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Altered Brain Reward Circuits in Eating Disorders: Chicken or Egg?

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Abstract

The eating disorders anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric disorders with high mortality. Our knowledge about the neurobiology of eating disorders is very limited, and the question remains whether alterations in brain structure or function in eating disorders are state related, remnants of the illness or premorbid traits. The brain reward system is a relatively well-characterized brain circuitry that plays a central role in the drive to eat and individuals with current or past eating disorders showed alterations in those pathways compared to controls. Here we propose that structural and functional alterations in the insula and frontal cortex, including orbitofrontal and cingulate regions, areas that contribute to reward and anxiety processing, could predispose to developing an eating disorder and that adaptive changes in those circuits in response to malnutrition or repeated binge eating and purging could further promote illness behavior, hinder recovery and contribute to relapse.

Keywords

Eating disorders; ED; Anorexia nervosa; AN; Bulimia nervosa; BN; Brain imaging; Reward; Anxiety; Circuitry; State; Trait; Dopamine; DSM-5; Psychiatry

Introduction

The eating disorders (EDs) anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric disorders with high mortality [1]. EDs usually begin during adolescence and occur most commonly in females [2]. The diagnostic criteria for AN are up to recently a body weight below 85 % of that expected for age and height, intense fear of gaining weight, feeling fat despite being underweight, and a loss of regular menses. This latter criterion was dropped in the new edition of the diagnostic and statistical manual for mental disorders (DSM-5), and the weight criterion has also been changed to weight that is below "minimally normal" [2]. A restricting type (AN-R), marked by food restriction and commonly over-exercising, has been distinguished from a binge-eating/purging type (AN-B/P),where

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Compliance with ethics Guidelines

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afflicted individuals eat large amounts of food in a relatively short period of time ("binge eating"), or engage in behaviors to counteract weight gain, such as self-induced vomiting or use of laxatives or diuretics ("purging"). BN individuals are usually at normal weight, and engage in recurrent binge eating and purging behavior at least twice a week for at least 3 months. Individuals with ED symptoms that do not meet full criteria for AN or BN are classified as Feeding or Eating Disorder Not Elsewhere Classified (FEDNEC). A new diagnosis, "binge eating disorder" (BED) is part of the ED diagnostic categories in DSM-5, which describes individuals with binge eating episodes as in BN, but without the behaviors to counteract weight gain.

While AN is mainly characterized by severe underweight and BN individuals by the regularly occurring binge and purge episodes at normal weight [3], there are many overlapping symptoms across both disorders, such as food restriction, episodic binge eating, purging or excessive exercise. Our knowledge about the neurobiology of EDs is yet very limited, and there are only few effective treatments for EDs [4–7], especially in youth [8]. If we had a better understanding of what are predisposing neurobiological factors and what are effects of the illness on brain function and resulting specific ED behaviors, this knowledge could help with early detection and possibly treatment development.

Importantly, research has shown that there may be a transition between full ED syndromes and stages of recovery [9]. It is therefore possible that state of illness and severity of ED symptoms are associated with degrees of adaptation of brain function [10••], and that different ED characteristics could be related to distinct neurobiological abnormalities. Thus, there could be shared as well as distinct trait related abnormalities of brain function across EDs that contribute to developing an ED while the pathologic ED behavior itself may then impact brain function and possibly contribute to difficulties with recovery and high relapse.

This review will describe brain circuits that may be altered premorbidly and contribute to EDs. The focus is primarily on reward pathways but I will also discuss other brain circuits that are involved in ED psychopathology.

