Neurobiological Perspectives on Mood and Eating Disorder Comorbidity: A Systematic Review

Sahana C Kanagala

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Recent mental health awareness has prompted research into the neurobiology of mood and eating disorders. Serotonin level fluctuations have been linked to depression, a well-known mood disorder, and selective serotonin reuptake inhibitors (SSRIs) are commonly used for its treatment. Alterations in the neutral circuits associated with food reward, along with a decrease in gray matter volume (GMV), have been implicated as markers for eating disorders, particularly anorexia nervosa. However, research into the neurobiological basis of the comorbidity of mood and eating disorders remains scant. This systematic review aims to synthesize existing research and identify the neurobiological mechanisms that may contribute to this co-occurrence. A systematic literature search was conducted across four databases: PubMed, PsychArticles, ScienceDirect, and BioMed Central. Through abstract and full-text screening, a total of eight papers met the inclusion criteria and were included. These papers were expected to be empirical studies that investigate a neurobiological mechanism hypothesized to facilitate the co-occurrence of mood and eating disorders in human and animal participants through measurements of mood disorders, disordered eating behaviors, and the suspected neurological process. The interventions in this review were investigated through the categorization of the included studies according to the neurobiological mechanism explored in each. Across the 8 eligible papers, the inquired processes are leptin dysregulation (N=3), abnormalities in the serotonergic pathway (N=2), hypothalamic-pituitary-adrenal axis impairments (N=1), variations in gray matter volume (N=1), and genetic variants (N=1). This study suggests that emotional dysregulation and reward system dysfunction may contribute to mood and eating disorder comorbidity. However, further empirical investigations are needed, given the limited research.

Keywords: neurobiological, eating disorder, mood disorder, comorbidity, review

Introduction

Awareness of eating and mood disorders has risen, driven by advocacy for timely treatment to prevent symptom escalation. Eating disorders (ED), more common among women, have an estimated prevalence of anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) at 0.9%, 1.5%, and 3.5% respectively [1]. For men, these rates are approximately 0.3%, 0.5%, and 2.0% [1]. AN is characterized as a restrictive ED, in which the heightened fear of gaining weight leads to aberrations in the self-perception of body weight and shape [2]. On the other hand, BN and BED are indicative of recurrent binge eating paired with intense feelings of stress and guilt, but in BN, binges are also followed by purging to prevent weight gain. Despite variations in the chronology of the onset of symptoms, EDs often co-occur with mood disorders (MD), which include major depressive disorder and bipolar disorder. Major depressive disorder entails a persistent depressive mood, loss of interest in previously enjoyed activities, reduced confidence, tiredness, inability to concentrate, and negative interference with a person's daily life [2]. Bipolar disorder is distinguished by periodic episodes of intense emotions, either manic or hypomanic, that disturb an individual's mood, energy, and function. Notably, 80% of both AN and BN patients also experience MD. When looking into a specific MD, such as bipolar disorder, there are parallels with ED: weight and eating weight and eating irregularities, behavioral activation disturbances, impulsivity, compulsivity, and emotional dysregulation.

Understanding the neurological markers associated with comorbidity is not only crucial for professionals to identify comorbid disorders in individuals with ED or MD but also for the mental health literacy (MHL) of the common public. MHL refers to how well-versed an individual, or group of people, is in the recognition, management, and prevention of a mental illness or illnesses. MHL levels tend to indicate the likelihood that an individual utilizes or seeks available mental health resources [3]. For example, one of the components of MHL is the awareness of risk factors and causes, and this could influence how individuals would engage in activities and resources for symptom management. Furthermore, as biological factors are occasionally overlooked due to common attributions to environmental factors in diagnoses, the assumption of a cause can influence

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health-seeking patterns and treatment response[4]. Awareness of neurobiological factors that underlie the co-occurrence of MD and ED could present a higher MHL, possibly reducing the risk of overlooking certain treatments and resources.

The interpretation of MDs like depression in ED varies based on chronology. If depression precedes ED, it implies that there is a risk of developing an ED, negative self-image, and serotonin-related biological irregularities. If depression follows an ED, it suggests that the length of the illness has an impact on a person's social life, indicating potential true comorbidity. Concurrent onset, however, may imply that depression results from significant malnutrition1. ED and MD, such as bipolar disorder, often share symptoms, complicating the distinction between a standalone and comorbid condition. While research on the biological markers for eating or mood disorders exists, the biological basis of their comorbidity remains elusive. This systematic review aims to address this limited availability of literature investigating neurological mechanisms underlying the comorbidity of MD and ED by analyzing existing empirical studies and their implications.

Methods

A systematic review of empirical studies was conducted to analyze current evidence on the neurobiological basis of the comorbidity between ED and MD. The current review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[5]. A search was undertaken across four databases, PubMed, PsychArticles, ScienceDirect, and BioMed Central, using the keywords ("neuro*" OR "biological" OR "base" OR "brain") AND (comorbid*" OR co-occurring" OR "shared mechanisms") AND ("mood disorder" OR "depression" OR "bipolar" OR "major depressive disorder") AND ("eating disorder' OR "anorexia" OR "bulimia" OR "binge"). Possible search bias was addressed through the incorporation of Boolean operators "OR" and "AND," truncation, synonyms, and particular MDs and EDs, such as depression and anorexia, respectively.

A total of 1,325 records identified through the database search underwent screening at the title and abstract levels. The criteria for inclusion were centered on studies focusing primarily on identifying the neurobiological mechanism that underlies the comorbidity of ED and MD. The full texts of the 43 resulting studies were then assessed for eligibility, leading to the 8 included studies in this systematic review.

These final 8 papers were selected following abstract and full-text screening based on the inclusion and exclusion criteria, as shown in the PRISMA flowchart in Figure 1. The studies, empirical and longitudinal, were conducted after 2000 and focused on the neurobiological nature of the co-occurrence of MD and ED by observing at least one group of participants diagnosed with an MD, exhibiting at least disordered eating behaviors, or both. In the instance that participants either displayed MD symptoms, ED characteristics, or disordered eating behavior, studies were expected to collect regular measurements of the comorbid disorder (or behavior). The neurobiological mechanism should have been investigated throughout data collection concerning neurological structures and chemicals. Studies that investigated only the previous or subsequent appearance of either an MD or ED following recovery from a previous disorder were excluded as they did not pertain to the focus of this systematic review on comorbidity.

