Cognitive Harms Associated with Regular Adolescent Marijuana Use

Timmen Cermak, MD

Executive Summary

Most people use marijuana because it affects their brains, producing a pleasing mental experience. Social and recreational use fall into this category. Because the human brain is still developing throughout adolescence, until approximately one's mid-20's, the impact of marijuana is greater on the adolescent brain; and, regular marijuana use presents a significantly greater hazard for adolescents than for adults.

Brain maturation during adolescence makes the developing brain more vulnerable to cannabinoid effects on both structure and function. Heavy or regular marijuana use, especially before age 18 is often associated with negative consequences not routinely found in occasional users. The effects are dose-dependent, with more subtle and transient impacts in less heavy users. Major youth risk factors appear to be early age at onset of use, regular or heavy use, and total dose over many years.

The primary effects of importance to adolescents involve reduced working memory, reduced higher order executive functions (abstraction, sequencing, reasoning, judgment, task flexibility, problem solving, planning and execution) and impacts on emotion. Alterations in the structure and activity of areas of the brain underlying these mental functions (the hippocampus, frontal lobes and amygdala) have been found in humans. Adolescents are more sensitive to these effects of marijuana and recover from them more slowly once abstinence occurs.

The impact of regular marijuana use on cognitive functions in adolescents can have a major negative effect on academic performance whether DSM-V diagnostic criteria for Cannabis Use Disorder (CUD) have been met or not. Neither a safe dose nor a definitely harmful dose of marijuana has been determined for adolescents.

Several important caveats must be considered when evaluating research on cannabis effects on neurological development and on higher brain functions. First, most functional and neuroimaging studies describe differences between marijuana users and matched control groups that do not use marijuana. Such studies have generally not tracked individual changes over time, or brain-imaged what is recovered after abstinence.

Second, prospective studies that follow individuals over many decades of neurodevelopment and maturation are rare. At this time they are best established in Australia and New Zealand. These prospective cohort studies to date have assessed cognitive functions more than imaging or brain structure.

Although findings are still many years away, the National Institute of Health (NIH) has begun a large 10 year prospective Adolescent Brain and Cognitive Development (ABCD) study to answer

many of the unanswered questions about neurodevelopment under the impact of marijuana and other drug use.

> The ABCD Study is a national longitudinal study that will assess the short- and long-term impact of substance use on brain development. The project will recruit 10,000 youths before they begin using alcohol, marijuana, tobacco and other drugs, and follow them over 10 years into early adulthood. ABCD Study investigators will use advanced brain imaging as well as psychological and behavioral research tools to evaluate brain structure and function. The study will track substance use, academic achievement, IQ, cognitive skills and mental health over time.
>
> *(http://addictionresearch.nih.gov/adolescent-brain-cognitive-development-study)*

Scientific research presents a coherent pattern across many levels. Regular, heavy adolescent marijuana users do not perform academically as well as nonusers. Cognitive functions important for academic performance, especially memory and higher order executive functions, are consistently shown to be reduced by heavy marijuana use. Physiological and structural changes are found in areas of the brain sub-serving memory and executive functions in heavy marijuana users. No single piece of evidence is as concerning as the overall pattern running through structure, function and performance in the real world consistently found in regular, heavy adolescent marijuana users.

Conclusions:

Sufficient research data currently exists to support the following conclusions:

- Cannabis dependence is most commonly a self-limiting problem; and, most youth show a "maturing out" effect in decreasing use in their 20's and 30's. The risks of addiction are exaggerated by "lifetime" metrics quoted in many discussions; and, regular and heavy use markers are better indicators for possible marijuana-related problems.
- The risks to educational progress are greater than the risks of addiction. The harms done to education are often greater than the harms done to the brain. The impact of regular marijuana use on cognitive functions in adolescents is likely to have a major negative effect on academic performance, leading students to perform beneath their natural capacity, whether DSM-V criteria for Cannabis Use Disorder have been met or not.
- Major youth risk factors from marijuana appear to be age at onset of use, regular or heavy use, and total dose over many years.
- Ongoing brain maturation in adolescence makes youth more vulnerable to cannabinoid effects on both structure and function. Youth marijuana use before age 18 appears to be the most vulnerable period.
- Heavy, regular marijuana use is often associated with negative consequences not found with occasional use. Effects are dose-dependent, with more subtle impacts in less heavy users.
- Neither a safe dose nor a definitely harmful dose of marijuana has been determined for adolescents.
- Marijuana use by adolescents carries sufficient risk to warrant marijuana tax revenue support for increased availability of cognitive/learning assessments, drug education, and counseling services in high schools.

Review of Scientific Data

Adolescent Neurodevelopment:

The details of brain development in adolescence are an area of active research [1] and there is already clear evidence that the endocannabinoid system plays a significant role in normal neural development [2] and connectivity patterns [1, 3, 4].

