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Neural Correlates of Comorbidity of Anxiety Disorders and Eating Disorders

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Neural Correlates of Comorbidity of Anxiety Disorders and Eating Disorders

by

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Abstract

The presence of eating disorder and anxiety disorder comorbidity has raised the question of whether or not there is a causal relationship between them. Previous studies have found that this comorbidity has been present in various patients with anxiety disorders and eating disorders, going further to try and determine which diagnosis came first (Swinbourne et al., 2012). By conducting a literature review, studies were examined to determine neurobiological regions impacted by both disorders. Prefrontal cortex abnormalities are consistent among both disorders, contributing to differences in behavior and reward systems. With the irregular structure and activation of the amygdala, emotion and fear regulation are disrupted in those with either illness. Hypothalamic dysfunction in regulating feeding and reward response is found to be an additional commonality. Deficiencies of gray brain matter indicate deterioration of neural connections in those with either disorder.

Introduction

Research over the past decade has made mental illness a frequent topic of discussion. However, it seems a disconnect remains in understanding these complex illnesses. Eating disorders, a type of mental illness, include various diagnoses based on types of eating behaviors and psychological tendencies that can result in severe malnutrition and even death. These illnesses' definitions are still being debated, even amongst medical insurance companies. However, studies have shown that eating disorders fit most well within the definition of "biologically based mental illness" due to the several categories of causation factors, including genetic, biological, and environmental (Klump et al., 2009). With several causal factors, the parts of the brain affected by these illnesses and how they are affected are in wide variety.

The two most well-known eating disorders are anorexia nervosa (AN) and bulimia nervosa (BN). AN is defined as significantly low body weight and extreme psychological tendencies about gaining weight and weight perception (Mayo Clinic, 2022). BN can include disrupted eating control resulting in the large consumption of food, known as binging, followed by purging (Mayo Clinic, 2022). A commonality shared between these diagnoses is affected dopamine activity, the basis of the neurological reward system. What makes these disorders different is how the system is affected, whether that be heightened neurological sensation caused by food in those with AN or lessened in those with BN (Weir, 2016). These neurological effects underlie the individuals' relationships with food across different eating disorders. Those with AN eat little to no food and often are anxious and overwhelmed when doing so while those with BN tend not to feel satisfied while eating, causing the consumption of large amounts of food at one time.

A common misconception about mental health is that all individuals experience similar emotions at one time or another. While anxiety is a familiar sensation involved in human nature and felt in various situations, there is a significant difference between being anxious and having a chronic anxiety disorder. Types of anxiety disorders include general anxiety disorders (GAD), obsessive-compulsive disorder (OCD), panic disorders, post-traumatic stress disorder (PTSD), social anxiety disorders (SAD), and several phobias (Meier et al., 2015). These disorders span an individual's life and have greater effects on their quality of life with feelings of severe stress, worry, and fear.

The relationship between eating disorders and the prevalence of mental illness among its victims has been a research interest of the biological and psychological disciplines for quite some time. The focus remains on determining if they share causal factors or if one disorder is caused

by the other. One study involved determining the types of psychiatric disorders their subjects were suffering from in addition to having BN and whether it began before or after their BN diagnosis. It was found that 64% of their subjects also suffer from some anxiety disorder (Bulik et al., 1996). In a similar study, female patients with eating disorders and others with anxiety disorders were considered to determine the presence of comorbidity, meaning patients displaying both an anxiety disorder and an eating disorder. It was found that 65% of those with an eating disorder also suffered from a comorbid anxiety disorder, and 13.5% of those with an anxiety disorder had a comorbid eating disorder (Swinbourne et al., 2012). Additionally, it is inferred that the most common anxiety disorder among those with eating disorders is OCD due to the effects of their compulsive tendencies on food consumption (Anxiety & Depression Association of America, 2022).

While it is clear that patients with eating disorders tend to have other mental health disorders, it remains to be determined which one came first and does that have any indication if one caused the other. Of the 64% of patients also suffering from an anxiety disorder, 92% expressed that it began before their BN diagnosis (Bulik et al., 1996). In the previous study including both female eating disorder and anxiety disorder patients, 69% of those with an eating disorder and a comorbid anxiety disorder said the anxiety began before their eating disorder diagnosis, and 71% of those with anxiety disorders and a comorbid eating disorder said that their anxiety disorder also began before their eating disorder diagnosis (Swinbourne et al., 2012). Although the anxiety disorders these patients suffer from could have preceded their eating disorder diagnosis, determining neurobiological regions affected by both anxiety disorders and eating disorders could suggest areas of future research exploring comorbidity.

Neural correlates of comorbidity of interest in this paper will be the prefrontal cortex, amygdala, hypothalamus, and gray matter atrophy.

Methods

This literature review utilized research already completed in the biological, psychological, and psychiatric disciplines. Accredited sources were found using the search engines Google Scholar and the Portland State Library database. Key phrases in a preliminary search for data included "eating disorders," "anxiety disorders," and "mental illness and eating disorders," as well as adding "neurobiology" in order to obtain articles with a neurobiological or anatomical approach. These articles were used to find correlate regions of interest by comparing anxiety disorder and eating disorder-focused articles. These regions of interest aided in a secondary data search using region names and general areas of interest as key searching phrases. These included "prefrontal cortex," "gray brain matter," "hypothalamus," and "amygdala" with "eating disorder" or "anxiety disorder," following each depending on the focus desired. Neural correlate regions were discussed to draw connections and note similarities in the different disorders.

