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Abstract

There are many types of anxiety disorders, all of which are most recognizable by their display of excessive fear or worry. In order to fully recognize and treat anxiety disorders, individuals must understand the neurobiological causes and neurocognitive expressions of the disorder. This review examines 16 studies on the neurobiology, cognitive symptoms, and treatment options for anxiety disorders. This revealed that the amygdala, prefrontal cortex, visual cortex, and superior temporal gyrus play a substantial role in anxiety disorders. These biological substrates are then linked to common cognitive symptoms of anxiety disorders, including executive function deficits. Finally, both neuropharmacological therapy and cognitive behavioral therapy are examined for their efficacy in helping patients with anxiety disorders. By drawing connections between these key aspects of anxiety disorders, this review concludes that it is important to understand each aspect thoroughly so that we can more readily and accurately diagnose patients, choose an effective treatment method for their needs, and help people of all ages manage the symptoms of these disorders.

Anxiety Disorders

Anxiety is defined by the American Psychological Association as an emotion associated with tension, worry, and physical changes such as increased blood pressure or sweating (American Psychological Association, 2020). There are several types of anxiety disorders, each characterized by recurring intrusive thoughts. Generalized anxiety disorder (GAD) is defined by the experience of uncontrollable and persistent worry (Anxiety and Depression Association of America, 2018). Social anxiety disorder (SD) is characterized by anxiety related to social situations, and panic disorder (PD) is anxiety associated with recurrent panic attacks (American Psychiatric Association, 2013). Post-traumatic stress disorder, obsessive-compulsive disorder, and specific phobias are also considered anxiety disorders by the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (American Psychiatric Association, 2013).

Globally, one in 13 individuals suffer from anxiety, making anxiety disorders the most common mental disorder worldwide (Anxiety and Depression Association of America, 2018). The occurrence of these disorders in the U.S. population is also staggering. Anxiety disorders affect around 18% of the total American population, or roughly 40 million people (Anxiety and Depression Association of America, 2018). The most common of these is SD, affecting around 15 million people, or 6.8% of the U.S. population (Anxiety and Depression Association of America, 2018). Anxiety disorders are also extremely prevalent in adolescents, as approximately 31.9% of children aged 13 to 18 years suffer from an anxiety disorder (National Institute of Mental Health, 2017). Because of its widespread presence in the country and across the world, it is vital that we do all we can to understand anxiety disorders and their effect on the population.

While each type of anxiety disorder has distinct symptoms, they all negatively impact the individual in similar ways. For example, all of the previously mentioned anxiety disorders cause recurrent and excessive fear or worry. In children, anxiety can cause problems in the child's academic and social life (Anxiety and Depression Association of America, 2018). The fear caused by anxiety can interfere with the individual's daily routines, as they attempt to avoid situations that they feel would cause them anxiety. It can also cause problems

in executive functions, such as verbal processing and memory, throughout adolescent development (Micco et al., 2009). Anxiety often persists to adulthood if left untreated, which can aggravate existing symptoms and lead to the development of new symptoms in adulthood. For example, anxiety disorders are often comorbid with symptoms of major depressive disorder (MDD) in adults (Hirschfield, 2001). Fortunately, interventions involving therapy and pharmacotherapy have been developed and shown to be highly effective (Sorsdahl et al., 2013). However, anxiety disorders often go unrecognized and untreated— which may be due to lack of awareness in the individual, social stigmas about therapy, lack of recognition from professionals, or the presence of other disorders that can mask anxiety symptoms (Stjernekla et al., 2019).

In order to recognize and treat anxiety, it is helpful to be familiar with the diagnostic criteria. In addition, it is important to understand the underlying causes of anxiety disorders. In recent decades, biotechnology has advanced to a point where we can take scans of the active brain using PET and fMRI machines. This has allowed psychologists and neuroscientists to better understand how the brain acts during specific situations. This advanced brain-imaging technology has been extremely helpful in identifying the neurobiological causes of mental disorders such as SD, PTSD, and other anxiety disorders (Etkin et al., 2009). By better understanding the neurological workings behind these disorders, more effective treatments could be developed. This review will examine the literature on the neurobiological roots and cognitive expressions of anxiety disorders and will consider the implications of neurobiology on treatment options for anxiety disorders.