The included 8 studies were evaluated to identify the neurobiological mechanisms increasing the risk for (or accounting for) the comorbidity of disordered eating behavior and mood disorder. For all eligible studies, the following data was extracted: Authors, design, sample, measurements of disordered eating behavior, measurements of mood disorders, neurobiological mechanism, and the main relevant findings. Following methodological recommendations from PRISMA, a component approach to quality assessment was employed. The quality of eligible papers was assessed using the Effective Public Health Practice Project tool (EPHPP) adapted to enable assessment of the specific methodological features of the primary studies pertinent to the research question under scrutiny[6]. Our quality assessment considered the following three domains: (a) selection bias, (b) study design, and (c) data collection methods. The risk of bias in the eight studies was assessed using the Cochrane ROBINS-I tool for non-randomized control studies[7]. Mills et al (2018), Mills et al (2019), Gauthier et al, Chandler-Laney et al, Yilmaz et al, and Liu et al exhibited low risk of bias, and Rybakowski et al and Zhang et al exhibited moderate risk of bias.

Results

The eight studies included in this review predominantly feature longitudinal studies conducted within the last two decades, focusing on empirical investigations into various neurobiological mechanisms. These mechanisms include leptin dysregulation, abnormalities in serotoninergic pathway functioning, hypothalamic-pituitary-adrenal (HPA) axis impairments, variations in gray matter volumes (GMVs), or genetic variants.

Of particular interest, three studies examined the role of leptin dysregulation in the comorbidity of eating and mood disorders. Mills et al. (2018) conducted a pioneering longitudinal study in Australia involving 123 adults. This study probed into leptin dysregulation and uncovered that log-leptin values exhibited minimal variation between individuals with major depressive disorder and control subjects. However, distinct patterns emerged based on appetite and weight changes. Females exhibiting decreased appetite/weight demonstrated lower log-leptin values. In contrast, those with increased or stable appetite/weight showed elevated log-leptin levels[8]. Subsequently,

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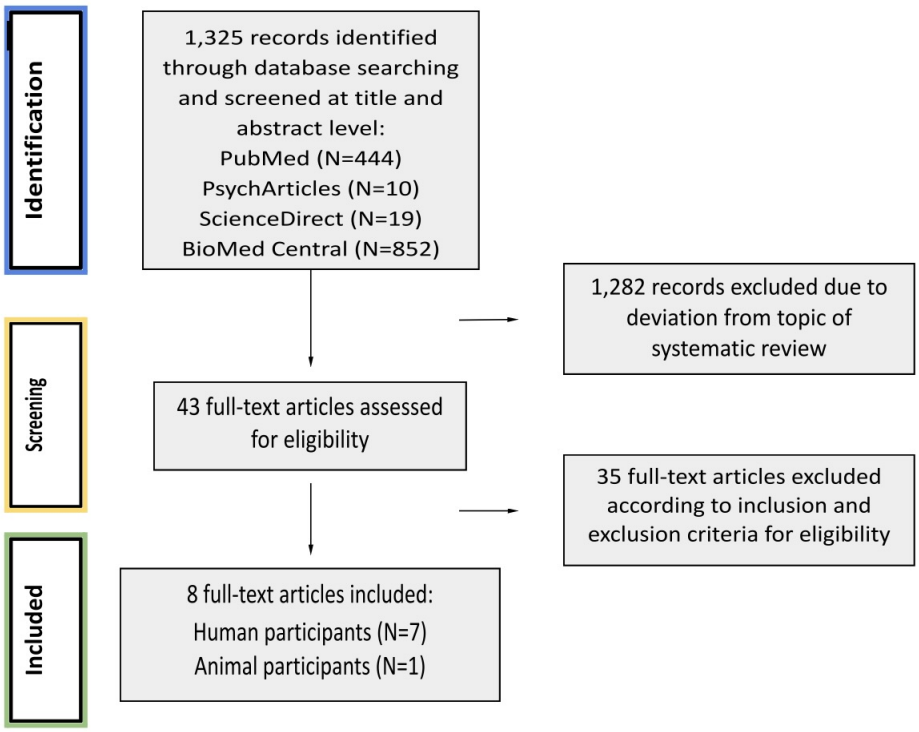

Fig. 1 Paper selection flow chart

Mills et al. extended this research with another longitudinal study involving 120 adults, examining the interplay between problematic eating behaviors, the severity of depression, and leptin dysregulation[9]. The findings indicated a positive correlation between leptin levels and disordered eating, while ghrelin, or appetite stimulant, levels were inversely related. Notably, abnormal eating behaviors were more prevalent among individuals diagnosed with major depressive disorder compared to their counterparts in the control group. A separate study conducted in Poland by Rybakowski et al. delved into the impact of leptin on ventral striatum circuits, examining its role in the dysfunction of the reward system[10]. The ventral striatum is a region of the brain that plays a significant role in reward processing as it is observed to be active in reward anticipation. Furthermore, this region is strongly connected to the limbic system, made up of components known for generating emotions[11]. This study revealed an inverse relationship between increased leptin levels following caloric restriction and the amelioration of depressive symptoms, suggesting a significant neurobiological link in the comorbidity context.

Two of the studies examined the atypical functioning of the serotonergic pathway, a crucial neuronal system that transports the key neurotransmitter serotonin[12]. Chandler-Laney et al. conducted a longitudinal study in the United States using 80 rats, investigating serotonergic pathway dysregulation[13]. The study found that high-calorie restriction led to reduced serotonin levels in the medial prefrontal cortex, with rats under high-calorie restriction displaying depressive-like behaviors in swim tests. The medial prefrontal cortex is key in combining info from various cortical and subcortical areas to be sent to the output structure. Abnormalities in its functioning could lead to impairments in cognitive processes, emotion regulation, motivation, and ability to socially interact. As a result, it is a cortical region suspected to play a role in the manifestation of numerous neurological and psychiatric illnesses, including depression and anxiety disorder[14]. In a separate longitudinal study in France conducted by Gauthier et al., which included 42 inpatients, a significant correlation was observed between disordered eating behavior and depression[15]. The study reported notably lower serotonin markers in patients with anorexia nervosa compared to controls and highlighted a correlation between increased tryptophan to large neutral amino acids (TRP/LNAA) ratio and reduced depressive symptoms. Tryptophan is an essential amino acid exclusively obtained through diet and the sole precursor to peripherally and centrally produced serotonin. Central production takes place in the raphe nuclei of the brain stem after tryptophan enters the

central nervous system after crossing the blood-brain barrier. As tryptophan competes with large neutral amino acids to cross the blood-brain barrier, the TRP/LNAA ratio following refeeding is an indicator of the proportion of tryptophan utilized to produce cerebral serotonin [16].

The role of HPA-axis impairments was investigated in a study by Yilmaz et al [17]. Conducted in Canada with 47 female participants, the study examined the relationship between HPA axis abnormalities and bulimia nervosa. The HPA-axis is the coordination of the central nervous system and peripheral tissues in the regulation of the body's adrenal hormones, including cortisol [18]. The findings indicated no correlation between current or behaviorally recovered bulimia nervosa and HPA-axis abnormalities. However, an inverse correlation was noted between depression scores and percent afternoon cortisol suppression.

