



Western Washington University
Western CEDAR

WWU Honors Program Senior Projects

WWU Graduate and Undergraduate Scholarship

Spring 2020

Consider the Ravens: An Exploration of Anxiety

Mckenzie Oliver
Western Washington University

Follow this and additional works at: https://cedar.wvu.edu/wwu_honors



Part of the [Psychology Commons](#)

Recommended Citation

Oliver, Mckenzie, "Consider the Ravens: An Exploration of Anxiety" (2020). *WWU Honors Program Senior Projects*. 378.

https://cedar.wvu.edu/wwu_honors/378

This Project is brought to you for free and open access by the WWU Graduate and Undergraduate Scholarship at Western CEDAR. It has been accepted for inclusion in WWU Honors Program Senior Projects by an authorized administrator of Western CEDAR. For more information, please contact westerncedar@wwu.edu.

Consider the Ravens: An Exploration of Anxiety

Mckenzie Oliver

Faculty Advisor: Dr. Mike Mana

WWU Honors Senior Capstone Project

Spring 2020

Introduction

We all worry. In this day and age, there are so many matters about which to worry. However, when worrying becomes excessive or irrational or leads to unreasonable behaviors, it would likely lead to the diagnosis of a medically recognized anxiety disorder. These disorders can take many forms, and as with any area of mental health, their definitions and manifestations are variable. They make up a significant component of mental health disorders worldwide and as such, it is important to be aware of and informed about them to foster understanding and connection with one another.

This exploration is rooted in my personal connection to anxiety disorders, as a large part of my life and college experience has involved handling my own anxiety. The title of this paper was inspired by a series of Bible verses that I have often read to bring some peace to my mind: “Therefore I tell you, do not worry about your life, what you will eat; or about your body, what you will wear. For life is more than food, and the body more than clothes. Consider the ravens: They do not sow or reap, they have no storeroom or barn; yet God feeds them. And how much more valuable you are than birds! Who of you by worrying can add a single hour to your life? Since you cannot do this very little thing, why do you worry about the rest?” (Luke 12:22-26, *The Holy Bible* NIV, 2011). I’d like to use this opportunity to reflect on my personal experiences and explore the “why” and the “how” behind these feelings that I have carried for most of my life, with the hope that it will be both personally therapeutic and impactful on others.

I have always recognized myself as an anxious person, a “Nervous Nellie,” a chronic worrier, but only recently was I diagnosed with generalized anxiety disorder or GAD. The story begins years and years ago, when I was a small child. One of the earliest anxious tendencies that

I can recall was that I often could not fall asleep if I had even the slightest need to pee. This affected me strongly at unfamiliar locations, and I could hardly ever stay through the night at a friend's house. In my mind, it was the end of the world if I could not fall asleep, so I would become panicky and upset (which only served to exacerbate my frequent trips to the bathroom). My parents had me examined for physical health issues and the doctors told them my behavior was caused by anxiety.

There were plenty of other instances like this in my childhood. There was a period of time when I could not leave the house if I felt the seams of my socks pressing against my toes inside my shoes. One day, I simply would not enter my second-grade classroom despite my mother persistently pleading with me outside the door because I was anxious about having to endure my stern and grumpy teacher. After an extensive argument I started *running away* from my mother, down the hallway, which was very contrary to my obedient nature. As I reflect on these experiences and more recent ones, I realize that even this obedient nature was often born out of anxiety about getting in trouble. I was always a well-behaved student because I was too nervous about being seen in a negative light or being punished to ever act out (and I am still like this, for the most part).

I have also always been known as a shy, quiet girl. Growing up with a father in the Air Force, our family moved around quite frequently, so I constantly had to make new friends and leave old ones behind. I was not talkative or outgoing, and was never part of the "popular crowd" in school. Making friends was not a very easy process for me. I also did not like to interact with strangers or people that weren't familiar to me. This was often explained by a casual remark about my shyness, but now that I'm reflecting on this, I'm realizing that this

shyness was probably a manifestation of the beginnings of social anxiety. I was (and still am) nervous about judgement from both familiar and unfamiliar people.

Many of these specific childhood anxious tendencies gently faded away as I matured, but new ones took their place as the amount of things I actually had to worry about increased. Some of the tendencies simply resolved into new variations of the same behaviors or worries. Before discussing more psychological and behavioral manifestations of anxiety, however, the scientist in me would like to take a step back and delve into the brain and body to investigate the physical basis behind these thoughts, feelings, and actions. Simply put, I'd like to explore *why* us anxious people are the way we are and *how* our physical selves function to influence our psychological selves.

Biological Aspects of Anxiety

A good place to start is with an exploration of the organ integral to our thoughts and actions: the brain. Many intricate relationships between different brain components are at play in anxiety disorders. This complicated dance is primarily carried out through interactions in the corticolimbic system, which regulates emotions, memories, and brain regions involved in higher cognitive processes. These interactions begin when a sensory or emotional stimulus is detected and relayed to a structure in the brain called the thalamus. This information can then take one of two pathways: a short, involuntary pathway that does not involve higher cognitive processes sends information straight to the amygdala (a central component in this dance, which will be discussed in detail shortly), while the long, voluntary pathway passes information to the prefrontal cortex and the hippocampus before it is sent to the amygdala. There are many reciprocal interactions between these and other areas of the brain. Information is then processed

by the amygdala and passed on to other brain and body structures, creating physiological and psychological responses commonly associated with anxiety or stress.

The long pathway to the amygdala is integral in anxiety disorders. Information received by the thalamus is passed on to the prefrontal cortex, which engages in higher cognitive processes that focus attention on the stimulus, organize memories of previous experiences, and determine the relative significance of the stimulus under consideration. Based on this calculation, the prefrontal cortex influences the amygdala's "decision" on generating an anxiety response. It can both reduce anxiety by reasoning out irrational fear, or it can increase it by causing us to imagine scenarios that could cause anxiety (*THE BRAIN FROM TOP TO BOTTOM*, n.d.). Specifically, the medial prefrontal cortex (mPFC) evaluates the threat level of the situation. The prelimbic region of the mPFC signals to the amygdala to create a response to a threat, and the infralimbic region signals to the amygdala to suppress a response to a threat (Calhoun & Tye, 2015). The prefrontal cortex is hypoactive in some people with anxiety disorders, and a higher level of activation is required to control an emotional reaction in anxious people (Gauthier & Nuss, 2015).

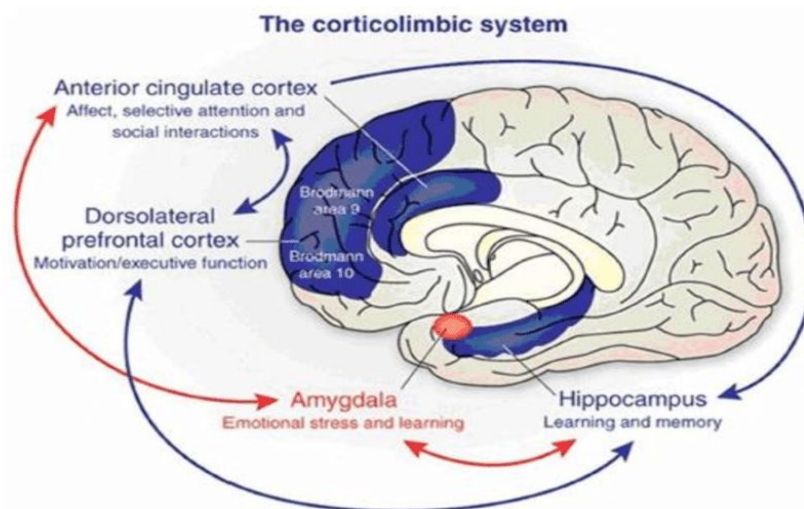
Connections between the dorsal anterior cingulate region of the PFC and the basolateral amygdala (BLA) are involved in maintaining correlations between memories and the fear or anxiety associated with them. This prevents the extinction of "fear memories," strengthening the association between the original anxiety-inducing situation and the anxiety itself. However, repeated exposure to the same "threat" can reduce the signaling between these regions and the anxiety response (Calhoun & Tye, 2015). This may be the basis of immersion therapy for the treatment of anxiety, which will be discussed later. The prefrontal cortex is also involved in

mediating between the anxiety or avoidance reaction and the reward reaction, in which a brain region called the nucleus accumbens is involved (Calhoun & Tye, 2015).

