A Review of Δ-9-Tetrahydrocannabinol's Effect on the Hippocampus and Evaluation of Behavioral Memory Impairment in Acute and Chronic Cannabis Users

by

TYLER COZY

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Brice A. Kuhl

The history of marijuana use for clinical and recreational purposes dates back centuries, but its legalization in the United States by several states has produced record sales. Therefore, there is also a record amount of people who are experiencing the acute, and potentially chronic, effects of Δ-9-Tetrahydrocannabinol, which is the psychoactive cannabinoid found in marijuana. The toxicity of THC to various brain regions has been underestimated for quite some time, and thus, this review seeks to evaluate the current scientific consensus on the dangers of THC neurotoxicity to hippocampal cells; another goal is to investigate the resultant impairment to memory that repeated endocannabinoid activation may proliferate. The results of this evaluative review indicate that chronically cannabis-dependent users do show poorer performance on behavioral memory tasks in comparison to light/non-users of marijuana. This is backed up by evidence in animal studies that found THC to produce decreased viability of hippocampal neurons. Although, while clinical trials may demonstrate inhibited performance on memory tasks in response to chronic THC exposure, the day-to-day effect of marijuana to an individual's memory may vary greatly depending on the total volume of marijuana that is consumed, and how often the brain is being insulted. In conclusion, increased chronic exposure to THC is associated with an increased risk for developing impairments to memory and deficits to optimal cognitive functioning.

Acknowledgements

I would like to express my esteemed gratitude to the advisors on my thesis committee: Dr. Brice Kuhl, Dr. Nathan Tublitz, and Dr. Barbara Mossberg. You all shaped my understanding of how to tackle such an interesting and pertinent topic, and inspired me to write with a passion and energy that I otherwise may have not realized on my own. I am so grateful to have had the support and encouragement of my advisors, and my family and friends who were never reluctant to extend me a word of advice whenever I felt like I was at a roadblock. I am indebted to these people who were willing to expend their own time and energy to contribute to my successes, and I cannot wait to pay it forward. A special thanks to Max Ralph and Nicholas Getz is in order, whom who were never even reluctant to answer my phone calls, and provided me with encouragement and insight to the thesis process even when they were busy with their own lives after graduation. Miriam Jordan, the amazing Thesis Coordinator at the Robert D. Clark Honors College at U of O, must definitely be thanked for perfectly answering my many questions along the way to completion of the thesis requirements. The successes I experienced in writing this thesis are most definitely not solely my own accomplishments, for I hope the pride I take in this literature is shared among those who have undyingly been there for me when I needed them; I could not have done it without you all!

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Background

Overview of Marijuana in Oregon

Cannabis use stems back far into history, being cultivated in China for its fibers, and used for medicinal purposes in the Middle East and India for over 5000 years.[1] Due to its long history of use, smoking marijuana is so commonly recognized in today's society, that scent of cannabis has become quite difficult to resist noticing. The popularity of the cannabis plant for recreational use has more recently come to the forefront, as several states have, in recent years, successfully passed legislative measures to allow for the recreational use, growing, and possession of marijuana for individuals 21 and above.

The states that gained enough support to pass majority votes include: Colorado, Washington, Alaska, the District of Colombia, and Oregon. The struggle of legalizing marijuana for recreational usage faced the same roadblocks as the proponents for clinical marijuana use did. There have been only 25 states (out of 50) in the U.S. to legalize marijuana for the clinical applications of exogenous cannabinoids found in marijuana.[2] This leaves an equal number of states that are in discordance with allowing for the trade-off of potential harms of marijuana use in lieu of the benefits that have been identified. Thus, it becomes more obvious that the troubling question for those states is: Are there any adverse risks of using marijuana, whether recreationally or for

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[1] Reisine, Terry, and Michael J. Brownstein. "Opioid and cannabinoid receptors." Current opinion in neurobiology 4.3 (1994): 406-412.

2 ProCon.org. "III. Sources for Legal Medical Marijuana States and DC." ProCon.org. 1 June 2012, updated 6/28/2016, medicalmarijuana.procon.org/view.resource.php?resourceID=004094

clinical applications, which would then expose different populations to the various cognitive deficits that may coincide with marijuana use? [3] This question becomes even more pertinent when thinking that those populations include teenagers, adults, and especially children with cancer who would then be at risk for experiencing impairment of their neuro-maturational development, which marijuana threatens through activation of the cannabinoid receptors throughout the brain; among the other potential side effects produced by the psychoactive THC molecule that will be mentioned in this thesis.[4]

Despite the inhibitions of many states to legalize marijuana for medicinal use, the four states that have legalized the recreational sale and usage of marijuana have already begun capitalizing on acquiring revenue from cannabis sales. Oregon has overshot all recreational sales records by millions of dollars, reaching $11 million in the first week of dispensary sales. After 6 months, total sales equated to a massive $102 million since January of 2016. At a 17% tax rate on recreational marijuana, $25.5 million in tax revenue was produced from those first six months of recreational marijuana sales, alone.[5]

From these sales figures, it is clearly notable that there are an equally large number of individuals being subjected to the cascade of reactions that result from THC binding to the cannabinoid receptors within many important brain regions such as the: medulla, cerebellum, basal ganglia, cerebral cortex, hypothalamus, spinal cord, and the hippocampus. As a result, there are a plethora of effects that proliferate from the

[3] Volkow, Nora D., et al. "Adverse health effects of marijuana use." New England Journal of Medicine 370.23 (2014): 2219-2227.

[4] Hill, Kevin P., and Roger D. Weiss. "Minimal Physical Health Risk Associated With Long-term Cannabis Use—But Buyer Beware." JAMA315.21 (2016): 2338-2339.

[5] Oregon Department of Revenue, August 22, 2016.

activation of the cannabinoid receptor. With the popularity of marijuana use, these effects pose risks to a substantial number of people. A study by Jacobsen, et. al. found that cannabis use is prevalent even among nearly half of all U.S. 12th graders, supporting that marijuana continues to be one of the most widely used illicit substances, even in some demographics which marijuana is not legally available to them.[6]

These younger populations may or may not be aware of the effects on memory that marijuana can cause; especially when they are going through their respective educational programs and being tested on their ability to recall knowledge and demonstrate mastery of various subjects. The effect that THC has on memory has been highly studied, as the risks of chronic cannabis use on memory is concerning, especially since marijuana is so commonly used. Therefore, this thesis seeks to evaluate the current scientific consensus on the effects of chronic and acute marijuana use on the hippocampus, and whether impairments to the hippocampus by THC can be a threat to successful and confident usage of one's memory.

Hippocampus overview and types of memory

Derived from the Greek words, "hippos," and, "kampos," the hippocampus is aptly named for its uncanny resemblance to the shape of a Sea Horse. The functionality of the hippocampus is essential to human life, as it allows for an entire lifetime of experiences to be recorded as they happen, and then stored in the brain for reflection at a later time. The conglomeration of memories and experiences that make up a person's

[6] Jacobsen, L. K., Mencl, W. E., Westerveld, M., & Pugh, K. R. (2004). Impact of cannabis use on brain function in adolescents. Annals of the New York Academy of Sciences, 1021(1), 384-390.

life are the basis from which their actions and decisions stem. In this respect, the foundation for a person's morals is bound to their hippocampus. Without a memory, life could not last longer than the moment you are currently living, with no way of conceptualizing any moments before or after. What's more, the hippocampus also pieces together fragments of memory to create hypothetical future events out of the bits and pieces of the past. The loss of functionality of the hippocampus would therefore be detrimental to what makes a person who they are, which is resultant of the memories of their life history.

The memory-recording organ is housed close to the center of the brain and lies within the medial temporal lobe, having major functionality within the limbic system.[7] Made up of many interconnected neural structures including the hippocampus, the limbic system can be understood as the part of the brain that reacts to emotional stimuli, in addition to being a memory-forming assembly line; this explains why memories are often accompanied by a filter of emotion (for example, remembrance of the loss of a family member may result in crying). Made up of an input/processing component via the hippocampus, and an output component, the limbic system is majorly interconnected to allow for all-inclusive memory formation.[8] See figure 1 below for some more information on the types of memory with which humans are equipped.