Regarding GMV abnormalities, Zhang et al. executed a longitudinal and mediation study in the United Kingdom with 1,594 adolescents [19]. GMV, consisting of unmyelinated axons, plays a crucial role in a myriad of bodily functions and is instrumental in enhancing brain functionality. The study observed lower GMVs in specific brain regions associated with emotional regulation and reward processing in adolescents who developed depression. Interestingly, these regions showed overlap with clusters associated with the development of purging behaviors.

Finally, a study by Liu et al. in China, involving genetic association data from 3,560 adults, investigated genetic variants linked to bipolar disorder and ED [20]. This study identified the SOX2-OT/FXR1 region on chromosome 3q26.33 as uniquely associated with both bipolar disorder and EDs. Additionally, the ABCG1 region was implicated in regulating eating behavior, highlighting the potential genetic foundations of these comorbidities.

Discussion

This systematic review examined eight studies that investigated neurobiological mechanisms potentially underlying MD and ED comorbidity, including leptin dysregulation, abnormal serotonin activity, variations in genomic regions such as the SOX2-OT, differences in GMV, and changes in hypothalamic-pituitary-adrenal (HPA) activity. As varied neutral pathways were involved, it was necessary to analyze each mechanism separately. However, despite the range of proposed mechanisms, a common finding across these studies is that impairments in emotional regulation and reward system functioning play a significant role in developing this comorbidity.

Leptin Dysregulation

Three studies underscored the role of leptin dysregulation in the comorbidity of mood and eating disorders. Notably, two studies conducted sequentially by Mills et al. provide significant insights into the relationship between leptin levels and problematic eating behaviors in individuals with Major Depressive Disorder (MDD) [8,9].

Leptin, a peptide hormone predominantly produced by adipose tissue, plays a crucial role in conveying information about adipose tissue size and energy storage status to the brain [21]. Additionally, Figure 2 displays how leptin functions as an appetite suppressant, inhibiting neural pathways that are activated by appetite stimulants, thereby reducing energy intake [22,23]. Accordingly, atypical leptin levels are hypothesized to play a role in the manifestation of disordered eating behavior (DEB) and ED, as these are characterized by unusual patterns in appetite. MDD, a heterogeneous mood disorder, often manifests in various symptoms, including changes in appetite and weight that are not related to motivated dieting [24]. These can include increased, decreased, or unchanged appetite or weight. Furthermore, depressive patients exhibited abnormal levels of leptin in existing clinical studies investigating the link between leptin and depression. However, it remains obscure whether increased or decreased levels play a more significant role due to a lack of consistency in results [25]. Despite this lack of definitive clarity, leptin remains a factor speculated in MD and ED.

The pilot study by Mills et al. revealed that leptin is more closely associated with sex-specific symptoms and physiology than with MDD as a whole [8]. According to the raw leptin levels, the mean for the MDD group was greater than the control, indicating the unusually high leptin levels suspected to be involved in comorbidity. However, this data was unreliable as it displayed a positively skewed distribution, an outcome of extreme data on the higher end. Therefore, the raw data was then natural-log transformed to prevent extreme data from skewing the mean levels of leptin in the control and MDD groups, hindering an accurate comparison [26]. As a result, the lack of a significant difference between the two average log-leptin levels demonstrates that leptin does not carry the expected significance in ED and MD comorbidity.

Further, a subset analysis focusing on food addiction and problematic eating behaviors in MDD indicated gender-specific patterns. Notably, females more frequently exhibited characteristics of food addiction according to the Yale Food Addiction Scale (YFAS) criteria. Consistent with leptin's role as an appetite suppressant, males with decreased appetite/weight displayed increased leptin levels. Conversely, females with increased appetite/weight had higher leptin levels, suggesting potential leptin resistance, characterized by elevated leptin levels and decreased sensitivity [8,27]. This pattern, indicating sex-specific symptoms and leptin resistance, was also observed in the subsequent study by Mills et al., reinforcing the evidence of problematic patterns in appetite and food intake, particularly in females [9]. On the other hand, the lower log-leptin levels in females with low weight in comparison with those with a stable or increased appetite also align with the normal function of leptin, which is

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produced by adipose tissue to regulate body weight[28]. Leptin resistance, shown in Figure 3, has been recurrently hypothesized to underlie obesity and extreme weight gain frequently associated with BN and BED due to the hormone's role in appetite suppression[2,23]. However, it is unclear whether leptin resistance may also play a significant role in the restrictive behavior of anorexic patients. In addition, further investigations are necessary to probe into the particular impairments of its underlying mechanisms, including leptin transportation, signaling, and neural networks

Complementing these findings, another study by Rybakowski et al. explored the relationship between leptin levels and depressive symptoms in female patients with anorexia nervosa, highlighting the involvement of a dysfunctional reward system10. This study observed the effects of leptin on reward behaviors mediated by the ventral striatum during treatment-induced weight gain in anorexic patients. This concordance in the resulting HDRS and BDI scores may be credited to the differences in the reliability of sources as HDRS is clinically administered while BDI is self-reported[29]. These results implicate leptin's role predominantly in somatic and motor depressive symptoms, suggesting its possible function as an inhibitor of the ventral striatum, a critical component of the brain's reward and motivational system[27].

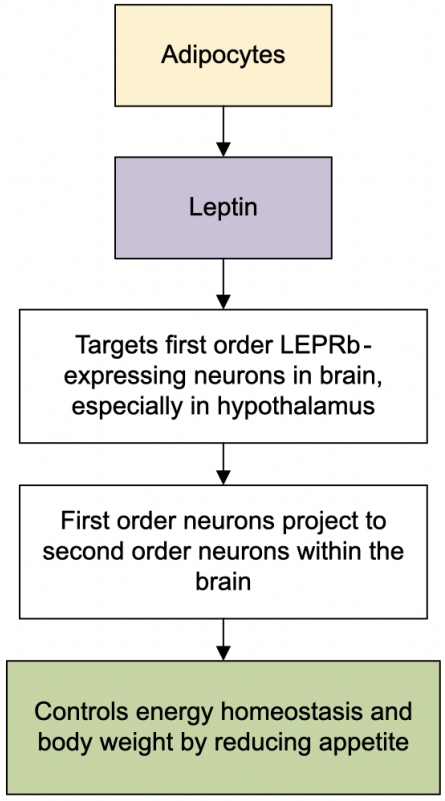

Fig. 2 Normal leptin signaling

Abnormalities in the Serotonergic Pathway

In the discourse on the comorbidity of MD and ED, two studies have provided evidence linking abnormalities in the serotonergic pathway with the characteristic depressive symptoms and caloric restriction seen in disordered eating behaviors. The pathophysiology of Major Depressive Disorder (MDD) remains incompletely understood, though the monoamine deficiency hypothesis, focusing on the serotoninergic system's role in synthesizing serotonin—a central nervous system neurotransmitter—has gained traction[30]. The prevalent use of SSRIs, a class of antidepressants, underscores the hypothesized significance of serotonin in depression. Serotonin disturbances have also been implicated in appetite dysregulation characteristic of disordered eating. These atypical eating patterns observed in DEB and ED are suspected to alter the amount of serotonin produced from its amino acid precursor tryptophan, which is exclusively obtained through diet[31]. The observed aberrations in neurochemical levels, particularly serotonin among patients with disordered eating, have spurred investigations into serotonergic pathway disturbances and serotonin dysregulation.

