Neurobiological Mechanisms of Restrictive Eating Behaviors: A Reinforcing Cycle

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Treatment for restrictive-type eating disorders (EDs) is mostly centered around therapy to tackle the psychological and cognitive motives for ED behaviors. However, many magnetic resonance imaging (MRI) studies on anorexia nervosa (AN) and bulimia nervosa (BN) patients, along with our current understanding of the effects of malnutrition on the brain, show that there are multiple structural and connectivity changes that cannot be accounted for through cognitive-based therapy. Therapeutics in the ED field have failed to take these neurobiological changes into account, thus lacking effective treatments for EDs. As 19% of ED patients end up with recurring symptoms/withdrawal, there is a need to identify novel targets for ED treatment. Neurobiological changes that are causal for and result from EDs provide promising targets that may prevent biological motives for ED behavior. This paper highlights specific neurobiological mechanisms by analyzing how the different changes in neurotransmitter pathways, connectivity, and plasticity that are caused by malnutrition, each play a role in reinforcing restrictive eating behaviors. These findings suggest that restrictive eating disorders are a self-reinforcing system and future research should focus on discovering more pharmaceutical approaches for recovery techniques.

Keywords: Eating Disorder (ED), Anorexia Nervosa (AN), Bulimia Nervosa (BN), Dopaminergic (DA), Ventral Tegmental Area (VTA), Nucleus Accumbens (NAc), Serotonergic (5-HT), L-tryptophan (Trp), Orbitofrontal Cortex (OFC), Depression (MDD), Brain-Derived Neurotrophic Factor (BDNF)

Introduction

Eating disorders (EDs) are often seen as mental disorders characterized by abnormal eating patterns paired with the impairment of mental health. For the purposes of this paper, we will be strictly looking at restrictive EDs, specifically anorexia nervosa (AN) and bulimia nervosa (BN). Individuals with AN often try to restrict energy intake, driven by the fear of gaining weight, usually through means of dieting, fasting, and over-exercising. Individuals with BN also engage in restrictive patterns but also have frequent bouts of overeating and binging, which are usually followed by intense feelings of guilt that are then compensated by purging intense dieting, and excessive exercise[1]. Most research into restrictive type EDs is usually done through a psychological lens by trying to discuss the role that our environment, childhood, and the content we consume have in the development of restrictive eating patterns to provide insight into new and accurate therapy approaches[2,3]. This research tends to focus on the effects of stress and personality on the proliferation of restricted eating habits and how those aspects can evolve over time. Recently, a more neurobiological approach toward ED research has been taking over in an attempt to find new drug treatments that can target specific pathways in the brain[4]. However, this is under the assumption that neurobiological findings, such as overactive dopaminergic (DA) pathways in ED patients, contribute to the development of EDs when they can rather be a result of restricted food intake that can further reinforce restrictive eating behaviors. While restrictive behaviors can occur outside of EDs, studying changes in brain connectivity can reveal how restrictive behaviors reinforce themselves, progressing into a disorder. By examining the specific mechanisms involved in the reinforcement of restrictive behaviors, we can identify potential pathways that can be targeted for specific drug treatments that can eventually be used to decrease ED recurrence. This paper aims to study current perspectives on the relationships between food intake and neurobiological changes in the brain while connecting them to the specified context of learning and reward processing in perpetuating restrictive behaviors.

Signaling Mechanisms Behind Reward Pathways and Habit Learning in the Context of Eating Disorders

Dopaminergic Pathways

Major functions of midbrain DA neurons consist of movement, motivation, reward, learning, and habit formation. These functions are associated with the DA neurons in the substantia ni-

gra pars compacta, the ventral tegmental area (VTA), and the retrorubral field[5]. The DA neurons in the VTA extend their axons into the nucleus accumbens (NAc) in the ventral striatum, which is most heavily involved in the reward and pleasure output of the DA pathway[6]. Activation of NAc DA neurons causes pleasurable feelings which in turn serves as a positive reinforcement for a behavior or stimulus. However, overactivation of these neurons can lead to intense cravings in the absence of stimuli with the increase of mesolimbic pathway activity[7]. With restrictive behaviors and the absence of food being the stimulus, overactivation of the mesolimbic DA pathways in ED patients can lead to positive reinforcement of these behaviors and an intense craving for restricted intake.

