we will use the term 'binding' for the various outcome parameters. It is not possible to disentangle receptor affinity (KD) and maximal binding capacity (Bmax) in a single PET measurement. The purpose of most investigations is to measure density and distribution of a single receptor molecule in the brain. The major advantage of PET imaging studies that they allow for studying distribution and density – and in some cases function – of single target molecules previously identified in animal and in-vitro research. The development of selective tracers for the 5-HT and DA systems has made in vivo study of receptor and transporter function possible using PET brain imaging. In turn, this offers the possibility of better understanding of neurotransmitter activity and dynamic relationships to behavior.

It should be noted that no single brain imaging technology provides a comprehensive spatial and temporal reflection of complex brain physiologic activity and neural circuit function. It is likely that symptoms in AN and BN involve complex and interconnected neural networks. While relatively few studies have been done in AN and BN, the findings tends to be relatively consistent, which may speak to the relative homogenetity of these disorders.

Serotonin function in AN

The 5-HT system has been intensively studied in AN patients because considerable evidence suggests that this neurotransmitter system could play a part in symptoms such as enhanced satiety[41], impulse control[42, 43], and mood[44, 45]. Indeed, there is much evidence of abnormal functional activity of the 5-HT system in AN patients.[46, 47] For example, underweight and malnourished AN patients have reduced cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), the major brain metabolite of 5-HT which is thought to reflect extracellular 5-HT concentrations[48]. By contrast, CSF 5-HT metabolite levels were elevated in recovered AN subjects.

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. Still, imaging studies of 5-HT functional activity are useful; although the complexity of 5-HT circuits cannot be fully elucidated in humans, such imaging studies can characterize potential state and trait differences between AN 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.

5-HT$_{1A}$ receptor—The 5-HT$_{1A}$ autoreceptor is located presynaptically on 5-HT somatodendritic cell bodies in the raphe nucleus, where it functions to decrease 5-HT neurotransmission[49]. 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. Studies in animals and humans implicate the 5-HT$_{1A}$ receptor in anxiety[50-52] and depression and/or suicide[45, 53, 54].

One means of imaging the binding of the 5-HT$_{1A}$ receptor is to use PET imaging with the radioligand [^{11}C]WAY100635. Bailer and colleagues[55] reported that ill AN individuals have a 50 to 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, recovered AN-B/P and BN subjects[56, 57] have a significant 20 to 40% increase in [^{11}C]WAY100635 BP in these same regions, compared to CW. While women recovered from AN-R had normal [^{11}C]WAY 100635 BP[57], [^{11}C]WAY 100635 BP values were markedly elevated in some subjects and were recently found to be significantly increased in lean and recovered AN-R individuals (using the radioligand [^{18}F]MPPF)[58].

Increased 5-HT$_{1A}$ postsynaptic activity has also been reported in ill BN subjects[59].

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 recovered BN individuals, whether or not 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[60], 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[61] 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[62] and 5-HT release in turn results in desensitization of the 5-HT$_{1A}$ receptor[63]. 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[64], 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[65], 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. Reduced [^{11}C]WAY100635 BP has been found in ill[66, 67] and recovered[68] depressed individuals, as well as in a primate model for depression[69]. Parsey[70] found no difference in carbonyl-^{11}C]WAY100635 BP in MDD, although a subgroup of never medicated subjects had elevated carbonyl-^{11}C]WAY100635 BP. Recent studies have found reduced [^{11}C]WAY100635 BP in social phobia[71] and panic disorder[72]. These findings suggest ED, mood, and depression share disturbances of common systems but are etiologically different.

5-HT$_{2A}$ receptor—Post-synaptic 5-HT$_{2A}$ receptors are in high densities in the cerebral cortex and other regions of rodents and humans[73, 74]. 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[41, 75-78].

Ill BN have been found to have normal 5-HT$_{2A}$ receptor binding.[79] However, studies of recovered BN women[80], 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. Moreover, studies using PET and [^{18}F]altanserin[81] investigated women who were

recovered from AN-R. recovered 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[78] found that women who were recovered from AN/B/P 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[82] 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 AN-R[83]. However, using PET and [^{18}F]altanserin we found similar 5-HT_{2A} receptor binding in a mixed group of ill AN-R and AN-B/P compared to CW[55]. 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.