[7] Wright, Anthony. "Limbic System: Hippocampus (Section 4, Chapter 5)." Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston. UTHealth, 1997-present. Web. 04 Feb. 2016.

[8] Swenson, Rand. "Chapter 9 - Limbic System." N.p.: n.p., n.d. N. pag. Review of Clinical and Functional Neuroscience. Dartmouth Medical School, 2006. Web. 05 Feb. 2016.

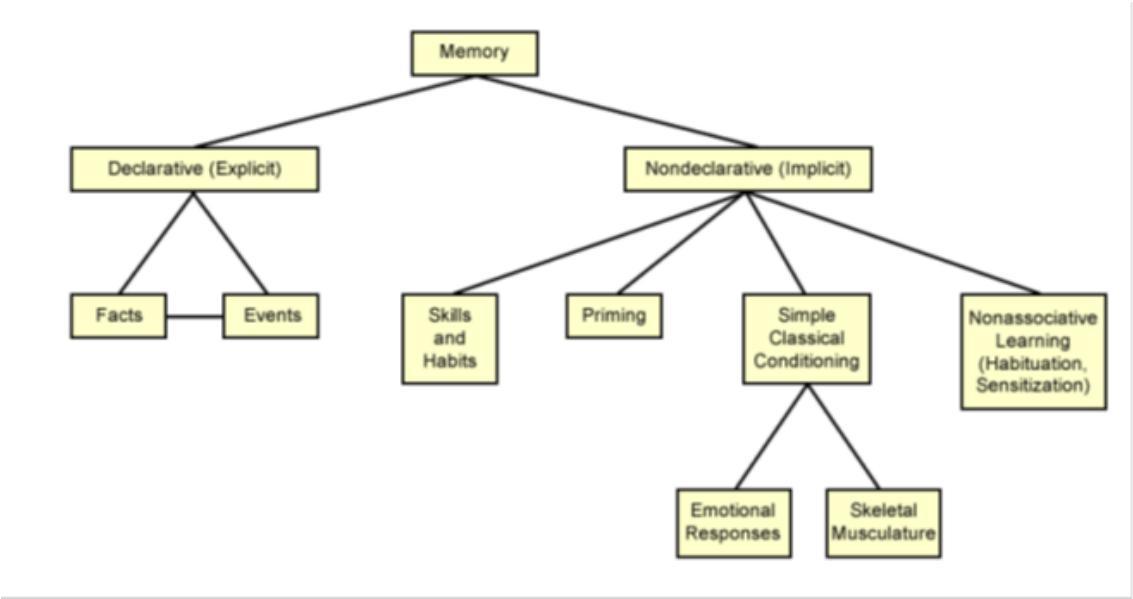

Figure 1. Diagram showing types of memory and their applications

The limbic system's production of memories can be divided into two subcategories, but specializes in the first: Declarative (explicit) and Non-declarative (implicit). Non-declarative memory is associated with, but not limited to, remembering mechanisms of motor function and is often sub-cortically controlled to produce movements such as walking or driving; in general can be described as "knowing how," and has less association with the limbic system and hippocampus. Declarative memory, which critically depends on the hippocampus, is the conscious ability to recall specific facts and events, or "knowing what". THC definitely impacts these skills when binding to the cannabinoid receptors that densely populate the hippocampus and other brain structures. But do these impairments last after the THC insult ends?

Henry Molaison (HM), a gentleman who had his hippocampus surgically removed as a strategy to help cease his recurring epileptic seizures, has allowed many studies to have since been pursued to uncover what the hippocampus does do, and also identify the functions for which it is not responsible. In many scientific cases, damage to a specific organ often reveals what function that organ primarily serves, because the function will be obviously absent. This case is no different, as the removal of HM's hippocampus immediately revealed that he struggled to form any new memories from

day-to-day, and the memories, events, and facts that he *could* remember, all had occurred previous to his surgery.

HM was a noble study subject, dedicating over 40 years of his life participating in thousands of memory-related experiments, each of which, ironically, felt entirely new to him no matter how many times they were repeated. Contrastingly, he did not struggle to show improvements while learning new motor skills; yet he still lacked the ability to acknowledge that he had learned these new skills. These discoveries that HM made possible not only revealed the major role that the hippocampus plays in the formation of new declarative memories, but also that memories are, in fact, stored elsewhere within the brain than the hippocampus and somehow maintain interconnectedness to emotions. HM demonstrated the ability to learn motor skills, showing that motor functions could still be utilized subcortically via non-declarative memory. This proves that the hippocampus is not entirely involved in reproducing motor functions stored in memory, and the process for recording and storing declarative information must be different than for non-declarative exercises. [9] There are many studies that have explored the impact of THC on the hippocampus and on memory that this thesis will explore, but before diving into human and animal studies, we will take a moment to examine some other notable behavioral side-effects that the psychoactive THC molecule can produce in its users, and how they influence the effect that marijuana can have on memory.

[9] Byrne, John H. "Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston." Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston. UTHealth, 1997-present. Web. 05 Feb. 2016.

Intro to the effects of THC on memory

There is plenty of research outlining the physical and behavioral effects of THC on memory, though various studies also include some other characteristic behavioral effects that THC produces that are related to its impending threat to memory, and so are important for marijuana users and potential marijuana users to be aware of.

Whether used clinically or recreationally, marijuana affects the nervous system in a robust fashion. There are two main types of cannabinoid receptors in our bodies that THC can affect us through: the CB1 receptor and the CB2 receptor. The highest densities of CB1 receptors are found in the cerebellum, striatum, and the hippocampus, whereas the CB2 receptors are located within the spleen and hematopoietic cells of the body.[10] These cannabinoid receptors produce the effects of marijuana through their G-protein coupled receptors (GPCRs). When THC binds to the CB1 cannabinoid receptor, there is a response mediated from the main G-*alpha* subunit, along with a set of second messengers that produce another cascade of reactions from the $G\beta$ and $G\gamma$ linked dimer subunits. As a result, the CB1 and CB2 receptors produce an assortment of effects throughout the body, as depicted on the following page in figure 2. There has been research completed on the physiology of cannabinoid signaling, but in order to maintain a narrow scope of research, this section will focus on some behavioral effects that are observed and experienced as a result of chronic cannabinoid activation by THC, and the threat to memory presented by such effects.

[10] Ameri, Angela. "The effects of cannabinoids on the brain." Progress in neurobiology 58.4 (1999): 315-348.

