THE NEUROSCIENCE BEHIND GENERALIZED ANXIETY DISORDER AND THE EFFECT OF VARIOUS LIFESTYLE FACTORS

By

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Abstract

Anxiety disorders are one of the most common mental health conditions in today's societies. Especially since the pandemic, numbers have risen so that close to 40% of U.S. have experienced some sort of anxiety disorder since 2020 (CDC, 2021). This makes it incredibly relevant to investigate generalized anxiety disorder (GAD). The papers studied in this literature review discuss how certain brain regions, neural pathways, and neurotransmitters are affected in GAD. The review also dives deeper into treatment options such as different medications used to treat GAD and how they work physiologically. The review also covers papers looking into different lifestyle factors such as daily movement or lack thereof, different diets, and mindfulness/meditation practices. It proposes potential future areas of study for GAD and what kind of lifestyle appears to be most beneficial for someone with GAD.

Introduction

The earliest written discussions of anxiety date back to as early as 106-43 BC. These writings, by Cicero and Seneca, are called the *Tuscalan Disputations*, although at the time anxiety was not recognized as an illness or a disorder. Cicero described anxiety and worry as medical illnesses even though many others were recognizing them. Around the same time, the Romans and Greeks were also trying to develop terms for anxiety-related emotions and states of mind (Crocq, 2015). Overtime, more research went into studying what is now known as 'anxiety', where it transitioned from solely considered a symptom of other disorders, to being recognized as its own disorder in the 19th century. As each Diagnostic and Statistical Manual of Mental Disorders (DSM) was published, more information has been included in diagnosing anxiety disorders and the branching of several types of anxiety disorders occurred (Crocq, 2015). Now, anxiety can be categorized as an umbrella of disorders that include generalized anxiety disorder, panic disorder, specific phobias, OCD, and PTSD. As medicine became more advanced, there has been more research on the neuroscience behind anxiety and what is physiologically happening in the brain and body to contribute to the mental effects of anxiety. The levels of neurotransmitters and hormones, changes in brain structures, and other organ functions all play a role in the progression of anxiety (Cosci, 2020; Nuss, 2015). The role of lifestyle factors such as exercise, diet, social life, and mindfulness also play into the alleviation and worsening of anxiety and overall mental health. Although there are a variety of anxiety disorders, this paper will briefly look into each one but dive mostly into the neuroscience of generalized anxiety disorder. It will also conclude with a discussion on which lifestyle factors seem to ease anxiety disorder symptoms.

Types of Anxiety Disorders and Diagnoses

Before diving into the neuroscience behind anxiety disorders, it is important to provide an overview of the major types of anxiety disorders. Although anxiety includes a number of subtypes, when someone thinks of anxiety in everyday language, they are most likely referring to generalized anxiety disorder. Generalized anxiety disorder is defined as worry and nervousness beyond the usual amounts. People with GAD tend to constantly be worrying about everything such as their family, job, finances, health, potential world catastrophes, grades, etc. (Anxiety disorders, 2017). Generalized anxiety disorder can prevent people from being able to function properly in everyday life because their minds are constantly cycling. According to a survey in 2014, about 3.1% of the U.S population was diagnosed with GAD although now it is higher and it has also been found that many of people will have the disorder for years without seeking therapy or medical help (Stein and Sareen, 2015). GAD is often diagnosed based off physical symptoms rather than just mental health. Someone with GAD will often report chronic headaches and gastrointestinal issues to their doctors. When questioned further, someone with GAD will also report feelings of helplessness, trouble breathing, excessive worry, and greater behaviors of alcohol consumption and drug use. GAD can be treated with medications, as will be discussed later, but some people who do not seek medical care will attempt to treat their anxious feelings with drug and alcohol use to mute the symptoms. This can cause numerous physical as well as mental problems. People with undiagnosed GAD are more prone to self-harm and suicidal thoughts as the worry takes up their mind. GAD is often, but not always, diagnosed with major depressive disorder as the psychological and physiological conditions can go hand in hand (Stein and Sareen, 2015).

