CANNABINOIDS AND ANXIETY MODULATION:

A FOCUS ON INLAND SOUTHERN CALIFORNIA

By

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ABSTRACT

Cannabis use is becoming increasingly common in the U.S. and particularly in the state of California and its intake has long been thought to decrease anxiety. This paper will discuss how cannabinoids and, specifically, endogenous cannabinoids modulate anxiety in different brain regions such as the hypothalamus, periaqueductal gray matter, habenula, hippocampus, prefrontal cortex, amygdala, substantia nigra, dorsal striatum, and stria terminalis. I will also discuss the therapeutic potential of cannabinoids in treating anxiety, given that the prevalence of anxiety is increasing in the U.S. I will discuss ways of measuring anxiety in rodent models and with human questionnaires. Along with the therapeutic potential of cannabis, however, comes its potential for abuse. Cannabis use disorder (CUD) is increasing in the U.S., especially in California and our region, Inland Southern California. I will analyze how cannabis use and CUD relate to anxiety in California and how CUD's effects can penetrate through all facets of society. Finally, I will discuss ways we can individually and collectively move forward towards a future with less CUD and more responsible cannabis use.

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INTRODUCTION

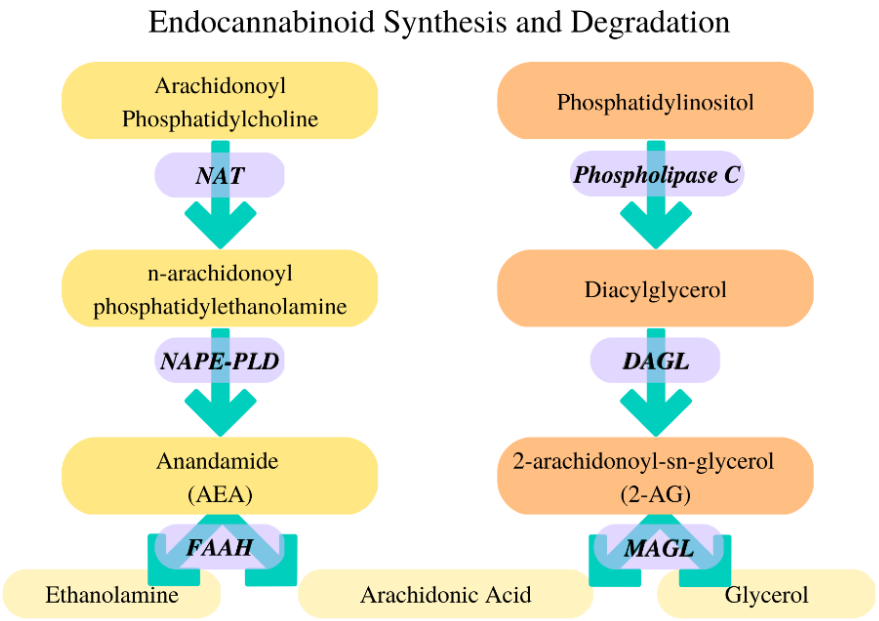
The Cannabis sativa plant has historically been perceived as an anxiolytic, or anxiety-reducing, drug. The earliest use of cannabis dates back to about 2800 BC, when it was first used under the reign of Emperor Shen Nung, who is considered to be the father of Chinese Medicine. Afterwards, several cultures ranging from Greeks and Romans to Assyrians and Hindus began using cannabis for its alleged healing effects for various health problems such as arthritis, epilepsy and amenorrhea (Lambert et al., 2022). More recently in the early 20th century, cannabis gained a reputation of being a dangerous drug that does not serve any medical purposes; a notion that is now being reevaluated by our modern research and contemporary society.

The main psychoactive compound in cannabis is Δ^9-tetrahydrocannabinol (THC), which has been known as a potent analgesic and sedative. The analgesic effects of THC can be attributed to its binding to cannabinoid receptors on nociceptive neurons in the periaqueductal gray matter and medulla oblongata in the brain, and the substantia gelatinosa, superficial dorsal horn and the dorsolateral funiculus in the spinal cord (Sañudo-Peña et al., 1999, Litchman et al., 1996, Manzanares et al., 2006). Additionally, the sedative effects of THC are still being mechanistically explored, but preliminary studies and clinical trials show that it can be sleep-inducing in humans. According to Nicholson et al. (2004) and Lafaye et al. (2018), it is thought to act on sleep/wake-related areas in the brain such as the suprachiasmatic nucleus, hypothalamus, and dorsal raphe nucleus, along with the another frequently studied cannabinoid: cannabidiol (CBD). Acute THC-intake can increase dopamine release and accelerate dopaminergic neuron activity in the nucleus accumbens, prefrontal cortex, and caudate nucleus (Pistis et al., 2002, Ton et al., 1988, Chen et al., 1990). THC and other cannabinoids exert physiological and behavioral effects via endogenously expressed G-protein coupled receptors called cannabinoid receptors. There are two different

cannabinoid receptors that are present on different tissue types in the body. Cannabinoid receptor 1 (CB_1R) is present in high density on nervous tissue, and in lower densities on other peripheral tissues such as gastrointestinal and reproductive organs. Cannabinoid receptor 2 (CB_2R) is present on nervous tissue in much lower densities than CB_1R; but also in the peripheral immune system (Pettit et al., 1998). Endocannabinoids (eCBs), are endogenously generated cannabinoids which bind to cannabinoid receptors and have similar effects to exogenous cannabinoids (Devane et al., 1992). The two principal eCBs are 2-arachidonoyl-*sn*-glycerol (2-AG) and Anandamide (N-arachidonoyl-ethanolamine, AEA).

eCBs are continuously being synthesized on demand from phospholipid-rich cell membranes, and they are rapidly degraded after they have served their respective functions. The enzymes responsible for synthesizing 2-AG and AEA are diacylglycerol lipase (DAGL) and N-arachidonoyl phosphatidylethanolamine phospholipase D (NAPE-PLD), respectively. 2-AG and AEA are degraded by monoacylglycerol lipase (MAGL) and Fatty acid amide hydrolase (FAAH) respectively, as shown in **Figure 1** (Mustafa et al., 2020). Endocannabinoids, along with their receptors, and the synthetic and degradative enzymatic machinery compose the endocannabinoid system (ECS). The ECS modulates multiple behavioral and physiological

