

NEURAL PLASTICITY
THE POWER OF THE MIND:
THE ART AND SCIENCE
OF TREATMENT
FOR DEPRESSION

by

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A THESIS

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The field of neuroscience has seen a major conceptual shift in the past forty years. Historically the brain has only been viewed as set in a definitive state from birth – defined by genes and biological structures to determine behaviors (Brady, *et al.*, 2024). These predetermined structures were believed to directly impact the expression of an individual's temperaments and their predisposition to mental health conditions.

Today medical research recognizes that the brain is adaptive in response to the environment, therapeutic interventions, and to the mind itself, potentially causing an upstream impact on neurochemical production and expression. Art and literature illuminate the complexity of the human mind as a hopeful avenue to provide participant-centered healthcare. These disciplines allow for a humane introspection of the mental psyche beyond the standard quantified assessment within the traditional field of psychology. The background and literature examples of depression will be briefed in Chapter One.

One of the ways that humans have been examined is in decision making. Consumer researchers typically find that individuals will make many decisions based on how they want to be perceived by others, and sometimes, these decisions result in negative consequences (Perez, *et*

al., 2021). Poor decision-making has long been considered a factor of the human condition. For example, according to a CDC study, the top four lifestyle causes of death in the United States are smoking, poor diet, sedentary lifestyle, and alcohol consumption (Mokdad *et al.*, 2000). All these causes are the result of numerous decisions made every day. In some cases, one could argue that an individual was not made aware of the negative implications these decisions would have on their overall long-term health. In most cases, however, health advocates, doctors, the media, and even family and peers make abundantly clear the negative effects of cigarettes, processed food, lack of exercise, and alcohol.

While the negative risk factors listed above do not have a direct link to depression, the concept of choice versus habit on health and wellbeing is clearly at play. Given the dangers these habits pose to one's health, self-preservation is not always the goal. With the growing rates of suicide in the age 10-24 population there is an extreme rise of escapism and mental suffering with the adolescent and emerging adult population (Curtin & Garnett, 2023). The role of impulsivity and decision making is one of many connects researchers are investigating to better understand suicidal behavior (Gvion, *et al.*, 2015).

It is important to note that suicide does not always mean that the individual experienced depression, yet there is some correlation as individuals with depression are at a higher risk for suicide when compared to the control group (Cai, *et al.*, 2021). In Chapter Two, there will be a clear list of depressive indicators provided by the DSM-5 that can construct a better understanding of how depression presents within daily life. An estimated 280 million people who live with depression experience these symptoms and occurrences worldwide, which is the focus of this thesis (WHO, 2023).

Using concepts like neural plasticity in Chapter Three, I will reinforce the connection between the power of the mind and the ability an individual has to change the ‘hard-wired’ neural networks of the brain through intentional thought and action. Most, if not all, mental health conditions, specifically depression, were historically viewed as a chemical deficit. A deficit denotes a lack or below functioning levels of a trait or compound. In the case of depression, it has been found that individuals with depression often have lower than normal serotonin levels. Chapter Four will highlight the relationship between serotonin and depression. While serotonin levels are clearly playing a role in the expression of depression, this thesis will express the complexity of depression that goes beyond a simple neurochemical deficit explanation.

The primary goal of this thesis is to better understand the benefits and pitfalls of common and emerging treatments for depression. Chapters Four through Eight will look at the effects of SSRIs, psilocybin, therapy, sleep intervention and exercise on individuals. I hope to use current research to find common trends each form of treatment has on individuals.

The brain is often compared to the hardwiring of a computer whereas the mind acts as the software (Chirimuuta, 2020). Although the hardware can be adjusted or damaged by manual manipulation, the software can be changed only through its use. For example, one could accidentally download a virus corrupting the computer’s hardware. If, however, this device was to be examined by physically inspecting the hardware, no damage would be observed, and the computer would appear to be functional, and closer inspection would reveal that the computer disproportionately was not functioning properly.

This analogy may be relevant to the treatment of depression in context. An individual afflicted with life disrupting depression might be assumed to be healthy based on traditional

medical approaches such as an MRI or CT scans, because the scans would not reveal any structural brain abnormalities. Because of the distinction between anatomical and psychological states of the human psyche, mental health is more than the physical brain itself. Mental health involves the mind. Diagnostic tools and clinical discretion allow healthcare providers the opportunity to investigate the software of the mind, providing more in depth, direct care.

To reduce one's mental narrative to the product of their decisions and environmental factors is to neglect the autonomy and free choice of the individual, reducing their long-term health to merely a product of their actions (Stanhope, *et al.*, 2013). In this thesis, my hope is not merely to identify singular habits or mindsets, but rather to provide an array of approaches and interventions that allow individuals to seek care that works for them even if it is beyond the traditional action plan most clinicians have prepared for depression. In the final Chapter, Chapter Nine, a call for "person-centered care," as proposed by the WHO and the Institute of Medicine, is emphasized as the main argument of this thesis (IOM; Rakel & Rakel 2016).

Entry Point

I experienced mild anxiety and emotional outbursts in high school and was immediately placed on prescription medication. My intuition knew that this was not a sustainable approach for myself as it created more anxiety within me to think that I would have to be on this medication for the rest of my life. Ever since this experience, I have always been interested in this form of psychological intervention. Many people have a subconscious voice in their mind, which can become disproportionately affected by external stimuli. Over time, the subconscious mind can influence the conscious mind in decision-making tendencies and perceptions of reality clinically referred to as thought distortions (American Psychological Association, 2017).

I have since come to realize that the emotions leading up to medical intervention are part of the human condition as they stem from deep-rooted empathy for others and fear of never being able to provide enough help and support for global issues. In my situation, it was not the emotions themselves that created my anxious or depressive state, but rather my views of them and my efforts to conceal them without further introspection. In my experience, emotions cannot be controlled as they act as an involuntary mental response to various conditions and stimuli. What can be adjusted, however, is emotional responsiveness, coping strategies, and perspective.

As I have come to be my own mental health advocate, I have realized that the lack of individualized mental health treatment and the need of the health care system to maximize productivity and efficacy have caused the psychological field to drift far away from person-centered care. This is not to say pharmaceutical intervention is not a viable option, but rather it does not have to be the only option. Through this thesis I hope to intrigue and inspire as I join the call for individual empowerment regarding seeking mental healthcare.

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“And as we do, struggling here and there, remember, there is nothing that can get between you and life’s deepest connection. Nothing, no matter how powerful, can ever take that away.”

– Casper Ter Kuile, *The Power of Ritual: Turning Everyday Activities into Soulful Practices*

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Chapter 1: Introduction to Depression

Depression is a condition often defined in scientific literature by one main criterion: anhedonia or “a lack of and/or a decreased capacity to experience pleasure” (Winer, *et al.*, 2019). Without the normal response to everyday activities and stimuli such as sunlight, food, movement, and social engagement, depression can make it difficult for individuals to uphold habits of selfcare, making recovery that much more difficult. Based on research, there appears to be an observable distinction in neural reward centers and reward response activation in individuals expressing depressive symptoms (Treadway, 2012). New research in neuroscience – merging the two historically separate disciplines of biology and psychology - is providing new insights towards the goal of a better understanding of depression's complexities (Altimus, *et al.* 2020).

Depression in Literature

Because of the internal nature of depression, the true patient experience cannot be denoted by clinical symptoms and checklists. Science is designed to be analytical and objective, which can make it difficult to embody the entire patient experience specifically considering that symptom expression differs in each person. For example, the major symptoms and effects of depression remain within an individual's mind, not only making it difficult to identify from an unfamiliar outside perspective but also difficult to treat adequately. Because a scientific description cannot capture the true gut-wrenching feelings one might experience when battling depression, I found it best to let the literature speak instead. Humans have such impeccable minds that they can mentally travel in time by recalling the past or planning the future. While this may seem like a skill, it can also become the gateway to feelings of anxiety and depression.

Within modern Western medicine there is a continuous effort to emphasize the individuality of patient experience and values to prevent inadequate healthcare (Tringale, *et al*, 2022). This could be due to the scientific method, requiring specific sets of groups to create an effective study and reducing individuals to one factor of 'n,' a single figure within a set sample size, as opposed to a person. Scientific research provides a universal lens to test a dependent variable's effectiveness against an independent variable to test and explore hypotheses. The trouble with this approach lies in the truth that people and their lives are not consistent across the globe.

Many people tend to live their lives lacking total fulfillment with the common mindset 'if it ain't broke, don't fix it.' Individuals struggling with depression are stuck in a negative lifestyle loop that is reinforced with behaviors that prevent the release of regulator neurotransmitters such as serotonin and dopamine (Cowen & Browning, 2015). When someone is caught in a pit of depression, activities like cooking, exercise, socializing, spending time outside, and other self-care activities can feel out of reach potentially due to the neural impairment of reward processing regions (Grahek, *et al.*, 2019). Activities like ordering fast food, watching TV, spending time inside and on social media, and canceling plans, feel more achievable.