Methods

This review aimed to collect empirical data regarding the neurobiological roots of anxiety and their impact on treatment methods. Using the search databases EBSCO, PyschInfo, and SCOPUS, I used search terms relating to anxiety disorders, causes, and treatments in the following combinations: “anxiety disorders AND causes or reasons or factors AND neuropsychology,” “anxiety

disorders AND neurobiology AND children or adolescents or youth or teen," and "anxiety disorders AND psychotherapy or therapy or treatment AND neuroimaging." The searches were then filtered by requiring the publishing date to be between 2000–2020 and by requiring peer-reviewed articles written in the English language. In the first two searches I was able to narrow my results to 300 and 663, respectively; in the third search, I was given 9,329 results.

From this point, I scanned the titles of the first 100 results to find articles relevant to my paper, then I read the abstracts of articles that seemed adequate to see whether the study was relevant to the review. Additionally, I scanned the references of particularly relevant studies to extract other useful research. I also used the databases to identify other articles which had cited my key articles, in an attempt to find more recent and relevant research. In the end, I had 16 articles to thoroughly analyze for this literature review.

Results

The Neurobiology of Anxiety Disorders

The literature identified several brain regions that appear to be deeply impacted by anxiety disorders, including the amygdala, the prefrontal cortex, the visual cortex, and the superior temporal gyrus. Each of these neurobiological substrates serve an important function in the brain. In patients with anxiety disorders, these functions were impaired or changed (Etkin et al., 2009; McCLure et al., 2006). To determine the extent of the impact of the neurobiological factors on anxiety disorders, literature on each brain region will be examined below.

Amygdala

One common thread in the literature is the important role of the amygdala in anxiety disorders. The amygdala is responsible for emotional processing, including the processing and consolidation of fear (Cummins & Ninan, 2002). By examining the relevant literature, we can more fully understand how the amygdala controls these processes, and how dysfunctions can occur to result in anxiety disorders.

Etkin et al. (2009) conducted a cross-sectional fMRI study investigating the connectivity patterns in the subregions of the amygdala in patients with GAD. Previous research by Garakani et al. (2006) had shown that connections between these specific regions of the amygdala process sensory information and send this information to the hypothalamus, which then produces behavioral and autonomic reactions. By comparing the scans of the GAD patients with a control group of healthy subjects, they were able to identify significant differences in the connectivity patterns of the basolateral amygdala and centromedial amygdala. In the control group, the basolateral amygdala and centromedial amygdala had clear and distinct connections with other sections of the brain, but in patients with GAD, the separation between their pathways was less distinct (Etkin et al., 2009). These differences imply an impairment in the amygdala's ability to communicate with the hypothalamus, which could cause differences to the physical and behavioral reactions produced. Additionally, the researchers found increased grey matter in the centromedial amygdala, and increased connectivity between the whole amygdala and the frontoparietal executive control network in subjects with GAD (Etkin et al., 2009). These abnormalities within the amygdala may explain some of the symptoms of anxiety disorders associated with emotional processing, such as excessive worry.

The following year, Etkin et al. (2010) conducted another study on the function of the amygdala in patients with GAD. This study investigated the regulation of emotional conflict through fMRI tasks. Compared to a healthy control group, the subjects with GAD were unable to activate the anterior cingulate in a way that dampened the amygdala activity, limiting their ability to regulate emotional conflict (Etkin et al., 2010). This suggested deficits in spontaneous emotional processing, which correlates to common anxiety symptoms. In conjunction, these studies show that dysfunction in the amygdala may be a defining characteristic of anxiety disorders due to its impact on emotions such as fear and worry, as well as its effect on autonomous reactions to emotional stimuli.

Prefrontal Cortex

As the largest region of the brain, the prefrontal cortex has a large impact on several different functions, including those associated with

anxiety. In an fMRI procedure involving continuous performance tasks and distractor tasks, it was found that adolescents with GAD had increased activation of the left medial prefrontal cortex and right ventrolateral prefrontal cortex in response to emotional images (Strawn et al., 2012a). Furthermore, connectivity between the right ventrolateral prefrontal cortex and bilateral medial prefrontal cortex was decreased in the GAD subjects when compared to the healthy control subjects (Strawn et al., 2012a). These abnormalities affect the individual's ability to regulate emotion and affect the process of mentalization, which correlates with known cognitive anxiety symptoms (Strawn et al., 2012a). Other research has shown that when viewing "angry" faces, the activity of the ventrolateral prefrontal cortex was increased in subjects with GAD compared to control subjects, which suggested a compensatory response to the inhibited amygdala activation (Monk et al., 2006; Strawn et al., 2012b). McClure et al. (2006) also found increased connectivity between the ventrolateral prefrontal cortex and the amygdala in patients with GAD, supporting this idea that the activity of the ventrolateral prefrontal cortex may be related to the activity of the amygdala (Strawn et al., 2012b).