Another anxiety disorder is called panic disorder. Panic disorder is not as strongly connected to the cognitive component of worry as in GAD, but rather manifests as repeated attacks of fear that can last minutes or an hour. These attacks come on suddenly and can often feel like a heart attack. Sometimes there is no trigger and they just occur on their own (Anxiety disorders, 2017). The common term for the attack itself is a "panic attack," which many people have experienced before. What distinguishes having an occasional panic attack versus experiencing panic disorder? Panic disorder involves many abnormal and uncontrollable panic attacks that involve prolonged fear. Panic disorder can involve the same symptoms as a panic attack which include things like sweating, overall discomfort, shortness of breath, dizziness, feeling out of one's body, etc. However, to have panic disorder, one needs to have a fear of having more attacks after one has occurred. The person is afraid of the feeling of being out of control of their emotions, thoughts, and body reactions (Perrotta, 2019).

Another common anxiety disorder is Post-Traumatic Stress Disorder, also known as PTSD. After experiencing a typically dangerous and sudden event, a person may have feelings of fear which can trigger their fight or flight response and a variety of other emotions. As time passes, many people will stop having these emotions and they will fully recover. However, if someone does not experience relief of these reactions after an extended period, they may be diagnosed with PTSD. Someone who has PTSD will experience fear and extreme stress even when they are now completely safe and away from the harm (Anxiety disorders, 2017). PTSD has been found to involves changes in how brain regions such as the amygdala, medial prefrontal cortex, and the hippocampus react to stimuli. In short, the amygdala, which is thought to control the fear response, has been found to be hyperresponsive people with PTSD, meaning they experience more fear responses than the 'normal' person. Moreover, the nearby hippocampus,

which is involved in learning and memory and is anatomically connected to the amygdala, has been found to have a decreased volume in people diagnosed with PTSD compared to people without PTSD, relating to the suppression of memories (Shin et al., 2006). To be diagnosed with PTSD, a person of any age must have re-experiencing symptoms such as flashbacks or nightmares, avoidance symptoms such as avoiding certain places or thoughts, two arousal symptoms, and two cognitive symptoms such as trouble remembering the traumatic event (Anxiety disorders, 2017). The person must experience all of these symptoms for at least a month to be diagnosed with PTSD.

There are a number of other types of anxiety disorders, but these 3 are some of the most common. The following sections will explore further into the neuroscience behind generalized anxiety disorder, potential medications and how they work, and lifestyle factors that may play a role in the relief or worsening of GAD symptoms and management.

Neuroscience Behind Generalized Anxiety Disorder

When diving into the neuroscience, it is important to start with an understanding of the physiological basis of relevant brain structures, and to consider how they change in someone with the disorder versus without it. From there, it is easier to look deeper into the specifics of each brain structure, their connections to other parts of the brain and body, the receptors present at neuronal connections, the neurotransmitters and hormones involved, and how this knowledge can be used to treat the disorder. With this in mind, the brain regions outlined below are often associated with generalized anxiety disorder.

The limbic system plays an important role in the regulation of human emotions, motivation, learning, and memory. The structures involved in the limbic system include the amygdala, hippocampus, and hypothalamus. The amygdala and hippocampus, specifically, are two of the parts that have been found to play a role in anxiety due to changes in their structure and connections. The amygdala is known to control our fear response and turn stimuli into a behavioral response (Calhoon and Tye, 2015). In many GAD patients, it has been found that the gray matter of the amygdala is increased compared to someone without GAD (Maron and Nutt, 2017). Gray matter is made up of neuronal cell bodies and unmyelinated axons and seems to be increase in the amygdala of GAD patients, especially women.

In one study conducted from 2010, the brains of 31 women were studied: 16 women with GAD and 15 otherwise healthy women. Social and demographic factors were matched across groups, including age, profession, education, and even handedness. The women were all given a questionnaire to assess their worries and beliefs. Then, the researchers conducted an MRI scan on each of the women's brains. Results revealed that the women with GAD had higher scores on the worry questionnaire and a greater volume of gray matter in the amygdala and anterior cingulate cortex, also associated with emotion and autonomic regulation (Schienle et al., 2010). Although it is hard to distinguish whether the increased volume of the amygdala causes GAD or is increased due to greater worry and responsiveness in GAD, more studies have been looking further into the causal mechanisms of GAD. Regardless, the amygdala is important in GAD because of its connection to other parts of the brain.

