Sexual Dimorphic Nature of the Amygdala and its Contribution to Females' Susceptibility to Depression

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Abstract

Depression is about twice as common in females as it is in males, which raises questions about the root of this significant disparity. Numerous studies have examined the role female hormonal changes at various stages of life, including the pre-menstrual, prenatal, and postnatal phases, have in this phenomenon. However, little emphasis is placed on the limbic system's contribution, particularly the amygdala. The processing of affective information takes place mostly in the amygdala, which is why affective disorders like depression have a significant impact on this brain structure. Furthermore, the amygdala is a subject of interest in studies of sex differences in the human brain due to its high concentration of sex hormone receptors. The recent developments of neuroimaging technologies also provide an opportunity to examine the distinct functions of the amygdala in males and females. This review's objective is to investigate the characteristics that make the amygdala a sexually dimorphic brain structure by placing a particular emphasis on its volume and function. It will also cover how the amygdala's sexually dimorphic characteristics contribute to the prevalence of depression in women.

1 Introduction

The limbic system comprises various brain areas crucial for processing emotional memory, along with motivation, social processing, learning, and spatial memory (Har00). The hippocampus and the amygdala are at the forefront of emotion regulation, with the amygdala processing emotion and the hippocampus creating a declarative episodic memory of the emotional event (RL04). The amygdala has received attention due to its essential role in processing emotionally salient information and developing adaptive responses subsequently (OB15). It is easily distinguishable in the temporal lobe due to the almond-shaped nucleus it

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contains (All21) and the fact that it has 13 nuclei total (Jan15; oMN). The sophisticated neuronal connections between the amygdala and other regions of the brain also make it a crucial structure in controlling both behavioral and physiological responses (Ham05). Therefore, learning about the amygdala's structure and function is worthwhile since any damage would disrupt many neurological processes.

Numerous studies have asserted that the amygdala is a sexually dimorphic structure (Nis81; Coo05; Uem12; Blu17; LO21) nevertheless, others have argued that the difference between males and females is not that significant (Fra00; Mar17). This review will focus on traits that are considered to make the amygdala a sexually dimorphic organ, notwithstanding the controversy. Amygdala's volume will be the first characteristic discussed in this review. Across all ages, males have a 9–12% larger average brain size than females (Kac19). This overall difference also correlates to variances in volume in individual brain areas, such as the amygdala (Mar17). Other factors, in addition to intracranial volume disparities, make the sex-related size difference in the amygdala apparent. For example, the amygdala's high number of sex hormone receptors renders it highly influenced by sex hormones such as androgen and estrogen, which play distinct roles in its volume (Ham05). Furthermore, the peak of amygdala development differs between males and females (Uem12). The aforementioned factors contribute to the alleged amygdala volume differential between males and females. Little is known about the functional significance of the volume differential. However, as neuroimaging technologies advance, there is room for discovery.

The function of the amygdala is another feature that makes it a sexually dimorphic organ. To begin with, the amygdala's primary role in the nervous system is processing threatening, fear-inducing stimuli, and activating fear-related behaviors to produce physiological and psychological responses (ˇSi21). It is also rarely activated and generates responses during emotionally neutral stimuli (Dav02). The functioning of the amygdala has revealed differences between the two sexes. The discrepancy is particularly evident in its response and hemispheric lateralization (Ham05). Although little is known about the clinical consequences of this differential, some studies have shown promise for future discovery (Sim14).

Apart from its sexual dimorphism, the amygdala's considerable participation in affective information processing (ˇSi21) is an appreciable trait. It helps to categorize sensory data and assign them the proper degree of relevance to elicit a response to the emotionally significant ones (ˇSi21). In light of the characteristics mentioned, the amygdala is the most afflicted brain structure in psychopathologies such as depression. Depression is one of the most common mental disorders (Kal20). Many studies have been conducted to determine the causes of this mental condition (Dav02; Fu09), and most of them have discovered greater amygdala involvement (Rub16; Zha21; ˇSi21). As a result, the amygdala is at the forefront of investigations into the neurological etiologies of depression.