The January 2015 American Academy of Pediatrics (AAP) technical report, *The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update*, describes the significance of adolescent neurodevelopment in the following manner [5]:

> New research on adolescent brain development has found that brain maturation, particularly that of the prefrontal cortex, proceeds into the mid-20s. This maturation includes substantial changes in specialization and efficiency, which occur through myelination and synaptic pruning. Synaptic pruning or refining consists of a reduction in gray matter, primarily in the prefrontal and temporal cortex areas and in subcortical structures through the elimination of neural connections [6-8]. Increased myelination also occurs, which allows increased neural connectivity and efficiency and better integrity of white matter fiber tracts [9, 10]. The prefrontal lobes are the last areas of the adolescent brain to undergo these neuro-maturational changes, which, when complete, allow more efficient communication between the higher-order areas of the brain and the lower-order sensorimotor areas [11, 12].

The AAP Technical Report [5] summarized studies of regular marijuana use during adolescence as showing poorer performance "on tests of working memory, visual scanning, cognitive flexibility, and learning [13]." Furthermore, "the number of episodes of lifetime marijuana use reported by subjects correlated with overall lower cognitive functioning [14]." The strongest and most consistent evidence of memory deficits is marijuana's impact on episodic memory (the autobiographical memory of specific events, situations, and experiences), which remains adversely impacted for up to 28 days following monitored abstinence [15-17].

School Performance and Adult Income:

One consequence of daily or near-daily cannabis use is that adolescents will experience cognitive impairment on a continuous basis and this impairment is highly associated with lower educational attainment [18] Nora Volkow, Director of the National Institute of Drug Abuse (NIDA) summarizes cognition data by asserting that "Since marijuana use impairs critical cognitive functions, both during acute intoxication and for days after use, **many students could be functioning at a cognitive level that is below their natural capability for considerable periods of time** [emphasis added]." [19]

A 2014 study based on three large prospective cohorts in Australia and New Zealand (n=2,537-3,765) found "clear evidence of a dose-response association in which increasing frequency of adolescent cannabis use was associated with declining rates of high-school completion and degree attainment, and increasing risks of cannabis dependence, other illicit drug use, suicide attempt, depression, and welfare dependence." [20]

Silins investigated the association between the maximum frequency of cannabis use before age 17 years and developmental outcomes assessed up to age 30 years. Individuals who were daily users before age 17 years had odds of high-school completion that were 63% lower than those who had never used cannabis [20-22].

The consequences of heavy marijuana use are also found in economic disparities. Pope found that heavy marijuana users (5,000 times) were 50% more likely to earn less than their parents [18]. Fergusson found that individuals who used marijuana 400+ times between 14-21 earned 76% of the average income of non-users at 25 years old [23]. And, Brook found that only 36% of chronic marijuana users had achieved financial independence at age 29 compared to 58% of those who had never used marijuana [24].

An important caveat whenever discussing problematic youth behavior is to recognize that "at-risk" youth usually experience multiple stressors, including poverty, physical and sexual abuse, hunger, living in an environment of violence and racism, to list only a few. In addition, a child's ability to succeed in school depends, to a great extent, on factors affecting the child's life well before the child begins school. Marijuana use never exists in isolation from other behaviors and constitutes only one risk factor for impaired learning. It is extremely difficult to tease out cause and effect for complex problems. However, the association between heavy marijuana use and social and educational difficulties is real and strong. Marijuana policy reform has the opportunity to partially mitigate this early-onset risk factor by preferentially allocating tax revenues for school-based services and outreach support for school dropouts rather than merely to universal educational drug prevention campaigns (e.g., public service announcements, school presentations, and billboards).

Lynskey [21, 22] acknowledges the complexity of at-risk youth when he writes that the link between early cannabis use and educational attainment…

> arises because of the social context within which cannabis is used. In particular, early cannabis use appears to be associated with the adoption of an anti-conventional lifestyle characterized by affiliations with delinquent and substance using peers, and the precocious adoption of adult roles including early school leaving, leaving the parental home and early parenthood.
>
> Early cannabis use shares a common set of risk factors (such as, social disadvantage, family problems, familial conflict and parental drug and alcohol problems) with a wide range of adverse social outcomes, such as delinquency, early sexual activity, teenage pregnancy, depression and attempted suicide. This suggests that efforts to prevent cannabis use should be part of broadly targeted strategies rather than the sole focus of a specific intervention [21].

It is important to avoid politically divisive either/or frameworks in favor of a more nuanced mutually interacting both/and perspective. By analogy, the question of whether the chicken or the egg came first is an either/or framework that works against a deeper understanding that both the hen and the egg are necessary for the chicken species to exist. In other words, social context certainly increases the risk of heavy marijuana use, and heavy marijuana use can compromise the ability to cope effectively with disadvantageous social contexts.

IQ Studies*:*

The media has paid considerable attention to a recent long-term study of the impact of marijuana use on IQ but often without correctly interpreting the study's results.

