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Synthetic Cannabinoids Effects on the Brain Versus Cannabis

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Abstract

Synthetic cannabinoids are marketed as a legal alternative to cannabis (Bush & Woodwell, 2014). In 2011 there were 28,531 emergency room visits related to the use of synthetic cannabinoids, which compared to cannabis use that resulted in 455,668 visits. There was an increase in 11,406 emergency room visits from 2010 to 2011, due to synthetic cannabinoid (SC) use. With increasing popularity of SCs, the aim of this literature review is to explain the effects of SC exposure on the brain in comparison to cannabis. A literature review will be completed on SCs and cannabis use effects on the brain, and then synthesized for the reader. Searches will utilize databases including Cochrane, CINAHL, PubMed, PsychInfo, and PsychiatryOnline. The literature will be peer reviewed and include studies on animals, and/or humans, with the goal of being published after 2006. Results will be distributed to the behavioral health consult services at Saint Cloud Hospital that includes a team of nurses, social workers, APRNs, PACs, and psychiatrists.

Keywords: synthetic cannabinoids, cannabis, THC, brain

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Out of 17 countries, the United States has the highest level of illicit and licit drug use despite legislative actions (Degenhardt et al., 2008). Cannabis use is especially popular, with forty-two percent surveyed in the United States had used it at some point. Drug use is in the adolescent and young adult population with the average first use of cannabis is between 15 and 21 years old (Degenhardt et al., 2008). SCs known as spice or K2, are promoted as a legal alternative to cannabis (Bush & Woodwell, 2014). The chemicals in SCs are not regulated (Drug Enforcement Agency, 2011). They are easy to find on the internet or retail stores. Although SCs first made an appearance in the United States in 2008, by 2011 SCs became a schedule 1 drug. In 2011, there were over 4.2 million web searches on Google utilizing the words synthetic marijuana, herbal incense, K2, spice, or synthetic weed; of which 87% of the searches ended at retail sites (Curtis et al., 2015). Cannabis has 9-tetrahydrocannabinol (THC) as the active ingredient, which SCs are supposed to mimic the effect of cannabis on the brain. SCs began when Huffman, Dong Dai, Martin, and Compton (1994) designed a new compound that was a cannabinoid-like substance and tested this on mice. Today you can find multiple SCs with varying names, being sold under the diversion of herbal incense and plant food with product warning for the consumer not to ingest (DEA, 2011).

Unfortunately, SCs ingestion occurs. Surveys collected from 13 different countries found the demographics of SC users were as follows; 90% Caucasian, 83% males, 48% had college degrees, and 9% unemployed (Vandrey, Dunn, Fry, & Girling, 2012). SC use via inhalation is the most common route of ingestion; alternative methods include vaporization, oral and anal ingestion. The subjective high lasted on average 93 minutes. There was a variety of reasons for the use of SCs including 78% curiosity, 58% enjoyment, 48% relaxation, and 30% to avoid urine

collection tests. Comorbid use of other drugs occurred 65% of the time. Along with comorbid drug use occurring in individuals, SCs have various unregulated chemical compounds. Out of 29 hospitalized patients, the most common SC included JWH-122 and JWH-210. Other compounds detected included JWH-015, CP-47,497-C8, JWH-018, JWH-073, JWH-081, JWH-250, and AM-694 (Hermanns-Clausen, Kneisel, Szabo, & Auwarter, 2013).

Similarly to cannabis use, SCs can be found affecting the youth with the average age of first use is 26 years old (Vandrey et al., 2012). The mean age of SC users in the Ghosh et al. (2013) study was also 26 years old. However, the range of users included 13 to 60 years old with 80% being male. Another study found similar demographic results with SCs users as 74.3 percent male, with an average age of 22.5 years old (Hoyte et al., 2011). Detrimental health effects occur with SC use with fifty-five percent drug-related emergency room visits occurred in patients age 12 to 20 years old compared to 26% due to cannabis use (Bush & Woodwell, 2011). Cannabis related emergency room visits overall still outnumber those from SCs; 455,668 versus 28,531. Overall in 2011, SC use made up 1.1 % of all drug-related emergency room visits. However, there appears to be a trend of advancing popularity or toxicity in SC use as from 2010 to 2011 an increase of 11,406 emergency room visits occurred.

Hospitals from New York to Anchorage, Alaska, have been affected by SC use. Anchorage, Alaska experienced an outbreak of SC use that caused the utilization of 1,351 ambulances (Cooper et al., 2016). In less than two months 167 emergency room visits related to SC use occurred with 6.6 % of patients ending up intubated. Ten people died during that surge of SC use or toxicity in Alaska. Samples of the products found during the outbreak were tested and found 11 different SC chemicals. The SC chemicals found were highly potent cannabinoid receptor agonist. Colorado hospitals had a similar event with 221 suspected cases of illness due

to SC use (Ghost et al., 2013). In three months in New York, there was less than one emergency room visit per day due to SC use (Nolan, Allen, Kunins, & Paone, 2016). That soon changed one weekend in July when 15 emergency room visits occurred with presenting symptoms of depression, tachycardia, intoxication, and mentally excited states.

Purpose

Clinically there is a substantial increase in the cases involving SCs, which correlates with the need for an expansion of clinical knowledge. The monetary loss due to SC use and cannabis on the healthcare system may be measurable, and includes emergency room visits and hospitalizations; however, the cost to families who have experienced loss is immeasurable. As we watch the youth experiment with drugs such as cannabis and SCs, one must ponder what the effects this will have on the developing brain.

The aim of this literature review is to describe the effects of synthetic cannabinoids on the brain versus cannabis. Since synthetic cannabinoids marketing includes as an alternative to cannabis, there is a duty to the public to explain the different effects cannabis can have on the brain versus SCs. Health care providers such as Advanced Practice Psychiatric Nurses (APPNs), nurses, and physicians have an important role in educating the public since they have free access to the public through multiple sources including publications, emergency rooms, public health, and clinic visits. The following literature review will synthesize information from current research to educate those in the health care field on the effects that synthetic cannabinoids have on the brain, and then compare this to the effects that cannabis has on the brain. With increased knowledge providers, can confidently educate patients to prevent or stop SC use. Inclusion criteria for the literature review will include research studies, systemic reviews, peer reviewed journal, written in English, published after 2006, describes the effects of SC and/or cannabis use

on the brain from imaging, cognitive testing, or observation of behaviors. Research may include experiments done on animals if the lack of research exists on humans with SC use.

Significance

From 2010 to 2015 there were 42,138 cases of toxic exposure found in 101 hospitals or clinics (Riederer et al., 2016). Out of 456 cases that had exposure to SCs in 277 cases it was the only agent, and the remaining were exposed to multiple agents. Further discrimination includes 415 of the cases had clinical signs of intoxication. The 277 that had the single agent exposure to SCs had symptoms including agitation, suppression of central nervous system, delirium, seizures, and hallucinations. Ultimately three deaths occurred. A small number (13) of the toxic exposure involved cannabis as the only agent. Furthermore, no antidote exists for SC exposure, and supportive care is the current standard treatment. Bassir, Medrano, Perkel, Galynker, and Hurd (2016) found a longer length of stay in the hospital, and more agitation occurred in the group who used only SCs when compared to cannabis users. The group exposed to SC and cannabis had an increase in aggression and required more as needed medication. Hoyte et al. (2011) review of data from the National Poison data system over a 9-month period in 2010 found 1353 SC single agent exposure with the following symptoms of exposure including tachycardia, agitation, lethargy, confusion, hallucinations, and rarely seizures. Clinical symptoms in the Colorado outbreak of SC use/toxicity were similar and included violence, confusion, and tachycardia (Ghosh et al., 2013). Most patients were treated and released; however, 13% admitted to the hospital with some of them needing intubation.

Two cases of patients hospitalized due to catatonia after high dose persistent SC use (Khan, Pace, Truong, Gordon, & Moukaddam, 2016). One case was a 21-year-old African American male that had a daily consumption of SCs for over a year. He had symptoms of

delayed responses, muteness, and hallucinations. Treatment of antipsychotics and benzodiazepines resolved the catatonia; however, cognitive deficits remained. The second case was a 17-year-old, Caucasian male that had two weeks of heavy use of synthetic cannabinoids, and one year of overall use. His symptoms included delays in speech, blank stares, muteness, and muscle rigidity. Treatment of antipsychotic, mood stabilizers and benzodiazepines helped to resolve the symptoms; however cognitive deficits remained. Both cases had no history of psychiatric or medical disorders. These cases cause growing concern that there is an underlying pathophysiological change occurring in the brain due to SC use.

Theoretical framework

Theory of Planned Behavior came from Theory of Reasoned Action (TRA), which originated from social psychologists that related on how beliefs affect behavior (McEwen &Wills, 2014). Theory of planned behavior begins with the assumption that people can make decisions. To help predict behavior, we must determine what the person intends to do, current beliefs, cultural norms, and self-efficacy of the person. This theory involves belief influences behavior. Knowledge and perceptions shape attitude and beliefs, and providers can influence knowledge base of their clientele. Essentially theory of planned behavior is a combination of concepts including beliefs, attitudes, and intention to act. This theory is reliant on that human behavior is predictable and can be deconstructed from thoughts and feelings (Ajzen, 2011). Human behavior is not an automatic process such as removing yourself from aversive stimuli. Conscious awareness is involved in the decision-making process.

The theory involves the concept that attitudes held by a person involving an outcome can be positive or negative (Ajzen, 2011). Attitudes towards SCs or cannabis use be negative or positive and may influence a person’s decision to use them or not. Behavioral control involves

the complex interactions of environment, intelligence, emotions, and support. Perceived behavioral control is what a person believes they can control, such as one may believe they have control over using SC or cannabis.

Health belief includes how a substance will affect a person (McEwen &Wills, 2014). A person must believe that they are susceptible to the effects on the brain due to SC use, like a cigarette smoker must believe that they are at risk for cancer for him or her to stop the behavior. Some may be under the false belief that SC is safe due to coming from a laboratory, or will produce that same effects as cannabis. Education and knowledge of the effects of SC use could change beliefs. The severity of illness is an important aspect of belief such as it is important to note if an illness would be a lifelong change due to exposure to a substance such as SC. If one can confidently say that SC may cause permanent brain damage, this will reduce the belief that experimentation of SC is acceptable. One must also believe that stopping or never using SC would provide a benefit in their life to prevent use. Social cues to change such as flyer or advertisements can promote the beliefs that change is beneficial. Ultimately a person must believe in self-efficacy and that they can change, and have control over one's behavior. Essentially the dangers of SC use and cannabis on the brain is not readily available to the public, and there is a great amount of misperception that may be driving use. Knowledge of the effects of SC and cannabis use on the brain when applied to the theory of planned behavior may reduce use.

Norms shape one's beliefs, and originate from social aspects such as friends, family, and public (McEwen & Wills, 2014). For example, in the United States illegal drug use is frowned upon in this society, which is exemplified by different laws. The use of SC would be against the norms of western society. Behavior is affected by norms, and is determined by expectations. SC

use is illegal, and socially unacceptable may deter a person from using it. However, laws have not been shown to be effective in reducing use as seen in Mathai et al. (2016) study where an increase of SCs related hospital presentations and consultations increased after a city-wide ban in Texas. Applying this theory to stopping SC use would include knowledge and information sharing via providers to the community to create beliefs and enhance change. Flyers and one on one patient education should help to create the belief that SC use is negative, and has negative influences on the brain beyond the punitive measures taken by the law.

The most important aspect of the theory of planned behavior is an intention to act, which influences belief and norms (McEwen &Wills, 2014). The concept of intention to act is predictive of actual change of behavior. Assessing one's intention to act can demonstrate how close they are to making actual life changes. One could make affirmation statements to clients when they notice change talk, and see hints of intention to change to promote the continuation of this intention into actual change.

Nurses can apply the theory of planned behavior to promote change in behaviors through publications, education, and one on one time. Public health nurses can effect change by tracking SC use and promoting education to the public. Psychiatric nurse practitioners can influence beliefs about SC and cannabis by giving reliable, evidence-based information. Information will not be laden with bias, but straightforward evidence of the effects SCs have on the brain. While changing the beliefs of a patient, then one can assess their intention to act or change their current behavior.

Definitions

Synthetic cannabinoids-Drugs that are made in attempts to act similar to cannabis, commonly called Spice, or K2. Chemical compound names include AB-PINACA, AB-FUBINACA, WIN-

55,212-2, WIN-55,21202, JWH-018, JWH-073, JWH-081, JWH-210, SR144528, JWH-391, CP55,940. In hospitalized patients the most common synthetic cannabinoid included JWH-122 and JWH-210, other compounds found; JWH-015, CP-47,497-C8, JWH-018, JWH-073, JWH-081, JWH-250, and AM-694 (Hermanns-Clausen et al., 2013).

Cannabis- 9-tetradrocannibinol (THC), marijuana, weed. Commonly used drug in the United States. Supposed to act as a partial agonist of cannabinoid receptors versus full agonist of SCs (Dresen et al., 2010).

Fractional anisotropy (FA)- White matter neuropathology can cause anisotropy to decrease which can show an increase in RD (Alexander, Lee, Lazar, & Field, 2007).

Mean diffusivity (MD)- may help to understand the changes that occur between the RD and FA (Alexandra et al., 2007)

Radial diffusivity (RD)- found by DTI and demyelination may cause RD to increase (Alexandra et al., 2007)

Diffusion Tensor Imaging-(DTI)- is a method to characterize microstructural changes in the brain as this is sensitive to change (Alexandra et al., 2007) Demyelination might show with RD increase, with minimal change on AD. Increased tissue water in edema will increase the MD, while cell increases in neoplasia may decrease the MD.

Prefrontal cortex-area with multiple reciprocal connections and integrates sensory input. Seen as the executive functioning area of the brain, and damage to this area can cause muteness, disinhibition, impairment in judgment (Waxman, 2000).

Dorsolateral prefrontal cortex (dlPFC)- impairment in this area to the brain can lead to difficulty with decision-making abilities, apathy, muteness, and indifference (Waxman, 2000).

Gray matter- contains to the functional cell bodies and synapses (Waxman, 2000)

White matter- lipid-rich area of the brain in which damage in this area would interfere with axonal conduction, unlike the gray matter it does not contain the synapses or cell bodies (Waxman, 2000)

Long-term potentiation- is where there in an enhancement of neuronal transmission at the synapses that follow high-frequency stimulation (Waxman, 2000). This was first seen in the hippocampus and may be associated with learning and memory. LTP depends on NMDA receptors in the postsynaptic membrane. Activation can lead to neuronal plasticity in the brain.

Purkinje cells-output of the cerebellar cortex, and form inhibitory synapses. Has apical dendrites reaching out toward surface, and basilar dendrites that are horizontal from the cell body, which makes the cell look like a tepee (Waxman, 2000)

Golgi cells- in the molecular layer and sends axons to granule cells to receive excitatory inputs (Waxman, 2000)

Corticospinal tracts- in the pyramid and crosses between the medulla and spinal cord, most of the axons are involved in sensory or motor cortex (Waxman, 2000)

Fornix- brings fibers from the hippocampus and the mamillary bodies in order to connect the hippocampus to the hypothalamus. Involved in afferent connection and autonomic and regulatory function (Waxman, 2000).

Precuneus-the posterior portion in between the parieto-occipatal fissure, and posterior cingulate cortex (Waxman, 2000)

Precentral gyrus- located in the frontal lobe (primary motor area), gyri are the cortical folds that allows the large area of the cortex to fit in the cranial vault (Waxman, 2000)

Superior Frontal Gyrus-dividing the frontal lobe in three parallel parts superior, middle, and inferior frontal gyri (Waxman, 2000)

Cingulate gyrus- located in the frontal lobe is crescent shaped, and located between cingulate sulcus and corpus callosum (Waxman, 2000)

Fusiform gyrus- is in the middle of the temporal lobe and lateral to inferior temporal gyrus (Waxman, 2000).

Anterior corpus callosum- large bundle of myelinated and nonmyelinated fibers and connects the hemispheres (Waxman, 2000)

Superior and Inferior longitudinal fasciculus (SLF)- connects the frontal lobe with occipital and temporal areas (Waxman, 2000).

Temporal lobe- primary auditory area and Wernicke's area where comprehension of language occurs (Waxman, 2000).

Thalamus-damage to this area can cause difficulties in discriminating sensations, and sensory deficits. Areas of the brain involved in long-term memory include amygdala, hippocampus, thalamus, frontal lobe, and basal forebrain (Waxman, 2000).

Amygdala-plays an important role in establishing the connection between sensory inputs and affective states. Increases during fear stimulation and plays a role in endocrine activity, sexual behavior and food and water intake (Waxman, 2000). Aggression and impulsivity linked with this area of the brain (Stahl, 2013)

Nucleus Accumbens- Considered the reward pathway and includes motivation. Negative symptoms of schizophrenia linked to this area of the brain (Stahl, 2013).

Literature Review

A cross-sectional cohort study by Zorlu et al. (2016) looked at SCs effects on the brain. This was the first study of its kind completed on humans. The purpose of the study included looking at the white matter of the brain using Diffusion Tensor Imaging (DTI) while comparing

SCs users and healthy controls. This was a small study with subjects of 18 healthy patients serving as controls, compared to 22 patients who used synthetic cannabinoids heavily for one year. Heavy SCs use was defined as at least five times a week for at least one year. All participants were active tobacco smokers. Exclusion occurred for the following reasons; if participants used another illegal drug more than 15 times in the last year, more than 12 alcohol drinks per week, history of mental illness, or brain injury. Exclusion also occurred if there was a diagnosis of neurological, liver, or renal disease. Statistically, there was a p-value set of less than 0.05. The method used to measure white matter was DTI.

The conclusions of Zorlu et al. (2016) included fractional anisotropy (FA) of the white matter was smaller in SC group than the control with a p-value of 0.023, which is statically significant. The parts of the white matter of the SC group that showed reduction included; left temporal lobe, subcortical, mostly the inferior fronto-occipital fasciculus of the brainstem, inferior longitudinal fasciculus, fornix, cingulum-hippocampus, and corticospinal tracts. The control group showed no reduction in FA of white matter. The duration of use, the amount of SC, or the age of first use was not associated with the reduction of white matter. Axial diffusivity (AD) did not differ between the groups in a significant way as p-value was 0.829. Radial diffusivity (RD) of the SC users were higher compared to controls and suggested demyelination and microscopic structural changes. Overall there may be toxic effects to the neurons in the hippocampus.

Limits to the study include that there is no way to control what was in the SC products that the individual ingested (Zorlu et al., 2016). Another limit was the cross-sectional nature of the study, which makes it impossible to say the changes occurred in the brain due to SCs use. There may have been neurodevelopmental changes in the brain that predisposed those to use

SCs; a longitudinal study would help to solve this dilemma. The study only included men, so unable to look at gender differences although most SCs users are male. Recall bias may be present as substance use was self-reported, which could mean people are under or over reporting the use of drugs and may have a different exposure than reported.

Another cross-sectional study completed with humans was Cohen et al. (2017) that looked at the effects of SCs on executive function comparing this to cannabis users and non-drug users. The study was slightly larger than the last with subjects of 38 people who used SCs, 43 cannabis users (CU), and 41 non-drug users. The average age of participants was 26 years old. The goal of the study was to find the effects of SCs on executive function in relation to cannabis use and no drug use.

Tools used to measure executive function included the stroop-word color task, n-back task, and free recall memory test (Cohen et al., 2017). The amount of SCs, cannabis, and non-drug use were all self-report. SCs users were recruited from drug treatment centers, while cannabis and nonusers were in the community. The inclusion of CUs occurred if they had consumed cannabis at least ten times in the last year, but had no SCs exposure. Non-users had reported no drug use. These groups were matched and demographically similar. SCs users were either on an inpatient or outpatient drug treatment, and the majority were males (29), and females (9). Inclusion criteria for SCs users were as follows, use at least ten times in the last year, but no more than four times in the last month. Psychiatrists also evaluated SC users and did not find any psychosis or comorbid psychiatric diagnosis.

Depression and anxiety assessments completed on all participants with Beck Depression Inventory (BDI), and Spielberger state-trait anxiety inventory (STAI) (Cohen et al., 2017). Both tools utilize self-report of symptoms. N-back test includes a one back method where participants

had to decide if a stimulus is identical to the previous stimulus, and a 2-back where the same concept used but two steps in between the decision instead of one. Stroop word-color task had the participants decide whether the words and color on the screen were congruent or incongruent for example blue. Long-term memory task was tested using 18 unrelated words, and then the participants must recall as many words from the list after they solve nine mathematic questions. The setting where the tests took place differed with the SCs group as it was done in a mental health center while CUs and nonusers completed testing at a University. Both settings were supposed to provide few distractions with only the researcher and participants present. The anxiety and depression scales were completed at a different time but within seven days of the cognitive testing.

The conclusion of the Cohen et al. (2017) included the mean scores of BDI was higher in the SCs group with 19.97, and similar between the CUs and non-user group with; 5.76 and 5.80. STAI average score was higher in SCs group with 53.39, while CUs and non-users had similar results of; 39.24 and 39.13. N-back test results of the accuracy of 1-back average scores of SCs group was 75.4, compared with CUs 97.25, and nonusers 97.39. 2-Back average scores of the accuracy of SCs users was 67.94, compared with CUs 91.54, and none user 90.56. Stroop-color test found reaction times were slower for all participants. The mean reaction time in milliseconds in SCs group was the longest at 2110.46, and similar between CUs and non-users; 1649.26 and 1669.88. Errors were higher in the SCs group with an average of 9.16, followed by CUs at 2.41, and 1.97. Long term memory recall showed on average the SCs group performed worse with recalling seven words, CUs 10.43 words, and non-users 11.05 words. In conclusion, SCs use appears to affect executive function negatively with cognitive performance of SCs users showing impairment in long-term and working memory when compared to non-users and cannabis users.

Minimal differences were present among non-users and cannabis users. Depression and anxiety symptoms were higher in the SCs group, with minimal differences between CUs and non-users.

Limitations of the Cohen et al. (2017) study included self-report which potentially leads to recall bias. There is no way to measure the compounds in the SCs that participants consumed, which new variations and compounds can lead to confounding variables. The testing centers and recruitment differed in SCs group (they were in drug treatment) while convenience sampling found CUs and nonusers. Other potential confounding variables included SCs group reported on average they smoked more cigarettes, and had lower education level than the other groups. A longitudinal study could help with the reduction of confounding variables.

Another cross-sectional study completed on humans by Nurmedov et al. (2015) in the region of Turkey to look at the effect of SCs on gray matter. SCs users were compared to controls who had never used cannabis. Participants were selected by chart review at an addiction clinic from the year 2013-2014. Out of 35 patient records, 15 charts were excluded due to not having enough data, leaving 20 patients included for participation. Inclusion criteria included a diagnosis of cannabis use disorder by two different psychiatrists. Participants were all male, and matched for age, level of education, sociodemographic status of the healthy controls with the SCs users to prevent confounding variables. Exclusion of participants occurred if there was an axis one disorder, other substance use disorders, or neurological disorder. The group of SCs users reported it as their drug of choice, and had used for at least for one year or had been using at least five times a week. The control group was 20 males with no history of drug use or psychiatric disorder. SCs users had to stop use for seven days before the study.

Depression and anxiety symptoms were assessed with the BDI and Beck Anxiety Inventory (BAI) (Nurmedov et al., 2015). A Symptom Checklist-90 (SCL-90) was used to keep

track of patterns of symptoms. Structural Magnetic Resonance Image (sMRI) was used to examine the brain as a whole with the gray matter analyzed by Voxel-based morphometry (VBM). A p-level of 0.05 was set as significant when analyzing different brain volumes. Results included that SCs users had a significant reduction in gray matter density in the right and left thalamus along with left cerebellum when compared with the control group. There was no association found between gray matter tissue density and age of first use, duration of use, or frequency of use in the last year. Limitations include confounding variables could lead to the reduction of gray matter. The study was not a longitudinal study so the abnormalities could have been present before the SC use. Recall bias could have been present due to self-report of drug use. Finally, this was a small sample and findings may not be replicated in a larger study, however it was the first study with humans looking the effects with SCs use on the gray matter.

Few studies have been done on SCs use and the effects on the human brain thus research completed on rats or mice are included. Kevin et al. (2017) utilized randomized control trial design (RCT) to study the effects of SCs use versus cannabis on adolescent rats. Biomarkers after repeated exposure were collected including plasma cytokines, corticosterone, plasma and cerebellar ethanolamides. These were measured as they have shown past sensitivity to cannabinoid receptor agonist. The control group was exposed only to cannabis to see if SCs caused more behavioral and biochemical changes.

Subjects of the testing included 64 albino rats with one rat excluded to sickness (Kevin et al., 2017). Each rat was given the same amount of handling time before testing. The experiment phase started at 31 days old for the rats to replicate the adolescent period. The same standard of care occurred with each rat. Rats were evenly divided between treatment groups with 16 rats assigned to cannabis group, 16 to AB-PINACA (SC) and 16 to AB-FUBINACA (SC).

Methods included intraperitoneal injections of six low and six high doses of the drug on alternating days, and received vehicle injection of a control solution on the other days. The behavioral assessment was completed during the 15 minutes after drug administration during ages 31 to 55 days and then a residual phase (no drugs for 2 weeks) from ages 69 to 94 days which represents the adulthood of the rats. Locomotor activity was observed after exposure to drugs by having rats able to explore freely in a dark chamber. Emergence test was utilized to follow anxiety behaviors. Rats were placed in a black box with lights positioned against the wall. The rats were scored for behaviors that included head protrusion, latency to emerge, and time spent outside of the box. Place conditioning was completed with each side of the box having different textural, visual or odor cues. The rats were then scored on their performance of cues which was shown by time spent on each side of the box. Rat vocalization demonstrated an aversion to a drug. The residual phase had tested the rats with novel object recognition. Social interactions were recorded between the mice. Then post-mortem samples were taken from the plasma and cerebellum. The significance set at p-level 0.05.