Neuroscience Aspects of Food Reward and Their Relevance to EDs

Food consumption is to a great degree driven by the tastes of food [11], which stimulate brain reward circuits, and brain reward mechanisms therefore could be important in the pathophysiology of abnormal eating [12, 13]. Taste inputs from the tongue, immediately after food contact and prior to gut involvement, project via brain stem and thalamus to the primary taste cortex comprised by insula and frontal operculum, and from there project to the ventral striatum and amygdala, and subsequently to hypothalamus, midbrain, and frontal cortex [14]. Hence a highly complex network is involved in taste processing. In addition to the transmission of taste quality, there are learned associations between food and more or less pleasurable experience that create an internal representation of food stimuli that get activated when we see, smell or think of food [11]. Those aspects of food reward have been distinguished in 1) a cognitive or cephalic phase that involves desire or craving, and 2) a consummatory phase in the food reward processing cycle. More basic "hardwired" pathways including the primary taste cortex in the insula as well as dopamine related circuits in the basal ganglia that form stimulus-behavior associations drive food approach, and those systems send learning signals to higher order brain regions to compare the current (food) experience with past experience and store new, or update previously stored, information on how much we value a particular food stimulus. Those higher order brain centers including in the prefrontal, orbitofrontal and cingulate cortex use this information to support the decision making process what type of food and how much we would like to eat in the future [15, 16]. This is further computed with input about the internal homeostasis of energy consumption

and expenditure, and hunger and satiety. Ideally, an individual bases the decision to eat on energy need together with food preference along the Latin saying “edimus ut vivamus, non vivimus ut edamus”, not for eating do we live, but for living, we eat. However, in EDs this reciprocal system may be disturbed in as such that the higher order brain centers are preoccupied with fears of eating and instead of contributing to healthy food intake may override the hardwired pathways that signal the desire or need to eat.

EDs are the product of a variety of biological, psychological and social factors coming together [17], however, it is conceivable that the effects of severe food restriction or chronic or episodic excessive food intake could be comparable to brain alterations found in animals that are subjected to underor over-feeding. This is important as knowledge of such mechanisms would help to distinguish state from trait alterations, as well as help develop neuroscience based models of and maybe more effective treatments for EDs. In fact, there have been recent advances with respect to describing ED brain neuro-circuitry [18, 19] and those results can now be put in the context of neuroscience research and help identify underlying neurotransmitter related alterations.

Food *restriction and weight loss* have been associated with heightened brain dopamine related reward response in rodents [20–22]. *Over-consumption of food* on the contrary showed addiction-like dopamine D2 receptor down regulation in rodents [23]. Those animal studies suggest that food restriction may sensitize, while excessive food intake may desensitize brain reward pathways. Human brain imaging studies indicated that obese individuals have reduced brain response in response to food receipt [24, 25] and reduced brain dopamine receptor availability [26]. Those studies support the notion that abnormally high or low body weight is associated with altered brain function that may involve dopamine pathways. Brain reward circuits are affected by malnutrition in animal studies also via other neurotransmitters and hormones, including leptin [27], ghrelin [28], glutamate [29] and opioids [30], but the dopamine system is particularly well characterized and can be studied empirically [31, 32].

Dopamine related brain circuits are critically associated with providing signals regarding the presence and amplitude of rewards [32, 33]. Such signals facilitate reinforcement learning [34], and code the value of stimuli [35, 36], maybe even including metabolic values of food [37], which could be disturbed in ED individuals. Further, computational models exist that allow making inferences regarding brain dopamine activation based on type and frequency of food stimulus exposure. Such a model is the temporal difference model [38], a computational theoretical framework for reward learning that is based on brain dopamine activation response to receiving of expected or unexpected reward stimuli. The primary areas that have been associated with that model are the ventral tegmental area and anteroventral striatum. In short, when we subject an individual to conditions of receipt or omission of expected or unexpected food stimuli, we can study brain dopamine associated reward pathways using brain imaging. This particular response is called ‘prediction error response’ as it is related to a computation in the brain that compares expected and received reward value. This model has been studied in dopamine neurons and adapted to human brain imaging [39]. Differences in brain response across ED and healthy individuals using this model then could provide us with information about possible dopamine related brain function and changes in EDs.