Dunedin Birth Cohort: Decrements in executive functions measured as components of IQ were shown to be diminished at age 38 in Meier et al.'s often-quoted study of persistent heavy marijuana users in a Dunedin, New Zealand birth cohort of 1,037 children, *but only if their heavy use began in early adolescence* and continued into adulthood [25]. IQ scores are composed of multiple sub-tests and the overall score decrements were composed of reductions in scores in five areas:

- Executive functioning
- Working memory
- Processing speed
- Perceptual reasoning
- Verbal comprehension

Deficits were found to persist after cessation of use for over one year. General IQ scores were diminished an average of 6 points (and 8 points for the earliest marijuana users) at age 38, but both adolescent onset and almost two decades of persistent cannabis use may be needed to obtain the magnitude and pervasiveness of long-term neuropsychological deficits reported by Meier et al. "In fact, adult-onset cannabis users did not appear to experience IQ decline as a function of persistent cannabis use. " [14]

Avon Longitudinal Study: Not all studies find the same results. In 2014, a large U.K. study (The *Avon Longitudinal Study of Parents and Children*, based on data from 2,235 children born in the Bristol area in 1991 or 1992) tested IQ at age 8 and again at age 15 [26]. The researchers found that there was no relationship between cannabis use and lower IQ at age 15, but that heavier cannabis users (50 times or more by age 15) showed marginally impaired educational abilities as manifested by 3% lower school exam results at age 16.

Unfortunately, the *Avon Longitudinal Study* is not comparable to the Dunedin Study. Meier et al.'s finding was that adults with long-term dependence on cannabis starting during adolescence and continuing 4 or more times per week during the 20 years after adolescence had lost IQ points by age 38. Those who lost the most IQ points were those who had started their cannabis use youngest. There is no reason to expect that teens who have used cannabis only 50 times would already show a loss of IQ points by age 15. The ALSPAC study would need at least 20 more years of follow up, and data on cannabis dependence, before it could be compared to the Dunedin Study [personal communication with Madeline Meier, Feb 2015]. For the time being, the Dunedin Study cannot be considered conclusive, and the planned ABCD US study will not replicate it. It is, however, important evidence that fits consistently into the implications of research reviewed in this briefing.

Psychosis:

Although not strictly a cognitive impact from marijuana, psychotic symptoms characteristic of schizophrenia have been reported in marijuana users. The lifetime rate of schizophrenia in the general population is ~1% [27] and meta-analyses of prospective studies have found a roughly two-fold increase in the incidence of schizophrenia and/or schizophrenia-like psychotic symptoms associated with cannabis use [28-30] A dose response effect has been demonstrated [31-33], and use in adolescence has been associated with the greatest risk [34].

The relationship between schizophrenia and cannabis use can currently only be described as an association. Whatever cause and effect relationship may exist is likely bi-directional, although the proportion in either direction is not clear. Luisa Degenhardt a long-term investigator of this interaction, concluded in 2002 that,

> The evidence is more consistent with the hypotheses that cannabis use may precipitate psychosis among vulnerable individuals, increase the risk of relapse among those who have already developed the disorder, and may be more likely to lead to dependence in persons with schizophrenia." [35]

By 2006 Degenhardt's perspective had evolved further,

> A contributory causal relation is biologically plausible because psychotic disorders involve disturbances in the dopamine neurotransmitter systems with which the cannabinoid system interacts…. It is most plausible that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia. [36]

This area of research is likely to remain fluid for the foreseeable future. Although the onset of schizophrenia can be devastating for the individuals and families involved, a potential doubling of a very low prevalence rate is unlikely to arouse sufficient public concern to significantly influence the current debate regarding marijuana policy reform.

Marijuana's Impact on Brain Structure & Mental Function:

A variety of measureable differences in cognitive functions and brain structure have been observed in marijuana users, especially in youth and in long-term heavy (daily, or almost daily) users [37-40], and especially in those with the earliest onset of marijuana use (before age 18). Exogenous cannabinoids appear to interact with the adolescent developing brain in ways that no longer occur in adults.

Human and animal studies reliably find anatomic differences compared to control subjects in several important brain structures when exposed to frequent marijuana stimulation. Studies also reliably find deficits in important mental functions associated with the altered brain structures. Functional impacts involve affect, temperament and dependence in addition to more easily measureable impacts on memory and cognition.

Three brain areas (hippocampus, frontal cortex and amygdala) with high concentrations of cannabinoid CB1 receptors appear to underlie most of the cognitive and affective impacts of heavy marijuana use. Regular use of marijuana reduces (down-regulates) CB1 receptors significantly [41-44], decreasing the normal cannabinoid tone and diminishing learning, memory and executive functions.

The Hippocampus and Memory:

Acute Effects: Short-term memory problems are among the most frequently self-reported consequences of cannabis use and are commonly cited as the reason for attempting to quit or reduce cannabis use [17]. While memory deficits are often the subject of numerous jokes and anecdotes about marijuana users, Fisk and Montgomery [45] have documented the reality of deficits in real-world measurements of everyday memory, cognitive failures and prospective memory in young adults consuming a mean of 4.5 joints per week for a mean of 4 years. In another

real world context, adult cannabis users exhibit poorer working memory than controls at the start of the work week, but only if they had used in the previous 24 hours [46].