In summary, when 5-HT_{2A} receptor binding is compared between subgroups, both recovered AN-R and AN-B/P have reductions in the subgenual cingulate, parietal, and occipital cortex. In comparison, only recovered AN-R have reduced 5-HT_{2A} receptor binding of the mesial temporal region and pregenual cingulate[81].

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 recovered AN-B/P had a negative relationship between the Eating Disorder Inventory – 2 Drive for Thinness[84] (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[78]. Furthermore, the AN studies described above[78, 81, 82] all found alterations in 5-HT_{2A} activity in the left parietal region. These findings raise the speculation that left parietal alterations in recovered AN-R and AN-B/P 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[85]. Theoretically, body image distortion might be related to the syndrome of neglect[86] 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[19].

Only recovered BN have reductions of the medial orbital frontal cortex[80]. 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[87]. 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.

5-HT transporter (5-HTT)—A recent study[88] used PET imaging with [^{11}C]McN5652 found that recovered AN-R had significantly increased [^{11}C]McN5652 BP compared to REC AN-B/P for the dorsal raphe and antero-ventral striatum. However, neither group was different from healthy CW. In addition, recovered BN were similar to CW and recovered AN-R. No other studies have been done in AN. However, other imaging and peripheral platelet studies have found evidence of reduced 5-HTT in BN[89, 90] and binge-eating disorder individuals[91]. Recent pilot data from our own group in recovered BN also suggest reduced 5-HTT availability in various cortical and subcortical brain regions.[92] A SPECT study

compared 5-HTT availability in the midbrain and thalamus in 13 female twins with BN (9 with purging and 4 with non-purging) versus 25 CW using a different radiologand for 5-HTT, [123I]ADAM[93]. 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 non-purging behaviors, across both studies.

While BN individuals show a response to higher doses of fluoxetine[94], the efficacy of such medication has been questioned, as relatively few individuals abstain from binge and purge behaviors, and relapse during treatment is common[95]. It remains controversial whether SSRIs are effective in AN individuals. Our clinical experience and data[96-98] suggest that individuals with AN respond better to fluoxetine than do those with AN-B/P. 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, recovered 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-B/P individuals tend to have higher binding of 5-HT_{1A} post-synaptic receptors and autoreceptors[57], which may be a compensatory means of downregulating raphe activity[99, 100]. Moreover, reduced 5-HTT activity, resulting from functional polymorphisms[101], 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[102]. Furthermore, in people with impulsive aggression reduced 5-HTT binding was found in the anterior cingulate cortex, a region involved in affect regulation[103].

Interactions between 5-HT_{1A} and 5-HT_{2A} receptors—Imaging studies provide insight into how disturbed 5-HT function is related to dysphoric mood in AN[104, 105]. That is, PET imaging studies show striking and consistent positive correlations between both 5-HT_{1A} and 5-HT_{2A} receptor binding potential and harm avoidance, a multifaceted temperament trait[106] that contains elements of anxiety, inhibition, and inflexibility. Studies in animals and healthy humans support the likelihood that 5-HT_{1A} and 5-HT_{2A} receptor activity has a role in anxiety[51, 107-109]. It is important to note that 5-HT_{2A} and 5-HT_{1A} postsynaptic receptors are highly co-localized (80%) in the rodent frontal cortex[110] and other cortical regions[111]. Through interneurons, they mediate, respectively, direct hyperpolarizing and depolarizing actions of 5-HT on prefrontal neurons that project to cortical and subcortical areas[112, 113]. Interactions between 5-HT_{1A} and 5-HT_{2A} receptors in the medial prefrontal cortex (mPFC) and related regions seem to modulate anxiety, attentional functioning[114], impulsivity and compulsive perseveration[113], and exploration of novel environments[115]. It remains to be determined whether the imbalance between enhanced 5-HT_{1A} and diminished 5-HT_{2A} receptor binding potential contributes to such symptoms in individuals with eating disorders.