Dopaminergic Pathways in the Context of EDs: There are many studies on the role of DA and its reward and motivational properties in both drug and non-drug-related behaviors, such as restrictive eating behaviors. DA signaling occurs in neurons along the mesolimbic pathway, which stretches from the VTA to the NAc. DA neurons are able to form reward associations by utilizing classical conditioning, which is a learning process that pairs two stimuli together after repeated paired exposure[8]. With the initial exposure to a food reward, the firing of DA neurons in this pathway increases. With repeated exposure to the food reward, the DA response is associated with a conditioned stimulus that serves as a predictor for the reward. A decrease in this region in the brains of obese mice resulted in compulsive food intake and increased activation in the somatosensory cortical regions that process palatability[9]. In the context of human AN, some studies have shown that there is a decrease in DA function among a recovered AN group whose weight was restored. This indicates that AN patients who are acutely ill may have higher DA pathway activity[10]. This finding suggests that AN individual with overactive DA pathways may feel less of a drive to compulsively eat and activate more of their reward circuit, favoring reinforcers other than food. DA activity has also been associated with the motivational salience required for performing behaviors to obtain food rewards[9], which can explain the resolve against hunger signals.

DA pathways, specifically in the ventral striatum region, are linked to reward processing and predicting rewarding or aversive experiences, which have been shown to be abnormal in AN patients as they do not feel motivated by typical stimuli, such as food, that healthy control individuals are[11]. A previous study by Frank et al. in 2014 looked at the brain activation of major DA pathway-related regions, such as the striatum, VTA, insula, and cingulate cortex, when unexpectedly giving or removing a sweet taste stimulus. Using statistical parametric mapping of activated DA neurons in AN patients, the authors found that the AN group had more activation of brain DA regions than the control group when given the unexpected sweet stimulus. The AN group also had a more negative response to the unexpected omission of the sweet stimulus than the control group. The results show that the DA reward pathway is overactive in AN patients[4], potentially explaining how quickly AN patients are able to adapt to the decrease in nutrition and create a stronger predictive relationship between food intake and body weight. These overactive DA pathways can also explain the increased motivation to engage in more extreme behaviors relating to restrictive eating. Using Bridges et al.'s reasoning[7], these overactive DA pathways can lead to positive reinforcement of food avoidance even in the absence of positive results, such as weight loss, which suggests the potential for relapse and the engaging in restrictive behaviors in a similar fashion to drug addiction relapses.

Serotonergic Pathways

There is less known about serotonin (5-HT) neurons in reward pathways, however, there is a way to measure the electrical activity of neurons when a specific behavior is being performed. Cohen et al. were able to distinguish 5-HT neuronal activation from non-serotonergic neuronal activation in thirsty mice through classical conditioning. In this study, a reward is defined as a drop of water, the neutral stimulus is nothing, and punishment is defined as a puff of air, each of which was preceded with a distinctive odor to cue an association. In the reward trial, the mice licked the tube when their reward was delayed, but not in the neutral or negative trials, indicating they made the conditioned association between the odors. This experiment showed that 5-HT neurons respond to reward and punishment by either short, intensive bursts of activity or by altering their baseline activity[12]. As AN patients have continually shown an abnormality in reward encoding, it is possible that typical stimuli that healthy controls may be received as a reward through intensive bursts of 5-HT neurons may actually be received as a punishment. The type of activity of 5-HT neurons in ED patients should be further researched as it can reveal whether food is viewed as a punishment or a reward.