Chandler-Laney et al. conducted an experimental study on rats to elucidate the effects of past caloric restriction and the frequency of palatable food intake on depressive symptoms and monoamine levels in the hypothalamus, nucleus accumbens, and medial prefrontal cortex (mPFC)[13]. The findings revealed that high-calorie restriction (HCR) combined with intermittent access to palatable food (PF) induced alterations in monoamine-mediated regulation of feeding and mood, evident through changes in serotonin turnover and levels. Methodologically, the study involved administering palatable foods and fluoxetine to both HCR and non-HCR rats with varied diet patterns, followed by measurements of monoamine level variations post-euthanasia. A noteworthy outcome was that HCR led to decreased serotonin levels in the mPFC compared to non-HCR, correlating with increased inactivity during the swim test, an indicator of depressive-like behavior. This aligns with findings that a restrictive diet reduces serotonin synthesis due to a drop in the monoamine precursor tryptophan. Furthermore, this decrease in mPFC serotonin is consistently linked to behaviors indicative of negative affect and mood disorders. Supporting evidence includes serotonin disturbances in the mPFC, with lowered serotonin concentration, release, and neurotransmission observed in preclinical chronic mild stress models of depression[32].

Another study investigated the serotonergic system in anorexic female patients, observing total blood serotonin and

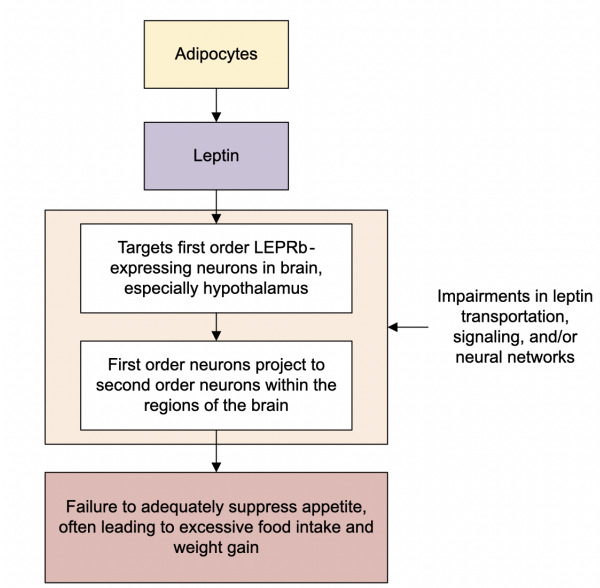

Fig. 3 Abnormal leptin signaling is representative of leptin resistance

plasma tryptophan post-refeeding [15]. The results confirmed the disruption of the brain serotonergic pathway during caloric restriction, typical of anorexia nervosa. At the beginning of the study, patients presented with exceptionally low tryptophan levels and TRP/LNAA ratios, and upon refeeding, a reduction in depressive symptoms was documented alongside an increase in the TRP/LNAA ratio. Tryptophan competes with large neutral amino acids to gain access to the central nervous system via the blood-brain barrier. The higher TRP/LNAA ratio suggests a greater proportion of tryptophan successfully transported to the brain and subsequently synthesized into cerebral serotonin. The association of an increase in the TRP/LNAA ratio with ameliorated depressive symptoms implicates the role of serotonin in the relationship between the restrictive behavior towards food in AN and depression, as shown in Figure 4 [16]. However, the study also recorded a paradoxical positive correlation between blood serotonin levels and depressive symptoms, suggesting that increased serotonin receptor activity might exacerbate dietary restriction. This unexpected correlation may hint at the possible engagement of other neurotransmission pathways, such as a dysregulated dopaminergic pathway, which has been posited as contributory to the pathophysiology of depression.

Changes in HPA Activity

The HPA axis is central to the body's response to stress, orchestrating a sequence of neuroendocrine actions that culminate in the secretion of cortisol, the primary stress hormone. This axis stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn regulates cortisol production**?** . Aberrations in HPA axis regulation are implicated in the pathophysiology of various mood and cognitive disorders, with 35% to 65% of patients diagnosed with Major Depressive Disorder (MDD) displaying abnormal HPA axis activity [33]. MDD patients also exhibit a dysfunctional negative feedback system of the HPA-axis as a reduced ability to decrease glucocorticoids, the steroid hormones produced by the adrenal gland, is observed [34]. Furthermore, the glucocorticoid cortisol, which is produced via the HPA axis, has been implicated in interfering with eating behavior, resulting in aberrant food and calorie intakes that are representative of DEB [35]. Speculations about the association of glucocorticoid levels, including cortisol, with MD and ED have led to investigations of the HPA axis to determine if it underlies comorbidity.

Investigating the HPA axis's role in comorbid depression and bulimia nervosa (BN), Yilmaz et al. measured the correlation between cortisol levels and depression scores using a dexamethasone suppression test (DST) [17]. The study involved women with behaviorally recovered BN, those with current BN, and controls with no psychiatric history. The pivotal discovery was that HPA axis irregularities may be more closely associated with comorbid depression rather than BN alone. This was evidenced by the lack of significant differences in cortisol levels between current/recovered BN patients and controls. A relationship primarily with BN would have resulted in a variation between the cortisol levels of the current/recovered BN and control groups. On the other hand, a subset analysis revealed that BN patients with depression exhibited elevated afternoon cortisol levels. The observed deviation of cortisol levels in the group of patients with comorbid BN and depression highlights the possible relationship between HPA-axis dysfunction and the comorbidity of MD and ED.