Reward Circuits in Eating Disorders When Ill and After Recovery

Research in AN indicated dopamine alterations such as altered levels of dopamine metabolites in the brain or number of dopamine receptors in specific brain regions [40–43], but we know little how such alterations may be clinically important. Functional brain

imaging may help bridge this gap. For instance, AN individuals' brain response was stronger than in controls to images of thin bodies in the ventral striatum [44]. Recovered AN showed reduced brain response to repeated sweet taste in insula and striatum [45], but increased caudate response to randomly given monetary [46] or taste stimuli [47]. A study that used randomly applied taste stimuli using the temporal difference model approach in AN and compared to obese individuals showed that AN had higher and obese had lower brain response to unexpected taste stimuli [48••], suggesting hypersensitive dopamine related brain function in AN, but the opposite in obese, consistent with the above described animal research. The discrepancy in response between repeated versus randomly applied taste stimuli across studies is most likely due to the random application stimulating the unconditioned dopamine related prediction error response while during the repeated application we expect that cognitive factors play a bigger role and affect reward response. For instance individuals with AN who know about a taste stimulus approaching as in the repeated application of a taste may constrain themselves in order to avoid an unwanted or as excessive perceived reward system response out of fear of overstimulation and food avoidance [49].

BN has been associated with addiction disorders [50] due to the episodic and often compulsive binging on palatable foods. The same neural pathways that reinforce motivation to approach food are also activated in response to addictive drugs [51]. This has lead to the hypothesis that prone individuals could get "addicted" to food, including increased tolerance as well as reduction of dysphoria, and such behaviors could be related to altered reward processing [52, 53].We recently found reduced prediction error response in BN [54] in insula, anteroventral striatum and frontal cortex, while higher binge/purge frequency predicted lower prediction error response, supporting that this constructmay play an important role in BN.

In summary, prediction error brain response is on opposite ends between AN and BN groups and promises to be an excellent construct to model brain reward function in EDs that could be related to dopamine function. This construct could also be useful in capturing state dependent and maybe also trait related brain response on trajectories of types or severity of ED related behavior.

Two other recent studies suggest possible state versus trait related brain alterations in EDs. First, a study in recovered AN and BN individuals that applied repeated caloric and non-caloric sweet taste stimuli during fMRI showed in recovered AN individuals reduced but in recovered BN subjects increased insula response compared to controls [55]. With the notion in mind that alterations after recovery could indicate premorbid or trait alterations in those individuals, those results implicate the insula as maybe important in the development of EDs. However, as it is a functional study, the altered response could be directly due to insula function, or could be due to altered input from other brain regions affecting insula activity. A recent structural study from our group showed that in ill and recovered AN as well as ill BN individuals orbitofrontal cortex gyrus rectus volume was higher compared to controls, suggesting that this could be a trait alteration across EDs [56]. That study further found that ill and recovered AN had higher right, while BN individuals had higher left insula volume. The right insula is not only important in taste perception but contributes to self-recognition, the "abstract representation of oneself" [57] and interoceptive awareness [58]. The fixed perception of being fat while severely underweight in anorexia nervosa [59] could thus be due to a right dysfunctional insula. The left insula activation responds to gastric distention [60] and self-reported fullness [61]. Thus, altered anterior insula volume could interfere with normal interoception in BN and an abnormal sense of "fullness" or satiation and then trigger the urge to purge after excessive food intake and guilt experienced over eating. Importantly, those results of higher insula volume [56] are discrepant from most other studies on brain

structure in AN that had found lower brain volumes compared to controls [62]. We believe this is due to the fact that subjects in our studies were assessed after 1–2 weeks of controlled food intake, which should have resolved effects from acute starvation and ideally identify regions that contribute to ED psychopathology. A caveat here is that all those studies will need replication in larger samples and whether the left and right distinctions will hold remains to be seen.