While individuals experiencing depression may observe consistent symptoms as documented in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5, the causes or influences underlying these cases can be vastly different, potentially calling for a range of interventions and/or treatments beyond a standardized approach. The distinction between intervention and a treatment method comes down to effectiveness and application. An intervention typically involves an outside source providing advice or prescriptive change to the

patient, whereas a treatment is typically a self-sought form of symptom alleviation to instigate conditional combat.

The American Psychological Association have recognized the validity of personalized care in the 2019 *Clinical Practice Guidelines for the Treatment of Depression Across Three Age Cohorts*. These guidelines emphasize the importance of individualized care in the context of standardized practices. The DSM-5 is a series of diagnostic tools developed by the American Psychiatric Association to provide clinicians with universal diagnostic criteria for a variety of mental health conditions.

Oliver Sacks, the writer and neurologist, argues that “each of us is a singular narrative, which is constructed, continually, unconsciously, by, though, and in us—through our perceptions, our feelings, our thoughts, our actions; and, not least, our discourse, our spoken narrations” (Sacks, 1998). The loss of a patient's narrative can create emotional turmoil with the patient leading to potential distrust in their healthcare provider.

A classical literary piece for a discussion of mental health is the renowned *The Yellow Wallpaper* by Charlotte Perkins Gilman. Asking the question: 'If a physician of high standing, and one's husband, assures friends and relatives that there is nothing the matter with one but temporary nervous depression – a slight hysterical tendency – what is one to do?' The author expresses the experience many individuals have faced when seeking mental healthcare (Gilman, 1892). Because of the commonness of abuse and mistreatment of patients within mental healthcare found in a meta-analysis done by Shields and colleagues, the World Health Organization has implemented new human rights efforts across the field (Shields, *et al.* 2018, WHO, 2021). The blurry origins of mental health issues can be overwhelming potentially

resulting in the oversimplification and over-generalization of an individual's experience with depression.

The psychosis experienced by the patient in *The Yellow Wallpaper* is exacerbated by the fact that she is trapped in a room of yellow wallpaper, which could potentially represent the restriction that the label 'depression' may impact individuals recovering. Within the short story, she is described pacing around the room, melting into a wallowing psychotic state to mirror the cyclic catastrophizing that she experiences without receiving the help she seeks from proclaimed healthcare professionals.

Gilman uses this story to emphasize the historically inappropriate treatment of women within medicine as if they are a subset species of men with a lack of judgement and personal understanding. Commonly referred to as gender bias, this issue is still being systematically tackled within medicine today (Alcalde-Rubio, *et al.*, 2020). The existence of gender bias further exacerbates the dangers of overcategorization, especially in mental healthcare, as it prevents the individual from being seen, heard, and respected. The role of gender is a primary focus in Gilman's short story and something that plays a role in her slow decay into madness, but depression is not an exclusively a female experience. Male writers like Edgar Allan Poe and Ernest Hemingway struggled with depression as well and express their experiences through their works (Boyd, 2020; Marckel 2020).

In the novel *Garden of Eden*, Hemingway writes, "Happiness in intelligent people is the rarest thing I know," which implies that intelligence can hinder one from experiencing happiness (Hemingway, 2014). To his point, one study found higher intelligence in youth to be associated with a reduction in self-reporting symptoms at age fifty potentially due to an over intellectualized

of emotions (Wraw, *et al.*, 2016). More specifically, the presence of chronic health conditions like diabetes also played a role in his depression onset (Herrera, *et al.*, 2021).

Edgar Allan Poe struggled with depression and substance abuse for most of his life, often turning to various vices to seek sanity. In a letter to a correspondent, he described his mental state as a “horrible never-ending oscillation between hope and despair which [he] could no longer have endured, without total loss of reason” (Poe, 1848). The shuffle between hope and despair is not uncommon when struggling with depression and provides a realistic example for how discombobulating and nonlinear recovery can be.

A recent publication, the memoir *Girl, Interrupted* deconstructs the implications of societal standards on the development of adolescent females into young women (Kaysen, 1993). The depressive impact of patriarchal standards on individuals that do not want to comply with the future planned for them comes to life in the lead character, Susanna. After a suicide attempt, Susanna is forced into a treatment center, which provides her with influences from other young women attempting to escape various expectations and standards placed upon them.

The lead character in *Girl, Interrupted*, is released from the center after having a realization that she is in fact in more control over her life and emotional state than she previously let on. The transition from adolescents into adulthood can bring upon a power struggle between parental guidance and internal intuition that at times can manifest as depression. When an individual feels as if they are living on the whim of others’ opinions or societal standards it can deprive an individual of their free will and self-expression.

The loss of individuality and control experienced by the lead character in *Girl, Interrupted* is reflected in the poem by Anne Sexton, *You, Doctor Martin*. The experience of slowly losing oneself to a facility designed to heal, Saxton writes, “I am queen of all my sins

forgotten. Am I still lost? Once I was beautiful. Now I am myself counting this row and that row of moccasins waiting on the silent shelf.” (Sexton, 1960). The overwhelming feeling of forgetting oneself in pain weaves its way through Sexton’s work, as the unnamed patient losing all self-confidence and train of thought as they begin counting rows of shoes that represent the patients surrounding her struggling in silence waiting for eternal release.

In her famous manifesto, *The Bell Jar*, Sylvia Plath explores the complexity of womanhood in a patriarchal society: “Sometimes we impose our thoughts upon the young. Why should not she see the whole book as an exciting story?” (Plath, 1963). While comparing one’s life to a book is not a unique notion, the recognition that viewing one’s life as an ‘exciting story’ as opposed to tainting it with externally imposed notions can allow someone to see themselves and their path as whole and beautiful. The common flow of literature typically requires a protagonist, mission, roadblock, and character development. Without components like those, literature would lack luster. Plath questions why the bildungsroman of youth cannot have the same artistic complexity.

Using literature from historic and current sources provides an introspective view of the patient's experience to better understand depression from a third person perspective. These authors and others have given voice to those afflicted with depression for hundreds if not thousands of years. Because an in-depth understanding of depression requires a historical perspective, the next chapter will consider the scientific history of depression.

Chapter 2: Historical Context

The notion of predetermined neural connections and infrastructure was a common perspective shared among most scientists in the preliminary stages of neuroscience during the 1800s. This notion was first challenged in 1911 by psychiatrist, Emil Kraepelin, when he argued that depression did not lead to permanent impairment as thought by his peers (Ebert & Bar, 2010). As the historically oppressive ramifications of the lack of research and clinical representation come to the forefront, treatment methods can be more effective and malleable based on the patient's needs. For example, for women the additional consideration of menopause or the use of hormonal contraception must be considered when determining the cause of a depressive state or prolonged emotional distress (Vivian-Taylor & Hickey, 2014; Fruzzetti & Fidecicchi, 2020)

Pharmacology within Mental Healthcare

Institutionalization typically prevents individuals from healing. Collectively, the need for integrative healing has been acknowledged in the previous literature making the overall claim that “you cannot find peace by avoiding life” (Cunningham, 1998). With the invention of more effective anti-depressants and more holistic mental health research intuitions in the United States, institutionalized long-term care steadily declined.

It is routine for individuals seeking professional help, especially in the United States, to be prescribed anti-depression medication after sharing signs of mental health concerns, especially among female adults. Spanning back to the use of "mother's helpers" beginning in modern America in 1963, Americans have learned to depend upon pharmaceutical medication to mediate intense feelings of anxiety, depression, or worthlessness (Atkins 2022). According to a brief released by the National Center for Health Statistics in 2020, the use of antidepressants

among female adults in the United States between the years of 2015-2018 has increased significantly enough to show an overall increase in usage for the total population (Brody & Qiuping, 2020).

In contrast, the National Institute of Mental Health (NIMH) has noted that there has been no significant increase in the use of antidepressants within the male population (NIMH, 2023). The difference in antidepressant use among the sexes could be due to a couple of factors. The mental health stigma around men could be preventing them from disclosing symptoms of depression and seeking proper mental healthcare, yet further studies are necessary (Mckenzie, 2022). This trend could also be related to the continuation of the historical mental healthcare view by professionals of women as hysterical. It is also possible that more women than men suffer from depression on a molecular level.

While the main argument of this thesis emphasizes the importance of personalized mental healthcare, understanding the social and societal context of the field of psychology is critical to interpreting treatment use in modern clinical settings. Without historical context, statistics reflecting the mistreatment and lack of representation of women and individuals of color would be lacking a significant explanation. The historically racist and patriarchal structure that nursed Western medicine into fruition is slowly being recognized and reconstructed, but the ramifications of those structures do not go unnoticed by marginalized patients (Seng, *et. al.*, 2012). Generational trauma is not something that can be consolidated into the treatment of a singular patient or diagnosis – it requires treating society. Because societal intervention is not the most realistic form of care, focusing efforts on the individual and their psychological needs can provide a more concise treatment plan.