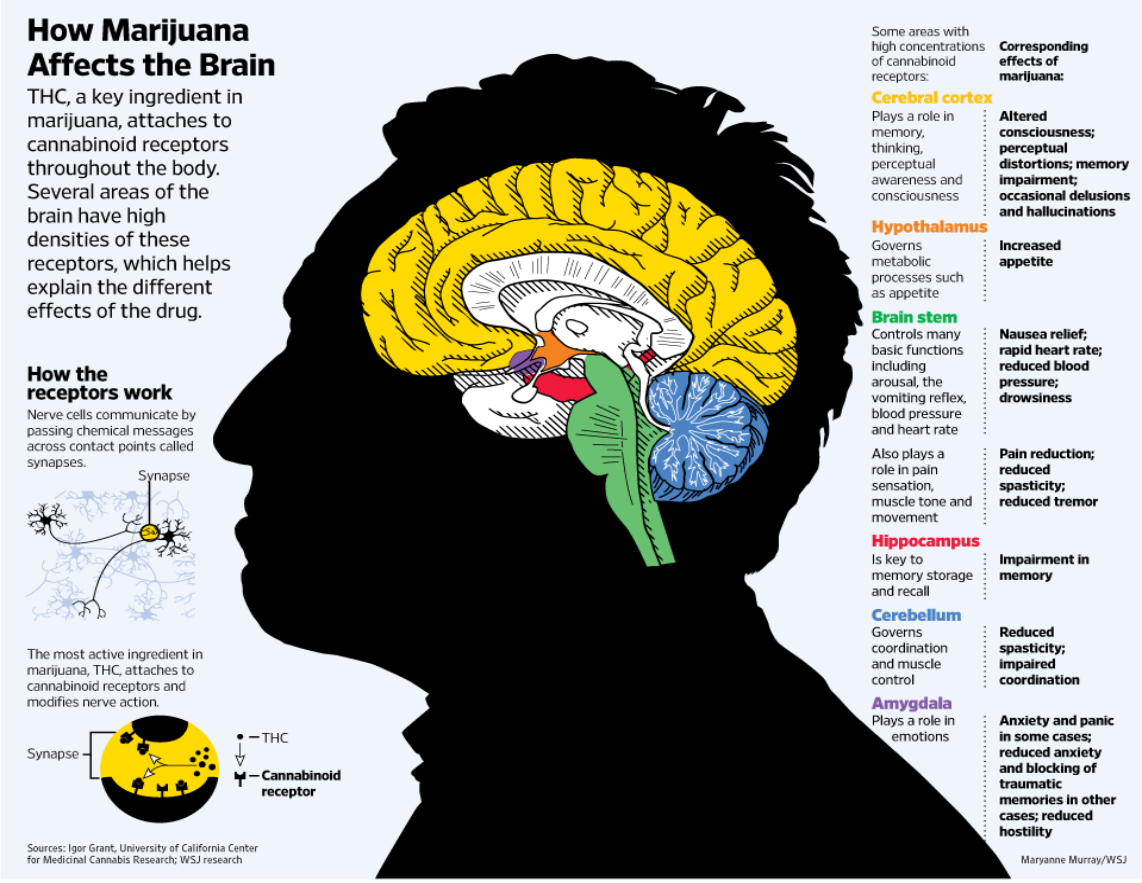

Figure 2. Color-coded diagram outlining the effects of THC on the Brain via areas of highly concentrated cannabinoid receptors

The effects of THC binding to the cannabinoid receptor produce a plethora of effects through at least 6 different brain regions, as can be seen by the list of metabolic processes that are being altered by THC in bold on the right.

Effect on memory through the addictive risk and withdrawals of chronic THC usage

The risk of damage to the hippocampus and memory is not solely related to THC activating the CB1 receptors within the brain, but also correlates to the decisions people make on how often to consume marijuana. The cognitive processes of decision making, planning, and self-regulation are known to be extensions of "executive functioning" that are controlled within areas of the prefrontal cortex.[11] There is another line of research that examines how the basal ganglia, and the nucleus accumbens in particular, may play a key function in the selection of executing actions.[12] Being another brain organ highly populated with cannabinoid receptors, the nucleus accumbens functions as the dedicated reward system of the brain. Activation of this system contributes to the feelings of euphoria experienced by cannabis users, and may additionally be linked to why marijuana has been known to be addictive when used extensively. A study by Tanda, et. al. examined the behavior of squirrel monkeys in response to being subjected to a self-administered injection of THC by repeatedly pressing a lever. When provided with THC the monkeys pressed the lever significantly more times and received more injections than when the self-induced injection was replaced with a saline solution. It is quite noticeable that the monkeys exhibited behavioral addictiveness to THC when looking at the graph from Tanda's study below.[13]

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[11] Purdy, M. (2011) Executive functions: Theory, assessment and treatment. In M. Kimbarow (Ed.), Cognitive communication disorders. New York: Plural publishing.

[12] Stephenson-Jones, M., Samuelsson, E., Ericsson, J., Robertson, B., & Grillner, S. (2011). Evolutionary Conservation of the Basal Ganglia as a Common Vertebrate Mechanism for Action Selection. Current Biology, 21(13), 1081-1091.

[13] Tanda, Gianluigi, Patrik Munzar, and Steven R. Goldberg. "Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel

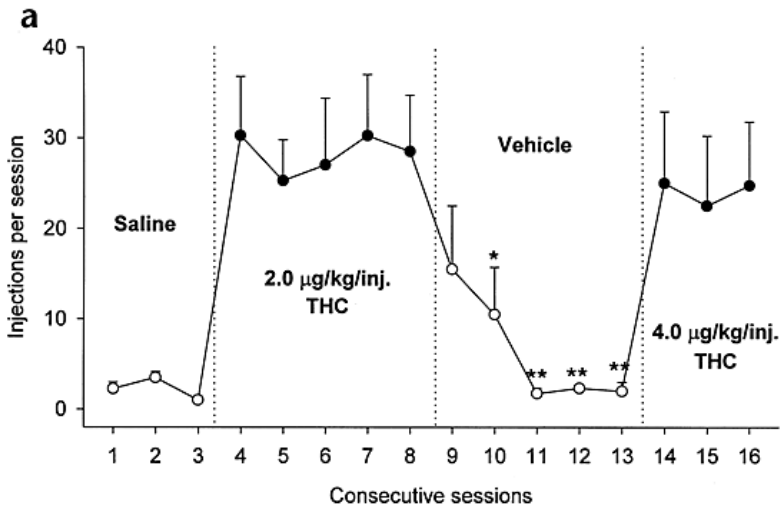

Figure 3. Graph displaying behavioral addiction of squirrel monkeys to the psychoactive constituent THC found in marijuana.[13]

This spike in drug usage is due to the fact that the squirrel monkeys are experiencing a comparable sense of euphoria that is experienced by human marijuana users; since it is so easy to attain that sense of euphoria simply by repeatedly pressing the lever, the animals then demonstrate the habitual desire/need to achieve that easy reward provided by THC. This is because their brain associates the lever with the euphoric sensation that will follow the injection. Humans can indeed also be at risk for developing this association in their brain over time as well, as the act of smoking marijuana can eventually be known, by the brain, to produce the euphoria or other side-effects deemed enjoyable by the user.[13] Such a cause-and-effect connection in the brain can then result in a user ultimately making the decision to repeatedly smoke marijuana in anticipation of that reward, without realizing that their hippocampal neurons are also being subjected to the consequences of THC toxicity.

monkeys." Nature neuroscience 3.11 (2000): 1073-1074.

Another issue with chronic THC usage is that users can develop dependence to the drug, as confirmed by the appearance of withdrawal symptoms that occur when usage is halted. A review of the significance and validity of cannabis withdrawal syndrome, completed by Budney, et. al. posited that marijuana withdrawal symptoms, when associated with long term, daily consumption of cannabis products, can be noticed within one day of smoking cessation.[14] In a human model outpatient study of daily cannabis users who smoked an average of 3.6 times per day, the severity of marijuana withdrawals on the parameters of aggression, restlessness, reduced appetite, and difficulty sleeping were assessed, as shown in figure 4:

[14] Budney, A. J., Hughes, J. R., Moore, B. A., & Vandrey, R. (2004). Review of the validity and significance of cannabis withdrawal syndrome. American journal of Psychiatry, 161(11), 1967-1977.

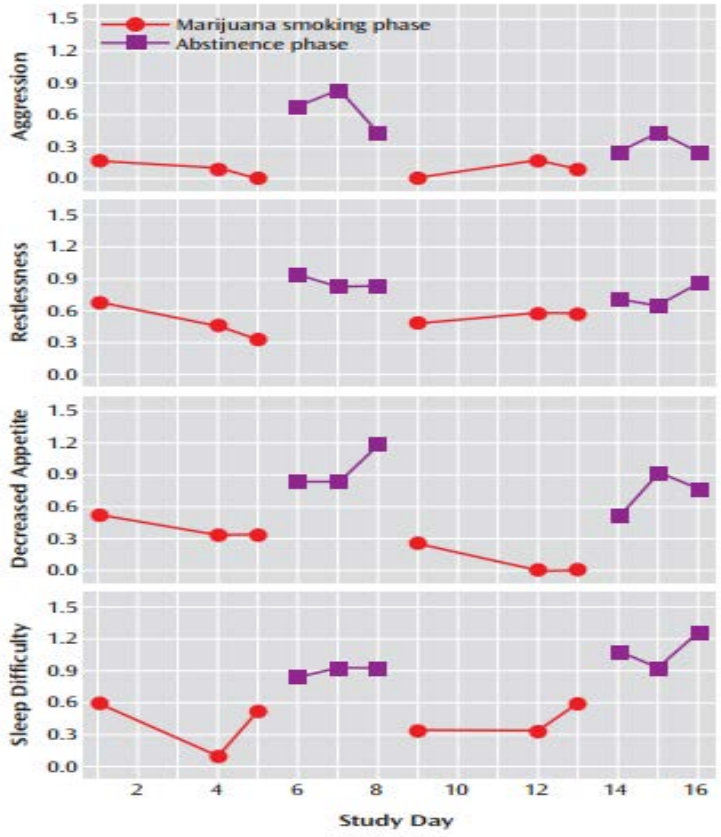

Figure 4. Mean Scores for Four Withdrawal Checklist Items Across Time in a 16-Day Study of Effects of Abstinence From Cannabis in Chronic Marijuana Users (N=12)