Results included in the locomotor test showed the distance of travel was less in the SC groups, but not in the cannabis group during the on drug phase (Kevin et al., 2017). Compared to the control days all high dose drugs decreased activity. Although there were no significant changes in low doses of the emergence test, there was a significant latency to emerge with high doses of all drugs, and reduced open field time. Higher rat vocalization occurred with low doses of AB-FUBINACA, and high doses of cannabis and the two SCs. Residual effects included SCs and cannabis caused a reduce time spent looking at the novel object. There was less social interaction with cannabis than SC treatment groups. There was no residual effect on locomotor activity or latency to emerge. There was less weight gain with the rats exposed to all the

cannabinoid groups during the on drug phase, however this resolved in the residual phase. There was no significant difference in the level of steroids. The cytokines levels in all samples fell below limits. All three drugs caused residual impairment for object recognition memory after two weeks. A reduction in cerebellar ethanolamides of Anandamide (AEA), Palmitoylethano (PEA), and Oleoylethanolamid (OEA) occurred in cannabis and AB-PINACA group of rats but not in AB-FUBINACA. Total social behavior tested after 19 days without drug administration was less in the cannabis group 51.8 seconds, when compared to 87.0 seconds, and 79.5 seconds of the two SCs groups.

In conclusion, all three drugs affected locomotor action by reducing it; caused anxiety as seen in emergence test, and had less weight gain during drug administration phase of testing (Kevin et al., 2017). Residual effects included that all drugs caused reduction of object recognition. Overall cannabis and the two SC products tested produced similar effects in the rats except cannabis was worse in the long-term for social interactions. Limitations include this study does not reflect the exposure of humans to unregulated SCs, and comorbid drug use. The study does provide an interesting debate that SCs in a controlled singular form may produce similar effects to cannabis during drug administration, and SCs were less harmful to social interactions than cannabis.

To see how SCs and THC affected neurotransmission in the brain Wiley et al. (2016) RCT study looked at the binding affinity of SCs at cannabinoid and noncannabinoid receptors. The purpose was to evaluate the range of cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors binding affinities utilizing functional observational battery (FOB). The subjects of adult male mice were used, and each mouse was exposed to a single dose of SC while

completing FOB. The mice were given the same standard of care with environmental controls and access to food.

All of the mice were given intravenous (IV) injections of SCs in the tail during FOB procedure (Wiley et al., 2016). Mice were randomly assigned to which SCs they would receive which included THC, JWH-018, JWH-073, JWH-081, JWH-210, and SR144528. The technician whom observed behavior was blind to the drug administered.

The results of the Wiley et al. (2016) study showed that all the compounds except JWH-391 had binding affinity for the CB1 receptor, and had a stronger affinity than THC. The highest CB1 receptor affinity was JWH-210, but all compounds also had an affinity for CB2 receptors. JWH-018 and JWH-391 had higher affinity to CB2 than CB1 receptors, while JWH-391 had weak affinity for either receptor. SCs were found to bind to noncannabinoid receptors, but the affinity was weak. No compounds showed affinity to norepinephrine, histamine, opioid, GABAnergic, or benzodiazepine receptors. THC did show affinity for dopamine, and along with JWH-391 had an affinity to muscarinic 1 receptor, however this was weak. All of the SCs did show affinity as an antagonist with serotonin at the 5-HT2b receptor except JWH-081. However, they were weak inhibitors of 5-HT2b. SCs inhibited hERG channels, except for JWH-081. For the behavior profile, THC was found to decrease arousal, rearing and overall activity in the open field. THC affected posture and gait causing more time spent in a flatten position. JWH-391 had a lack of affinity for the CB1 receptor, and showed minimal change in the observed behavior of the mice. The other six SCs included JWH-018, JWH-073, JWH-210, AM-2201, JWH-167 and JWH-081 all correlated with behavior changes such as decreased wakefulness, rearing and overall decrease activity. Ataxia, and flatten body poses were seen. More abnormal muscle tone was seen with SCs administration than THC. Ease of handling measured central nervous system

(CNS) excitability. With administration of SCs, CNS excitability was higher when compared to THC group. The observed behavior of jumping and vocalizations were common with higher doses of SCs. Limitation of the study includes all the mice were male.

A commonly abused SC (MAM-2201) was looked at to see how it altered brain function (Irie et al., 2015). The goal of the RCT study was to explore whether MAM-2201 activates CB1 receptors. The study investigated SC on synaptic transmission, and in humans it looked at SC in CB1 receptor with AtT-20 cells. SCs of MAM-220, JWH-018, AM215 were utilized in the experiment, and WIN5,212-2 known as a CB1 and CB2 receptors agonist was used as a positive control. The procedure looking at the AtT-20 human cells included a whole-cell patch-clamp recordings, then staining of CB1 receptor proteins. The electrophysiology recorded utilizing potassium currents. The cerebellum of mice of either sex was used.

The results included that MAM-2201 acts as an agonist on CB1 receptors which was demonstrated in both mice and human cells (Irie et al, 2015). The activation of the presynaptic CB1 receptors leads to the inhibition of glutamatergic presynaptic transmission and suppression of the GABAnergic synaptic transmission at the Purkinje cell interneurons. MAM-2201 was more potent than JWH-018 and THC at decreasing parallel fiber-Purkinje cell excitatory postsynaptic current. There was a reduction in action potentials in Purkinje cells postsynaptic currents with MAM-2201. The effects of this SC is likely due to inhibition of neurotransmitter release due to activation of CB1 receptor. MAM-2201 inhibits synaptic transmission in the cerebellum. Cerebellum motor movements may dysfunction with MAM-2201 use and clinical you may see that a client be unable to complete a finger to finger test.

Renard et al. (2015) RCT study looked at adolescent exposure to SC (CP55,940) a synthetic cannabinoid agonist in order to explore if it interferes with the remodeling and

organization of the cortical and limbic regions of the brain. This study was completed in Europe, and is an important study as cognitive deficits could occur if damage to prefrontal and hippocampal areas of the brain. The study was done to see if chronic exposure to SCs during adolescence would lead to cognitive deficits due to disruption in the prefrontal and hippocampal network. Adult rats that were exposed to SCs during the adolescent period were used to measure synaptic plasticity in the hippocampus and prefrontal cortex network.

Methods of Renard et al. (2015) study included exposing adolescent rats age 29-50 days old to the synthetic cannabinoid CP55,940 by intraperitoneal injections. All the rats were male, and received the same standard of care. Dendritic morphology of pyramidal medial prefrontal cortex neurons was examined by the Golgi-Cox method. Five control rats and five rats received SCs and then their 49 neurons were measured by dendritic complexity index (DCI). Electrophysiology was performed on adult rats, nine from the control group and ten rats from SC group. Western blot analysis done on six adult rats from the control group and six rats that were given SC. The PFC and hippocampus were dissected post-mortem.

Results included that chronic exposure to SC during adolescence showed a decrease in the number of dendrites in the PFC of the adult rat (Renard et al., 2015). There was a reduction in the length of dendrites. The reduction in length and number of dendrites occurred in basal dendrites but not in the apical dendrites. Chronic exposure leads to an overall decrease in DCI in the basal dendrites, but not in the apical dendrites. Long-term potentiation was impaired in the hippocampus-PFC circuit in the SC exposed group. The results suggest the chronic SC exposure may lead to extended memory deficits at the postsynaptic level due to changes in the PFC. Protein levels of postsynaptic marker PSD-95 and presynaptic markers of synaptophysin and vesicular glutamate transporter type 3 (VGLUT3) were taken from the PFC, and hippocampus

which are involved with memory function. PSD-95 is a protein that helps organize N-methyl-D-aspartate (NMDA) receptors and others. Synaptophysins is a synaptic vesicle protein and VGLUT3 is a subtype of a glutamate transporter. PSD-95 decreased in the PFC of the SC group, however VGLUT3 and synaptophysin remained unaffected. The hippocampus had a slight decrease in PSD-95 in the SC group, which was not statistically significant, and neither VGLUT3 or synaptophysin were affected (Renard et al., 2015).

Carvalho et al. (2016) RCT study looked at the chronic exposure of SC, CB1 receptor agonists affect the morphology of the dendrites of the pyramidal neurons in the medial prefrontal cortex, medium spiny neurons in the nucleus accumbens. Thirty-six adolescent rats were utilized age 27-30 days, along with adult rats who were age 55-60 days. Subjects were exposed to the same environment including rotating light, access to food or water, and temperature. SC used was WIN 55,212-2 which was injected interperitoneally.

Methods included six adolescents, and six adults were given daily injections for 14 days, after which post-mortem dissection of the brain occurred (Carvalho et al., 2016). Golgi-cox stain was used to look at the structural morphology of the reconstructed dendrites. The dendrites including the number of spines, length, overall arrangement were looked at in the area of the pyramidal neurons in the medial prefrontal cortex and medium spiny neurons in the nucleus accumbens. Six to ten neurons were reconstructed from each animal. The rats were tested for aversion to SC as they were conditioned by being injected twice a day by either a control shot or shot with SC.

The results of the study showed that SC increased the basal and apical dendrite length and branches in the medial prefrontal cortex only in adult rats, and can lead to more excitatory transmission but only in the adult rats and not in adolescent rats (Carvalho et al., 2016). This

difference could be related to a decrease in CB1 receptor expression in adults compared to adolescents. In the nucleus accumbens of adult rats, there was a decrease in dendrite length and branches in those exposed to SC, which suggests a decreasing effect on the GABAergic transmission and this could be linked to why adult rats have more aversion to SC. Spine density was reduced in both adolescent and adult rats in the nucleus accumbens, which shows that SC may decrease glutamatergic transmission in the nucleus accumbens. During the conditioning, it was found that adult rats exposed to SC spent less time in the chamber where the drug exposure occurred than adolescent rats. Findings suggest adolescent rats have less aversion to SC and may be at greater risk for addiction than adult rats. Limitations of the study include that the most common way SC are used is through smoking so injecting them may not resemble exactly what is occurring in the actual patient. Also outside of a lab SCs are used without control of the chemical makeup or doses.

Next we will look at how cannabis affects the brain, Cheng et al. (2014) cross-sectional study looked at the effects of heavy cannabis use on brain activity. The study utilized fMRI with the participants in a resting state. Multi-voxel pattern analysis (MVPA) measured connectivity. The goal of the study was to look at the networks affected in the brain of chronic cannabis users by examining the brain activity. Participants included 25 adult male volunteers with 13 in the control group and 12 cannabis user (CU) group. Exclusion criteria for the CUs included the use of other illicit drugs in the last three months, or a psychopathological disorder other than cannabis abuse or disorder. Exclusion of heavy alcohol users occurred along with anyone with a hearing impairment, cardiovascular disease, learning disability, neurological disease, or history of head trauma. Inclusion criteria included cannabis use at least once a week for the last month, adulthood, and a high school degree. Before the tests, there was an abstaining period from any

cannabis use for at least 12 hours. Drug screens were utilized to test the validity of self-reported cannabis use.

The procedure included having participants in a resting state for the MRI, but not sleeping (Cheng et al. 2014). During the fMRI, the motion is limited in the patient as much as possible. The analysis focused on the gray matter, and MVPA analysis was completed to look at the connectivity. Results included several regions in the brain that are different in cannabis users and the control. A greater strength in connectivity was in the cannabis users' brain in comparison to nonusers. Accuracy rate higher than 80%, with a p-value less than 0.05 was statistically significant. The CUs had higher connectivity in the following clusters (Precentral Gyrus, Middle Frontal Gyrus), (Precentral gyrus, Superior Frontal Gyrus), (Middle frontal gyrus, Cingulate gyrus), (Cingulate gyrus, Superior frontal gyrus) and (Inferior frontal gyrus, Fusiform gyrus). Over 84 percent of the time MPVA was able to classify CUs brain over a normal brain. Findings suggest that CU have more difficulty processing information due to the dysfunctional connectivity throughout the brain.

Limitations include this was a cross-sectional design so unable to say cannabis causes hyperconnectivity in the brain (Cheng et al., 2014). The study was a small sample size, and the gender was male for all the subjects. There could be multiple confounding variables that lead to hyperconnectivity such as downregulation of cannabinoid receptor, a neurodevelopmental difference that predisposes a person to substance use, or cannabis withdrawal.

Becker, Collins, Lim, Muetzel, and Luciana (2015) completed a longitudinal study of white matter microstructure of those who had exposure to heavy cannabis use. Diffusion tensor imaging (DTI) was utilized to look at the microstructure of the white matter with fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD). This was the first

longitudinal study that looked at the white matter microstructure due to sustained cannabis use during adolescence. This study looked at axonal fiber organization. Adolescence with regular use of cannabis and control groups were looked at two different points. Axonal fiber organization was measured by FA (increasing) and RD (decreasing).

The sample size included 37 cannabis users who were recruited through university advertisements (Becker et al., 2015). CUs were included if they used at least five times per week for at least one year. Exclusion occurred if they smoked cigarettes daily or excessive alcohol use. Of the 36 participants, 27 CUs returned for the two-year follow-up, which two no longer meet criteria due to lack of cannabis use. Researchers selected 23 controls for comparison. Inclusion criteria included for all participants were English-speaking, right-handed with normal vision and hearing. Exclusion occurred due to neurological problems, intellectual disability, axis 1 diagnosis, or pregnancy. No cannabis use could occur for at least 24 hours before testing.

Methods included MRI scanning and partial neuropsychological testing at the beginning of the study, and two years later (Becker et al., 2015). Rey auditory verbal learning test (RAVLT) was used to look at the verbal and memory skills. During RAVLT there are 15 words to recall. Participants must repeat four items after recalling the 15 words, recall immediately, and then after 30 minute delay.

Groups were matched due to gender, racial background, years of education, and approximate IQ to reduce confounding variables. Most of the study participants were Caucasian and had above average intelligence quotients (IQs) (Becker et al., 2015). There was a significant difference in the FA change between CUs and non-users. Controls had more positive FA change over cannabis users. The largest positive change in the control group versus cannabis user (CU) group occurred in the right hemisphere along the superior longitudinal fasciculus (SLF), and this

extended to the corticospinal tract. The next peak of FA in cluster of parietal operculum in the left hemisphere. More positive two-year FA change was in CUs group in two clusters in the left hemisphere; one cluster was in the anterior corpus callosum, and then in the posterior thalamus. There were significant differences in the two-year follow-up between CUs and control. The RD change was more positive for the CU group in the right hemisphere, inferior parietal, precuneus, and posterior cingulate cortex. The cluster peak overlapped the posterior cingulum. RD change increased in the control group versus CUs in the left hemisphere cluster along the CST.

Cannabis use had a negative association with FA change over two years (Becker et al., 2015). The maximum cannabis use during the last year had a negative association with the FA change in the right SLF/CST junction. Age of onset of cannabis use did not correlate with FA changes. RAVLT did not have a significant change in longitudinal testing; however, CU group showed poorer performance when compared to controls in verbal learning, and memory. Overall FA change over time in CU group was less than in the control group, and RD change was increased in the CU group when compared to control group. In CUs showed less FA change in the central and parietal regions of the right and left SLF, left superior frontal gyrus, in the left CST, and right anterior thalamic lateral to the corpus callosum. An increase in FA and decrease in RD in CU group occurred in posterior genu, rostral body, and posterior thalamic white matter which suggests better organization. Increased activation of alternative information processing pathways by CUs, which may reflect a functional compensation. The amount of cannabis use correlated with the FA change with the right SLF, and left SLF. Heavy cannabis use affected the white matter microstructure in the superior longitudinal fasciculus, corticospinal tract, and corpus callosum. Limitations include the small size of the study; self-reporting of cannabis use can lead to recall error.

Gorka et al. (2016) completed RCT study on the effects of cannabis on cognitive reappraisal process that relies on frontolimbic functioning. The goal of the study included looking at the acute effects of cannabis on activation of neurons, and connectivity during the cognitive appraisal. Either a cannabis or placebo was administered before cognitive reappraisal task during MRI.

There were 78 subjects that volunteered for the study all of them were right handed. Exclusion of participants occurred if taking any psychoactive medications, axis 1 diagnosis, daily cigarette smoker, neurological or medical illness present. Past exposure to cannabis had to be less than ten times, and they confirmed a negative urine drug screen at the time of the study. Random assignment to placebo (36 participants) and cannabis group (39 participants). Participants recruited from the University of Michigan or the University of Illinois. The ages of participants ranged from 21 to 45 years old.

The study protocol was completed the same at the University of Michigan and University of Illinois (Gorka et al., 2016). Two hours before MRI scan the participants either received a capsule of dextrose filler or synthetic cannabis (Marinol 7.5 mg). Participants viewed images that were negative or neutral for about 5 seconds and then had to respond how negative they felt. Researchers educated the participants on the reappraisal process on how to use cognitive strategies against these images. Look condition was where participants looked at images, maintain condition was where participants processed images, reappraise condition was where participants attempted to decrease the effect that the images caused.

Results in the THC included activation of the amygdala increased during maintain condition when compared to look condition but did not reach significance during reappraise (Gorka et al., 2016). The placebo group did not have a difference in the amygdala between

maintain and look or between maintain and reappraise. When comparing groups, THC increased left amygdala activity during reappraise with the placebo. There was no difference between placebo and THC in regards to left amygdala activation during maintain or look conditions. THC decreased left amygdala to dorsolateral prefrontal cortex (dlPFC) and right amygdala to dlPFC functional coupling during reappraise condition, while right amygdala to dlPFC coupling decreased with THC. THC compared to placebo increased left amygdala to dlPFC functional coupling during look condition. Overall the participants reported that cognitive reappraisal was successful in decreasing negative affect in both placebo and THC groups. THC group did have some differences and showed higher left amygdala activation and less amygdala connectivity with dlPFC functional coupling during cognitive reappraisal when compared to the placebo group. Left amygdala activation was higher in the THC group during reappraise and maintain when this was compared to look condition. THC appears to affect the amygdala, but not the amygdala-dlPFC functional connectivity during cognitive reappraisal. The increasing of left amygdala to dlPFC functional connectivity during look, and decreased right amygdala to dlPFC functional connectivity during maintain could be that THC causes difficulties to engage the dlPFC to respond to negative stimuli or THC causes difficulty accurately assessing visual or affective information. However, this would need to be further studied to come to a conclusion. The strength of this study included the RCT design. The limitations include two different university sites ran the testing, and two different scanners were used for MRI (Gorka et al., 2016).

Lorenzetti et al. (2015) a European study looked at the morphological changes of multiple brain regions of 15 heavy CUs when compared with 15 controls. This was a cross-sectional study. Participants of the CUs were 15 adults with heavy cannabis use occurring for

years, on average about 21 years of regular use. There were 16 participants in the control group who were similar in age, IQ, and educational years matched with CUs. Participants had less than ten exposures to other drugs along with no medical, neurological or psychiatric disease. CUs had on average used 28 days and consumed about 212 joints in a month time span. MRIs were utilized to look at the anatomy of the brain.

The results include CUs have decreased hippocampus and amygdala volumes, but no changes in orbitofrontal, anterior cingulate cortices, or pituitary gland when compared to control group (Lorenzetti et al., 2015). There was not a significant difference in interaction between the hemisphere on the brain regions. Chronic heavy cannabis use appears to lead to decreasing hippocampal volume. Chronic cannabis use largely affects the mediotemporal region of the brain and volume reductions to the amygdala which this is the first study to show the reduction in the amygdala. Limitations of this study include the small sample size, but it does suggest that heavy and long-term cannabis use has a negative impact on the mediotemporal brain region.

Morrison and Stone (2011) RCT study looked at if synthetic THC could produce the negative symptoms of schizophrenia. The European study completed at the Institute of Psychiatry. Subjects included 22 healthy males that came to two different sessions. Under random and double-blind conditions participants received either IV dronabinol a synthetic THC or a placebo. The IV administration occurred slowly over 5 minutes for a total dose of dronabinol 2.5 mg. The dosage was supposed to replicate a cigarette of cannabis. The measurement of negative symptoms included psychological assessments utilizing Community Assessment of Psychic Experiences (CAPE-state). Negative symptoms were rated with the positive and negative syndrome scale (PANSS) along with self-rated sedation checklist to differentiate the sedation with cannabis use from actual negative symptoms of schizophrenia.

Assessments completed at baseline, then 30, 80, and 120 minutes after injection. Validation instrument was used.

Overall this was a small study, 19 out of 22 subjects completed both sessions of receiving IV synthetic THC or a placebo (Morrison & Stone 2011). One subject refused the questionnaire so was disqualified, two subjects were unable to complete it due to nausea or anxiety. Authors set a statistical p-value of 0.05. The results of the self-rated negative symptom scores did not increase with the placebo administration, however, at 30 minutes post injection of synthetic THC, there was an increase of any average of 4 points which returned to baseline after 120 minutes. The most common endorsement of items relating to negative symptoms of schizophrenia appeared with the questions discussing a lack of desire to communicate, lacking motivation or spontaneity, and feeling little to no emotions. There was a slight increase in the PANSS-negative subscale from a mean 7 to 7.7 at 30 minutes post injection of synthetic THC. There was no relationship between self-rated sedation and the reporting of negative symptoms. Overall the synthetic THC appears to produce an acute effect of negative symptoms of schizophrenia that is not related to the sedation of the drug. Limitations of the study include the small effect size and using a pure synthetic THC product which may not be comparable to what you would find outside a controlled setting.

Prior to now, we have explored mostly the pathophysiological changes that occur in the brain. Next, we will look more at the symptom expression of SCs or cannabis in clinical practice. A retrospective study compared clinical symptoms, treatment, and length of hospitalization between CUs and SC users (Bassir et al., 2016). The authors reviewed electronic charts from a dual diagnosis inpatient unit going back one year. Symptoms examined included psychosis, mood, suicidality, agitation, and aggression. Inclusion occurred if substance use was in the last

three months prior to hospitalization. Out of 594 charts reviewed, 7.9% had exposure to both marijuana and SCs, 35.2% only exposure to marijuana, 5.9% had exposure to only SCs, and 51% were negative for exposure to both SCs, and marijuana. There was a higher number of African Americans that had exposure to SCs, and marijuana than were negative for both drugs.

In conclusion, authors found increased number of psychotic symptoms, psychotic diagnoses, and antipsychotics used in those who used only SCs (Bassir et al., 2016). Followed by those exposed to both marijuana and SCs, and then those only exposed to marijuana who experienced the least number of symptoms. Longer length of hospitalization and an increase in agitation occurred in the group which exclusively used SCs. The group that exposed to SCs and marijuana had an increase in aggression and usage of as needed medication to sedate the individual. There was no association between mood symptoms or suicidality due to exposure of SCs, and marijuana. Limitation of the study includes the setting of an inpatient unit suggests that patients were of higher acuity, and this information may not fit the community as a whole.

A systematic review of articles regarding SCs and the physical and psychological consequences completed by Courts, Maskill, Gary, and Glue (2016). The review of literature included case reports in emergency room settings, reports from national databases, and poison control centers. Out of 484 articles identified from databases, 77 included in the literature review, postmortem studies excluded. This lead to information collected on a total of 3695 individuals in which 75% were males, with the average age of 23 years old.

Conclusions of the review included the finding that agitation was the second most common symptom reported after tachycardia (Courts et al., 2016). Agitation was more commonly seen with SCs use than with cannabis. Anxiety was reported more in smaller studies at 21.4% compared to 2% of larger studies. Out of the 3695 individuals who used SCs, 264 had

symptoms of hallucinations, 250 irritability, 206 psychosis, 192 delusions, 130 disorganization, 95 aggression, 79 depression, 52 suicidal, and 47 paranoia. Very rarely were symptoms of delirium seen (10 out of the 3695) mania (5), stroke (5), and catatonia (4). Courts et al. (2016) suggest emergency room physicians should suspect SCs use if they have a young adult male presenting with tachycardia and agitation.

Methods

Searches for peer reviewed literature was completed through the University of North Dakota online Library utilizing databases of Cochrane, Psychiatryonline, PsychInfo, CINAHL, and PubMed. Literature was included in the review if it was on the effects of SCs or cannabis on the brain with human or animal studies. The studies included were published after 2006. The research could include reports on the pathophysiological changes in the brain or clinical symptoms that resulted from use. The inclusion criteria was rather broad due to lack of studies completed on synthetic cannabinoids effects on the brain, which could be related to SCs being a newer drug of abuse. Research was excluded if it was published before 2006 or discussed other effects of SCs on the body or focused on demographics, however those studies were used as background material. Primary sources were the focus of the literature review; however one systematic review was included. American, European, and Australian studies were included due to being written in English. All the studies on SCs were recently published and the oldest study was 2015. The oldest study included on cannabis was 2011. The goal of the literature review was to find studies that either compared SCs to cannabis effects on the brain, use of SCs effect on the brain, or studies exploring the use of cannabis on the brain. Longitudinal or randomized control studies on humans were preferred, however the fact that SCs is a newer drug of abuse, very few were actual found, and cross-sectional studies needed to be utilized.

The search engine of Cochrane yielded poor results with the term “synthetic cannabinoid” revealed one unrelated result, and with the terms “cannabis AND brain”, revealed one unrelated result. PsychInfo search with the term “synthetic cannabis” produced 227 results with three studies of relevance included in the literature review. PsychInfo search with terms “synthetic cannabis AND brain” had 41 results with five studies included. Using similar terms on PsychInfo of “synthetic cannabinoids AND brain” had 154 results with two studies used for the literature review. Psychiatryonline was searched with terms “Synthetic Cannabinoids” with 46 results, however none were used for the literature review. CINAHL gave 166 results of “Synthetic Cannabinoids AND brain”, which gave several articles for background information. One article out of 150 was used from CINAHL after searching “cannabis AND brain”. PubMed database yielded good results for this project with “Synthetic Cannabinoids AND brain” giving 8 studies that were included out of 532 results. Search terms “Cannabis and Brain” on PubMed gave one study that was used.

Results

The results of the searches yielded 15 peer-reviewed articles, with the oldest article included was 2011. Five studies were cross-sectional in nature, while one study was longitudinal, one retrospective, one systematic review, and seven studies were randomized controlled trials. Three studies compared the effects of SC use versus cannabis, seven exclusively looked at SCs use effects on the brain, while five studies completed on CU effects on the brain. Five studies were done on rats either adolescent or adults while the rest were completed on humans.

The information was presented to psychiatrists, nurses, physician assistants, and APRNs at the Saint Cloud Hospital. The presentation occurred at a quarterly hospital consult team meeting. The participants who attended the education worked for Saint Cloud Hospital, and are

part of the acute care team that works throughout the hospital managing complex psychiatric patients on medical floors. One hour of continuing medical education was provided for those that attended. Information was distributed to University of North Dakota graduate students.

The presentation revealed positive results. Nursing staff reported it helpful in knowing signs of SCs use such as agitation. Psychiatric providers were able to discuss their own cases and apply this to the information provided in the presentation. Overall it was reported that staff that attended the presentation that the information on SCs assisted with population they have seen in practice.