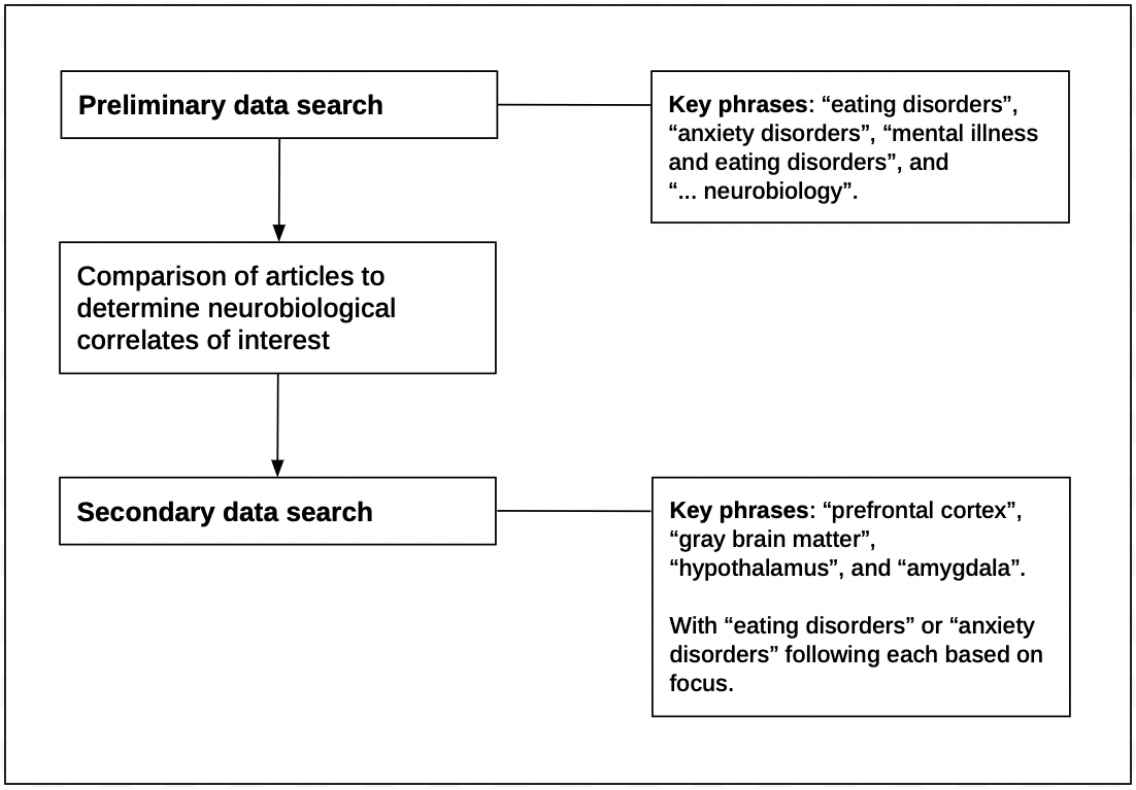

Figure 1 Literature search and neurobiological correlate determination. A literature search was performed in the interest of establishing known anatomical factors in both anxiety disorder and eating disorder pathologies known to occur simultaneously. Key phrases from the preliminary literature search informed those utilized in the secondary search.

Results

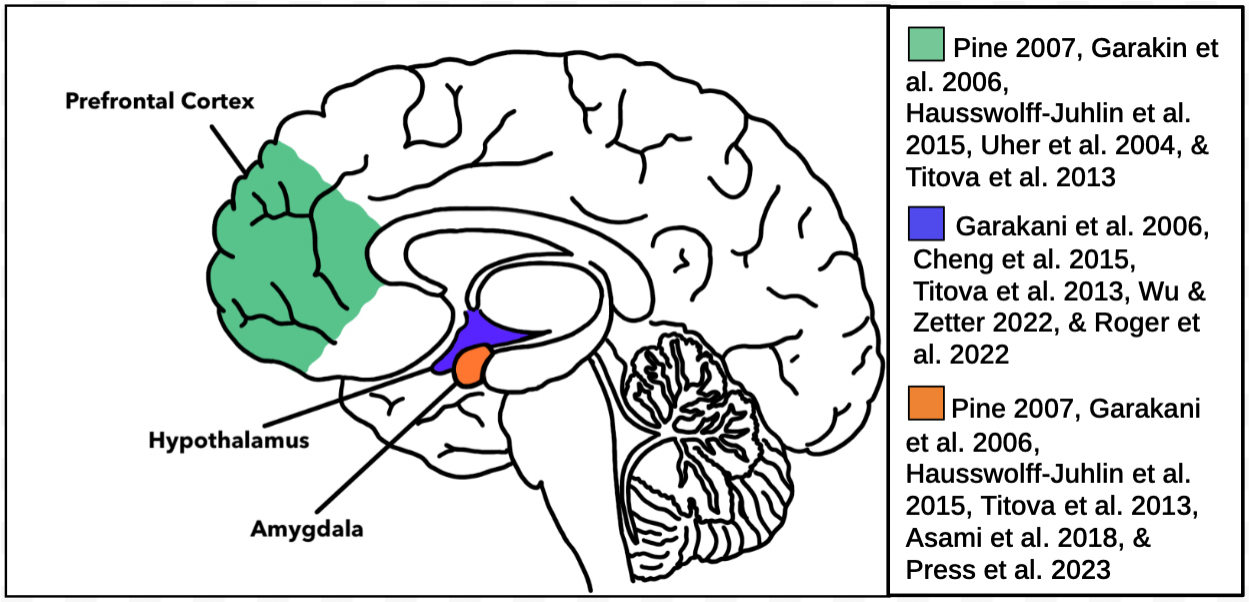

Figure 2 Correlates of interest between anxiety disorders and eating disorders. Anatomical regions were identified based on correlation to comorbidity of both anxiety disorders and eating disorders. A literature review revealed common areas to include the prefrontal cortex, hypothalamus, and amygdala.

In Pine 2007, the focus was placed on specific brain regions participating in threat response for future research on pediatric development and anxiety disorders. Two regions mentioned include the amygdala and the ventral and medial prefrontal cortices. The amygdala is of importance due to its role in threat response regulation. The ventral prefrontal cortex is of interest with its connections to the amygdala. This circuitry is thought to be involved in emotion and behavioral regulation. Pine explains that threat regulation is the system that is interrupted in anxiety disorders like social phobia, separation anxiety disorder, and GAD (Pine, 2007). The threat regulation system includes threat-attention interaction, threat appraisal, and memory & learning (Pine, 2007). This system is interrupted by the genetic and environmental influences on different brain circuitry involved in threat regulation, including the amygdala and the prefrontal

cortex. These brain circuits can be impacted by structural change, which has been found in the amygdala, hippocampus, and the medial and ventral prefrontal cortices (Pine, 2007). Such changes need to be further researched to determine the specific direction of structural change; however, any change like this could potentially impact the region's function and the circuitries they are involved in. Another study found increased activation of the amygdala and ventromedial and ventrolateral prefrontal cortices in adults with mood and anxiety disorders compared to a healthy control group when presented with threats.