This study provides evidence that withdrawal symptoms can arise in chronic daily cannabis users even after one day of abstinence, and in turn exemplifies how cessation of marijuana use can present unpleasant symptoms that may cause for a desire to use marijuana to alieve those symptoms, so that it may be easier to sleep or eat.[15] However, light/non-daily users were less prone to experiencing the same severity of withdrawal symptoms.[14,16,17]

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[15] Budney AJ, Hughes JR, Moore BA, Novy PL: Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry 2001; 58:917–924

[16] Lichtman AH, Martin BR: Marijuana withdrawal syndrome in the animal model. J Clin Pharmacol 2002; 42:20S–27S

[17] Harris RT, Waters W, McLendon D: Evaluation of reinforcing capability of delta-9 -tetrahydrocannabinol in rhesus monkeys. Psychopharmacologia 1974; 37:23–29

These findings are important to consider when thinking about the threat that extended marijuana use poses to the memory. A chronic user's cognitive decision making process may be swayed by their brain's addiction to getting "high," or even affected by the desire to relieve the unpleasant symptoms that arise when daily use is halted. These reasons to continue using marijuana do not evaluate whether the hippocampus is being damaged, and additionally threaten the healthy functioning of one's memory because continued daily THC exposure might be personally justified from user to user by the reasons mentioned above, leaving hippocampal neurons at risk for impairment that only worsens as the duration of THC dependence lengthens.[15]

Direct effects of THC on the hippocampus and impact on memory

In order to evaluate the way that marijuana physiologically impacts the hippocampus and therefore affects behavioral memory, findings from acute and chronic animal studies will be presented, followed with information extracted from a number of acute and chronic human studies. This will provide a good overview of how THC physiologically affects the hippocampus, in addition to examining effects on memory experienced by cannabis users across a variety of conditions.

Memory & marijuana in animal models

THC's effect on hippocampal neurons in animal models

While no rats were harmed in the making of this thesis, a number of Sprague-Dawley rats bravely underwent rigorous memory testing and subsequent heroic sacrifice to allow for the development of knowledge on how hippocampal neurons respond to THC dosages. Thankfully their sacrifice was not in vain, as several studies were able to uncover previously unknown information about the way that THC produces memory impairment through activation of the CB1 cannabinoid receptor. A study by Guy Chan, et. al. discovered the risk of hippocampal neuron toxicity that is associated with marijuana use in 1998. He and his cohorts treated hippocampal neuron slices from rat brains with THC ex vivo (meaning they produced the results by experimenting with rat brains that have been removed from their bodies) and saw reduced viability of the hippocampal neuron cells as a result of THC's exerted effect.[18] They also

[18] Chan, Guy Chiu-Kai, et al. "Hippocampal neurotoxicity of Δ9-tetrahydrocannabinol." The Journal of neuroscience 18.14 (1998): 5322-5332.

experimented with antagonists of the CB1 receptor to identify whether it was the CB1 receptor activation via THC that was mediating the neurotoxic effects. When the CB1 receptor was being blocked by an antagonist (neuronal slices were pre-soaked for 20 minutes), THC would no longer able to activate the receptor even after 5 hours of treatment, and the hippocampal cells were able to maintain a greater degree of viability.[18]

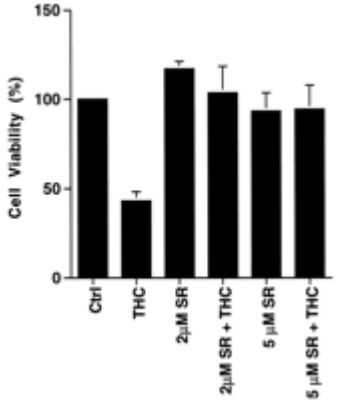

Figure 5. Impact of THC on hippocampal neurons and attenuation by CB1 antagonists

The results of this study show that THC reduced hippocampal cell viability by more than 50%, showing significant impairment to these cells and evidence for hippocampal neurotoxicity of THC. The antagonists shown as 2μM SR and 5μM SR both presented no deleterious effects to the hippocampal neurons, and even seemed to protect the cells from degrading by effectively blocking the pathway cascade produced by THC. This is because the antagonists compete with THC to bind to the receptor, and therefore disallow THC to bind because the receptors are occupied by the antagonists. As a result the CB1 receptor is not activated, and there is no observed loss of function or synaptic damage.[21]

The evidence presented above for hippocampal neurotoxicity of THC leads researchers to the next question: How does THC produce the observed damage to hippocampal cells? The same researchers mentioned above were able to discover that

the enzyme Phospholipase A2 is activated by the CB1 receptor, which results in the production and release of arachidonic acid.[18] Moving right along to 2014, a study by Rongqing Chen, et. al. discovered the importance of the cyclooxygenase-2 (COX-2) enzyme within the cascade of reactions following CB1 activation by THC. The visual aid produced by Chen and his partners may help to follow how the G protein coupled receptor leads to the formation of COX-2 and subsequent causation of memory impairment; see the following page.[19] They also began discussion of the use of non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen to help attenuate the negative impacts to memory because of their ability to block the production of COX-2.[19] Although, there was no mention of the impending dangers of these drugs, which can be harmful to the lining of the stomach with excessive use. So while such NSAIDs may be effective protectors of memory, there are side effects that limit their usefulness in the long term treatment of cancer symptoms, for example.

[19] Chen, Rongqing, et al. "Δ9-THC-Caused Synaptic and Memory Impairments Are Mediated through COX-2 Signaling." Cell 3.156 (2014): 618.

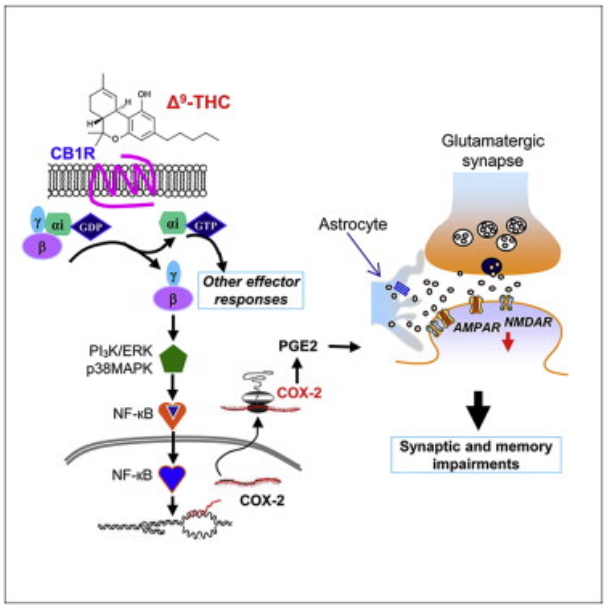

Figure 6. Diagram of the CB1 receptor's cascade of reactions following THC activation

Exposure to THC is associated with the induction of COX-2 via the beta and gamma subunits of the CB1 receptor's GCPR colored in blue and purple above. Once cyclooxygenase-2 is produced, it enzymatically reacts with arachidonic acid to form prostanoids in the brain, represented by PGE2. Prostanoids function to induce anaphylactic and inflammatory responses, which effectively produce damage to the synapses by causing downregulation and internalization of glutamate receptor subunits. Alterations to dendritic spine density of these hippocampal neurons are also observed as a result of repeated THC exposure. These effects cause synaptic inefficacy, and resultant inability of hippocampal neurons to function normally, producing the impairment to memory that can be experienced by cannabis users.[19]