Within the past decade, the field of neuroscience has taken a significant turn not only in understanding of the human brain and fruition of thoughts but also the understanding of the function and coordination between neurons within the brain (Altimus, *et al.* 2020). The concept of a “fixed verse growth mindset” has been a key factor in understanding the human mind (Dweck & Yeager, 2019). Having a “fixed mindset” implies that an individual believes they have no autonomy or authority over skill sets whereas a growth mindset is a mental state where an individual feels autonomous and empowered to use intentionality to learn new things and grow beyond their current state.

For the past 50+ years, studies have found that the brain is highly adaptive and will tailor an individual's experience to the environment (Akil & Nestler, 2023). Understanding the role of intentionality can potentially not only change the messaging of the subconscious mind but influence the connection and communication between neurons.

Diagnostic Tools

Currently the DSM-5 is the most accurate and reliable and foremost tool to diagnose mental health conditions such as depression. Throughout its clinical use, this diagnostic manual has received criticism and revisions as psychology adapts to new scientific findings (Lasalvia, 2015). The historical narrative around depression has created a binary diagnostic decision that often limits the expression of an individual's experience – leaving diagnosis to an affirmation or denial of the presence of depression. The presence or absence of certain behaviors listed in the DSM-5 assessment criteria determine the validity of a diagnosis. With the subjective nature of emotional experiences, it can be difficult to capture an individual's mental state. That is not to say it is impossible, despite the many revisions and editions of the DSM, to provide an encompassing description of depression. Clinical discretion is also pivotal in the diagnostic

process for many reasons, one of which is the variation in vernacular between population groups as terminology used by individuals can vary based on a multitude of demographic identities. Psychologists must make a significant effort to understand their patients while developing a holistic understanding of who their client used to be before the onset of depression (Meyer, *et al.*, 2021).

According to the 5th edition of the DSM-5 “The individual must be experiencing five or more symptoms during the same 2-week period, and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5. Fatigue or loss of energy nearly every day.
6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide” (American Psychiatric Association, 2013).

This style of assessment has the potential to lead into psychological stereotypes of what it looks like to have depression, causing individuals to seep through the cracks of care if the criteria does not represent their experience. For example, an individual that is the primary breadwinner for their household may have depression, but symptoms like indecisiveness or slowing down may not apply. The distinction of having five out eight criteria could still include the breadwinner, but if they only meet four out of eight criteria, would they automatically not receive a diagnosis? Here lies the importance of clinical discretion. Furthermore, emotional tolerance varies between individuals, and those chronically struggling may denote symptoms like

fatigue or guilt. One study, done in China analyzing the misdiagnosis of bipolar disorder found that out of one-hundred seventeen cases in an outpatient population 70.6% were misdiagnosed as depression (Shen, *et al.*, 2018).

Because this study was done outside of the United States it can serve as an example for the influence culture can play on diagnostic trends. The lack of representation of various identities, genders, and races in psychological research can negatively influence the foundation for all clinical practice and intervention. Miller and Adams (2021) cataloged examples of the lack in inclusivity in psychological research and argued that psychological research must take a more expansive approach (Miller and Adams, 2021).

Due to the possibility of human error in the practice of psychological intervention, it is no wonder that an emphasis is placed on identifying and eliminating personal bias within the mental health field (Snowden, 2003). As the public and professional discussion widens regarding the role healthcare professionals play in health disparities across medical disciplines, researchers like Gonzalez and colleagues are providing educational materials and guidance to healthcare workers at large with the hope of improving care for women and minority groups (Gonzalez, *et al.*, 2021). Many mental models and factors such as bias are at play in an individual's mind, including mental health professionals.

Implicit bias, which often manifests subconsciously, can be difficult to detect in oneself and can uphold stereotypes. In comparative study of 599,421 individuals, the African American and Hispanic populations were found to have lower rates of depression treatment when compared to the Caucasian population (McGregor, *et al.* 2020). There are many systematic components affecting the access and application of effective treatment, one of which is social stigma within the healthcare system (McGregor, *et al.* 2020). Research has found that cognitive

behavior therapy (CBT) can be a technique used to work on overcoming bias experienced by health care professionals (Woud & Hofmann, 2023). CBT can allow mental health professionals to overcome unfair and unjust bias that may plague their work, preventing their clients from receiving a justified diagnosis and adequate treatment (Prieto, 2021).

In psychology, there is an important distinction between clinical discretion and personal judgement. Clinical discretion relies on scientific reasoning whereas personal judgement involves bias and opinion. Mental health professionals are human and will build a natural rapport with some patients, but not necessarily with everyone. Finding a mental health professional that matches the aspirations and needs of the patient is crucial in effective care.

Often discussed in scientific and professional communications, confirmational and blind spot biases are consistently prevalent in highly educated individuals (Kenski, 2016). Because professionals have above-average knowledge of a specific topic, they can find sources and information to reinforce their opinions even if that causes them to neglect essential information. While confirmational and blind spot bias can be observed in everyday life, research has shown that individuals are more likely to consider the strength of an argument when it is confirmatory or in alignment with their own opinions (Kappes, *et al.*, 2019). The Kappes paper suggests that the participants may not have paid as much attention to alternative viewpoints – preventing themselves the opportunity to objectively reflect. Their study further emphasizes the value of mindfulness and bias consideration when receiving additional information or forming a diagnosis or treatment plan.

That is not to say, however, that there is no place for labels within psychological care, as they can provide individuals with a term to describe their current state, leading to more effective treatment and care. Some clinicians explicitly state that a diagnosis does not inflict an immutable

identity upon the individual, but rather it is used to predict future feelings and behavioral trends (Windham & Vernoy, 2022). In the case of depression, the treatment goal is to reduce or even terminate depressive symptoms.

Chapter 3: Neuroplasticity Mechanisms That Could Underlie Depression

This section provides a current overview of potential hypothetical neuroplasticity mechanisms that could underlie depression. It is important to note at the outset that there has been no direct link between the neural plasticity mechanisms described in this chapter and depression. There has, however, been much speculation among neuroscientists and psychologists that mechanisms like these might be involved in depression. By better understanding the following mechanisms, the function of the brain in depression might be revealed. A caveat: one should not infer from my thesis that a deficit or malfunction within these mechanisms is the cause of depression. Instead, my thesis argument is meant to illuminate the potential involvement of these systematic distortions' role in a greater network of influences.

Long-Term Potentiation and Long-Term Depression

The study of neural plasticity is an important subarea within neuroscience. Its premise is that the brain can grow, withdraw, or alter neural connections based on input specific interactions. Both Long-Term Potentiation (LTP) and Long-Term Depression (LTD) are well known cellular mechanisms that have been proposed to explain how the brain learns and creates memories. It is important to emphasize here that LTD is a completely different concept than depression. In this study, LTD will be used to refer to a specific cellular neurobiological process, and depression will refer to the mental condition. Both LTP and LTD work in a positive feedback loop: a self-reinforcing, cyclical process leading to an increase in the result of neural growth or depression, respectively.

Both LTP and LTD work at the level of a synapse, the connection point in the nervous system between neurons. A synapse is where chemical information, in the form of a neurotransmitter, is sent from a sending or pre-synaptic neuron to the receiving or post-synaptic

neuron. In LTP, once sending or pre-synaptic neuron is initially excited, the post synaptic or receiving cell will continue to provide positive feedback to the pre-synaptic cell, enhancing the connection between the two neurons. The synapse will remain strengthened for hours or sometimes days.

Current research on LTP is using a variation in stimuli intensity to better understand how cells respond to LTP-inducing stimuli. In figure 1 the intensity of signaling response in relation to the stimuli can be observed between pathways 1 and 2 as the amplitude of the pathways varied in response to frequency level (Purves, *et al.*, 2001). Pathway 1 is provided with a high stimulus whereas pathway 2 is provided with a control level of stimulus. As seen in graph B there is a higher response within pathway 1 over fifty milliseconds when compared to pathway 2. Furthermore, in figure C spanning across a one-hour window, the heightened stimulus response in pathway 1 is observed to remain at a heightened level even sixty minutes after the stimulation. Pathway 2 remains constant throughout the one-hour period appearing to reach baseline around seventy-five milliseconds as seen in graph B.