Discussion and Implications for Nursing

Synthetic cannabinoids appear to be associated with disruption of the connectivity in the white matter in the brain and demyelination that may underlie cognitive impairment and vulnerability to psychosis seen with human SCs users (Zorlu et al. 2016). SCs users compared to healthy controls had lower FA in inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, fornix, cingulum-hippocampus and corticospinal tracts. A longitudinal study on humans showed microstructure changes in the white matter after chronic heavy cannabis use (Becker et al., 2015). The findings suggested that heavy cannabis use leads to functional compensation in the brain. Gross morphological brain changes also occur with heavy cannabis use (Lorenzetti et al., 2015). CUs had a reduction in mediotemporal regions especially with the hippocampus and amygdala volumes, however did not exhibit gross changes in orbitofrontal, anterior cingulate cortex, and pituitary in a small crossectional study with nonusers. The differences were associated with dose and frequency of cannabis use. Findings suggest that heavy cannabis users would struggle with complex cognitive tasks and processing. Heavy cannabis users had higher connectivity strength compared with controls in the cingular gyrus,

middle frontal gyrus, precentral gyrus, superior frontal gyrus, posterior cingulate cortex, and cerebellum (Cheng et al., 2014). This suggests that CUs may have changes in the brain that cross the span of the cerebellum to the PFC, which may cause difficulty for heavy CUs to perform processing tasks and disrupts information communication across the brain.

The changes in the gray matter density was also affected by SCs use (Nurmedov et al., 2015). Chronic use of SCs compared to healthy adults showed a reduction gray matter density in the left and right thalamus, and left cerebellum. SCs chronic use in adolescent mice compared to adult mice showed chronic use suggest long lasting effects with visual and spatial short-term working memories, which may lead to deficits in cognitive function as an adult (Renard, et al., 2015). Findings suggest adolescent rats have less aversion to SC and may be at greater risk for addiction than adult rats (Carvalho et al., 2016). Executive function was affected in humans who used SCs when compared to CUs and nonusers (Cohen et al., 2017). SCs users were less accurate when tested on recall with the n-back task, had a slower response and less accuracy with Stroop task, and long-term memory was affected as they could recall fewer words than the other groups. SCs users had higher rates of depression and anxiety than nonusers and CU.

Synthetic cannabinoid MAM-2201 was more potent than THC or SC JWH-018 and acted as an agonist on the CB1 receptor (Irie et al., 2015). This lead to slower action potentials and inhibition of neurotransmitter release especially in the cerebellum. Cannabis showed greater amygdala activation but less amygdala to dlPFC during cognitive reappraisal when compared to placebo group, which shows cannabis affects the amygdala but not PFC during cognitive processing of emotions (Gorka et al. 2016). Comparing the effects of THC on rats with SCs of AB-PINACA and AB-FUBINACA found THC and SCs produced similar results (Kevin et al., 2017). The residual effect showed THC caused less observed social interaction than SCs. SCs

versus THC had a stronger affinity for CB receptors, and possibly have a greater potency to CB1 receptors or CB2 receptors when compared to THC (Wiley et al., 2016). THC did show affinity to dopamine and M1 receptors, but binding was weak. SCs did bind weakly to noncannabinoid receptors. THC and SCs were found to affect behavior in the mice in relation to CNS activation and muscle function, however SCs impaired behavior at a wider dose range, and increased CNS excitability, autonomic dysfunction, and sensorimotor reaction. Even conditioned rats tried to avoid the SC injections by staying out to box where it occurred (Carvalho et al., 2016).

Acute cannabis use mimics the negative symptoms of schizophrenia (Morrison & Stone, 2011). On systematic review the largest symptom seen after SCs use is tachycardia followed by agitation (13.5%), and a small number of hallucinations of (7.6%) (Courts et al., 2016). Agitation was found to be the most common feature of SCs users when compared to CUs (Bassir et al., 2016). In the retrospective review of charts in an inpatient mental health unit setting SCs users had increased psychotic presentations, diagnosed psychotic disorders, needed higher doses of antipsychotics, and had longer hospitalization. In an acute care setting SCs users appear sicker than CUs.

The effects of SCs and cannabis on the brain has widespread implication on practice, depending on where the provider works. SCs users in an acute setting may appear more agitated and need a higher dosage of medication to reduce symptoms of psychosis and agitation. In primary practice or chemical dependency treatment centers, providers may see the cognitive deficits that occur with heavy cannabis or SC use. This means a provider or treatment center may need to alter their routines with patients such as giving more time for the patient due to the disruption in brain relating to processing information and executive functioning tasks. Patients who use SCs may have less working and long-term memory, so ensuring information is written

done for the patient, and involvement of family members is necessary. Little is known about how SCs use affects the females versus males, so this will make treating female patients more complicated.

Education for the public will be difficult due to several factors. Due to the limited current research it is difficult to surmise the cause and effect relationship between SCs use and dysfunction in the brain, however research suggests more harm occurs to the brain especially with chronic heavy use of SCs when compared to cannabis use possible related to a stronger affinity as a CB1 receptor agonist. Chronic heavy use of cannabis is also detrimental to the brain. Some SCs appear worse for the brain than others, which is difficult as patients are unaware of what they are ingesting. Little research has been done with females in regards to SC use so information cannot be generalized to the public as a whole. Few longitudinal studies or RCTs have been completed on humans with SCs use at this time so unable to provide family members or patients education on what the future may look like for users. Studies were also focused on chronic and heavy use of SCs that occurred in adults or as seen in mice so unable to predict someone who experiments one time on SCs as an adolescent, and what their future may entail relating to cognitive function. Education should utilize the theory of planned behavior and focus on young adults before use of SCs, and anyone who is using SCs to promote change behavior or prevent use by explaining the harms associated with use.

Education to providers should start early in nursing programs, residency, and include those in practice. SCs have been around since 2008, and continue to cause emergency room visits, and inpatient mental health stays. Education on SCs and their effects are essential to emergency room physicians so they can recognize agitated young adults that may have been exposed especially since confirmatory testing takes too long to impact acute treatment. Primary

care providers and those at chemical treatment centers need to be aware of potential long-term effects of SCs on the brain especially in regards to processing information. Lastly psychiatric providers in outpatient and inpatient settings need to be aware of complications related to SCs use especially in regards to psychosis that is more difficult to treat, and cognitive deficits that may remain even after the psychosis clears.

Implication on health policy includes needing more funding for research on synthetic cannabinoids. Currently there is a lack of knowledge and research related to synthetic cannabinoids long-term effects on the brain. Grants, and governmental funding could help bridge this gap. Money can be focused on supporting longitudinal studies comparing SCs users and cannabis users. Since SCs have been around longer in Europe than the United States an international research team would be a benefit in reducing SCs use. Banning and legal implications have not reduced SCs nor cannabis use. Less focus should be on legal consequences and more on educating the public of potential health consequences of use as we see young adults experiment with SCs without fully knowing the potential consequences. Funding for education and research should be dispersed among those in emergency rooms, primary care, psychiatric mental health treatment centers, and chemical dependency workers.

Although harm reduction policies are controversial, one could consider a harm reduction policy related to SCs and cannabis. Although the heavy chronic use of cannabis is shown to have harmful effects on the brain especially in regards to executive functioning; SCs are shown to reduce gray matter and executive function in comparison to cannabis. Legalizing cannabis may deter people from looking at SCs as a “legal alternative” or safer than cannabis. This would be proposing less harm to come from cannabis use than SCs use. Harm reduction policy would be fact based, and promote the education of what consumers are using, however it would still

allow potential harm to occur to consumers' brains due to cannabis use. Harm reduction policy may be of benefit as Food and Drug Administration could oversee cannabis distribution and safety profiles.

Overall more studies need to be completed on SCs effect on the brain as relatively few have been completed when it comes to human subjects. No longitudinal studies have been completed on the effects of SCs on the brain. Future studies could improve by having Randomized Control Trial design with humans. Increased longitudinal studies on SCs would help to provide a cause and effect relationship between the changes in the brain. Studies on SCs need to be larger as most studies were relatively small and either did not include women or had few female subjects. More studies on SCs are needed with human subjects, however RCT designs would be difficult to justify due ethical concerns of the potential harm of SCs.

Summary

In conclusion it appears SCs affect white matter of the brain and leads to demyelination and microscopic changes, which chronic heavy cannabis use also affects the microscopic white matter in the brain negatively and leads to poorer learning and memory (Zorlu et al., 2016; Becker et al., 2015). SCs may be toxic to the hippocampus, which is exhibited by the reduction in long-term memory (Zorlu et al. 2016; Kevin et al., 2017). This was also supported by the Renard et al. (2015) study where SC impacted long-term potentiation from hippocampus to the PFC circuit. Heavy cannabis use was associated with decreases in the hippocampus and amygdala volumes, which SCs users had a decrease in gray matter in the thalamus and cerebellum (Lorenzetti et al., 2015; Nurmedov et al., 2015). Cerebellum dysfunction by SC was demonstrated by the Irie et al. (2015) study. Cannabis causes higher amygdala activation, but less amygdala connectivity with dlPFC (Gorka et al., 2016). Heavy cannabis use is correlated

with hyperconnectivity in the brain (Cheng et al., 2014). More depression and anxiety symptoms were seen in SCs users compared to CU (Cohen et al., 2017). Rats had higher vocalizations, jumping, and avoided exposure to SCs (Wilet et al., 2016; Cavalho et al., 2016). This may be related to the fact that SCs have a stronger affinity to CB1 receptor than THC (Wiley et al., 2016). SC is an agonist on CB1 receptor and can be seen with motor dysfunction (Irie et al., 2015). Adolescents may especially vulnerable to SC use and addiction as in the case of rats they have shown less aversion to SC than adult rats (Carvalho et al. 2016).

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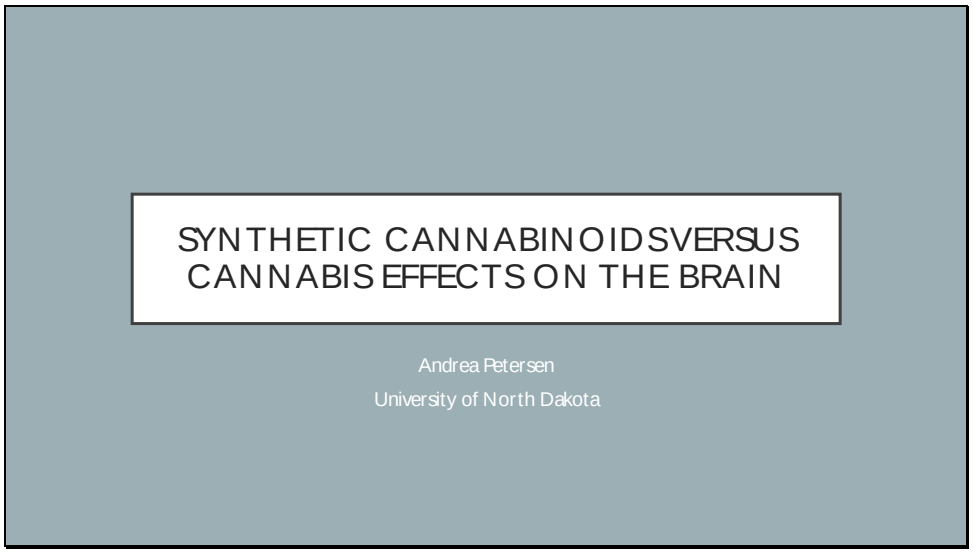
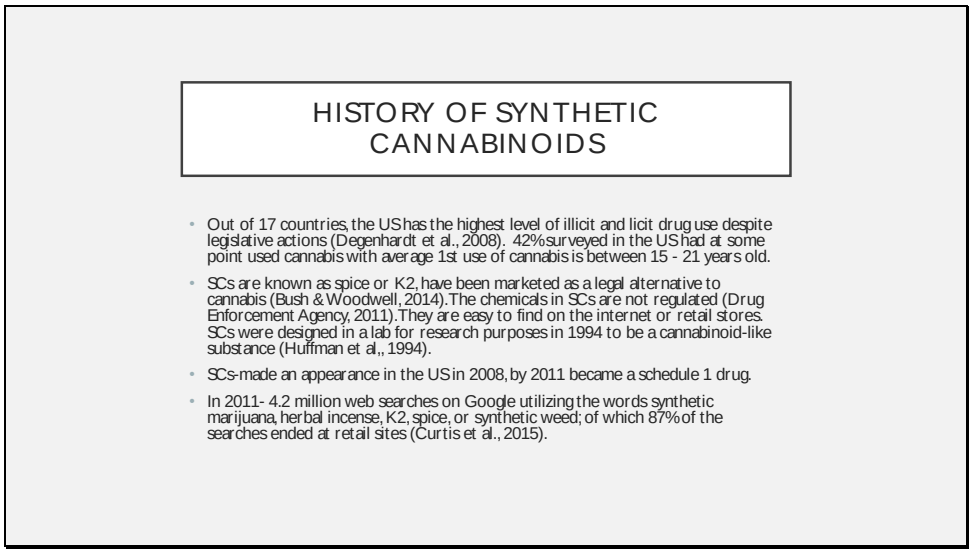
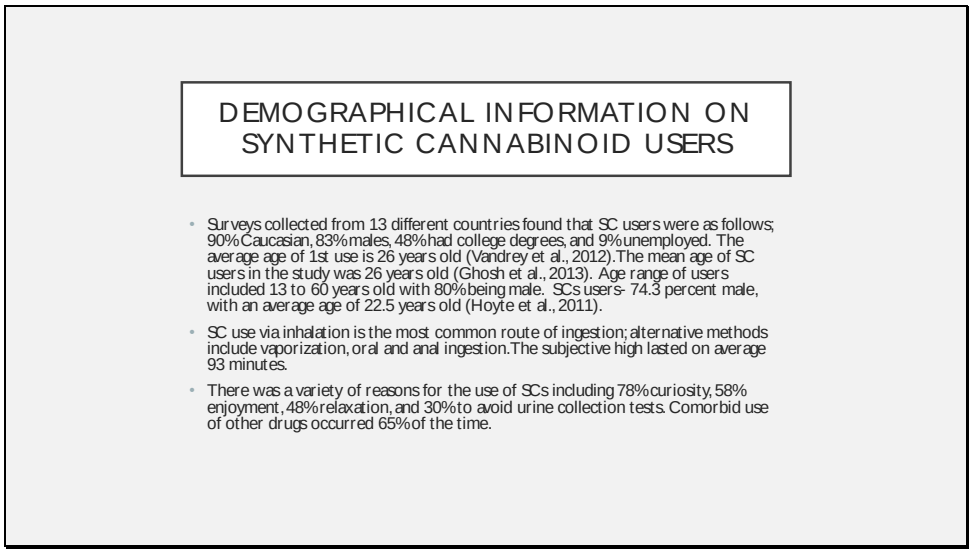
Appendices:


SYNTHETIC CANNABINOIDS VERSUS CANNABIS EFFECTS ON THE BRAIN
Andrea Petersen
University of North Dakota

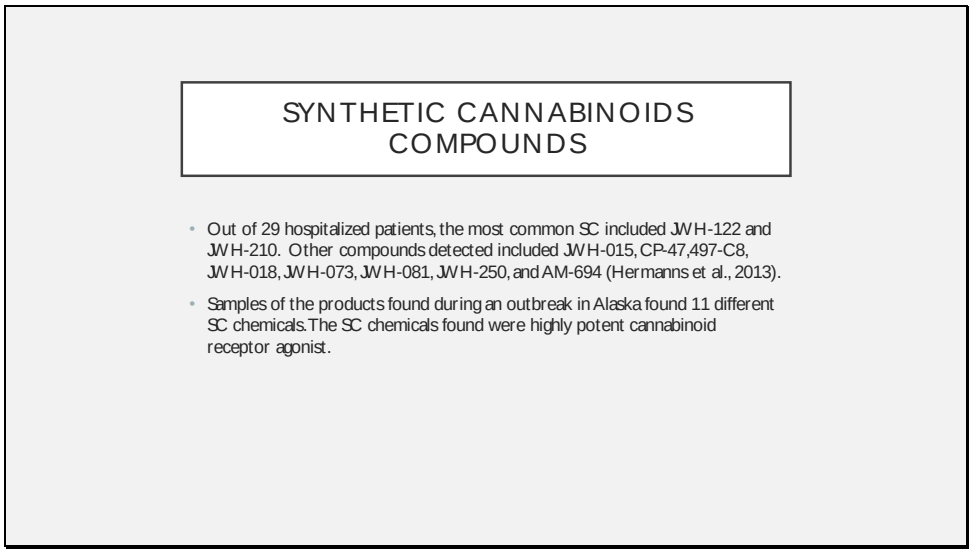
Slide 2


HISTORY OF SYNTHETIC CANNABINOIDS
Out of 17 countries, the US has the highest level of illicit and licit drug use despite legislative actions (Degenhardt et al., 2008). 42% surveyed in the US had at some point used cannabis with average 1st use of cannabis is between 15 - 21 years old.
SCs are known as spice or K2, have been marketed as a legal alternative to cannabis (Bush & Woodwell, 2014). The chemicals in SCs are not regulated (Drug Enforcement Agency, 2011). They are easy to find on the internet or retail stores. SCs were designed in a lab for research purposes in 1994 to be a cannabinoid-like substance (Huffman et al,, 1994).
SCs-made an appearance in the US in 2008, by 2011 became a schedule 1 drug.
In 2011- 4.2 million web searches on Google utilizing the words synthetic marijuana, herbal incense, K2, spice, or synthetic weed; of which 87% of the searches ended at retail sites (Curtis et al., 2015).

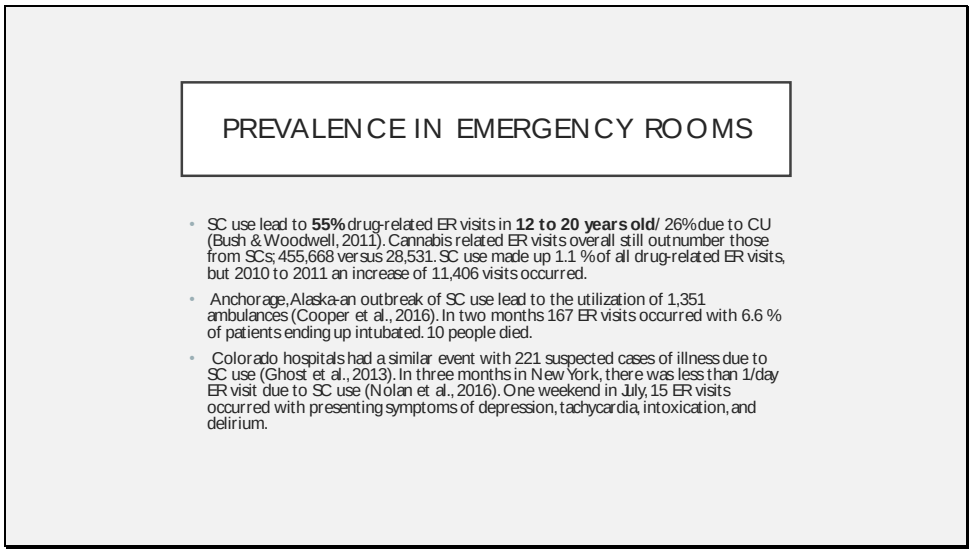
Slide 3


DEMOGRAPHICAL INFORMATION ON SYNTHETIC CANNABINOID USERS
Surveys collected from 13 different countries found that SC users were as follows; 90% Caucasian, 83% males, 48% had college degrees, and 9% unemployed. The average age of 1st use is 26 years old (Vandrey et al., 2012).The mean age of SC users in the study was 26 years old (Ghosh et al., 2013). Age range of users included 13 to 60 years old with 80% being male. SCs users- 74.3 percent male, with an average age of 22.5 years old (Hoyte et al., 2011).
SC use via inhalation is the most common route of ingestion; alternative methods include vaporization, oral and anal ingestion.The subjective high lasted on average 93 minutes.
There was a variety of reasons for the use of SCs including 78% curiosity, 58% enjoyment, 48% relaxation, and 30% to avoid urine collection tests. Comorbid use of other drugs occurred 65% of the time.

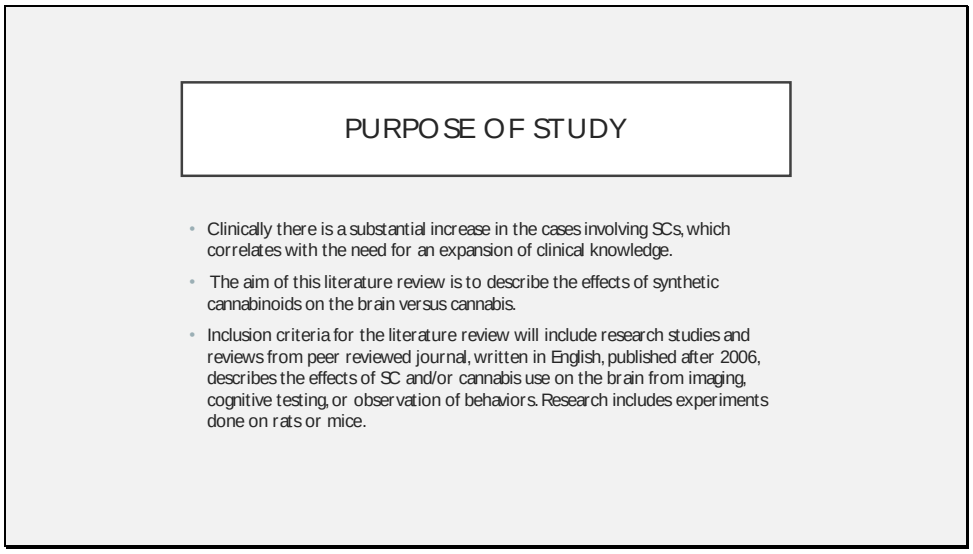
Slide 4


SYNTHETIC CANNABINOIDS COMPOUNDS
Out of 29 hospitalized patients, the most common SC included JWH-122 and JWH-210. Other compounds detected included JWH-015, CP-47,497-C8, JWH-018, JWH-073, JWH-081, JWH-250, and AM-694 (Hermanns et al., 2013).
Samples of the products found during an outbreak in Alaska found 11 different SC chemicals. The SC chemicals found were highly potent cannabinoid receptor agonist.

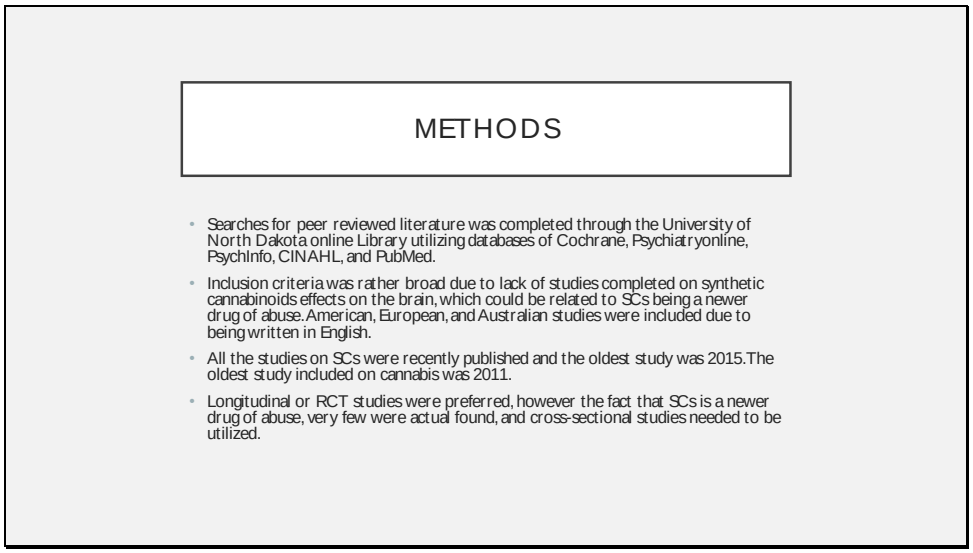
Slide 5


PREVALENCE IN EMERGENCY ROOMS
• SC use lead to **55%** drug-related ER visits in **12 to 20 years old**/ 26% due to CU (Bush & Woodwell, 2011). Cannabis related ER visits overall still outnumber those from SCs; 455,668 versus 28,531. SC use made up 1.1 % of all drug-related ER visits, but 2010 to 2011 an increase of 11,406 visits occurred.
• Anchorage, Alaska-an outbreak of SC use lead to the utilization of 1,351 ambulances (Cooper et al., 2016). In two months 167 ER visits occurred with 6.6 % of patients ending up intubated. 10 people died.
• Colorado hospitals had a similar event with 221 suspected cases of illness due to SC use (Ghost et al., 2013). In three months in New York, there was less than 1/day ER visit due to SC use (Nolan et al., 2016). One weekend in July, 15 ER visits occurred with presenting symptoms of depression, tachycardia, intoxication, and delirium.

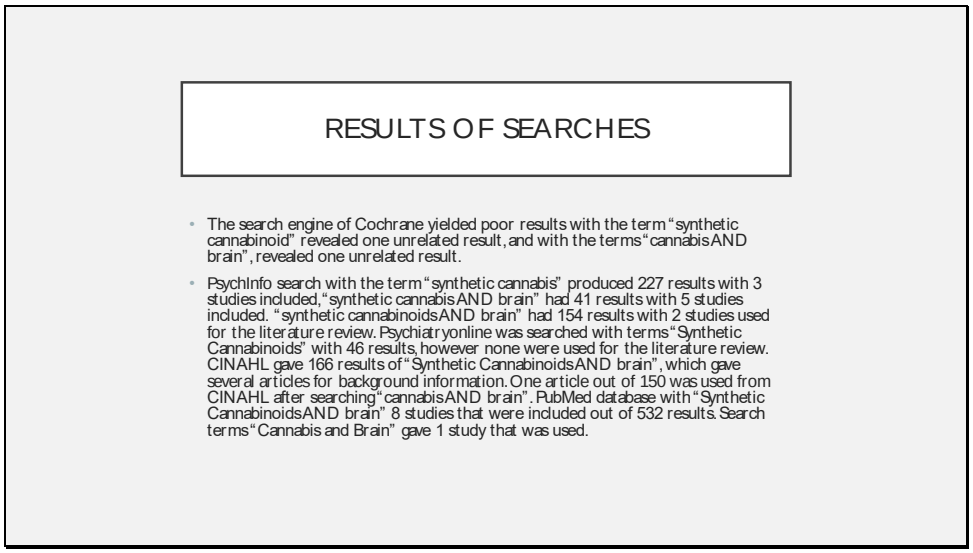
Slide 6


PURPOSE OF STUDY
Clinically there is a substantial increase in the cases involving SCs, which correlates with the need for an expansion of clinical knowledge.
The aim of this literature review is to describe the effects of synthetic cannabinoids on the brain versus cannabis.
Inclusion criteria for the literature review will include research studies and reviews from peer reviewed journal, written in English, published after 2006, describes the effects of SC and/or cannabis use on the brain from imaging, cognitive testing, or observation of behaviors. Research includes experiments done on rats or mice.