Figure 1: Synthetic and Degradative Pathways for AEA and 2-AG

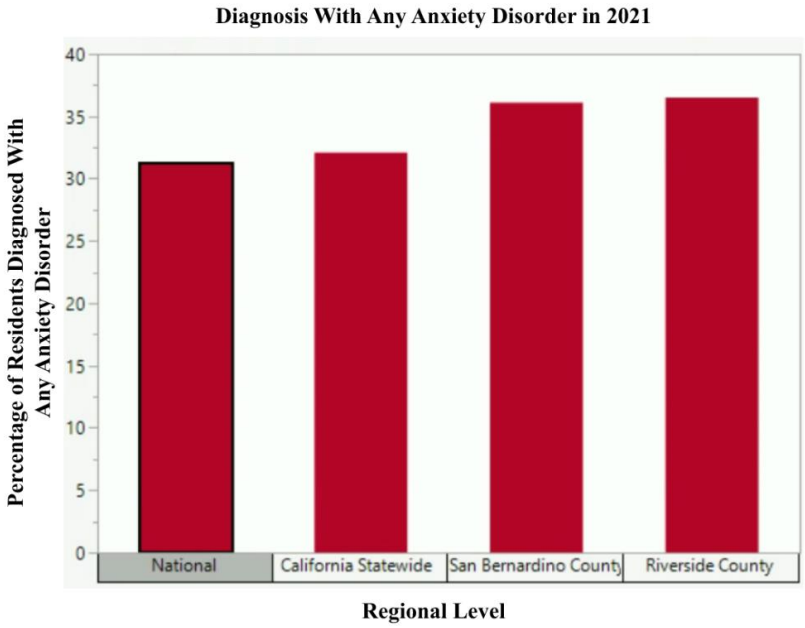


processes, including those relating to anxiety, conditioned fear, averse memory extinction, and post-traumatic stress (Ashton et al., 2008, Butler et al., 2008, Ganon-Elazar et al., 2009, and Pamplona et al., 2006.)

Although fear and anxiety are adaptively-beneficial biological responses that prepare us to face or evade threats, the prolonged presence of these processes can negatively impact our overall health (National Institutes of Health, 2019). According to the National Institute of Mental Health (NIMH), as of 2020, 31.3% of American adults have experienced anxiety disorders in their lifetime. As a matter of fact, the NIMH is estimating that this number could be up to 10% higher because of those who don't seek help, are misdiagnosed, or are unaware that they could potentially have anxiety (National Institute of Mental Health, 2021). These statistics worsen when examining the state of California, where 32.1% of adults have experienced an anxiety disorder in their lifetime. In our own backyard of Inland Southern California (Riverside and San Bernardino Counties), an average of 36.3% of adults have experienced an anxiety disorder in their lifetime, as shown in **Figure 2** (Riverside County Health Indicators. 2021)**.** The most common comorbidities of anxiety disorders are major depressive disorder (MDD) and substance abuse disorder (SUD) (National Institute of Mental Health, 2022). This makes anxiety a highly consequential medical concern that must be addressed through both social interventions and biomedical research solutions. A large workforce of researchers is exploring how ECS modulation can reduce generalized anxiety and anxiety related to conditioned fear and posttraumatic stress (Vimalanathan et al., 2020). The importance of synthesizing a new anxiolytic therapy is not only a pressing matter because of increasing anxiety rates in the U.S. and globally, but also because chronic side effects of current anxiolytic medications can be as severe as memory loss, confusion, and sexual dysfunction (Garakani et al., 2020). Synthetic cannabinoids or ECS modulators can be anxiolytic,

while carrying less severe side effects than current anxiety medications (National Library of Medicine, 2017). It is difficult to replicate innate anxiety disorders in animal research because usually anxiety is idiopathic in humans. Additionally, we exhibit multiple psychological, cognitive, and physiological symptoms of anxiety that are also shared by other disorders, making anxiety difficult to diagnose. Plenty of animal models replicate conditioned fear responses which differ from innate anxiety because it is learned. This makes animal models of anxiety slightly different from human anxiety, which is why it is important to rigorously test the model using multiple different behavioral approaches.

Figure 2: National, Statewide, and Regional Anxiety Trends



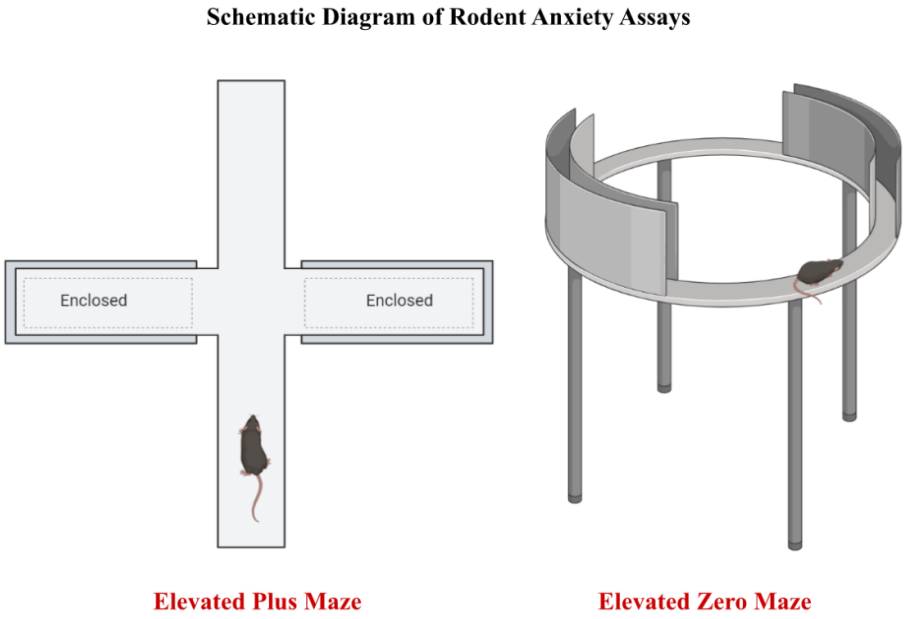
MEASURING ANXIETY

Animal Models

It is difficult for researchers to measure anxiety in both animals and humans. Since animals cannot explicitly communicate their feelings of anxiety, a certain pattern of behaviors has been associated with increased and decreased anxiety. This pattern can be observed in unconditioned, approach-avoidance tests that depend on the innate conflict that all rodents, and prey animals to a larger extent, have to forage in the wild versus to hide and avoid predation. As described by Cryan & Sweeney in the 2012 review, the ratio of foraging-to-hiding is the essential measurement of

rodent anxiety. One commonly used assay is the elevated-plus maze test (EPM), which consists of a platform that is elevated above the ground. This platform contains four perpendicular arms, extending from the center, each being about as wide as the experimental animal it is suited for. Two of the four arms contain high walls, while the other two contain very low walls (Sweis et al., 2015). A camera records the behavior of the mice in the EPM, and the time spent in the high-walled areas versus the low-walled areas. Longer time spent in the high-walled areas, as opposed to the low-walled areas, is associated with increased anxiety, and vice-versa (Walf et al., 2007). The Elevated-zero maze (EZM) is a newer version of the EPM test that, with repeated trials, is yielding more consistent results when working with C57BL/6J transgenic mice (Tucker et al., 2017). The EZM consists of an elevated circular platform that is divided into four quadrants, with two of those quadrants containing high walls, similar to the EPM, and the other two quadrants containing low walls (La-Vu et al., 2020).