Other Circuits

Clinically, individuals with EDs stand out to be anxious and cautious, and research has suggested both anxious traits such as harm avoidance as well as increased prevalence of premorbid anxiety disorders [63, 64]. Thus, anxiety has been suggested to be a key vulnerability factor for the development of EDs [65]. In addition, AN and BN have been found to have emotion regulation difficulties [66, 67], and ED individuals appear to control their eating, weight and shape as a way to address their perceived lack of control over interpersonal and overall life stressors and overwhelming anxiety [64, 68]. This need for control could be driven by highly elevated scores of intolerance of uncertainty in both AN and BN [69]. In summary, with the high anxious behaviors observed in EDs, fear related brain pathways should be involved in those disorders.

Food and related weight gain are still the primary fear inducing stimuli for ED individuals. Various studies have applied pictures of high and low calorie foods during brain imaging to elicit brain response in relation to anxiety ratings. In AN for instance high-calorie food pictures provoked anxiety and led to greater temporo-occipital activation and mesial temporal as well as left insular and bilateral anterior cingulate activity, and these results were thought to be consistent with anxiety provocation and related limbic activation [70]. In another study [71] food images stimulated medial prefrontal and anterior cingulate cortex in recovered and ill AN, but lateral prefrontal regions only in recovered AN. In recovered AN, prefrontal cortex, anterior cingulate cortex and cerebellum were more highly activated compared to both controls and chronic AN after food presentation. This suggested that higher anterior cingulate cortex and medial prefrontal cortex activity in both ill and recovered AN compared to controls may be a trait marker for AN. These are areas of executive function, decision-making, error monitoring and also reward expectancy. Such alterations could suggest heightened vigilance or processing activity in response to visual food stimuli. Taken together, these studies suggest that the frontal cortex is active in the capacity to appropriately or inappropriately restrict food, possibly via heightened fear related activation and anxious cognitions that drive food restriction. Just recently, we applied diffusion tensor imaging (DTI) in AN, a technique that investigates integrity of white matter tracts in the brain [72]. That study indicated the there are white matter alterations in AN in particular in the bilateral fimbria fornix regions, outflux pathways from the hippocampus and connecting to frontal cortical regions and subcortical reward processing areas such as the ventral striatum, and importantly fimbria fornix white matter alterations in AN predicted harm avoidance. This study thus suggests that alterations in white matter could be directly involved in the pathophysiology of anxiety processing in AN. In BN, presentation of food images was also associated with increased response in frontal, cingulate, occipital and insula cortex, and suggesting anxious response as in the AN group [71].

In summary, one could hypothesize the following model of a functional disconnect between brain regions. The AN individual is initially learning to overvalue extreme ideals of thinness, and the amygdala get sensitized to food and body related stimuli as threatening and starts to restrict food. With illness progression there is an increasing lack of connectivity between frontal cortex and amygdala, possibly related to altered white matter connectivity

[72]. This may lead to an inability of prefrontal brain regions to control excessive amygdala activity, which continues to drive weight related fears, even if an AN individual tries to reverse course. This continuous fear response could be a reinforcing mechanism that further worsens known poor cognitive flexibility in AN [73] in reevaluating actual danger of shape and weight related stimuli, and an inability to test and adapt to new behaviors such as re-feeding and weight gain. Additionally, a pathologic integration of signals from the body periphery may disturb normal body image and drive the perception of being fat despite being thin.

A Possible Mechanism of Premorbid and Illness Related Brain Structure and Function