Another study performed in 2001 used the enzyme activator forskolin to induce synaptic formation within hippocampal cells in vitro ("in glass", like in a test tube) while simultaneously inducing activation of the cannabinoid receptor by THC. Forskolin and THC produce opposite effects, in that forskolin increases cyclic adenosine monophosphate (cAMP) concentrations by activating adenylyl cyclase. On the other hand, THC inhibits adenylate cyclase, effectively reducing levels of cAMP

through CB1 activation.[20] Since cAMP is an important signal carrier that allows for cell communication, forskolin should aid in synapse functionality, whereas THC produces impairment to synapse communication. The findings of this 2001 study by Daniel Kim and Thayer Stanley showed that the synaptic formation that was being induced by forskolin was inhibited and rendered ineffective when the CB1 receptor was activated by THC. Chan and his research team also found that a transcription blocker, actinomycin D, was indeed able to prevent THC-induced toxicity.[18] These results demonstrate how THC can modulate synaptic plasticity independent of neurotransmitter release, and again prove that hippocampal neurons are at risk of neurotoxicity by exposure to THC, possibly through transcription dependent cell death, leaving memory at stake.[21]

Evidence for acute behavioral memory impairment in animal models

Since the mechanism for memory impairment in the hippocampus has been conceptualized, the next question is whether or not the physiological evidence of hippocampal damage actually produces observable impairments to the usage of memory.

In order to determine the effects of THC on memory in animal models, many studies utilize a radial arm maze, or water maze test in order to assess the ability of rats to remember specific target locations and demonstrate learning by completing the

[20] Ameri, Angela. "The effects of cannabinoids on the brain." Progress in neurobiology 58.4 (1999): 315-348.

[21] Kim, Daniel, and Stanley A. Thayer. "Cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture." The Journal of neuroscience: the official journal of the Society for Neuroscience 21.10 (2001): RC146-RC146.

assigned tasks more quickly upon repetition. Observations from these studies varied in their results, but most often the rats acutely dosed with THC (6-10 mg/kg) would perform the tasks at a slower rate, in addition to producing redundant actions within the tests. For example, when completing the radial arm maze test (example pictured below), rats treated with THC in several experiments were observed to move at a reduced speed of locomotion as compared to the control group, and would even re-enter the same arms where they had already found a food pellet. These results contrasted the control groups who had no issues completing the maze without error after being taught the procedure (controls finished radial maze in ~57 s, and those treated with 6 mg/kg THC finished the maze in ~257 s, making up to 5x more errors). [22,23]

[22] Mishima, Kenichi, et al. "Characteristics of Learning and Memory Impairment Induced by. DELTA. 9-Tetrahydrocannabinol in Rats." The Japanese journal of pharmacology 87.4 (2001): 297-308.

[23] Molina-Holgado, F., M. I. Gonzalez, and M. L. Leret. "Effect of Δ 9-tetrahydrocannabinol on short-term memory in the rat." Physiology & behavior 57.1 (1995): 177-179.

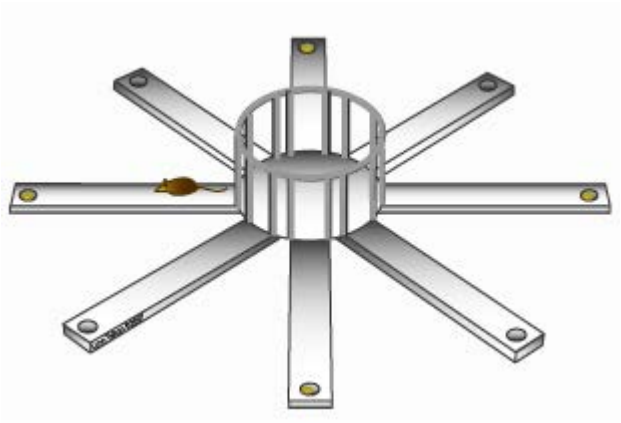

Figure 7. Image of an 8-arm radial maze used for testing memory in rat models

Rats begin in the middle and then complete the maze by traveling down the arms to find each of the food pellets, and the maze is successfully completed once each of the pellets have been found/consumed.

Another study exemplifying behavioral memory impairment in response to THC assigned various tasks to rhesus monkeys that had been trained to puff marijuana cigarettes. Their ability to complete a delayed matching-to-sample task effectively showed how THC impairs memory because the THC dosed monkeys would perform at a lesser degree of accuracy than the control groups. Another set of monkeys were administered an oral dosage of THC and similar results were produced. In these monkeys, who would be classified as non-users, there were significant impairments to memory, but the effects to memory did not last into the next day. This supports that very acute dosages of THC do no cause memory impairments that last longer than it takes for the insult to resolve.[24]

[24] Zimmerberg, B., S_ D. Glick, and M. E. Jarvik. "Impairment of recent memory by marihuana and THC in rhesus monkeys." (1971): 343-345.

Finally, another 8-arm radial maze experiment evaluated whether memory impairments were dose related, and aimed to observe the direct effects of various cannabinoids via intrahippocampal injections. The following cannabinoids were injected directly within the hippocampi of Sprague-Dawley rats:

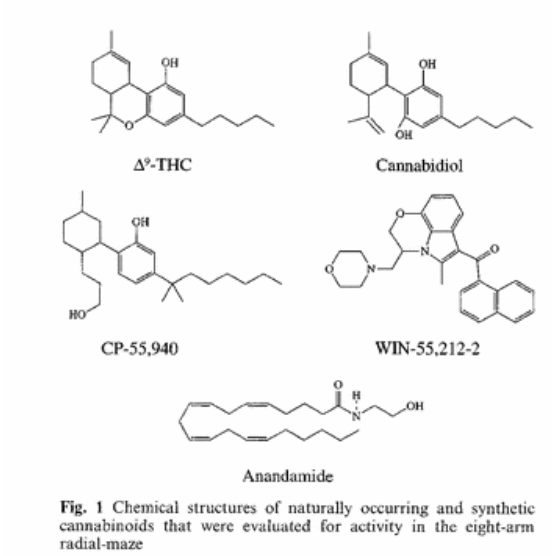

Fig. 1 Chemical structures of naturally occurring and synthetic cannabinoids that were evaluated for activity in the eight-arm radial-maze

Figure 8. Chemical structures of naturally occurring and synthetic cannabinoids that were used to test performance on the radial arm maze

Due to the similar functional groups and stereochemistry of the cannabinoids shown above, the CB1 receptor allows for the similar shapes to fit like a lock and key into its active site, and therefore exert its metabolic effects on memory and those otherwise mentioned previously in this thesis. The results of this study saw that the disruptive effects on memory associated with marijuana were only present in the dosages of THC, WIN, and CP. There were no apparent effects on memory from any volume of Cannabidiol (CBD) or anandamide injected to the hippocampus. It is also quite interesting to note that injection of these cannabinoids within the hippocampus seemed to specifically alter cognition, because no other pharmacological effects such as anti-

nociception, hypothermia, catalepsy, etc. were observed. This suggests that the effects on memory produced by marijuana are specifically localized to the cannabinoid receptors that reside within the hippocampus.[25]

Effect of chronic THC usage on memory in animal models

There are fewer studies available on the chronic use of marijuana in animals; the studies available that were completed on animal models observed the impact that chronic exposure to THC had on the developmental period of the brain during adolescence and how memory was then affected during adulthood. This section will present these findings on animals before going on to examine the effects that THC has on the more complex human brain.

In order to evaluate if adolescent chronic use of marijuana can lead to cognitive deficits in memory due to changes in brain infrastructure as a result of the endocannabinoid system being activated during development, Rubino and his colleagues studied two groups of rats from birth.[26] Two groups of mice were treated with THC and a placebo at 35 days post-natal twice a day until 45 days post-natal, and were then let mature without THC insult. They then began testing the groups at a mature age of 75 days post-natal. The differences between the placebo and THC groups were analyzed via different memory tests such as a water maze to test spatial and aversive memory. In a water maze, there is a tub of water that mice swim around in and

[25] Lichtman, A. H., Dimen, K. R., & Martin, B. R. (1995). Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats.Psychopharmacology, 119(3), 282-290.