The long pathway to the amygdala also involves the hippocampus, which is a key structure for both emotional regulation and memory creation in the brain. The hippocampus can create context for and store memories of events and therefore can increase the anxiety response in similar events. Signaling from the amygdala to the hippocampus can strengthen such “fear memories” (Calhoun & Tye, 2015). Additionally, signaling from the ventral hippocampus (vHPC) to an area in the middle of the forebrain called the lateral septum (LS) can generate an anxiety signal. This then leads to inhibition of the anterior hypothalamus, activation of a specific region of the hypothalamus called the paraventricular nucleus, and activation of the periaqueductal gray in the brainstem, creating an anxiety state (Calhoun & Tye, 2015).

Interestingly, the hippocampus can also be involved in negative feedback or reduction of the anxiety response: it contains receptors for stress hormones and when these hormones bind, they can reduce signaling to the hypothalamus and result in reduced downstream signaling (Herman et al., 2012). The hippocampus therefore has many complex roles in the anxiety response.

A diagram containing these long pathway components is pictured below in Figure 1.

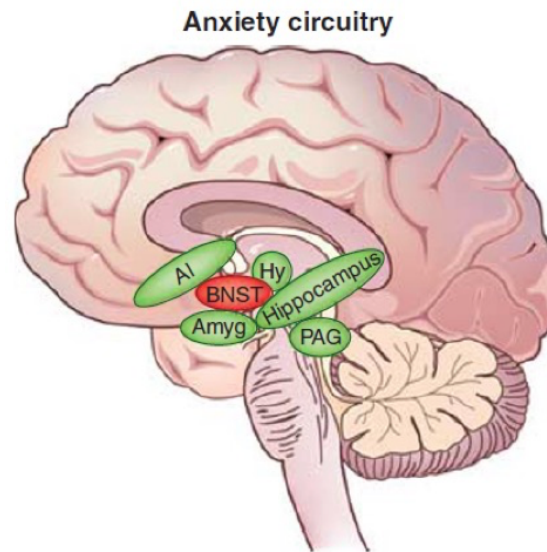


(Leisman, 2013)

Figure 1. Diagram depicting brain structures in the corticolimbic system, including those involved in the long pathway.

The central component in these complex circuits is the amygdala, which is responsible for one's emotional response to a stimulus. After receiving information via one of the two aforementioned pathways, the basolateral amygdala (BLA) activates the central amygdala (CeA). This can then activate the hypothalamus and brainstem to create the physiological manifestations of anxiety (Gauthier & Nuss, 2015). The BLA also activates the bed nucleus of the stria terminalis (BNST), which further signals to other areas of the brain to increase “fear learning” and create a fear response. The BNST is specifically involved in the freezing response during stress. The periaqueductal gray or PAG can also be a downstream target of the amygdala, and it is involved in this freezing behavior as well (Calhoun & Tye, 2015). The amygdala can also signal to the ventral tegmental area in the midbrain and the locus coeruleus in the pons of the brainstem, which may create the uneasiness felt in anxiety (Gauthier & Nuss, 2015).

A diagram containing some of the brain regions involved in these interactions is pictured below in Figure 2.



(Avery et al., 2015)

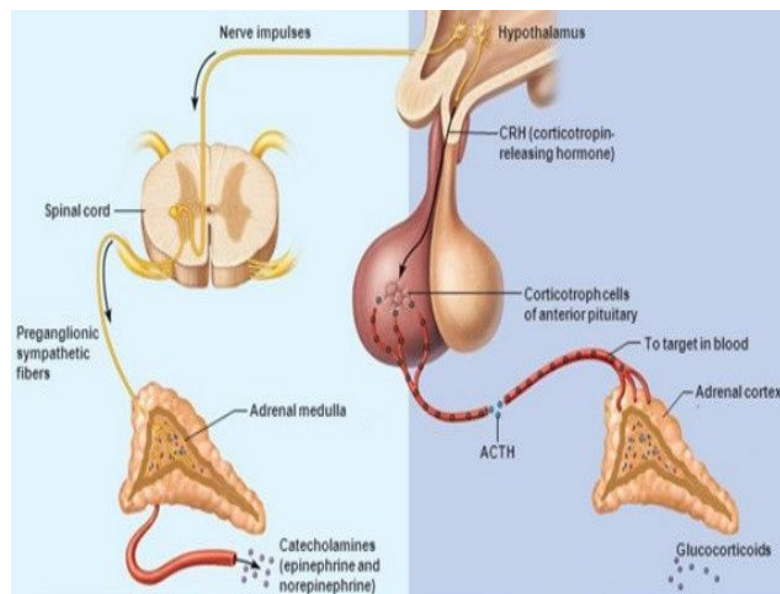
Figure 2. Diagram depicting brain regions involved in the anxiety response, including those downstream of the amygdala.

The physiological symptoms commonly associated with anxiety can be a result of the activation of the sympathetic nervous system. The sympathetic nervous system is responsible for the “fight or flight” response that is necessary in survival situations. Essentially, the hypothalamus activates the adrenal medulla, a component of the adrenal glands (which are located just above the kidneys), via the sympathetic ganglia (neurons in the spinal cord). This causes them to release epinephrine, more commonly known as adrenaline. This hormone increases heart rate, breath rate, blood pressure, and release of energy sources such as sugars and fats into the bloodstream (Harvard Health Publishing, 2018a). If one isn’t using all of this excess energy in an actual fight or flight response, but is instead in a non-threatening but

anxiety-producing situation, this can lead to physical shaking, which is a commonly experienced symptom in anxiety.

A slower pathway termed the HPA (hypothalamic-pituitary-adrenal) axis is also receptive of signals from the amygdala, hippocampus, and prefrontal cortex, and is heavily involved in the neuroendocrine response in anxiety. When the amygdala is activated by the presence of a stressor, it activates the paraventricular nucleus of the hypothalamus. This then activates the pituitary gland, which is involved in the regulation of many hormonal glands (Watson & Breedlove, 2018). The pituitary gland releases a hormone that travels to and activates the adrenal cortex of the adrenal glands. These glands then release cortisol, a glucocorticoid or stress hormone that has many physiological effects in the body (Watson & Breedlove, 2018). Hippocampus and mPFC signaling to this axis inhibit this stress response (Smith & Vale, 2006).

A diagram tidily depicting these two pathways is pictured below in Figure 3.

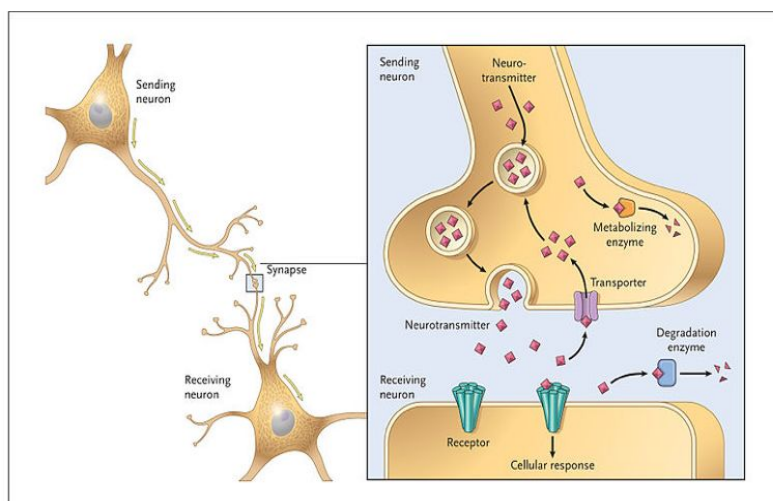


(Bassi, 2017)

Figure 3. Diagram depicting two main brain-body pathways activated in the anxiety response.

The “signaling” involved in all of these intricate pathways is carried out via communication between neurons, in which electrical and chemical signals are involved. Essentially, neurons fire an electrical signal called an action potential when a certain membrane potential threshold is reached in the neuron. This electrical signal causes the release of chemical messengers into the synapse, or the space between neurons. The waves of electrical signals exist at different frequencies, and one in particular that can be measured by an EEG, called the theta rhythm, has been shown to play a significant role in anxiety. Theta rhythms that originate in the hippocampus can drive and synchronize with the rhythms in the mPFC and amygdala, which has been shown to create anxiety (Calhoun & Tye, 2015). The hippocampus is basically recognizing and signifying a threat. Theta rhythms that originate in the PFC, however, have been shown to create a “safety signal” and reduce anxiety when synchronized with the amygdala’s rhythms (Calhoun & Tye, 2015).