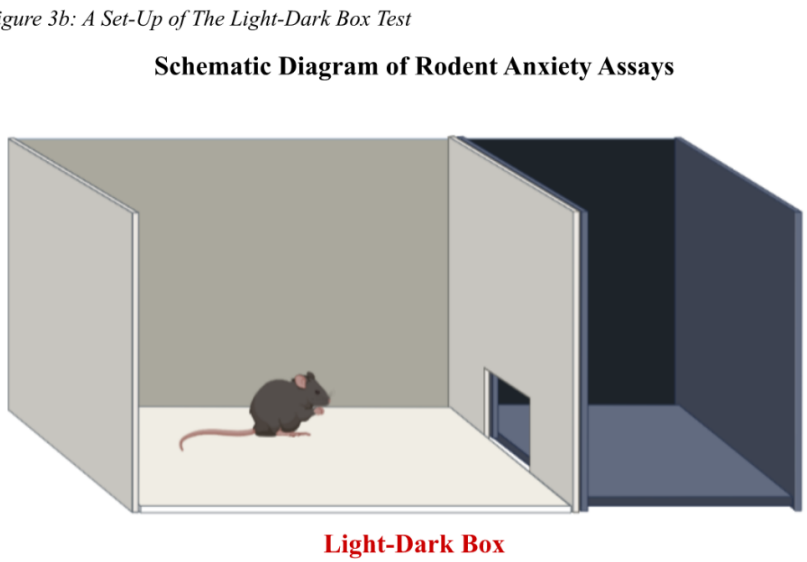
Figure 3a: A Set-Up of Elevated Mazes



Another rodent anxiety assay is the light-dark box (LDB) test, which measures the time that rodents spend in a tinted box that does not allow light to enter versus a transparent, well-lit box. The results of this test, again, depend on the concept that rodents are prey animals that would

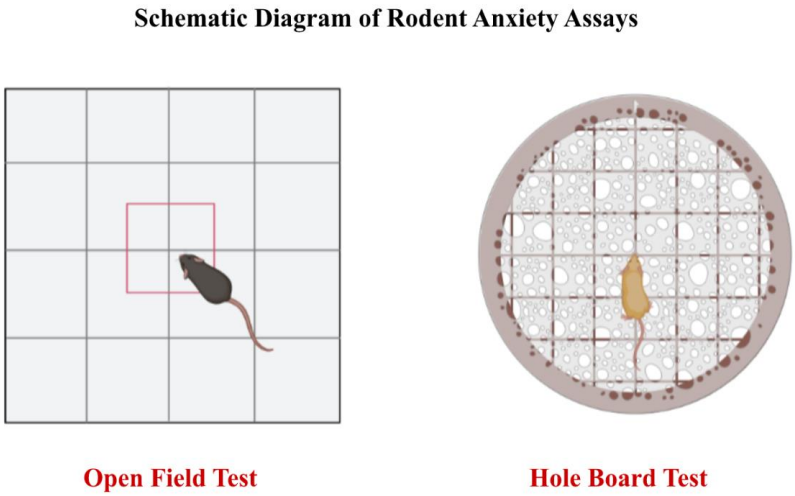
spend more time in the dark if they are more anxious, and more time in lit environments if they are less anxious (La-Vu et al., 2020). A test that employs a similar concept to that of the LDB test is the open field test (OFT). The OFT measures exploratory behaviors of rodents in a large, square box. Exploratory behaviors that would ideally be exhibited when rodents are less anxious, include crossing the entire field, risk-taking, defined by spending time in the center of the field, and rearing, defined by the rodent standing on its hind legs (Valvassori et al., 2017). When rodents are more anxious, they can display more manic-like, hyperactive, and repetitive behaviors characterized by repeated grooming and sniffing of their surroundings, while staying in or near the corners of the field (Lucca et al., 2009).

Figure 3b: A Set-Up of The Light-Dark Box Test



One shortcoming of the OFT is that it does not give rodents the choice to explore much, except for the center of the field, which is the riskiest position they can place themselves in (Brown et al., 2008). In the OFT, it is difficult for experimenters to distinguish between

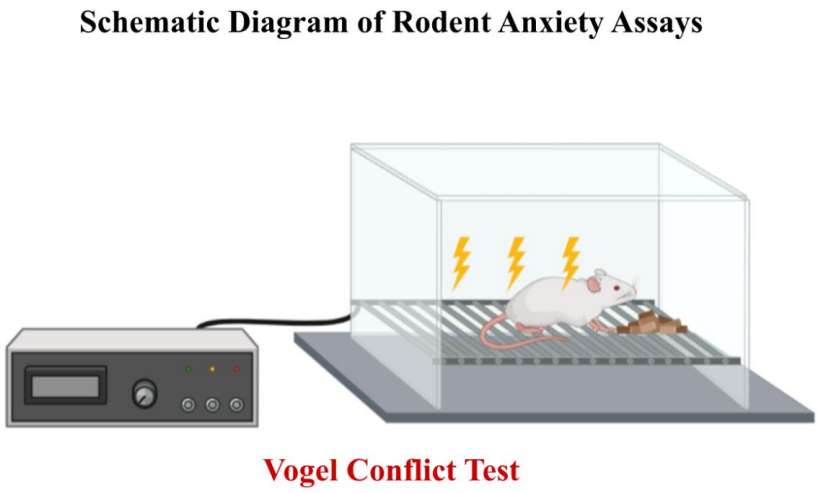
Figure 3c: A Set-Up of the Open Field Test and the Hole Board Test



exploration, which occurs when anxiety is reduced, and locomotion, which occurs at any state of anxiety (Kliethermes and Crabbe, 2006). Thus, changes and nuances have gradually been added to the OFT, and eventually a completely new assay, the hole board test (HBT), emerged. The HBT set-up is almost identical to that of the OFT, with the difference mainly being that, instead of the flat flooring present in the OFT, the HBT adds the nuance of holed-flooring that experimental rodents can burrow into. Burrowing into these holes can only be characterized as exploratory, neophilic behavior; the epitome of a reduced-anxiety phenotype in rodents (Hoshino et al., 2004). Generally, in most rodent anxiety assays, body stretching behaviors, along with frequent surveillance, urination and defecation are all signs of increased anxiety (Wooten et al., 2015).

Unlike the previously discussed unconditioned approach-avoidance tests, the Vogel conflict test (VCT) is a conditioned response test designed to identify anxiolytic drugs (La-Vu et al., 2020). In the Vogel test, animals are firstly deprived of water for a period of time at the experimenter's discretion, and then given access to water again during the experiment. The rodents are punished haphazardly when they attempt to drink water by electrical shocks, administered through the metal drinking straw (Millan et al., 2003). The amount of times that they attempt to drink naturally decreases over time because they develop aversive reactions to the electric shock. However, if the drug administered to the rodents is anxiolytic, the amount of times they attempt to get

Figure 3d: A Set-Up of the Vogel Conflict Test



water will not decrease as significantly or as rapidly (Millan et al., 2003). This anxiety assay, in particular, has several sensitivities and should be done alongside other assays to ensure that the experimental results are clear and consistent. If electrical shock voltage, nociception, motivation, learning, or thirst are slightly increased or decreased, anxiolytic drug effects can be masked and results may be ambiguous to experimenters (Patrick et al., 2019). Schematic diagrams of all the described anxiety assays can be found in **figure 3**.

