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Review

Amygdala and anorexia nervosa: a narrative review

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SUMMARY

The amygdala, with its ability to attribute emotional value to stimuli and to certain events, is believed to play a role in the etiopathogenetic processes underlying Eating Disorders. In particular, this review will briefly summarize data concerning the alterations found in the structure and functional pathway of the amygdala, in relation to the pathological profile of Anorexia Nervosa (AN). Appropriate keywords and medical subject headings were identified and searched for in PubMed/MEDLINE. References of original articles and reviews were screened, examined, and selected. Numerous studies have identified alterations in the functioning of the amygdala in patients suffering from AN, often with significant differences. Patients showed a significantly reduced amygdala volume, probably because of starvation and malnutrition. In some studies, an hyperactivation of the amygdala was highlighted, while in other hypoactivation was found. In individuals with AN, dysregulated eating patterns are associated with an imbalance between reward-related and cognitive control processing regions. Hyperactivation of the amygdala was highlighted in response to stimuli with salient characteristics for the AN (such as body or nutrition).

Key words: amygdala, food intake, eating behaviors, anorexia nervosa

Introduction

Anorexia nervosa

Eating disorders (EDs) are complex mental health conditions characterized by dysfunctional thoughts, behaviors, and perceptions related to food and body image [1]. These disorders can severely impact the daily lives of affected individuals, leading to significant deficits in social, occupational, and emotional functioning. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the currently classified EDs include anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant/restrictive food intake disorder, other specified feeding and eating disorders, pica, and rumination disorder [1].

Anorexia nervosa (AN) is a severe form of ED marked by restrictive caloric intake, a disturbed body image, intense fear of weight gain, and denial of the medical severity of the condition [1]. These features contribute to significantly low body weight, which can precipitate numerous medical complications [1,2]. While the overall incidence of AN has remained stable, there is evidence suggesting an increased incidence among younger girls (< 15 years) [3]. The gold standard for AN treatment is a multidisciplinary approach encompassing nutritional counseling, psychotherapy, and pharmacological support [4]. However, treatment is often challenging, and many patients achieve only partial or total remission years after the onset of symptoms [5]. AN is associated with notably high relapse rates [4,6], and individuals with AN are at a greater risk of mortality compared to those with other EDs and psychiatric disorders [7].

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Given these epidemiological insights, it is crucial to elucidate the etiological correlates of AN to explore new therapeutic avenues. Currently, the etiology of AN remains largely unknown, though it is hypothesized to involve a combination of biological, psychological, psychosocial, and behavioral factors [8].

Extensive research has been conducted to understand the neurobiology underlying AN. Both functional and structural brain deficits appear to be present in individuals with AN. Evidence points to the involvement of brain structure volumes and dysfunctions in the functional resting-state connectivity of various brain networks [9]. The reward circuit, cognitive control, and habit-formation systems, as well as dopaminergic regulation, are implicated in AN [10]. Serotonin, given its role in mood, anxiety, and obsessiveness, is also considered crucial in maintaining dysfunctional symptoms in AN [11]. Additionally, findings indicate hypoperfusion in certain brain areas and overall glucose hypometabolism in the brains of some AN patients [12].

AN imposes a significant burden of disease. Despite extensive research, it remains essential to deepen our understanding of its etiology to uncover new therapeutic possibilities.

Overview of physiological aspects of amygdala

The amygdala, an almond-shaped subcortical structure located in the medial temporal lobe, comprises several anatomically and cytoarchitecturally distinct regions [13]. Its primary function is currently understood to be the maintenance of emotional homeostasis through connections with other brain regions. These include the prefrontal cortex (involved in stress-reactive rumination), the anterior cingulate cortex (involved in memory formation, cognitive flexibility, planning, and behavioral inhibition), the insula and parahippocampal gyrus (both activated by hunger-related cravings), and the nucleus accumbens (involved in the cognitive processing of motivation, reward, fear, and aversion) [14-17].