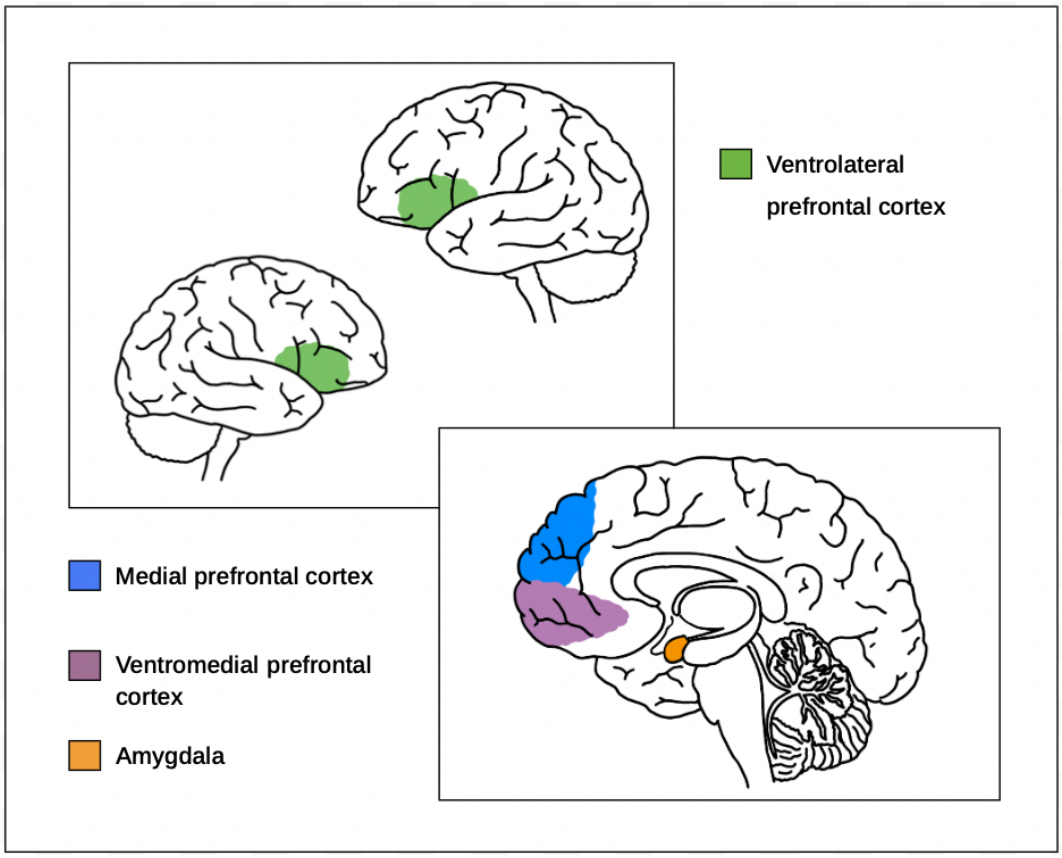

Figure 3 Anatomy of the threat response. Patients experiencing anxiety disorders often demonstrate hyperactivated threat responses. Regions in the prefrontal cortex which connect to the amygdala have been shown to be involved in threat response interruption in anxiety disorder patients (Pine 2007).

A study involving panic disorder (PD) patients by Asami et al. 2018 focused on the volumetric differences in the amygdala within its several nuclei. Previous studies have observed overall volumetric amygdala changes in those with PD. Imaging revealed a volumetric deficit in the right whole amygdala and specifically in the right lateral nucleus and basal nucleus in those with PD compared to healthy control (Asami et al., 2018). These nuclei connect to larger brain regions, including the medial prefrontal cortex and the orbitofrontal cortex, thus involving them in sensory communication. The volumetric deficits present are noted to likely negatively affect the function of these regions leading to PD symptoms.

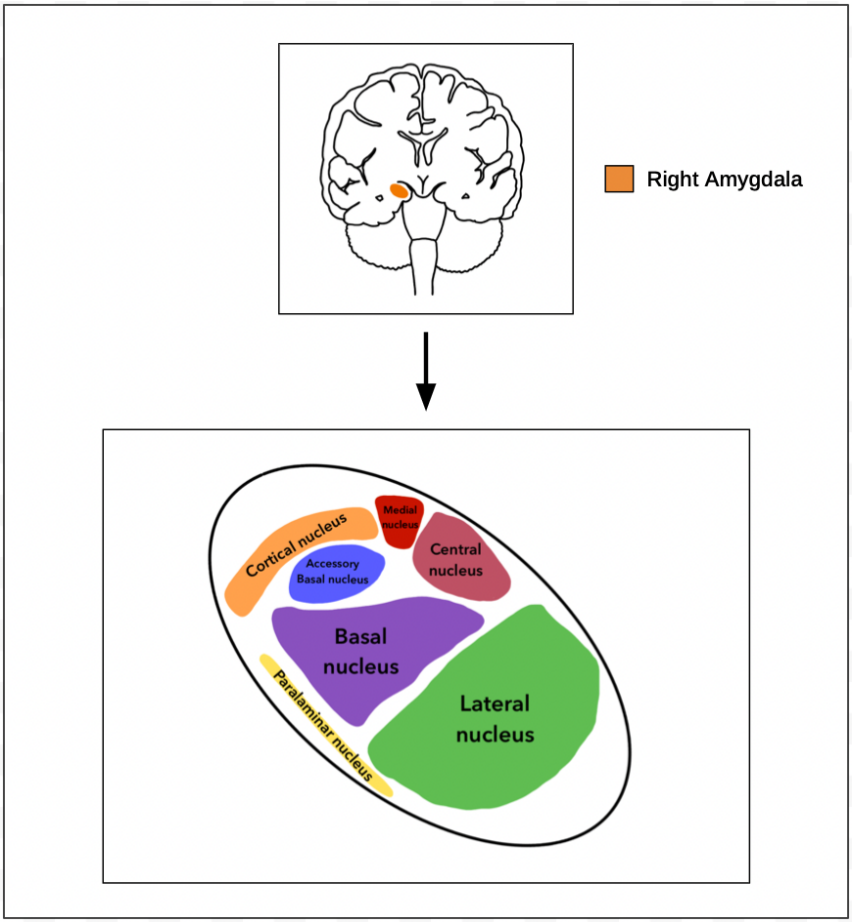

Figure 4 Anatomy of PD. Volumetric deficits have been observed in the right amygdala, right lateral nucleus, and basal nucleus in PD patients which could influence abnormal function (Asami et al., 2018).

Wu & Zetter 2022 discussed the influence of the hypothalamic paraventricular nucleus (PVN) in anxiety disorders in hopes of improving treatments for these illnesses. PVN has several roles, including stress response, and is involved in several brain circuitry through its neurons extending to brain regions including the central amygdala, dorsomedial hypothalamus, medial prefrontal cortex, and ventromedial hypothalamus (Wu & Zetter, 2022). These circuits are thought to be interrupted in those with anxiety disorders. The dorsomedial hypothalamus regulates stress response through an inhibitory role on the PVN. The prefrontal cortex and medial amygdala are also involved in PVN regulation. The PVN has specialized neurons innervating several parts of the brain, releasing different neuropeptides (Wu & Zetter, 2022). This ability allows the PVN to influence many regions of the brain and their subsequent functions, including those mentioned to be involved in the PVN circuitry above.