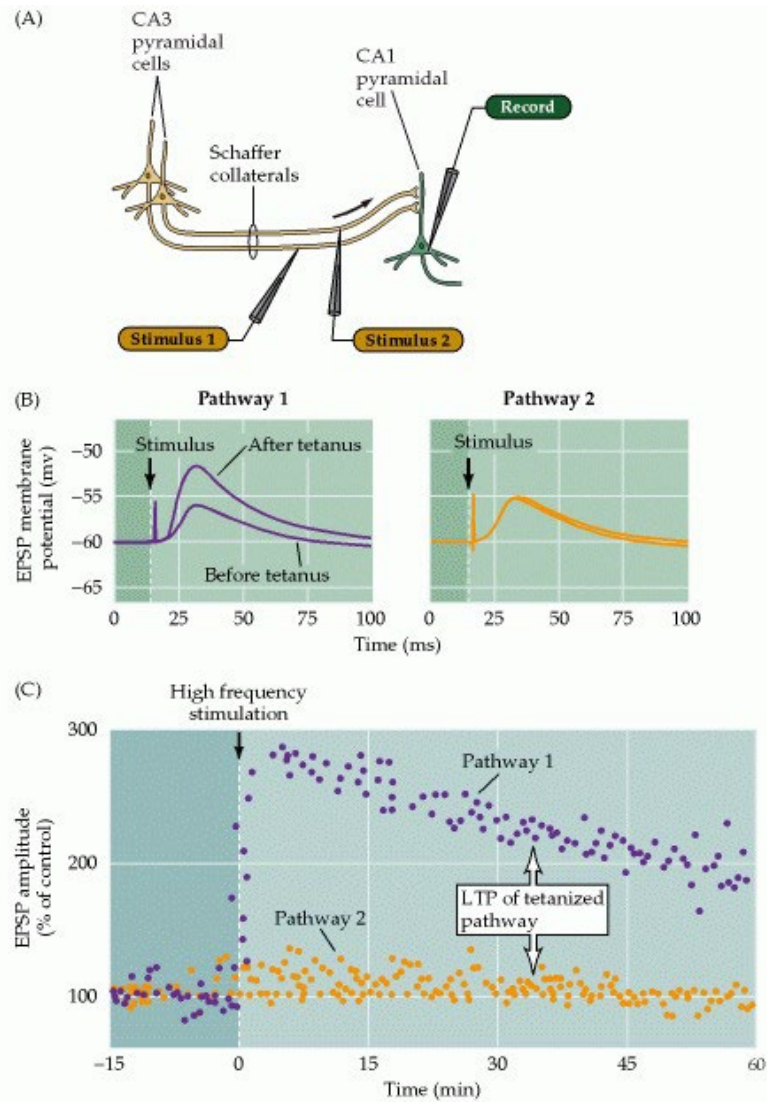


Figure 1: Long-term potentiation of Schaffer collateral-CA1 synapses.

(A) Setup for measuring nerve cell communication (B) Left: Pathway 1 nerve response recorded after a high-frequency stimulation showing increased activity with the heightened spike nearing -50. Right: Pathway 2 did not get high-frequency stimulation, and there was no change in activity as the spikes remained at the -55 mark. (C) High-frequency stimulation of pathway 1 led to long-lasting increased activity as shown by the heightened dots after zero minutes (purple), activity in pathway 2 (orange) remained unchanged with no initial stimulation. (After Malinow *et al.*, 1989.) (Purves, *et al.* 2001)

In contrast to LTP, LTD occurs at a synapse when it has not been excited by the pre-synaptic cell. The lack of stimulation causes the synapse to weaken. Because this process utilizes

positive feedback, a synapse that is experiencing LTD will continue to be depressed unless it is excited by another presynaptic cell. LTD can result in the loss of synapses due to the long-term lack of input.

LTP and LTD are examples of neural plasticity mechanisms that, in theory, might underpin the ability of a person to grow beyond a current mental self through therapies such as dialectical behavioral therapy (DBT) and cognitive behavioral therapy (CBT). These molecular mechanisms might allow individuals to develop emotionally and intellectually; however, the linkage between what occurs at the cellular and molecular levels and the behavior of an individual is far from understood.

Although the original studies on LTP and LTD were performed on cells in a region of the brain known as the hippocampus, subsequent research has shown that both mechanisms are found in many other brain regions, suggesting that these mechanisms occur throughout the brain (Mulkey, *et al*, 1994; Bear & Abraham, 1996; Massey & Bashir 2007). Although completely speculative at present, it is possible that in the future intentional manipulation of specific neurons to evoke these mechanisms could allow individuals to create or disrupt connections in memory, potentially helping individuals recover or move past a traumatic loop causing their depression (Lever, *et al.*, 2002).

Another trait of LTP at synapses is association, which enhances another synapse on the receiving cell if it is close to the synapse that was originally activated (Yang, *et al.*, 2019). This phenomenon could be one of the underlying mechanisms that permits the human brain to create even more connections and generate new, learned behaviors.

One type of learning which might utilize LTP is classical conditioning, a type of associative learning in which two stimuli, one that elicits a behavioral response and the other that

is originally ineffective, are presented together. After multiple repetitions of the two stimuli together, it is often the case that the ineffective stimulus becomes “conditioned” and triggers the response in the absence of the other stimulus (Spielman, 2020).

Pavlov performed the traditional example of classical conditioning. He did an experiment in which he showed his dogs a piece of meat which caused them to salivate. After multiple trials in which he paired the ringing of a bell with the presentation of meat, the dogs began to salivate to the sound of the bell without the presentation of meat (Rehman, *et al.*, 2023). The dogs associated the bell ring with the presentation of meat and thus learned to produce the salivation response only to the bell's sound.

LTP and LTD might underpin classical conditioning and provide a possible explanation for how individuals can create links between experiences and information regardless of how factual the connection may be in the physical world. Research has yet to elucidate the role of LTP and LTD in other complex cognitive processes but that does not mean they do not have potential roles in higher cognitive functions.

Based on much research on LTP, LTD and other forms of neural plasticity, the malleability of the brain to create physical connections from external input can be extremely beneficial. However, making mental short cuts regarding the stimulus from the outside world can also lead to irrational fears or behaviors. Associative learning is the process in which an individual consciously or subconsciously uses context clues and worldly experiences to develop a biological and psychological response to certain stimuli. For example, if an individual grew up associating the sound of an abusive guardian arriving home with mistreatment, they may still feel uneasy hearing the distant sound of the front door or garage opening when living with others. Furthermore, that same individual may unlearn that response after moving in with someone more

supportive and may associatively begin experiencing a sense of relaxation or excitement when hearing them arrive home.

Although this example discusses a specific situation, the aftermath of various associative processes could over time contribute to a depressive state. Depression is almost certainly the result of a variety of factors, yet the distinction between causation and correlation is essential. Correlation is a statistical term that implies connection between two variables whereas causation implies a confirmed cause and effect relationship.

A zero-order correlation has been noted between the number of adverse childhood experiences (ACEs) occurring within an individual's lifetime, exposure to stress, and the onset of depression (Hammen, *et al.*, 2000). Because this study did not control for any variables outside of the predetermined testing variables, the zero-order classification applies. The research does not suggest that ACEs always cause depression, however they have been found to have some statistically correlated with depression in many instances (Desch, *et al.*, 2023). A study by Hammen and coworkers (2000) suggests that individuals experiencing high stress conditions have an increased potential of depression onset ($p= 0.045$) independent of ACEs. Individuals experiencing low stress conditions that have also experienced major adversity are more likely to become depressed ($p= 0.045$; Hammen, *et al.*, 2000).

One effect of ACEs is that they can cause individuals to experience a suppressive response within their reward pathways potentially heightening the threshold needed to elicit a reward response (Casement *et al.*, 2018). Reward pathways are brain areas that activate when an individual is anticipating or receiving a reward. In 2018, Casement and colleagues hypothesized that the activity in two brain regions, the medial prefrontal cortex (mPFC) and the ventral striatum (VS), should be monitored using functional Magnetic Resonance Imaging (fMRI) in

depressed adolescent girls. The mPFC is a region of the brain associated with social and reward processing while the VS is involved in the generation of positive emotional responses in the neural circuit known as the dopamine reward pathway (Casement *et al.*, 2018).

Casement *et al.* (2018) found that the activity of the mPFC and VS were reduced in 16-year-old depressed females who were in families with minimal parental warmth. They postulated that there may be a positive relationship between low parental warmth and the appearance of depressive symptoms (Casement *et al.*, 2018). The results of the Casement study suggest that throughout child development individuals have associative learning processes. An individual's ability to anticipate potential rewards and respond positively potentially stems from the perspective gained throughout childhood development.

To better understand the reward process during childhood, researchers are actively working to determine where in the brain these processes occur and how childhood trauma plays a role (Hanson, *et al.*, 2016). One study found that when exposed to a rewarding scenario, individuals who experienced a traumatic event early in life, specifically between kindergarten and third grade, exhibited decreased activation of the VS (Hanson, *et al.*, 2016).

The hypothesis that early childhood may influence the later appearance of depression is supported by a 2019 meta-analysis, which showed that the onset of depression was associated with all five forms of child maltreatment studied (Garder, *et al.*, 2019). Child maltreatment can manifest in many forms such as sexual abuse, physical abuse, emotional abuse, neglect, and exposure to intimate partner violence (Garder, *et al.*, 2019).

As children become adolescents, many typically begin to solidify their self-identity (Pfeifer & Berkman, 2018). This is followed by the transition to adulthood, and it is at this stage that conditions like depression begin to rise partly because the shift from adolescence to

adulthood can be unpredictable with new responsibilities. According to the CDC in 2019, the age range with the highest rates of depression was 18–29-year-old emerging adults, with 21% of the total cases of depression in the United States (Villarroel, M & Terlizzi, E., 2020).

How people learn to process or overcome a traumatic response varies (Center for Substance Abuse Treatment, 2014). The underlying mechanisms may involve LTP and LTD in areas of the brain associated with social processing and reward function such as the mPFC and ventral striatum. Although, to my knowledge, there is no current research that is testing this hypothesis, this hypothesis provides a promising approach for future studies.