Ranganathan and D'Souza detailed the acute effects of THC on memory as a transient deficit in

> …immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner. In particular, cannabinoids increase intrusion errors. These effects are more robust with the inhaled and intravenous route and correspond to peak drug levels. This profile of effects suggests that cannabinoids impair all stages of memory including encoding, consolidation, and retrieval. [47]

Decrements in short-term, or working memory, defined as the ability to manipulate small amounts of information for a short period of time in order to facilitate a goal has been linked to lower academic performance[16]. Substantial impairment in working memory is found in treatment-seeking youth with primary cannabis dependence [48] Decreased learning, memory and the executive functions discussed below almost certainly make a major contribution to the reduced educational achievements documented in regular marijuana users.

Long-Term Effects: A review of the long-term effects on memory were reported by Solowij and Montgomery [17] as "not dissimilar to those associated with acute intoxication." Solowij's research shows that long-term cannabis users performed more poorly on tests of memory and attention than shorter-term users and controls, between which she found no difference. Decrements, but not severe problems, were found in learning, retention, and retrieval for chronic users with a mean of 24 years, but not 10 years. "The fact that the frequency of use was near daily among long- and shorter-term users suggests that the duration of cannabis use is a more salient contributor to the development of cognitive impairment than quantity or frequency of use."

Memory and Abstinence: Memory decrements after discontinuation of marijuana use do not appear to be permanent. Pope et al. [18] studied heavy cannabis users (5000 times) compared to individuals who had smoked no more than 50 times. Heavy users exhibited significant deficits on memory of word lists on Days 0, 1, and 7 of abstinence, but by Day 28 the differences between users and controls had narrowed and were mostly non-significant. He concluded that one consequence of ongoing daily or even near-daily cannabis use is that individuals will "effectively experience cognitive impairment on a continuous basis [and] this impairment might contribute to the lower educational attainment and household income of heavy cannabis users."

In a study of college students after a supervised overnight period of abstinence, heavy users (median of 29 out of the previous 30 days) showed decreased mental and reduced learning, as seen on the California Verbal Learning Test compared to light users (median of 1 time in the previous 30 days) [49].

Verbal Learning: Solowij [17, 50] compared performance indices from one of the most widely used measures of learning and memory—the *Rey Auditory Verbal Learning Test*—in adolescents aged 16–20 who were cannabis users, alcohol users and non-user controls matched for age, education and premorbid intellectual ability (assessed prospectively). Cannabis users performed significantly worse than alcohol users and non-users on all performance indices. They recalled significantly fewer words overall, demonstrating impaired learning, retention and retrieval The adolescent cannabis users learned fewer words across the five learning trials, recalled significantly fewer words in total over the five trials and after interference and a delay, forgot more words after interference and delay, and recognized fewer words from a less well-learned list than both alcohol users and controls.

The degree of impairment was associated with the duration, quantity, frequency and age of onset of cannabis use. Despite relatively brief exposure (less than 2.5 years on average), adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy users. Light users who consumed on average 1.5 joints four times/month, did not exhibit impaired performance relative to alcohol users and non-users of any substance. The heavier cannabis users "were not seeking treatment, were not dependent on cannabis, nor were they using on a daily basis or particularly heavily; average use was approximately 3 days per week, 17.5 joints per month, equating to approximately 1.25 joints on each occasion of use. Our results show that this level of use (but not use at once/week) was sufficient to produce memory decrements in adolescents" [50]. The fact that the young cannabis users within the current study, with their far lesser exposure to cannabis (an average 2.4 years), showed similar significantly impaired performance relative to their age-matched counterparts as adult users with 24 years use, suggests indeed greater adverse effects of cannabis use on the developing brain [50].

Young adolescents are not only more quickly impacted by marijuana than adults; the impact also lasts longer after stopping use [51]. Schwartz demonstrated that 14-16-year-olds fail to show significant improvements in short term memory after 6 weeks of abstinence [51, 52] in contrast to Pope's finding recovery of 61% of the decrement in 7 days and complete recovery from memory decrements by day 28 [53]

Hippocampal Brain Volumes: Most people are more interested in the functional impacts of cannabis than on how marijuana alters the anatomy and physiology of the hippocampus – the brain structure most directly involved in memory and learning. Changes in hippocampal volume are the most consistently reported findings in a review of structural brain alterations in cannabis users. Long-term heavy cannabis users (most days of the week for 20 years) [42] sustain significant dose-related reductions in hippocampal volume. A study by Cheetham [54] puts these results in perspective by showing that the volume of the hippocampus at age 12 does not predict initiation of cannabis use by age 16. Therefore, structural changes in the hippocampus appear to be a consequence of chronic cannabis exposure rather than a premorbid vulnerability. This conclusion is consistent with before-and-after animal studies that demonstrate hippocampal changes in direct response to cannabis administration.