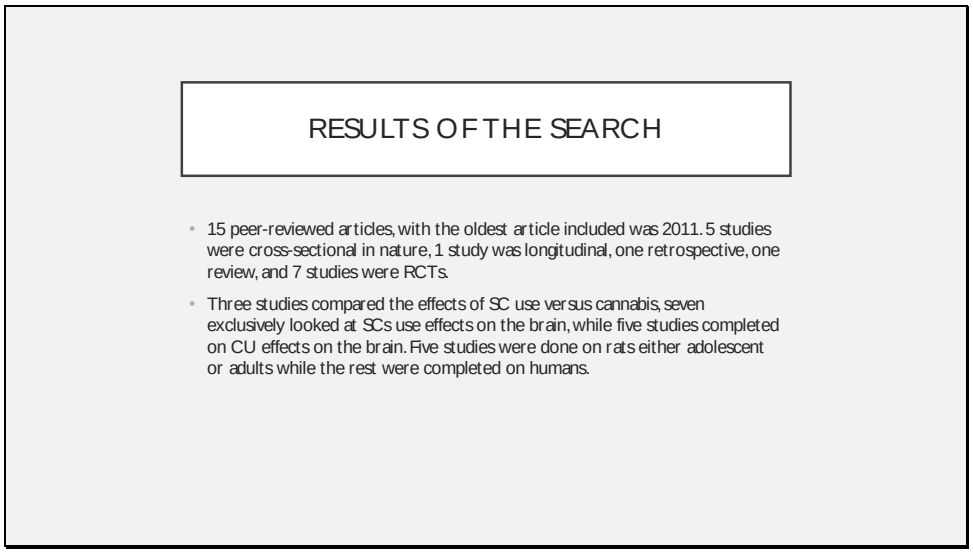
Slide 7


METHODS
Searches for peer reviewed literature was completed through the University of North Dakota online Library utilizing databases of Cochrane, Psychiatryonline, PsychInfo, CINAHL, and PubMed.
Inclusion criteria was rather broad due to lack of studies completed on synthetic cannabinoids effects on the brain, which could be related to SCs being a newer drug of abuse. American, European, and Australian studies were included due to being written in English.
All the studies on SCs were recently published and the oldest study was 2015. The oldest study included on cannabis was 2011.
Longitudinal or RCT studies were preferred, however the fact that SCs is a newer drug of abuse, very few were actual found, and cross-sectional studies needed to be utilized.

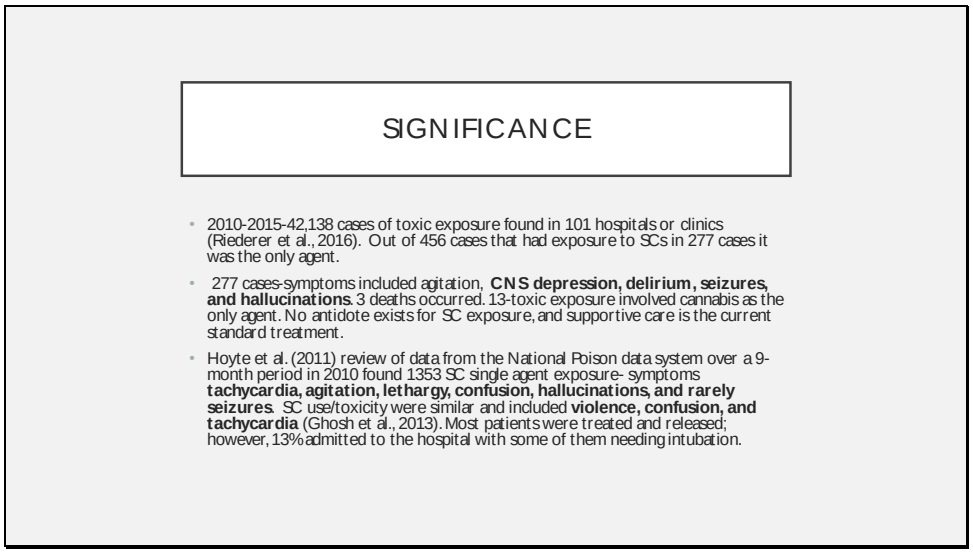
Slide 8


RESULTS OF SEARCHES
The search engine of Cochrane yielded poor results with the term "synthetic cannabinoid" revealed one unrelated result, and with the terms "cannabis AND brain", revealed one unrelated result.
PsychInfo search with the term "synthetic cannabis" produced 227 results with 3 studies included, "synthetic cannabis AND brain" had 41 results with 5 studies included. "synthetic cannabinoids AND brain" had 154 results with 2 studies used for the literature review. Psychiatryonline was searched with terms "Synthetic Cannabinoids" with 46 results, however none were used for the literature review. CINAHL gave 166 results of "Synthetic Cannabinoids AND brain", which gave several articles for background information. One article out of 150 was used from CINAHL after searching "cannabis AND brain". PubMed database with "Synthetic Cannabinoids AND brain" 8 studies that were included out of 532 results. Search terms "Cannabis and Brain" gave 1 study that was used.

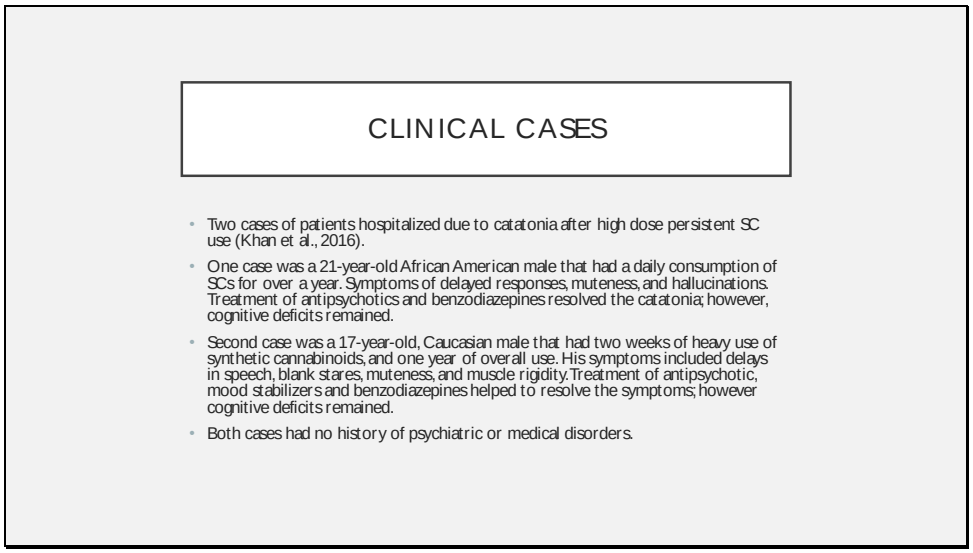
Slide 9


RESULTS OF THE SEARCH
• 15 peer-reviewed articles, with the oldest article included was 2011. 5 studies were cross-sectional in nature, 1 study was longitudinal, one retrospective, one review, and 7 studies were RCTs.
• Three studies compared the effects of SC use versus cannabis, seven exclusively looked at SCs use effects on the brain, while five studies completed on CU effects on the brain. Five studies were done on rats either adolescent or adults while the rest were completed on humans.

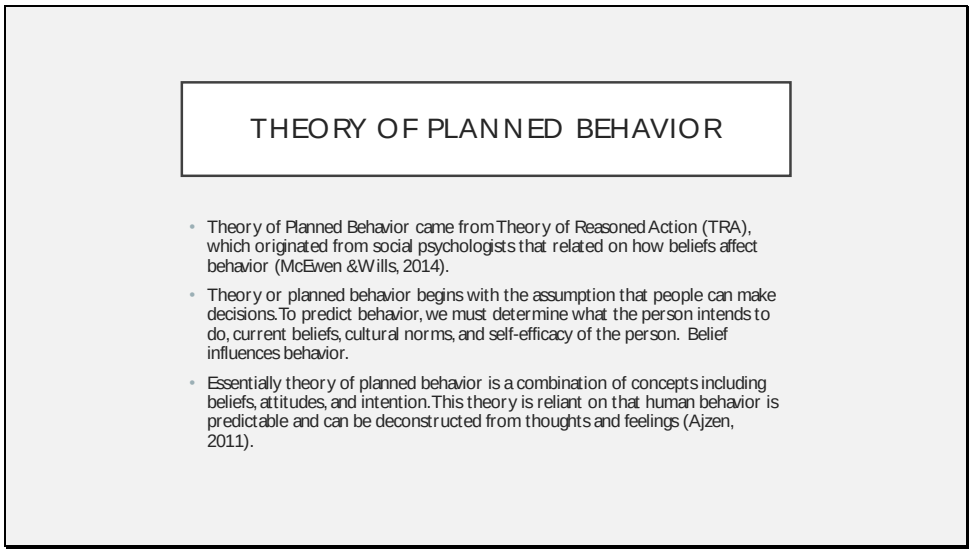
Slide 10


SIGNIFICANCE
• 2010-2015-42,138 cases of toxic exposure found in 101 hospitals or clinics (Riederer et al., 2016). Out of 456 cases that had exposure to SCs in 277 cases it was the only agent.
• 277 cases-symptoms included agitation, **CNS depression, delirium, seizures, and hallucinations**. 3 deaths occurred. 13-toxic exposure involved cannabis as the only agent. No antidote exists for SC exposure, and supportive care is the current standard treatment.
• Hoyte et al. (2011) review of data from the National Poison data system over a 9-month period in 2010 found 1353 SC single agent exposure- symptoms **tachycardia, agitation, lethargy, confusion, hallucinations, and rarely seizures**. SC use/toxicity were similar and included **violence, confusion, and tachycardia** (Ghosh et al., 2013). Most patients were treated and released; however, 13% admitted to the hospital with some of them needing intubation.

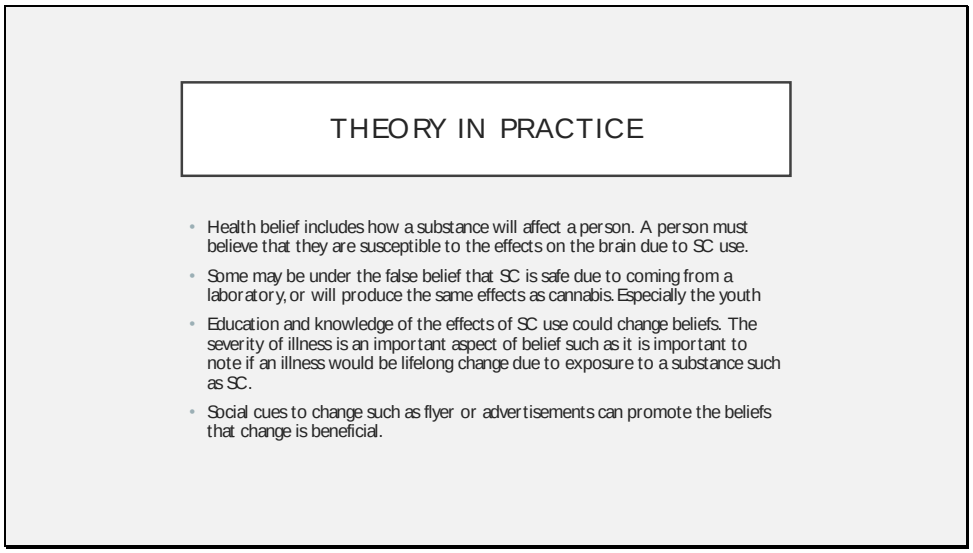
Slide 11


CLINICAL CASES
Two cases of patients hospitalized due to catatonia after high dose persistent SC use (Khan et al., 2016).
One case was a 21-year-old African American male that had a daily consumption of SCs for over a year. Symptoms of delayed responses, muteness, and hallucinations. Treatment of antipsychotics and benzodiazepines resolved the catatonia; however, cognitive deficits remained.
Second case was a 17-year-old, Caucasian male that had two weeks of heavy use of synthetic cannabinoids, and one year of overall use. His symptoms included delays in speech, blank stares, muteness, and muscle rigidity. Treatment of antipsychotic, mood stabilizers and benzodiazepines helped to resolve the symptoms; however cognitive deficits remained.
Both cases had no history of psychiatric or medical disorders.

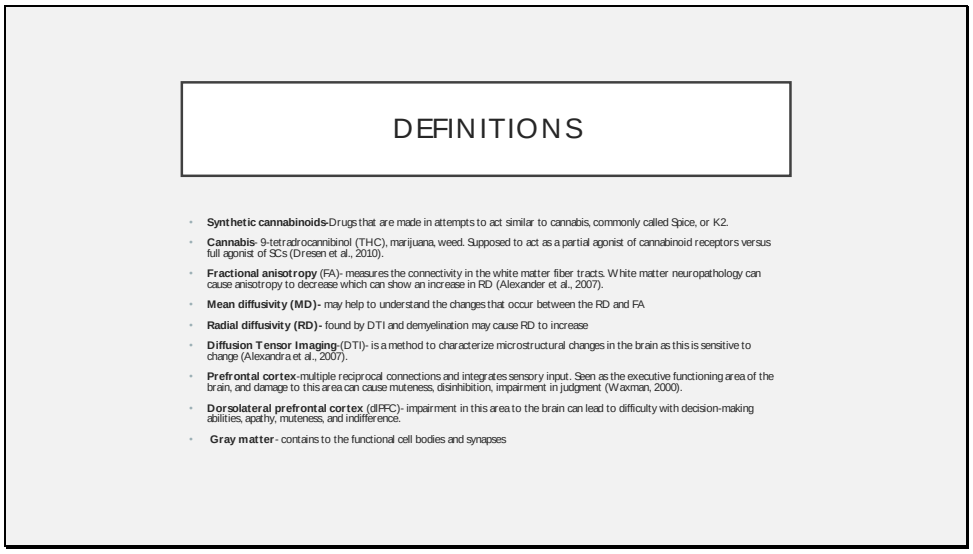
Slide 12


THEORY OF PLANNED BEHAVIOR
• Theory of Planned Behavior came from Theory of Reasoned Action (TRA), which originated from social psychologists that related on how beliefs affect behavior (McEwen &Wills, 2014).
• Theory or planned behavior begins with the assumption that people can make decisions. To predict behavior, we must determine what the person intends to do, current beliefs, cultural norms, and self-efficacy of the person. Belief influences behavior.
• Essentially theory of planned behavior is a combination of concepts including beliefs, attitudes, and intention. This theory is reliant on that human behavior is predictable and can be deconstructed from thoughts and feelings (Ajzen, 2011).

Slide 13


THEORY IN PRACTICE
Health belief includes how a substance will affect a person. A person must believe that they are susceptible to the effects on the brain due to SC use.
Some may be under the false belief that SC is safe due to coming from a laboratory, or will produce the same effects as cannabis. Especially the youth
Education and knowledge of the effects of SC use could change beliefs. The severity of illness is an important aspect of belief such as it is important to note if an illness would be lifelong change due to exposure to a substance such as SC.
Social cues to change such as flyer or advertisements can promote the beliefs that change is beneficial.

Slide 14


DEFINITIONS
Synthetic cannabinoids-Drugs that are made in attempts to act similar to cannabis, commonly called Spice, or K2.
Cannabis- 9-tetradrocannibinol (THC), marijuana, weed. Supposed to act as a partial agonist of cannabinoid receptors versus full agonist of SCs (Dresen et al., 2010).
Fractional anisotropy (FA)- measures the connectivity in the white matter fiber tracts. White matter neuropathology can cause anisotropy to decrease which can show an increase in RD (Alexander et al., 2007).
Mean diffusivity (MD)- may help to understand the changes that occur between the RD and FA
Radial diffusivity (RD)- found by DTI and demyelination may cause RD to increase
Diffusion Tensor Imaging-(DTI)- is a method to characterize microstructural changes in the brain as this is sensitive to change (Alexandra et al., 2007).
Prefrontal cortex-multiple reciprocal connections and integrates sensory input. Seen as the executive functioning area of the brain, and damage to this area can cause muteness, disinhibition, impairment in judgment (Waxman, 2000).
Dorsolateral prefrontal cortex (dlPFC)- impairment in this area to the brain can lead to difficulty with decision-making abilities, apathy, muteness, and indifference.
Gray matter- contains to the functional cell bodies and synapses

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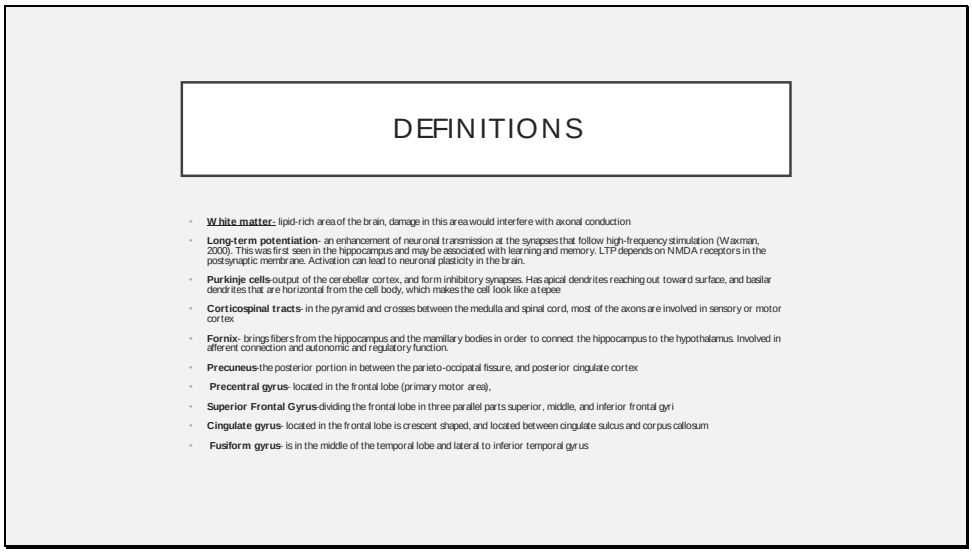
DEFINITIONS
White matter- lipid-rich area of the brain, damage in this area would interfere with axonal conduction
Long-term potentiation- an enhancement of neuronal transmission at the synapses that follow high-frequency stimulation (Waxman, 2000). This was first seen in the hippocampus and may be associated with learning and memory. LTP depends on NMDA receptors in the postsynaptic membrane. Activation can lead to neuronal plasticity in the brain.
Purkinje cells-output of the cerebellar cortex, and form inhibitory synapses. Has apical dendrites reaching out toward surface, and basilar dendrites that are horizontal from the cell body, which makes the cell look like a tepee
Corticospinal tracts- in the pyramid and crosses between the medulla and spinal cord, most of the axons are involved in sensory or motor cortex
Fornix- brings fibers from the hippocampus and the mamillary bodies in order to connect the hippocampus to the hypothalamus. Involved in afferent connection and autonomic and regulatory function.
Precuneus-the posterior portion in between the parieto-occipatal fissure, and posterior cingulate cortex
Precentral gyrus- located in the frontal lobe (primary motor area),
Superior Frontal Gyrus-dividing the frontal lobe in three parallel parts superior, middle, and inferior frontal gyri
Cingulate gyrus- located in the frontal lobe is crescent shaped, and located between cingulate sulcus and corpus callosum
Fusiform gyrus- is in the middle of the temporal lobe and lateral to inferior temporal gyrus

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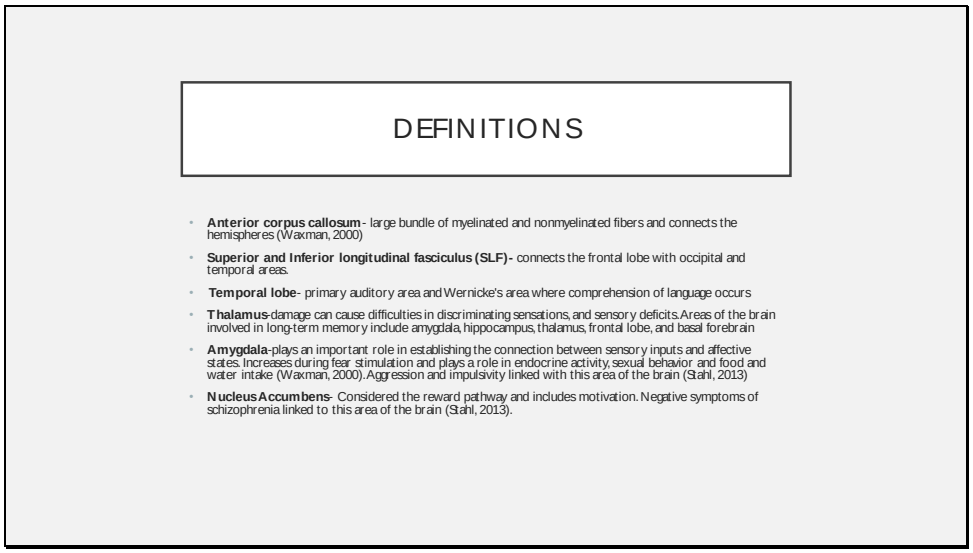
DEFINITIONS
Anterior corpus callosum- large bundle of myelinated and nonmyelinated fibers and connects the hemispheres (Waxman, 2000)
Superior and Inferior longitudinal fasciculus (SLF)- connects the frontal lobe with occipital and temporal areas.
Temporal lobe- primary auditory area and Wernicke's area where comprehension of language occurs
Thalamus-damage can cause difficulties in discriminating sensations, and sensory deficits. Areas of the brain involved in long-term memory include amygdala, hippocampus, thalamus, frontal lobe, and basal forebrain
Amygdala-plays an important role in establishing the connection between sensory inputs and affective states. Increases during fear stimulation and plays a role in endocrine activity, sexual behavior and food and water intake (Waxman, 2000). Aggression and impulsivity linked with this area of the brain (Stahl, 2013)
Nucleus Accumbens- Considered the reward pathway and includes motivation. Negative symptoms of schizophrenia linked to this area of the brain (Stahl, 2013).

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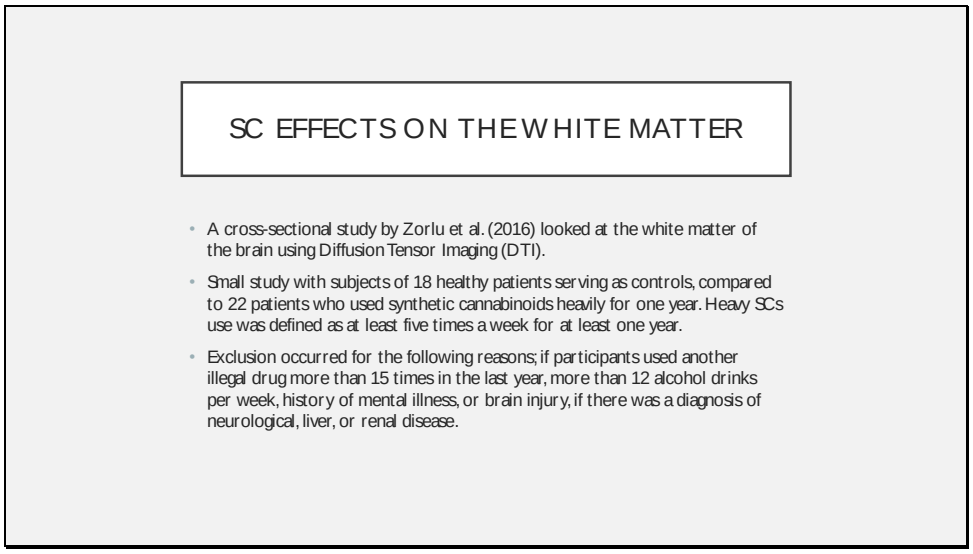
SC EFFECTS ON THE WHITE MATTER
• A cross-sectional study by Zorlu et al. (2016) looked at the white matter of the brain using Diffusion Tensor Imaging (DTI).
• Small study with subjects of 18 healthy patients serving as controls, compared to 22 patients who used synthetic cannabinoids heavily for one year. Heavy SCs use was defined as at least five times a week for at least one year.
• Exclusion occurred for the following reasons; if participants used another illegal drug more than 15 times in the last year, more than 12 alcohol drinks per week, history of mental illness, or brain injury, if there was a diagnosis of neurological, liver, or renal disease.

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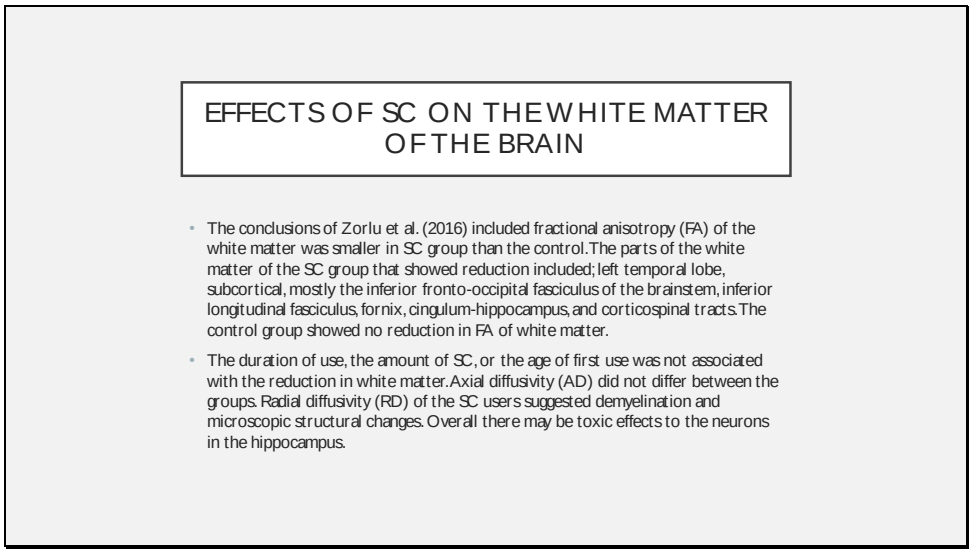
EFFECTS OF SC ON THE WHITE MATTER OF THE BRAIN
• The conclusions of Zorlu et al. (2016) included fractional anisotropy (FA) of the white matter was smaller in SC group than the control. The parts of the white matter of the SC group that showed reduction included; left temporal lobe, subcortical, mostly the inferior fronto-occipital fasciculus of the brainstem, inferior longitudinal fasciculus, fornix, cingulum-hippocampus, and corticospinal tracts. The control group showed no reduction in FA of white matter.
• The duration of use, the amount of SC, or the age of first use was not associated with the reduction in white matter. Axial diffusivity (AD) did not differ between the groups. Radial diffusivity (RD) of the SC users suggested demyelination and microscopic structural changes. Overall there may be toxic effects to the neurons in the hippocampus.