Brain Derived Neurotropic Factor

While the research to better understand how the brain can make new neural pathways and connections is still in pilot stages, one particularly fascinating compound, Brain Derived Neurotrophic Factors (BDNF) has been implicated in the facilitation of neural plasticity. BDNF was first identified in 1982 as a factor involved in maintaining neuron signaling (Barde, *et al.*, 1982). More recent studies have demonstrated that BDNF may also impact neural activity in the brain cells (Song, *et al.*, 2017). BDNF has been linked with depression and neuroplasticity when dysregulated or decreased and has been associated with LTP, the process discussed earlier in this chapter. (Yang, *et al.*, 2020).

Figure 2 shows a simplified, hypothetical chain of events regarding the influence of BDNF on synaptic plasticity and the onset of depression (Yang, *et al.*, 2020). Research has found an inverse correlative relationship between the expression of BDNF and intensity of depression (Yang, *et al.*, 2020). In a postmortem brain analysis, Guilloux *et al.* (2012) identified a decreased expression of not only BDNF in the presence of stress, but also a reduction in the levels of its corresponding receptor in the samples of depressed patients (Guilloux, *et al.*, 2012). Given the

low sample size, the use of post-mortem brains with substantial cellular and molecular degeneration, and the lack of controls, the results from the Guilloux study must be viewed as preliminary and call for further exploration.

The three molecular mechanisms – LTP, LTD and BDNF – together provide groundwork mechanisms within the brain for further exploration of their involvement in depression. It must be noted that even if these processes are involved in depression, they are a small subset of the many components connected to the onset of this disorder. By furthering the understanding of mechanisms within the brain, therapies and treatment methods can become more effective with fewer risks or side effects. Neuroplasticity provides hope for those experiencing depression and the potential for long term neural change.

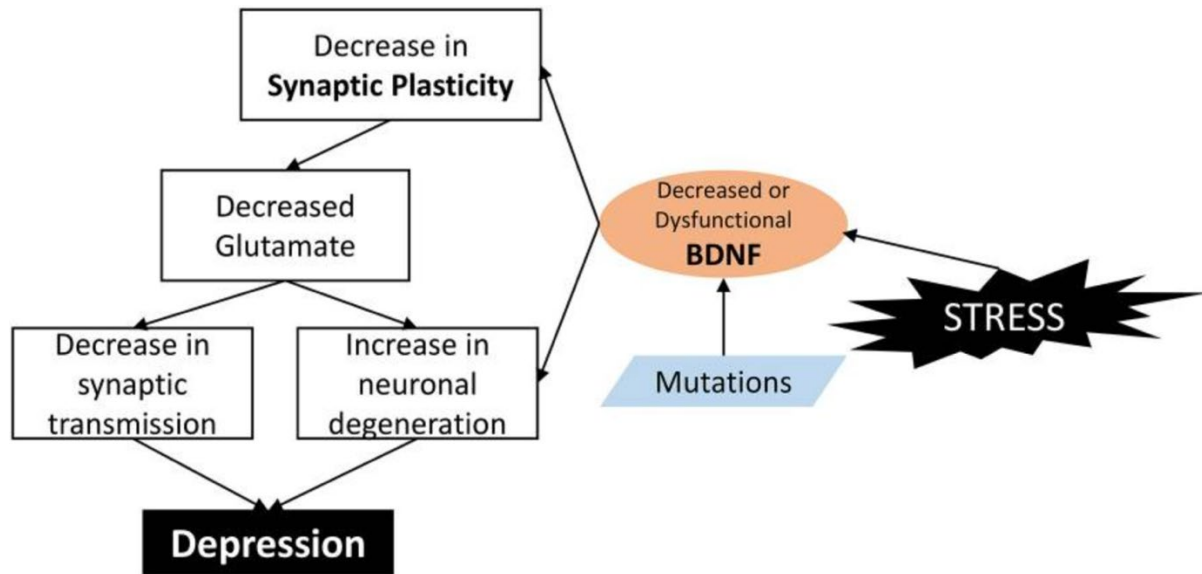


Figure 2: How alteration of functional BDNF results in depression.

BDNF is a molecule involved in the control of synapse formation and regulation of changes in synapse structure and function. BDNF stimulation increases synaptic spine density. Dysfunction or decreased BDNF leads to malfunction of synaptic plasticity; and eventually leads to depression (Yang, *et al.* 2020).

Chapter 4: Selective Serotonin Re-Uptake Inhibitors (SSRIs)

There is a clear debate over the rise of mental health conditions within society. Some speculate that these discussions come from more awareness and destigmatization of mental health concerns, while others suggest that industrialization and financial emphasis within the community creates constant self-doubt and lack of social and emotional fulfillment (Pescosolido, *et al.*, 2021; Wulsin, *et al.*, 2014). Regardless of the root of these conditions and feelings within individuals, there is a wide array of methodologies and practices used to reduce or treat these conditions.

Many studies are working to determine the effects of typical medication such as SSRIs and other on- and off-label antidepressants. Other research is focused on alternative therapies such as exercise, dialectical behavior therapy (DBT), and psilocybin, all of which are purported to provide a holistic long-term effect and which will be discussed in later chapters (Edinoff, *et al.*, 2021; Cowen, 2023). Part of the reason that SSRIs became the gold standard in depression treatment is the fact that historically, research has shown a transmitter imbalance in depressed patients, with a specific emphasis on a deficit in the neurotransmitter serotonin or 5-hydroxytryptamine (5-HT; Ebert & Bar, 2010). Studies such as these paved the way for the development of SSRIs as a treatment for depression.

Because of the growing need for effective mental health treatments, many individuals are turning to the use of SSRIs to manage the symptoms of several mental health conditions including anxiety, depression, bulimia, anorexia, and other psychological disorders (Chu and Wadhwa 2023).

As discussed in the Entry Point and Introduction, part of the human experience is occasional the inappropriate judgment within decision making potentially due to the interplay of

emotions and bias (Perez, *et al.*, 2021). This pertains to the neural circuitry that evokes perception within an individual (Merfeld, *et al.*, 2015). The premise that individuals are likely to fall into patterns of routine, regardless of whether they are beneficial or harmful to their overall health plays a role in the questions being asked about neural plasticity. It is unclear whether the noticeable variation in neural functionality of depressed individuals is the cause or an effect of depression.

The primary way to adjust these neural pathways is to actively work against negative and harmful thoughts and implement goals to create healthier habits and perspectives (Berkman, 2019). In one meta-analysis, the implications of fluoxetine, a common SSRI, and physical exercise were compared across various neurological and mental health conditions including depression (Micheli, *et al.*, 2018). Regarding creating new neural pathways and networks, the research studied rodents and found that long-term cardiovascular enhancement programs such as running were comparable to fluoxetine as they both increased levels of BDNF (Micheli, *et al.*, 2018). Not only does that result underscore the role BDNF may play in symptom alleviation, but it also creates a connection between SSRIs and their potentially positive influence on neural plasticity.

The ability to enhance neural plasticity in rodents occurs through an increase in dendritic complexity and number of spines, which are the location of synapses (Micheli, *et al.*, 2018). The denser and more complex the dendritic spines, the more neural space and connectivity neurons will have across a given area (Runge, *et al.*, 2020). Even though this study was done on animal models, it suggests that the same neuroplastic mechanisms might occur in humans.

One of the primary initial treatment recommendations for individuals experiencing depression within the United States is to prescribe SSRIs with the goal of regulating the

emotional experience of patients (American Psychiatric Association, 2013). Currently, there is evidence suggesting the connection between serotonin and reward responses, which can impact an individual's emotional state (Michely, *et al.*, 2020). Yet, there is no definitive causal evidence that depression is simply due to a neurotransmitter imbalance. Rather, it is equally possible that this imbalance is a symptom of depression rather than a direct cause (Cowen & Browning, 2015). A recent meta-analysis published in the scientific journal, *Nature*, challenges the serotonin theory, which argues that individuals with depression simply have lower concentrations of serotonin in the brain (Moncrieff, *et al.*, 2022). Because of the findings relating SSRIs to the functionality of multiple mechanism beyond serotonin receptors such as dopamine receptors and BDNF levels, it is possible that this medication provides more therapeutic effects than previously understood (Kobayashi, *et al.*, 2012, Moncrieff, *et al.*, 2022).

Neuroscientists are still uncertain of the true mechanism(s) that SSRIs use to achieve their effects. Historically, SSRIs were believed to aid in the prevention of serotonin uptake at the synapse for individuals lacking a normal serotonin level as depicted in Figure 3. In this model, SSRIs cause serotonin to remain in the synaptic cleft instead of being reabsorbed by the pre-synaptic cell or broken down by enzymes. Because of the synaptic changes observed in LTP, the effects of SSRIs on synapses must be re-considered in further research. Hypothetically, if serotonin is more bioavailable in the synapse, then the post-synaptic cell will potentially create more serotonin receptors in response. Although this is purely speculative, given the receptor changes neurons undergo in other stimulations it is possible that serotonin receptors will be upregulated in response to higher serotonin levels (Kobayashi, *et al.*, 2012 & Salvan, *et al.*, 2022). This upregulation phenomenon has been observed in nicotine users as neurons will

increase the nicotinic receptor count in response to higher levels of nicotine in the brain (Henderson, 2019).