Detailed animal studies, impossible in human research, consistently show a wide variety of changes in the hippocampus when exposed to cannabinoid stimulation, from shrinkage of neural cell nuclei and bodies [55, 56], to reductions in cell density [57], dendritic length [58], number of CB1 receptors by 30% [43], and number of synapses (reduced by 44% even 7 months after THC is discontinued) [55, 59]. Caution needs to be observed in applying the effects of cannabis on other animals to humans. Nonetheless, rodents given THC five times a week for 8 months (approximately 30% of the rat life-span) sustain the same degree of reduction in hippocampal volume as humans who have heavily used marijuana for 20 years [58],

The amount known about the role of the hippocampus in memory and the details of the profound extent of marijuana's impact on hippocampal physiology occupy too many volumes to be ignored. For example, neural models form in the hippocampus during classical conditioning before evidence of behavioral learning appears [60], with the speed of learning directly related to the percentage of theta rhythm (3-7 Hz) present [61]. Cannabinoids alter theta rhythm, which has been shown to impair memory [62]. Cannabinoids also acutely reduce glutamate release in the hippocampus, thereby blocking long-term potentiation, considered to be the mechanism for strengthening neuronal connections to form the substrate for learning and memory [63]. After 7 days of

cannabinoid administration, the complete blockade of long-term potentiation persists for 3 days and full reversal does not occur for up to 14 days, thereby reducing synaptic plasticity. Administration of cannabinoid antagonists significantly increases long-term potentiation. Consistent with this impact on long-term potentiation, social recognition in rodents, a measure of short-term memory, has been shown to decrease with cannabinoid stimulation and increase with cannabinoid antagonism [64].

Finding one's way around an environment (spatial memory) and remembering the events that occur within it (episodic memory) are crucial cognitive abilities that most neuroscientists agree are linked to the hippocampus [65]. Differences in hippocampal structure, volume [42, 66, 67] and physiology all contribute to decrements in working memory for heavy marijuana users' memory [17, 48] compared to non-users, even during early abstinence.

The Frontal Lobes and Executive Functions:

The frontal lobes, which are the last portion of the brain to mature fully at approximately 24 years old, provide the substrate for our most advanced intellectual abilities, the executive functions, which include abstraction, sequencing, reasoning, judgment, task flexibility, problem solving, planning and execution. Daily use of marijuana reduces the natural cannabinoid receptors by 20% in the frontal lobes [7, 41]. Hirvonen demonstrated that the reversible down-regulation of brain cannabinoid CB_1 receptors in human subjects who chronically smoke cannabis correlates with years of cannabis. After ~4 weeks of continuously monitored abstinence from cannabis on a secure research unit, CB_1 receptor density returned to normal levels [41].

Adolescents using marijuana chronically score worse than controls on a battery of test assessing executive functions, with early onset users scoring worse than late-onset users, illustrated by the graph at right by Fontes of scores on a battery of executive function tests of early onset users, late onset and nonusers. [68]

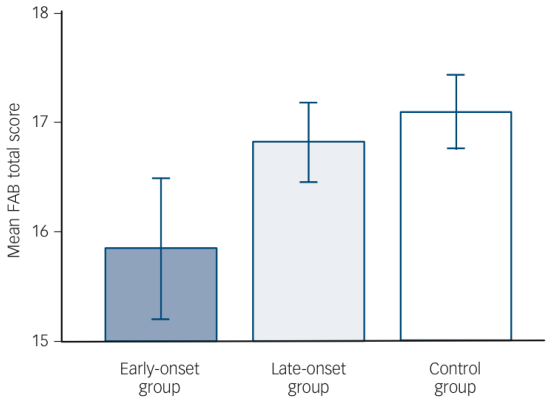


Fig. 4 Frontal Assessment Battery (FAB) total score in early-onset, late-onset and control groups.

Three studies illustrate decrements in executive function associated with regular marijuana use.

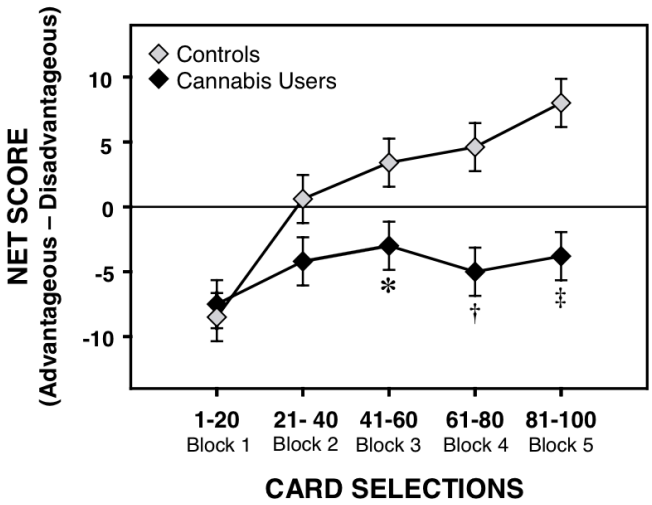
Wisconsin Card Sort: The Wisconsin Card Sort Test assesses abstract reasoning, strategy formation and the ability to shift cognitive strategies in response to changing contingencies. Test subjects are asked to discover the correct way to sort cards with symbols of different characteristics. After subjects demonstrate understanding of the correct way to sort the cards, the rules are arbitrarily changed, which requires abandoning the original strategy to discover the new correct one. The earlier someone has started using marijuana, even after 4 days of abstinence, the more difficulty they have discovering the correct strategy and the more frequently they perseverate with the old, incorrect strategy. [68]