Given the amygdala's role in depression and its sexually dimorphic trait, it is a crucial brain structure to examine when discussing females' propensity to

depression. According to current statistics, depression is 50% more common in women than men (Org23). Many studies have attempted to investigate the causes of this immense gap (Alb15; Li17; Kue17). However, their focus was on the alterations that occur during distinct stages of female life, such as menstruation, pregnancy, and menopause, with minimal emphasis on sexually dimorphic brain structures such as the amygdala. The primary goal of this review is focusing on defining the characteristics that distinguish the amygdala as a sexually dimorphic organ, and demonstrating how they can be relevant in determining the causes of female susceptibility to depression.

2 Amygdala

2.1 Structure of the amygdala

The amygdala is a brain structure in the temporal lobe that is part of the limbic system (OB15). It contains neuronal cells that transport electrical and chemical impulses, as well as glial cells that support the neuronal cells (Cli23). The amygdala was named after the Greek word for almond because of the almond shape of its basal nuclei (All21). Also, due to its almond shape, it can be clearly distinguished in its anatomic position, which is anterior to the hippocampus (OB15). Although it varies depending on the overall size of the brain, it is a small structure placed near regions that transport information from the senses (OB15). It is a paired structure, with one in the left hemisphere and the other in the right (OB15). It has 13 nuclei that fall into four major categories: the basolateral group (which includes lateral, basal, accessory basal, and para laminar nuclei); the superficial (which encompasses centro medial and cortical nuclei); the medial and central (which share functional similarities but have distinct roles at times), the anterior amygdaloid area, and the amygdalohippocampal area (ˇSi21). Among these nuclei, the basolateral nuclei, which emerges from the lateral amygdala, plays a predominant role in the whole amygdala (ˇSi21). It sends efferent projections to other amygdala nuclei and other cortical areas (ˇSi21).

2.2 Function of the amygdala

The limbic system is a group of brain regions involved in information processing, memory storage and retrieval, setting emotional states, and connecting the conscious and unconscious activities of the brain (Har00). The amygdala is a prominent component of the limbic system that plays a crucial role in the processing of emotional information (ˇSi21). It is mainly engaged in recognizing fearful and threat-inducing stimuli and activating physiological responses to them (OB15). As a result, it is at the forefront of emotional learning and behavior because it assists the nervous system in forming adaptive responses when an individual is exposed to these stimuli (OB15). The fear the amygdala mediates can be both innate and learned (Iso15). The amygdala is crucial for regulat-

ing emotions and producing adaptations due to its complex interactions with sensory modalities, which are vital for processing both types of fears (Iso15). Emotion regulation refers to the process by which the amygdala determines risks at the unconscious level and modulates behavioral and physiological responses at the cognitive level (ˇSi21). Furthermore, the amygdala is prominently implicated in both negative and positive valence emotion encoding, following which it assigns a label to each emotion (ˇSi21). It generates reactions to emotionally relevant ones after assigning labels (ˇSi21). The categorical model assumed that the amygdala was primarily involved in negative emotions; however, advances in neuroimaging techniques revealed that the amygdala is also involved in emotionally neutral stimuli (Bon15). It can be inferred that the amygdala is only marginally involved in emotionally pleasant stimuli, but its involvement is prominent in emotionally unpleasant stimuli. Besides, the amygdala has sophisticated neural connections with other brain parts, namely sensory structures, and brain regions such as the hippocampus and hypothalamus (Ham05). This link is especially crucial in information processing between the prefrontal cortex and hypothalamus (oMN), and memory formation in the hippocampus. Also, it processes diverse types of emotions through its connections with structures engaged in the senses (Cli23). As a result, abnormalities in the amygdala's functioning may result in difficulty with proper emotion regulation, which leads to psychopathologies.