Neurotransmitters are the chemical messengers that carry out the signaling between neurons. They are released from one neuron (termed the pre-synaptic neuron) and bind to receptors on another neuron (termed the post-synaptic neuron) to induce a response. The neurotransmitter can either be excitatory, increasing the signaling potential of the post-synaptic neuron, or inhibitory, decreasing the signaling potential of the post-synaptic neuron. An illustration of this communication between neurons is depicted below in Figure 4.



(NIDA, 2011)

Figure 4. Diagram depicting neuron signaling.

The most common inhibitory neurotransmitter and one that is highly involved in anxiety pathways is gamma aminobutyric acid, or GABA. It inhibits cell firing because it can be ionotropic: essentially, the binding of GABA causes the opening of chloride channels on the neuron. Chloride ions, which are negatively charged, then flow into the post-synaptic cell. This hyperpolarizes the membrane potential, decreasing the neuron's chance of firing an action potential (Watson & Breedlove, 2018). GABA can also be metabotropic, meaning it indirectly opens chloride channels after a sequence of other events; this causes it to induce a slow and prolonged inhibitory response (Gauthier & Nuss, 2015).

GABA plays a major role in the regulation of the central nucleus of the amygdala, which, as mentioned before, is a key component of anxiety pathways in the brain. Clusters of GABAergic neurons (neurons containing GABA receptors) in the amygdala limit the activity of the central nucleus, which when activated can induce an anxiety response after a sequence of

downstream actions. These GABAergic neurons are activated in response to signaling from glutamatergic neurons (neurons containing glutamate receptors) in the prefrontal cortex. If GABA functioning is impaired, the inhibition of the amygdala is reduced and it engages in overactive signaling (Meyer & Quenzer, 2018). This also means there is less control of the amygdala by the prefrontal cortex. The prefrontal cortex can allow us to reason out of our fear response, so it is essential to have properly functioning and adequate amounts of GABA to control anxiety.

There are multitudes of pharmaceutical treatments used for anxiety disorders, and those that act similarly to GABA are quite common. Benzodiazepines are a class of drug that bind to some kinds of GABA receptors and increase the probability of chloride channels opening in response to GABA, therefore making it more potent (Gauthier & Nuss, 2015). Barbiturates are another class of drug that bind to a spot on the GABA receptor and prolong the opening of chloride channels. They can act without GABA present, which potentially makes them more dangerous (Meyer & Quenzer, 2018). Neuroactive steroids are another treatment option that can act similarly to benzodiazepines and also directly activate the GABA receptor (Gauthier & Nuss, 2015). A specific drug called etifoxine can modulate neurosteroids and allosterically bind to the GABA receptor, also reducing anxiety (Gauthier & Nuss, 2015).

Although it plays a crucial role, GABA is not the only neurotransmitter involved in anxiety. Serotonin, a versatile neurotransmitter involved in numerous functions such as mood regulation, also plays a part. Serotonin increases amygdala-mediated activity, and a hyperactive amygdala can increase anxiety. It has also been shown to inhibit the periaqueductal gray, allowing it to mediate the fight or flight response involved in anxiety (Bandelow et al., 2016). It

doesn't seem to strictly increase or decrease anxiety, but rather affects it in different ways across various areas of the brain; it seems to be more involved in balance than unidirectional change. Drugs that mimic serotonin or cause it to accumulate can reduce anxiety, and are increasingly being used as treatments for anxiety disorders. The most common are SSRIs, or selective serotonin reuptake inhibitors, which prolong serotonin's effects by allowing it to accumulate in the synapses between pre-synaptic and post-synaptic neurons instead of immediately recycling it back into the pre-synaptic cell (Meyer & Quenzer, 2018).

Dopamine, the "pleasure" or "motivation" neurotransmitter, also plays many roles in the brain and in anxiety. There are many projections of neurons with dopamine receptors from the ventral tegmental area of the brain to the mPFC and the amygdala. These are activated by stressful stimuli and inhibit prefrontal cortex control of the amygdala, leading to a hyperactive amygdala and increased anxiety response (Meyer & Quenzer, 2018). Increased turnover (presence, transport, and use) of dopamine in the prefrontal cortex has also been shown to enhance the anxiety response. Benzodiazepines, the drug previously mentioned in the discussion about GABA, can decrease dopamine turnover (Meyer & Quenzer, 2018).

The major neurotransmitters mentioned thus far are not the only small molecules involved in biological anxiety; numerous other hormones and neuropeptides influence the physiological responses that we often associate with such disorders. The HPA axis, previously mentioned as a downstream pathway of amygdala, HPC, and PFC signaling, involves many of these hormones. When activated by the amygdala, the paraventricular nucleus of the hypothalamus releases a hormone or neuropeptide called corticotropin-releasing factor, or CRF. CRF is what activates the anterior pituitary gland, which releases a hormone termed

adrenocorticotrophic hormone, or ACTH (Meyer & Quenzer, 2018). ACTH travels through the blood to activate the adrenal glands. These glands then release glucocorticoids, which have many effects on the body (Meyer & Quenzer, 2018).

The major stress hormone or glucocorticoid in humans is cortisol. Cortisol can participate in negative feedback by binding to the hippocampus, hypothalamus, and pituitary gland and decreasing HPA axis signaling (Meyer & Quenzer, 2018). Glucocorticoids such as cortisol can have other effects on the brain and body: in acute stress, they can activate brain-derived neurotrophic factors (BDNFs), which increases neuroplasticity. However, in chronic stress, they can have the opposite effect, suppressing BDNFs and decreasing neuroplasticity (Bandelow et al., 2016). This means the brain cannot change and adapt as easily, which may make people more prone to repeating their same anxious behaviors. Levels of cortisol vary widely among people with various anxiety disorders, so it is not the sole determining factor of anxiety (Bandelow et al., 2016).

CRF, also called corticotropin releasing hormone (CRH), has additional effects in the brain. Sensitivity to lower levels of CRF can increase the release of norepinephrine or NE, a neurotransmitter involved in the physiological responses associated with anxiety (Meyer & Quenzer, 2018). Anxious people can develop this sensitivity because their bodies are exposed to CRF frequently, so it engages in a sort of positive feedback. The turnover of NE is then increased in the amygdala, hippocampus, hypothalamus, and prefrontal cortex (Meyer & Quenzer, 2018). A region in the brainstem called the dorsal pons contains a collection of noradrenergic cells (cells that respond to NE) called the locus coeruleus, or LC. This area,

involved in arousal and sensory processing, is activated by CRF and inhibited by GABA and serotonin (Meyer & Quenzer, 2018).

Norepinephrine is a neurotransmitter and hormone that is primarily involved in the activation of the sympathetic nervous system. It is released at sympathetic nervous system organ sites and causes increased heart rate, pupil dilation, and other physiological responses that commonly occur in anxiety. It is also involved in the formation of emotional memories, associating certain events with feelings of anxiety and therefore increasing the anxiety response when a similar event occurs (Meyer & Quenzer, 2018). Hyperfunction of NE and the stimulation of the locus coeruleus in the brain are often associated with anxiety (Bandelow et al., 2016).

Interestingly, numerous drugs used in the treatment of anxiety disorders act on both serotonin and norepinephrine. Certain drugs called SNRIs (serotonin and norepinephrine reuptake inhibitors) act similarly to SSRIs and prevent the reuptake of both serotonin and norepinephrine, which can have anxiolytic effects (Farach et al., 2012). A class of drugs called tricyclic antidepressants (TCAs) act similarly, increasing the levels of both of these neurotransmitters (Roy-Byrne, MD, 2019). Monoamine oxidase inhibitors, or MAOIs, inhibit the activity of the enzyme monoamine oxidase, which is involved in the breakdown of serotonin and norepinephrine. This means it also increases the levels of these neurotransmitters in the brain (Anxiety Disorders Association of America, 2009). It seems odd that increasing levels of norepinephrine can have anxiolytic effects, since norepinephrine generally acts to increase anxiety-related physiological responses. This “noradrenergic paradox” has been investigated, and a possible explanation is that norepinephrine can activate “autoreceptors” on the neurons

from which it was released, which in turn inhibits those neurons from releasing more norepinephrine. As such, it participates in a sort of negative feedback (Blier & Briley, 2011).