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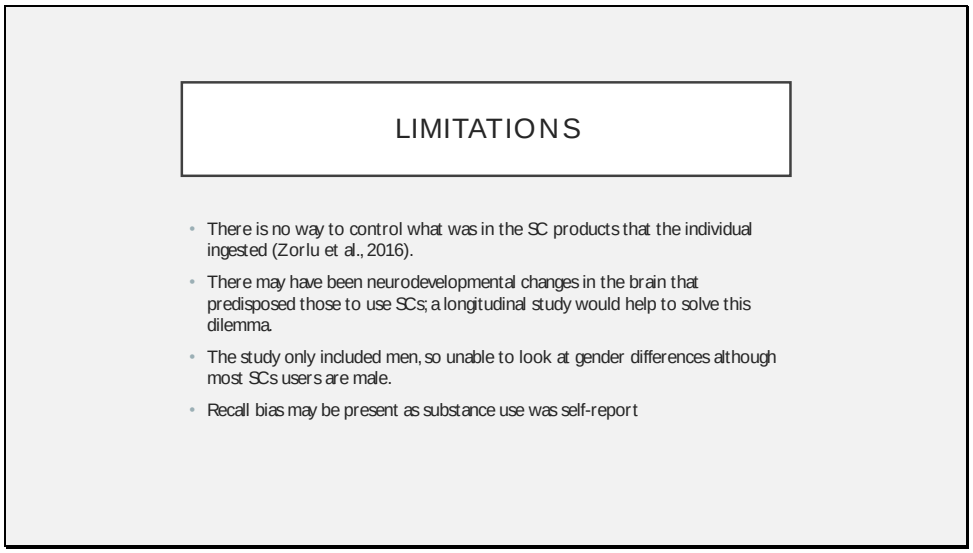
LIMITATIONS
There is no way to control what was in the SC products that the individual ingested (Zorlu et al., 2016).
There may have been neurodevelopmental changes in the brain that predisposed those to use SCs; a longitudinal study would help to solve this dilemma.
The study only included men, so unable to look at gender differences although most SCs users are male.
Recall bias may be present as substance use was self-report

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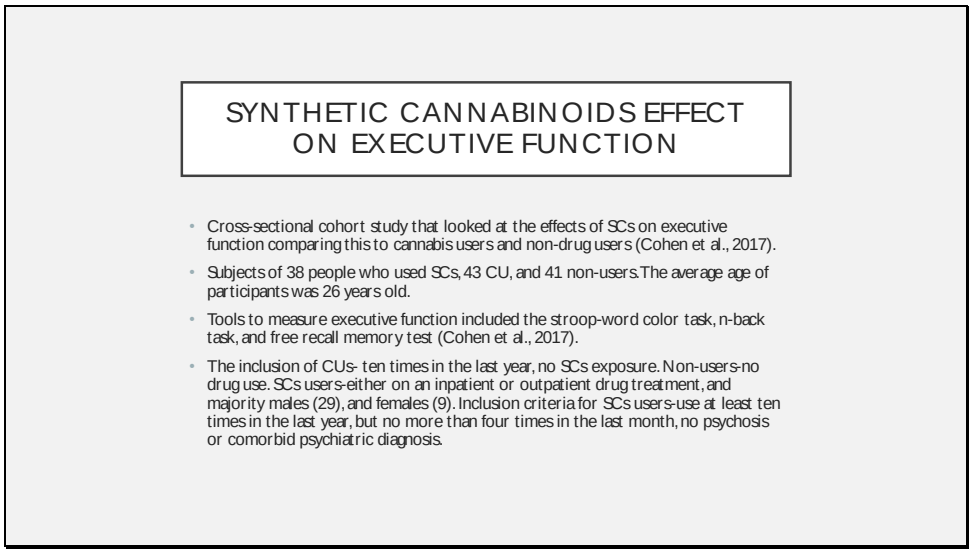
SYNTHETIC CANNABINOIDS EFFECT ON EXECUTIVE FUNCTION
Cross-sectional cohort study that looked at the effects of SCs on executive function comparing this to cannabis users and non-drug users (Cohen et al., 2017).
Subjects of 38 people who used SCs, 43 CU, and 41 non-users. The average age of participants was 26 years old.
Tools to measure executive function included the stroop-word color task, n-back task, and free recall memory test (Cohen et al., 2017).
The inclusion of CUs- ten times in the last year, no SCs exposure. Non-users-no drug use. SCs users-either on an inpatient or outpatient drug treatment, and majority males (29), and females (9). Inclusion criteria for SCs users-use at least ten times in the last year, but no more than four times in the last month, no psychosis or comorbid psychiatric diagnosis.

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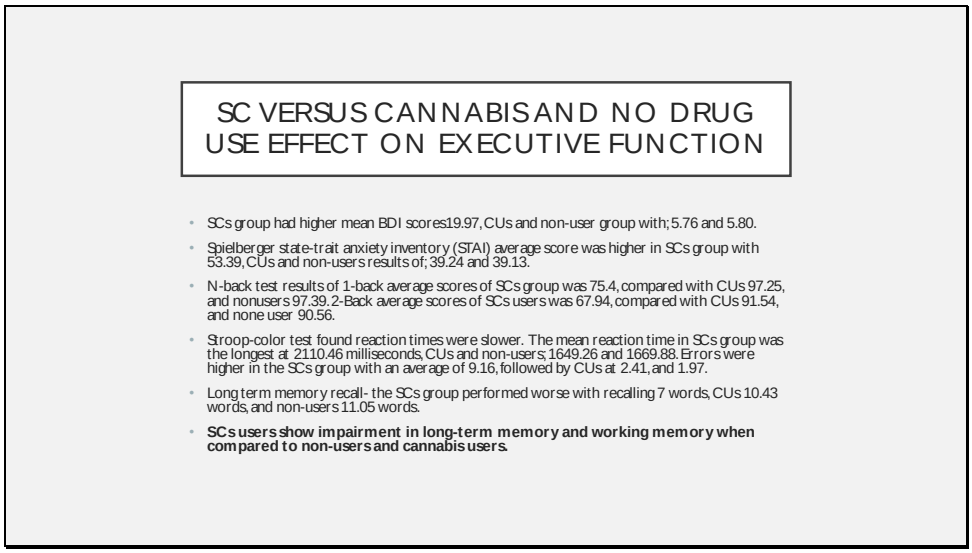
SC VERSUS CANNABIS AND NO DRUG USE EFFECT ON EXECUTIVE FUNCTION
SCs group had higher mean BDI scores 19.97, CUs and non-user group with; 5.76 and 5.80.
Spielberger state-trait anxiety inventory (STAI) average score was higher in SCs group with 53.39, CUs and non-users results of; 39.24 and 39.13.
N-back test results of 1-back average scores of SCs group was 75.4, compared with CUs 97.25, and nonusers 97.39. 2-Back average scores of SCs users was 67.94, compared with CUs 91.54, and none user 90.56.
Stroop-color test found reaction times were slower. The mean reaction time in SCs group was the longest at 2110.46 milliseconds, CUs and non-users; 1649.26 and 1669.88. Errors were higher in the SCs group with an average of 9.16, followed by CUs at 2.41, and 1.97.
Long term memory recall- the SCs group performed worse with recalling 7 words, CUs 10.43 words, and non-users 11.05 words.
SCs users show impairment in long-term memory and working memory when compared to non-users and cannabis users.

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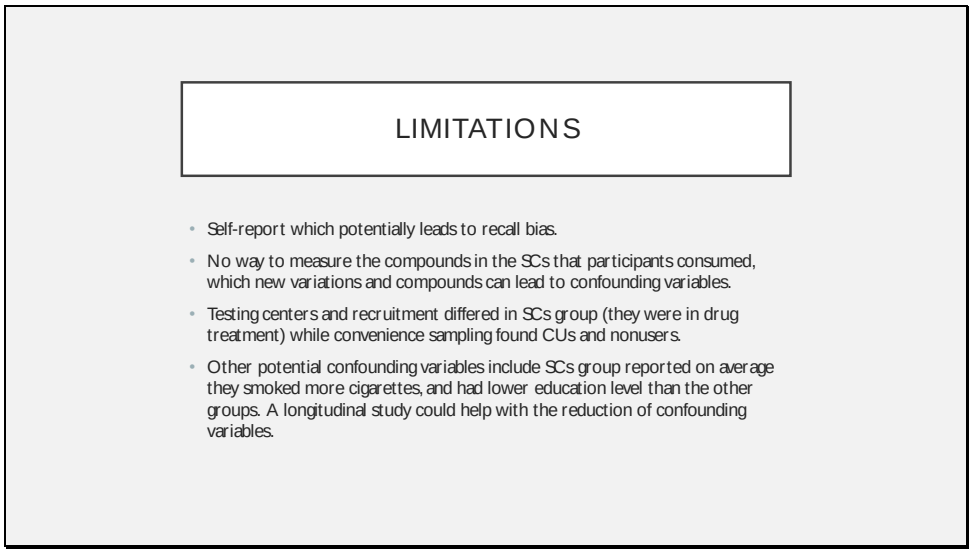
LIMITATIONS
Self-report which potentially leads to recall bias.
No way to measure the compounds in the SCs that participants consumed, which new variations and compounds can lead to confounding variables.
Testing centers and recruitment differed in SCs group (they were in drug treatment) while convenience sampling found CUs and nonusers.
Other potential confounding variables include SCs group reported on average they smoked more cigarettes, and had lower education level than the other groups. A longitudinal study could help with the reduction of confounding variables.

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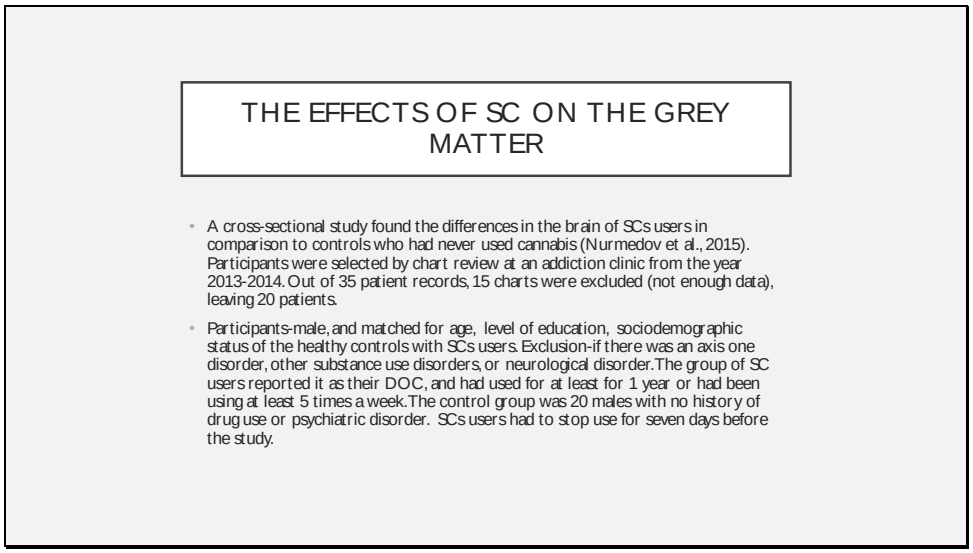
THE EFFECTS OF SC ON THE GREY MATTER
• A cross-sectional study found the differences in the brain of SCs users in comparison to controls who had never used cannabis (Nurmedov et al., 2015). Participants were selected by chart review at an addiction clinic from the year 2013-2014. Out of 35 patient records, 15 charts were excluded (not enough data), leaving 20 patients.
• Participants-male, and matched for age, level of education, sociodemographic status of the healthy controls with SCs users. Exclusion-if there was an axis one disorder, other substance use disorders, or neurological disorder. The group of SC users reported it as their DOC, and had used for at least for 1 year or had been using at least 5 times a week. The control group was 20 males with no history of drug use or psychiatric disorder. SCs users had to stop use for seven days before the study.

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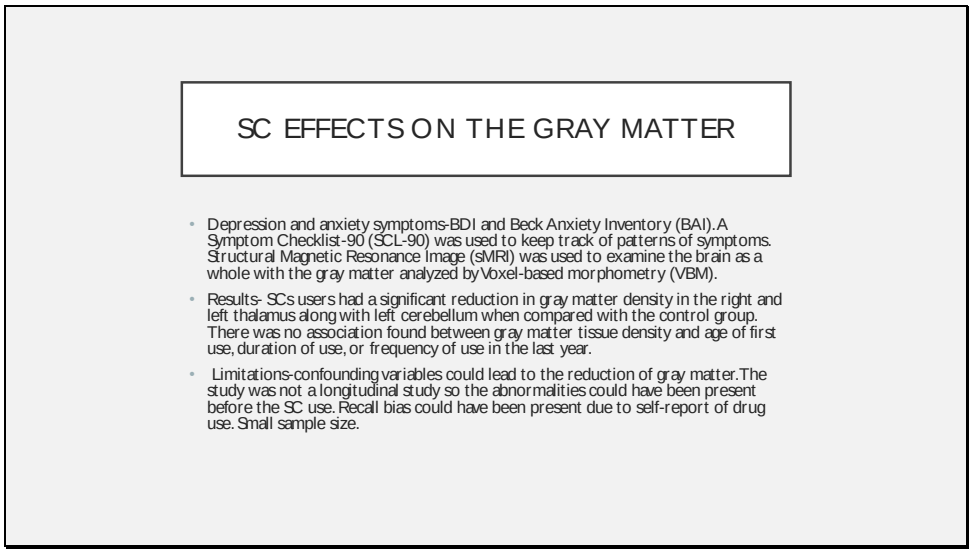
SC EFFECTS ON THE GRAY MATTER
• Depression and anxiety symptoms-BDI and Beck Anxiety Inventory (BAI). A Symptom Checklist-90 (SCL-90) was used to keep track of patterns of symptoms. Structural Magnetic Resonance Image (sMRI) was used to examine the brain as a whole with the gray matter analyzed by Voxel-based morphometry (VBM).
• Results- SCs users had a significant reduction in gray matter density in the right and left thalamus along with left cerebellum when compared with the control group. There was no association found between gray matter tissue density and age of first use, duration of use, or frequency of use in the last year.
• Limitations-confounding variables could lead to the reduction of gray matter. The study was not a longitudinal study so the abnormalities could have been present before the SC use. Recall bias could have been present due to self-report of drug use. Small sample size.

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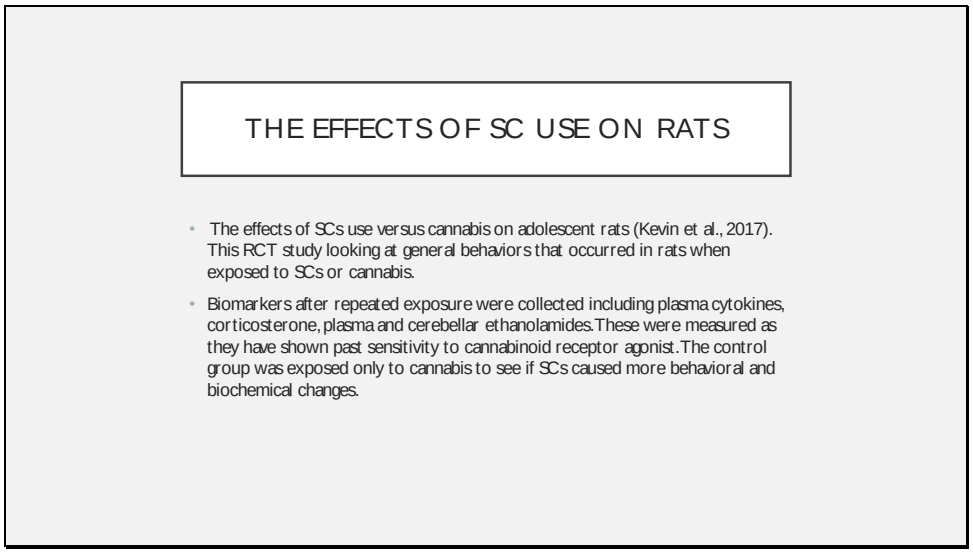
THE EFFECTS OF SC USE ON RATS
• The effects of SCs use versus cannabis on adolescent rats (Kevin et al., 2017). This RCT study looking at general behaviors that occurred in rats when exposed to SCs or cannabis.
• Biomarkers after repeated exposure were collected including plasma cytokines, corticosterone, plasma and cerebellar ethanolamides. These were measured as they have shown past sensitivity to cannabinoid receptor agonist. The control group was exposed only to cannabis to see if SCs caused more behavioral and biochemical changes.

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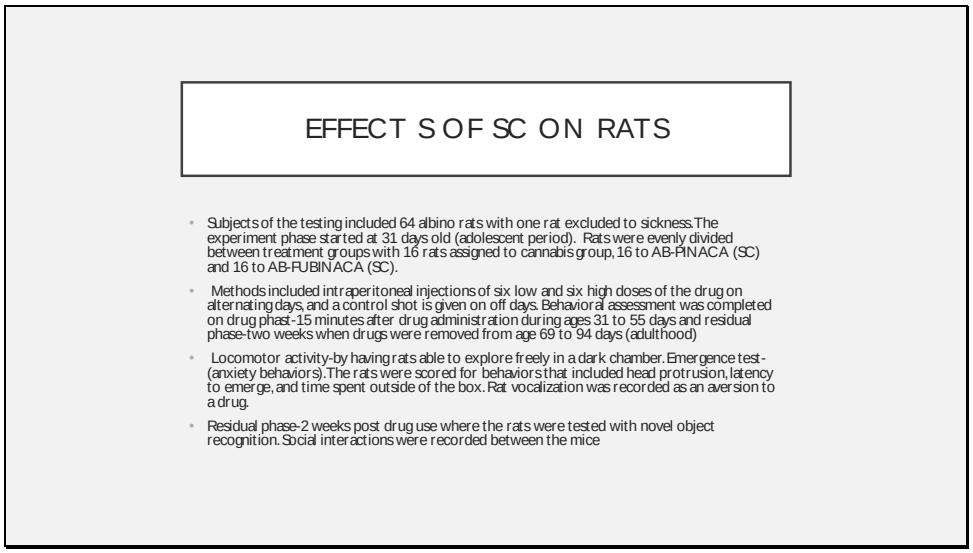
EFFECTS OF SC ON RATS
Subjects of the testing included 64 albino rats with one rat excluded to sickness.The experiment phase started at 31 days old (adolescent period). Rats were evenly divided between treatment groups with 16 rats assigned to cannabis group, 16 to AB-PINACA (SC) and 16 to AB-FUBINACA (SC).
Methods included intraperitoneal injections of six low and six high doses of the drug on alternating days, and a control shot is given on off days. Behavioral assessment was completed on drug phast-15 minutes after drug administration during ages 31 to 55 days and residual phase-two weeks when drugs were removed from age 69 to 94 days (adulthood)
Locomotor activity-by having rats able to explore freely in a dark chamber. Emergence test-(anxiety behaviors).The rats were scored for behaviors that included head protrusion, latency to emerge, and time spent outside of the box. Rat vocalization was recorded as an aversion to a drug.
Residual phase-2 weeks post drug use where the rats were tested with novel object recognition. Social interactions were recorded between the mice

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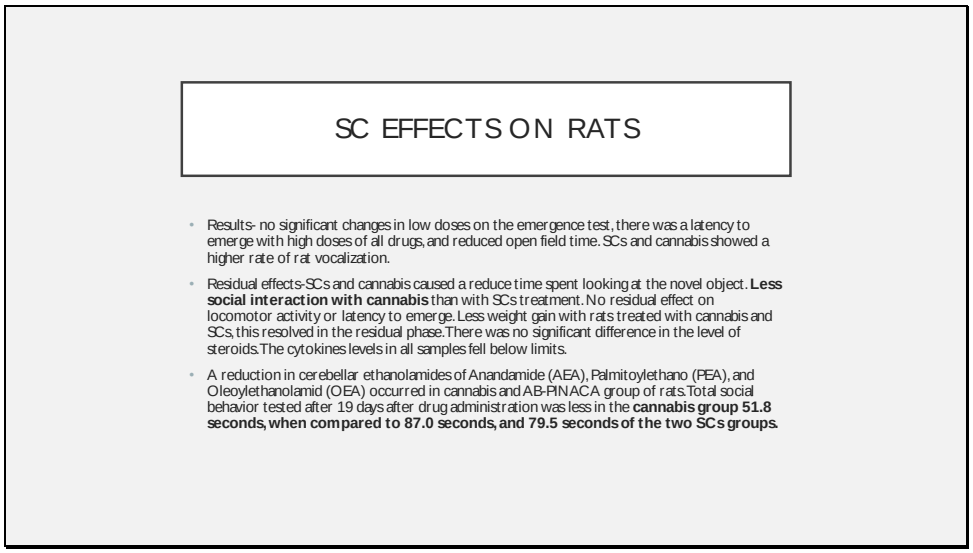
SC EFFECTS ON RATS
Results- no significant changes in low doses on the emergence test, there was a latency to emerge with high doses of all drugs, and reduced open field time. SCs and cannabis showed a higher rate of rat vocalization.
Residual effects-SCs and cannabis caused a reduce time spent looking at the novel object. Less social interaction with cannabis than with SCs treatment. No residual effect on locomotor activity or latency to emerge. Less weight gain with rats treated with cannabis and SCs, this resolved in the residual phase. There was no significant difference in the level of steroids. The cytokines levels in all samples fell below limits.
A reduction in cerebellar ethanolamides of Anandamide (AEA), Palmitoylethano (PEA), and Oleoylethanolamid (OEA) occurred in cannabis and AB-PINACA group of rats. Total social behavior tested after 19 days after drug administration was less in the cannabis group 51.8 seconds, when compared to 87.0 seconds, and 79.5 seconds of the two SCs groups.

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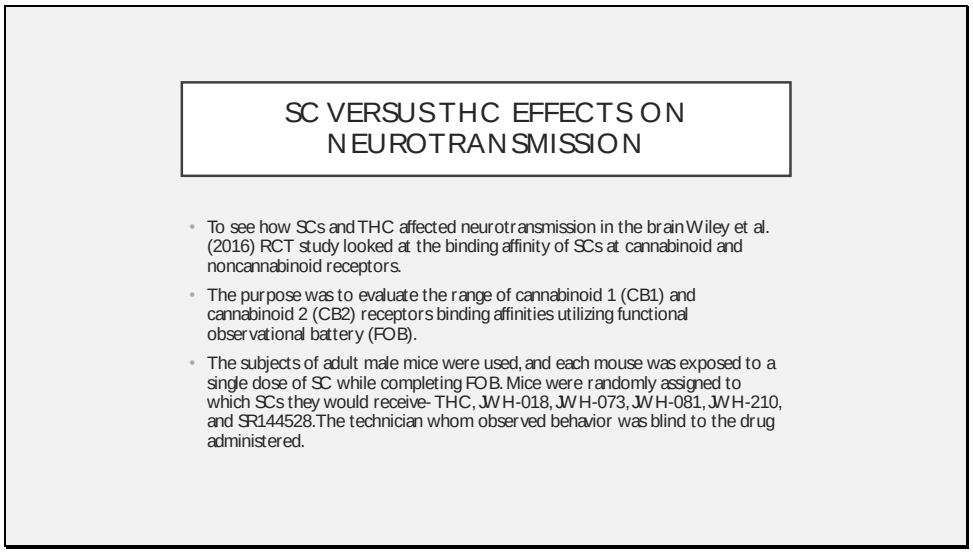
SC VERSUS THC EFFECTS ON NEUROTRANSMISSION
• To see how SCs and THC affected neurotransmission in the brain Wiley et al. (2016) RCT study looked at the binding affinity of SCs at cannabinoid and noncannabinoid receptors.
• The purpose was to evaluate the range of cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors binding affinities utilizing functional observational battery (FOB).
• The subjects of adult male mice were used, and each mouse was exposed to a single dose of SC while completing FOB. Mice were randomly assigned to which SCs they would receive- THC, JWH-018, JWH-073, JWH-081, JWH-210, and SR144528. The technician whom observed behavior was blind to the drug administered.