Human Questionnaires

When measuring human anxiety, experimenters rely on self-reporting from potential anxiety patients or study participants. There are several scales that are used to evaluate, quantify, and compare how much anxiety is being reported: one of which being the Hamilton Anxiety Scale (HAM-A). HAM-A was one of the first widely used anxiety scales, designed by Dr. Max Hamilton in 1959. HAM-A includes 14 points that allow patients to self-report both psychological stresses, and somatic symptoms of anxiety (Hamilton, 1959). The following are the 13 items that patients are to self-report, on a Likert scale, while taking the HAM-A questionnaire: anxious mood, tension, newly emerged fears, insomnia, intellectual difficulties, depressed mood, muscular aches, sensory abnormalities, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and, autonomic symptoms (Hamilton, 1959). The 14^{th} item, the patient's behavior during their doctor's visit, is evaluated by the physician administering the HAM-A questionnaire. This scale has been praised for its thoroughness and the fact that it encompasses a wide range of symptoms that, at the time of its novel use, were not all readily attributed to anxiety by physicians (Porter et al., 2017). These symptoms include muscle twitches, tinnitus, hot or cold flashes, dyspnea, abdominal pain, dryness of palate, and night sweats (Hamilton, 1959). At the time of its development, HAM-A was meant to measure the severity of "neurotic anxiety states",

(Hamilton, 1959). In 1959, that terminology was medically adequate to characterize what we now refer to as generalized anxiety disorder (GAD). Recently, HAM-A has been criticized for being too general, having listed diagnostic symptoms of anxiety, panic disorder, and depression. This makes sense given that GAD first appeared in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980, two decades after HAM-A was first developed (Crocq, 2017).

Following the addition of GAD to the DSM, several people sought to create more comprehensive and specific questionnaires for anxiety. In 1983, the Hospital Anxiety and Depression Scale (HADS) was created by English psychiatrists, Zigmond and Snaith, to be used in the outpatient setting (Zigmond and Snaith, 1983). The HADS contains 14 items, 7 relating specifically to anxiety and 7 relating specifically to depression, similar to those present on the HAM-A scale and participants are to self-report the severity of their symptoms on a scale from 0-3. Collective scores of more than 11 on either subscale are categorized as severe cases of clinically significant anxiety, or depression (Jarvandi et al., 2003). Yet, one disadvantage of the HADS is that it is not sensitive enough, in this day and age compared to more recent tests, at detecting both anxiety and depression (Powell et al., 2019).

In 1970, , Spielberger et al. developed the State Trait Anxiety Inventory (STAI), which was finalized in 1995. Their approach to measuring anxiety was very novel, in that they tried to measure both ‘state anxiety”, which they defined as temporary and acute, and “trait anxiety”, which they defined as long-lasting and chronic (Heeren et al., 2018). STAI was criticized for having inadequate minimum scores for diagnosing anxiety disorders (McDowell, 2006). At around the same time, the Beck Anxiety Inventory (BAI) was developed, consisting of 21 items which can each be self-reported by patients on a Likert scale from 0-3 (Beck et al., 1997). While this test

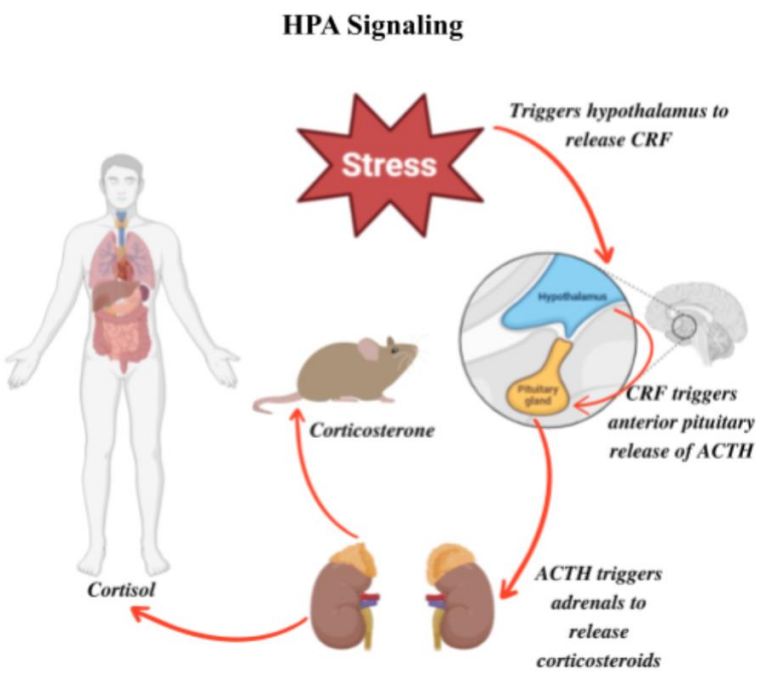
had valid consistency and adequacy in terms of scoring, it was inadequate in measuring anxiety symptoms relating to trauma. Most of the BAI questionnaire's inquiries were regarding physiological symptoms that more closely resembled panic attacks, rather than also focusing on psychological symptoms of anxiety that would stem from disorders such as post-traumatic stress disorder (Cox et al., 1996). Now, the GAD-7 score range is more conventionally and universally used to measure anxiety because it has proven to be valid and consistent across many populations and age groups, especially when measuring changes in anxiety levels over various periods of time (Spitzer et al., 2016).

THE NEUROBIOLOGY OF ANXIETY

Hypothalamus

The hypothalamic-pituitary-adrenal (HPA) axis is responsible for provoking the secretion of several hormones and neurotransmitters in response to psychological and physiological stressors (Sheng et al., 2021). While HPA signaling is almost instantaneous, downstream hormonal signaling is rather slow-acting. As shown in **figure 4**, the hypothalamus responds to chronic stress by releasing corticotropin releasing factor (CRF), which then triggers the anterior pituitary gland to secrete adrenocorticotropic hormone

Figure 4: Basic Hypothalamic-Pituitary-Adrenal Signaling

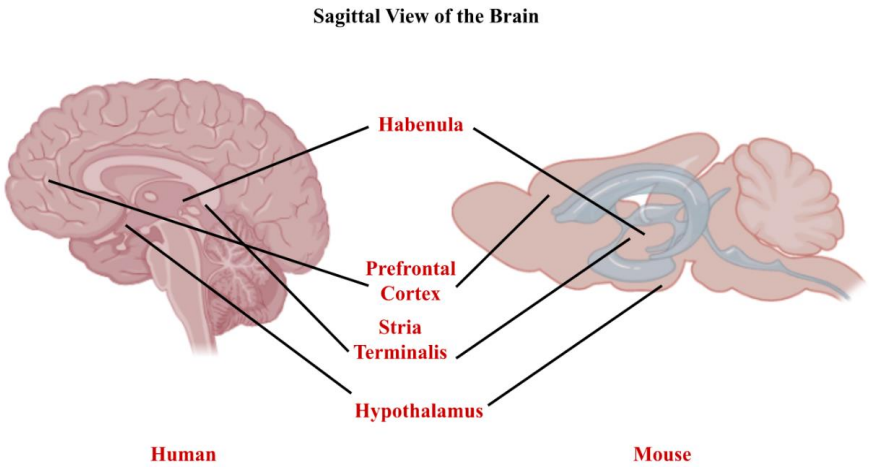


(ACTH). ACTH in turn stimulates the adrenal glands to release corticosteroids, cortisol and corticosterone (CORT) for humans and rodents respectively (Rivier and Vale, 1983, Vale et al., 1981). Cortisol/CORT halts insulin release and stimulates glycogen release, thereby elevating blood glucose levels to enable the fight or flight response. It has been found, in both animal and human research studies, that administering cannabinoids in low doses yields an anxiolytic response, while administering high doses of cannabinoids can increase anxiety while also causing other adverse effects such as paranoia and lethargy. This is referred to as a biphasic, dose-dependent effect (Margulies and Hammer Jr., 1991, Hill et al, 2021). The hypothalamus and all of the following regions, in the mouse and human brain, will be portrayed in **figure 5**. Endocannabinoid signaling can negatively modulate the HPA axis in some cases, which suggests a therapeutic potential for the pharmacological amplification of endocannabinoid signaling in treating anxiety disorders (Patel et al, 2004). Specifically, AEA-mediated CB_1R activation in the ventromedial nucleus of the hypothalamus (VMH) has been shown to reduce panic and anxiety of C57BL/6 mice in response to a live predator (Dos Anjos-Garcia et al, 2020).