In addition, the prefrontal cortex may be useful in identifying adolescents at risk for anxiety disorders. Clauss et al. (2016) found that inhibited adults (shy, avoidant of social situations) and adults with anxiety disorders exhibit less engagement of the prefrontal cortex than healthy control subjects. They then conducted a study observing the activation of the prefrontal cortex of adolescents in response to threat stimuli and social stimuli. They compared inhibited adolescents with a control group of uninhibited adolescents. They found that the inhibited adolescents had increased activation of the medial prefrontal cortex and dorsolateral prefrontal cortex, as well as reduced connectivity between prefrontal and limbic regions and reduced connectivity between distinct prefrontal cortex regions (Clauss et al., 2016). This was linked to the subjects' inability to properly prepare for social threats and their heightened reactions to social stimuli (Clauss et al., 2016). Thus, we can see that altered functions and abnormal connectivity of the prefrontal cortex in both adolescents and adults can be indicative of anxiety disorders and is associated with the expression of anxiety disorder symptoms.

Other Regions

There are several other regions of the brain involved in anxiety disorders. For instance, Ameringen et al. (2004) found that social anxiety caused deactivation of the visual cortex and the orbitofrontal cortices, regions of the brain responsible for visual attention, visual processing, and connecting stimuli with emotional response. The deactivation of these areas suggested that subjects with SD tend to focus their attention away from the social stimuli and towards their (often negative) thoughts, resulting in a negative emotional response (Ameringen et al., 2004). Additionally, DeBellis et al. (2002) found that the white matter and gray matter volumes of the superior temporal gyrus were larger in adolescents with GAD than in control subjects, suggesting developmental alterations to brain structure in pediatric GAD. These studies show that individuals with anxiety disorders show observable neurocognitive differences in many regions of the brain when compared to individuals without similar disorders.

Neurocognitive Expression of Anxiety Disorders

Considering the examined neurobiological components at work in the brain of patients with anxiety disorders, we can see how they may be associated with the cognitive functions of anxiety. For example, Toren et al. (2000) assessed the neurocognitive functions of adolescents with an anxiety disorder compared to a healthy control group using standard neuropsychological tests. They found that the anxiety group scored higher on the Revised Children's Manifest Anxiety Scale (RCMAS), a self-reported measure of anxiety, which was expected. The anxiety group also scored lower on the California Verbal Learning Test (CVLT), a measure of verbal processing, and had more errors on the Wisconsin Card Sorting Test (WCST), a measure of several executive functions, indicating that these subjects struggled with verbal or linguistic skills. However, there were no significant differences between the two group's scores on the Rey-Osterrieth Complex Figure Test (ROCF), a measure of non-verbal processing. This showed that adolescents with anxiety have trouble with linguistic skills but are not limited in their non-verbal

skills (Toren et al., 2000), suggesting that the regions of the brain specifically associated with verbal processing may be impacted by anxiety disorders.

Murphy et al. (2018) conducted a similar test in which adolescents underwent a comprehensive set of neurocognitive assessments, including both self-reports and executive functioning exams. Their results showed that children with anxiety symptoms experienced increased planning time, increased inhibition, and higher cognitive flexibility (Murphy et al., 2018). In addition, children with anxiety demonstrated poorer working memory skills compared to the healthy control subjects (Murphy et al., 2018). Each of these deficits can cause problems in the child's academic and social life.

Another important factor to consider is whether these cognitive functions can act as a predictor for anxiety disorders, or if they emerge only in currently affected patients. Micco et al. (2009) conducted a study investigating this dilemma by evaluating the executive abilities of offspring at risk of anxiety disorders (due to parental diagnosis). They found that executive function deficits were present in adolescents who currently had anxiety disorders, but there was no correlation between offspring risk and executive function— showing that these deficits in cognitive abilities are not a marker for future disorders, but could be useful in identifying existing anxiety disorders (Micco et al., 2009). The researchers suggest that children exhibiting problems in executive function should have a neuropsychological assessment done to identify the disorder early.