As part of the HPA axis, the corticotropin-releasing hormone (CRH), which is secreted from the hypothalamus, signals the anterior pituitary gland to release the adrenocorticotropic hormone (ACTH). Subsequently, ACTH stimulates the release of the stress hormone cortisol and androgens. The increase in cortisol then acts on the hypothalamus to reduce the amount of CRH released in a negative feedback loop [36]. The DST, which administers the synthetic ACTH dexamethasone, should typically result in suppressed cortisol levels due to the HPA axis's negative feedback mechanism. In a well-functioning system, which is displayed in Figure 5, increased cortisol, induced by ACTH, would inhibit the release of CRH, the HPA axis's central regulatory hormone [37,38]. Yet, the study yielded atypical results: cortisol was not suppressed in the afternoon in BN patients with depression, as shown in Figure 6, suggesting a dysregulated HPA axis in individuals with comorbid BN and depression [17]. This dysregulation points to the complex interplay between physiological stress responses and psychiatric conditions, underlining the need for integrated approaches to understanding and treating

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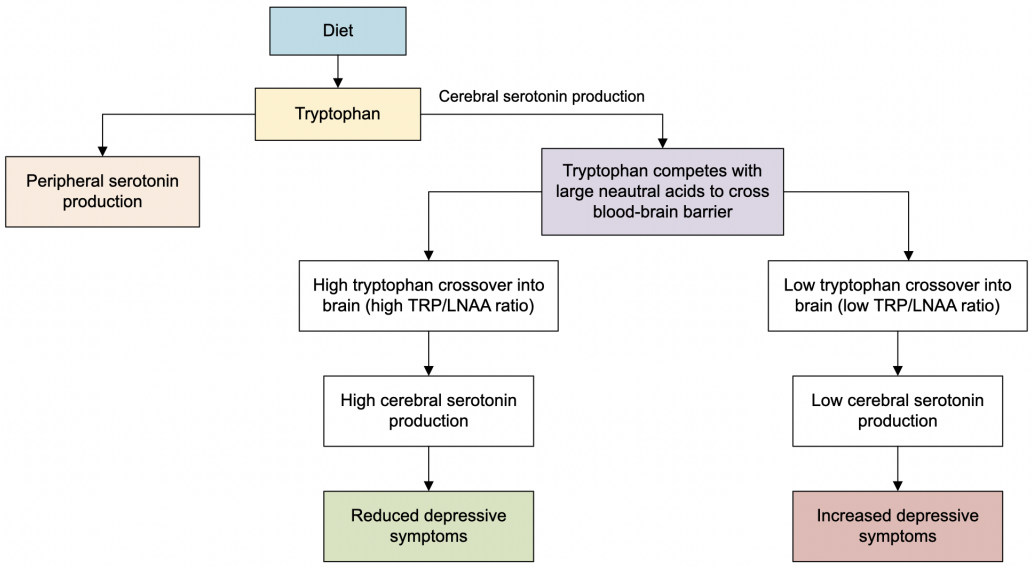

Fig. 4 Production of cerebral serotonin production

these disorders.

Abnormal GMVs

A study by Zhang et al. discerned abnormalities in GMVs within specific brain regions associated with emotional regulation and reward processing, which may contribute to the co-occurrence of depression in individuals with DEBs, particularly those involving purging and binge eating[19]. Gray matter is one of two macroscopic brain tissue types and is made up of neuronal somata, dendrites, and synapses[39]. This tissue makes up the cerebral cortex, the outer layer of the cerebrum that is responsible for high-level processes, such as emotions[40]. Therefore, GMV aberrations in brain regions with significant involvement in neural activities and regulation are suspected to contribute to neurological and psychiatric disorders such as MD and ED.

The research utilized voxel-based morphometry to examine variations in GMVs across the brain, aiming to pinpoint risk factors for the development of DEBs and concurrent mental health issues[19]. The study's whole-brain VBM analysis revealed reduced GMVs in two brain region clusters[19]. These clusters encompassed the medial and left lateral orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), mid-cingulate cortex (MCC), supplementary motor area, dorsomedial prefrontal cortex (PFC), and left dorsolateral PFC. Notably, these regions demonstrated an overlap with those linked to purging behavior development, particularly within the ACC, MCC, medial OFC, and dorsomedial and left dorsolateral PFC[19].

Moreover, the investigation identified brain regions commonly associated with binging or purging (BoP) and depressive symptoms[19]. These findings indicate shared neurobiological pathways, as evidenced by the low GMVs observed in the ACC and medial OFC regions, shown in Figures 6 and 7, respectively. These areas are critical for encoding action-reward associations in reward-based decision-making and for top-down emotion regulation. The study posits that impairments in emotion regulation and reward processing may underlie the intersection of potential future purging behaviors and depression. In agreement with observed GMV decreases in brain regions responsible for emotional dysfunction, cognitive, and stress response, aberrant emotional and cognitive processing in MDD has been commonly associated with ACC among others[41]. Despite the multiple papers that noted a significant gray matter decrease in the ACC, there are also contradicting findings that detected a less prominent GMV reduction in comparison to other areas of the brain. In addition, while the OFC has been suggested as another cortical region involved in MDD manifestation, there has not been as much research into this involvement. In investigations between GMV and ED, GMV reductions in the ACC and OFC areas of women have also been reported in AN. However, there are variations between AN and BN/BED, as those with BN or BED exhibited contrasting increases in the ACC's GMV[42]. Different regions, such as the hippocampus and insular cortex, have also been observed in ED or MD patients in addition to the OFC and ACC. These differences can be attributed to the varying symptomatology among AN, BN, BED, and MD. However, the commonalities found in brain regions exhibiting abnormal GMVs between DEBs and depression still underscore a com-

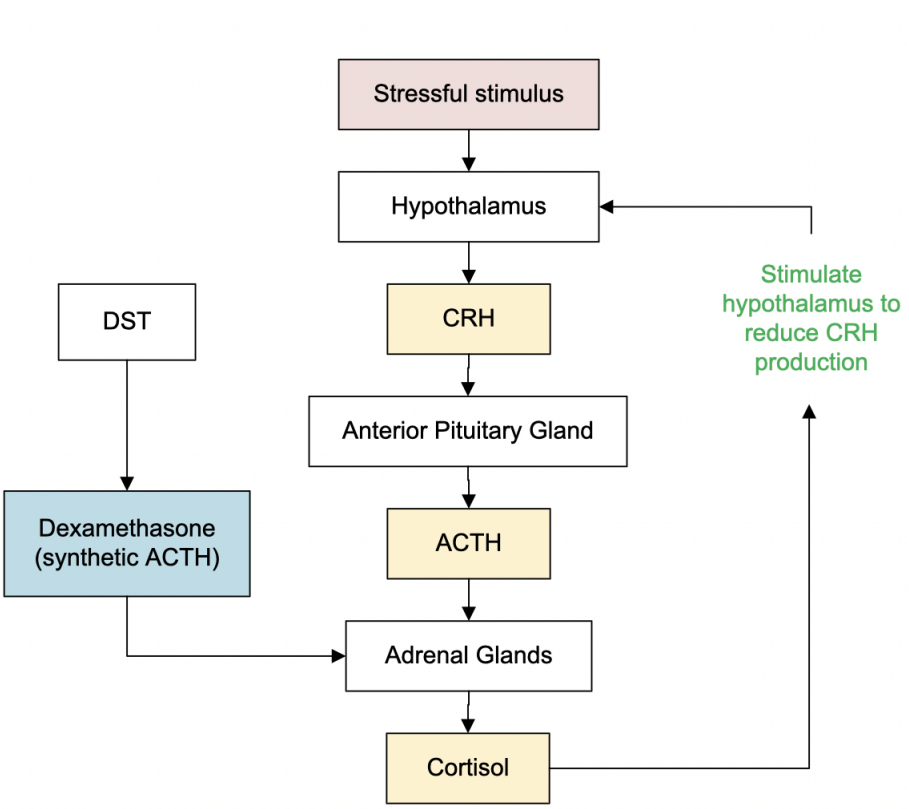

Fig. 5 Normal HPA-axis response to stress

mon neurobiological substrate, enhancing our understanding of the interrelation between these disorders.