Periaqueductal Gray Matter

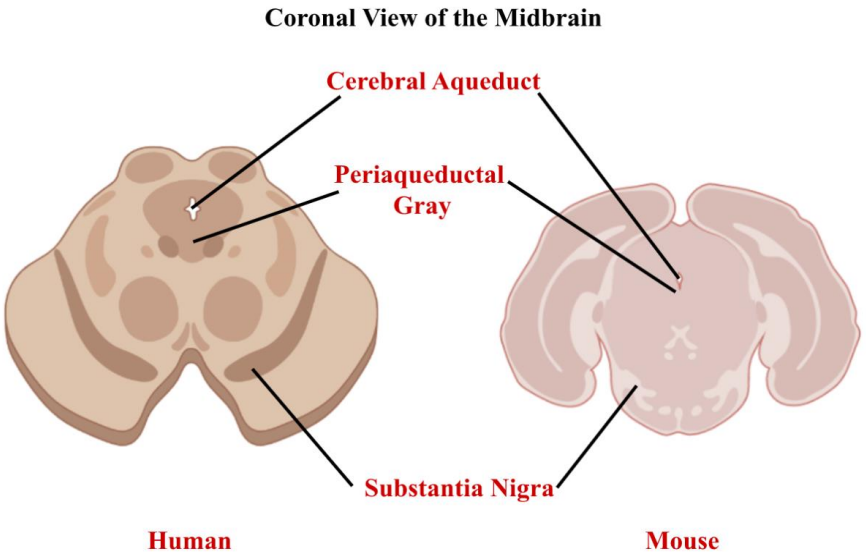
In the periaqueductal gray (PAG), injection with CB_1R agonists yields several anxiolytic response types in animal models. For instance, dorsolateral PAG

Figure 5a: Neurological Loci of Anxiety-Modulating Endocannabinoid Signaling



injections with 50 pmol 2-AG was correlated with an increase of times that mice went into open arms of the EPM. Additionally, 100 pmol injections of URB602, a compound that inhibits hydrolysis of 2-AG and severely extends its physiological effects, perpetuated this effect (Santos et al, 2013). AEA injections in the dorsolateral PAG yielded an overall anxiolytic response in Wistar rats. This anxiolytic response was evident in both the OFT and when being exposed to a live cat predator (Lisboa et al., 2014). The CB_1R agonist and a stable analogue of AEA, Arachidonyl-2-chloroethylamide (ACEA), mimicked the anxiolytic effects of AEA when injected into the dorsolateral PAG. The anxiolytic effect of AEA was also reversed by the selective CB_1R ligand AM251 - showing that this is a CB_1R-mediated effect (Moreira et al, 2007).

Figure 5b: Neurological Loci of Anxiety-Modulating Endocannabinoid Signaling



HU210 is a synthetic cannabinoid that is much more potent than THC. While the effects of THC can be observed in humans for about 2 to 4 hours, the effects of HU210 can be observed for 26 to 30 hours (McMahon et al, 2014). HU210 injections in the dorsomedial PAG yielded decreased hyperlocomotion and flight responses in mice, in the VCT (Finn et al, 2003).

Additionally, in rat models of contextualized fear-conditioning, dorsolateral PAG injections of AEA and another selective CB_1R agonist, AM404, were associated with the reduction of fearful behavior. In a more naturalistic setting with rats being exposed to a live predator,

dorsolateral PAG injections of AEA and MAGL inhibitor were associated with reducing anxious behavior (Lisboa et al, 2014). The reduction in anxious behavior is still being mechanistically explored, but research suggests that PAG CB_1R activation, modulated by adenosine release and adenosine A_1 receptors, inhibits glutamate release (Hoffman et al., 2010, Manzoni et al, 2011). While the role of glutamate in anxiety is also still being investigated, rodent forced swim tests show that stress increases glutamate release and inhibits its neuronal reuptake in the hippocampus and prefrontal cortex (Popoli et al., 2011). Glutamate activates the N-methyl-D-aspartate NMDA receptor which, if antagonized using MK-801, has been shown to have anxiolytic effects (Sharma et al., 1991).

Habenula

Emerging research points to cholinergic habenular neurons when considering endocannabinoid signaling. Unexpectedly, in the habenula, GABA release is not inhibitory as it is in most other brain regions, but rather excitatory. Habenular neurons rarely express KCC_2, a potassium-chloride cotransporter that pumps chloride out of the neuron against its electrochemical gradient in response to GABA (Kim and Chung, 2007). Therefore, down-regulation of GABA release in the medial habenula can have anxiolytic and anti-depressive effects. Experiments analyzing the forced swim test, OFT, and EPM, performed by Vickstrom et al. (2021), found that CB_1 receptor activation, whether by endogenous 2-AG or exogenous WIN 55, 212-2, leads to suppression of GABA release in ventromedial habenular cholinergic neurons, suggesting that this neurological site is an important target for anxiety modulation. Results from the same study indicate that the knockout of CB_1R in the nucleus of the diagonal band of Broca's area yielded anxiolytic effects in the OFT and EPM. Likewise, exploratory rodent research indicates that CB_1R in medial habenular neurons may modulate the retrieval of aversive memories. Researchers

demonstrated that CB_1R-knockout mice exhibit increased anxiety symptoms in response to aversive conditioning because of the lack of CB_1-mediated inhibition of glutaminergic and acetylcholinergic neurons in the medial habenula (Soria-Gomez et al., 2015).

Hippocampus

The prefrontal cortex and the amygdala, crucial structures for modulating anxious and defensive behaviors, have several connections to the septo-hippocampal system, which modulates these behaviors via neuroendocrine inhibition of the HPA axis. Ventral hippocampal injections of AM404 were anxiolytic in rats exposed to the VCT (Campos et al., 2010). Additionally dorsal hippocampal injections of AM404 or URB597, a selective irreversible FAAH inhibitor, yielded anxiolytic responses in both the EPM and VCT (Lisboa et al., 2015). This reinforces the critical importance of the hippocampus in learning and memory, along with conditioned anxiety responses. Conditioned anxiety or contextualized fear situations are important when considering human therapeutic agents that can help patients overcome habitual phobias such as fear of driving and fear of heights (Graham et al., 2011).