There are other neuropeptides involved in anxiety that are not as well-known but are worth discussing. For example, cholecystokinin (CCK) is a neuropeptide found in anxiety-related areas of the brain such as the basolateral amygdala, hypothalamus, periaqueductal gray, and anterior cingulate cortex or ACC (Bandelow et al., 2016). CCK activates neurons in the amygdala, interacts with neurotransmitters such as serotonin and GABA, and increases production of glutamate (an excitatory neurotransmitter) in the ACC (Bandelow et al., 2016). The ACC is involved in processing negative emotions and anticipating unpleasant stimuli, so overactivity could be a biological explanation for the unnecessary apprehension felt in anxiety (Martin et al., 2009). An interesting side note is that CCK is also involved in digestion, as it stimulates the release of digestive enzymes from the pancreas and bile from the gallbladder to aid in digestion (*Cholecystokinin*, 2020). This may explain why people experience a “nervous stomach” during periods of anxiety; their digestion may be accelerated by CCK.

Atrial natriuretic peptide (ANP) is also involved in the modulation of anxiety. ANP specifically inhibits the release of ACTH and cortisol, acting as an anxiolytic hormone and decreasing HPA axis activation. Physical activity can actually increase ANP levels, which may be part of the reason why exercise is beneficial for anxiety reduction (Bandelow et al., 2016). Finally, oxytocin (the “love hormone”) decreases activation of the amygdala and brainstem in response to stress (Martin et al., 2009). It has specifically been shown to ease social anxiety by activating GABAergic neurons in the amygdala and increasing the likelihood of pleasant social

interactions (Labuschagne et al., 2010). Perhaps this is why we feel so comforted around our loved ones; oxytocin is creating that feeling of safety.

It is apparent that there are multitudes of factors that contribute to the mental state known as anxiety, and it is interesting to consider how all of this can affect one's overall health. To begin, a consistently activated sympathetic nervous system has detrimental effects on cardiovascular health. For example, frequent release of adrenaline increases the risk of heart attacks and strokes by damaging blood vessels and increasing blood pressure (Harvard Health Publishing, 2018a). In addition, increased levels of HPA activity and release of cortisol can cause fat buildup and weight gain, which can have further negative effects on the body (Harvard Health Publishing, 2018a). It doesn't appear that there are many other well-studied direct causations between anxiety and other aspects of physical health, but various studies have been conducted to investigate the correlations between anxiety disorders and conditions such as gastrointestinal disorders, chronic respiratory disorders, and heart disease. Correlations between respiratory disorders such as chronic obstructive pulmonary disease (COPD) and anxiety disorders in individuals are high. In addition, the likelihood of a heart attack in individuals with heart diseases is higher for those with anxiety disorders (Harvard Health Publishing, 2018b). A specific study looking at an elderly population reported an association between gastrointestinal disorders, such as irritable bowel syndrome and Crohn's disease, and anxiety and depression (Kang et al., 2017). Although exact mechanisms are not well understood, it is apparent that anxiety is not beneficial to overall physical health.

There are numerous biological factors involved in anxiety. But this begs the question of why some people's brains repeatedly trace the stress circuit, or have less potent responses to

inhibitory neurotransmitters, or possess any of these other traits that cause anxiety. Is it preordained, in our genetics, or does it all depend on the environment in which we were raised? Both can come into play. Anxiety is such a complex phenomenon; numerous genes are involved and therefore a direct causal relationship between genetics and anxiety is difficult to pin down. However, various genes that affect factors such as serotonin transport and necessary proteins such as BDNF (which is important in the growth and development of neurons) can play roles in anxiety (Sharma et al., 2016). Studies have been conducted in animals that show that epigenetics, which is the control of gene expression via methods such as DNA methylation, can alter the expression of genes such as these that contribute to the “stress circuits” in the brain and body (Meyer & Quenzer, 2018). There is evidence that experiencing stress and trauma early on in life can affect genetic expression and brain development and increase the likelihood of anxiety later on, so genetics and environment are undoubtedly linked (Meyer & Quenzer, 2018).

I have often wondered how genetics and environment have affected my anxious tendencies. As was mentioned earlier, I’ve had these tendencies since I was a young child, but to my knowledge I didn’t experience intense amounts of stress or any trauma. I had a very safe and sheltered childhood. But perhaps this safe and sheltered childhood contributed just the same. I was constantly warned about the dangers in the world and heavily protected from them by my parents, which likely influenced the amount of fear I carried with me in many situations. Perhaps some of my anxious tendencies are attempts to harness control over my life, given that there are so many things I was taught I do not have control over. My mother also has anxious tendencies, and only now that I’m older do I realize that perhaps I subconsciously adopted similar ones when I was younger. It also supports the idea of a genetic component; if anxiety

runs in my family, perhaps I was genetically predisposed. It's all very interesting to speculate on, and although there is no clear-cut way to explain the cause, it's likely that many factors have come into play in my personal experiences.

It is clear that anxiety has its roots in the physical body. Much of what we think and feel can be attributed to chemical and electrical messages traveling around the brain and body. But the stimuli that can trigger these messages, and their manifestations, make up another side of anxiety that has its own form of complexity. The psychological and behavioral aspects of anxiety disorders are equally if not more important in studying this multifaceted phenomenon. To explore this side of anxiety disorders, it's important to distinguish the fact that anxiety disorders are often categorized based on what sets off the anxiety response and how the individual reacts. For this exploration, I'd like to focus on three forms: generalized anxiety disorder (GAD), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). I have had personal experiences with GAD and SAD, and have not been diagnosed with OCD, but I take an interest in it given some of the forms in which my personal anxiety manifests.

Psychological and Behavioral Aspects of Anxiety

A good starting point for the discussion on this side of anxiety disorders is generalized anxiety disorder, or GAD. The most recent *Diagnostic and Statistical Manual of Mental Disorders*, the DSM-V, gives criteria for diagnosing GAD. These include "the presence of excessive anxiety and worry about a variety of topics, events, or activities" that is experienced for at least six months and is "very challenging to control" (Glasofer, PhD, 2020; American Psychiatric Association, 2013). Essentially, it seems that the anxiety response isn't necessarily triggered by a specific situation, but is rather a frequent underlying mindset. GAD is diagnosed

when an individual has uncontrolled worry in addition to at least three other symptoms, which include things such as sleep trouble, muscle tension, and restlessness (Glasofer, PhD, 2020; American Psychiatric Association, 2013). Many of these physiological symptoms are logical results of the previously discussed stress response in the body.

I was recently diagnosed with GAD by my primary care doctor. Interestingly enough, she didn't ask me any specifics about how long my worry had been going on or if I experienced any characteristic symptoms. She just noticed that I pick at my skin and asked if I was stressed, and when I said yes, it became "official." I do agree that I often worry about *many* things. When I have to enter an unfamiliar situation or undergo something that has caused me stress before, I get extremely worried beforehand and exhibit lots of the symptoms commonly associated with anxiety - shaky hands, nervous stomach, racing heart. These symptoms often persist for some of the actual event, but are usually worse prior to it. Even when no dire consequences are likely, my nerves like to take over; it's almost habitual at this point. Now I know that this is likely due to the links between my amygdala, prefrontal cortex, and hippocampus, strengthening the association between bad memories and the anxiety response.

An example of this would be my experiences in science labs as an undergraduate. I took Honors Chemistry my freshman year at WWU, and I found the labs to be very stressful due to their level of difficulty and my inexperience. I tend to put a lot of pressure on myself in my academics, so I wanted to get good grades, and these grades depended on how well experiments turned out in the lab. But science experiments aren't as easy to control as other types of assignments, and the restrictions on resources and time limits did not help (I do not do well under time pressure). I think part of my anxiety surrounding these labs was due to my lack of control -

I couldn't *make* the science "go right" all of the time. My nerves also caused my hands to shake, which made handling the equipment and doing just about everything that required dexterity very difficult. This would exacerbate my anxiety, and thus began a perpetual unpleasant cycle. From there on out, I would get very nervous before every chemistry lab I had to take, and even some biology labs. As a cell and molecular biology major, I've had to take many labs, so this anxious state was quite frequent.