Implications for satiety and the benefit of starvation

It is thought that in individuals with AN dietary restraint reduces anxiety, whereas eating stimulates dysphoric mood[105, 116, 117]. 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.[118105] 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.[119] This is consistent with increased CSF 5-HIAA levels in recovered AN individuals.[119] Increased 5-HT concentrations inhibit appetite, perhaps through activation of the 5-HT_{2C} receptor[120]; however, 5-HT_{2C} receptor

binding has not been measured by imaging studies in individuals with AN. Increased 5-HT_{1A} binding potential is positively associated with harm avoidance in recovered AN individuals,[57] and enhanced anxiety and harm avoidance are traits that are present premorbidly and persist after recovery from AN. Thus, it is possible that carbohydrate-induced increases in extracellular 5-HT levels drive anxiety and harm avoidance though 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, decreases brain 5-HT synthesis.[118, 121, 122] Indeed, malnourished and emaciated AN patients have reduced plasma tryptophan availability[123, 124] and reduced CSF 5-HIAA[65]. Importantly, experimental manipulations that reduce brain tryptophan levels decrease anxiety in both ill and recovered AN subjects[105]. However, starvation in AN seems to be associated with a compensatory increase in postsynaptic 5-HT_{1A} receptor binding potential[55]. Moreover, 5-HT_{2A} receptor binding is also positively related to harm avoidance in ill AN patients. 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 so spiral out of control.

Dopamine and reward processing in AN

Patients with AN often exercise compulsively, are anhedonic and ascetic, and find little in life that is rewarding aside from the pursuit of weight loss[125]. Such temperament persists, in a more modest form, after recovery[126, 127], indicating that these characteristics are traits rather than being state-related. DA dysfunction, particularly in striatal circuits, might contribute to altered reward and affect, decision-making, and executive control, as well as stereotypic motor movements and decreased food ingestion in AN patients[128]. Evidence that the DA system is involved in AN includes reduced CSF levels of DA metabolites in both ill and recovered AN individuals[129], functional DA D2 receptor gene polymorphisms in AN patients[130] and impaired visual discrimination learning[131], which is thought to reflect DA-signaling function, in AN patients.

A recent study from our group,[128] found that REC AN had increased binding of D2/D3 receptors in the anteroventral striatum (AVS), a region that contributes to optimal responses to reward stimuli[132-134]. This could indicate increased D2/D3 densities, decreased extracellular DA, or both, in recovered AN individuals. In addition, there were positive correlations between DA D2/D3 binding in the dorsal caudate/dorsal putamen and anxiety measures in REC AN[128]. The AVS and dorsal caudate are components of limbic and executive-associative pathways[135-137]. Thus striatal DA dysfunction might contribute to altered reward and affect, decision-making, and executive control, as well as stereotypic motor activity[136] and decreased food ingestion[138] in AN. The brain dopamine system dynamics can be tested by using for instance the D2/D3 receptor ligand raclopride and the dopamine-release challenge drug amphetamine. This approach provides information about the interplay between the amount of dopamine released and number of DA receptors available. In a small pilot study REC AN and controls showed similar levels of dopamine receptors after amphetamine challenge, but D2/D3 receptor binding in the caudate was associated with anxiety in AN. Food intake and reward processing is associated with DA release in the basal ganglia including the striatum, and an exaggerated anxiety response in AN following DA release could explain why food-related DA release produces anxiety in AN.[139] Cannabinoid receptors have also been associated with brain reward function and a

recent study in AN found increased availability of the type 1 cannabinoid receptor, but it is yet unclear how this finding may relate to AN behavior.[139, 140]

5-HT, DA, and harm avoidance—The PET imaging studies in ill and recovered AN and BN subjects described above have found significant correlations between harm avoidance and binding for the 5-HT_{1A}, 5-HT_{2A}, DA D2/D3 receptors in mesial temporal and other limbic regions. Bailer[78] found that recovered AN-B/P subjects showed a positive relationship between [^{18}F]altanserin BP in the left subgenual cingulate and mesial temporal cortex and harm avoidance. For ill AN subjects, [^{18}F]altanserin BP was positively related to harm avoidance in the suprapragenual cingulate, frontal, and parietal regions. 5-HT_{2A} receptor binding and harm avoidance were shown to be negatively correlated in the frontal cortex in healthy subjects[109] and in the prefrontal cortex in patients that attempted suicide[141].