Serotonergic Pathways in the Context of EDs: 5-HT, as a neurotransmitter, is dependent on the amino acid L-tryptophan (Trp). The amount of Trp entering the brain depends on its ratio to other large neutral amino acids (LNAAs). When there is a large decrease in the plasma ratio between Trp and other amino acids, there is a reduced influx of Trp to the brain. Without the necessary dietary carbohydrates to increase the plasma Trp/LNAAs ratio[13], AN patients experience a depletion of Trp concentration in the brain, causing a decrease in 5-HT levels and an increase in anxiety. Yokokura et al. believe that this depletion of Trp can induce AN patients to restrict energy intake, further reducing Trp levels[14]. However, AN patient also shows an increase in postsynaptic 5-HT neuronal activity that is associated with starvation. This suggests that when AN patients are forced to eat, there is an increase in extracellular 5-HT concentrations, causing dissatisfied or despondent feelings. To avoid these consequences, ED patients will likely pursue starvation

instead[15].

Davidson et al. hypothesize that we use hunger and satiety cues to retrieve episodic memories of food rewards and our most recent memory of eating. Through experimentation on rats, they realized that the Western-style diet, which has a high-fat content, weakened the hippocampus blood-brain barrier, impairing the ability of interoceptive satiety cues to modulate appetite suppressive memory retrieval. This behavior caused excessive eating, even after a recent meal, which led to excessive weight gain in the mice[16]. It is believed that 5-HT disturbances can facilitate the encoding of allocentric episodic memory[17], which is the recalling of events through an outside, third-party perspective[18]. The disturbances of 5-HT levels present in anorexic patients may amplify the encoding of food reward memories as episodic memory. Expanding on Davidson et al. findings, we can believe the opposite effect may hold true, where decreased dietary fat intake may increase interoceptive and satiety signaling to retrieve recent episodic memories of eating. The effects of restrictive fat intake on interoceptive and satiety signaling in the context of episodic memory formation should be further studied, as this can play a role in the strict and controlling tendencies anorexic patients have around mealtimes that are amplified due to the role of abnormal 5-HT signaling (Fig. 1).

Changes in Neural Connectivity in Restrictive Eating Models

Orbitofrontal Cortex

The orbitofrontal cortex (OFC) controls reward and punishment-related perception. For example, the OFC assigns reward values to aversive and pleasant tastes to encode taste perception. This taste perception is then used to influence reward-seeking behaviors, such as eating. However, there is a strong correlation between a subject's preferences towards specifically sweet food and their body mass index (BMI) to the functional connectivity of the OFC. This suggests that the differences in the functional connectivity in the OFC between individuals with varying BMI can lead to variation in assigned award values to the same food stimulus, changing how each person may perceive a food reward and intake food[18]. This study indicates obese patients assign more positive reward values to food, while individuals with decreasing BMI as a result of food restriction may assign less positive or even negative reward values to the same food stimulus[19].

Effective connectivity is defined as the influence one brain region has on another. Recent Functional magnetic resonance imaging (fMRI) studies, measuring brain activity and connectivity between regions, show that individuals with either AN or BN have larger OFC volumes and higher effective connectivity from the medial OFC and insula to the inferior OFC. However, both groups have lower connectivity strength between the middle OFC and hypothalamus, as well as between the gyrus rectus and medial PFC (Fig, 2). Frank et al. believe that the altered functioning between the frontal hypothalamic circuits could promote the formation of associations between food and weight gain in ED patients, promoting it as a 'punishment.' However, the higher functional connectivity in the OFC could impact the computed value of sweet taste perception and experience, reinforcing food-avoidant and restrictive behaviors[4].

Similar patterns of OFC effective connectivity are found in patients with depression (MDD)[20], as well as reduced sensitivity to different rewards as the OFC has higher activation when presented with a non-reward condition rather than a reward condition. These findings suggest that those with MDD have an increased sensitivity to non-reward, or not receiving an expected reward, which provides evidence for the hypothesis that individuals with MDD experience decreased medial OFC activation from typical, pleasantly rewarding stimuli[21]. Similar OFC connectivity patterns between ED and MDD patients should be further examined, as the decreased sensitivity to pleasantly rewarding stimuli observed in MDD patients could reveal how ED patients assign reward values to food and weight gain. There may be a possible decrease in sensitivity to typical food reward values while there is an increase in sensitivity to abnormal rewards, such as weight gain. This could explain the shifting of ED patients' perspectives to a more non-reward, or unexpected reward stimuli, such as the restriction of food. As many antidepressant medications affect activity and connectivity in the OFC[21], we may be able to repurpose existing anti-depressants for ED patients to change their perception of food stimuli and alleviate restrictive eating behaviors.