It's interesting that I was diagnosed with GAD, because as is apparent in the example above, it seems as if my anxiety is almost always triggered by a specific situation - it's just that there are many situations that can trigger it. Aside from chemistry labs, I get nervous about driving unfamiliar routes, driving other people around, talking on the phone, interpersonal conflicts and having to resolve them, speaking up, and making decisions, to name a few. But it seems to me that GAD often puts one into a state of anxiety where one can't even distinguish a cause. Perhaps I am often spun up into an anxious state without a real cause, but my rational mind won't accept this, and thus pins it on something concrete so my mind can explain itself to me.

I'd next like to discuss a specific form of anxiety that I feel I've had experiences with my whole life: social anxiety. The DSM-V gives diagnostic criteria for SAD that include "marked fear or anxiety about one or more social situations in which (one) might be scrutinized by others" and "fear that (one) will humiliate or embarrass (one)self and be rejected by others." The anxiety is often "out of proportion to the actual threat of the situation" and "interferes with many areas of life" (Cuncic, 2019; American Psychiatric Association, 2013). SAD is a relatively common anxiety disorder that often starts in early childhood and can be contributed to by both

environmental and genetic factors (*NIMH » Social Anxiety Disorder: More Than Just Shyness*, 2018). People with social anxiety often experience typical anxiety symptoms such as trembling and nausea when in many social situations, and can be very self-conscious in or avoidant of such situations (Cuncic, 2019). This obviously has detrimental effects on day-to-day life.

I mentioned before that I was extremely shy at a young age. As a child, I was always very nervous about meeting new people, and sometimes had trouble making friends or feeling fully included and accepted. This has improved since I've gotten older, but I am still not one for "putting myself out there." Most people would describe me as very quiet and introverted, which are not bad things in and of themselves, but some of the reasons behind why I am those things isn't great for my mental health. I am often afraid to speak up because I am afraid of what people will think of me. Unfamiliar or potentially uncomfortable social situations make me very nervous, and I tend to avoid them unless I am with people around whom I feel comfortable. Even simple phone calls give me adrenaline rushes.

I have also struggled with having the confidence to speak out in academic settings, and rarely am able to make voluntary verbal contributions in class, even if I think I know the answer or have an interesting thought. It's like my brain physically blocks my hand from going up or my mouth from forming words, and I feel that I cannot speak. When I do have to speak out in front of people, my sympathetic nervous system decides to throw a party and my heart races, my stomach churns, and my hands tremble. Interestingly enough, this has gotten worse as I've gone through college. I think it's partially because I'm surrounded by incredibly intelligent peers, and I am (irrationally) terrified of their judgement. However encouraging people are to me about sharing my thoughts, my brain convinces me that I will get something wrong and then, due to my

brain's tendency to perpetually replay my mistakes, I will never forget it. This also makes me enthusiastically uninterested in public speaking. I think making myself do these things will help - I just have to overcome the mental barriers, which is not easy.

A final anxiety-related disorder that I haven't been diagnosed with but I feel a connection to is obsessive-compulsive disorder, or OCD. Interestingly, OCD was previously included under the umbrella of anxiety disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, but in the most recent DSM-V, OCD is under its own category of "Obsessive-Compulsive and Related Disorders." Anxiety still does play a role. The DSM-V provides criteria for diagnosis of OCD, which is defined as the "presence of obsessions, compulsions, or both." Obsessions are described as "Recurrent and persistent thoughts, urges, or images that are experienced...as intrusive and unwanted, and that...cause marked anxiety or distress" that the person "attempts to ignore or suppress... or to neutralize... with some other thought or action" (Fenske, MD & Petersen, MD, 2015; American Psychiatric Association, 2013). Compulsions are described as "repetitive behaviors... or mental acts...that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly" that are "aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation." The compulsions may be directly connected to the obsessions (such as hand washing in response to obsessive thoughts about contamination) but may not have a logical connection to the obsessive thoughts (Fenske, MD & Petersen, MD, 2015; American Psychiatric Association, 2013). The thoughts and behaviors are generally quite difficult to control, and compulsions typically tend to take up a significant amount of time in day-to-day life (*Obsessive-Compulsive Disorder (OCD) | ADA*, 2019).

I don't want to self-diagnose, or undermine the severity of this actual disorder with my potentially less potent experiences. I just think it's interesting to examine some of my anxious tendencies through this lens. I've already mentioned that I consider myself a chronic worrier, but I don't know how obtrusive I should consider my thoughts to be, because I sometimes feel that there is a logical reason for my worries. I wash my hands more often than the average person and if I touch someone else's hands or something my brain considers "contaminated," I have the thought of that contamination in the back of my mind until I wash my hands. I've also always been a person of routine, but sometimes, it does seem to get out of hand. For example, even if I *know* that I checked to make sure the back door was locked, my brain will tell me to check it again, because what if it was actually unlocked and someone broke in? These types of thoughts aren't omnipresent, but do play a large part in my life.

Something that I do repetitively, uncontrollably, and irrationally is ruminate on past mistakes. When I make a mistake that my brain decides to fixate on, whether it actually has an impact on my life or (more often) does not, it becomes like an itch in my brain that I can't scratch unless the issue is resolved. The issue often cannot be resolved because it happened in the past, so it is very difficult for my brain to ignore it. The mistake starts playing in a repeating loop in my head, and sometimes the track wears out quickly, but other times it sticks around for an absurd amount of time; sometimes it'll even fade away but then come back much later on and start replaying again. This frustrating unpleasantness exacerbates my fear of making mistakes and therefore my overall anxiety in many situations. I also have a tendency to pick at my skin, especially when I'm in a stressful situation or stuck in a bout of rumination. There is a disorder that is categorized under the same heading as OCD in the DSM-V that involves compulsive

skin-picking (*Diagnostic and Statistical Manual of Mental Disorders and OCD* | *OCD-UK*, 2013). I often have trouble controlling this behavior, however unwanted it is. It is interesting to examine how the symptoms I personally experience can overlap and connect with symptoms experienced in other mental health disorders, as this sort of connection can increase the empathy we feel for each other.

Having anxiety-related disorders can obviously be detrimental to physical and mental health and can make everyday life difficult. However, there are numerous treatments available, ranging from medications that directly target the neurochemical aspects to behavioral therapies that target the psychological side. Anxiety disorders are so complex, it is logical that treatments work differently for different people, and it is not able to be entirely streamlined. There are, however, common therapies that work well for large groups of people. I'd like to discuss these in a little more depth.

Treatment

To start, we can touch back on the pharmacological side of anxiety treatment. There are many medications currently on the market for anxiety disorders, and they use varying mechanisms to alleviate symptoms in the brain. One of the most well-known classifications of drugs is the central nervous system (CNS) depressants, which include the aforementioned benzodiazepines and barbiturates. These drugs enhance the effects of the inhibitory neurotransmitter GABA, reducing feelings of stress (Meyer & Quenzer, 2018). This is especially significant because research has shown that lower numbers of GABA receptors and abnormalities in the regulation of GABAergic neuron signaling have been observed in people with anxiety disorders (Martin et al., 2009). Benzodiazepines in particular have been commonly

prescribed for GAD, SAD, and OCD, and can be used regularly or in cases of situational anxiety (Meyer & Quenzer, 2018). However, current research is suggesting that they are not the best option for primary treatment, as they may cause dependence when taken over extended periods of time and withdrawal symptoms when attempting to stop taking them (Bandelow et al., 2017). They may also have serious side effects involving depression of the CNS, manifesting in symptoms such as slower reaction time and dizziness, and may have detrimental cognitive effects (Bandelow et al., 2017).

Drugs commonly classified as antidepressants are also useful in the treatment of anxiety disorders (Anxiety Disorders Association of America, 2009). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly prescribed for pharmacological treatment of anxiety disorders. They sometimes take a few weeks to have any beneficial effects, and can initially make anxiety symptoms worse (Bandelow et al., 2017). However, after this initial time, these drugs are often effective. For example, in a meta-analysis study, Jakubovski et al (2019) found that both SSRIs and SNRIs have significantly beneficial effects on anxiety symptoms compared to placebo treatments, specifically in SAD. SSRIs in particular have better efficacy with increased dosage, but this also increases unpleasant side effects, so a balance must be attained (Jakubovski et al., 2019). Other antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are also occasionally prescribed to treat anxiety disorders. However, TCAs have more detrimental side effects and overdoses are lethal, so they are more risky (Farach et al., 2012). MAOIs can have disastrous interactions with other medications and dietary tyramine, so they are not often used (Bleakley & Davies, 2014).