Genetic abnormalities and SNPs

Liu et al. conducted a study employing Genome-wide association (GWA) strategies to elucidate the genetic underpinnings that may predispose individuals with bipolar disorder (BD) to eating disorders (ED)[20]. The study uncovered notable findings within the SOX2-OT and ABCG1 genomic regions[20]. The SOX2-OT genomic region is a long noncoding RNA with diversified functions, including the transcription of the SOX2 gene, which regulates the ability of embryonic stem cells to become any cell type. The reduced expression of this region has been found to result in single-nucleotide polymorphisms (SNPs) linked to mental illnesses such as anorexia nervosa[43]. The definitive function of the ABCG1 gene is not conclusive, but it is speculated to play a role in macrophage cholesterol efflux regulation[44]. Specifically, in the comparative analysis between individuals with co-occurring BD and ED (BD+ED) versus control subjects (CTL), researchers identified 13 single nucleotide polymorphisms (SNPs) in linkage disequilibrium within the SOX2-OT/FXR1 region on chromosome 3q26.33[20]. This region has also been previously linked to anorexia nervosa, suggesting a genetic intersection that may contribute to the susceptibility of ED in the context of BD. However, the peak of p-values in the data implies that the observed differences between the two groups are likely due to chance[45]. Despite this uncertainty of a relationship, the p-value does not confirm the degree of accuracy of the hypothesis, allowing for further investigation into this mechanism[46].

The association of the SOX2-OT region with both BD and ED underscores the potential of genetic factors to play a role not only in the manifestation of ED but also in the shared etiological pathways underlying both conditions. The study by Zhang et al. (2016) further complements these findings, indicating a second region of interest: the ABCG1 locus on chromosome 21q22[19]. This gene is posited to be involved in G protein signaling relevant to serotonin synthesis. ABCG1 encodes for ATP-binding cassette sub-family G member 1, a transporter protein implicated in the uptake of tryptophan—the precursor to serotonin. Since serotonin is a critical neurotransmitter that modulates

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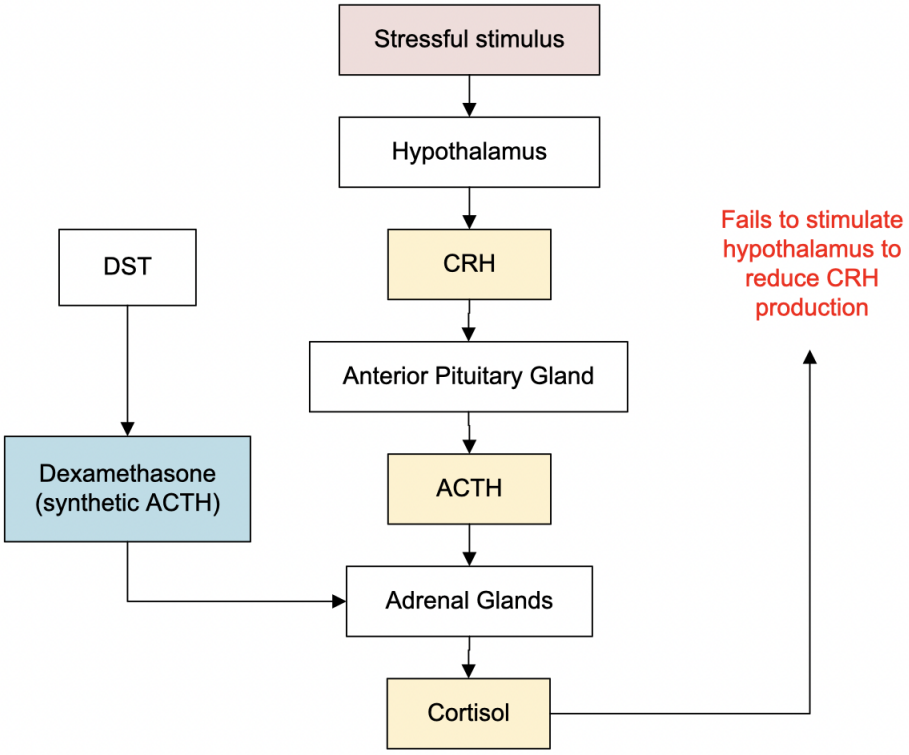

Fig. 6 Abnormal HPA-axis response to stress

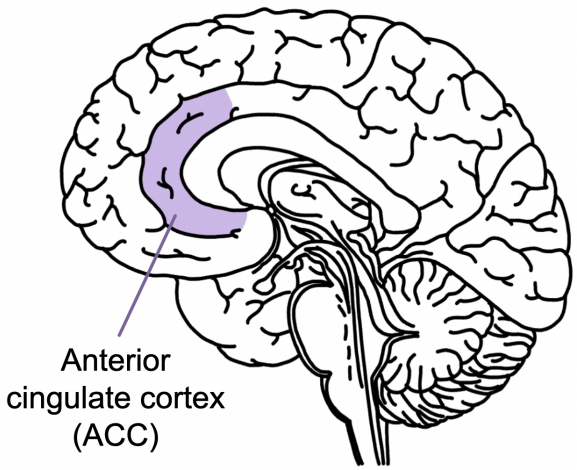

Fig. 7 ACC region in the lateral section of the brain

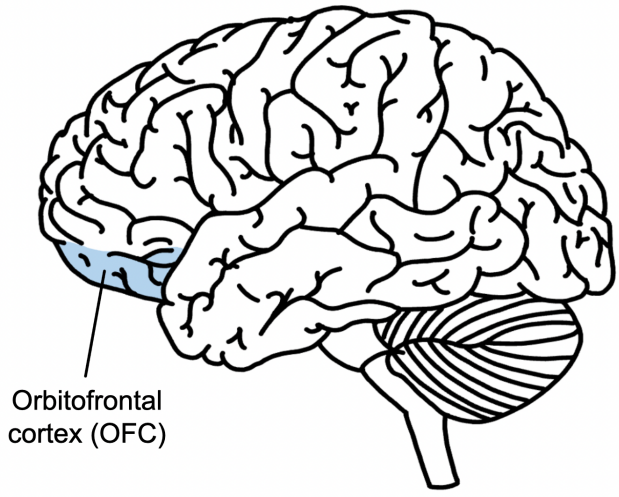

Fig. 8 OFC region in lateral view of the brain

eating behaviors, genetic variations affecting the serotonergic

pathway may influence the predisposition to ED. Together, these insights into specific genetic regions contribute to a deeper understanding of the molecular mechanisms that may underlie the comorbidity of BD and ED, pointing to potential targets for future research and therapeutic interventions.