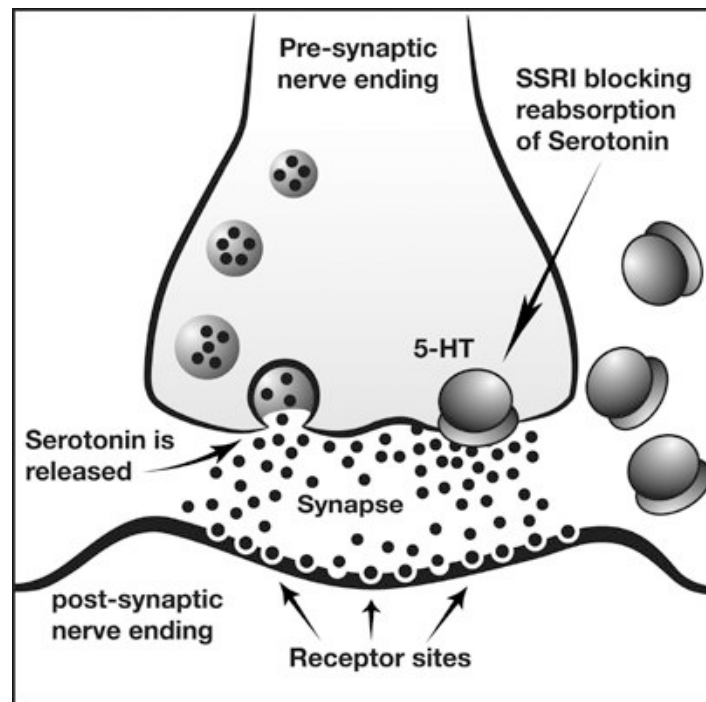


Figure 3: Diagram of a synapse in relation to serotonin release and SSRI functionality.

Serotonin is released from the presynaptic nerve-ending into the synaptic cleft. From the synaptic cleft the serotonin binds to receptor embedded in the post synaptic nerve. SSRIs block serotonin from reabsorbing into the pre-synaptic cell increase the chance of binding to the post synaptic receptors (Lattimore, et al., 2005).

A recent brief regarding antidepressants from the Centers for Disease Control published in September 2020 found that between 2015 and 2018, 13.2% of adults used antidepressants in the past month (30 days), which translates to over 1 in 8 Americans using pharmaceuticals (Brody & Qiuping, 2020). It is important to consider that these data could include patients using antidepressants for off-label use. Also of note, this information was collected before the COVID-

19 pandemic, which exacerbated symptoms of mental illness. According to the World Health Organization, the COVID-19 pandemic contributed to a 25% increase in the prevalence of anxiety and depression globally (WHO, 2023). One might wonder if this trend continues, will society reach a point where many individuals depend on pharmaceuticals for emotional regulation?

While effective treatment is essential for ensuring the quality of life for someone with depression, a societal dependence on pharmaceuticals limits the potential for total recovery from depression. SSRIs have been seen to lead to some degree of withdrawal-like symptoms upon their cessation, making the transition of medication a challenge (Davies & Read, 2019). Allowing individuals to be reliant on a medication may result in a heightened potential for the development of psychological treatment dependence. This is especially relevant if patients experience withdrawal symptoms when attempting to terminate medication (Chiappini, *et al.*, 2022). For example, an individual may desire to end SSRI use due to the range of adverse effects including an increased risk of suicidality in children and young adults aged 18–24 (Edinoff, *et al.*, 2021). Because of this predicament, SSRI use can be controversial, specifically as an indefinite treatment, which underscores the importance of conjunctive therapy alongside medication use.

The overall mechanisms of why depression occurs, as well as how SSRIs work, are still not fully understood. Likewise, psilocybin has been seen to improve symptoms and potentially 'cure' depression in some individuals without the need for long-term daily use (Smigielski, *et al.*, 2019). Because cure is a definitive state, I used quotes to denote the potential for relapse and the undefined rates of lifelong effectiveness. Both molecules have been used to chemically aid in symptom relief in individuals with depression.

However, SSRIs require habitual use, whereas psilocybin, the subject of the next chapter, can be used in a shorter timeframe for longer-lasting relief (Santos & Marques, 2021).

Chapter 5: Psilocybin

In the 1950s and 1960s so called “magic mushrooms” were all the rage among a subset of the population for their healing properties, after Robert Gordon Wasson published a piece in *Time* magazine discussing his experience during a traditional Mazatec ritual (Wasson, 1957; Zeiss, *et al.*, 2021). These fungi contain a chemical identified as psilocybin. This compound been investigated and found to create a euphoric state where individuals felt as if they were able to create connections better and understand themselves and the world around them better (Mortaheb, *et al.*, 2024). Psilocybin can aid individuals with terminal illnesses who are anxious about the idea of death and what may happen to them after death (Yu, *et al.*, 2021).

Unfortunately, after the war on drugs began in the late 1970s, psilocybin research was halted. As rates of clinically diagnosed SSRI treatment resistant depression rise in the United States, psilocybin research is beginning to bloom again in hopes of providing another scientifically backed treatment method (Zhdanova, *et al.*, 2021). Treatment resistance is difficult to definitively declare with entire certainty because there are a range of SSRIs that could provide a variation of the magnitude of relief experienced (Stein, *et al.*, 2021).

Although psilocybin therapy is not covered by insurance, which limits access and large-scale implementation, individual testimonies provide a basal level of understanding for the personal benefit this therapy can provide. Psilocybin treatment appears to give individuals space to consider their habits and routines along with more deep-rooted issues such as personal beliefs or traumatic experiences (Breeksema, *et al.*, 2024). Considering these life details in a slowed relaxed state can help people to comprehend past events and their current effects on the present without feeling the need to escape or distract from the emotions they experience in everyday situations (Johannesdottir & Sigurdsson, 2022).

Individuals seeking psilocybin therapy will typically schedule several initial sessions with a provider to mentally prepare them for the psilocybin experience, including ensuring a proper dosage and safe environment (National Center for Complementary and Integrative Health). In some cases, some individuals may be eligible to engage in clinical research with psilocybin if certain conditions or criterium are met, which vary given the research objective (National Institute of Health).

In a study done by Carhart-Harris, *et al.* (2018), participants were found to have a positive outcome from psilocybin treatment with a reduction in depressive symptoms at five weeks, three and six months later using a self-rated QIDS-SR16 questionnaire. The QIDS-SR16, a 16-prompt questionnaire used to self-assess symptoms of depression within the past week (National Institute on Drug Abuse, 2016). Limitations of this study include the low, 26-person sample size. This study focused exclusively on female participants, a substantial benefit to the field because historically, psychological research used men as the default group.

The Carhart-Harris study was also notable because it was performed using women who had previously sought more classical pharmaceutical treatment and had been clinically determined to be treatment resistant to SSRIs (Carhart-Harris, *et al.*, 2018). Even though SSRI treatment is the gold standard for depression care, psilocybin is emerging as a treatment method that can be effective in individuals unable to obtain successful results with SSRIs. Carhart-Harris and colleagues followed up their 2018 work with a double-blind, Phase 2 clinical trial on fifty-nine patients comparing psilocybin to escitalopram, a frequently prescribed SSRI commonly known as the brand names Lexapro and Ciprallex (Carhart-Harris, *et al.*, 2021). Using the QIDS-SR-16 self-reporting assessment tool, researchers measured depression symptoms within the past week scoring scale with scores ranging from 0-27 (National Institute on Drug Abuse, 2016).

Initially, the mean scores at baseline were 14.5 in the psilocybin group and 16.4 in the escitalopram group before receiving their respective treatments (Carhart-Harris, *et al.*, 2021).

After the experimental treatments were completed, each group experienced a substantial decrease in scores and symptoms six weeks into the trial (Carhart-Harris, *et al.*, 2021). The psilocybin group's average score decreased by -8.0 ± 1.0 points to 6.5 ± 1.0 and the escitalopram group's average score decreased by -6.0 ± 1.0 to 10 ± 1.0 (Carhart-Harris, *et al.*, 2021). The major decline in depressive symptoms provides promise for both forms of treatment as the researchers call for larger and longer trials as the overall significance of the treatment groups within this small study was negligible. The positive anecdotal reports about the effectiveness of psilocybin in treating depression, including those patients with SSRI resistant depression, suggest that this form of depression treatment should be the subject of future research studies.