Some groups suggest that eCB modulation in the hippocampus acts as a switchboard, deciding whether the appropriate response in different situations is fear extinction or fear reconsolidation. In multiple conditioned fear tasks, De Oliveira et al., 2008 that AM251, a CB_1R inverse agonist, perpetuated fear and prevented fear extinction. They also found that AEA facilitates fear extinction, while 2-AG blocks it. Of note is that all 3 of these CB_1R ligands were injected bilaterally into the hippocampus. Additionally, in the dorsal hippocampus, it has been shown that NMDA receptor activation, via AP7 injections, along with nitric oxide (NO) formation is associated with a CB_1R blockade. These results were found after pre-treatment with Bicuculline,

which is an anxiogenic $GABA_A$ antagonist. This is thought to result from excessive excitatory glutamate signaling to NMDA receptors (Spiacci et al., 2016).

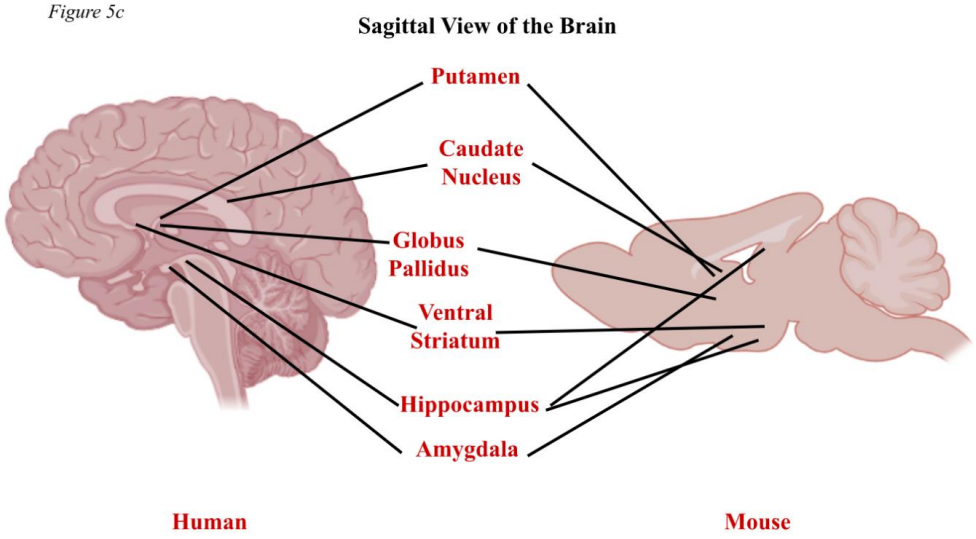
Prefrontal Cortex

The prefrontal cortex (PFC) is a modulatory hub for a wide range of bodily functions, including neurotransmission, endocrine signaling, and behavioral regulation. It is also the main neurological center for executive function, which is a mental process controlling attention, prioritization of tasks, planning and multitasking (Welsh et al., 1991, Cristofori et al.. 2019). In rodents, the medial PFC is divided into ventromedial and dorsomedial regions. The ventromedial region is further subdivided into prelimbic, infralimbic, and medial orbital cortices that each connect to and modulate mood, emotional responses, and anxiety behaviors in other brain regions (Kolb et al., 2003). It has been found that endocannabinoid receptors are more commonly expressed on GABAergic interneurons than glutamatergic interneurons in the rodent PFC, suggesting that they strongly facilitate inhibitory, anxiolytic, neurotransmission more so than excitatory, anxiogenic, neurotransmission (Lafourcade et al., 2007). Under stressful situations, such as the VCT, it has been found that plastic changes take place in the ventromedial PFC. For example, a down-regulation of AEA signaling has been observed by Rubino et al (2008) and linked to increased-anxiety behaviors in the EPM. Additionally, the same group found that overexpressing FAAH via PFC lentivirus injections resulted in increased-anxiety phenotypes. When trying to reverse this effect to confirm that endocannabinoid signaling was responsible for anxiety modulation, the group administered URB597, inhibiting FAAH release, which consequentially inhibits AEA degradation. This led to a decreased-anxiety phenotype in the EPM.

Amygdala

The amygdala is located just anterior to the hippocampus, in the frontal region of the temporal lobe (AbuHasan et al., 2022, Paxinos and Franklin, 2004). The amygdala is a complex structure subdivided into several nuclei. The amygdala consists of the lateral, basal, and basomedial nuclei, along with cortical-like regions, and the extended amygdala. The function of the amygdala in the brain is to regulate emotional responses to fearful or threatening events. The amygdala is responsible for detecting such stimuli and tying those memories to the emotions of fear or aggression (Suboski et al., 1970). In rats, bilateral intra-amygdala infusions of AM251 were associated with the prevention of fear memory reconsolidation (Lin et al., 2006). Similarly, this same group found that AM404, sped-up the process of fear extinction when infused into the amygdala. Similar results were found by Ganon-Elazar and Akirav in 2009, with a different CB_1R agonist, WIN 55, 212-2, suggesting that agonizing the CB_1 receptors in the amygdala can reverse learned fear, specifically inhibitory avoidance. This has major implications in PTSD. In this investigation, WIN 55, 212-2 was infused into the basolateral amygdala and stress responses were measured in three assays: the OFT, EPM, and VCT.

Figure 5c



Substantia Nigra

The substantia nigra is a part of the basal ganglia, along with the dorsal striatum, globus pallidus, and subthalamic nucleus (Stelt et al., 2003, Paxinos and Franklin, 2004). The substantia nigra is made up of the pars compacta and pars reticulata. The substantia nigra pars compacta along with the ventral tegmental area are the main structure that contain dopaminergic neurons. However, the substantia nigra pars reticulata mainly contains GABAergic neurons (Lanciego et al., 2012). The substantia nigra controls voluntary movements and dopamine-related reward responses (Sonne et al., 2022). In a clinical observational study by Gao et al. (2022), it was shown that patients with traumatic brain injuries were more likely to have a smaller substantia nigra and were more likely to exhibit anxiety and depression symptoms. Patients self-reported their symptoms using the HADS questionnaire.

Dorsal Striatum

The dorsal striatum consists of the caudate nucleus and the putamen, while its counterpart, the ventral striatum, consists of the nucleus accumbens and the olfactory tubercle. The term "striatum", anatomically, describes the white and gray matter striped appearance of this structure (Telford et al., 2014, Paxinos and Franklin, 2004). The dorsal striatum is a part of the basal ganglia and is responsible for voluntary movement, decision making and habit formation, especially in the context of reward-reinforcement (Chang et al., 2002). Investigations have shown that CB_1 receptor activation, through HU-210 and WIN 55, 212-2, is associated with a decrease in excitatory postsynaptic glutamate currents (Gerdeman et al., 2001). The dorsal striatum is very tightly connected with the dorsomedial PFC and this has implications in cannabis-related reward and cannabis dependence, also referred to as cannabis use disorder (CUD) (Haber et al., 2006).