Other medications on the market for treatment of anxiety disorders include anticonvulsants, such as pregabalin, which blocks voltage-gated calcium channels involved in neurotransmitter release and has similar inhibitory effects as benzodiazepines with less adverse side effects (Farach et al., 2012). A noteworthy drug called buspirone, which has been effective in treating GAD, acts similarly to SSRIs and also has similar anxiolytic effects to benzodiazepines, with less adverse side effects on the CNS and less risk of dependence (Meyer & Quenzer, 2018). There are many others, and this is an ever-expanding field in which much research is being conducted. As more is discovered about the neurochemistry behind anxiety, more pharmacological solutions will likely take form.

Medication is a very valid treatment option for many people with anxiety disorders. As with any sort of medical treatment, different medicines work in varying capacities for different individuals - there is no “one size fits all” mentality when it comes to pharmacology and anxiety. Personally, I have always been skeptical of anti-anxiety drugs for treatment of my anxiety. The first thing my primary care doctor suggested when she diagnosed me with GAD was for me to start medication, which is interesting to me, because there are lots of other options out there. I guess it feels almost like a personal defeat if I can’t control my anxiety with my own willpower and strength of mind. I also don’t want to become dependent on a substance or have things “messing with my mind;” again, this is mostly a personal-strength dilemma, but there is the possibility of physiological dependence with some of these medications. I’m sure there are many opinions on whether or not anti-anxiety medication is over-prescribed, and I don’t want to make a judgement. Nevertheless, although medication works for lots of people, it is not the only treatment for anxiety.

A fairly well-known and very common method of treatment for anxiety disorders and many other mental health disorders is cognitive behavioral therapy, or CBT. CBT is defined as “psychotherapy aimed at correcting negative thinking and consciously changing behaviors as a way of changing feelings” (Watson & Breedlove, 2018). One of the major forms of CBT is exposure therapy, in which the person is repeatedly exposed to the anxiety-inducing stimulus in a controlled setting (like a therapy session) to gradually reduce the fear associated with it. This works by essentially re-wiring the “associative networks” or “cognitive fear structures” in the brain (Kaczurkin & Foa, 2015). These are likely made via connections between the amygdala, prefrontal cortex, and hippocampus when establishing irrational “fear memories” in response to non-harmful stimuli, as mentioned earlier (Calhoun & Tye, 2015). The controlled repeated exposure to the anxiety-inducing stimulus and formation of new memories feeds “corrective information” into this fear circuit, allowing one to “relearn” the situation, replace the fear memories with pleasant ones, and experience reduced anxiety when the stimulus is encountered in a real-life situation. This exposure could be in the person’s imagination or in real life (Kaczurkin & Foa, 2015). For GAD and SAD, this could take the form of imagining and talking through worry-inducing situations, or putting oneself in feared social situations. For OCD, this could take the form of exposing oneself to an inducer of obsessive thoughts (such as contamination) and *not* performing the compulsive ritual afterward (such as not washing the hands x amount of times). Many studies have been conducted that show that this method of therapy is effective (Kaczurkin & Foa, 2015).

Another form of CBT is simply called cognitive therapy. This method essentially targets negative thoughts with the hopes of then changing negative feelings and behaviors (Kaczurkin

& Foa, 2015). It seems that the general idea behind this method is for a professional, such as a therapist, and an anxious patient to have discussions about the patient's negative thoughts. The professional talks with the patient about the reasoning behind irrational thoughts and encourages the patient to analyze those thoughts, recognize faults in said thoughts, and gradually become able to convince themselves to lend less weight to them. For example, in GAD, a patient could be encouraged to identify thoughts that "overestimate risk" in certain situations. In SAD, a patient could be taught that the reason certain social situations are anxiety-inducing is because they tend to have a weak self-image and overestimate the harm a mistake could cause, and the patient would hopefully be able to implicate better patterns of thought to address this and reduce their fear (Kaczkurkin & Foa, 2015). In OCD, a patient may be encouraged to identify connections between triggers, obsessive thoughts, and the importance they place on these thoughts that leads to compulsive behaviors, and then begin to work through these connections. Cognitive therapy alone has not been shown to be significantly effective in GAD and OCD treatment, but it has proven effective in SAD compared to controls (Kaczkurkin & Foa, 2015). More study is needed on this type of therapy.

I personally like the idea of cognitive-behavioral methods of treatment for anxiety more than medication, possibly because they give one more control over the situation and allow one to make noticeable, active steps towards wellness. Another medical professional whom I've talked to about anxiety recommended that I start seeing a counselor or therapist, and although I haven't yet, I know plenty of friends who do and they say it makes a large difference on their mental health. No doubt exposing oneself to anxiety-inducing situations, talking about one's deepest fears, and convincing oneself to engage in different patterns of thought is a very difficult

journey, but it has beneficial outcomes in the long run. I sometimes try these methods on my own, especially engaging in different thought patterns, and it is definitely difficult to maintain; the “anxious portion” of my brain often wins out. But with willpower and practice, perhaps it will improve.

Medication and cognitive behavioral therapy are not mutually exclusive; in fact, some people engage in both methods of treatment. However, in studies conducted to determine the effectiveness of a combination of the two types compared to each individually, the results vary. For example, Crits-Christoph et al. conducted a study comparing the effectiveness of venlafaxine (an SNRI) and CBT alone and a combination of the two, and did not find any significant benefit of the combination treatment (2011). Other studies have found that a combination of benzodiazepines and CBT can be worse than one form individually (Singewald et al., 2015). However, one meta-analysis study that compared many of these studies did find that a combination could be effective (Bandelow et al., 2017). In addition, certain drugs (such as SSRIs and noradrenergic agonists) that act on biological components involved in anxiety can act as “cognitive enhancers” and improve the effectiveness of CBT by decreasing the potency of fear memories (Singewald et al., 2015). Considering the fact that anxiety is both biological and psychological, it makes sense that a more holistic treatment approach could be beneficial. More studies are needed to determine a consistent trend.

One rather unorthodox method of treatment I came across while researching is neural circuit reprogramming. This plays off of the idea of rewiring the associative or cognitive fear networks in the brain, as mentioned for CBT. In CBT, this is accomplished through thought patterns and behaviors. By contrast, in neural circuit reprogramming, the idea is to physically

manipulate these circuits in the brain via methods such as transcranial magnetic stimulation (TMS) or focal ultrasound targeting certain positions in these fear memory circuits (Calhoun & Tye, 2015). By up-regulating or down-regulating activity in certain circuits of the brain, beneficial downstream effects such as reduced fear memories could occur (Calhoun & Tye, 2015). There are many considerations to take into account with this sort of study, such as other effects on the brain, safety, invasiveness, and ethical concerns (Tye, 2014). Although this is an interesting idea, it seems to me as if it crosses personal boundaries and it's not something I would ever want to undergo.

A holistic therapeutic method for anxiety treatment is exercise. Numerous studies have shown the benefits of exercise on both the body and the brain, and it is encouraged as a therapeutic strategy for countless diseases and disorders. Physically, exercise activates the sympathetic nervous system and the HPA axis, increasing the production of glucocorticoids such as cortisol (Stranahan et al., 2008). This activation induces physical symptoms such as fast heart rate, which is crucial in exercise and occurs unnecessarily in anxiety. The exact mechanism of how this reduces overall anxiety isn't clear, but perhaps it has something to do with the autoreceptors and negative feedback idea mentioned earlier in the discussion about the noradrenergic paradox. Purposeful, healthy stimulation of the sympathetic nervous system may reduce the likelihood of activation in non-threatening but anxiety-inducing situations. Additionally, as mentioned previously, glucocorticoids can activate brain-derived neurotrophic factors (BDNFs), increasing neuroplasticity (Bandelow et al., 2016) and providing more opportunities for re-wiring of fear circuits. BDNFs can also have anxiolytic effects (Anderson & Shivakumar, 2013). Exercise can also increase blood flow to the brain and levels of beneficial

neurotransmitters such as serotonin, norepinephrine, and the endogenous opioids known as endorphins, which can have beneficial effects on mood (Anderson & Shivakumar, 2013). Also, muscle tension can be reduced in physical activity, further contributing to feelings of relaxation (Ratey, 2019).