Intrinsic Connectivity Networks

Several Intrinsic Connectivity Networks may play a role in AN: the default mode network (DMN), which is activated when the brain is not involved in a specific mental task and is involved in introspection, the executive control network (ECN), which makes decisions for goal-directed behaviors, and the basal ganglia network (BGN), which is involved in processing rewards. Chen et al. conducted a study with 693 healthy undergraduate students and measured the association between network connectivity and eating disorder symptoms. They found that individuals who reported higher levels of ED symptoms had weaker internetwork functional connectivity. The ECN is responsible for attention and goal-directed eating behaviors, and those with irregular ECN connectivity often exhibit strange eating behaviors as they have lower dietary self-control than is exhibited in individuals with BN. AN and BN individuals in this study also showed lower BGN activation and BGN-ECN-associated connectivity. Researchers hypothesize that AN patients may dysfunctionally process rewards but have increased cognitive control. Whereas, BN patients have decreased cognitive control

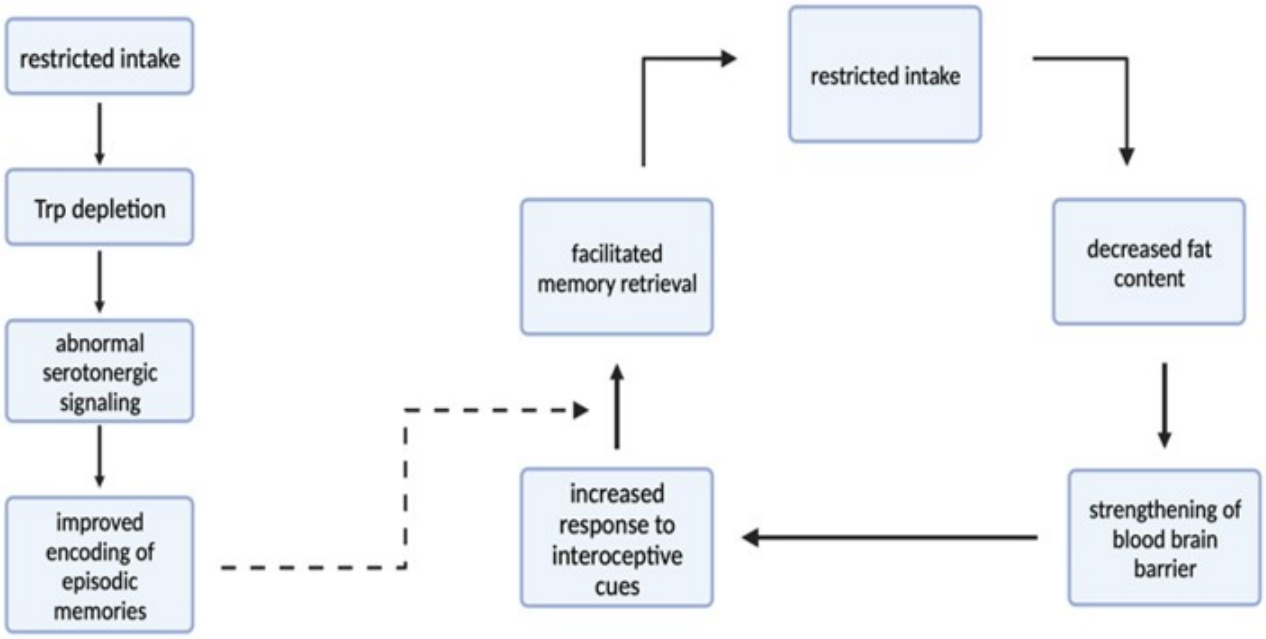

Fig. 1 Reinforcing role of restrictive intake through memory retrieval (Riva et al., 2016)[17], (Davidson et al., 2022)[16]. There are two different pathways that potentially interact with each other to create a reinforcing cycle for restrictive food intake. The first pathway shows how restrictive intake can reduce Trp concentration in the brain as a large portion of Trp is derived from dietary intake. As Trp is an essential element of 5-HT signaling, the depletion of Trp in the brain can alter 5-HT pathways. According to Riva et al.[17], abnormal 5-HT signaling can facilitate the encoding of episodic memory, which plays a vital role in the second pathway involving the facilitation of memory retrieval utilizing interoceptive cues. The second pathway is also triggered by the restriction of nutritional intake, which similar to the reduction of Trp, can also reduce fat content in the brain. Using the findings of Davidson et al.