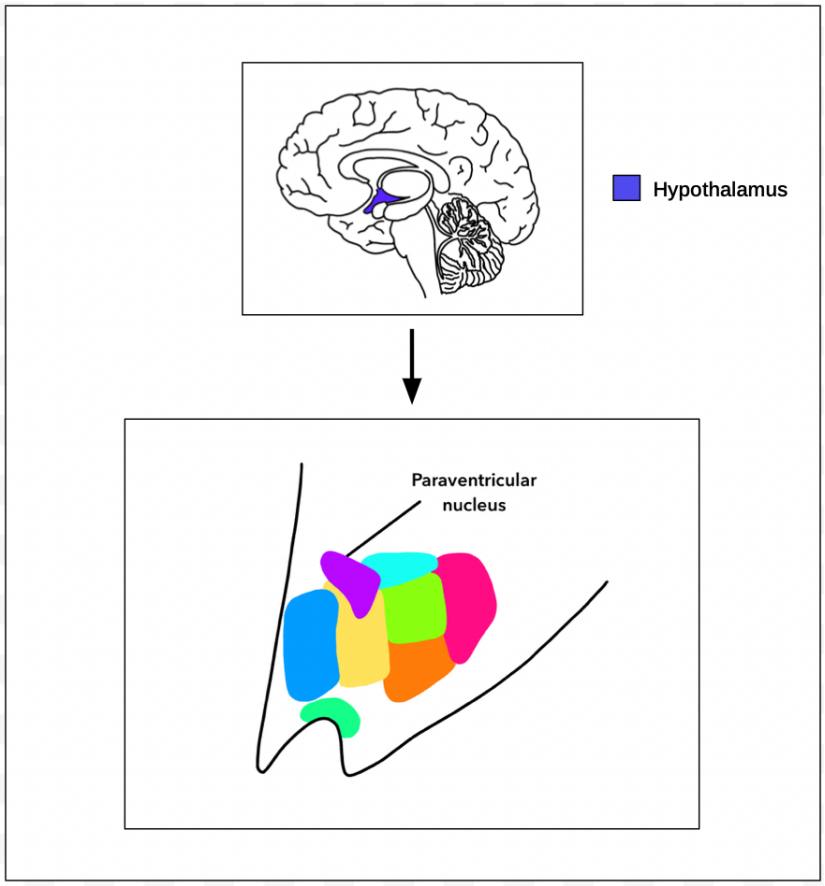

Figure 5 Anatomy of the Stress Response. Interruption of PVN related circuitry involved in stress response was observed in anxiety disorder patients. The PVN has the potential to influence several brain regions connected to it via neuron released neuropeptides (Wu & Zetter, 2022).

Gray matter alterations in those with varying anxiety disorders were compared by Cheng et al. 2015 in order to draw a contrast between the different diagnoses. With magnetic resonance imaging (MRI), gray matter reduction was observed in all patients with either OCD, PTSD, or SAD. In the left hypothalamus, both OCD and SAD subjects had a decrease in gray matter volume. PTSD subjects had a greater decrease of gray volume matter in this region. Due to being responsible for hormone regulation, the hypothalamus is involved in the body's reactions to stress and influences behavior which could be disrupted by this deficit. In the left inferior parietal lobule, OCD subjects had the least gray matter deficit, followed by SAD subjects and PTSD

subjects with the most significant gray matter deficit. The inferior parietal lobule aids in emotion regulation and gray matter alterations could result in dysregulated emotion (Cheng et al., 2015).

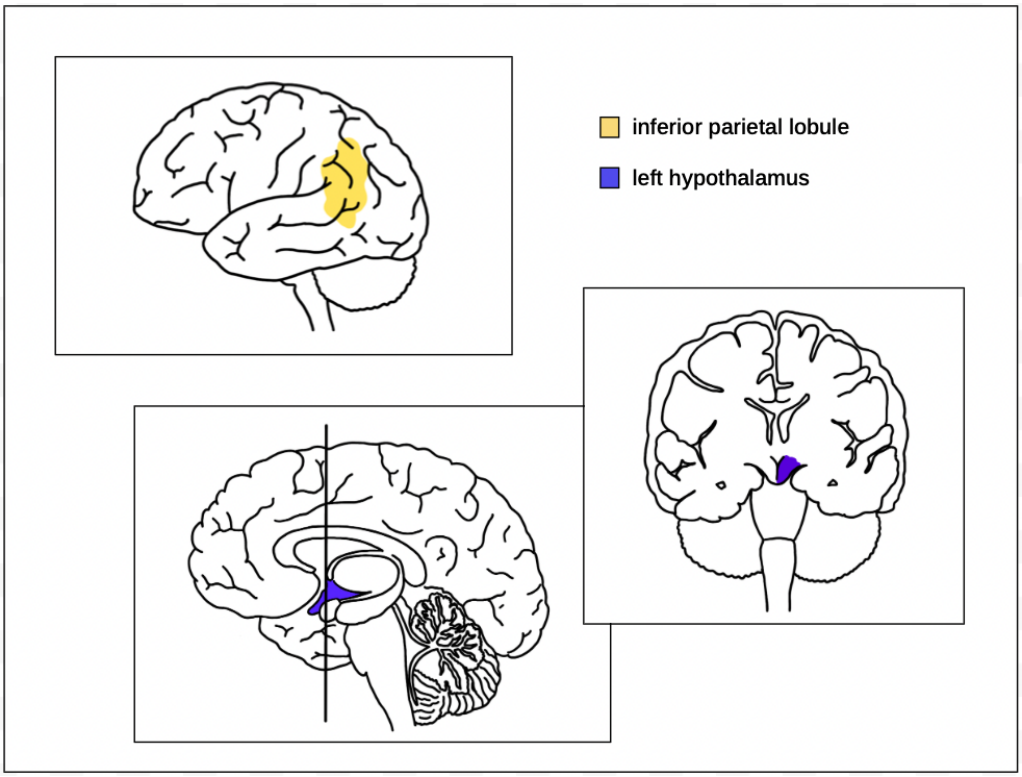

Figure 6 Gray matter deficit in anxiety disorder patients. All OCD, PTSD, & SAD patients had gray matter deficits in the left hypothalamus and the inferior parietal lobule. PTSD patients had the greatest gray matter deficit in both brain regions (Cheng et al., 2015).