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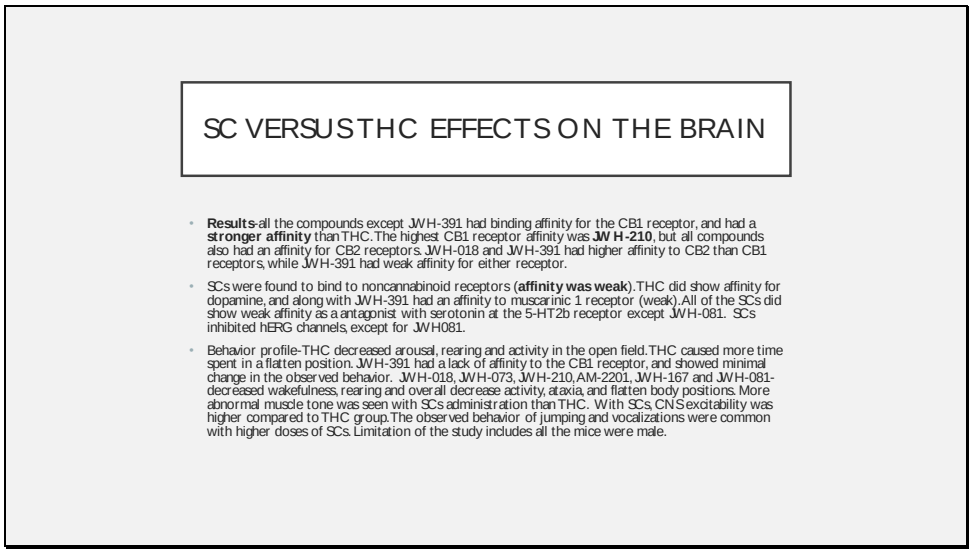
SC VERSUS THC EFFECTS ON THE BRAIN
Results-all the compounds except JWH-391 had binding affinity for the CB1 receptor, and had a stronger affinity than THC. The highest CB1 receptor affinity was JWH-210, but all compounds also had an affinity for CB2 receptors. JWH-018 and JWH-391 had higher affinity to CB2 than CB1 receptors, while JWH-391 had weak affinity for either receptor.
SCs were found to bind to noncannabinoid receptors (affinity was weak). THC did show affinity for dopamine, and along with JWH-391 had an affinity to muscarinic 1 receptor (weak). All of the SCs did show weak affinity as a antagonist with serotonin at the 5-HT2b receptor except JWH-081. SCs inhibited hERG channels, except for JWH081.
Behavior profile-THC decreased arousal, rearing and activity in the open field. THC caused more time spent in a flatten position. JWH-391 had a lack of affinity to the CB1 receptor, and showed minimal change in the observed behavior. JWH-018, JWH-073, JWH-210, AM-2201, JWH-167 and JWH-081-decreased wakefulness, rearing and overall decrease activity, ataxia, and flatten body positions. More abnormal muscle tone was seen with SCs administration than THC. With SCs, CNS excitability was higher compared to THC group. The observed behavior of jumping and vocalizations were common with higher doses of SCs. Limitation of the study includes all the mice were male.

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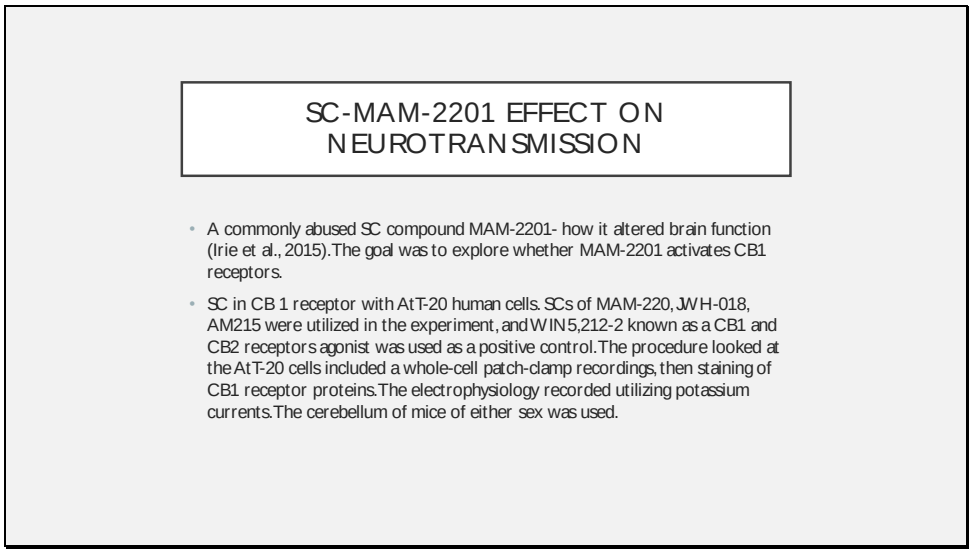
SC-MAM-2201 EFFECT ON NEUROTRANSMISSION
• A commonly abused SC compound MAM-2201- how it altered brain function (Irie et al., 2015). The goal was to explore whether MAM-2201 activates CB1 receptors.
• SC in CB 1 receptor with AtT-20 human cells. SCs of MAM-220, JWH-018, AM215 were utilized in the experiment, and WIN 5,212-2 known as a CB1 and CB2 receptors agonist was used as a positive control. The procedure looked at the AtT-20 cells included a whole-cell patch-clamp recordings, then staining of CB1 receptor proteins. The electrophysiology recorded utilizing potassium currents. The cerebellum of mice of either sex was used.

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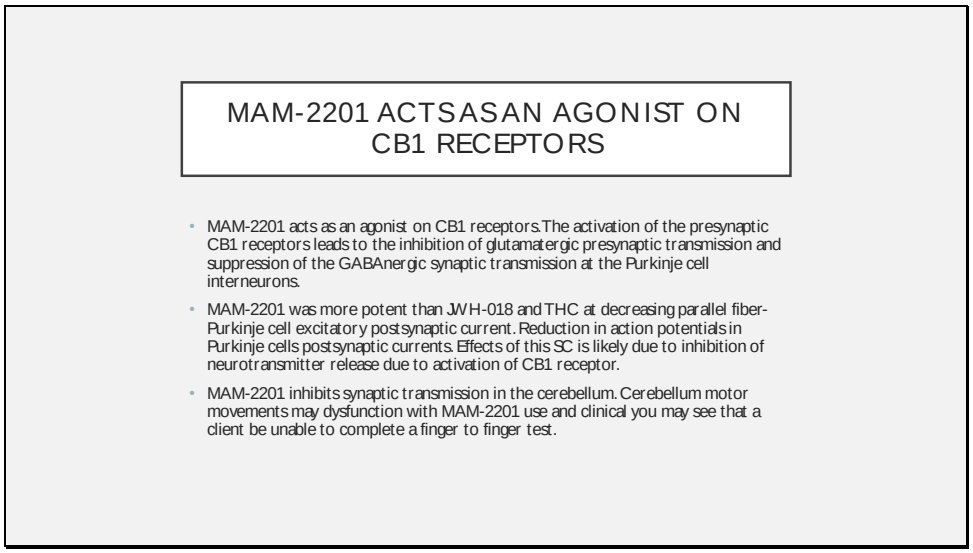
MAM-2201 ACTSASAN AGONIST ON CB1 RECEPTORS
• MAM-2201 acts as an agonist on CB1 receptors.The activation of the presynaptic CB1 receptors leads to the inhibition of glutamatergic presynaptic transmission and suppression of the GABAnergic synaptic transmission at the Purkinje cell interneurons.
• MAM-2201 was more potent than JWH-018 and THC at decreasing parallel fiber-Purkinje cell excitatory postsynaptic current. Reduction in action potentials in Purkinje cells postsynaptic currents. Effects of this SC is likely due to inhibition of neurotransmitter release due to activation of CB1 receptor.
• MAM-2201 inhibits synaptic transmission in the cerebellum. Cerebellum motor movements may dysfunction with MAM-2201 use and clinical you may see that a client be unable to complete a finger to finger test.

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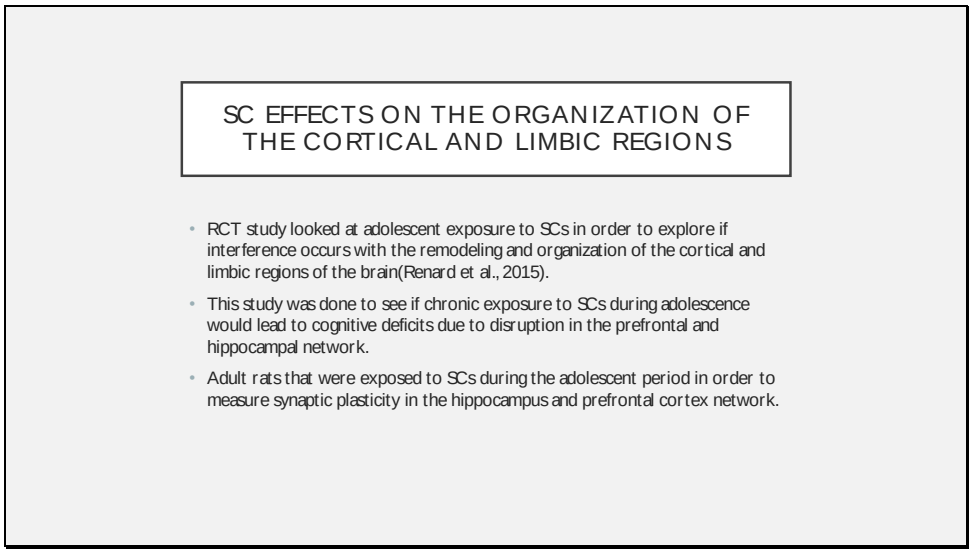
SC EFFECTS ON THE ORGANIZATION OF THE CORTICAL AND LIMBIC REGIONS
• RCT study looked at adolescent exposure to SCs in order to explore if interference occurs with the remodeling and organization of the cortical and limbic regions of the brain(Renard et al., 2015).
• This study was done to see if chronic exposure to SCs during adolescence would lead to cognitive deficits due to disruption in the prefrontal and hippocampal network.
• Adult rats that were exposed to SCs during the adolescent period in order to measure synaptic plasticity in the hippocampus and prefrontal cortex network.

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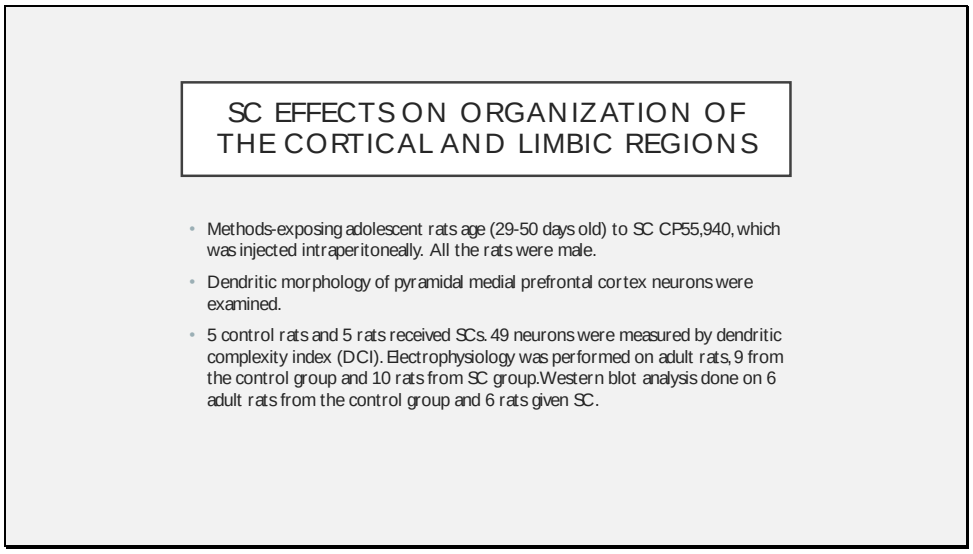
SC EFFECTS ON ORGANIZATION OF THE CORTICAL AND LIMBIC REGIONS
Methods-exposing adolescent rats age (29-50 days old) to SC CP55,940, which was injected intraperitoneally. All the rats were male.
Dendritic morphology of pyramidal medial prefrontal cortex neurons were examined.
5 control rats and 5 rats received SCs. 49 neurons were measured by dendritic complexity index (DCI). Electrophysiology was performed on adult rats, 9 from the control group and 10 rats from SC group. Western blot analysis done on 6 adult rats from the control group and 6 rats given SC.

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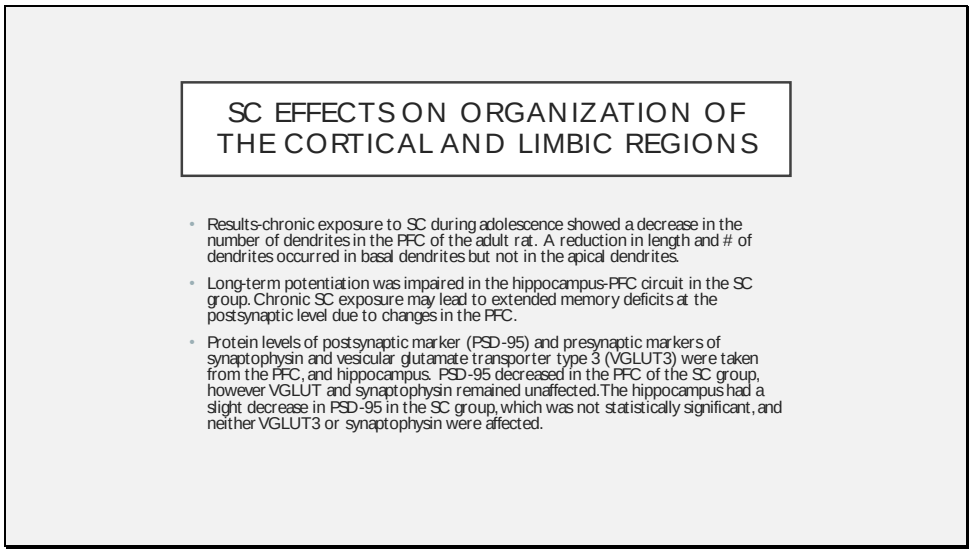
SC EFFECTS ON ORGANIZATION OF THE CORTICAL AND LIMBIC REGIONS
Results-chronic exposure to SC during adolescence showed a decrease in the number of dendrites in the PFC of the adult rat. A reduction in length and # of dendrites occurred in basal dendrites but not in the apical dendrites.
Long-term potentiation was impaired in the hippocampus-PFC circuit in the SC group. Chronic SC exposure may lead to extended memory deficits at the postsynaptic level due to changes in the PFC.
Protein levels of postsynaptic marker (PSD-95) and presynaptic markers of synaptophysin and vesicular glutamate transporter type 3 (VGLUT3) were taken from the PFC, and hippocampus. PSD-95 decreased in the PFC of the SC group, however VGLUT and synaptophysin remained unaffected. The hippocampus had a slight decrease in PSD-95 in the SC group, which was not statistically significant, and neither VGLUT3 or synaptophysin were affected.

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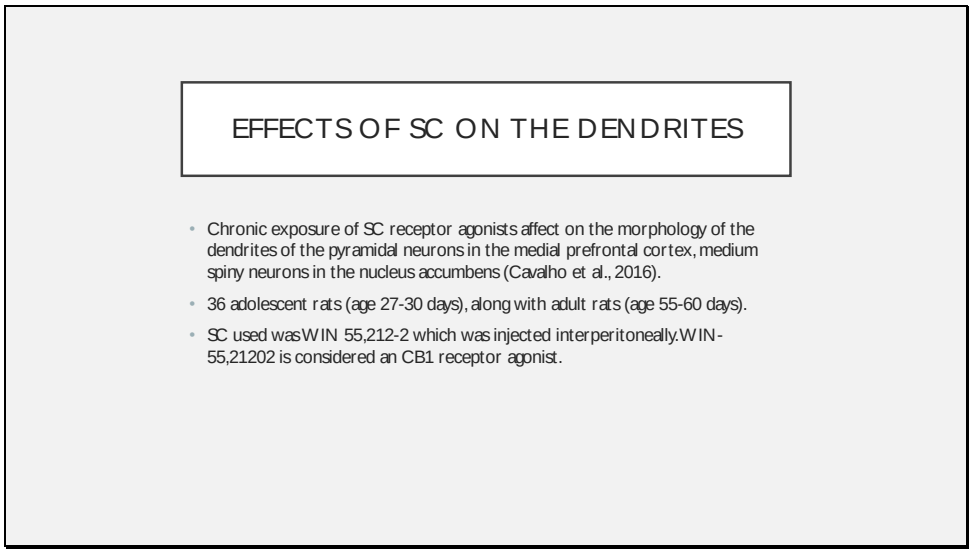
EFFECTS OF SC ON THE DENDRITES
• Chronic exposure of SC receptor agonists affect on the morphology of the dendrites of the pyramidal neurons in the medial prefrontal cortex, medium spiny neurons in the nucleus accumbens (Cavalho et al., 2016).
• 36 adolescent rats (age 27-30 days), along with adult rats (age 55-60 days).
• SC used was WIN 55,212-2 which was injected interperitoneally. WIN-55,21202 is considered an CB1 receptor agonist.

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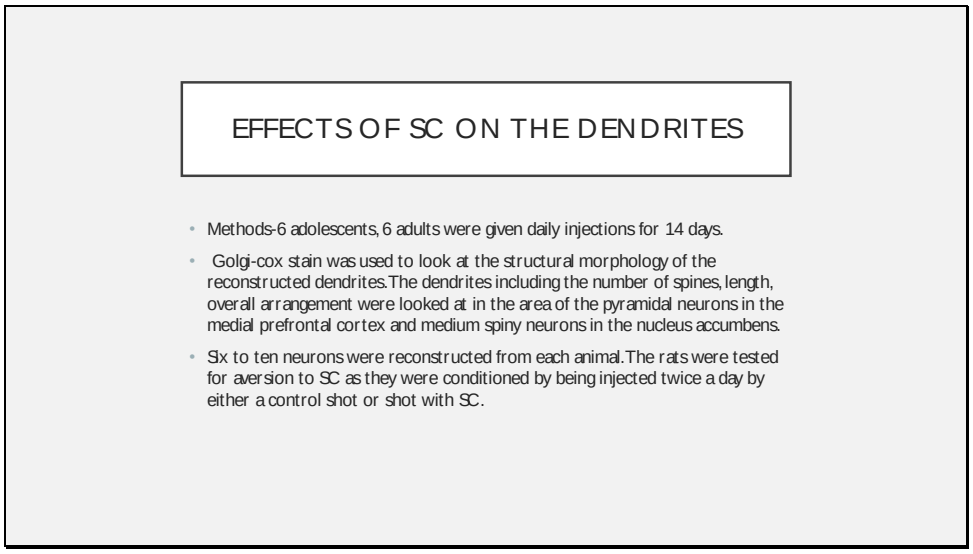
EFFECTS OF SC ON THE DENDRITES
Methods-6 adolescents, 6 adults were given daily injections for 14 days.
Golgi-cox stain was used to look at the structural morphology of the reconstructed dendrites. The dendrites including the number of spines, length, overall arrangement were looked at in the area of the pyramidal neurons in the medial prefrontal cortex and medium spiny neurons in the nucleus accumbens.
Six to ten neurons were reconstructed from each animal. The rats were tested for aversion to SC as they were conditioned by being injected twice a day by either a control shot or shot with SC.

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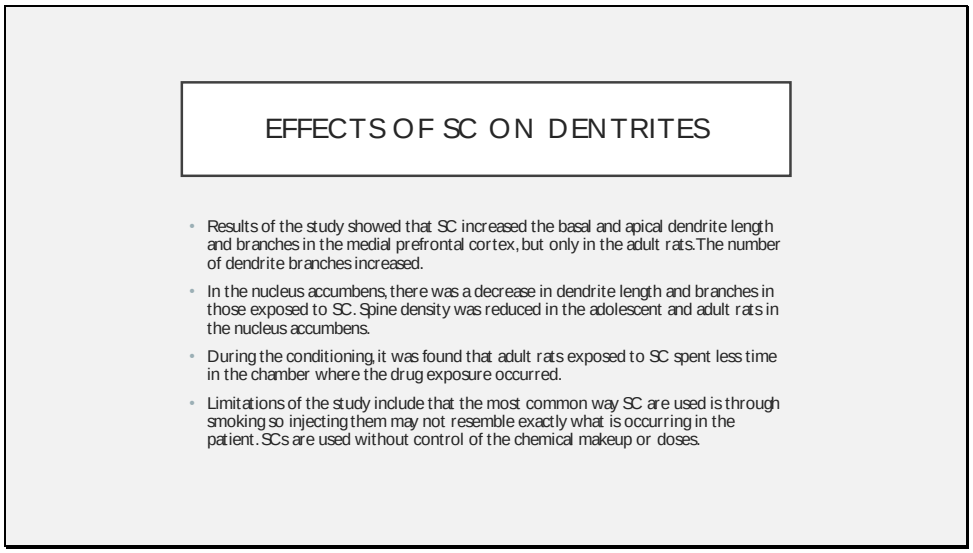
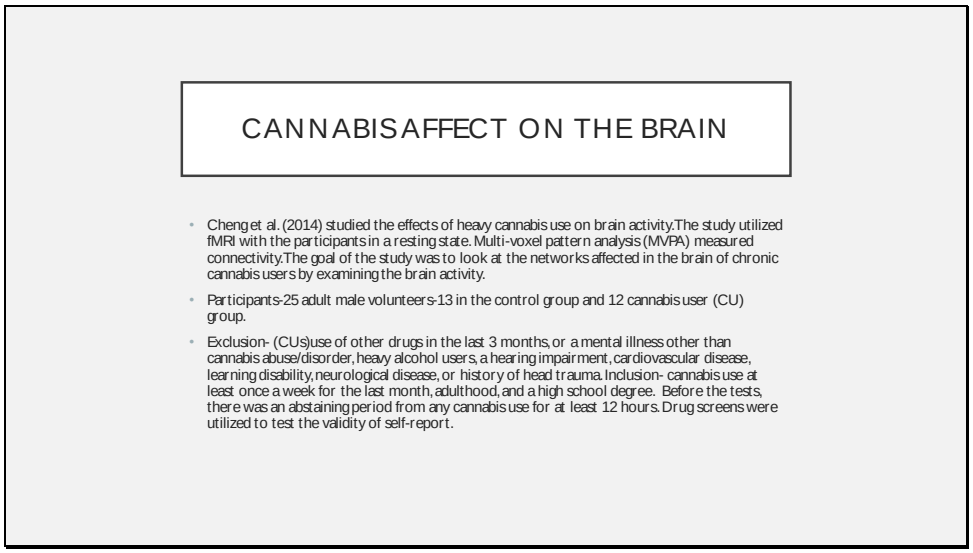

EFFECTS OF SC ON DENTRITES
Results of the study showed that SC increased the basal and apical dendrite length and branches in the medial prefrontal cortex, but only in the adult rats. The number of dendrite branches increased.
In the nucleus accumbens, there was a decrease in dendrite length and branches in those exposed to SC. Spine density was reduced in the adolescent and adult rats in the nucleus accumbens.
During the conditioning, it was found that adult rats exposed to SC spent less time in the chamber where the drug exposure occurred.
Limitations of the study include that the most common way SC are used is through smoking so injecting them may not resemble exactly what is occurring in the patient. SCs are used without control of the chemical makeup or doses.

Slide 38


CANNABIS AFFECT ON THE BRAIN
• Cheng et al. (2014) studied the effects of heavy cannabis use on brain activity. The study utilized fMRI with the participants in a resting state. Multi-voxel pattern analysis (MVPA) measured connectivity. The goal of the study was to look at the networks affected in the brain of chronic cannabis users by examining the brain activity.
• Participants-25 adult male volunteers-13 in the control group and 12 cannabis user (CU) group.
• Exclusion- (CUs) use of other drugs in the last 3 months, or a mental illness other than cannabis abuse/disorder, heavy alcohol users, a hearing impairment, cardiovascular disease, learning disability, neurological disease, or history of head trauma. Inclusion- cannabis use at least once a week for the last month, adulthood, and a high school degree. Before the tests, there was an abstaining period from any cannabis use for at least 12 hours. Drug screens were utilized to test the validity of self-report.

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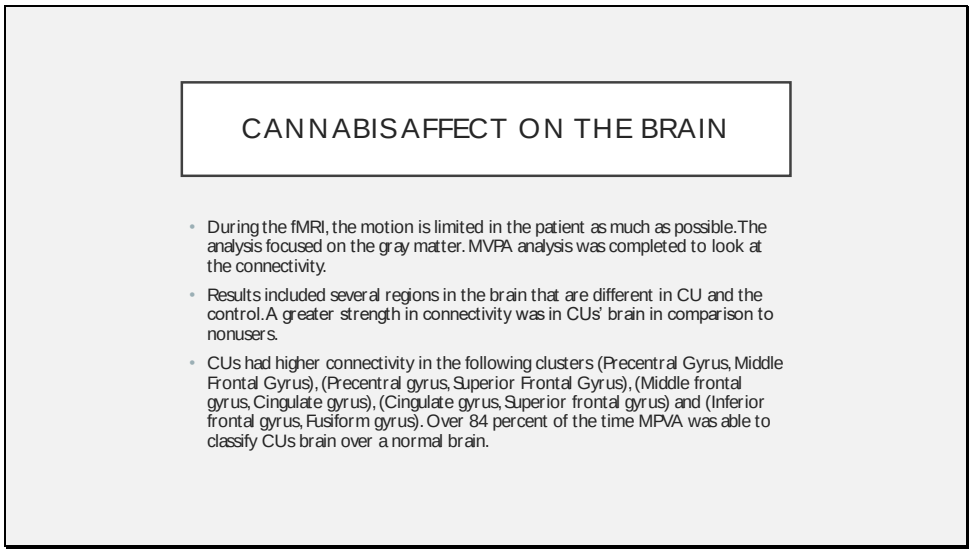
CANNABIS AFFECT ON THE BRAIN
During the fMRI, the motion is limited in the patient as much as possible. The analysis focused on the gray matter. MVPA analysis was completed to look at the connectivity.
Results included several regions in the brain that are different in CU and the control. A greater strength in connectivity was in CUs' brain in comparison to nonusers.
CUs had higher connectivity in the following clusters (Precentral Gyrus, Middle Frontal Gyrus), (Precentral gyrus, Superior Frontal Gyrus), (Middle frontal gyrus, Cingulate gyrus), (Cingulate gyrus, Superior frontal gyrus) and (Inferior frontal gyrus, Fusiform gyrus). Over 84 percent of the time MPVA was able to classify CUs brain over a normal brain.