[17], we can hypothesize that decreased fat content strengthens the blood-brain barrier to increase sensitivity to interoceptive satiety cues and modulate appetite-suppressive memory retrieval. At this step, the improved encoding of episodic memory from the first pathway is reintroduced, as these interoceptive cues can more easily retrieve recent memories of eating and feelings of satiety. These recent memories of eating can lead ED patients to further restrict their intake as they induce satiety, feeding into the reinforcing cycle of restrictive intake. Trp: tryptophan, 5-HT: serotonergic, ED: eating disorder.

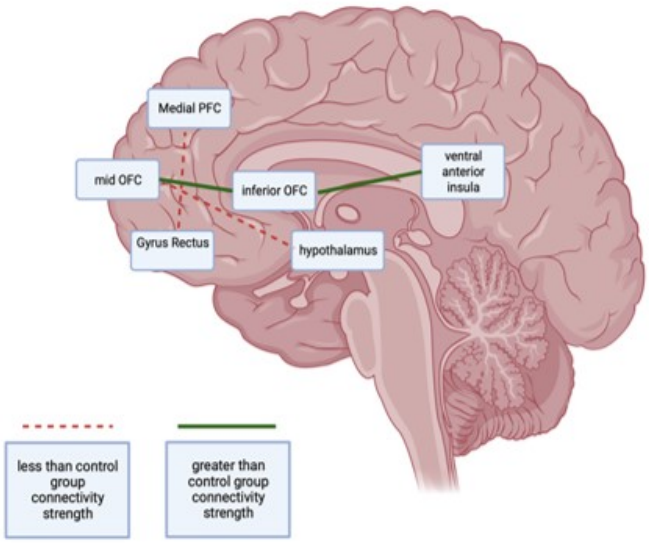

Fig. 2 Summary of brain region connections weakened or strengthened in ED patients (Frank et al., 2016). Both AN and BN patients, when compared to a control group, showed higher effective connectivity from the medial OFC and ventral anterior insula to the inferior OFC. Additionally, both patient groups had lower connectivity strength between the middle OFC and hypothalamus, and the gyrus rectus and the medial PFC[4]. AN: anorexia nervosa, BN: bulimia nervosa, OFC: orbitofrontal cortex.

but exhibit more erratic eating behaviors. This suggests that there may be lower functional connectivity between the BGN and ECN pathways since ED patients often exhibit an inverse relationship between reward reactivity and dietary self-control[22].

The Implications of Altered Plasticity on Learning and Relapse

Myelin Plasticity and White Matter Alterations

Many studies cite white matter abnormality as a common finding in AN MRI studies. White matter organization is measured based on water diffusion analysis: fractional anisotropy (FA), which describes the maximum direction of water diffusion, and the mean diffusivity (MD), which measures the degree of diffusion. Both factors have a negative correlation to white matter intensity[23]. Kazlouski et al. studied a group of 16 AN patients and found FA decreases in many white-matter bundles, particularly in the bilateral fimbria-fornix. Additionally, they found MD increases in frontoparietal and parieto-occipital bundles. The fornix is a white matter track stretching from the hippocampus to the midline, playing an important role in episodic memory recall. The fornix is primarily known for transmitting information through the reward processing network, and damages to it can alter the connections within the limbic system, primarily by affecting food processing[24].