In Hausswolff-Juhlin et al. 2015, the neurobiology of eating disorders and other psychiatric disorders is examined through neuroimaging to improve eating disorder treatment through similarities. Two areas noted included the hypothalamus and the basal ganglia due to their roles in feeding. Hausswolff-Juhlin et al. note that the amygdala, a part of the basal ganglia, might affect the emotions toward food (Hausswolff-Juhlin et al., 2015). Functional magnetic resonance imaging (fMRI) of eating disorder patients revealed gray and white brain matter deficits. Images also revealed activation of the medial orbitofrontal cortex, lateral orbitofrontal cortex, and specifically the dorsolateral prefrontal cortex in those with AN when food image

stimulus was involved. During exposure to food images, patients with BN displayed decreased activation in the prefrontal cortex, while activation was heightened in the medial orbitofrontal cortex (Hausswolff-Juhlin et al., 2015). Decreased activation in this region could explain the compulsive nature of this disorder.

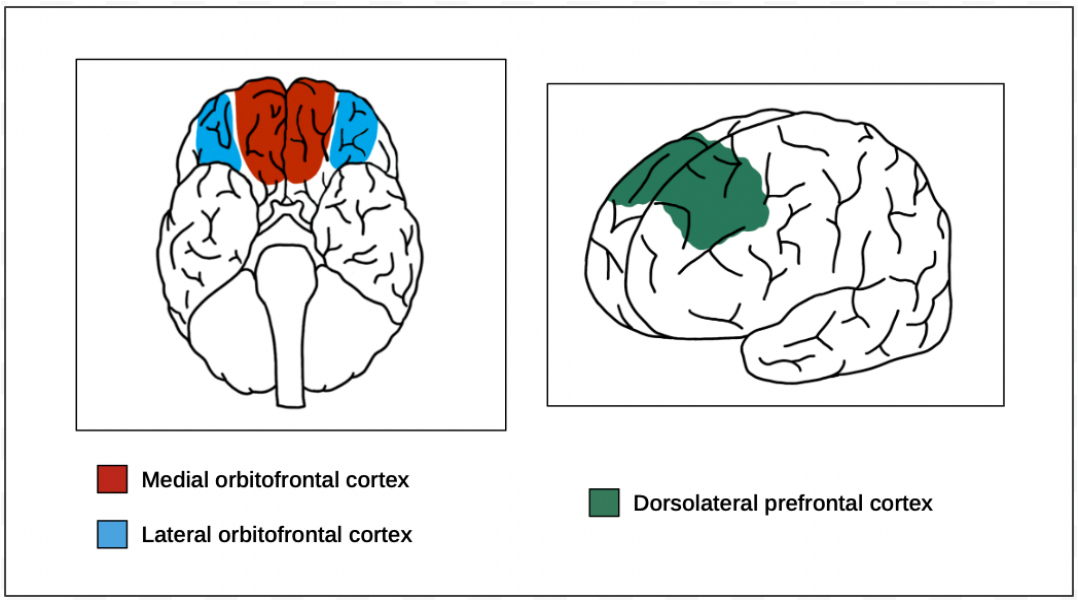

Figure 7 Brain regions of activation in AN patients. When food image stimuli was presented, AN patients showed activation in the medial and lateral orbitofrontal cortex and the dorsolateral prefrontal cortex according to fMRI (Hausswolff-Juhlin et al., 2015).

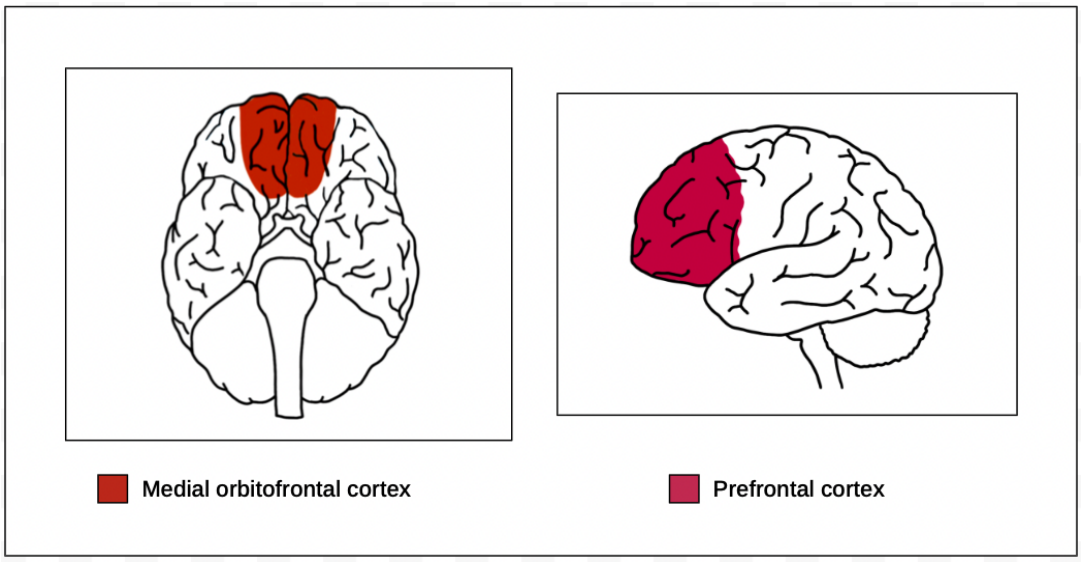

Figure 8 Brain regions of activation in BN patients. When food image stimuli was presented, BN patients showed activation in the medial orbitofrontal cortex and the prefrontal cortex according to fMRI. Increased activation was observed in the medial orbitofrontal cortex while activation in the prefrontal cortex was decreased (Hausswolff-Juhlin et al., 2015).

Uher et al. 2004 studied activation in regions of the prefrontal cortex in female patients with eating disorders through the presentation of food image stimuli in order to contribute to proper eating disorder classification. The presentation of food image stimuli made the subjects with eating disorders uncomfortable and threatened. Activation areas of interest observed in fMRI images of the eating disorder patient group included the left orbitofrontal cortex (Brodmann's area 11) and the left lateral prefrontal cortex (Brodmann's area 10) (Uher et al., 2004). While the inferior parietal lobule and left cerebellum were activated in the healthy control group, the subjects with eating disorders instead had activation in the medial prefrontal cortex and the anterior cingulate.

Also, compared to the healthy group, it was found that the left medial orbitofrontal cortex activation was heightened. In contrast, the eating disorder subjects' left lateral prefrontal cortex and the left inferior parietal lobule activation were lessened. It is noted that the orbitofrontal

cortex is also known to be involved in OCD and affective disorders. A decrease in anterior and lateral prefrontal cortex activation was found in subjects with BN. Due to the lateral prefrontal cortex being involved in regulating behavior, this could indicate the dysregulation of compulsive behavior. Both subjects with AN and BN displayed greater medial prefrontal cortex activation (Brodmann's area 9). With these results, Uher et al. suspect a system involved in compulsivity and mood could exist within the medial prefrontal cortex that is a part of stimuli response in those with OCD, eating disorders, and affective disorders (Uher et al., 2004).