[26] Rubino, T., Realini, N., Braida, D., Guidi, S., Capurro, V., Vigano, D., ... & Parolaro, D. (2009). Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. Hippocampus, 19(8), 763-772.

try to find the location of a small invisible block that they can climb onto. By using visual cues such as posters on the wall near the water maze, mice can learn the location of this stand and find it faster, demonstrating a process of learning. Results showed that aversive memory was not affected between groups but the THC pretreated groups demonstrated impairments to their spatial memory, as their water maze completion times rarely shortened. Aversive memory was not affected because early THC usage did not impair the rats' ability to learn and remember that they feared being placed in the water, and therefore being forced to swim until they found the safety of the perch. This shows that the rats demonstrate the ability to perform contextual learning, which plays a role in aversive memory, both having been shown to be linked to the function of the hippocampus.[27] It is important to note that these rats were not exposed later in their life to THC, only during adolescent years. So the poorer performance on the water maze could be derived from alterations to proper brain development in adolescence as a result of endocannabinoid activation.[29] O'Shea also provided evidence in 2004 that younger rats are at risk of more cognitive deficits (such as anxiety and impaired memory function) than rats who were subjected to THC usage after peak maturity. This research suggests that the impairments experienced by younger rats may be due to the improper functioning of their brain caused by THC being activated by the cannabinoid receptor during their development, when synaptic pruning and myelination of their axons is being regulated. On the other hand, adult rats that have already developed and matured

[27] Goosens, Ki Ann. "Hippocampal Regulation of Aversive Memories." Current opinion in neurobiology 21.3 (2011): 460–466. PMC. Web. 8 Sept. 2016.

are less likely to experience deficits that would persist because the development of their brain machinery was unaltered. [28]

Prelude to human studies

Before examining the acute and chronic effects of THC observed in humans, this section will show that the evidence of impairment to memory in developmental animal studies above shows similar results to a human study. By looking at the response to THC exposure in a human study that examines the effects on development of the adolescent human brain, this section hopes to display that findings in animal studies can be translatable to effects experienced by humans.

An fMRI study on 3 groups of human adolescents, all around age 17, evaluated the differences in performance on memory tasks for 7 cannabis users who also smoke tobacco, 7 tobacco users without history of cannabis use, and 7 non-smokers who served as the control group. The cannabis-smoking group contained individuals who began smoking at a median age of 13, an age where neuro-maturational changes are at risk for effect by THC exposure. They were all tested on measures of sustained attention, as well as selective and divided attention by using a word-recognition test. The adolescent cannabis users presented with deficits in sustained attention, and also were less accurate than controls for working memory tasks, as demonstrated in figure

[28] O'Shea, Melanie, et al. "Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats."Journal of Psychopharmacology 18.4 (2004): 502-508.

10. During the working memory task, functional Magnetic Resonance Imaging showed interesting discrepancies between the brain activation patterns of each group.

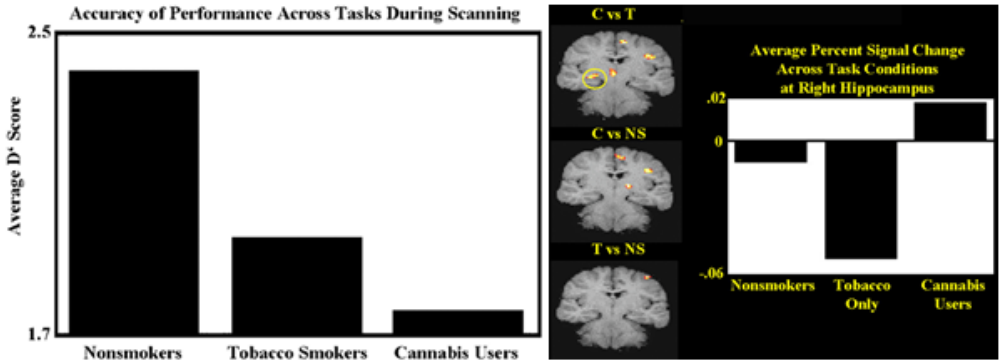

Figure 9. fMRI images alongside results of memory performance demonstrating cognitive deficits caused by adolescent marijuana use from Jacobsen's study.

The cannabis users were marked with the inability to deactivate the right hippocampus, while tobacco users and non-smokers were able to perform the same task without using that part of the hippocampus. Jacobsen's study posited that this is because hippocampal neurons play an important role to produce inhibition during mnemonic processing. And since the assigned tasks in this study necessitate the use of mnemonic processing, like remembering words 1-back or 2-back, the inability to perform at a high degree of accuracy on these tasks may be attributed to the failure of the inhibitory interneurons within the hippocampus to be functioning appropriately. Their team assumes that this effect may be due to THC-mediated inhibition of neurotransmitter release, which could in turn disrupt synaptic plasticity within hippocampal neurons or even be resultant of cannabis-induced apoptosis of the cells within the hippocampus. [29]

[29] Jacobsen, L. K., Mencl, W. E., Westerveld, M., & Pugh, K. R. (2004). Impact of cannabis use on brain function in adolescents. Annals of the New York Academy of Sciences, 1021(1), 384-390.

Additionally, it seems possible that the failure to deactivate portions of the hippocampus may be related to the cannabis-effected adolescent brain being unable to perform the same functions as non-users brain's without recruiting more neurons. As a result, they are functioning at a sub-optimized cortical efficiency, which could be linked to their early-onset of use. This suggests that there is danger of developing altered cortical activation patterns and an inability to efficiently localize specific brain functions, at least not as well as a matured brain that was not exposed to THC during development.[31,30] Though there is a caveat in that working memory is distinct from declarative memory; this suggests that deficits to performance on the working memory tasks in this study would not generally depend on the functions of the hippocampus. So this fMRI study appears to be of weaker relevance to the impending threat of THC to the hippocampus, and instead suggests the possibility of impairment to other structures within the brain.

[30] Becker, B., Wagner, D., Gouzoulis-Mayfrank, E., Spuentrup, E., & Daumann, J. (2010). The impact of early-onset cannabis use on functional brain correlates of working memory. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34(6), 837-845.

Marijuana and memory in human models

Acute effects of THC and CBD on memory observed in human models

While animal studies provide a solid outlet for proving that there is evidence of acute memory impairment as a result of THC use, human use of cannabis varies. A review of the acute effects of marijuana in humans confirms that cannabinoids impair many stages of memory, including encoding, consolidation, and retrieval. These effects are mediated through various mechanisms of depression, and long-term inhibition of neurotransmitter (GABA, dopamine, glutamate, and acetylcholine) release within the hippocampus.[31] However, there are many different strains of marijuana that contain varying percentages of exogenous cannabinoids, which can produce separate effects alongside THC. These differing strains produce different effects on memory, a study produced in 2010 suggests.

Two main cannabinoids found in marijuana are those known as delta-9-tetrahydrocannabinol and cannabidiol (CBD). The study by Morgan, et. al. focused on the acute effects of marijuana with high percentages of THC, as compared to the effects of marijuana with high percentages of CBD on memory. Their findings reflect evidence that CBD helps to attenuate the negative effects on memory that THC produces via activation of the cannabinoid receptor.[32] They found that marijuana low in CBD and high in THC produced more deleterious effects on memory than strains of

[31] Ranganathan, Mohini, and Deepak Cyril D'souza. "The acute effects of cannabinoids on memory in humans: a review." Psychopharmacology 188.4 (2006): 425-444.

[32] Morgan, C. J., Schafer, G., Freeman, T. P., & Curran, H. V. (2010). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. The British Journal of Psychiatry, 197(4), 285-290.

marijuana that were cannabidiol-rich.[32] Another team of researchers, once again led by Morgan, completed a study in 2012 that aimed to replicate the neuroprotective effects of CBD that they discovered in their 2010 study.

