# Neurological Insights into Generalized Anxiety Disorder: Exploring the Vital Roles of the Amygdala and GABA

Alyssa Molock

Class of 2024, Sussex Technical High School, Georgetown, Delaware

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**Abstract**

Generalized Anxiety Disorder (GAD) is a disorder that has affected individuals worldwide for centuries. Though it falls under the umbrella of Anxiety Disorders, GAD patients have symptoms that affect them differently than any other anxiety disorder. This research paper investigates the neurobiological mechanisms that make up GAD. Findings below have a specific focus on the roles of the Amygdala and GABA levels. Through a comprehensive review of existing studies and literature, the research shows positive connotations between an overactive Amygdala and low levels of GABA in the brain. The goal of this study is to dig deeper into the neurochemical basis of GAD, in hopes to develop medications to prevent this disease or to assist the already affected patient.

**Generalized Anxiety Disorder, Defined**

Generalized Anxiety Disorder (GAD) is a psychiatric disorder characterized by excessive and persistent feelings of worry and dread about many daily activities—that of which negatively interferes with the individual's everyday function. GAD is identified with psychological symptoms consisting of restlessness, fatigue and irritability along with physical symptoms of muscle tension and headaches. (Mayo Clinic, 2017) Many believe the etiology of the disease may include, stress, genetic factors and environment-based disruptions in the individual's lives. Findings that that at around 4% of the global population, around 301 million people suffer from an anxiety disorder worldwide, (Javaid et al., 2023) though not all are GAD-related. Risk factors include being female, low socioeconomic status and childhood adversity. (Madonna et al., 2019) Though there is no cure for GAD, it is a treatable illness, commonly managed with prescribed medicines and therapeutic inventions.

Because it is an uncurable disorder, it is inferred that quality of life for these patients is considerably lower than those unaffected. A major complication for those who have GAD is depression. Studies show that depression is a common result for those who have been diagnosed with Anxiety. In a research article describing the relationship between Anxiety and depression posted on the American Journal of Psychiatry, Ned. H. Kalin, MD., comments that Anxiety and depression are "comorbid" with each other. Additionally, in his study, Kalin found that 43% of patients with Generalized Anxiety Disorder were diagnosed with depression. (Kalin, 2020) Additionally, insomnia, social isolation, and suicide potential are considerable complications for GAD patients. (Munir & Takov, 2022)

Many scientists believe the disorder arises from hyper-reactivity in the Amygdala. The Amygdala is the part of the brain that process the body's emotions, including fear. (C.C Medical) When the amygdala is hyper-reactive, the human might face a higher risk of going in "fight or flight" mode, resulting in a constant state of fear or worry. Also, low levels of the neurotransmitter Gamma-aminobutyric acid (GABA), may also be the cause. The following research describes the brain function of patients with Generalized Anxiety Disorder and demonstrates the neurological differences between GAD Patients and those unaffected, while focusing on the roles of the Amygdala and GABA in the brain.

**History / Background**

Austrian Neurologist Sigmund Freud was the first person to recognize Anxiety as the disorder it is now. The physician coined the term "anxiety neurosis" in 1895, when he came up with the etiological theory of the phenomenon. His second symptom the "anxious expectation" is a key symptom in what Generalized Anxiety Disorder is today. (Crocq, 2017) Freud listed an example "A woman, for instance, who suffers from anxious expectation will think of influenza pneumonia every time her husband coughs when he has a cold, and, in her mind's eye, will see his funeral go past." Essentially, visualizing the situation of fear and worry in a situation similar to his at the time. That women's reaction was Freud's version of modern-day Anxiety. Centuries later, the term Anxiety, as a whole, has changed drastically in history.