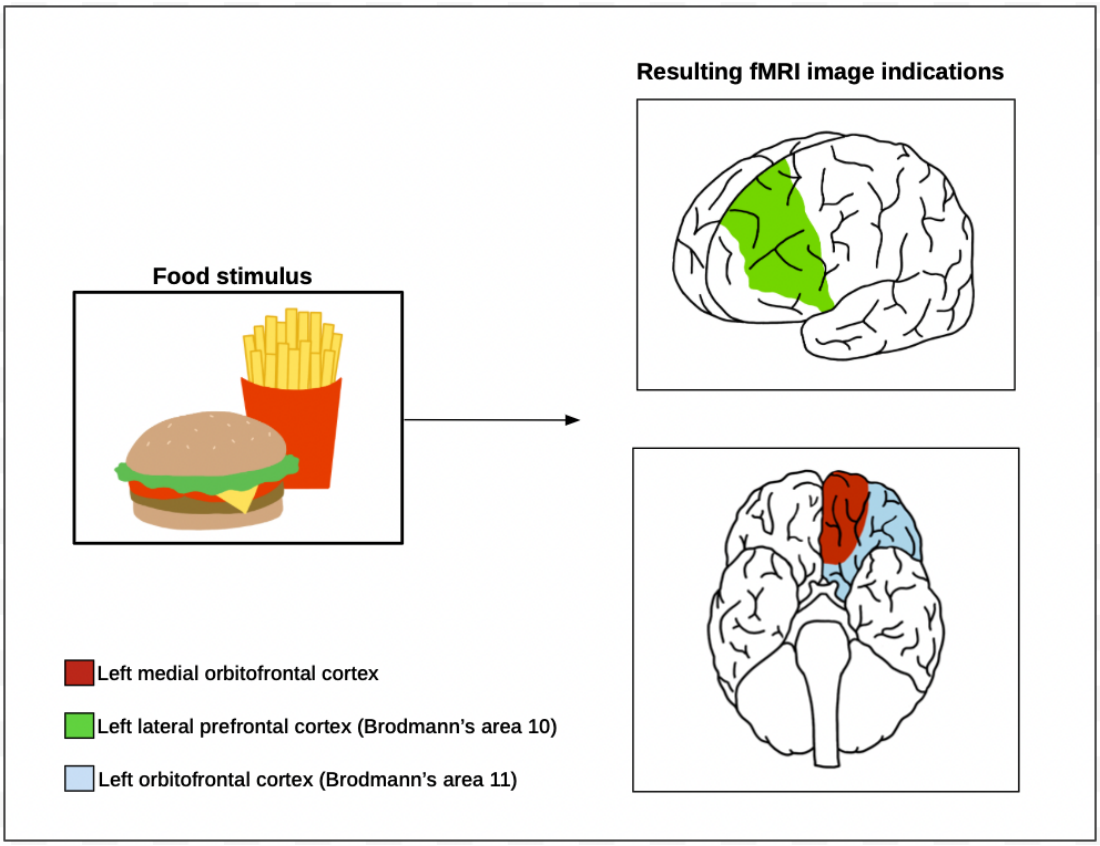

Figure 9 Brain regions of hyperactivation in AN & BN patients. In comparison to a healthy control, heightened activation of the left medial orbitofrontal cortex, left lateral prefrontal cortex, and left orbitofrontal cortex was observed in AN & BN patients in response to food image stimuli (Uher et al., 2004).

The activation of emotion-related brain regions was examined by Press et al. 2023 in female patients with binge eating disorder (BED) to try and determine neural correlates of interest for future research. This was done using neuroimaging to examine brain activation, specifically the insula and amygdala, when patients were presented with images of negatively attributed body parts of themselves or others similar in size. Negatively attributed body parts were of focus due to previous studies determining that those with eating disorders show increased attention to these areas. Compared to a healthy control group, higher activation of the amygdala and insula was found in those with BED, especially when presented with images of negatively attributed body parts of themselves specifically (Press et al., 2023). This was also found in similar studies completed with female patients with AN and BN. This increased activation was further examined, and increased amygdala activation was most associated with negative responses to the image stimuli (Press et al., 2023).

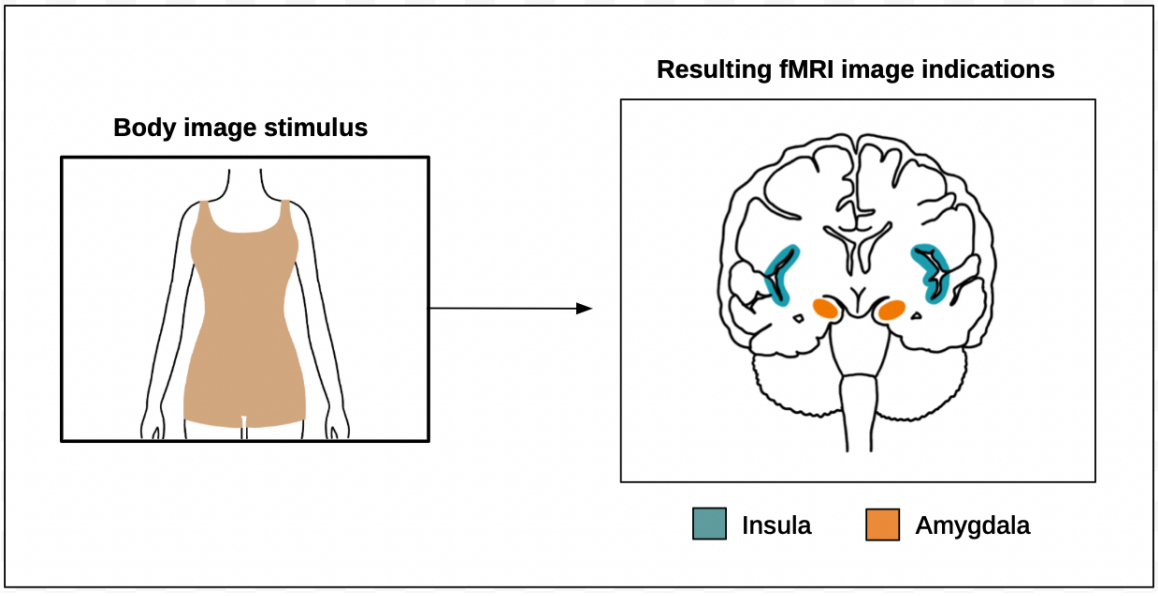

Figure 10 Brain regions of hyperactivation in BED patients in response to negative image stimuli. Heightened activation was found in the insula and amygdala in response to negatively attributed body part image stimuli in those with BED (Press et al., 2023).