According to Zhou et al. (2018), there is a dysfunction in regulatory control that drives the shift from voluntary actions to addictive ones. This dysfunction in regulatory control occurs as a result of a reward-related override. This same group conducted a clinical observational study with 24 cannabis-dependent individuals to explore the aforementioned dysfunction in their regulatory control. Using structural and functional MRI, they found that cannabis-dependent participants had a disconnect between both the dorsal and ventral striatal regions, and the dorsomedial PFC. Additionally, these participants also had an increased connectivity between the ventral striatum and the rostral anterior cingulate cortex, a structure that surrounds the frontal region of the corpus callosum, and is responsible for integrating emotion, attention, cognition, and memory development (Shi and Cassell, 1998, Paxinos and Franklin, 2004).

Stria Terminalis

The stria terminalis is heavily implicated in anxiety and PTSD because it mediates the startle response to fearful stimuli (Walker et al., 2003, Walker et al., 2010). It is a white matter projection located between the thalamus and the caudate nucleus (Nieuwenhuys et al., 1988, Paxinos and Franklin, 2004). The bed nucleus of the stria terminalis is a part of the extended amygdala, receiving nerve connections from the hippocampus, basolateral amygdala, and medial PFC (Heimer et al., 1988). In male Wistar rats, the injection of CBD into the bed nucleus of the stria terminalis was associated with an increase in open arm exploration in the EPM (Gomes et al., 2010). Additionally, these CBD injections were also associated with an increase in punished water intake in the VCT. Interestingly, the group found that the mechanism of this anxiolytic response was not through cannabinoid receptors, but rather through serotonergic 5-HT_1A receptors. The group found this mechanism by performing the same experiment again, but with additional pretreatment with WAY 100635, a serotonin receptor antagonist.

CANNABIS USE DISORDER

Classification, Symptoms, and Complications

Cannabis use disorder (CUD), as defined by DSM-V, is a type of substance use disorder, characterized by consistent, unhealthy dependence on cannabis, leading to clinically significant cognitive impairment and interruptions to daily life. According to DSM-V, oftentimes individuals with CUD take larger doses of cannabis, and for a longer period of time than they originally intended. Additionally, CUD individuals may spend a large amount of time attempting to obtain cannabis, or recover from its use, disrupting important occupational, recreational, and social activities. CUD individuals, particularly teenagers and college students, are more likely to recurrently use cannabis in situations when it is hazardous or unfitting. This makes sense, given that cannabis can be associated with an increase in risky driving and sexual behaviors (Lane et al., 2005, Bryan et al., 2012). This phenomenon is exacerbated by the frequent labeling inaccuracies found on cannabinoid and hemp-derived products (Spindle et al., 2022, Vandrey et al., 2015). Because there is not enough regulation on the labeling of these substances, oftentimes the steps required to accurately measure CBD and THC content are omitted. A study conducted by the University of Wisconsin-Madison (2022), finds that only 15% of CBD products currently sold in stores were labeled accurately; specifically, they had a significantly higher percent composition of CBD than advertised. Shockingly, this group also showed that many of these alleged CBD-only products actually contained measurable amounts of THC. This would not have been the case if strict regulations were placed on CBD product manufacturers to accurately and appropriately measure the amounts of CBD and THC their products contain. In the laboratory, a sophisticated and experienced researcher can tell the difference between the nearly identical collision-induced dissociation (CID) fragmentation patterns of THC and CBD in mass spectrometry, a task that is

extremely difficult for most cannabis manufacturers to do with their lack of technique and laboratory equipment necessary (Huang et al., 2021).

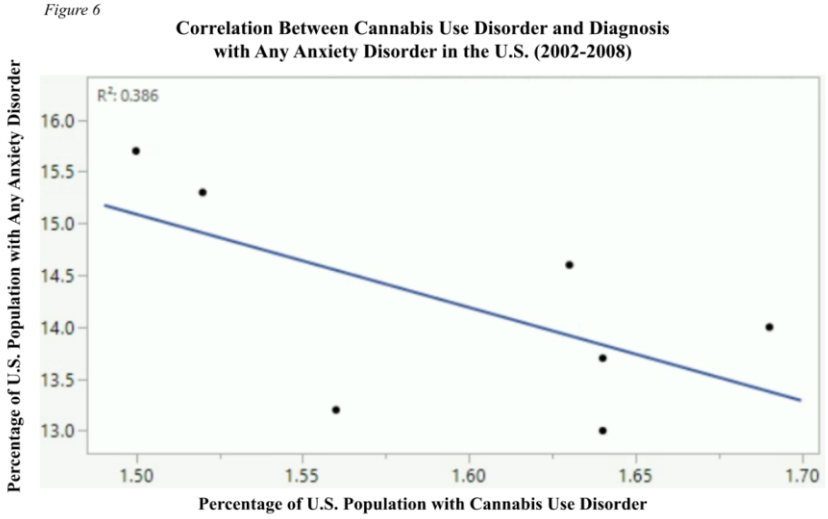
The most common cannabis withdrawal symptoms are sweating, muscle tension, bouts of anxiety and irritability, disturbed sleep cycles, loss of appetite, stomach pain, and chills (Hughes, 2005, DSM-V). Cannabis withdrawal symptoms start within 2 days to a week of abstinence from cannabinoid products (Goodwin et al., 2012). This is due to the downregulation and desensitization of CB_1 receptors (Landfield et al., 1988). This means that CUD individuals may need a higher dosage of cannabis to experience the same effects because they have become tolerant to it. Chronic, high-dosage exposure to cannabis can be neurotoxic. Complications of CUD may include chronic hyperemesis, suicidal ideations, and psychosis (Karila et al., 2014). According to the CDC (2022), CUD also increases the risk of myocardial infarction, stroke, coronary artery disease, heart failure, heart valve complications, arrhythmia, pregnancy complications, and other vascular diseases.

National, Statewide, and Regional Cannabis Use Demographics

According to the CDC (2022), about a third of cannabis users in the U.S. have been diagnosed with CUD. Based on the 2022 Gallup Consumption Habits Survey, among Americans between the ages of 18 to 34, 33% use cannabis; while among older Americans aged between 35-54 16% use cannabis and from those above 55 years of age, 7% use cannabis. People without a college degree were reported to use cannabis 6% more than those with a college degree, and men were reported to use cannabis 4% more than women. When Gallup first polled about cannabis use in 2013, only 7% of Americans reported trying cannabis at least once. Now this number has jumped to 48% of Americans. The Substance Abuse and Mental Health Services Administration (SAMHSA) conducts an annual National Survey on Drug Use and Health (NSDUH). The 2021 survey showed that 69.13% of cannabis users in the U.S. were Caucasian,

13.13% were Hispanic or Latino, 11.84% were African American, 2.74% were Asian, 0.77% were Native American, and 2.74% were biracial. According to this same survey, 50% of those experiencing CUD also experienced a comorbid mental health disorder. **Figure 6** shows a regression analysis between the prevalence of CUD and any anxiety disorder in the U.S. between 2002 and 2008. This data was gathered from Walters et al. (2012) and Compton et al. (2016).