Stroop Test: The Stroop Test is designed to demonstrate interference in the reaction time of a task. When the name of a color (e.g., "blue", "green", or "red") is printed in a color not denoted by the name (e.g., the word "red" printed in blue ink instead of red ink), naming the color of the word

takes longer and is more prone to errors than when the color of the ink matches the name of the color. After 4 days of abstinence, the earliest onset marijuana users demonstrated more intrusion errors, an indication of reduced ability to inhibit irrelevant stimuli. [68, 69]

Iowa Gambling Task: The Iowa Gambling Task was designed to simulate real-life decision-making. Subjects are presented with 4 virtual decks of cards on a computer screen. Each card chosen wins some game money except for an occasional card that causes them to lose some money. The goal is to win as much money as possible. The decks differ in the number of losses each contains. Thus, some decks are "bad decks" that lead to losses over the long run and other decks are "good decks" that lead to gain.

Most control subjects stick to the good decks after sampling about 40 or 50 cards from each deck. Subjects known to suffer frontal lobe damage, however, continue to perseverate with the bad decks, a sign of reduced judgment. Chronic cannabis consumption, produces similar decrements in performance on the Iowa Gambling Task. "Subjects focusing on the highest win are less aware of losses or simply underestimate losses" and this difference was related more to the amount of cannabis consumed than to measured personality traits [70].



MRI brain imaging shows greater frontal lobe activity in response to losses in controls compared to marijuana users, suggesting that marijuana users are less sensitive to negative feedback during strategy development [71]. Interestingly, subjects in both groups initially chose cards primarily from the decks with higher immediate rewards, but subjects in the control group change their deck preference as they experience the large monetary losses associated with the disadvantageous decks [72].

On the basis of demonstrated reductions in frontal lobe executive functioning, Fontes [68] concluded that "exposure to cannabis in early adolescence may lead to lower mental flexibility". The blunted response to negative stimuli leading to less advantageous decision making strategies is consistent with data presented in the amygdala section below, specifically regarding the tendency to forget aversive experiences and a blunted response to negative emotional stimuli found in chronic marijuana users.

Medina [13] focused her attention on adolescents to explore how long executive functions remain diminished after abstinence is established. She found decreased psychomotor speed, complex attention, story memory, planning and sequencing ability in adolescent marijuana users compared with controls after >23 days of monitored abstinence, even after controlling for lifetime alcohol use. Furthermore, dose-dependent relationships were observed between lifetime marijuana use and poorer cognitive performance. She states that her

> neuropsychological findings differ from those of Pope and colleagues [53], who found that deficits in attention, short-term memory, and psychomotor speed were no longer measurable among adult marijuana users following 28 days of abstinence. One possible explanation for this discrepancy is that marijuana use during adolescence may negatively

> impact neuromaturation and cognitive development, resulting in more severe cognitive consequences compared with use during adulthood. For example, introduction of cannabis during adolescence may interrupt pruning of gray matter or disruption of white matter myelination, especially in the prefrontal cortex [73-75], which continues to develop into early adulthood [6, 11, 76, 77]. The current findings are consistent with animal studies that found more severe cannabis-induced learning impairments among adolescents compared with adults [78-81] and findings that early onset use is associated with increased morphometric, electrophysiological, and cognitive abnormalities among adult marijuana users [82-85] .

Gruber demonstrated that adolescents who started smoking marijuana regularly prior to the age of 16 performed significantly more poorly on measures of executive function than controls. The early initiators in her study also smoked twice as often and nearly three times as much marijuana per week than their later smoking counterparts [86]. These findings further demonstrate that earlier marijuana onset is related to poorer cognitive function.

Amygdala and Attention*:*

Many of the effects of marijuana come from its stimulation of the highly concentrated cannabinoid receptors in the amygdala, a portion of the brain containing neural circuitry important in emotions, appetites, and attention to novel stimuli. Acute stimulation of the amygdala by marijuana contributes to increased appetite, lessened anxiety (in most people and at lower doses) and an interesting dis-habituation to sensory stimuli, leading people to notice sensations they had long ago stopped paying attention to.

Emotion: Chronic marijuana uses have been found to have reduced amygdala size of 7% compared to controls [42] and the number of cannabinoid receptors can be reduced as much as 25% [42, 43, 87]. Gruber demonstrated that these reductions lead regular users to process some emotional stimuli differently [88], When shown subliminal images of an angry face, the amygdala in non-users becomes active; but, no response to the emotional stimuli occurred in the amygdala of regular marijuana users. This reduced sensitivity to emotional cues is consistent with the typical complaint of partners that regular marijuana users are “stoned” or “less present.” The reduction of cannabinoid receptors in the amygdala may also contribute to boredom.

Anxiety, a documented symptom of withdrawal from marijuana [89], is characteristic of a cannabinoid deficiency state. After regular marijuana use reduces the number of cannabinoid receptors in the amygdala below normal, anxiety lasts up to 4-6 weeks while the full complement of receptors is rebuilt. During this early period of abstinence there is a risk of restarting marijuana use to keep the remaining receptors stimulated enough to reduce the anxiety [90-92]. The impacts outlined above happen to nearly all daily, or near-daily, marijuana users.