Comparisons with Existing Literature

To address the degree of agreement across existing literature, the findings in similar systematic reviews investigating the basis of ED and MD comorbidity will be held in the context of the interpretations in this study. Due to the limited research carried out on this topic, only two reviews have been identified for a comparative analysis. Nonetheless, this comparison will promote a deeper understanding of existing literature and evidence.

The first review, conducted by Donofry et al, asserted that MD and ED comorbidity is a result of emotional dysregulation, including factors such as abnormal BMV changes in neural regions responsible for emotional and stress responses[47]. In its investigation, similar findings across the included studies were reduced volumes in the amygdala, striatum, nucleus accumbens, ACC, and dorsolateral PFC (dlPFC). Furthermore, a more prominent decrease was observed in MD than ED, resulting in the argument that these impairments in areas associated with emotional regulation are more exceptional for the basis of MDD instead of ED. In accordance with this systematic review, the paper by Donofry et al highlighted the role of the ACC. On the other hand, Donofry et al also emphasized the significance of the changes in amygdala and dlPFC volumes. Despite these contrasting observations, another common finding was the different volume changes across BN, BED, AN, and MD. This further implicates the difficulty in evaluating patterns due to neural heterogeneity.

The second study, carried out by Fornaro et al to probe into AN and bipolar disorder comorbidity, explored neurotransmitters, HPA-axis functioning, and genetic variants in addition to the emotional dysregulation systems previously explored in the review by Donofry et al[1]. In consonance with the findings of this study concerning serotonin, Fornaro et al noted abnormalities in neurotrophic factors involved in mood and appetite synthesized in cerebral regions. HPA-axis neurotransmitters and the SOX2-OT genetic region, responsible for neurodevelopmental and protective mechanisms, were also implicated. However, in the respective literature, Fornaro et al also distinguished an emphasis on variations in neurotrophic tyrosine kinase receptor 3 and PRR5-ARHGAP8 genes.

Limitations and Implications for Future Studies

The scope of research examining the neurobiological basis of comorbidity between EDs and MDs remains narrow. Current mechanisms, while compelling, are not yet definitive due to the complex interplay of internal and external factors, along with diverse neurological pathways. Not all studies provided large sample sizes, potentially introducing variability in the results. Additionally, the research often focused on specific pairings of eating and mood disorders, limiting the generalizability of the findings to the broader spectrum of comorbid conditions. Gender representation was another limitation, as some studies exclusively included female participants, neglecting potential sex-based differences in coping mechanisms, biology, and hormone levels that could affect the outcomes. Given the paucity of empirical studies, this domain necessitates more rigorous research to decipher the neurobiological mechanisms underlying the comorbidity of MD and ED. Future studies should strive for greater comprehensiveness and seek to corroborate the preliminary findings. Elucidating the neurobiological underpinnings may significantly refine treatment modalities and inform preventive strategies to mitigate symptom progression.

Furthermore, the presence of multiple possible mechanisms to underlie comorbidity exhibits the complexity of the brain and how this co-occurrence of MD and ED may be influenced by varying abnormalities in the brain's processes. Educational interventions addressing mental health and illnesses could be bolstered by incorporating information about possible biological factors, such as leptin dysregulation and serotonergic irregularities, associated with MD and ED comorbidity. By increasing affected individuals' awareness of the several options, patients would seek the advice of mental health professionals for personalized treatment. However, the uncertainty concerning the neurobiological basis of comorbidity affirms that educators, policymakers, and mental health professionals must remain open to considering environmental influences in treatment methods. This concordance in findings and lack of solid understanding regarding mental illnesses further implicate the necessity for thorough testing.

Conclusion

In conclusion, the tentative neurobiological mechanisms for the comorbidity of MD and ED—comprising leptin dysregulation, serotonergic pathway anomalies, HPA-axis dysfunction, unusual gray matter volumes, and genetic variations—are implicated in emotional dysregulation and aberrant reward-system processing within the central nervous system. The existing evidence shows the potential of the investigated mechanisms to play a role in this comorbidity. For example, the increased emphasis on areas involved in and connected with emotional and stress regulation warrants further investigations. On the other hand, the concordance among literature affirms caution against immediate generalization of an individual study's results as certain suspected mechanisms may be associated with an individual disorder or characteristic, such as the prominent role of leptin in appetite regulation as opposed to emotional processes. Furthermore, due

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to the inconsistencies between literature, including the eligible studies, as well as the heterogeneous nature of the brain, a definite conclusion concerning the neurobiological underpinnings of ED and MD can not be reached yet. Confirmatory and expansive research is essential to substantiate these initial observations. By bringing to light the current neurological processes speculated to play a role in the co-occurrence of MD and ED, this review emphasizes the significance of informing affected individuals, professionals, and educators of these biological factors. Higher mental health literacies among individuals would drive beneficial patient-professional interactions through increased utilization of resources and interventions.

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References

1 M. Fornaro, F. Daray, F. Hunter, A. Anastasia, B. Stubbs, D. D. Berardis, J. Shin, M. Husain, E. Dragioti, P. Fusar-Poli, M. Solmi, M. Berk, E. Vieta and A. Carvalho, *Journal of Affective Disorders*, 2021, **280**, 409–431.

2 A. P. Association, *Diagnostic and statistical manual of mental disorders*, 5th edn, 2022.

3 A. Freţian, P. Graf, S. Kirchhoff, G. Glinphratum, T. Bollweg, O. Sauzet and U. Bauer, *International Journal of Public Health*, 2021, **66**, year.

4 A. Jorm, *The British Journal of Psychiatry*, 2000, **177**, 396–401.

5 A. Liberati, D. Altman, J. Tetzlaff, C. Mulrow, P. Gøtzsche, J. Ioannidis, M. Clarke, P. Devereaux, J. Kleijnen and D. Moher, *BMJ*, 2009, **339**, year.