In generalized anxiety disorder, it has been found that the connection between the amygdala and the prefrontal cortex (PFC) is different in someone with the disorder versus someone not diagnosed with the disorder. A little more on the prefrontal cortex: the prefrontal

cortex is located in the anterior (front) of the brain, and plays a role in our decision-making, planning, thinking about the consequences of our actions, and overall social behavior (Martin et al., 2009). Specifically, the ventromedial region of the PFC has been found to play an important role in regulating negative emotions, in this case, anxiety (Patriquin and Mathew, 2017). The connection between the amygdala and PFC has been found in adults and adolescents to be reduced, signifying a main identifier in the brain of someone with GAD. This decreased connectivity has been found to be increased with the use of medications in which will be discussed later. It was also found that the reduction in connection between PFC and amygdala got worse as symptoms of GAD worsened (Hilbert et al., 2014). This is particularly intriguing because it gives an exact pathway in the brain to dive deeper into when studying GAD and coming up with potential treatments for it.

Some neurotransmitters studied in relation to anxiety disorders are serotonin (5-HT), norepinephrine (NE), dopamine (DA), and GABA. Interestingly, 60-90% of people diagnosed with major depressive disorder also have an anxiety disorder, and these neurotransmitter pathways are heavily involved in both (Liu et al., 2018). The comorbidity of MDD and GAD can make it hard to distinguish what pathway is causing which condition, however in many cases, the abnormalities of various pathways contribute to both symptoms of MDD and GAD.

Within in the amygdala lies the pathway of GABA. GABA is an inhibitory neurotransmitter that counteracts the excitatory pathways of the CNS. GABA receptors can be found throughout the CNS; in fact, 1/3 of the neurons in the CNS are estimated to use GABA as their neurotransmitter. GABA is especially important in the amygdala because its inhibitory effects reduce fear and anxiety reactions (Nuss, 2015). GABA is the main neurotransmitter and receptor for the basolateral amygdala complex to regulate the central nucleus of the amygdala

and then also connects these sections of the amygdala to the prefrontal cortex, the connection discussed earlier (Nuss, 2015). There are two types of receptors for GABA: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are the key receptors in the pathway for generalized anxiety disorder. In a person without generalized anxiety disorder, $GABA_A$ binds the inhibitory neurotransmitter GABA. When GABA binds, it causes a conformational change that opens the receptor and it becomes an ion channel that allows chloride to flow into the neuron, causing hyperpolarization. This hyperpolarization inhibits the neuron, making it less likely to fire. This is what counteracts the excitatory signals in the central nervous system, allowing the brain to be more relaxed (Neuroscientifically Challenged, 2018). For someone with generalized anxiety disorder, studies have shown that $GABA_A$ receptors have a reduction in sensitivity, causing them to have difficulty binding GABA as readily as someone without GAD (Nutt, 2001). It is not entirely clear whether this reduction in sensitivity is due to the individual receptors themselves having trouble binding GABA or if it is due to a reduction in the total number of receptors, but regardless most medications like benzodiazepines have been formulated to target GABA receptors and is one of the clinical ways GAD is treated.

Another neurotransmitter that has been studied in relation to generalized anxiety disorder is norepinephrine (NE). Although there has not been much certainty in its role in GAD yet, many studies have looked into the comorbidity of depression with GAD and how NE levels are altered in both. In an older study from 1998, it was found that melancholic depressed patients had a significantly higher amount of NE levels in their plasma compared to controls without any mental disorders. The researchers then took this data and decided to look at GAD patients and found that although not as significant of a difference, GAD patients had higher levels of NE in their plasma as well compared to the controls (Nutt, 2001). This suggested that the sympathetic

nervous system was more active in someone with generalized anxiety disorder compared to someone without, making sense of the common symptoms of faster heart rate, breathing rate, and racing thoughts; the "fight or flight" symptoms of the sympathetic nervous system. NE has been found to be a key component in regulating the HPA (hypothalamic-pituitary-adrenal) axis which is the system that controls acute and chronic stress levels. When there is a dysregulation of NE due to chronic stress, this is what has been found to lead to depression and generalized anxiety disorder (Goddard et al., 2010). This led to greater studies and the development of a class of drugs called SNRIs (serotonin norepinephrine reuptake inhibitors) although it is not entirely understood how these drugs work since NE is elevated in GAD patients and these drugs stop NE and serotonin from being taken out of the synapses, leading to higher levels of NE (Goddard et al., 2010).