Furthermore, the amygdala is one of the brain areas that exhibit laterality in functioning (Mar99). According to Mar99, in an experiment where the cerebral blood flow variations in response to emotional valence were evaluated, unpleasant stimuli substantially stimulated the left hemisphere of the amygdala. Meanwhile, the right amygdala was involved in the recovery, non-detailed, and shallow processing of emotional information (Mar99). This demonstrates that in addition to playing similar roles in emotion processing (All21), the two hemispheres of the amygdala have distinct functions in how emotion is processed.

3 Sexual dimorphic nature of the amygdala

Sexual dimorphism is defined as a "distinct difference in size or appearance between the sexes of an animal in addition to the sexual organs themselves" (DO223). One of the supposed sexually dimorphic organs is the human brain. A study of 48 healthy individuals, 21 females and 27 males of the same age, educational background, ethnicity, socioeconomic situation, handedness (right), and reading level, concluded that there are variations in the brains of males and females (Gol01). The study also revealed that the difference is more pronounced in brain regions with higher levels of sex hormone receptors; it is also worth noting that earlier exposure to sex hormones contributes to brain sexual dimorphism (Gol01). Considering cerebral size disparities, the study Gol01 found that males have larger volumes in limbic and paralimbic regions, such as the amygdala and the hippocampus, since they contain more sex hormone receptors.

Many studies on sex differences in the human brain have focused on the amygdala (Nis81; Coo05; Uem12; Blu17; LO21). Other studies have claimed that the amygdala is not a sexually dimorphic organ (Fra00; Mar17). Regardless of the debates, it is critical to examine sexual dimorphic features because they may have ramifications for various psychopathologies. For example, a study in rats discovered that exposure to testosterone in the neonatal period triggers synaptogenesis during postnatal development, resulting in variations in female and male amygdala's later in life (Nis81). Furthermore, another study by Coo05 on rats revealed that gonadal steroid hormones have a strong influence on the medial amygdala early in life, and it is also lateralized before puberty. After gonadal steroid hormone exposure, female rats had 80% more excitatory synapses in the left hemisphere of the medial amygdala than males (Coo05). Additionally, the amygdala's increased number of sex hormone receptors makes it sexually dimorphic in adulthood due to the hormones ingested during the neonatal period (Gol01). The Amygdala's sexual dimorphism can be seen in its volume and function.

3.1 Amygdala's volume difference between males and females

Male brains are 9-12% larger than female brains across all ages, and this total intracranial difference is also attributable to individual brain structures such as the amygdala (Mar17). However, according to Fra00 and Mar17, the size difference is only evident when the total brain size difference is not considered; hence they claim that the size difference is insignificant. On the other hand, a study conducted by Uem12 on 109 healthy individuals ranging in age from 1 month to 25 years old, with 57 males and 52 females, discovered that amygdala volume is higher in males. Furthermore, as reviewed in Kac19, after correcting for intracranial volume, 400 subjects aged 8 to 30 years revealed higher amygdala volume in males compared to females.

Several factors can contribute to the size difference between the sexes, of which is the male and female sex hormones. As previously stated, the amygdala contains sex hormone receptors (Ham05), making it susceptible to those hormones. As an illustration, a study conducted on sixty-day-old male and female rats by Coo99 revealed that castration of testosterone in male rats resulted in equal volumes with female rats. Moreover, the study by Coo99 claimed that the volume difference between males and females relies on the gonadal hormone androgen, and the difference is evident before puberty, though to a smaller extent than in adulthood. Another study by Wan19 on 563 healthy adults, 250 males, and 313 females, found that before the peak of amygdala development, males' amygdala growth fit the quadratic model, while females suited the linear model. This study Wan19 indicated that sex hormones play a substantial role in the pace of expansion and decline of the amygdala's volume.

Aside from sex hormones, the peak at which the amygdala matures differs between males and females, which contributes to the size differential. According to a study by Uem12, females reached the local maximum volume one and a half

years earlier than males. In addition, females had a slower growth rate, which contributed to a smaller amygdala volume (Uem12). The peak age also differed between the right and left amygdala; for males, the right amygdala peaked at 12.6 while the left peaked at 11.1; for females, the right amygdala peaked at 11.4, and the left peaked at 9.6. Further, the study by Uem12 found that before the peak, the size difference between males and females was not significant, but after, there was a substantial difference.