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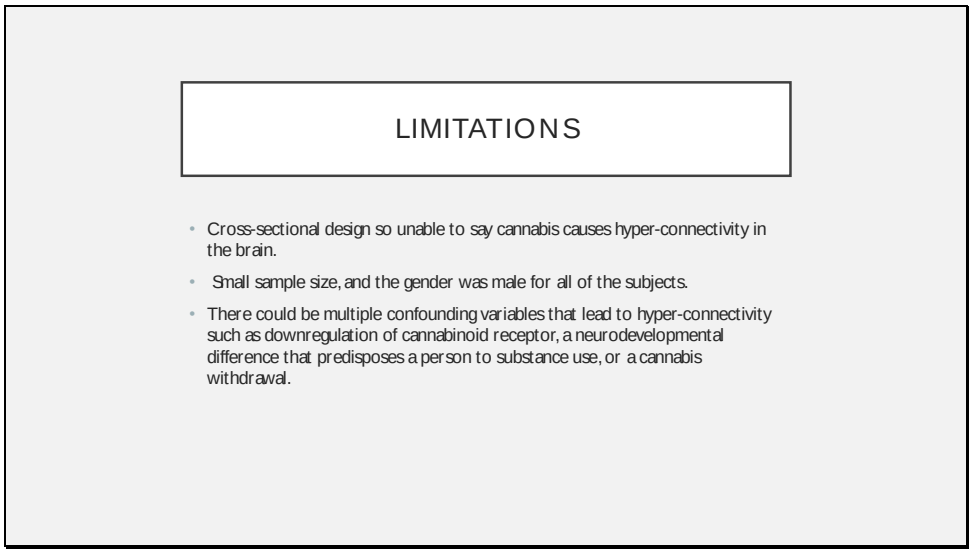
LIMITATIONS
Cross-sectional design so unable to say cannabis causes hyper-connectivity in the brain.
Small sample size, and the gender was male for all of the subjects.
There could be multiple confounding variables that lead to hyper-connectivity such as downregulation of cannabinoid receptor, a neurodevelopmental difference that predisposes a person to substance use, or a cannabis withdrawal.

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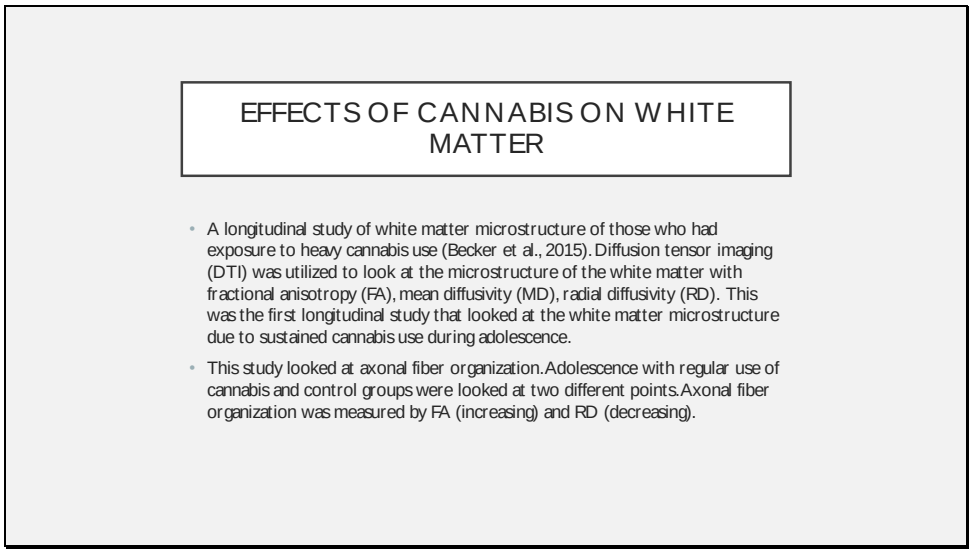
EFFECTS OF CANNABIS ON WHITE MATTER
• A longitudinal study of white matter microstructure of those who had exposure to heavy cannabis use (Becker et al., 2015). Diffusion tensor imaging (DTI) was utilized to look at the microstructure of the white matter with fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD). This was the first longitudinal study that looked at the white matter microstructure due to sustained cannabis use during adolescence.
• This study looked at axonal fiber organization. Adolescence with regular use of cannabis and control groups were looked at two different points. Axonal fiber organization was measured by FA (increasing) and RD (decreasing).

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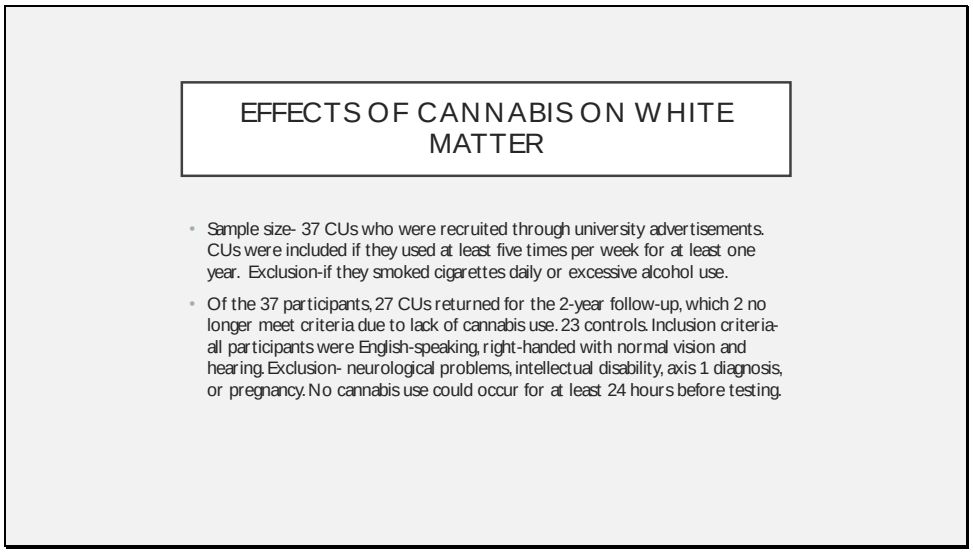
EFFECTS OF CANNABIS ON WHITE MATTER
Sample size- 37 CUs who were recruited through university advertisements. CUs were included if they used at least five times per week for at least one year. Exclusion-if they smoked cigarettes daily or excessive alcohol use.
Of the 37 participants, 27 CUs returned for the 2-year follow-up, which 2 no longer meet criteria due to lack of cannabis use. 23 controls. Inclusion criteria- all participants were English-speaking, right-handed with normal vision and hearing. Exclusion- neurological problems, intellectual disability, axis 1 diagnosis, or pregnancy. No cannabis use could occur for at least 24 hours before testing.

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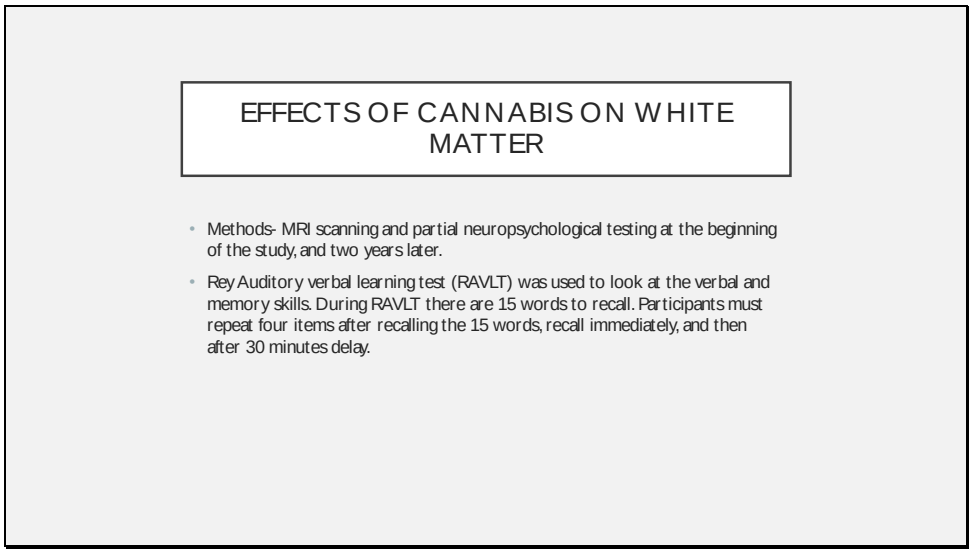
EFFECTS OF CANNABIS ON WHITE MATTER
Methods- MRI scanning and partial neuropsychological testing at the beginning of the study, and two years later.
Rey Auditory verbal learning test (RAVLT) was used to look at the verbal and memory skills. During RAVLT there are 15 words to recall. Participants must repeat four items after recalling the 15 words, recall immediately, and then after 30 minutes delay.

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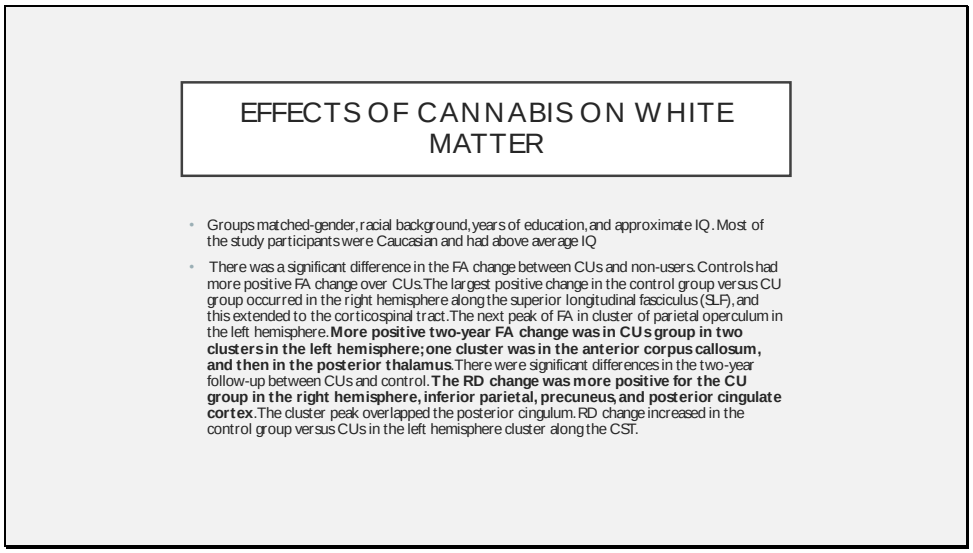
EFFECTS OF CANNABIS ON WHITE MATTER
Groups matched-gender, racial background, years of education, and approximate IQ. Most of the study participants were Caucasian and had above average IQ
There was a significant difference in the FA change between CUs and non-users. Controls had more positive FA change over CUs. The largest positive change in the control group versus CU group occurred in the right hemisphere along the superior longitudinal fasciculus (SLF), and this extended to the corticospinal tract. The next peak of FA in cluster of parietal operculum in the left hemisphere. More positive two-year FA change was in CUs group in two clusters in the left hemisphere; one cluster was in the anterior corpus callosum, and then in the posterior thalamus. There were significant differences in the two-year follow-up between CUs and control. The RD change was more positive for the CU group in the right hemisphere, inferior parietal, precuneus, and posterior cingulate cortex. The cluster peak overlapped the posterior cingulum. RD change increased in the control group versus CUs in the left hemisphere cluster along the CST.

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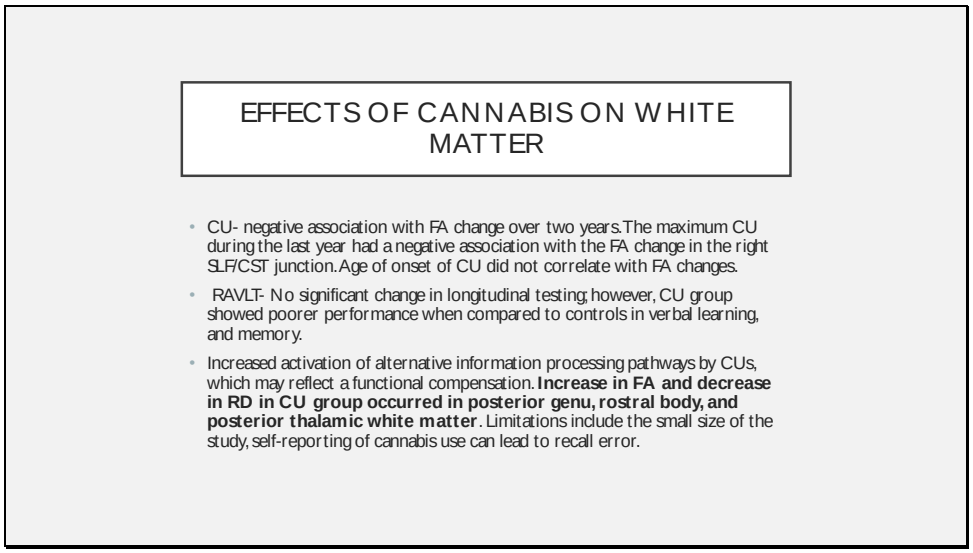
EFFECTS OF CANNABIS ON WHITE MATTER
• CU- negative association with FA change over two years. The maximum CU during the last year had a negative association with the FA change in the right SLF/CST junction. Age of onset of CU did not correlate with FA changes.
• RAVLT- No significant change in longitudinal testing; however, CU group showed poorer performance when compared to controls in verbal learning, and memory.
• Increased activation of alternative information processing pathways by CUs, which may reflect a functional compensation. Increase in FA and decrease in RD in CU group occurred in posterior genu, rostral body, and posterior thalamic white matter. Limitations include the small size of the study, self-reporting of cannabis use can lead to recall error.

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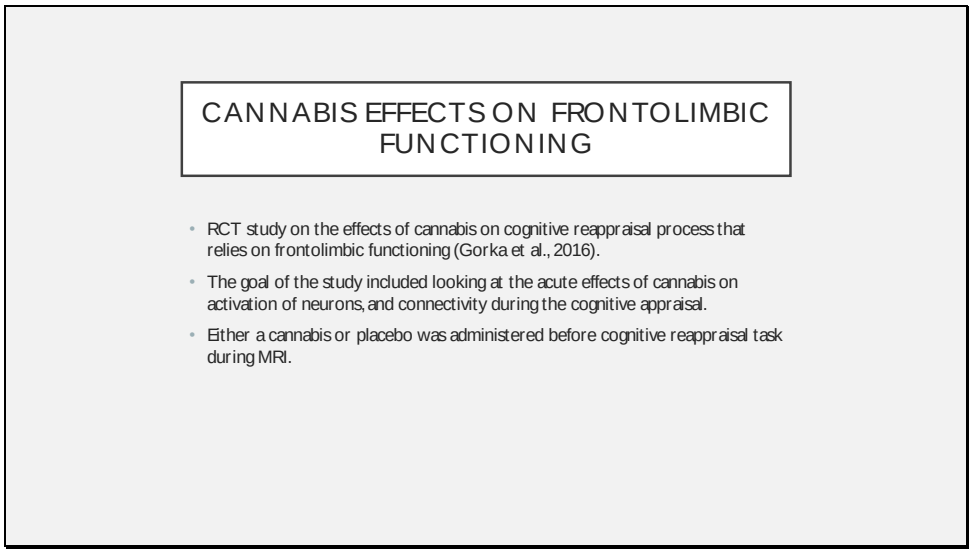
CANNABIS EFFECTS ON FRONTOLIMBIC FUNCTIONING
• RCT study on the effects of cannabis on cognitive reappraisal process that relies on frontolimbic functioning (Gorka et al., 2016).
• The goal of the study included looking at the acute effects of cannabis on activation of neurons, and connectivity during the cognitive appraisal.
• Either a cannabis or placebo was administered before cognitive reappraisal task during MRI.

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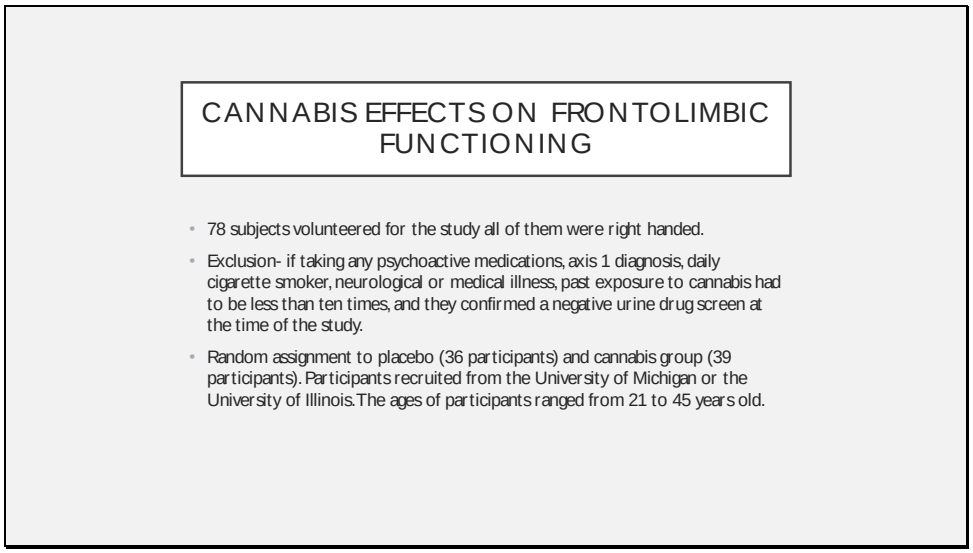
CANNABIS EFFECTS ON FRONTOLIMBIC FUNCTIONING
78 subjects volunteered for the study all of them were right handed.
Exclusion- if taking any psychoactive medications, axis 1 diagnosis, daily cigarette smoker, neurological or medical illness, past exposure to cannabis had to be less than ten times, and they confirmed a negative urine drug screen at the time of the study.
Random assignment to placebo (36 participants) and cannabis group (39 participants). Participants recruited from the University of Michigan or the University of Illinois. The ages of participants ranged from 21 to 45 years old.

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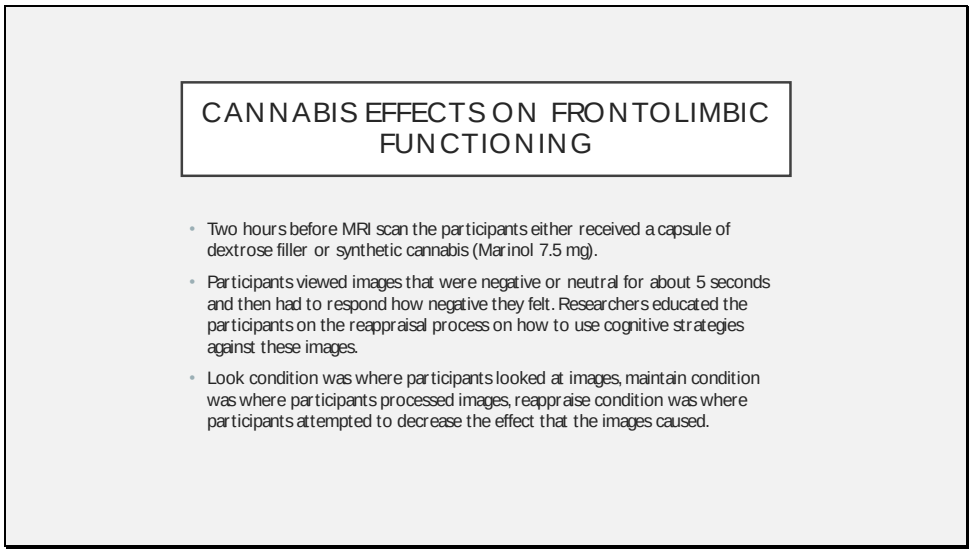
CANNABIS EFFECTS ON FRONTOLIMBIC FUNCTIONING
• Two hours before MRI scan the participants either received a capsule of dextrose filler or synthetic cannabis (Marinol 7.5 mg).
• Participants viewed images that were negative or neutral for about 5 seconds and then had to respond how negative they felt. Researchers educated the participants on the reappraisal process on how to use cognitive strategies against these images.
• Look condition was where participants looked at images, maintain condition was where participants processed images, reappraise condition was where participants attempted to decrease the effect that the images caused.

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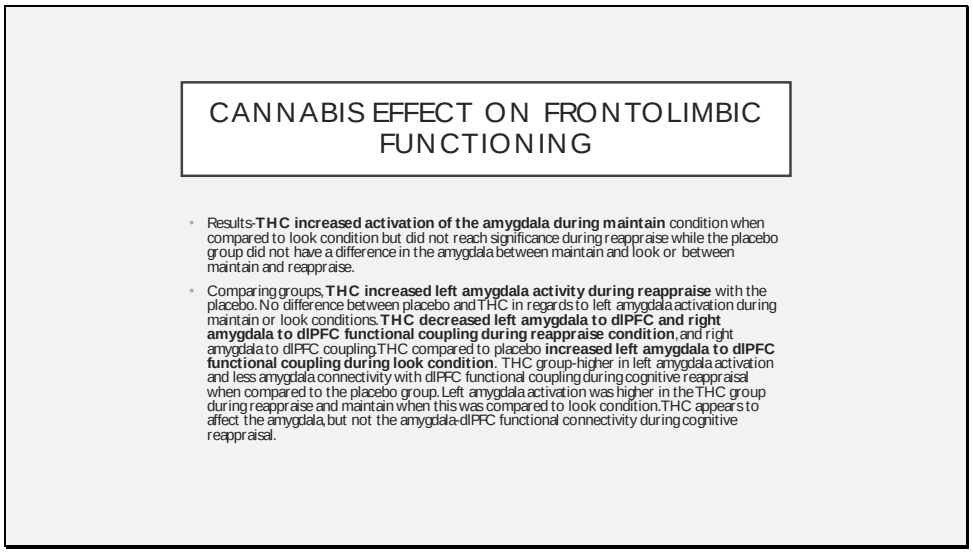
CANNABIS EFFECT ON FRONTOLIMBIC FUNCTIONING
Results-**THC increased activation of the amygdala during maintain** condition when compared to look condition but did not reach significance during reappraise while the placebo group did not have a difference in the amygdala between maintain and look or between maintain and reappraise.
Comparing groups, **THC increased left amygdala activity during reappraise** with the placebo. No difference between placebo and THC in regards to left amygdala activation during maintain or look conditions. **THC decreased left amygdala to dlPFC and right amygdala to dlPFC functional coupling during reappraise condition**, and right amygdala to dlPFC coupling. THC compared to placebo **increased left amygdala to dlPFC functional coupling during look condition**. THC group-higher in left amygdala activation and less amygdala connectivity with dlPFC functional coupling during cognitive reappraisal when compared to the placebo group. Left amygdala activation was higher in the THC group during reappraise and maintain when this was compared to look condition. THC appears to affect the amygdala, but not the amygdala-dlPFC functional connectivity during cognitive reappraisal.

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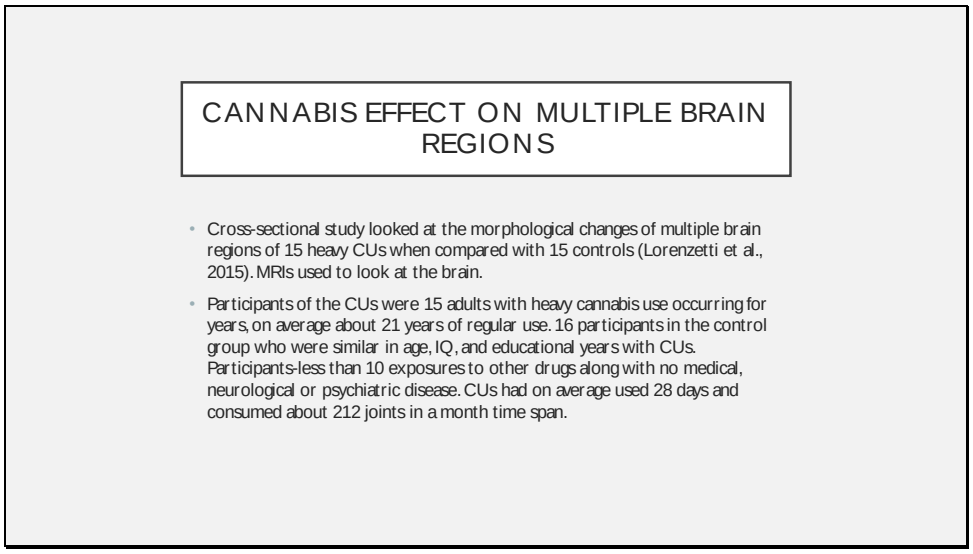
CANNABIS EFFECT ON MULTIPLE BRAIN REGIONS
• Cross-sectional study looked at the morphological changes of multiple brain regions of 15 heavy CUs when compared with 15 controls (Lorenzetti et al., 2015). MRIs used to look at the brain.
• Participants of the CUs were 15 adults with heavy cannabis use occurring for years, on average about 21 years of regular use. 16 participants in the control group who were similar in age, IQ, and educational years with CUs. Participants-less than 10 exposures to other drugs along with no medical, neurological or psychiatric disease. CUs had on average used 28 days and consumed about 212 joints in a month time span.

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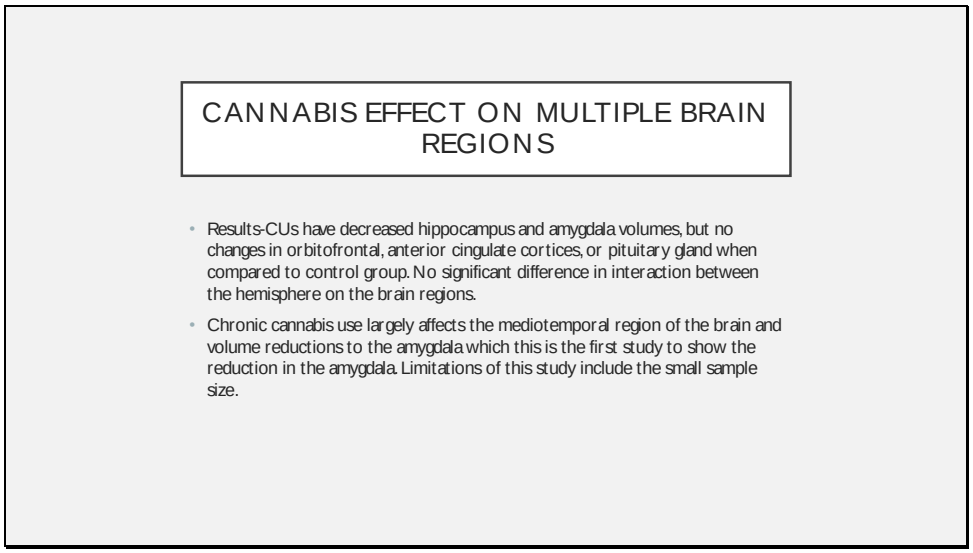
CANNABIS EFFECT ON MULTIPLE BRAIN REGIONS
Results-CUs have decreased hippocampus and amygdala volumes, but no changes in orbitofrontal, anterior cingulate cortices, or pituitary gland when compared to control group. No significant difference in interaction between the hemisphere on the brain regions.
Chronic cannabis use largely affects the mediotemporal region of the brain and volume reductions to the amygdala which this is the first study to show the reduction in the amygdala. Limitations of this study include the small sample size.