These cognitive abnormalities can be linked back to the brain regions previously examined. For instance, the prefrontal cortex is responsible for planning, impulse control, and attention. The neurocognitive studies above show that adolescents with anxiety disorders do exhibit problems with planning and attention, and we know from neurobiological research that the prefrontal cortex is highly altered in individuals with anxiety disorders (Strawn et al., 2012a). Problems in working memory are also present in individuals with anxiety, which is primarily controlled by the amygdala, frontal lobe, and prefrontal cortex. These links show how understanding the

neurobiological occurrences in individuals with anxiety disorders can help us understand the symptoms they exhibit.

Treatments for Anxiety Disorders

Treatment for anxiety disorders can come in many forms, dependent on the severity of the disorder, the type of anxiety disorder, and the patient's responsiveness. Pharmacotherapy uses medicines, such as benzodiazepines or selective serotonin re-uptake inhibitors (SSRIs), to target the areas of the brain that are impacted by the disorder, while psychotherapy uses behavioral therapy to help the patient recognize and receive the behavioral symptoms of their disorder. Using the research about the neurocircuitry of anxiety disorders, we can examine the efficiency of each kind of treatment and find a balance of methods that can be effective in treating youth with anxiety disorders.

Pharmacotherapy

Several neuropharmacological drugs have been identified as effective treatment options for anxiety disorders, including sertraline, fluoxetine, venlafaxine, and benzodiazepines (Strawn et al., 2016b). Sertraline has been shown to be effective in treating adolescents with anxiety disorders, especially GAD and SD (Strawn et al., 2012b). Fluoxetine showed significant improvement in youth with anxiety disorder, according to the Screen for Anxiety-Related Emotional Disorders and the Pediatric Anxiety Rating Scale (Strawn et al., 2012b). Venlafaxine, a selective serotonin norepinephrine re-uptake inhibitor (SSNRI), was used as an extended-release medication in treating youth with GAD and resulted in significant improvements in anxiety symptoms (Strawn et al., 2012b). Benzodiazepines have typically been used to treat adults with anxiety, but more research is needed on their efficacy in treating adolescents (Strawn et al., 2012b). Each of these medicines target the neurological substrates that are impacted by anxiety disorders in a way that helps correct the deficits in the brain's function.

Although all of these medications have been shown to be effective in sample populations, the type of medication prescribed will likely

vary based on the specific kind of anxiety disorder the patient experiences. Sorsdahl et al. (2013) analyzed data from the 1997–1999 American Psychiatric Institute for Research and Education Practice Research Network Study of Psychiatric Patients and Treatments records relating to the diagnoses and treatment of anxiety disorders. They found that patients with an anxiety disorder were most likely to be given benzodiazepines or SSRIs over any other type of medication (Sorsdahl et al., 2013). However, they also found that anxiety disorders may be under-recognized and under-diagnosed, based on community surveys and interviews with the psychiatrists (Sorsdahl et al., 2013). This research offers insight into the variety of pharmacological treatments patients receive for anxiety disorders and lays the foundation for future research into this topic.

Garakani et al. (2006) took a different approach—rather than SSRIs, they suggested using protein blockers to prevent memory consolidation for patients with anxiety disorders. Although more research is needed, they proposed that the drug propranolol could block the recall of traumatic memories without impeding on the integration of new memories. This method could prove highly effective, especially for patients suffering from PTSD.

Psychotherapy

Another common way of treating anxiety disorders is through cognitive behavioral therapy (CBT). This is a type of therapy wherein a therapist helps a patient to challenge their problematic thinking patterns and change their behavioral patterns with specific and individualized action-based strategies (American Psychological Association, 2017). Research has shown that CBT is highly effective in both adults and children with anxiety disorders (Strawn et al., 2012). However, there are several different programs of CBT that could be used, and there are more being developed each year. For instance, Queen et al. (2014) found that trans-diagnostic treatment for anxiety and depression, two highly comorbid illnesses, could result in positive trajectories for both. Additionally, Garber et al. (2016) found that when a target-specific treatment is used on patients with both an anxiety disorder and major depressive disorder, cross-over effects

help to treat both illnesses. Thus, they proposed that an augmented therapy module with both anxiety-specific and depression-specific treatments could efficiently treat both disorders (Garber et al., 2016).