The functional importance of the size differential between males and females is yet unknown (Ham05), but certain studies have shown promise. For instance, according to a study by Qin16 conducted on 176 people between the ages of 19 and 30, 100 of whom were males and 76 of whom were females, whole brain size as well as intracranial brain structure size were substantially associated with function. It can be deduced from this that, with developments in neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), functional significance of the amygdala size difference between males and females may be identified.

3.2 Amygdala's function difference between males and females

The amygdala is a crucial brain structure for processing emotions, particularly threatening and frightening ones (˘Si21). The mechanism by which these emotions are processed in the amygdala differs between men and women (Ham05). For example, a study conducted on female and male rats by Blu17 discovered a significant sex difference in the activity of the basolateral amygdala (BLA). Females had higher excitatory synaptic inputs to the lateral and basal nuclei of the BLA, which was especially noticeable during the estrus cycle (Blu17). Females with higher BLA activities had a stronger glutamatergic drive, and there was also increased presynaptic protein synaptophysin in BLA (Blu17). This resulted in increased lateral amygdala-dependent cued freezing and basal amygdala-dependent contextual freezing (Blu17). According to the study by Blu17, the increased activity of the BLA in females is accountable for the physiological difference between female and male amygdala. Additionally, in a study conducted on 14 adult females by Lis12, the neuropeptide oxytocin boosted amygdala activation in response to threatening faces. The hormone oxytocin is widely known for its powerful effects on lowering amygdala reactivity in threat processing in males; however, the study Lis12 demonstrated the converse to be true in females. The above differences in amygdala functioning between males and females can be observed in its response to unpleasant stimuli and hemispheric lateralization during emotion processing.

The amygdala is significantly involved in our bodies' behavioral and physiological responses to aversive stimuli (˘Si21). The amygdala's response to these stimuli differs between males and females (Ham05). According to a study by And14 conducted on 45 healthy adults between the ages of 18 and 35, with 16 males and 29 females, there were disparities in amygdala reactivity between males and females. In the study And14, both male and female volunteers viewed

evocative visuals varying in novelty and valence, and females' amygdala response was more persistent to negative valence visuals over repeated trials. According to the study by And14, persistent responses in females relate to a negative effect, which has implications for affective disorders. Another study Can02 on 12 females and males found that females remembered emotional occurrences more. In the study Can02, both males and females were exposed to neutral and emotionally negative images; their brains were recorded using fMRI; and their memories were assessed three weeks later. To begin with, both males and females remembered more emotionally aversive images, and females remembered the emotionally aversive images better than males, with more vivid and intense recollections (Can02). According to the findings above, the difference in amygdala response to aversive stimulus between males and females can be demonstrated by a more persistent amygdala response as well as a stronger recollection of aversive events in females.

The amygdala is one of the brain regions that has shown laterality, with the left and right hemispheres being involved in information processing in distinct ways (Mar99). This laterality has also been demonstrated to differ by sex, with females' and males' left and right amygdala participating in emotion processing differently (Ham05). Cah04 conducted a study on 11 males and females in which both female and male subjects underwent fMRI scan while viewing slides ranging from emotionally neutral to extremely arousing. When memories were assessed two weeks later, males showed a stronger activation of the right hemisphere of the amygdala, whereas females showed a greater involvement of the left hemisphere (Cah04). Besides, the blood oxygen level-dependent (BOLD) signal was detected in the left hemisphere of the amygdala in females and the right hemisphere in males (Cah04). Another study Sch11 included 235 male and female adolescents who were age and handedness matched. The subjects completed an emotional face perception fMRI test, and the results revealed that boys had greater right amygdala involvement (Sch11). According to the study by Sch11, sex-dependent hemisphere lateralization in teens is a forerunner for emotional memory in adulthood. It also suggested that hemispheric lateralization could have implications for the etiology of mental disorders (Sch11).