Roger et al. 2022 examined the hypothalamus's role in food-related regulation and its state in AN patients. Hypothalamic dysfunction in those with eating disorders has been found in previous studies. This dysfunction was further studied to reveal structural differences in the hypothalamus compared to healthy control, including gray matter deficit in the left hypothalamus (Roger et al., 2022). Once more, gray matter abnormalities are theorized to impact the function of the brain structure and, here, specifically, impact the food reward system. Connectivity involving the hypothalamus was also studied to reveal fiber and connectivity abnormalities in the hypothalamic nuclei themselves and the circuitries involving the hypothalamus. Functional connectivity in AN patients is most impacted in homeostasis and reward circuitry regions. When presented with food image stimuli high in calories, AN patients were found to have increased activation in the hypothalamus, amygdala, and anterior insula (Roger et al., 2022). However, areas of activation have abnormalities in whether they increase or decrease due to differences found in those currently ill and those recovering. Overall, Roger et al. state that what is supported is a dysregulation of the food reward system, including the hypothalamus, with its reduced reactivity and connectivity (Roger et al., 2022).

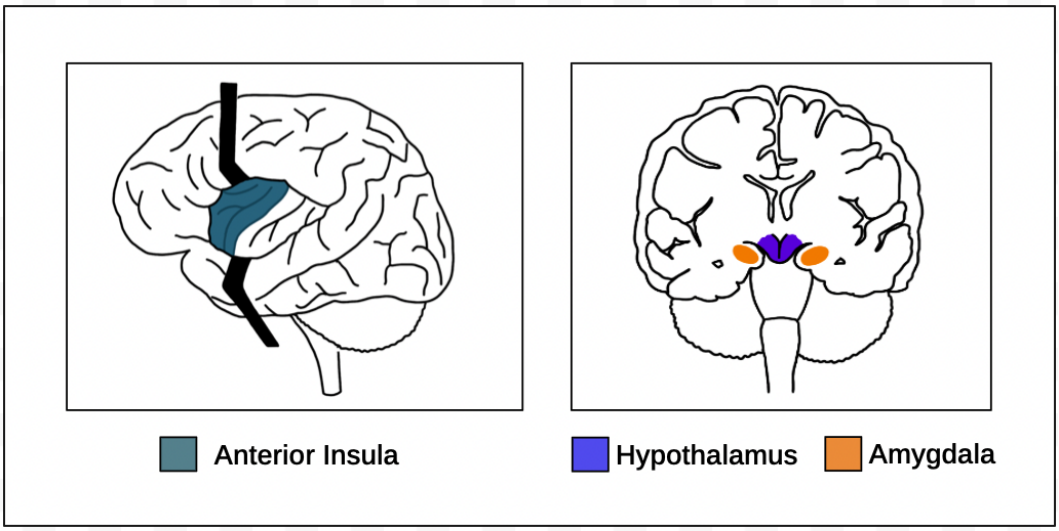

Figure 11 Brain regions of hyperactivation in AN patients in response to food image stimuli. In response to high calorie food image stimuli, a greater activation in the hypothalamus, amygdala, and anterior insula was observed in AN patients (Roger et al., 2013).

Brain matter volume in the brains of females currently ill with AN was compared with a healthy control group to determine volume trends by Titova et al. 2013. MRI imaging displayed a gray and white matter deficit in the entirety of the brain. One of the specific regions of gray matter loss was the hypothalamus. In addition, other studies have found changes in gray matter in the amygdala. There has been observed decreased activation of the midbrain, including the hypothalamus and amygdala, in those with AN while also having increased activation in the prefrontal cortex regions. Titova et al. conclude that functions based in this region are impacted in those with AN.

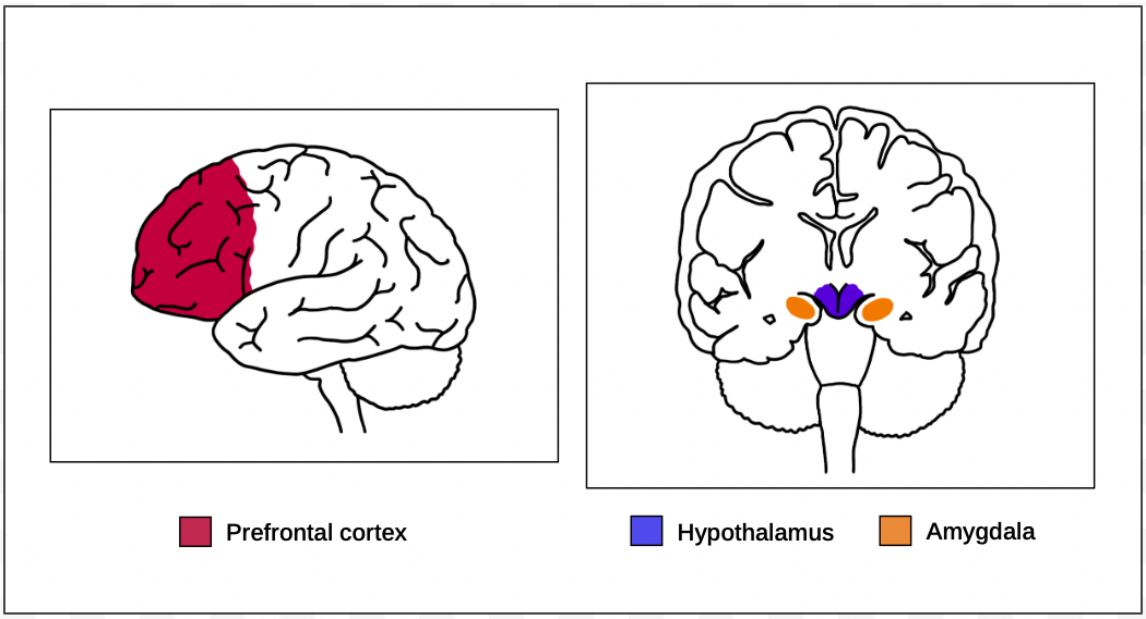

Figure 12 Brain regions of varying activation in AN patients. In AN patients, decreased activation in the hypothalamus and amygdala was found while there was an increase in activation of the prefrontal cortex (Titova et al., 2013).