Chapter 6: Therapy

Traditional therapeutic interventions such as dialectical behavior therapy (DBT) and cognitive behavioral therapy (CBT) have been shown to provide comparable improvement in depressive symptoms with SSRIs (Hofmann *et al.*, 2017). The utilization of DBT and CBT have helped many individuals undergo these perspective and behavioral changes, easing depressive and anxiety symptoms (Cranford *et al.*, 2009). This may be because these applications provide individuals with the space to untangle and feel their emotions while breaking down daily and long-term stressors. The need for human connection may lead individuals to struggle when their social needs are not being met. When individuals work in isolated jobs, live alone, or find themselves trapped in a digital world, it makes sense that depressive symptoms might increase. Seeking out human-based therapeutic support allows individuals to receive personalized and human-based guidance.

The APA recommends coupling therapeutic intervention with pharmacological intervention to allow individuals to receive advisory and monitoring medications (American Psychiatric Association, 2013). Because mental healthcare is not one size fits all, seeking support from a therapist, psychologist, and or psychiatrist can empower individuals to seek out treatment options that work best for them. Many treatments discussed in this thesis can be used in conjunction with others as individuals seek out patient-centered care.

Dialectical Behavioral Therapy (DBT)

Dialectical behavior therapy, which is also referred to as talk therapy, is often used for a variety of mental health conditions in a long-term approach to develop a variety of mindfulness and emotional regulation skills (Robins & Chapman, 2005). Some skills developed through DBT can be used in daily life, including improvement of interpersonal relationships, distress

management, and increased self-awareness (Robins & Chapman, 2005). DBT can be practiced both in a one-on-one setting with a clinical professional or in a group setting led by a clinical professional (Robins & Chapman, 2005). In a randomized-control trial taking place over a ten-week treatment period, it was found that the mindfulness and emotional regulation skills associated with DBT did not prevent depression relapse but significantly reduced depressive symptoms in the participant group (Elices, *et al.*, 2017).

Cognitive Behavioral Therapy (CBT)

While general talk therapies such as DBT can play a direct role in managing and potentially overcoming depression in the long-term, CBT has been shown to improve one common symptom of depression, poor sleep (Taylor *et al.*, 2014). Cognitive behavioral therapy is a short-term, goal-oriented intervention plan utilizing several core principles as defined by the American Psychological Association (American Psychological Association, 2017). CBT identifies and attempts to resolve psychological problems to be associated with distorted thinking patterns and unhelpful coping strategies (American Psychological Association, 2017).

Intervention utilized by CBT involves unlearning unhelpful behaviors and thinking modalities commonly referred to as thought distortions (American Psychological Association, 2017). Some examples of cognitive distortions include all-or-nothing thinking, jumping to conclusions, comparison, catastrophizing, and overgeneralization (Grinspoon, 2022). CBT also provides emotional regulation strategies and mindfulness techniques to provide coping strategies to relieve symptoms of psychological distress such as anxiety and depression (American Psychological Association, 2017).

Patients who have undergone CBT for depression show improvements in several sleep metrics, including the time it takes an individual to fall asleep known as sleep latency and onset,

sleep effectiveness, and insomniac manifestations (Taylor *et al.*, 2014). Researchers found that college students treated with CBT improved their sleep, reduced their daytime fatigue, and increased their cognitive performance throughout the day (Taylor *et al.*, 2014). The importance sleep plays in emotional regulation and management will be discussed in the following chapter.

Multiple Treatment Approach

Of the various treatment methods discussed in this thesis, therapy, like the others, does not need to be employed on its own. As mentioned previously, it is often the case and usually highly recommended that an individual should follow a comprehensive treatment plan involving both SSRIs and CBT or DBT as initial interventions (American Psychiatric Association, 2013). Vasile (2020) reviewed seventeen international studies and found that a combination of pharmacological and therapeutic interventions (CBT) was the most effective (Vasile, 2020). A clear limitation of this review is the lack of consistency used to measure the efficacy of treatment in detail, yet the overall effectiveness is found to be positive. Therapy also can be effective without SSRIs or with an alternative lifestyle-based intervention such as sleep or exercise, which will be discussed in Chapters 7 and 8, respectively.

Chapter 7: Sleep Intervention

Although sleep superficially appears to be a passive activity without a direct link to emotional regulation, many studies point to the importance of a full night's rest to reduce depressive symptoms and control emotional regulation turmoil (Emens, *et al.*, 2009; Park, *et al.*, 2020). Sleep facilitates physical and mental regeneration and allows for heightened levels of neural plasticity to occur as the brain makes connections from information absorbed throughout the day (Dierickx, *et al.*, 2017; Weiss & Donlea, 2021).

Sleep is often the first form of self-care to be impacted in depressed individuals and a constant state of fatigue tends to be a consistent symptom of depression (American Psychiatric Association, 2013). Other sleep issues are related to depression; there is a positive correlation between nocturnal insomnia symptoms (NIS) and the onset of depression (Casement, *et al.*, 2024). It has been suggested that this might be due to the disruption of reward processing in the frontal cortex by NIS, causing a reduction in feelings of satisfaction or achievement (Casement, *et al.*, 2024).

Improving sleep hygiene and introducing sleep intervention methods such as an earlier bedtime or morning light exposure can help reduce the intensity of depressive symptoms while improving an individual's overall mood (Casement, *et al.*, 2021). Studies in adolescent and young adult populations have shown that increasing sleep quality reduces the risk of depression (Bruce, *et al.*, 2017). Sleep provides the brain time to regulate memory storage and other various neural processes to ensure that individuals can engage appropriately with the world when awake (Dewald-Kaufmann, *et al.*, 2014).

Sleep is often the first area of wellness to decline when individuals feel overloaded. Because sleep is an inactive process it can feel useless for many and often goes neglected. The

current hustle culture many Americans fall victim to inadequate sleep, resulting in poor emotional management and regulation. Minkel *et al.*, (2016) found that sleep-deprived individuals exhibited a higher average of subjective stress, anger, and anxiety when exposed to low-stress conditions when compared to the control group. The same response was not observed in the advent of high-stress conditions as there was no significant difference between the experimental and control groups' subjective scores (Minkel, *et al.*, 2016).

There are several possible explanations for these results. The low-stress activity was completed first and this might have provided time to prepare for the high-stress activity (Minkel, *et al.*, 2016). It is also possible that a reduction in sleep causes mild agitation during low-stress situations, whereas the high-stress activity created a high amount of stress regardless of sleep (Minkel, *et al.*, 2016).

Researchers expected to find a significant response in both the low- and high-stress conditions given previous research, (Chuah, *et al.*, 2006; Yoo, *et al.*, 2007). Heightened anger in the sleep deprived group could signify the influence sleep deprivation has on emotional regulation in future elongated studies (Tomaso, *et al.*, 2021). The reasons for the Minkel results remain unclear. Further research between the relationship between sleep efficiency and stress response is clearly warranted.

Another study found a relationship between shortened or disturbed sleep and an increase in stress markers, specifically cortisol, which could potentially exacerbate the stress response in participants (Akerstedt, 2006). With this study in mind, it would have been beneficial for Minkel and his colleagues (2016) to measure cortisol levels to better understand the stress response in their participant population. Determining their levels of cortisol could have allowed for the study to have a more objective analysis component. As mentioned earlier, the only metric the Minkel

study (2016) used was self-reporting measures on subjective stress. It is possible that participants in the Minkel study who experienced sleep deprivation regularly could adjust their perception of stress.

Both Facer-Childs *et al.*, (2019) and Regehr, Glancy, and Pitts (2013) used intentional lifestyle intervention to adjust the stress response, which was assessed by measuring cortisol levels throughout the intervention process. Although Facer-Childs *et al.* (2019) had an overall goal of decreased depression symptoms in night owls and Regehr, Glancy, and Pitts (2013) had an overall goal of reducing anxiety symptoms in university students, the combination of self-reported symptoms and hormonal metrics such as melatonin and cortisol allowed for more quantitative results. While cortisol is a useful indicator of stress response, melatonin provides insight into sleep onset. One study found that daily administration of melatonin over six weeks in rats experiencing chronic stress reduced anxiety tendencies brought on by heightened cortisol levels (Gomaa, *et al.*, 2017).

Facer-Childs *et al.* (2019) initiated a two-hour advancement in the treatment group's sleep/wake timing, utilizing targeted light exposure monitored by dim light melatonin onset, fixed mealtimes, and regulated caffeine intake and exercise timing. Dim light melatonin onset requires a participant sample to be taken every thirty minutes to monitor melatonin levels as bedtime approaches. The researchers assessed the effects of the treatments using the Depression, Anxiety, and Stress Scale (DASS; Facer-Childs *et al.* 2019). The DASS is a frequently utilized tool in both general and clinical populations to assess depression, anxiety, and overall physiological distress (Cowles, *et al.*, 2022). The scores indicate the intensity and presence of both depression and anxiety with the participant population. A higher DASS score correlates with heightened levels of depression, anxiety, and stress. After the three-week-long intervention

period, the intervention group showed an average decrease of 8.7 ± 2.4 points when compared to the pre-intervention score of range of 11.2-19.8 (Facer-Childs *et al.*, 2019). In contrast, the control group's DASS scores did not show any notable change (Facer-Childs *et al.*, 2019). The overwhelming decrease in DASS scores in the experimental group denotes the effectiveness of the sleep intervention program on the participants' mental wellbeing.