In an assessment of the sub-chronic impact of THC and CBD usage, a mixed group of 120 daily and recreational cannabis users were sorted into two groups, one consisting of users who revealed the presence of CBD in their system via hair sampling, and the other with no CBD detected. Assessments were conducted to evaluate degrees of psychosis-like symptoms, evidence of depression/anxiety, and usage of memory (specifically prose recall and source memory) in each group. The results of this study showed that individuals with higher levels of THC in their hair expressed increased feelings of depression and anxiety, while there were fewer psychosis-like symptoms found in individuals with CBD present in their hair. Once again, the individuals with higher levels of THC performed more poorly on memory tasks, and those with more CBD displayed better recognition memory. The results of this study indicate that there are potential benefits of CBD that attenuate the negative impacts of THC to memory via antagonistic effects mediated through interactions that are still being investigated.[33] Unfortunately the marijuana strains that dominate the market are high in THC, but the above studies suggest that CBD strains may be able to aid in reducing the amount memory-related impairments induced through endocannabinoid activation by THC.[32,33]

[33] Morgan, C. J. A., Gardener, C., Schafer, G., Swan, S., Demarchi, C., Freeman, T. P., ... & Wingham, G. (2012). Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychological medicine, 42(02), 391-400.

Impact of chronic marijuana use on behavioral memory for cannabis users

According to marijuana statistics from the University of Oregon Office of the Dean of Students, over 69 million Americans claim to have tried marijuana at least once.[34] This statistic is concerning when we look at the short history of research that has been conducted on cannabis. It was not until the 1940s that scientists discovered through analysis of hemp resin, the tetrahydrocannabinol nature of the THC molecule, and not until 1964 that the

Δ-9-THC molecule was fully identified by Goani and Mechoulam.[35] This means that in Oregon on July 1st, 2015, just 51 years after the discovery of the THC molecule, cannabis possession and recreational use was made legal to those over the age of 21— long before substantial testing could be done on the drug. There have since been a number of studies trying to discover any long term impacts of chronic marijuana usage, and there is evidence across these studies that cannabis users are unable to match the memory capabilities of non-users. [36,37,38,39] These studies are not just concerned with recreational marijuana usage, but also aim to discover risks associated with using marijuana for clinical use— as cancer patients want to keep proper usage of their memories too.

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[34] "Marijuana: Did You Know? ." Marijuana: Did You Know? University of Oregon Office of the Dean of Students, 2013. Web. 29 Oct. 2015. <http://uodos.uoregon.edu/Programs/SubstanceAbusePreventionandStudentSuccess/MarijuanaDidYouKn ow.aspx>.

[35] Goani, Y. and Mechoulam, R. (1964) Isolation, structure and partial synthesis of an active constituent of hashish. Journal of the American Chemical Society, 86, 1646-1647.

[36] Fletcher, Jack M., et al. "Cognitive correlates of long-term cannabis use in Costa Rican men." Archives of General Psychiatry 53.11 (1996): 1051-1057.

[37] Harvey, M. A., Harvey, M. A., Sellman, J. D., Harvey, M. A., Sellman, J. D., Porter, R. J., & Harvey, M. A. (2007). The relationship between non-acute adolescent cannabis use and cognition. Drug and alcohol review, 26(3), 309-319.

There is an ethical challenge involved with studying the deleterious effects of increasing marijuana exposure, so most studies on chronic marijuana usage are obviously retrospective.[38] This way, the healthy memory of a non-cannabis user would not be put at risk for means of scientific discovery. The current retrospective studies, however, provide interesting results that show how differing magnitudes of cannabis use can produce varying degrees of neurocognitive deficits that can last weeks after the cessation of smoking.[39,40] For example, Schwartz and his team performed neurocognitive testing on cannabis-dependent adolescents (and non-users for control) at a baseline of initial cessation, and then tested them again on a battery of 7 psychological tests after 6 weeks of supervised abstention. While the cannabis-dependent adolescents did show improvement to their test scores after 6 weeks, they failed to achieve statistically significant difference from their baseline scores. Based on this data, chronic marijuana usage can indeed produce selective short-term memory deficits that last for at least 6 weeks after the last consumption of marijuana, as demonstrated by the inability of the chronic users to achieve scores that were equivalent to their controls who never had exposure to marijuana.[39]

Schwartz's study provides evidence that there are costs associated with the chronic use of marijuana, and that memory is one of the cognitive functions that lays

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[38] Pope Jr, Harrison G. "Cannabis, cognition, and residual confounding." Jama 287.9 (2002): 1172-1174.

[39] Schwartz, R. H., Gruenewald, P. J., Klitzner, M., & Fedio, P. (1989). Short-term memory impairment in cannabis-dependent adolescents. American Journal of Diseases of Children, 143(10), 1214-1219.

[40] Battisti, R. A., Roodenrys, S., Johnstone, S. J., Respondek, C., Hermens, D. F., & Solowij, N. (2010). Chronic use of cannabis and poor neural efficiency in verbal memory ability. Psychopharmacology, 209(4), 319-330.

victim. In an attempt to determine whether abstaining from marijuana use after being chronically exposed to THC reduces those impairments to memory, another study by Hanson et. al. tested the effects of abstinence after they found evidence of persisting neurocognitive deficits at 1 month of ceased marijuana use in their initial 2007 study.[41] The second study they completed in 2011 examined adolescent users, aged 15-19, who had used marijuana over 200 times and who had smoked at least four times in the past month before the study. They excluded users with evidence of alcohol or other drug dependencies to eliminate those confounding variables. These users and their demographically similar controls were tested at 3 days, 2 weeks, and 3 weeks post-cessation. The results of their cognitive testing showed some improvements over time, as displayed in figure 11 on the following page.

[41] Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF J Int Neuropsychol Soc. 2007 Sep; 13(5):807-20

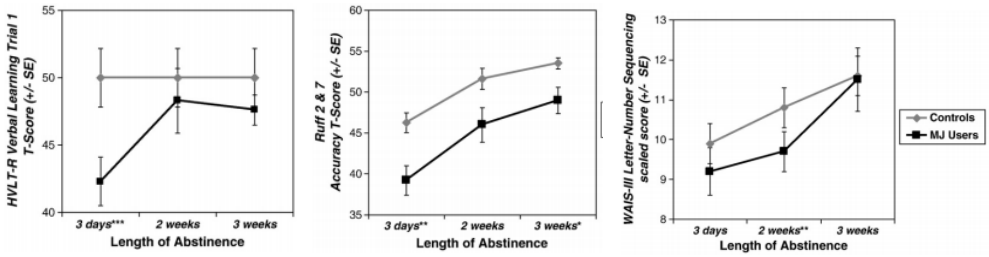

Figure 10. Results from 3 weeks of neuropsychological testing in: verbal list learning, attention accuracy, and verbal working memory in chronic and non-user adolescents.

Cannabis users demonstrated poorer performance than their control counterparts in each of the evaluations of neurocognitive functioning, confirming that there are deficits to memory that continue to effect cognitive performance for 3 weeks post-cessation. [42]

While abstinence from marijuana use after chronic usage shows evident deficits to competent memory functionality in scientific testing, other studies focus on the effects to memory through varying degrees of cannabis usage; these include studies of light usage to daily cannabis dependence, and even from <10 years of dependence to >30 years of repetitious THC exposure. [40,43,44]

Results from these studies demonstrated that after 12 hours of abstinence, regular daily users perform significantly more poorly on the cognitive functions of attention, spatial working memory, strategy, and learning than non-regular users of cannabis. They chose 12 hours of abstinence in order to attempt to control for the conflicting forces of the acute effects of marijuana intoxication, and the withdrawal effects produced by disuse. Surprisingly, a different study by Battisti revealed that

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[42] Hanson, K. L., Winward, J. L., Schweinsburg, A. D., Medina, K. L., Brown, S. A., & Tapert, S. F. (2010). Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. Addictive behaviors, 35(11), 970-976.

[43] Fletcher, Jack M., et al. "Cognitive correlates of long-term cannabis use in Costa Rican men." Archives of General Psychiatry 53.11 (1996): 1051-1057.