Interactions between the amygdala and hippocampus facilitate the translation of various sensory stimuli into behavioral responses. Consequently, the amygdala's role in certain psychiatric disorders, including eating disorders (EDs), has been the subject of extensive scientific investigation in recent years [18]. Within the amygdala, the basolateral and central nuclei have been particularly studied in relation to EDs, as they are central to associative fear learning, leading to conditioned behavioral responses such as weight loss [19,20].

The potential impact of the amygdala on the anorectic phenotype has also been explored from a neuroendocrine perspective. Animal studies have demonstrated high densities of receptors for various neurohormones, including leptin, in the amygdala [21]. Leptin, a hormone produced by adipose tissue that regulates hunger, has been a focal point of recent scientific research. Hypoleptinemia, in particular, may be associated with alterations in the rostral-medial amygdala, a brain region involved in olfactory and food-related reward processing [13]. Furthermore, leptin's role in the neurogenesis of structures such as the amygdala and hippocampus, as well as in axon growth and synaptogenesis, has been highlighted [22].

Another noteworthy neuroendocrine factor is the orexin system. Orexins (also known as hypocretins) are excitatory neuropeptides with well-documented roles in regulating wakefulness, arousal, energy homeostasis, and anxiety [23]. These peptides are localized in the lateral hypothalamus and dorsomedial hypothalamic nuclei, and they project to the amygdala. The highest density of orexinergic fibers in the amygdala is found in the central nucleus [23]. Additionally, a direct functional connection has been demonstrated between orexin enhancement of locus coeruleus activity and amygdala-dependent memory processes, indicating that orexins play a crucial role in learning about harm-predictive stimuli [24].

Orexins are released during caloric restriction, aiming to increase external food intake while simultaneously increasing energy expenditure. This typically results in a net effect of decreased body weight [25], often manifesting as the increased hyperactivity and restlessness commonly observed in anorexic patients [26].

The present study, which involved a search of the literature, aimed to gather evidence from the studies published to date to clarify the current knowledge on the functioning of the amygdala in EDs, with a focus on AN. Ethical approval was not sought for the present study because it retrieved and synthesized data from already published studies.

Two researchers (F.M. and V.B.) conducted independent searches of the PubMed/MEDLINE database for relevant literature, including original articles, meta-analyses and reviews, between October and November 2023. The search terms "Amygdala", "Eating disorders" and "Anorexia nervosa" were used to identify appropriate keywords and medical subject headings.

The following criteria were applied in the selection of articles for inclusion: (1) addressing the issue of amygdala functioning in AN, (2) published after 1990, (3) peer-reviewed, (4) written in the English language, and (5) available in full text. Articles were excluded if they involved (1) a non-target population (i.e., EDs but not AN), (2) a non-target topic (i.e., descriptive articles about EDs or amygdala's functioning), and (3) a non-target design (i.e., thesis).

In the preliminary stage, the abstracts were screened for inclusion and exclusion criteria, and then selected articles were comprehensively examined in full text. In addition to keyword searching, citation chaining was

employed in the full-text screening process to identify content that the original searches may have missed. Papers were screened, selected when appropriate, and discussed. Of the 112 PubMed/MEDLINE results, 73 met the inclusion criteria for full-text reading. At the end of the process, 46 articles were included after a full-text review.

Amygdala and anorexia nervosa: what do we know?

A variety of cognitive functions mediated by the amygdala are key elements of anorexia-related psychopathology. Specifically, the role of the amygdala in emotions is of clinical interest [27]. One of the most well-known and extensively studied aspects of the amygdala is its role in emotional regulation and the attribution of emotions in response to internal and external stimuli. In AN, there appears to be widespread difficulty in the processing of emotions, both in their recognition and processing. This suggests a possible correlation between amygdala dysfunction, and this increasingly characterized psychopathological dimension in eating disorders [28]. Furthermore, the amygdala facilitates the consolidation of memories related to significant emotional content. In AN, the presence of an over-general autobiographical memory could be related to a possible avoidance of emotions [29,30]. Finally, in light of the amygdala's role in the reward circuit, it is noteworthy to observe the existence of altered food-related reward in AN [31].