A survey of 1,125 students aged seventeen to twenty-four revealed that students often have delayed sleep/wake timing and are at higher risk for sleep deprivation (Lund *et al.*, 2010). Based on these results, Hershner & O'Brien (2018) designed a virtual sleep intervention program targeting college students aged eighteen and older. Among many index tools and assessments used, the Pittsburgh Sleep Quality Index (PSQI) and the Patient Health Questionnaire (PHQ-9) provided the most beneficial information in terms of sleep and depression (Buysse, *et al.*, 1989; Kroenke, *et al.*, 2001).

After completing the eight-week intervention program, which involved action steps such as keeping a regular sleep schedule, ceasing electronic use earlier in the evening, and having an earlier wake time, there was significant improvement in mean sleep quality (PSQI) and depression scores (PHQ-9) (Hershner and O'Brien, 2018). Not only do these results reiterate the benefits of sleep intervention; they also underscore the value of sleep when attempting to reduce symptoms of depression. By creating a virtual intervention and survey system, Hershner and O'Brien made their study accessible through the internet to maximize participation access. By doing so researchers gathered a more diverse and representative dataset of college-aged individuals.

The reduction in mental well-being impacts sleep quality and reduces the overall benefits of sleep on emotional regulation and cognitive function. The relationship between cortisol and

melatonin, mentioned previously, is a key component to effective sleep. Regehr, Glancy, and Pitts Study (2013) performed a systematic review of twenty-four studies that utilized mindfulness interventions and showed that these in general resulted in an overall decrease in symptoms of anxiety and cortisol levels. While this meta-analysis does not relate directly to sleep and depression, the overall benefit of mindfulness intervention and hormonal metrics demonstrate the potential relationship between the cortisol stress response and mental wellbeing (Lovibond & Lovibond, 1995).

Chapter 8: Exercise

When it comes to lifestyle intervention, exercise is recommended for improved overall mental and physical health (Rippe, 2018). Due to the increasingly sedentary lifestyle in America, many individuals are not spending enough time moving their bodies, thus depriving them of the positive benefits of exercise (Park, *et al.*, 2020).

Many people think exercising is done to achieve physical fitness, but it has the potential to aid in achieving mental fitness as well. Exercise can increase the release of Brain Derived Neurotropic Factors (BDNF) and the hormone dopamine, which help regulate emotions (Hackney, *et al.*, 2015; Bastioli, *et al.*, 2022). Exercise also aids in circadian rhythm management allowing for more effective sleeping patterns, further aiding in emotional regulation (Shen, *et al.*, 2023; Park, *et al.*, 2020). It is also known that physical inactivity can cause heart disease, strokes, and other metabolic diseases (Ghodeswar, *et al.*, 2023). Not only do these conditions place a threat on an individual's immediate health, but they also pose future risk for an individual's mental health balance potentially resulting in the onset of depression due to the stress that accompanies illness (Booth, *et al.*, 2002).

As mentioned previously in Chapter 2, the concentration of BDNF is correlated with maintenance of synaptic connections, and in one study it was found that humans experience a significant elevation in BDNF levels in response to exercise (Ferris, *et al.*, 2006). This study measured the concentration of BDNF before and after two 30-minute cycle rides at either high or low intensity with an average rest period of forty-eight hours between each test. In conjunction with sampling BDNF levels pre- and post-exercise, participants also completed the Stroop color and word test as a tool to assess cognitive function (Scarpina & Tagini, 2017). The study found a

significant increase in both BDNF levels and Stroop scores for the high intensity exercise group (Ferris, *et al.*, 2006).

An increase in the concentration of BDNF was observed directly after the two high intensity thirty-minute rides. However, the study did not provide information on how a consistent long term exercise regimen could improve an individual's baseline BDNF levels nor did it demonstrate how long levels are risen before returning fully to baseline (Ferris, *et al.*, 2006). However, in theory, this study might provide some beneficial information. It suggests that at least thirty minutes of high intensity aerobic activity at least every forty-eighty hours will cause an increase in BDNF, with a resultant heightened cognitive function.

During a metanalysis of twenty-nine studies, Szuhany and colleagues (2015) confirmed a correlation between regular exercise and a slight increase in resting BDNF levels. In conjunction with finding a small correlation between BDNF levels and a consistent exercise routine, researchers also found that the sex of participants played a role in the magnitude of the stimulatory effects of exercise on BDNF levels (Szuhany, *et al.*, 2015). The effects of exercise on BDNF levels appear to be moderated by sex as the female population showed less BDNF fluctuation compared to the male population (Szuhany, *et al.*, 2015).

Oxidative Stress

Oxidative stress causes cellular destruction when there is an unbalanced accumulation of reactive oxygen species (ROS), which disrupts normal cellular activity (Bhatt, *et al.*, 2020). It has been proposed that oxidative stress in the brain and the neurodegeneration it causes play a role in the onset of depression (Bhatt, *et al.*, 2020). Mitigating levels of ROS with suitable antioxidants has the potential to reduce depression symptoms as some cases of depression are

associated with lower antioxidant levels. However, a causal relationship between oxidative stress and depression has not yet been observed (Bhatt, *et al.*, 2020).

Exercise and Oxidative Stress

In a randomized clinical trial, researchers found that the introduction of an aquatic exercise program reduced levels of oxidative stress, anxiety, and depression in an elderly population (Silva *et al.*, 2019). Exercise may provide a non-pharmacological intervention to reduce oxidative stress and can be used with other treatment methods. While oxidative stress and ROS reduction are contemporary issues in the study of depression, there is a potential for a novel intervention method for depression treatment that investigates underlying mechanisms linking ROS levels to depression. This intervention method may provide interesting new evidence to better understand the pathogenesis of depression (Correia, *et al.*, 2023).

Chapter 9: A Holistic Intervention Plan

Based on the research findings and discussion of this thesis, and the fact that there is not one all-encompassing cure or treatment for depression, the most effective form of treatment might be the simultaneous use of more than one form of treatment. In 2016, the *Journal of the American Geriatrics Society* published a paper emphasizing eight essential components of what they called person-centered care. While this paper is designed with an elderly population in mind and might not be effective for younger generations, it is worth noting for overall implications.

An effective treatment plan for depression should begin with, a goal-focused care plan using an inter-disciplinary (American Geriatrics Society, 2016). To ensure consistent and continual communication with both the care team members and the patient, there must be a designated lead person who actively coordinates all healthcare team members. Health care providers should undergo continual education and training due to the constant development of the mental health field and aid with the goal of developing self-determination in the patient. In addition, utilizing performance measurement[s] and feedback from team members can provide affirmative metrics and/or suggest the potential need for treatment adjustment (American Geriatrics Society, 2016).

Starting with dialectical behavioral therapy (DBT), therapy gives patients the ability to verbally discuss their lifestyle and emotional landscape, and cognitive behavioral therapy could also be used as a springboard for other treatments depending on the discretion of the provider and patient (American Psychiatric Association, 2013). DBT also allows the mental health provider to act as a lead point of contact as they work with the patient to expand the care team based on their needs. For example, patients can be referred to a psychiatrist who might prescribe selective serotonin reuptake inhibitors depending on the severity of the patient's symptoms.

Based on the discretion of the therapist, the patient might also receive an exercise plan and/or sleep intervention guidance from a health/wellness coach or sleep expert. In some cases, psilocybin treatments might be useful based on the advice of the health care team and at the discretion of the patient.

A multi-faceted treatment plan for depression could enable patients to find workable solutions to their depressive symptoms. These types of plans must be individually tailored and must always be corrected or adjusted based on the success or failure of each type of treatment. It is important to note that in many cases the patients are their own experts of themselves and their experiences. The value of mental health professionals allows patients to be an active participant in identifying a single- or multi-pronged treatment plan. Instilling confidence in patients at all levels of healthcare allows for more effective and appropriate treatment and has the benefit of addressing the patient's feeling of being misunderstood or hopeless when struggling with untreated depression as discussed in Chapter 1 using literary testimonies.

Conclusion

This is an exciting time for the field of neuroscience as new findings are allowing for further development of theoretical modeling of the biological mechanisms of depression in conjunction with scientific and clinical applications. There is a common theme in the biomedical sciences of working to understand how a system responds to a decrease or dysregulation with the aim of engineering more effective clinical care. The study of depression is no different, and research laboratories across the world are analyzing the brain to create a more holistic, clinical understanding of the mind-brain connection.

This project's purpose is to emphasize the importance of personalized clinical care. Based on the research evidence of this thesis, a multi-faceted treatment plan may be the most effective approach. Furthermore, it is important to note that treatments that may have worked for individuals in the past can lose their effectiveness. It is up to the clinical team to help navigate treatment changes within an individual's health plan.

I look forward to furthering my understanding of the intricacies of the human brain alongside the scientific community as I begin to embark on my professional academic journey. I aspire to use my scientific knowledge and literacy to help others better understand themselves and find the most effective ways to nurture and heal their minds.

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