Medications for Generalized Anxiety Disorder

One last neurotransmitter to highlight is serotonin (5-HT). Serotonin is the neurotransmitter responsible for mood regulation and is also involved in sleeping patterns. It is unclear how drugs such as selective serotonin reuptake inhibitors (SSRIs) aide in GAD; however, they have been shown to significantly increase the well-being of adult with GAD. Since serotonin levels do not seem to be different in someone with GAD versus a control, there is no clear reason why they work. However, many researchers seem to believe that it could be due to the suppression of anxious thoughts due to a boost in mood from excess serotonin when taking SSRIs (Cassano et al., 2002). SSRIs act by blocking the reuptake of serotonin so that it remains in the synapse longer therefore giving it a better chance of binding to 5-HT receptors and boosting mood. SSRIs have been used to treat GAD and depression disorders and have been

successful as they are highly used by doctors all over the world (Strawn et al., 2018). Escitalopram is one of the newest and commonly used SSRIs in the U.S. and its effects have been shown compared in a double-blind study to placebos to boost mood and lessen anxiety. It is absorbed by the GI tract in 2-4 hours and remains active in the blood for a long time to block the reuptake of serotonin (Strawn et al., 2018).

Another similar yet different class of anti-depressant and anti-anxiety drugs called SNRIs (selective serotonin and norepinephrine reuptake inhibitor) work to reduce anxiety symptoms by stopping the reuptake of serotonin and norepinephrine as mentioned earlier. Previously, it was discussed that NE is elevated in someone with GAD, so why would SNRIs help this dysregulation if they increase the presence of NE? SNRIs help stop neurons in the brain from absorbing NE as quickly, so they allow NE to work its usual effects of making someone more alert, but in a slower manner. They slow down the use of NE, effectively regulating panic attacks that may occur due to excess NE being utilized all at once (Strawn et al., 2018).

The last and the most common class of drugs used to treat generalized anxiety disorders is benzodiazepines. Benzodiazepines work on GABA and GABA receptors as mentioned earlier. SSRIs and SNRIs tend to focus on the psychic symptoms of anxiety such as worry and irritability, whereas benzodiazepines work on the somatic symptoms of GAD, making them more effective as they are treating the physiological issues occurring in the brain/body (Cassano et al., 2002). The deficiency in GABA neurotransmission is critically linked to GAD, whereby GABA does not bind to GABA receptors as easily in GAD (Nemeroff, 2003). To fix this, benzodiazepines bind to GABA receptors as an agonist. However, benzodiazepines do not bind to the same binding sites on $GABA_A$ that GABA binds to. Instead, they bind onto two different subunits on the same receptor. This interaction of GABA and benzodiazepine on the same

receptors is called an allosteric effect because it causes a change in conformation of the receptor (Neuroscientifically Challenged, 2017). This conformation change is thought have two possible effects: it increases the chances of GABA binding to $GABA_A$ and activating the receptor and/or it increases the effects that GABA has on the receptor by allowing more chloride ions to rush in and hyperpolarize the neuron, significantly reducing the ability of the neuron to fire action potentials (Gielen et al., 2012). The inhibition of these neurons is what helps mute the pathways involved in anxiety and arousal. $GABA_A$ receptors were closely studied by isolating GABA neurons and using diazepam (a benzodiazepine) and taking electrode voltage clamp recordings to see the activity. It was found that $GABA_A$ receptors ability to be activated by GABA was increased when diazepam was used (Gielen et al., 2012). Benzodiazepines have been used to treat GAD because they have been found in multiple studies to reduce symptoms of GAD in less than 2 weeks and the tolerance of the patients did not increase quickly, making it effective in low dosages for longer periods of time (Cassano et al., 2002). Untreated GABA dysregulation can lead to a variety of other conditions, one being irritable bowel syndrome- diarrhea (IBS-D). As shown in the following section, the health of our brain truly does affect the rest of our body.