4 Amygdala's involvement in depression

Depression is one of the most common psychopathologies, affecting around 280 million people worldwide, with females being twice as afflicted as males (Org23). A mix of psychological, social, and biological factors can contribute to it (Org23). Because of its involvement in emotion processing, the amygdala is thought to play a key role in depression (Rub16; ˇSi21). "Feelings are conscious, emotional experiences of these activations that contribute to neuronal networks mediating thoughts, language, and behavior, thus enhancing the ability to predict, learn, and reappraise stimuli and situations in the environment based on previous experiences" (ˇSi21, p.1]). Consequently, feelings or emotional experiences have a significant impact on people's lives. Since the amygdala is the

key brain structure responsible for processing emotions and feelings, any disturbance in the amygdala could result in a fault in cognitive reasoning, making us vulnerable to psychopathologies like depression. Amygdala hyperactivation has been identified in major depressive disorder (MDD) (Rub16; Zha21;˘Si21). The amygdala hyperactivation may potentially influence the initial judgment as well as the response to incoming information, resulting in cognitive biases towards unpleasant or emotionally salient information (Dav02). This mechanism is also hypothesized to be caused by norepinephrine, which is found at abnormally elevated levels in MDD (Dav02). Norepinephrine is involved in amygdala-mediated learning and is impacted by glucocorticoid secretions, which are similarly elevated in depression (Dav02).

A postmortem study conducted on 13 people with MDD and 10 healthy controls by Rub16 revealed differences in amygdala structure. Depressed participants exhibited a larger lateral nucleus and more total BLA neurovascular cells than controls (Rub16). This study also has important implications for how structural disturbances in the amygdala lead to depression. Another study Ram14 included 55 patients with MDD who met the DSM-IV criteria and 19 healthy controls. The subjects underwent a 3-T fMRI scan, and those with MDD exhibited impaired intrinsic connectivity with other brain areas involved in emotion processing and regulation (Ram14). According to the study, these reduced intrinsic connections of the amygdala may be one of the causes of decreased sensations and perceptions, which leads to cognitive disturbances in MDD (Ram14). The studies reviewed above provide concrete evidence for the critical role of the amygdala in depression.

5 New Idea: The amygdala's sexual dimorphism and its role in females susceptibility to depression

Women are more prone to depression than men since they experience it twice as often (Org23). It can be due to different causes, including hormonal changes at critical life stages such as menstruation, pregnancy, and menopause (Kue17; Li17). However, the neurological origins of this tendency have received little attention. According to Gol01, the human brain is sexually dimorphic, with some of its regions demonstrating anatomical and functional differences between males and females. The difference is especially noticeable in brain areas with a high concentration of sex hormone receptors, such as the amygdala (Gol01; Ham05). The amygdala has shown sexual dimorphism in volume and function, and studies reporting the difference have also argued that this has clinical implications (Sch11; Uem12).

The difference in amygdala volume between males and females can be seen in males having a greater amygdala volume than females (Uem12; Kac19). Though studies have not determined the functional or clinical importance of the differential, it is worth noting that certain studies have discovered that larger or smaller

amygdala volumes have induced psychopathologies (Xu20; Zha21). Given that the amygdala is the main structure engaged in emotion processing and is involved in depression (Dav02; Si21), any volumetric variation between males and females can have medical consequences. As an example, one of the factors driving hyperactivation of the amygdala in females during producing responses to unpleasant stimuli (Dav02; Ham05) could be a smaller volume of the amygdala, although further research is needed to prove it. The smaller volume of the amygdala, which results in fewer neuronal and glial cells, may disturb the amygdala's normal function in emotion processing. This may make women more prone to faulty and disrupted cognitions, resulting in depression. Moreover, the difference in the peak of amygdala maturation between males and females is notable. Since males reach their peak of maturity one and a half years later (Uem12), their amygdala could have a higher potential to form efficient connections with other brain regions. As a result, earlier amygdala maturation in females may have a negative impact on emotion regulation and render them more susceptible to depression.