In 1980, when the American Psychiatric Association published the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), GAD was first introduced. Then, it had been described as "Generalized, persistent anxiety". In the DSM-5, it had been described as "Excessive anxiety and worry [apprehensive expectation] about a number of events or activities. Difficult to control the worry." (Crocq, 2017) Prior to this, in DSM-1, Anxiety was mentioned in a chapter titled "psychoneurotic disorders", where anxiety was seen to be a danger signal which was produced by a threat from within the person. The 'anxiety reaction" was seen to be the reaction to said danger signals; though the reactions were differentiated from normal apprehensiveness or fear. In DSM-II, the reaction of DSM-I had been renamed "neuroses", then characterizing the term "anxiety neurosis" as anxious over-concern extending to panic

and frequently associated with somatic symptoms. Which then became the precursor to the Generalized Anxiety Disorder commonly known to psychiatrists in modern times. (Crocq, 2017)

As noted before with Dr. Kalin's study, when the DSM-III defined Generalized Anxiety disorder, many commentators acknowledged the comorbidity of GAD and depression. Because of this, some suggested the disorder should be "conceptualized as a prodrome, residual, or severity marker than as an independent disorder." Though, as research went on, data showed that "generalized anxiety disorder is a common disorder that, although often comorbid with other mental disorders, does not have a higher comorbidity rate than those found in most other anxiety or mood disorders." (Munir & Takov, 2022).

**The Causes**

As the Amygdala activates the "fight-or-flight" response within the individual, for GAD patients, this means they are constantly on high alert. Anxiety is rooted within the stress hormones the hyperactive Amygdala sends the body. With these responses, the body responds with fear-actions including an increased heartbeat, tense muscles and heavier breathing. For Generalized Anxiety Disorder patients, there does not need there to be a stressor for them to experience these symptoms. It is common for patients to have no specific reason for their actions. (Harvard Health, 2014) Additionally, in a study found with the Stanford School of Medicine, research has shown that the amygdala regions in GAD patients had less connectivity to the brain responsible for determining the importance of stimuli. (Pappas, 2009). From this, patients have demonstrated their inability to discern the level of concern with situations they are put in.

Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the nervous system. It is a chemical messenger that sends signals to the brain. The purpose of GABA is to reduce neuronal excitability by inhibiting nerve transmission, in result decreasing the level of neuronal stimulation in the brain. (Allen et al., 2023), However, low levels of GABA have been shown to be linked to GAD. Research provides proof that decreased levels of GABA can lead to a feeling of anxiousness with individuals who have abnormalities in the neuro-transmitter.

Some studies demonstrate low levels of GABA could be a part of the GAD patient's genetics—however, genetics in relevance to GAD are seen to be less substantial than other anxiety disorders. Though studies have proved that first-degree relatives of family members who have GAD have higher rates of mood and anxiety disorders in general, scientists have presumed it to be the same with an increased risk of the disease in general. Findings in brain scans for pediatric patients with GAD demonstrate high rations of gray matter to white matter in the temporal lobe. (Martin et al., 2023) This study suggests the pediatric subjects have been subjected to stress-induced amygdala hypertrophy after prolonged exposure to the illness. Additionally, in a finding with adolescent GAD patients compared to healthy subjects, GAD patients have found resting activity in the ventrolateral prefrontal cortex (vlPFC) to be elevated compared to healthy subjects. This is presumed to be a compensatory response to the disease. (Madonna et al., 2019)

**Demographics Affected**

However, it should be noted that brain imaging scans between GAD patients tend to be inconsistent—leading to the conclusion that the disease affects each person differently. Females tend to be affected with Generalized Anxiety Disorder as compared to men. Regarding age, in a study concluded debating the age of GAD patients and how it affects them, results led to younger-middle aged adults showing more symptoms of anxiety, worry, negative affect and depression while compared to older adults. In addition, younger adults experienced fewer somatic anxiety symptoms, but higher worry and negative affect than middle-aged adults. Additionally, tending to race, African-Americans were found to

be less likely to be taking medications and seeing mental health providers as compared to their white counterparts in the study. (Brenes et al., 2008)

There are many theories that GAD can affect people based on their race, genetics, age, etc., but there needs to be more studies before the conclusion can be drawn. With the help of neuroimaging and additional data, only then can scientists find the link to who is most likely to be affected by this disorder.