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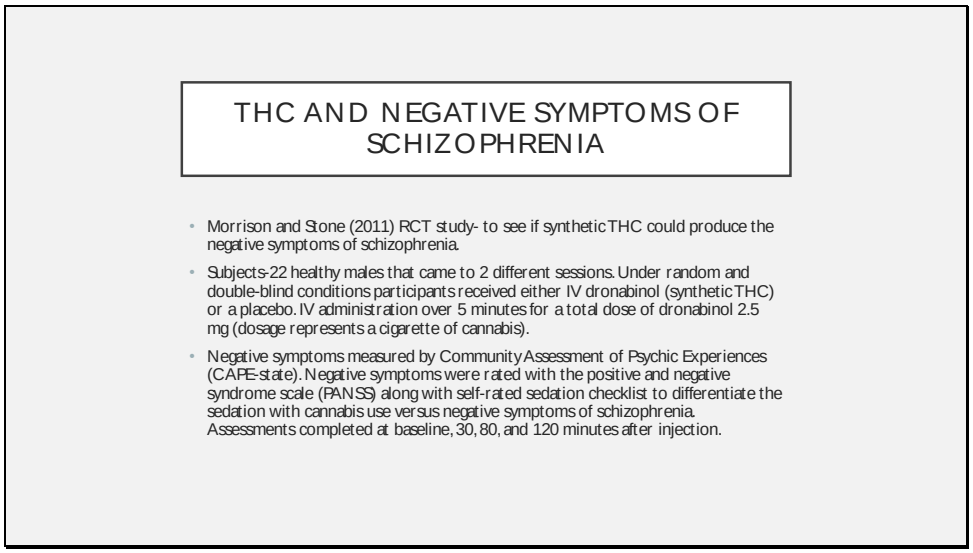
THC AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA
Morrison and Stone (2011) RCT study- to see if synthetic THC could produce the negative symptoms of schizophrenia.
Subjects-22 healthy males that came to 2 different sessions. Under random and double-blind conditions participants received either IV dronabinol (synthetic THC) or a placebo. IV administration over 5 minutes for a total dose of dronabinol 2.5 mg (dosage represents a cigarette of cannabis).
Negative symptoms measured by Community Assessment of Psychic Experiences (CAPE-state). Negative symptoms were rated with the positive and negative syndrome scale (PANSS) along with self-rated sedation checklist to differentiate the sedation with cannabis use versus negative symptoms of schizophrenia. Assessments completed at baseline, 30, 80, and 120 minutes after injection.

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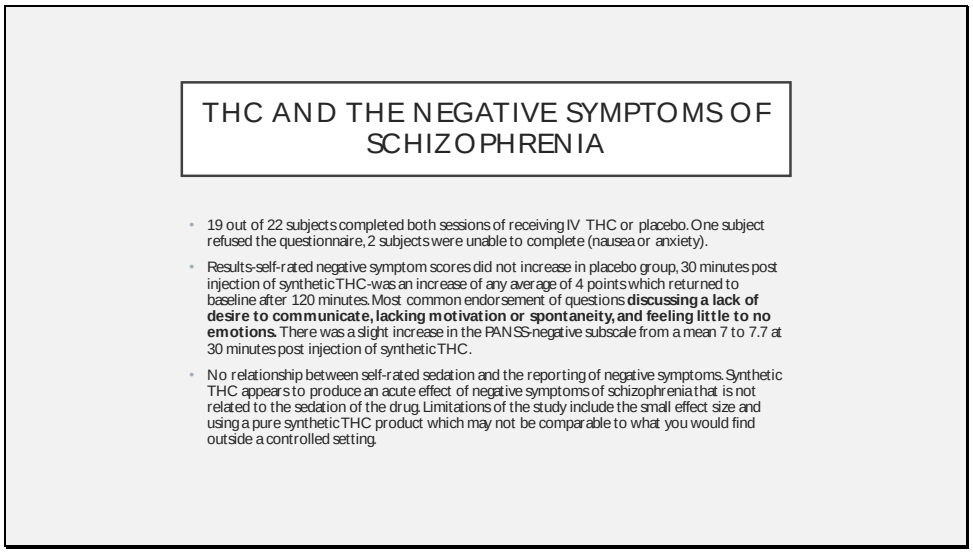
THC AND THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA
19 out of 22 subjects completed both sessions of receiving IV THC or placebo. One subject refused the questionnaire, 2 subjects were unable to complete (nausea or anxiety).
Results-self-rated negative symptom scores did not increase in placebo group, 30 minutes post injection of synthetic THC-was an increase of any average of 4 points which returned to baseline after 120 minutes. Most common endorsement of questions discussing a lack of desire to communicate, lacking motivation or spontaneity, and feeling little to no emotions. There was a slight increase in the PANSS-negative subscale from a mean 7 to 7.7 at 30 minutes post injection of synthetic THC.
No relationship between self-rated sedation and the reporting of negative symptoms. Synthetic THC appears to produce an acute effect of negative symptoms of schizophrenia that is not related to the sedation of the drug. Limitations of the study include the small effect size and using a pure synthetic THC product which may not be comparable to what you would find outside a controlled setting.

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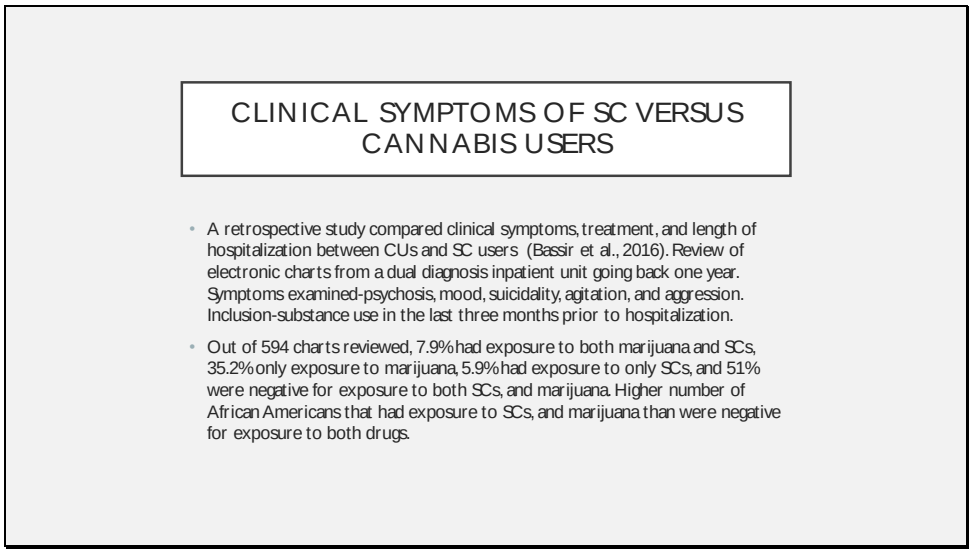
CLINICAL SYMPTOMS OF SC VERSUS CANNABIS USERS
A retrospective study compared clinical symptoms, treatment, and length of hospitalization between CUs and SC users (Bassir et al., 2016). Review of electronic charts from a dual diagnosis inpatient unit going back one year. Symptoms examined-psychosis, mood, suicidality, agitation, and aggression. Inclusion-substance use in the last three months prior to hospitalization.
Out of 594 charts reviewed, 7.9% had exposure to both marijuana and SCs, 35.2% only exposure to marijuana, 5.9% had exposure to only SCs, and 51% were negative for exposure to both SCs, and marijuana. Higher number of African Americans that had exposure to SCs, and marijuana than were negative for exposure to both drugs.

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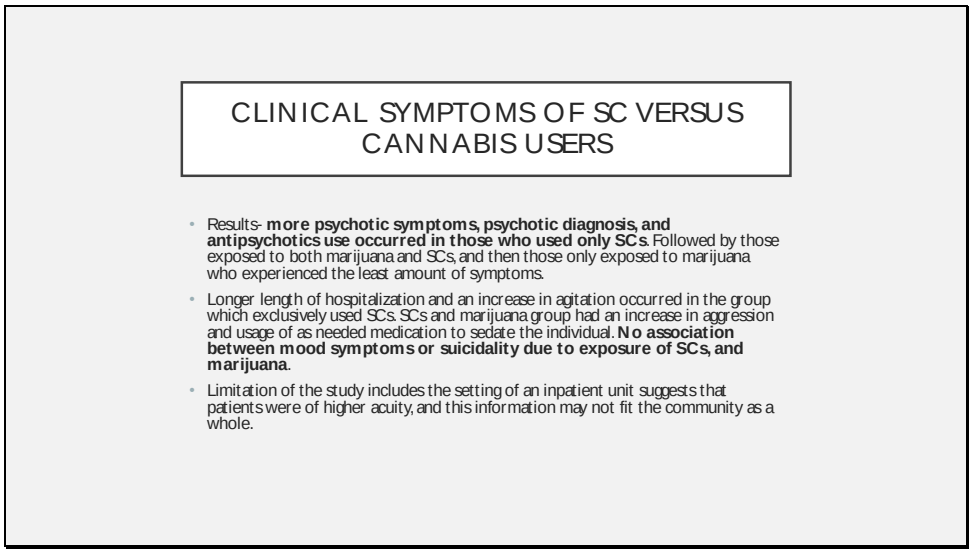
CLINICAL SYMPTOMS OF SC VERSUS CANNABIS USERS
Results- more psychotic symptoms, psychotic diagnosis, and antipsychotics use occurred in those who used only SCs. Followed by those exposed to both marijuana and SCs, and then those only exposed to marijuana who experienced the least amount of symptoms.
Longer length of hospitalization and an increase in agitation occurred in the group which exclusively used SCs. SCs and marijuana group had an increase in aggression and usage of as needed medication to sedate the individual. No association between mood symptoms or suicidality due to exposure of SCs, and marijuana.
Limitation of the study includes the setting of an inpatient unit suggests that patients were of higher acuity, and this information may not fit the community as a whole.

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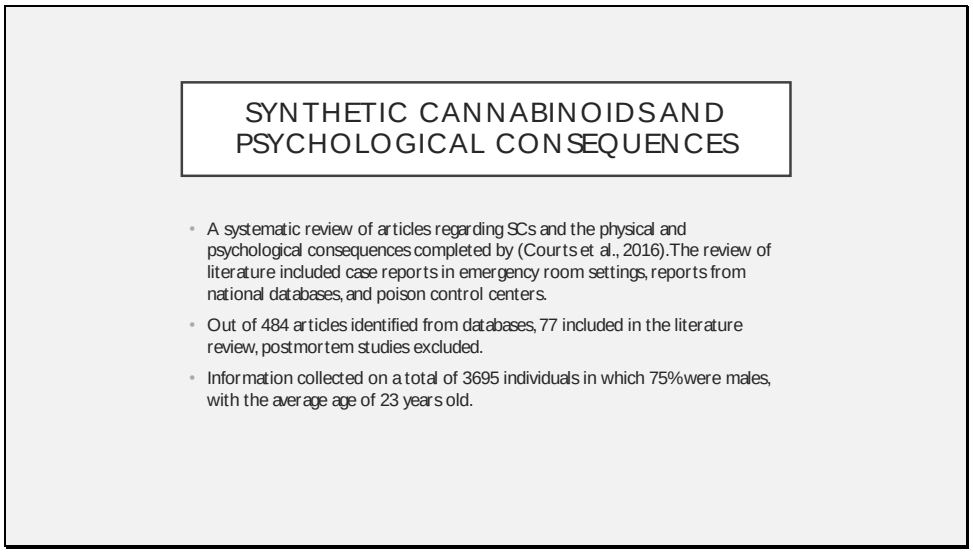
SYNTHETIC CANNABINOIDS AND PSYCHOLOGICAL CONSEQUENCES
• A systematic review of articles regarding SCs and the physical and psychological consequences completed by (Courts et al., 2016). The review of literature included case reports in emergency room settings, reports from national databases, and poison control centers.
• Out of 484 articles identified from databases, 77 included in the literature review, postmortem studies excluded.
• Information collected on a total of 3695 individuals in which 75% were males, with the average age of 23 years old.

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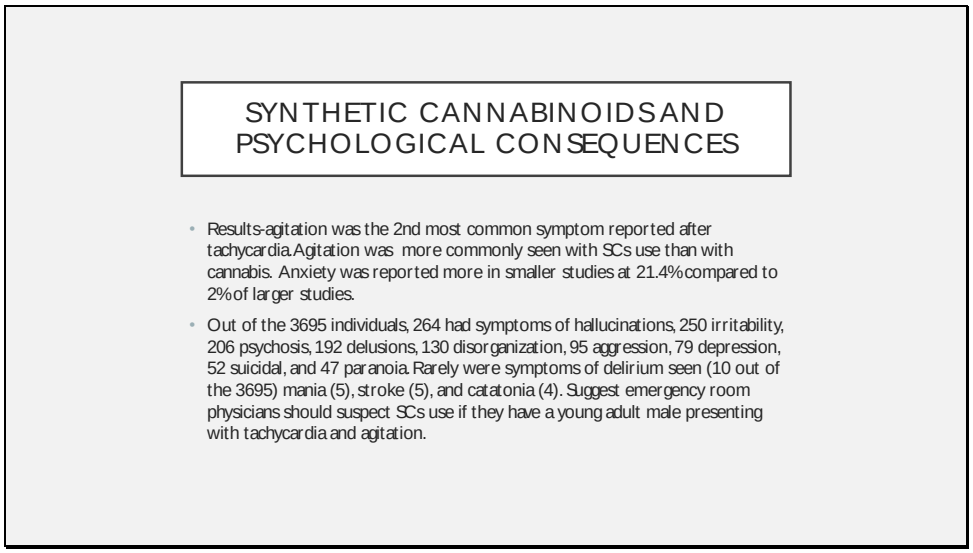
SYNTHETIC CANNABINOIDS AND PSYCHOLOGICAL CONSEQUENCES
Results-agitation was the 2nd most common symptom reported after tachycardia. Agitation was more commonly seen with SCs use than with cannabis. Anxiety was reported more in smaller studies at 21.4% compared to 2% of larger studies.
Out of the 3695 individuals, 264 had symptoms of hallucinations, 250 irritability, 206 psychosis, 192 delusions, 130 disorganization, 95 aggression, 79 depression, 52 suicidal, and 47 paranoia. Rarely were symptoms of delirium seen (10 out of the 3695) mania (5), stroke (5), and catatonia (4). Suggest emergency room physicians should suspect SCs use if they have a young adult male presenting with tachycardia and agitation.

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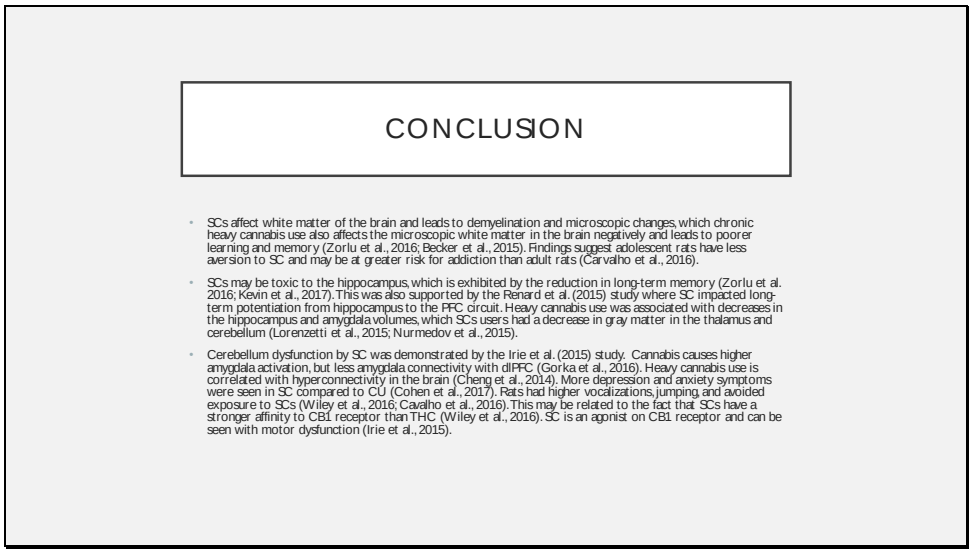
CONCLUSION
SCs affect white matter of the brain and leads to demyelination and microscopic changes, which chronic heavy cannabis use also affects the microscopic white matter in the brain negatively and leads to poorer learning and memory (Zorlu et al., 2016; Becker et al., 2015). Findings suggest adolescent rats have less aversion to SC and may be at greater risk for addiction than adult rats (Carvalho et al., 2016).
SCs may be toxic to the hippocampus, which is exhibited by the reduction in long-term memory (Zorlu et al. 2016; Kevin et al., 2017). This was also supported by the Renard et al. (2015) study where SC impacted long-term potentiation from hippocampus to the PFC circuit. Heavy cannabis use was associated with decreases in the hippocampus and amygdala volumes, which SCs users had a decrease in gray matter in the thalamus and cerebellum (Lorenzetti et al., 2015; Nurmedov et al., 2015).
Cerebellum dysfunction by SC was demonstrated by the Irie et al. (2015) study. Cannabis causes higher amygdala activation, but less amygdala connectivity with dlPFC (Gorka et al., 2016). Heavy cannabis use is correlated with hyperconnectivity in the brain (Cheng et al., 2014). More depression and anxiety symptoms were seen in SC compared to CU (Cohen et al., 2017). Rats had higher vocalizations, jumping, and avoided exposure to SCs (Wiley et al., 2016; Cavalho et al., 2016). This may be related to the fact that SCs have a stronger affinity to CB1 receptor than THC (Wiley et al., 2016). SC is an agonist on CB1 receptor and can be seen with motor dysfunction (Irie et al., 2015).

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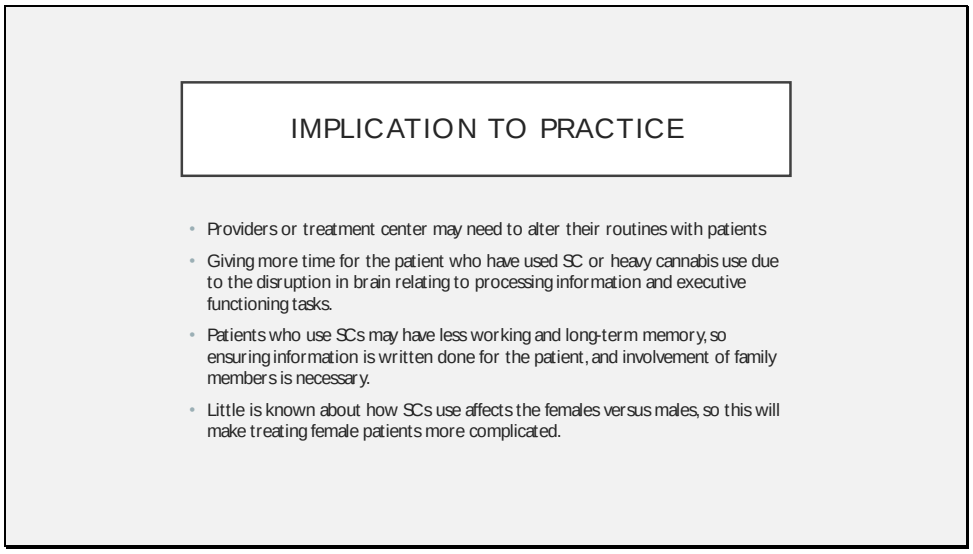
IMPLICATION TO PRACTICE
Providers or treatment center may need to alter their routines with patients
Giving more time for the patient who have used SC or heavy cannabis use due to the disruption in brain relating to processing information and executive functioning tasks.
Patients who use SCs may have less working and long-term memory, so ensuring information is written done for the patient, and involvement of family members is necessary.
Little is known about how SCs use affects the females versus males, so this will make treating female patients more complicated.

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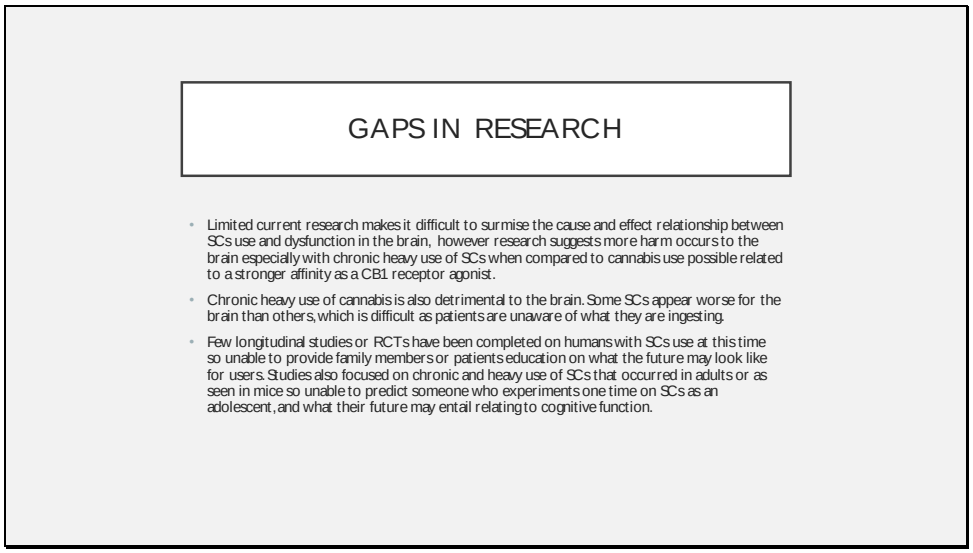
GAPS IN RESEARCH
Limited current research makes it difficult to surmise the cause and effect relationship between SCs use and dysfunction in the brain, however research suggests more harm occurs to the brain especially with chronic heavy use of SCs when compared to cannabis use possible related to a stronger affinity as a CB1 receptor agonist.
Chronic heavy use of cannabis is also detrimental to the brain. Some SCs appear worse for the brain than others, which is difficult as patients are unaware of what they are ingesting.
Few longitudinal studies or RCTs have been completed on humans with SCs use at this time so unable to provide family members or patients education on what the future may look like for users. Studies also focused on chronic and heavy use of SCs that occurred in adults or as seen in mice so unable to predict someone who experiments one time on SCs as an adolescent, and what their future may entail relating to cognitive function.

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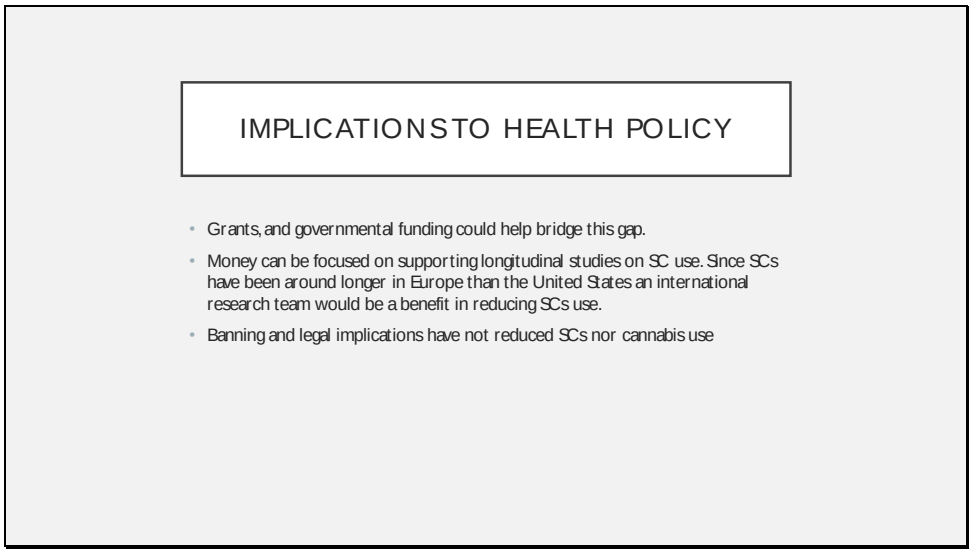
IMPLICATIONS TO HEALTH POLICY
Grants, and governmental funding could help bridge this gap.
Money can be focused on supporting longitudinal studies on SC use. Since SCs have been around longer in Europe than the United States an international research team would be a benefit in reducing SCs use.
Banning and legal implications have not reduced SCs nor cannabis use

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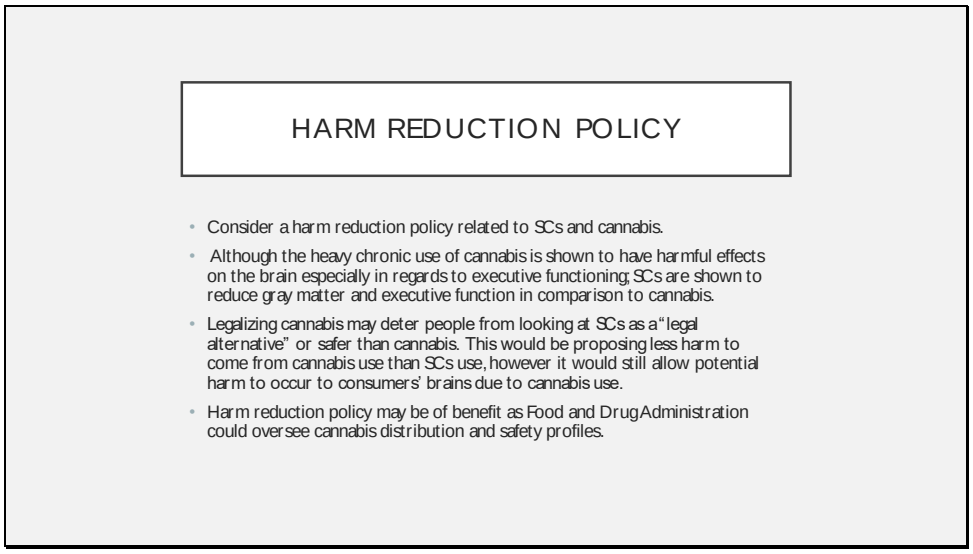
HARM REDUCTION POLICY
Consider a harm reduction policy related to SCs and cannabis.
Although the heavy chronic use of cannabis is shown to have harmful effects on the brain especially in regards to executive functioning, SCs are shown to reduce gray matter and executive function in comparison to cannabis.
Legalizing cannabis may deter people from looking at SCs as a "legal alternative" or safer than cannabis. This would be proposing less harm to come from cannabis use than SCs use, however it would still allow potential harm to occur to consumers' brains due to cannabis use.
Harm reduction policy may be of benefit as Food and Drug Administration could oversee cannabis distribution and safety profiles.