However, there are also some limitations to CBT, especially in treating adolescents. Many adolescents do not get professional care due to high costs, inaccessibility, and social stigma surrounding therapy (Stjerneklar et al., 2019). Thus, several researchers have begun designing internet-based CBT (ICBT) as an alternative to therapy. Stjerneklar et al. (2019) studied a Danish version of the ICBT program called ChilledOut and found that patients had significantly improved after 14 weeks of treatment. ICBT could be a smart alternative for adolescents because there is less social stigma, more anonymity, reduced costs, and allows for independent progress. Adolescents are also highly familiar with technology and may feel more comfortable using an online program than seeing a therapist in person (Stjerneklar et al., 2019). This would be especially helpful for adolescents with social anxiety, as going to a therapist may be difficult for them. By evaluating the different options for therapy and medication, psychologists can determine the best treatment plan for patients on an individual basis.

Discussion

The literature review has revealed several insights on anxiety disorders, including the neurobiological substrates involved in anxiety disorders, the neurocognitive expressions of anxiety, and potential treatment options for patients with anxiety disorders. The amygdala controls emotional processes but can have connectivity issues in patients with GAD and other anxiety disorders, causing problems in their emotional processing (Etkin et al., 2009). This can lead to problems in the working memory and may disrupt the process of memory consolidation and association of emerges with an emotional response. SSRIs can target receptors in the amygdala, changing the way emotional events are processed, and protein blockers may be able to interfere with the recollection of traumatic memories (Garakani et al., 2006). In addition, the prefrontal cortex is involved in complex functions such as mentalization, linguistic

skills, and planning—all of which have been shown to be impeded in adolescents with anxiety disorders (Strawn et al., 2012a; Toren et al., 2000). CBT can also be extremely helpful in improving these skills and correcting the deficits in executive function. Another brain region affected by anxiety disorders is the visual cortex, which can be deactivated as attention drawn away from external stimuli and towards internal worries, creating negative associations with the stimuli (Ameringen et al., 2004). This can cause individuals with an anxiety disorder, especially SD, to internalize more often and ignore the positive aspects of social interaction due to an excessive focus on worries or insecurities (Ameringen et al., 2004). CBT can help patients become aware of this problem and can help combat the tendency to internalize; medications, such as SSRIs, can also help by adjusting the way situations are processed. By examining these key aspects of anxiety, we can determine whether CBT or medication alone would be preferable, or if a combination therapy may be most effective for the patient's needs.

It is important to look at this research in light of its limitations. Although best efforts were taken to ensure that all relevant studies were assessed, it is possible that more research exists which could help strengthen or refute this conclusion. Additionally, the study of anxiety disorders is difficult because there are so many different kinds of disorders, with unique symptoms and a unique neurobiological makeup. Therefore, it may be fruitful to investigate one specific anxiety disorder, such as GAD or SD, and examine its literature, so as to bring together a more cohesive understanding of that disorder. Further research could also be done on anxiety disorders in adolescents, as it could help us understand the development and emergence of anxiety disorders.

The literature that does exist on anxiety in adolescents has important implications for the diagnosis and treatment of anxiety disorders. The structural problems identified above in the prefrontal cortex were found in youth as well as in adults, which may provide an easier way to identify signs of an anxiety disorder in all stages of life (Micco et al., 2009). Furthermore, adolescents with anxiety disorders had a much larger volume of the white and gray matter of the STG,

showing early developmental differences in youth with GAD (DeBellis et al., 2002). Additionally, the executive function deficits were found in children and adolescents through simple tests, which could also be used to identify youth with anxiety disorders through schools. If children seem to be having issues with executive functioning tasks in school or at home, brain-imaging technology could help determine whether the child has an anxiety disorder. By identifying the problem early on, treatments can begin, which can help prevent long-term issues from emerging (Micco et al., 2009). Thus, it is important to understand each of these aspects of anxiety disorders thoroughly so that we can more readily and accurately diagnose patients, choose an effective treatment method for their needs, and help people of all ages overcome the impairments of anxiety disorders.

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