Exercise has lots of physical benefits, as is apparent, but it can have psychological benefits as well. Exercise can increase self-efficacy, or the idea that one is competent and able to manage potential threats (Anderson & Shivakumar, 2013). It can also serve as a distraction from worries, or a healthy escape from the anxiety of everyday life. Interestingly, it can also work as a form of exposure therapy: if the person is worried about physical symptoms of anxiety such as fast heart rate and this is attained safely in aerobic exercise, the associated fear could decrease (Anderson & Shivakumar, 2013). It is clear that exercise has many beneficial effects on physical and mental health, and can serve as a very helpful and low-risk therapeutic strategy. I am trying to implicate exercise regularly into my life, and it does sometimes make me feel more relaxed. It's a good disperser of "anxious energy" for me.

The form of exercise that I am most inclined to participate in is dance. I started dancing when I was four years old, and I took classes all the way up through sophomore year of high school. I then continued dancing in musical theater throughout high school. I have also been participating in WWU Glee Club throughout my entire college experience and was the dance coordinator for the past three years. I consider dance a therapeutic activity. It takes my mind off of worries and instead focuses my thoughts on my movements and how my body feels as I push through those movements. I truly feel at home and confident when I dance, and it's one of the only things that I hardly ever get anxious about doing in front of people; in fact, I love

performing dance routines. The therapeutic aspect of it likely comes in part from the beneficial physiological effects of exercise mentioned above. I think a large part of it is the confidence it instills in me; lack of self-confidence is a weakness I possess that contributes to my anxiety, but when I'm dancing, I'm secure in who I am and sure of myself.

Another one of my favorite personal therapeutic activities (and one that I know I share with lots of people) is listening to music. Music is incredibly powerful; it can evoke poignant memories and emotional responses. There is biological evidence that listening to music can reduce stress by activating numerous portions of the brain, increasing dopamine release and decreasing cortisol levels in the blood (Suttie, 2015). Music has been an omnipresent entity in my life; it's played a large role in my dance and musical theater experience, and often accompanies me in my day-to-day activities. It is definitely therapeutic for me: it's amazing that some songs have the power to mentally transport me away from my present anxious thoughts and immerse my mind in the experience and emotions that the music is creating. It feels like the act of processing the music and the emotions it evokes can overpower the anxiety circuitry firing away rapidly in my brain. This love of music is a shared quality worldwide, which goes to show how incredible of a phenomenon it is.

Something that I love to do in an almost therapeutic way is read books. I've been an avid reader since I was very young, often choosing to step into a fantastical story with imaginary characters over actively engaging with real people. I've started to wonder why I love it so much, and I think it has to do with the fact that when I read a book, it allows me to momentarily escape my own life and problems and enter someone else's story. It can give me temporary relief from anxious thoughts. It can also open up my mind to different perspectives, which helps me put my

own life into perspective and appreciate all of the things I should be grateful for instead of worrying about relatively miniscule personal issues. Books are monumentally impactful.

A final aspect of my life that helps with my anxiety is my spirituality. I was raised a Christian and grew up attending church semi-regularly, and I still make a habit of doing so. However, the organized portion of my religious life is not necessarily the most impactful part. It is comforting to be able to trust in a higher presence, because so many things are outside of our control and unknowable to us, and I think this is why so many people choose to be religious. I personally believe that life has a deeper and higher meaning to it than what can be explained by humans, and this is what spirituality means to me. It is difficult, but I use my spirituality to work on trusting the idea that everything happens exactly as it should, which can greatly decrease my anxiety.

It is clear that anxiety is a multifaceted entity, encompassing biological and behavioral components that intricately integrate to create experiences. The experiences involved aren't necessarily pleasant, but being informed about how and why they occur both satiates my academic curiosity and helps attenuate some of the negativity surrounding my thoughts and experiences. It is also evident that although anxious tendencies can seem unbeatable at times, there are many ways to go about alleviating them. Anxiety disorders are prevalent in society, and understanding their mechanisms can increase acceptance of and compassion towards ourselves and others. This exploration has been personally therapeutic and will hopefully foster awareness and understanding, allowing us to "consider the ravens" and achieve peace both within ourselves and with each other.

References

- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. <https://doi.org/10.1176/appi.books.9780890425596>
- Anderson, E., & Shivakumar, G. (2013). Effects of Exercise and Physical Activity on Anxiety. *Frontiers in Psychiatry, 4*. PMC. <https://doi.org/10.3389/fpsyt.2013.00027>
- Anxiety Disorders Association of America. (2009). *MEDICATIONS*.
- Avery, S. N., Clauss, J. A., & Blackford, J. U. (2015). The Human BNST: Functional Role in Anxiety and Addiction. *Neuropsychopharmacology, 41*(1), 126–141. <https://doi.org/10.1038/npp.2015.185>
- Bandelow, B., Baldwin, D., Abelli, M., Bolea-Alamanac, B., Bourin, M., Chamberlain, S. R., Cinosi, E., Davies, S., Domschke, K., Fineberg, N., Grünblatt, E., Jarema, M., Kim, Y.-K., Maron, E., Masdrakis, V., Mikova, O., Nutt, D., Pallanti, S., Pini, S., ... Riederer, P. (2016). Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. *The World Journal of Biological Psychiatry, 18*(3), 162–214. PMC. <https://doi.org/10.1080/15622975.2016.1190867>
- Bandelow, B., Michaelis, S., & Wedekind, D. (2017). Treatment of anxiety disorders. *Dialogues in Clinical Neuroscience, 19*(2), 93–107. PMC. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5573566/>

- Bassi, G. (2017, October 30). *A Sympathetic-Adrenal Neuroimmune Reflex Linked to the Immunosuppressive Effects of Spinal Cord Injury*. *BrainImmune: Trends in Neuroendocrine Immunology*.
<http://www.brainimmune.com/sympathetic-adrenal-neuroimmune-reflex-spinal-cord-injury/>
- Bleakley, S., & Davies, S. J. (2014). The pharmacological management of anxiety disorders. *Progress in Neurology and Psychiatry*, *18*(6), 27–32.
<https://doi.org/10.1002/pnp.357>
- Blier, P., & Briley, M. (2011). The noradrenergic symptom cluster: clinical expression and neuropharmacology. *Neuropsychiatric Disease and Treatment*, *7*(Suppl 1), 15–20. <https://doi.org/10.2147/NDT.S19613>
- Calhoun, G. G., & Tye, K. M. (2015). Resolving the neural circuits of anxiety. *Nature Neuroscience*, *18*(10), 1394–1404. <https://doi.org/10.1038/nn.4101>
- Cholecystikinin*. (2020). Colostate.Edu.
<http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/gi/cck.html>
- Crits-Christoph, P., Newman, M. G., Rickels, K., Gallop, R., Gibbons, M. B. C., Hamilton, J. L., Ring-Kurtz, S., & Pastva, A. M. (2011). Combined medication and cognitive therapy for generalized anxiety disorder. *Journal of Anxiety Disorders*, *25*(8), 1087–1094. PMC. <https://doi.org/10.1016/j.janxdis.2011.07.007>
- Cuncic, A. (2019, June 25). *Symptoms and Diagnosis of Social Anxiety Disorder*. Verywell Mind; Verywell Mind.

<https://www.verywellmind.com/social-anxiety-disorder-symptoms-and-diagnosis-4157219>

Diagnostic and Statistical Manual of Mental Disorders and OCD | OCD-UK. (2013).

OCDUK.Org.

<https://www.ocduk.org/ocd/clinical-classification-of-ocd/dsm-and-ocd/>

Farach, F. J., Pruitt, L. D., Jun, J. J., Jerud, A. B., Zoellner, L. A., & Roy-Byrne, P. P.

(2012). Pharmacological treatment of anxiety disorders: Current treatments and future directions. *Journal of Anxiety Disorders*, 26(8), 833–843. PMC.

<https://doi.org/10.1016/j.janxdis.2012.07.009>

Fenske, MD, J. N., & Petersen, MD, K. (2015). Obsessive-Compulsive Disorder:

Diagnosis and Management. *American Family Physician*, 92(10).