A progressively deeper understanding of the neurobiological basis of disease is essential for the advancement of neuroscience research and clinical practice in mental health. This could lead to better outcomes through more targeted treatments and improved survival rates. Numerous scientists worldwide have undertaken this challenge, studying the human brain in both health and disease to identify the brain pathways involved in different clinical presentations [32]. Recent technological advances in techniques that allow examination of whole-brain connectivity are contributing to the field, providing evidence that major psychiatric disorders result from perturbations in a complex network of highly connected, anatomically distributed neural systems rather than dysfunction of limited brain regions [33].

The amygdala, with its ability to attribute emotional value to stimuli (both internal and external) and to certain events (occurred or possible), is believed to play a role in the etiopathogenetic processes underlying EDs [34]. In particular, this discussion will offer an overview of the alterations found in the structure and functional pathways of the amygdala in relation to the pathological profile of AN in all its complexity (Fig. 1). Numerous studies have identified alterations in the functioning of the amygdala in patients suffering from AN, often with significant differences.

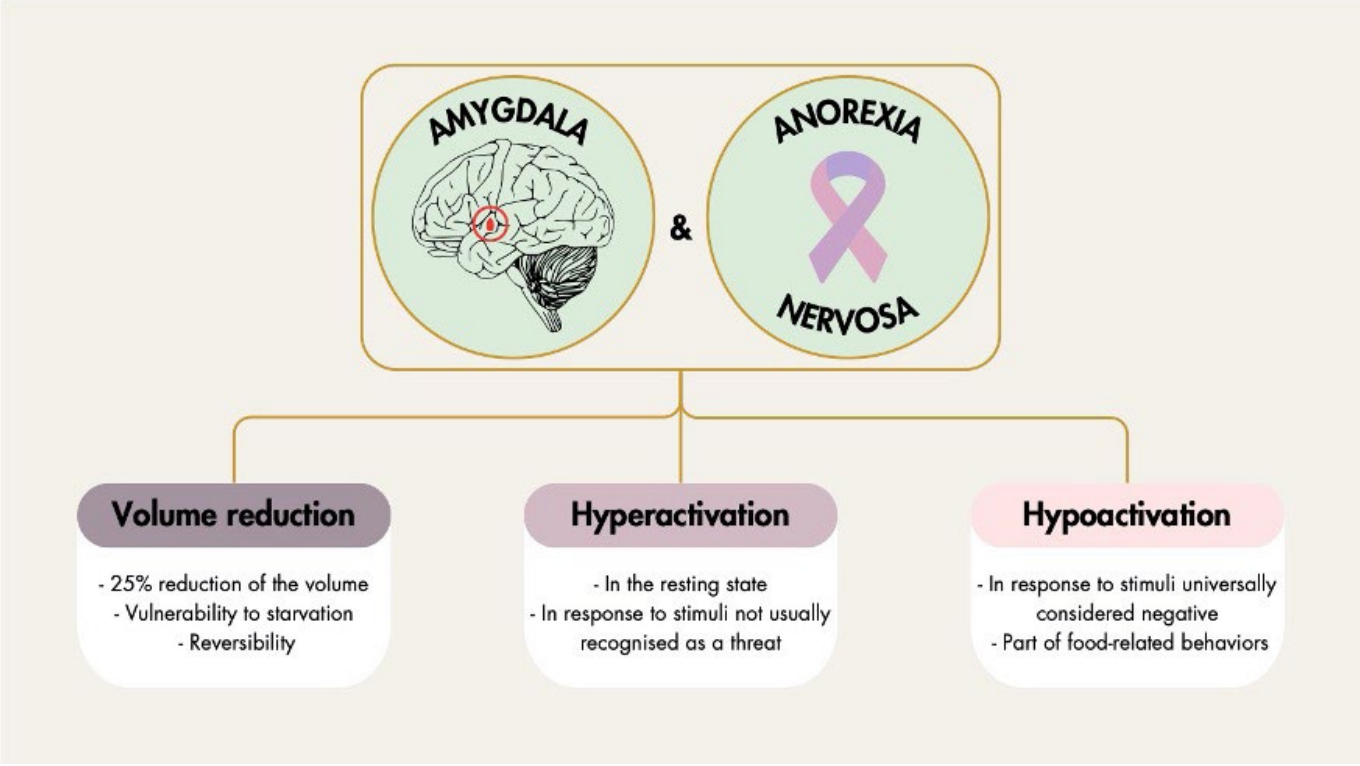


FIGURE 1. *Overview of findings regarding the correlation between amygdala and AN.*

One of the first experimental studies focusing on the amygdala in patients with AN, conducted by Giordano et al. (2001), aimed to evaluate the volume of the Hippocampal-Amygdala Formation (HAF), given its role in processing stress-related information, using magnetic resonance imaging (MRI) [35]. The study demonstrated that patients with AN showed significantly reduced HAF volumes (approximately 25%) compared to healthy controls. The HAF volume reduction in Cushing's syndrome reversed with the correction of endocrine abnormalities, while in depression and PTSD, the HAF volume reversed months to years after the last depressive episode or acute trauma, a time when patients no longer hypersecreted glucocorticoids [38]. Given that no correlation was found between HAF volume and hormonal parameters or BMI, reversibility of HAF volume reduction in AN was deemed unlikely [35]. Subsequent studies have largely confirmed the finding of alterations in the size of cerebral gray matter in patients with AN, particularly demonstrating volume reductions in certain brain structures, such as the accumbens, pallidum, putamen, and amygdala [39-42]. These regions are hypothesized to be more vulnerable to hunger and malnutrition [39,41]. All the studies report a reduction in the total volume of the amygdala [39-42]. Severe volume loss in the rostral-medial nuclei of the amygdala, involved in olfactory/food-related reward processing, may represent a structural correlate of AN-related symptoms [13]. Lower HAF volumes in individuals with AN appear to be a result of chronic exposure to excessive cortisol levels due to chronic stress [42]. Hypercortisolemia in AN may also serve as a compensatory mechanism, increasing gluconeogenesis and providing vital nutrients [43]. Reduced amygdala volume in AN patients has been associated with less body image uncertainty and reduced phobia scores, possibly contributing to disease maintenance [44]. Unlike the initial study by Giordano et al. (2001), subsequent research suggests that amygdala volume may increase with weight and hormonal normalization [39-42].

Takano et al. conducted one of the first studies to analyze the correlation between EDs and the amygdala in terms of altered functioning [45]. This study highlighted significant activation – hyperfunctioning – in the resting state of various structures, including the amygdala, in patients with AN compared to controls [45]. Single photon emission computed tomography (SPECT) demonstrated hyperactivation, indicating a condition of hyperperfusion. Other studies have also reported findings of hyperactivation of the amygdala in AN patients and have investigated the stimuli triggering this hyperactivation. Miyake et al. conducted three studies highlighting amygdala hyperactivation in AN patients using fMRI [46-48]. Hyperactivation, interpreted as a reaction to a dangerous stimulus, was found in response to stimuli not usually recognized as a threat by the general population, such as the perception of one's own overweight body and words related to physical fitness, perceived as overwhelming and aversive [47,48]. The vision of food images also led to greater activation of the amygdala, as demonstrated by Joos et al. [49]. The task of eating, even in a state of hunger, led to intense amygdala activation, reflecting the fear of weight gain, a main symptom of AN [50]. These results suggest multimodal amygdala reactivity independent of sensory mode [42].

Miyake et al. also found significant amygdala activation during an emotional decision-making task, not followed by activation in the anterior cingulate cortex, a region involved in cognitive processing of emotional information and emotional regulation [46]. The increased amygdala activity and decreased cingulate cortex activity likely represent parts of a negative feedback loop of emotional processing characterizing this clinical presentation. This deficit in the cognitive evaluation of negative emotions could represent the neural basis of alexithymia (inability to identify, understand, or describe one's own emotions) often observed in AN patients [46].