Figure 6



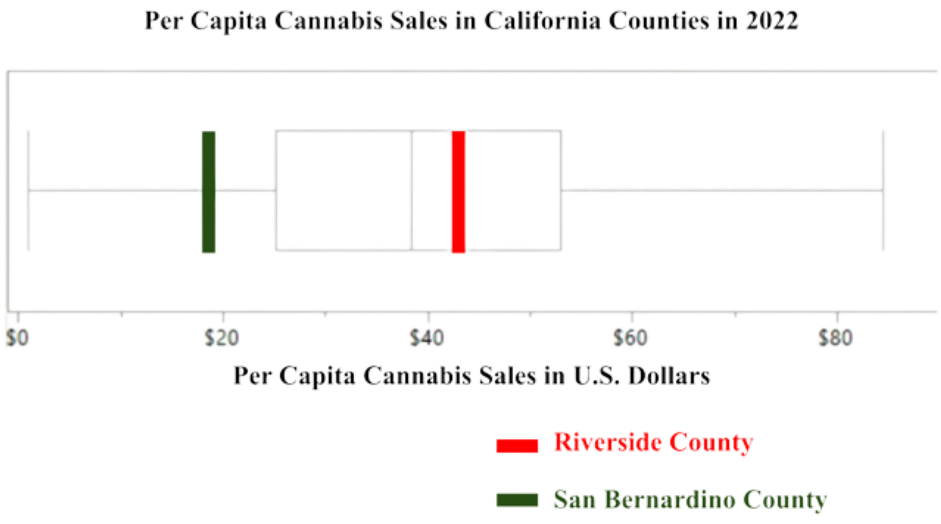
There is a weak correlation ($R^2 = 0.386$) between diagnosis with CUD and diagnosis with any anxiety disorder, however, there is not enough statistical power to state definitively whether the two are strongly related.

Based on a 2021 Cannabis Use report published by the California Department of Public Health, 12.8% of California 7th, 9th, and 11th graders reported using cannabis within a month previous to the survey. A further analysis of this showed that 23% of these youth cannabis users were Caucasian, 17% were African American, 14.3% were Hispanic or Latino, 4.2% were Asian, 14.7% were Native American, 11.9% were Pacific Islanders or Native Hawaiian, and 14.4% were of mixed racial background. The more concerning findings of this report were maternal cannabis use rates. An average of 4.2% of Californian women who had a recent live birth reportedly used cannabis during their pregnancy. This average was weighted based on race and age and the most prevalent cannabis users during pregnancy were African American women aged 15-19. Of note is that 59.7% of these women were living below the federal poverty line. These findings are

concerning because THC can cross the placental barrier (Bailey et al., 1987). While it is unclear exactly how THC can affect the developing fetus, research suggests that perinatal use may alter fundamental aspects of fetal development (Bernard et al., 2005, Antonelli et al., 2005, Antonelli et al., 2003). A study by Varner et al. (2014), found that mothers who had used cannabis during pregnancy were more likely to experience stillbirth. In 2020, Corsi et al. showed that maternal cannabis use during pregnancy is linked to an increased likelihood of pediatric Autism Spectrum Disorder (ASD). Finally, low birth weight — an ASD risk factor — is also linked to maternal cannabis use during pregnancy (Michalski et al., 2020). The California Cannabis Use Report also showed that 10.5% of Californians used cannabis consistently for 20 days each month. This means that 4,084,951 Californians were consistent cannabis users, and of those individuals, 16%, or about 676,000 people met the criteria for CUD. However, of those individuals, only 17,782, or 2.63% were admitted to California CUD treatment programs. 41% of these individuals were younger than 17 years of age. Overall, 15% of individuals at California substance abuse treatment facilities were there due to CUD. Another troublesome finding from that report is that the number-one drug of abuse consumed by drivers involved in motor vehicle crashes was cannabis.

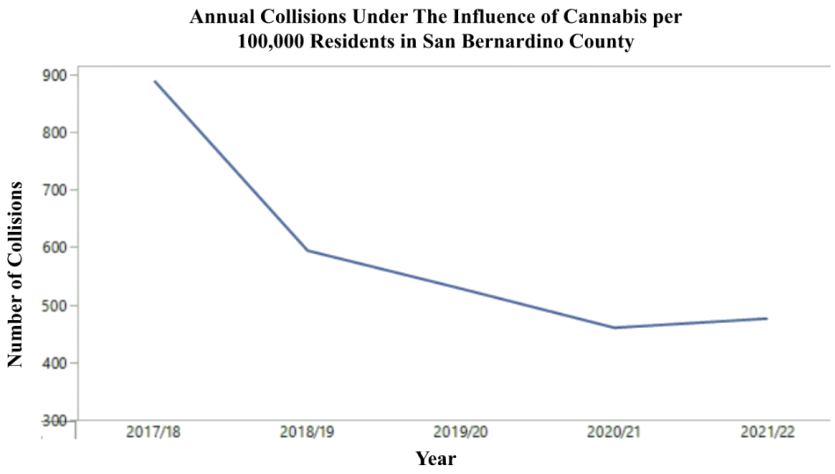
The statistics and health indicators referring to cannabis use in Riverside and San Bernardino counties were scarce and generic. Meanwhile, for other more seriously abused drugs such as amphetamines and

Figure 7a



opioids, the data was more extensive and up to date. According to the California Department of Tax, as shown in **figure 7a**, Riverside County's per capita cannabis sales in 2022 were in the 60th percentile of California sales tax, at $44.45, while San Bernardino's per capita cannabis sales were in the 23th percentile of California sales tax, at $19.09. **Figure 7b** shows the number of cannabis-related motor vehicle collisions in San Bernardino County (San Bernardino 2020 Health Indicators Report). There were not many more reliable reports run by each county to indicate the local rates of CUD. However, this only shows that more research and attention need to be allocated to CUD in our region to truly understand more about the demographics and treatment trends and to improve the health of our community in Inland Southern California.

Figure 7b



CONCLUSION

More research is necessary to assess the therapeutic potential of cannabinoids and cannabinoid-derivatives and to ensure the safety of recreational cannabis users. Though academic research on cannabis is expanding and becoming more sophisticated, cannabis' schedule 1 federal designation remains a roadblock for a staggering number of labs. This designation makes it difficult for researchers to obtain cannabis and to adequately research it. Reconsidering the schedule 1 classification of cannabis may be a necessary step in advancing our knowledge surrounding CUD and its long-term impacts on human health. Academic research has the potential to be a useful resource in the midst of growing social and educational concerns relating to cannabis

use. It is clear by the lack of reporting in the Inland Southern California Region that County authorities need to consider CUD to be a more serious health indicator just as opioid and amphetamine addiction. Many users are misinformed about the safety of cannabis use and its potential side effects following chronic exposure. Hence, more community health education that is delivered by non-biased medical professionals is needed for safe and responsible cannabis use. In particular, this education needs to take place in areas with socioeconomically and educationally disadvantaged individuals because these are the areas with the largest safe-cannabis-usage knowledge gaps. K-12 education must also contain some curricula about the effects of cannabis consumption on neurological development because, as shown in some aforementioned reports, cannabis use can start as early as 7th grade for some individuals. Additionally, there needs to be a stricter regulation system for labeling cannabinoid products and ensuring that they have the correct, advertised amount of CBD and THC, so that consumers do not unknowingly develop a tolerance for these CB_1 receptor modulators. As a scientific community, we've made incredible strides in improving public knowledge of cannabis and its impact on individual and societal health outcomes, but we still have much to accomplish. I hope that this review will serve as one step in the right direction.

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