Clinical and epidemiological studies have consistently shown that one or more anxiety disorders occur in the majority of people with AN or BN[142-145]. Silberg and Bulik[146], using twins, found a unique genetic effect that influences liability to early anxiety and eating disorder symptoms. When a lifetime anxiety disorder is present, the anxiety most commonly occurs first in childhood, preceding the onset of AN or BN[147-149]. Anxiety and harm avoidance remain elevated after recovery from AN-R, AN-B/P, and BN[126], even if individuals never had a lifetime anxiety disorder diagnosis.[145] Finally, anxiety[150] and Harm Avoidance from the Cloninger (TCI)[106] Temperament and Character Inventory have been a robust signal in our (WK PI) genetic studies[151]. In summary, the premorbid onset and the persistence of anxiety and harm avoidance symptoms after recovery suggest these are traits that contribute to the pathogenesis of AN and BN. The PET imaging data suggest that such behaviors are related to disturbances of 5-HT and DA neurotransmitter function in limbic and executive pathways.

Serotonin – Dopamine interactions

Do interactions between 5-HT and DA systems contribute to symptoms in AN? It has been theorized that 5-HT is the crucial substrate of an aversive motivational system which might oppose a DA-related appetitive system[152, 153]. Indeed, animal studies show that 5-HT_{2C} receptors tonically inhibit DA neurons[154, 155]. A PET study in recovered eating disorder subjects found positive correlations between 5-HT transporter and D2/D3 receptor binding in the ventral striatum and dorsal caudate.[56] From another perspective, studies suggest that 5-HT has a role in action choice by controlling the timescale of delayed rewards through differential effects on ventral and dorsal striatal circuits[156, 157]. This is consistent with evidence that reduced and increased 5-HT activity are associated with impulsive, aggressive behaviors and behavioral inhibition, respectively[43, 158156]. Considered together, AN individuals might have a trait towards an imbalance between 5-HT and DA pathways, which could play a role in an altered interaction between ventral and dorsal neurocircuits.

Despite considerable evidence of 5-HT abnormalities, ill AN patients show little response to selective serotonin reuptake inhibitor (SSRI) administration[64], in terms of improvement of mood or reduction of core eating disorder symptoms. The efficacy of SSRIs is dependent on neuronal release of 5-HT[62] and 5-HT release in turn results in desensitization of the 5-HT_{1A} receptor[63]. 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[65], 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. Preliminary data raise the possibility that olanzapine — which has effects on both DA and 5-HT receptors — and

possibly other atypical antipsychotics might be useful for increasing weight gain and reducing anxiety and obsessionality in AN[159].

Implications—Phillips[135] has described a ventral limbic system, which includes the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex, which identifies the emotional significance of a stimulus and the production of an affective state in response to that stimulus. In addition, these regions are important for regulation and mediation of autonomic responses to emotional stimuli and contexts accompanying the production of affective states.

The findings described above offer evidence that individuals with ED have brain function alterations within brain regions that constitute limbic circuits. There are fear related responses to food and body related stimuli, altered reward response and altered sensory taste response, as well as increased or decreased 5-HT and DA receptor dysregulation. In general, such alterations tend to be present in the ill state and persist after recovery. At this point, fMRI studies may provide us with pathways that mediate behavior of EDs and may help identify brain pathways of disturbance. PET studies in turn may directly point toward altered brain chemistry with the hope of developing pharmacologic targets for intervention. Furthermore, the combination of fMRI and PET studies may provide a comprehensive insight how ED behavior is determined by specific brain networks and neurotransmitter receptor function.

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