Studying ED individuals premorbidly is difficult because of the low incidence of the disorder. Studying individuals after recovery may be the closest to reflect brain function that may have been before start of the illness. There is of course always the question whether results after recovery are a “scar” from the illness and this question is difficult to resolve. Here we consider results found after long term recovery, that is for at least 1 year at normal body weight, no binge/purge behaviors, normal food intake and regular menses, as possibly reflecting premorbid brain function. Based on the above described studies we propose (Table 1) that individuals with EDs have as trait abnormality larger orbitofrontal cortex volumes compared to controls, which may contribute to early satiety and disturbed valuation of food stimuli. ED subjects are generally anxious and this is reflected in high frontal and anterior cingulate cortex activation, which may also be a premorbid trait. When environmental stress and low self valuation trigger fear of fatness, this hyperactive circuitry will be high jacked by those fears and provide the neurobiological correlate for preoccupation with body related fears and food concerns. Times of food restriction in AN then may sensitize insula and striatal reward pathways and contribute to overstimulation of an already hypersensitive salience response [49] and drive food avoidance from a biological level. Low response to repeated and thus predictable food stimuli may be due to higher order cognitive processes controlling the lower brain circuitry in order to avoid too strong salient stimulus stimulation. Heightened response to random stimuli may occur because of the inability to “prepare” for the stimuli and this response highlights a biological alteration of high sensitivity. In BN, fear driven food restriction may collide with a possibly trait related hypo-responsive reward system that predisposes to binge eating, and that behavior then even more decreases reward sensitivity in response to excessive food intake. The high fear of weight gain together with the vulnerability to overeat then may drive the recurrent interplay of binge eating, purging and food restriction in between binge/purge episodes.

During acute food restriction or episodes of purging, brain volumes may decrease due to the lack of fluids [74], but higher orbitofrontal and insula cortex volumes may be present before, during and after recovery, when controlling for acute malnutrition. It is possible that increased right insula volume predisposes especially restricting type AN individuals to have disturbed interoception and body experience [59] and while a possible trait of higher left sided insula volume in BN could prejudice those individuals to be more sensitive to gastrointestinal perception [60, 61] and promote the need to alleviate fullness by self induced vomiting.

The functional responses to reward (increased in AN, decreased in BN) and anxiety (increased in AN and BN) specific tasks will adapt during the course of illness of EDs and will be exaggerated compared to the premorbid state.

With ongoing illness, food restriction will further heighten sensitivity to salient stimuli in AN, while binge eating and purging behavior will more and more reduce reward

responsiveness in BN. By the same time AN and BN individuals both struggle with shape and weight related fears, which drive the seemingly illogical presentation of rather continuing the ED illness behavior than work on recovery. This is because the fear and anxiety are just so intolerable for them and the particular illness behavior at least in the moment alleviates their fears more than normalization of eating behavior.

Conclusion

EDs are multifactorial illnesses with a variety of bio-psychosocial aspects, yet they run in families and there should be strong biological factors that predispose ED individuals to developing those disorders. In this synthesis of some of the most recent ED brain imaging literature I proposed a model of potential predisposing structural and functional brain alterations that could contribute to the development of EDs and why it may be so difficult to overcome them. The origins of alterations in premorbid brain structure or function is unclear, however genes and environment are most likely responsible for specifically shaping brain development during childhood and adolescence in individuals susceptible to develop EDs. Studies along developmental trajectories will be needed to disentangle trait from state related underlying neurobiology in EDs and to study interventions that could prevent EDs in individuals at risk.

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Table 1

A proposed model of dynamic trait and state related brain changes in eating disorders

	Possible premorbid trait			Active illness		
	Diagnostic group	**Alteration**	**Laterality**	**Diagnostic group**	**Alteration**	**Laterality**
Brain structure						
Insula volume	AN	Increase ↑	Right	AN	Increase ↑	Right
	BN	??		BN	Increase ↑	Left
Orbitofrontal cortex volume	AN	Increase ↑	Left	AN	Increase ↑	Left
	BN	??		BN	Increase ↑	Left
Brain function (activation)						
Random (unpredictable) Taste reward stimulation						
Insula	AN	Increase ↑	Right	AN	Increase ↑	Right
	BN	??		BN	Decrease ↓	Right, Left
Ventral striatum	AN	Increase ↑	Left	AN	Increase ↑	Left
	BN	??		BN	Decrease ↓	Right
Repeated (predictable) Taste reward stimulation						
Insula	AN	Decrease ↓	Right	AN	??	
	BN	Increase ↑	Right	BN	??	
Anxiety provocation						
Frontal cortex with anterior cingulate	AN	Increase ↑	Right, Left	AN	Increase ↑	Right, Left
	BN	Increase ↑	Right, Left	BN	Increase ↑	Right, Left