Another study by Kim and Whalen found that white matter pathway integrity is negatively correlated to Trait Anxiety. Trait Anxiety is a stable experience of negative emotions that persist across many different situations, not just in particularly stressful ones. This type of anxiety is commonly associated with EDs as it takes form through avoidance of social eating and low self-esteem. The correlation between Trait Anxiety and white matter pathways indicates that ED individuals with high levels of anxiety have lower white matter density, suggesting that white matter density can be used to predict anxiety levels and can directly affect anxiety, potentially contributing to Trait Anxiety to drive EDs[25].

Alterations to the white matter fornix pathways and findings about Trait Anxiety levels could be due to abnormal myelin plasticity, where white matter gets its color and nutrients from[26], in ED individuals. Pappaianni et al. used ultra-high field MRI to measure intracortical myelin in AN and control patients. On average, AN patients had lower intracortical myelin levels compared to controls. The team hypothesized this was due to malnutrition since myelin contains a large amount of lipids and proteins. Myelin volume has been used as a marker of plasticity, and the myelin loss in AN patients can point to reduced cognitive flexibility and the inability to change beliefs and behaviors[27]. Oligodendrocyte precursor cells (OPCs) proliferate and differentiate into new oligodendrocytes, which then integrate themselves as myelin sheaths around axons, and can undergo plasticity by altering the length and thickness of each layer[28]. Recent theories that correlate white matter structural changes with increased myelin density suggest that myelination may be a factor in learning[29]. If this is the case, this may correlate malnutrition with the inability to change beliefs and behaviors, attributed to myelin plasticity, in ED patients. This inability to change beliefs that accompany a decrease in nutritional intake suggests that recovery without adequate nutritional intake can result in relapse and reverting back to harmful beliefs and behaviors, such as low self-esteem and avoidance of social eating. Since malnutrition has been proven to impact myelin concentration, it would also directly impact white matter tracts, such as the fornix, that control reward and food processing as well as anxiety levels in the context of plasticity (Fig. 3). One way to limit chances of relapse in recovering ED patients is to target white matter levels in the brain through diets with a surplus of healthy fats and potential dietary supplements.

Brain-Derived Neurotrophic Factor

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin that plays a role in the survival and differentiation of developing neurons as well as the regulation of matured neurons. BDNF expression is dynamic, with epigenetic factors playing a crucial

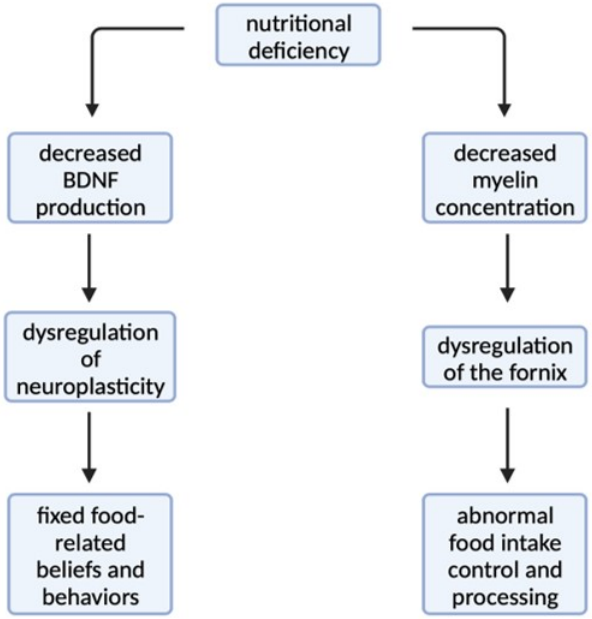

Fig. 3 Effects of neuroplasticity changes on food reward processing and psychological beliefs (Kazlouski et al., 2011). The lack of nutrients can affect neuroplasticity in two ways. The lack of nutrients can affect myelin plasticity, decreasing the concentration of myelin, specifically in white matter bundles involved in the reward processing network, like the fornix[27]. Changes in myelin plasticity and concentration can affect the fornix's ability to process food rewards and control intake[24]. Another potential factor of neuroplasticity that can be affected by nutritional deficiency is the BDNF in the brain. Since BDNF is known to enhance neuronal plasticity, which can help rewire our beliefs and change our way of thinking[30], decreases in BDNF concentrations can make changing ED-related beliefs and behaviors harder to eliminate. These are two potential pathways for how the lack of nutrients can change the role that neuroplasticity plays on the brain, and how those changes feed into the reinforcing cycle of restrictive eating. BDNF: brain-derived neurotrophic factor, ED: eating disorder.