Along with the volume difference, the functional difference in the amygdala of males and females may increase female depression susceptibility. The amygdala's response and hemispheric lateralization are manifestations of the differential. Primarily, females' amygdala exhibits a persistent response to fear or unpleasant stimuli compared to males (And14), and this response could result in amygdala hyperactivation. Thus, hyperactivation may cause a higher metabolism in the body, resulting in needless physiological reactions and maladaptive cognitions that lead to depression. Furthermore, women may be predisposed to depression due to their more vivid and powerful recall of emotionally charged memories (Dav02). Women employ their left hemisphere during emotional memory processing (Cah04), and the left hemisphere is generally involved in the detailed processing of aversive stimuli (Mar99), which can lead to the formation of solid memories in women. Emotional memories are more important to individuals and will be recalled more frequently than other memories. These memories may also bring back the pain alongside the negative thoughts felt and disrupt females' mental health. It may also result in physiological and behavioral responses such as insomnia or hypersomnia and social isolation.

6 Discussion

6.1 Implications

This review paper explored the amygdala's sexual dimorphic characteristics and their role in female depression vulnerability. To begin with, it defined the amygdala by describing its anatomy and function, along with discussing the amygdala's role in depression. It demonstrated some of the amygdala's sexually dimorphic characteristics. The amygdala's volume was the first attribute examined in this review, and it stated that females have a smaller amygdala volume. Also, it implied that the decreased volume would result in fewer neuronal and

glial cells, obstructing proper functioning and triggering amygdala hyperactivity when exposed to adverse stimuli. The review also looked at the amygdala's earlier maturity in females. It suggested that this occurrence might render the female amygdala less effective in connection with itself and other brain structures. This may jeopardize emotion regulation and predispose women to depression. The function of the amygdala was the other sexually dimorphic feature examined. The first functional difference observed was in the amygdala's sensitivity to unpleasant stimuli, with females exhibiting a more persistent response. According to the review, this may cause unnecessary physiological reactions in our bodies, resulting in maladaptive cognitions. In addition, this review looked at females' acute and vivid recall of emotional memories. It also claimed that women's left hemisphere lateralization while processing emotion may contribute to this. In essence, emotional memories will be more retained in females, bringing back the pain or bad sentiments they had at the time. As a result, it will have a negative impact on their mental health, rendering them susceptible to depression.

6.2 Limitations

One limitation of this review was the scarcity of studies on the sexual dimorphic feature of the amygdala. This narrowed the scope of the review and limited the reasons for sexual dimorphism to the effects of sex hormones. Furthermore, the focus of this review is the amygdala's sexual dimorphism as a neurological etiology for female depression vulnerability. However, since the amygdala has a high density of sex hormone receptors, it is difficult to determine whether its effects are neurological or sex hormone influenced. Another limitation is that the notions stated in this review are only suggestions based on the studies done so far. As a result, numerous studies are needed to determine whether these may be plausible linkages between the amygdala's sexual dimorphism and female depression susceptibility.

6.3 Future directions

According to the studies discussed in this review, the amygdala is a sexually dimorphic brain structure. As neuroimaging techniques advance, more extensive and thorough investigations of the amygdala's sexual dimorphism will be possible. Researchers will then be able to explore the therapeutic ramifications of this trend once they have an in-depth understanding of the similarities and differences between the amygdala of males and females. Thus, the amygdala may be of interest in researching the neurological origins of females' susceptibility to depression.

7 Conclusion

This review aimed to investigate the amygdala's sexual dimorphism and discover how it affects women's susceptibility to depression. As previously mentioned, the amygdala exhibits sexually dimorphic characteristics in its volume and function. Nevertheless, more research is needed to have a broad understanding of the extent of the discrepancies. Additionally, because the amygdala plays a role in depression, it is imperative to have an extensive grasp of the distinctions when examining the significant sex disparities in the prevalence of depression.

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