More recently, Seidel et al. found that AN patients, compared with controls, showed hyperactivation of the amygdala and the right dorsolateral prefrontal cortex (DLPFC) during the passive viewing of negative stimuli [51]. These findings indicate impaired processing of salient emotional stimuli in AN but do not suggest a general deficit in the regulation of negative emotions. The DLPFC is involved in executive functions, such as decision-making, self-monitoring, inhibition, and planning. Increased DLPFC activation in AN supports the hypothesis that the disorder may be characterized by excessive self-control [52].

Contrary to the studies above, Holsen et al. found premeal hypoactivation of the amygdala in AN patients exposed to high-calorie foods, suggesting that these deficits may contribute to disrupted food-related behaviors [53]. Other studies demonstrating less amygdala activation compared to healthy controls did so only in response to universally negative emotional or situational stimuli, not specific to EDs, suggesting a greater rational processing of stimuli (due to hyperactivation of the prefrontal cortex) compared to emotional processing [14,54,55]. This interpretation suggests that people with AN tend to react emotionally cold and detached to negative emotionally provoking stimuli [56,57]. Meanwhile, other case-control studies suggested that the brain's response to a fear stimulus (evaluated by increased activity in the amygdala, uncus, and insula) was not different between AN patients and controls [58,59].

Discussion and conclusion

In this review of the literature, despite the scarcity of

specific studies which do not allow us to exhaust the doubts about it, we have reported the major neurobiological mechanisms regarding the relationship between the functioning of the amygdala and AN.

To briefly summarize, in individuals with AN, dysregulated eating patterns are associated with an imbalance between reward-related and cognitive control processing regions [31,60-62]. The amygdala tends to activate not only due to fear or the presence of negative stimuli, as was supposed in the past, but rather due to the intrinsic emotional value of the stimulus itself. It is no coincidence that some studies have highlighted hyperactivation of the amygdala, particularly when the stimuli had salient characteristics for AN (body, nutrition). Conversely, for conventionally negative stimuli that are probably less emotionally resonant for AN, hypoactivation is found in patients [54]. The concurrent hyperactivation of the DLPFC could indicate significant involvement of cognitive regions in the processing of emotions [51,55].

These findings underscore the close implication of the amygdala in the neurobiological activity that characterizes the clinical pattern of AN. Given this correlation, it can be assumed that these results have potential clinical implications. Various intervention strategies have proven effective in modifying the activity state of the amygdala in other psychiatric disorders, such as anxiety, posttraumatic stress disorder (PTSD), and schizophrenia. These interventions range from psychotherapy to mindfulness meditation interventions, as well as invasive techniques such as deep brain stimulation [63-66]. Even some pharmacological therapies have proven effects on the amygdala. This applies not only to benzodiazepines but also to antipsychotic and antidepressant drugs [67-69]. Selective serotonin reuptake inhibitors (SSRIs), for example, have the ability to increase amygdala activity in response to positive stimuli and decrease activity in response to negative stimuli [70]. By understanding how the function of the amygdala is modulated in relation to the symptomatic spectrum of AN, we could also intervene to modify its functioning to benefit the clinical spectrum of the disorder.

One of the major complexities linked to the study of the amygdala and its functional alterations in relation to AN is the great variety of conflicting articles. The presence of contradictory articles could be due to biases in the studies, such as the recruitment of patients in different stages of the disease or the use of external stimuli that are too different from each other. It is also possible that in conditions of acute AN, the cognitive and physiological systems are seriously compromised, making it difficult to determine whether certain anomalies are the cause or consequence of starvation [71,72]. Consequently, we recognize that there is still a long way to go to define precise neurofunctional correlates of EDs, and further studies are necessary.

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Conflicts of Interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Conception of the work: MF; design of the work: MF, AAR; Drafted the work: MF, CG, FG, BV; Revision of the work: TVS, AAR, DRD.

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