[44] Harvey, M. A., Harvey, M. A., Sellman, J. D., Harvey, M. A., Sellman, J. D., Porter, R. J., & Harvey, M. A. (2007). The relationship between non-acute adolescent cannabis use and cognition. Drug and alcohol review, 26(3), 309-319.

longer term chronic users of marijuana were able to perform better on word recall tasks than users who had experienced significantly less exposure to the effects of THC in their lifetime. This study also included the use of an EEG to examine the patterns of electrical activation in relation to memory tasks. They suggest that the superior performance of extreme chronic cannabis users in relation to shorter-term chronic users may be attributed to neuroadaptation of the hippocampus to the deficits instilled by THC. The EEG results demonstrated that additional recruitment of compensatory regions of the brain may help facilitate task performance. The less experienced cannabis users therefore have not had adequate time to adapt to the deleterious effects of THC, and we see poorer performance on their memory tasks as a result.[45] Although, with increasing concentrations of THC appearing in today's strains of cannabis, the neuro-adaptive ability of the brain and hippocampal neurons may not be as successful in future studies.

In regards to the lasting effects of residual marijuana, H.G. Pope Jr completed a study that examined the effects of chronic heavy marijuana as compared to light use in college students. After a period of supervised abstinence from marijuana for at least 19 hours, both groups were tested on the same types of standard neurophysiological testing that have been observed in previous studies. The results of their study presented that heavy users showed significant impairment on attentional and executive functions as compared to light users on tasks of card sorting and learning of word lists (though card

[45] Battisti, R. A., Roodenrys, S., Johnstone, S. J., Respondek, C., Hermens, D. F., & Solowij, N. (2010). Chronic use of cannabis and poor neural efficiency in verbal memory ability. Psychopharmacology, 209(4), 319-330.

sorting does not depend much on the hippocampus, while learning of word lists is a function of declarative memory, which the hippocampus is responsible for). These differences remained significant between groups when they controlled for the potential confounding variables of premorbid cognitive functioning and the use of other drugs and alcohol. [46]

To continue the trend seen in this thesis, they concluded that there are apparent residual cognitive deficits that last into the days following marijuana use, even if usage is halted. These findings assume that college students who use marijuana on a daily basis may be at risk for performing on a sub-optimal level of cognition and memory, especially if they smoke the night before an exam. It is unknown, however, whether this impairment is due to a residue of THC still present in the brain, an inherent withdrawal effect, or a direct result of neurotoxicity of THC to hippocampal neurons.[46]

In one last observation that was particularly striking, a study by Fletcher, et. al. found that older users (median age of 45) who had been exposed to THC for a median of 34 years were unable to perform as well as a younger population (median age of 28) who smoked for up to 8 years. The results of neurocognitive testing showed that after a 72 hour abstention period there was a notable difference between the performance levels of older and younger cannabis users. The older users (age~45) who were exposed to THC for a much longer portion of their lives performed more poorly than non-users of similar age. The younger users (age~28) who had been exposed to THC for only about 8 years were able to out-perform the older cannabis-users after the 3 day break

[46] Pope HG, Jr, Yurgelun-Todd D. The Residual Cognitive Effects of Heavy Marijuana Use in College Students. JAMA. (1996); 275(7):521-527.

from ingesting THC, and even performed without statistically significant difference from their controls. [47] This demonstrates that less exposure to THC provides the hippocampus more of a chance to bounce back from the deficits produced by THC, especially when users begin using marijuana after reaching peak maturity, as did the younger users in this study.

[47] Fletcher, Jack M., et al. "Cognitive correlates of long-term cannabis use in Costa Rican men." Archives of General Psychiatry 53.11 (1996): 1051-1057.

Conclusion

In summary of this review, there are many scientific studies that repeatedly demonstrate the impairments to memory experienced as a result of the suggested neurotoxicity of THC to hippocampal neurons. Several scientific studies done in vitro demonstrated this neurotoxic effect, which was evidenced by decreased viability of hippocampal neurons in response to THC dosage. This is assumed to be a result of the changes to synaptic plasticity of hippocampal neurons when the CB1 cannabinoid receptor produces its cascade of effects, which include the inhibition of adenylyl cyclase, and the production of inflammatory pathways in the hippocampus via prostanoids that are produced in response to THC activation. Different groups of rats and monkeys were tested to see if this threatened damage to the hippocampus displayed impairment in using various aspects of their memory, and many of these studies found that the THC-absent control groups performed with much less error as compared to the animals acutely dosed with THC. Animals displayed less memory-impairing effects only if the cannabinoid receptor was protected by an antagonist, meaning that it is the activation of the CB1 receptors within the hippocampus that is at least partly responsible for the negative effects that are observed in memory tasks. Although, there needs to be more research done on what other physiological pathways contribute to the deficits on memory that are experienced, as some results displayed differing characteristic effects depending on the types of memory that were being tested, such as working memory.

Chronic usage of THC in animals during development also displayed the risk of an impaired functionality to raw memory machinery, which was similarly observed in a

study on humans who chronically used THC while maturing. These results require that emphasis be placed on the importance that the brain needs to be allowed to fully develop before it is better able to handle the insults of drugs like cannabis. There is substantial evidence that adult humans display memory impairment in response to THC's acute effects as well, but the majority of the human studies were completed retrospectively, and focused on the longitudinal impact of chronically exposing the hippocampus to THC. These studies were conclusive in that the magnitude of impairment to memory experienced by users, and the degree to which memory deficits last following abstinence, both positively correlate to the total amount of THC exposure that is endured by a long term user. Risk of altered cortical activation and sub-optimized task localization in the brain was also demonstrated in these studies of chronic marijuana dependence. To be clear, it appears that the longer a user is exposed to the effects of THC, there is an increased risk of damage to the hippocampus, though the memory-impairing effects may be less severe if marijuana is used less frequently. Ultimately, abstinence seems to be the most efficient way to allow for recuperation of efficient hippocampal function.

It appears that memory is not the only variable at risk from chronic THC exposure though, as other metabolic processes were proven to be under the influence of endocannabinoid activation by THC; daily usage and dependence to marijuana was shown to impact day-to-day activities such as eating and sleeping through withdrawal symptoms. To complicate things, some studies in this thesis only allowed people to participate if they were actively seeking help to cease the usage of marijuana, and other studies included people who did not view their marijuana usage as an impedance to

their daily life. This suggests that there is a discrepancy in the ways that users feel about how marijuana impacts their daily life, even in chronic users. So, it might be beneficial to create studies that examine the difference in memories of people who are struggling with a marijuana addiction versus people who identify with sole recreational use of marijuana.

It is also difficult to translate a scientific test of neurophysiological performance to the everyday use of ones memory in real life. Therefore, a subjective study could be used to interview various users of marijuana on their autobiographical memories of their lives. This would give information about how well their hippocampi are recording and storing declarative memories; and, give a subjective look at how marijuana usage may affect an individual's ability to actively recall memories. It would also be beneficial to identify whether there are gaps in autobiographical memory as a result of THC's effect on the hippocampus. However, this research style presents a caveat in that people, or their brains, may develop strategies to compensate for impairments to their raw memory machinery. So the benevolence of this research would be limited to identifying how well different individuals may be able to atone for the impairments produced by THC, but would not be a good predictor for deficits to declarative memory that exist as a result of THC exposure to the hippocampus.

A really interesting study included in this thesis was one that did memory experiments on rats who had THC injected directly into the hippocampus. The effects produced from this study were interestingly only memory-related, as no other systemic effects were observed. This study allowed for rats to be studied solely on the variable of how CB1 activation in the hippocampus produced effects on memory. It would be really

interesting to test humans on a battery of memory tests if there were a way to only activate the cannabinoid receptors within the hippocampus. This way, a lab-based study could be used to identify the direct effect that THC has on the hippocampus, and thus the resultant memory performance would be affected by less variables presented by activation of THC throughout the brain's cannabinoid system. This would then cause for users to truly experience the effects that THC causes to memory, without feeling the simultaneous sensations of euphoria that make marijuana so popular. Though this study idea might be considered unethical, it would allow for further understanding of how marijuana directly affects the different types of memory that require use of the hippocampus.

In an effort to discover ways to reduce the amount of harm dealt to the hippocampus by marijuana, there should also be more studies completed that assess the potential neuroprotective benefit of CBD that was briefly mentioned. The impact of different strains of marijuana plants and concentrates should also be evaluated to identify if some are less deleterious to memory than others, perhaps acutely and over time, so that the amount of damage done can be at least reduced.

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