Temperament: Genetic variations in the density of CB1 receptors in the amygdala influence temperament [93]. The temperamental characteristic of novelty seeking is inversely correlated with global CB1R availability, most pronounced in the amygdala. The degree of receptor down-regulation observed in humans with regular marijuana use is well within the parameters underlying significant genetically-associated temperamental differences. High density of CB1 receptors in the amygdala leads to an inhibited temperament that tends to avoid novelty, while a low density of CB1 receptors leads to a more uninhibited novelty seeking temperament. Regular use of marijuana leads to a reduction of CB1 receptors in the amygdala of 25%, similar to the range of genetic variations.

The Importance of Forgetting: Increasing cannabinoid stimulation in the amygdala has also been shown to enhance the forgetting of aversive experience [94]. Extinction of aversive memories is an active process. Marsicano [94] used classical conditioning to teach rats that a shock soon follows a tone leading the rats to freeze when they heard the tone. Once he no longer administered the shock he measured how long it took for the animal to extinguish their fear response to the tone. Rats bred with a deficiency of CB1 receptors were unable to extinguish their fear response, demonstrating that a functioning cannabinoid system is necessary to forget aversive experiences. While the tone caused release of endocannabinoid in the amygdala, CB1 receptors are necessary for the neural circuitry to produce forgetting.

The chronic increased stimulation of CB1 receptors produced by regular marijuana use could reasonably be expected to complicate adolescent marijuana users' ability to develop effective coping strategies. While under the influence of marijuana, aversive memories are more easily forgotten and their lessons left unlearned.

Brain Imaging:

A vast literature documents decrements in frontal lobe based executive functions, but there is far less detailed evidence regarding structural or physiological changes associated with marijuana use.

Human research is limited to gross imaging of brain structure and activation. Chronic exposure to marijuana reduces gray mater in the frontal cortex, though the permanence of this change has not been determined [37, 67, 95]. Studies of frontal lobe volume in adolescents are few and yield differences based on gender still requiring exploration.

Inhibition of impulsivity is an important executive function. A quantitative estimate of white matter (the neural tracts connecting the left and right frontal lobes) integrity at the microstructural level (diffusion tensor imaging) reveals significant reductions in directional coherence in marijuana smokers relative to non-users. Age of onset of marijuana use was correlated with the degree of abnormalities. These data represent the first report of significant alterations in frontal white matter tracts and were associated with measures of impulsivity in chronic marijuana smokers [96].

Functional brain imaging (PET scans and fMRI) of the frontal lobes have shown altered activity in response to tasks that require executive functions. Marijuana users show less activity in the left frontal cortex compared to controls when administered the Stroop test, which requires inhibition of verbal stimuli and attention to the physical color, a task that marijuana users do more poorly [97].

In a go/no-go task requiring readiness to respond combined with the ability to inhibit a response to a defined stimulus, Tapert [98] demonstrated that adolescents who regularly use marijuana performed as well as controls. However, even after 28 days of abstinence, marijuana users showed increased areas of brain activity in the frontal lobes during the task relative to non-users. The study concluded that a pattern of increased activation with comparable performance is consistent with functional compensation, which supposes that loci of functional activity are spread to more and larger regions. Therefore, adolescent marijuana users appear to recruit more neural tissue in executive control areas to adequately perform the task.

ENDNOTES

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Endnotes (Annotated)

Ammerman, S., et al. (2015 (Mar)). "The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update." Pediatrics **135**(3).

This technical report updates the 2004 American Academy of Pediatrics abstract technical report on the legalization of marijuana. Current epidemiology of marijuana use is presented, as are definitions and biology of marijuana compounds, side effects of marijuana use, and effects of use on adolescent brain development. Issues concerning medical marijuana specifically are also addressed. Concerning legalization of marijuana, 4 different approaches in the United States are discussed: legalization of marijuana solely for medical purposes, decriminalization of recreational use of marijuana, legalization of recreational use of marijuana, and criminal prosecution of recreational (and medical) use of marijuana. These approaches are compared, and the latest available data are presented to aid in forming public policy. The effects on youth of criminal penalties for marijuana use and possession are also addressed, as are the effects or potential effects of the other 3 policy approaches on adolescent marijuana use. Recommendations are included in the accompanying policy statement.

Arseneault, L., et al. (2002). "Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study." BMJ **325**(7374): 1212-1213.

Arseneault, L., et al. (2004). "Causal association between cannabis and psychosis: examination of the evidence." Br J Psychiatry **184**: 110-117.

Berry, S. D. and M. A. Seager (2001). "Hippocampal theta oscillations and classical conditioning." Neurobiol Learn Mem **76**(3): 298-313.

Burgess, N., et al. (2002). "The human hippocampus and spatial and episodic memory." Neuron **35**(4): 625-641.

Cheetham, A., et al. (2012). "Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study." Biol Psychiatry **71**(8): 684-692.