6 B. Thomas, D. Ciliska, M. Dobbins and S. Micucci, *Worldviews on Evidence-Based Nursing*, 2004, **1**, 176–184.

7 J. Sterne, M. Hernán, B. Reeves, J. Savović, N. Berkman, M. Viswanathan, D. Henry, D. Altman, M. Ansari, I. Boutron *et al.*, *BMJ*, 2016, **355**, year.

8 J. Mills, S. Thomas, T. Larkin, N. Pai and C. Deng, *Journal of Affective Disorders*, 2018, **240**, 137–145.

9 J. Mills, T. Larkin, C. Deng and S. Thomas, *Journal of Affective Disorders*, 2019, **279**, 244–251.

10 F. Rybakowski, A. Slopien and M. Tyszkiewicz-Nwafor, *Neuro Endocrinology Letters*, 2014, **35**, 64–67.

11 V. Sturm, C. Haase and R. Levenson, *Genomics, circuits, and pathways in clinical neuropsychiatry*, Elsevier Academic Press, 2016, pp. 345–364.

12 Y. Charnay and L. Léger, *Dialogues in Clinical Neuroscience*, 2010, **12**, 471–487.

13 P. Chandler-Laney, E. Castaneda, C. Pritchett, M. Smith, M. Giddings, A. Artiga and M. Boggiano, *Pharmacology Biochemistry and Behavior*, 2007, **87**, 104–114.

14 P. Xu, A. Chen, Y. Li, X. Xing and H. Lu, *Physiological Genomics*, 2019, **51**, 432–442.

15 C. Gauthier, C. Hassler, L. Mattar *et al.*, *Psychoneuroendocrinology*, 2014, **39**, 170–178.

16 T. Jenkins, J. Nguyen, K. Polglaze and P. Bertrand, *Nutrients*, 2016, **8**, 56.

17 Z. Yilmaz, A. Kaplan and R. Levitan, *Eating and Weight Disorders - Studies on Anorexia, Bulimia, and Obesity*, 2013, **17**, 17–21.

18 C. Weng, T. Lin and B. Hsu, *Handbook of Cognitive Behavioral Therapy by Disorder*, Elsevier Academic Press, 2023, pp. 307–320.

19 Z. Zhang, L. Robinson, T. Jia *et al.*, *Biological Psychiatry*, 2020, **19**, 853–862.

20 X. Liu, J. Kelsoe, T. Greenwood and the Bipolar Genome Study (BiGS), *Journal of Affective Disorders*, 2015, **189**, 141–149.

21 H. Münzberg and C. Morrison, *Metabolism*, 2014, **64**, 13–23.

22 M. Obradovic, E. Sudar-Milovanovic, S. Soskic *et al.*, *Frontiers in Endocrinology*, 2021, **12**, year.

23 Y. Zhou and L. Rui, *Frontiers of Medicine*, 2013, **7**, 207–222.

24 A. P. Association, *What is Depression?*, `https://www.psychiatry.org/patients-families/depression/what-is-depression#section_1`, 2020, Accessed: 2024-08-24.

25 X. Zou, L. Zhong, C. Zhu *et al.*, *Frontiers of Neuroscience*, 2019, **13**, 378.

26 C. Feng, H. Wang, N. Lu *et al.*, *General Psychiatry*, 2014, **26**, 105–109.

27 L. Schmidt, E. Medawar, J. Aron-Wisnewsky, L. Genser, C. Poitou, K. Clément and H. Plassmann, *Brain Communications*, 2021, **3**, year.

28 Y. Yingzhong, Y. Droma, G. Rili and K. Kubo, *Internal Medicine*, 2006, **45**, 941–946.

29 B. Hajduska-Dér, G. Kiss, D. Sztahó, K. Vicsi and L. Simon, *Frontiers in Psychiatry*, 2022, **13**, year.

30 D. Sarrouilhe, N. Defamie and M. Mesnil, *Biomedicines*, 2021, **9**, year.

31 W. Kaye, *Physiology and Behavior*, 2008, **94**, 121–135.

32 E. L. Belleau, M. T. Treadway and D. A. Pizzagalli, *Biological Psychiatry*, 2018, **85**, 443–453.

33 F. B. Almeida, G. Pinna and H. M. T. Barros, *International Journal of Molecular Sciences*, 2021, **22**, 5495.

34 E. Sarno, A. J. Moeser and A. J. Robison, *Advances in Pharmacology*, 2021, **91**, 259–292.

35 S. Kuckuck, E. S. van der Valk, A. J. W. Scheurink, B. van der Voorn, A. M. Iyer, J. A. Visser, O. J. D. Delhanty, S. A. A. van der Berg and E. F. C. van Rossum, *Obesity Reviews*, 2023, **24**, year.

36 S. D. Gonzalez, A. J. Williams, C. J. Blacker, J. L. Voort, K. M. Schak, C. B. Nemeroff, A. S. WIDGE and M. Tohen, *Personalized Medicine in Psychiatry*, 2017, **1**, 39–58.

37 W. Vale, J. Spiess, C. Rivier and J. Rivier, *Science*, 1981, **213**, 1394–1397.

38 M. J. Allen and S. Sharma, *Physiology, Adrenocorticotropic Hormone (ACTH)*, StatPearls Publishing, Treasure Island, 2023.

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39 P. V. Bayly, L. A. Taber and C. D. Kroenke, *Journal of Mechanical Behavior of Biomedical Materials*, 2014, **29**, 568–581.

40 K. Javed, V. Reddy and F. Lui, *Neuroanatomy, Cerebral Cortex*, StatPearls Publishing, Treasure Island, 2023.

41 M. Y. Du, Q. Z. Wu, Q. Yue, Y. Liao, W. H. Kuang, X. Q. Huang, R. C. Chan, A. Mechelli and Q. Y. Gong, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2012, **36**, 11–16.

42 S. J. Brooks, G. J. Barker, O. G. O'Daly, M. Brammer, S. C. Williams, H. B. Schiöth, J. Treasure and I. C. Campbell, *BMC Psychiatry*, 2011, **11**, 179.

43 P. Y. Li, P. Wang, S. G. Gao and D. Y. Dong, *BioMed Research International*, 2020, **2020**, year.

44 J. Klucken, C. Büchler, E. Orsó, W. E. Kaminski, M. Porsch-Ozcürümez, G. Liebisch, M. Kapinsky, W. Diederich, W. Drobnik, M. Dean, R. Allikmets and G. Schmitz, *Proceedings of the National Academy of Sciences*, 2000, **97**, 817–822.

45 T. P. Dahiru, *Annals of Ibadan Postgraduate Medicine*, 2008, **6**, 21–26.

46 F. S. Nahm, *The Korean Journal of Pain*, 2017, **30**, 241–242.

47 S. D. Donofry, K. A. Roecklein, J. E. Wildes, M. A. Miller and K. I. Erickson, *Neuroscience & Biobehavioral Reviews*, 2016, **68**, 911–927.

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