**Common Medications**

Medications are commonly prescribed to patients suffering from Anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) and Serotonin-norepinephrine reuptake inhibitors (SNRIs) are, generally, Doctor's first choice medication for GAD patients. They consist of drugs such as Citalopram, Fluoxetine and Paroxetine, all medications that increase levels of serotonin in the brain. Drugs such as these are preferred as they have 'broad spectrum' efficacy in both short-term and long-term treatment, and are generally well tolerated; and for these reasons, the British Association for Psychopharmacology stated that SSRI's "are widely considered to be the first-line pharmacological approach in patients with anxiety disorders" (Strawn et al., 2018) Though, some SSRIs are at risk of withdrawal symptoms at the end of treatment.

If not prescribed with SSRIs, a second choice medicine is Benzodiazepines. Studies show that 55 to 94% of anxiety patients have been treated with benzodiazepines. This medicine is used as a depressant, which provides sedation and can reduce anxiety within the patients. In the patient, Benzodiazepines tell the brain to release GABA neurotransmitter signals, in attempt for the nervous system to have slowed activity. This is ideal for GAD patients as benzodiazepines do not lead to increased jitteriness or insomnia. Though, there are negatives to the medication. It can lead to CNS depression—fatigue, dizziness and impaired driving skills are a few negatives. Additionally, after prolonged use, the patient might get dependent on the drug. The withdrawal symptoms are much more adverse than withdrawal symptoms to an SSRI.

Phytotherapy, the use of plants or herbs as a medication has shown positive results in many studies. There are theories that a lavender pill could be used as a medication to GAD, however there have been inconsistent results to the study. (Bandelow et al., 2017) For older patients, there are risks of sensitivity to the medications as they have higher fall risks and risks of cardiovascular events.

Antipsychotics and Buspirone are also medicated choices for patients.

For those who choose to not take medication for their diagnosis, Cognitive Behavior Therapy (CBT) is a choice. Some examples of CBT include psychoeducation, changing maladaptive thought patterns, and gradual exposure to anxiety-provoking situations. (Munir & Takov, 2022). CBT is a way for GAD patients to be in touch with their feelings towards the disorder so they can work out and analyze their thoughts, feelings and behavior patterns towards themselves and their diagnosis.

**Possible Solutions**

Additional emerging research shows that scientists have been doing studies regarding serotonin, melatonin and neuropeptides in the brain in an attempt to find more medications to fight anxiety-related diseases (Murrough et al., 2018), medications that work positively similar to SSRI's and SNRI's.

Additionally, natural remedies utilizing the Kava plant have been considered. It contains kavapyrones, which many think can "exert anxiolytic effects through activity on sodium and calcium channels or most likely from action on GABA-A receptors (like benzodiazepines)" Findings support that there were reductions in anxiety, however it was noted Kava could be recommended for short-term use, though is not recommended to replace long-term medications. Scientists have noted severe liver toxicity when using kava. Several other natural remedies include ashwagandha, passionflower, echinacea, ginkgo,

chamomile, lemon balm and valerian, though none show as much promise as the kava plant. (Garakani et al., 2020)

It should be noted that there are not many studies that are finding positive results when it comes to treatment for Generalized Anxiety Disorder.

**Final Remarks – Summarizing the Findings**

Research and findings are constantly being done in attempt to find more medications and learn more about the disorder known as Generalized Anxiety Disorder, though there are theories, there is always more to know about the brain. Some key takeaways in my research highlight that the cause of GAD is from a hyperactive amygdala, which then provides the fight-or-flight actions in the body and possibly an abnormally low level of GABA in the patient's brain, which leads to the symptoms of a constant state of fear with the GAD patient. Findings cannot conclude that there are patterns concerning genetics or demographics for affected patients. These are highly supported claims, though more research is being done to treat and find the cause of this disorder in the patients.

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