Discussion

Neural correlates of comorbidity of anxiety disorders and eating disorders emerged by completing the literature review and three of those regions are of focus in this paper. The prefrontal cortex quickly became prevalent in these articles due to the activation modification in those with either disorder. The prefrontal cortex is important in patients with anxiety disorders due to its role in threat regulation (Pine, 2007). Specifically, the regions of interest include the ventral and medial prefrontal cortices. The ventral prefrontal cortex was examined due to being a part of the emotional and behavioral circuitry together with the amygdala (Pine, 2007). Pine suspects threat regulation to be impacted in those with anxiety disorders, stemming from the initial influence on brain structures like the prefrontal cortex. Pine states that the initial impact has been found in structural change in the medial and ventral prefrontal cortices. This could suggest impacted function in these regions. Additionally, a heightened activation in the same

prefrontal cortices in adults with mood and anxiety disorders was noted. In a food image stimuli study, comparison to a healthy control group revealed that eating disorder patients' brain activation areas differed (Uher et al., 2004). While the fMRI showed activation in the inferior parietal lobule and left cerebellum in the healthy control, the prefrontal cortex and the anterior cingulate were activated in eating disorder patients. The different activation regions in the healthy and eating disorder patient groups raises the question of whether these regions indicated are involved in causation or are being influenced as a result of the illness itself. Activation abnormality of the prefrontal cortex is a similarity between anxiety disorder and eating disorder patients. This could be indicative of the behavioral changes that present themselves in those with these disorders. If a pediatric patient with either of these disorders, underdevelopment of the prefrontal cortex might have further implications.

Increased activation of the medial orbitofrontal cortex (Brodmann's area 9) and lesser activation in the left lateral prefrontal cortex (Brodmann's area 10) and the left inferior parietal lobule has been found in eating disorder patients (Uher et al., 2004). More specifically, a decrease in anterior and lateral prefrontal cortex activation was found in subjects with BN (Uher et al., 2004). Similarly in another study, AN patients were found to have increased activation in the medial orbitofrontal, lateral orbitofrontal, and dorsolateral frontal cortices while those with BN also had increased activation in the medial orbitofrontal cortex but less in the prefrontal cortex (Hausswolff-Juhlin et al., 2004). The orbitofrontal cortex has also been found to be associated with OCD and affective or mood disorders (Uher et al., 2004). This suggests that the orbitofrontal cortex could be impacted by both anxiety disorders and eating disorders. While having various responsibilities, its role in sensory integration, behavior, and reward response for both is most pertinent in this discussion (Rolls, 2004). Impacted reward response for sensory and

behavior could explain feelings of overstimulation and erratic behavior in those with either disorder. Another possibility could be that the impact on the orbitofrontal cortex differs in each disorder. For example, the sensory of food might be altered in eating disorder patients while behavior is more significantly disrupted in anxiety disorder patients.

The amygdala is an area of focus in patients with either disorder due to its involvement in fear and threat response and its several connections in other brain circuitry. Volumetric abnormalities were of interest in Asami et al. 2018 in those specifically with PD, finding that the right amygdala and, more specifically, the right lateral nucleus and basal nucleus were impacted by a volumetric deficit the most. This causes concern for the circuitries the nuclei are a part of as function could be impacted, and in this case, sensory communication (Asami et al., 2018). In BED patients, increased amygdala activation was observed and further supported in a similar study with the same findings in AN and BN patients (Press et al., 2023). This could open up possibilities of hyperactivation in related circuitries, leading to additional abnormalities in brain function. Studies utilized in this paper suggest that increased activation might be correlated with volumetric abnormalities. This could be a result of attempting to compensate for the loss of connectivity or a dysregulation issue resulting from these illnesses.

With the connections to the amygdala and the prefrontal cortex, the hypothalamus is important in both disorders due to its potential to influence many brain regions. In particular, the hypothalamic paraventricular nucleus (PVN) was examined to determine the potential impact its dysregulation in those with anxiety disorders could have on its involved circuitries. The PVN is involved in stress response and brain regions connected with it, including the central amygdala and medial prefrontal cortex, can have regulatory roles in its function (Wu & Zetter, 2022). The PVN can directly impact these and other connected regions via neuropeptides, suggesting that its

dysregulation could affect several brain regions. The hypothalamus in those with eating disorders has consistently been of focus due to the pathology of eating disorders being most connected to dysfunction of the reward system and food-related regulation (Roger et al., 2022). Connectivity and activation abnormalities in the hypothalamus and its nuclei have been observed, entailing differences in fibers and functional connectivity, especially in homeostasis and reward circuitry regions. Activation abnormalities were found in the hypothalamus, amygdala, and anterior insula, with differentiation in those currently ill and those recovering (Roger et al., 2022). Anxiety disorder and eating disorder patients exhibit stress and reward response abnormalities which may underlie other phenomena including distress, excess satisfaction, or lack of satiety. Capability of such widespread effect on the body could suggest that the hypothalamus is a region of causation for these illnesses rather than a result of their influence.

In addition to the three correlates of focus, a commonality between the two disorders was a gray brain matter deficit. A study completed with patients with either PTSD, OCD, or SAD led to an observation of overall gray matter deficit in the brain of all disorders. Specifically, the left hypothalamus and the left parietal lobule were affected in all patients, with the most significant gray matter deficit present in those with PTSD (Cheng et al., 2015). In a similar imaging study, Titova et al. 2013 also found an overall gray and white matter deficit in the brains of patients with AN. In these patients, regions of this deficit included the hypothalamus and amygdala (Titova et al., 2013). The gray matter deficit in the hypothalamus could display a commonality between anxiety disorders and eating disorders that could be explored in future research about their comorbidity. Both studies examined the possibility of the roles of each of these regions being impacted by a gray matter deficit and possible explanations of symptoms in those with these disorders. For example, the left hypothalamus and left parietal lobule influence behavior

and emotion, and a loss of nerve cells could lead to decreased or improper function due to a lack of signal amplification (Cheng et al., 2015). This could be consistent in the amygdala and other brain regions, impacting several functions of the brain. The presence of a gray matter deficit in these brain regions could possibly be a result of decreased use or activation of the region leading to degeneration of neural connections. If true, gray matter deficits could indicate additional brain regions impacted by these disorders that could be explored in future research.

The possible correlates of comorbidity discussed in this paper could lead to several research opportunities. What seems to be lacking on this topic is specificity and proving causation rather than correlation. Image stimuli-based studies hold promise in discovering how these brain regions differ in those with these illnesses. This study type might be applied to more specific parts of these three correlates to observe how image stimuli most negatively associated with the specific illness affects patients' brains. Another path for research could be diving deeper into whether brain abnormalities came before or after these disorders. While it has been found that these correlates have abnormalities in function, structure, and regulation, it is still unknown whether these abnormalities are causation for both anxiety disorders and eating disorders or that they are the result from having these illnesses. Determining this factor could reveal that these disorders do not share causation but instead have similar impact on these brain structures, only future research will tell. Studies relating the comorbidity of anxiety disorders and eating disorders provide an excellent framework for the exploration of novel patient treatments. Thus, continued research in this area is likely to yield fruitful outcomes.

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