Lifestyle Factor Effects on Generalized Anxiety Disorder

The everyday choices someone makes in their life for things such as diet, daily movement, social life, mindfulness, time spent outside, and more all factor into how anxiety disorders present themselves. For someone with generalized anxiety disorder, there are decisions to be made in these lifestyle factors that can positively or negatively affect how the symptoms of GAD present themselves.

One lifestyle factor to investigate is level of daily activity and/or exercise. It is known that movement everyday has many health benefits like lowering blood pressure and bettering overall heart health, lowering risk of disease, improvement of mental health; one of being reduction of anxiety symptoms. The U.S. Department of Health and Human Services collected data that showed daily activity or exercise for all genders can reduce causes of mortality up to 30% (Anderson and Shivakumar, 2013). Some researchers even compared daily exercise from walking to weightlifting as psychoactive drug due to its effect of regulating bodily systems (Vina et al., 2012). Although the exact way in which exercise reduces anxiety is not known, there are many systems related to anxiety that studies have found are affected by anxiety, such as the HPA axis. In GAD, the HPA Axis is dysregulated due to an increase in ACTH levels and glucocorticoids. According to a study where participants voluntarily exercised regularly, the exercise began to alter CRH and ACTH levels. CRH appeared to be lowered in release from the hypothalamus thus leading to a lowered ACTH secretion from the pituitary gland as well. This is evidence that regular exercise can lower our stress response system, therefore decreasing symptoms in anxiety (Anderson and Shivakumar, 2013). In another study, 30 women with GAD were taken and split into three groups: one doing resistance training, one doing cardio and another control group just doing daily necessary tasks. After 6 weeks, results on a physical exam as well as results from a patient survey on physical, emotional, and mental health were compared from scores taken before the trial. It was found that these women with GAD who completed either the resistance training or the cardio significantly improved in all categories whereas the control group did not change much (Herring, 2016). This shows that daily activity really can improve overall health quickly and in the long-term as well.

Exercise has also been shown to increase levels of brain-derived neurotrophic factor (BDNF) as well. BDNF is a key to keep our neurons healthy by helping them grow, maintaining them, and aiding in forming new connections. Lowered BDNF levels in the hippocampus and dorsal raphe nucleus have been linked to anxiety and depression symptoms. In a study with rats, it was found that rats who ran on wheel compared to those that did not, increase the mRNA levels responsible for making BDNF after 20 days of voluntary running. Increasing BDNF keeps our brain healthy and allows for improved functioning of serotonergic systems, aiding in anxiety symptoms (Anderson and Shivakumar, 2013).

Diet is crucial to the health of many systems in the body that affect our brain and anxiety. Although a newer development of research, many studies are finding a connection between diet, the gut microbiome, and mental health. Diet can vary depending on the culture or normalcy of the environment someone lives in. A few studies have focused on comparing diets full of whole grains, vegetables, fruits, and unprocessed meats aka the "healthier diet" to diets considered "Western" which includes highly salted foods, pizza, candy/chocolate, fried food, alcohol, processed meats, etc. One of these studies was conducted on women in Australia where some reported having the healthier diet and others reported having a western diet. They were then given a questionnaire evaluating anxiety and depression symptoms and it was found that those with the healthier diet were significantly less likely to have GAD and MDD and less likely to have anxiety symptoms as well (Sarris et al., 2012). Another study found that men and women on what is called a "pylori" diet, consisting of the same foods as the "healthier" diet, compared to those who had a "western" diet, were less likely to develop symptoms of MDD and GAD. Those who consumed western foods as their main diet were found to have heightened likelihoods of anxiety but not depression symptoms (Sarris et al., 2012). These studies showed a correlation