role in gene expression. It is important to note that as a neurotrophic factor, BDNF plays a very significant role in regulatory mechanisms surrounding weight and metabolism. However, this section of the paper will focus most on the linkage between BDNF to long-term potentiation (LTP) and the formation of memories, which leans into the theory that BDNF mediates plastic changes in the brain[30]. Nakazato et al. researched the possible involvement of BDNF in individuals with EDs by comparing BDNF serum levels in female AN and BN patients and control non-patients. They found that ED patients have lower levels of serum BDNF, which is positively correlated with BMI, meaning an increase in weight[31]. They also found in a previous cross-sectional study that a partially recovered AN group had slightly higher levels of BDNF than the current AN group. However, this difference was not statistically significant[32]. This cross-sectional study only studied a recovered AN group, which was defined as a group of women who had a regular menstrual cycle for at least one year. However, this definition only takes into account physical recovery, not the mental recovery that may be affected by changes in BDNF levels. Since physical weight is not always an indicator of cognitive thoughts and motives in ED individuals, it is important to do further research on BDNF levels in ED patients who have variations in physical symptoms of malnutrition. Gravesteijn et al. compared 48 papers and articles that studied the effects of dietary supplements, vitamins, minerals, probiotics, polyphenols, etc. on the concentrations of BDNF in the brain. While there was no clear cause-and-effect relationship found, most studies showed that a boost to these dietary factors correlated to an increase in BDNF levels or suggested a trend toward it[33]. However, individuals with restrictive eating patterns often have a less-than-adequate intake of many dietary and nutritional necessities, such as zinc, vitamin D, and amino acids[34]. The findings of Gravensteijn et al. suggest that the lack of these nutrients can correlate to a decrease in BDNF concentrations in the brain. Additionally, the reduced levels of BDNF can be explained by its linkage to leptin, an appetite-suppressant hormone, as leptin indirectly stimulates the synthesis of BDNF mRNA and protein by activating BDNF-expressing neurons[35]. Since leptin is strongly reduced in AN patients, it is possible that BDNF-expressing neurons were not adequately activated, leading to a decrease in BDNF expression[36]. Milos et al. performed a study that revealed when AN patients were given metreleptin supplements, which are typically used to treat leptin deficiency, they displayed a decreased fear of weight gain and an improvement in anxiety-related mood. This study and the linkage between BDNF and leptin show how lower levels of BDNF may also be correlated to common cognitive and psychological aspects of EDs, such as food and weight-gain anxiety[37].

BDNF is known to enhance neuroplasticity, which can help rewire our beliefs and change our way of thinking. Likewise, decreases in BDNF can perpetuate the restrictive thoughts often

associated with EDs by making it more difficult to change beliefs and behaviors, often making recovery more difficult (Fig. 3). Since many antidepressant and antipsychotic medications have been shown to increase BDNF by targeting synaptic availability of 5-HT, a similar approach can be utilized in medications for restrictive ED patients as increasing local BDNF levels can reduce the likelihood of relapse and the recurrence of harmful eating pattern.