Gauthier, I., & Nuss, P. (2015). Anxiety disorders and GABA neurotransmission: a

disturbance of modulation. *Neuropsychiatric Disease and Treatment*, 11, 165.

PMC. <https://doi.org/10.2147/ndt.s58841>

Generalized Anxiety Disorder (GAD) | Anxiety and Depression Association of America,

ADAA. (2019). ADAA.Org.

<https://adaa.org/understanding-anxiety/generalized-anxiety-disorder-gad>

Glaser, PhD, D. R. (2020, April 3). *Generalized Anxiety Disorder: Symptoms and*

Diagnosis. Verywell Mind; Verywell Mind.

<https://www.verywellmind.com/dsm-5-criteria-for-generalized-anxiety-disorder-1393147>

Harvard Health Publishing. (2018a, May 1). *Understanding the stress response - Harvard Health*. Harvard Health; Harvard Health.

<https://www.health.harvard.edu/staying-healthy/understanding-the-stress-response>

Harvard Health Publishing. (2018b, May 9). *Anxiety and physical illness - Harvard Health*. Harvard Health; Harvard Health.

https://www.health.harvard.edu/staying-healthy/anxiety_and_physical_illness

Herman, J. P., McKlveen, J. M., Solomon, M. B., Carvalho-Netto, E., & Myers, B.

(2012). Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Brazilian Journal of Medical and Biological Research*, 45(4).

PubMed. <https://doi.org/10.1590/S0100-879X2012007500041>

How does exercise impact your brain? (n.d.). Lifestyle Essentials. Retrieved May 25, 2020, from

https://www.lifestyleessentials.com.au/blog/how-does-exercise-impact-your-brain_106s88

Jakubovski, E., Johnson, J. A., Nasir, M., Müller-Vahl, K., & Bloch, M. H. (2019).

Systematic review and meta-analysis: Dose-response curve of SSRIs and SNRIs in anxiety disorders. *Depression and Anxiety*, 36(3), 198–212.

<https://doi.org/10.1002/da.22854>

Kaczurkin, A. N., & Foa, E. B. (2015). Cognitive-behavioral therapy for anxiety

disorders: an update on the empirical evidence. *Dialogues in Clinical Neuroscience*, 17(3), 337–346. PMC.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610618/>

- Kang, H.-J., Bae, K.-Y., Kim, S.-W., Shin, H.-Y., Shin, I.-S., Yoon, J.-S., & Kim, J.-M. (2017). Impact of Anxiety and Depression on Physical Health Condition and Disability in an Elderly Korean Population. *Psychiatry Investigation*, *14*(3), 240. PMC. <https://doi.org/10.4306/pi.2017.14.3.240>
- Kelly, PhD, O. (2019, August 26). *The 5 Types of Obsessive-Compulsive Disorder*. Verywell Mind; Verywell Mind. <https://www.verywellmind.com/what-are-the-different-types-of-ocd-2510663>
- Khdour, H. Y., Abushalbak, O. M., Mughrabi, I. T., Imam, A. F., Gluck, M. A., Herzallah, M. M., & Moustafa, A. A. (2016). Generalized Anxiety Disorder and Social Anxiety Disorder, but Not Panic Anxiety Disorder, Are Associated with Higher Sensitivity to Learning from Negative Feedback: Behavioral and Computational Investigation. *Frontiers in Integrative Neuroscience*, *10*. PMC. <https://doi.org/10.3389/fnint.2016.00020>
- Labuschagne, I., Phan, K. L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., Stout, J. C., & Nathan, P. J. (2010). Oxytocin Attenuates Amygdala Reactivity to Fear in Generalized Social Anxiety Disorder. *Neuropsychopharmacology*, *35*(12), 2403–2413. <https://doi.org/10.1038/npp.2010.123>
- Leisman, G. (2013). The Development of the Frontal Lobes in Infancy and Childhood: Asymmetry and the Nature of Temperament and Affect. *Frontal Lobe: Anatomy, Functions, and Injuries*. <https://doi.org/10.13140/RG.2.1.4461.7041>
- Martin, E. I., Ressler, K. J., Binder, E., & Nemeroff, C. B. (2009). The Neurobiology of Anxiety Disorders: Brain Imaging, Genetics, and Psychoneuroendocrinology.

Psychiatric Clinics of North America, 32(3), 549–575. PMC.

<https://doi.org/10.1016/j.psc.2009.05.004>

Meyer, J. S., & Quenzer, L. F. (2018). *Psychopharmacology: Drugs, the Brain, and Behavior* (3rd ed., pp. 560–599). Oxford University Press.

Montoya, A., Bruins, R., Katzman, M., & Blier, P. (2016). The noradrenergic paradox: implications in the management of depression and anxiety. *Neuropsychiatric Disease and Treatment*, 12, 541. PMC. <https://doi.org/10.2147/ndt.s91311>

NIDA. (2011, March 16). *English: Generic Neurotransmitter System*. Wikimedia Commons.

https://commons.wikimedia.org/wiki/File:Generic_Neurotransmitter_System.jpg

NIMH » *Anxiety Disorders*. (2019, February 8). NIH.

<https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml>

NIMH » *Obsessive-Compulsive Disorder*. (2019, January 15). NIH.

<https://www.nimh.nih.gov/health/topics/obsessive-compulsive-disorder-ocd/index.shtml>

NIMH » *Social Anxiety Disorder: More Than Just Shyness*. (2018, December 4). NIH.

<https://www.nimh.nih.gov/health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml>

Obsessive-Compulsive Disorder (OCD) | Anxiety and Depression Association of America, ADAA. (2019). ADAA.Org.

<https://adaa.org/understanding-anxiety/obsessive-compulsive-disorder-ocd>

Ratey, J. J. (2019, October 24). *Can exercise help treat anxiety? - Harvard Health Blog.*

Harvard Health Blog.

<https://www.health.harvard.edu/blog/can-exercise-help-treat-anxiety-2019102418096>

Roy-Byrne, MD, P. (2019). *What Medications Are Used to Treat Anxiety Disorders?*

Adaa.Org.

<https://adaa.org/learn-from-us/from-the-experts/blog-posts/what-medications-are-used-treat-anxiety-disorders>

Sharma, S., Powers, A., Bradley, B., & Ressler, K. J. (2016). Gene × Environment

Determinants of Stress- and Anxiety-Related Disorders. *Annual Review of Psychology*, 67(1), 239–261. PMC.

<https://doi.org/10.1146/annurev-psych-122414-033408>

Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., & Ressler, K. J. (2015).

Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacology & Therapeutics*, 149, 150–190.

<https://doi.org/10.1016/j.pharmthera.2014.12.004>

Smith, S. M., & Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis

in neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, 8(4), 383–395. PMC. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181830/>

Stranahan, A. M., Lee, K., & Mattson, M. P. (2008). Central Mechanisms of HPA Axis

Regulation by Voluntary Exercise. *NeuroMolecular Medicine*, 10(2), 118–127.

PMC. <https://doi.org/10.1007/s12017-008-8027-0>

- Suttie, J. (2015, January 20). *Five Ways Music Can Make You Healthier*. Greater Good Magazine; Greater Good Science Center, UC Berkeley.
https://greatergood.berkeley.edu/article/item/five_ways_music_can_make_you_healthier
- THE BRAIN FROM TOP TO BOTTOM*. (n.d.). TheBrain.Mcgill.Ca. Retrieved February 26, 2020, from
https://thebrain.mcgill.ca/flash/i/i_04/i_04_cr/i_04_cr_peu/i_04_cr_peu.html
- The Holy Bible, New International Version* (p. 948). (2011). Zondervan.
- Tye, K. M. (2014). Neural Circuit Reprogramming: A New Paradigm for Treating Neuropsychiatric Disease? *Neuron*, 83(6), 1259–1261. PMC.
<https://doi.org/10.1016/j.neuron.2014.08.022>
- Watson, N., & Breedlove, S. M. (2018). *The Mind's Machine: Foundations of Brain and Behavior* (2nd ed.). Oxford University Press.
- Zakhary, MD, PhD, L. (2018, November 28). *Picking your skin? Learn four tips to break the habit*. Harvard Health Blog.
<https://www.health.harvard.edu/blog/picking-your-skin-learn-four-tips-to-break-the-habit-2018112815447>