between diet and mental health however more research was needed to see if diet could be changing the symptoms of one's mental state. A more recent study from 2019 aimed to evaluate this using the fecal microbiome of 36 people with GAD and 24 otherwise healthy individuals. In individuals with GAD, it was found that they had a less diverse microbiome in their feces compared to healthy individuals. Although this study did not look specifically at their diets, it did show that there is some relationship between gut microbiota and mental disorder (Chen et al., 2019). Our microbiome is key to defending against disease and keeping us healthy so it is no surprise that it may correlate to mental health. Lastly, one case study from 2016 was conducted on a 15-year-old female with GAD. The female also had hypoglycemia and focused on eating carbohydrates; however, she was reporting severe anxiety symptoms that medication did not seem to help. Her daily diet was recorded, as reported by her, and it consisted of mostly carbohydrates and very minimal proteins, fiber, and fats. To see if diversifying her diet changed her anxiety symptoms, researchers gave her a diet consisting of all macronutrients and more micronutrients. After just a week and especially after a few months of her new diet, the female reported significantly less anxiety symptoms, greater energy, and less frequent problems with her hypoglycemia (Aucoin & Bhardwaj, 2016). Although in this specific study they did not take samples of her microbiome, it is consistent with other findings in which diversifying one's diet leads to a more diverse gut microbiome, less cases of disease, and less likely to have mental health issues such as anxiety or depression (Sarris et al., 2012).

Although diet and exercise are very important aspects of one's life, another often overlooked aspect of lifestyle is one's mindfulness of one's thoughts, emotions, and surroundings. Mindfulness can be cultivated with a practice, including activities such as meditation, self-affirmations, yoga, journaling, etc (Desrosiers et al., 2013). Meditation dates

back 2500+ years but has only more recently reached western culture. Meditation promotes awareness of one's thoughts and being present in processing them and focusing on breathing and being in the moment as well (Desrosiers et al., 2013). It was thought that those who meditated exhibited fewer signs of anxiety and depression and overall reduced mental health issues. However, now MRI studies are finding physical evidence that this may be true. MRI studies looking at the brains of people who regularly practice meditation and mindfulness are finding increased gray matter in various brain regions such as the prefrontal cortex, right anterior insula, and hippocampus (Sarris et al., 2012). As mentioned previously, these areas have all been associated with GAD pathways and neurotransmitters important in anxiety symptoms. A study in 2011 using infrared spectroscopy found the levels of oxygenated hemoglobin in the prefrontal cortex to be increased and increased serotonin levels in the blood throughout the body within 5-30 minutes of meditation and controlled breathing (Yu et al., 2011).

Yoga is another form of mindfulness and self-awareness that has been studied and shown to improve symptoms of anxiety and depression. In a review of 8 separate studies, it was concluded that practicing yoga improved symptoms of anxiety and awareness of self (Kirkwood et al., 2005). In a study conducted in 2015, patients who were already diagnosed with generalized anxiety disorder were "prescribed" Sudarshan Kriya Yoga (SKY) which involves yoga and controlled breathing techniques. Check-ins were taken every few weeks-months and it was found that after 6 months, anxiety symptoms of these patients greatly improved. Self-image and self-confidence also improved along with mental health (Doria et al., 2015).

Discussion/Conclusion

All anxiety disorders are an interesting topic of study because of their prevalence in all communities. No matter where a person is from or what their background is, anyone can develop an anxiety disorder. Research into GAD is important because it affects a large amount of people, and it is still unknown as to what exactly causes it in the brain. A study that could be created to answer more questions could relate to the volume of the amygdala. Previously, a study was discussed where it was uncertain whether an increased volume of the amygdala is what causes GAD and its symptoms or if the symptoms and increased worry from GAD is what causes the amygdala to become larger. Looking into this could help create more effective treatment options for those with GAD since we are also unsure of how some medications such as SSRIs and SNRIs are helping anxiety. The connection between the prefrontal cortex and the amygdala should also continue to be researched because of other studies showing the connection between the two to be affected in a person with GAD compared to a healthy individual.

Generalized anxiety disorder affects a number of neurotransmitters, regions, and connections in the brain. Although research into GABA/benzodiazepine receptors and pathways is promising, there are many other drugs that help treatment of the disorder yet still need explanation to how exactly they are working. Lifestyle factors play a large role in how GAD presents itself in a person and how well it can be managed. A lifestyle with a balanced diet containing all macronutrients and a variety of foods seems to be the best diet for the brain and body such as gut health. Gut health is an area of study for research to look further into and how it connects to our mental health. An active lifestyle with daily movement and time to reflect and be mindful of one's own thoughts also are crucial to staying healthy and minimizing the symptoms

of anxiety. There is so much more to learn about anxiety disorders and how we can treat them effectively in the future because of the increasing prevalence they have in our societies.

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