Discussion

Currently, most recovery options for EDs only include cognitive-based therapy that aims to reduce harmful thoughts and habits. However, a range of studies show that more than 25% of AN patients relapse after receiving official treatment and therapy[38]. This can be explained by the studies outlined in this paper that show multiple pathway and structural changes in AN patients, suggesting that restrictive eating behaviors are self-reinforcing, and cognitive-based therapy may not adequately address the neurobiological grounds for restrictive eating behaviors. Malnutrition can alter our reward processing mechanisms by directly affecting neurotransmitter reward pathways; overactive DA pathways can create a stronger predictive relationship between food intake and body weight while increasing motivation to engage in extreme behaviors, while abnormal 5-HT pathways may amplify the use of interoceptive and satiety signaling to retrieve recent episodic memories of eating, resulting in more self-controlling and restrictive eating behaviors. Changes in neural connectivity in AN patients can alter reward association abilities; altered functional connectivity can promote the formation of associations between food and weight gain as 'punishments', and lower BGN activation and BGN-ECN-associated connectivity in ED patients can reveal an inverse relationship between reward reactivity and dietary self-control. Finally, the very mechanisms of change and learning in the brain are altered with malnutrition; malnutrition can affect myelin plasticity and white matter pathways that control food processing, and studies that reveal lower concentrations of BDNF in AN patients can affect their neuroplasticity and their ability to change beliefs and behaviors. These multiple structural and activation changes in the brain of AN patients suggests that malnutrition and restrictive eating behaviors are part of a positive feedback loop, where prolonged malnutrition reinforces the very behaviors that cause it at a neurobiological level. This understanding can help researchers, doctors, therapists, nutritionists, and other health professionals to better treat ED patients with the understanding that behaviors are reinforced and caused by chemical and connectivity imbalances rather than controllable changes in mentality and psychology. As many of the chemical changes in AN patients are similar to the changes in the brains of clinically depressed patients, current research aimed at targeting these overlapping pathways to treat depressive symptoms can be applied to ED research to better aid physical recovery with mental recovery. In addition, many other neurobiological changes that are linked to changes in food and reward processing, such as 5-HT neuronal activity, computation of reward values, and BDNF levels in a larger variation of patients should be further researched to find a larger variety of approaches to drug therapy for ED patients.

Although the potential connection between neurobiological changes in neurotransmitter pathways, effective connectivity, plasticity mechanisms and ED progression could yield novel therapeutics for ED patients, the field is currently limited by several factors. One factor is that many studies referenced in this review only compare ED patients to a control group that displays no restrictive eating symptoms, meaning many of the associations between findings and ED behaviors could be affected by confounding factors unrelated to EDs. A more adequate approach to finding a stronger correlation between the neurobiological findings of ED behaviors is to compare ED patients with both a control group and a recovered ED patient group. This would assist in determining that these neurobiological changes are a result of malnutrition that continues to reinforce ED behaviors rather than innate characteristics of ED brains.

Further areas of study include the type of 5-HT neuron activity and how that correlates to the processing of rewards and punishments in relation to typical food rewards. Another potential area of study that should be researched further is the connection between restrictive EDs and MDD. Since these two disorders often co-occur, their relationship in OFC connectivity patterns and sensitivity to non-rewards can reveal more about the neurobiology of EDs to yield better targeted and sustained medication and treatments.

Conclusion

By analyzing specific AN and BN studies or known effects of malnutrition on reward and reinforcement pathways, connectivity changes in the brain that imply changes in reward association, and abnormal neuroplasticity, we can hypothesize there is a reinforcing pathway that is responsible for the proliferation of restrictive eating habits. ED individuals often spend most of their lives in a cycle of recovering and relapsing due to insufficient treatments. Utilizing the neurobiological findings of reinforcement and learning mechanisms, we can shift towards more drug-based therapies that target specific neurotransmitters and connectivity pathways, which creates a more targeted approach to recovery alongside current therapy-based treatments.

Methods

In this paper, I used search engines like PubMed to find research papers and review articles. I searched for more review papers

on known changes in DA and 5-HT pathways in ED patients, specific MRI studies on connectivity changes in the brain, and research papers on the relationship of plasticity to learning and memory. For each subtopic, I initially searched for papers relating to "anorexia" or "eating disorders," with additional searches using keywords like "eating" or "diet." I cited the studies from these papers if they had a sample size of more than 20 animals per group or more than 50 human subjects per group. Additionally, I made sure the papers I was citing were published in the last ten years. If I used any paper published prior to the last ten years, I made sure it was cited along with and relevant to the findings of more recent studies and papers. If there was a potential limitation or bias I noticed in the study, I made sure to mention it along with my citation.

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