BACKGROUND: There is growing evidence that long-term, heavy cannabis use is associated with alterations in regional brain volumes. Although these changes are frequently attributed to the neurotoxic effects of cannabis, it is possible that some abnormalities might predate use and represent markers of vulnerability. To date, no studies have examined whether structural brain abnormalities are present before the onset of cannabis use. This study aims to determine whether adolescents who have initiated cannabis use early (i.e., before age 17 years) show premorbid structural abnormalities in the amygdala, hippocampus, orbitofrontal cortex, and anterior cingulate cortex. METHODS: Participants (n = 121) were recruited from primary schools in Melbourne, Australia, as part of a larger study examining adolescent emotional development. Participants underwent structural magnetic resonance imaging at age 12 years and were assessed for cannabis use 4 years later, at age 16 years. At the follow-up assessment, 28 participants had commenced using cannabis (16 female subjects [57%]), and 93 had not (43 female subjects [46%]). RESULTS: Smaller orbitofrontal cortex volumes at age 12 years predicted initiation of cannabis use by age 16 years. The volumes of other regions (amygdala, hippocampus, and anterior cingulate cortex) did not predict later cannabis use. CONCLUSIONS: These findings suggest that structural abnormalities in the orbitofrontal cortex might contribute to risk for cannabis exposure. Although the results have important implications for understanding neurobiological predictors of cannabis use, further research is needed to understand their relationship with heavier patterns of use in adulthood as well as later abuse of other substances.

Cousijn, J., et al. (2012). "Approach-bias predicts development of cannabis problem severity in heavy cannabis users: results from a prospective FMRI study." PLoS One **7**(9): e42394.

Cousijn, J., et al. (2012). "Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls." Neuroimage **59**(4): 3845-3851.

Degenhardt, L. and W. Hall (2002). "Cannabis and psychosis." Curr Psychiatry Rep **4**(3): 191-196.

Degenhardt, L. and W. Hall (2006). "Is cannabis use a contributory cause of psychosis?" Can J Psychiatry **51**(9): 556-565.

ECNP (Claire Mokrysz) (2014). "No Relationship Between Moderate Adolescent Cannabis Use, Exam Results or IQ, Large Study Shows." Science Daily. from http://www.sciencedaily.com/releases/2014/10/141020212410.htm.

A large UK study has found that occasional adolescent cannabis use does not lead to poorer educational and intellectual performance, but that heavy cannabis use is associated with slightly poorer exam results at age 16. The results come from the Avon Longitudinal Study of Parents and Children (ALSPAC, also known as "Children of the 90's") a long-term study that follows the health of children born in the Bristol area (UK) in 1991 and 1992. The work is being presented at the annual congress of the European College of Neuropsychopharmacology (ECNP) in Berlin. The researchers analysed data from 2,612 children who had their IQ tested at the age of 8, and again at the age of 15. These children's examination results were then factored in via the National Pupil Database. At the age of 15, each person in the study completed a survey on cannabis use. The researchers then used

regression analysis to look at how cannabis use affected both intellectual and educational performance. A number of children could not be included in the final analyses (for example because they had experienced a head injury), leaving a total sample size of 2,235.

The researchers found two main points:

1. Cannabis use appeared to be associated with decreased intellectual performance. Cannabis use was, however, highly correlated with other risky behaviours such as alcohol, cigarette and other drug use. When the researchers took these other behaviours into account, they found there was no relationship between cannabis use and lower IQ at age 15.

2. Heavier cannabis users (at least 50 times by age 15) however, did show marginally impaired educational abilities. These children tended to have poorer exam results (3% lower) on compulsory school exams taken at age 16, even after adjusting for childhood educational performance, as well as alcohol, cigarette and other drug use.

Ferdinand, R. F., et al. (2005). "Cannabis use predicts future psychotic symptoms, and vice versa." Addiction **100**(5): 612-618.

Filbey, F. M., et al. (2014). "Long-term effects of marijuana use on the brain." Proc Natl Acad Sci U S A **111**(47): 16913-16918.

Fisk, J. E. and C. Montgomery (2008). "Real-world memory and executive processes in cannabis users and non-users." J Psychopharmacol **22**(7): 727-736.

The relationships between executive processes, associative learning and different aspects of real world memory functioning were explored in a sample of cannabis users and nonusers. Measures of executive component processes, associative learning, everyday memory, prospective memory, and cognitive failures were administered. Relative to nonusers, cannabis users were found to be impaired in several aspects of real world memory functioning. No other group differences were apparent. The absence of cannabis related deficits in those executive component processes and aspects of learning that are believed to support real world memory processes is surprising given that cannabis related deficits were obtained in real world memory. The present results are discussed within the context of neuroimaging evidence which suggests that cannabis users may exhibit different patterns of neural activation when performing executive tasks while not always exhibiting deficits on these tasks.

Fontes, M., et al. (2011). "Cannabis use before age 15 and subsequent executive functioning." The British Journal of Psychiatry **198**: 442–447.

Galve-Roper I., et al. (2008). "Mechanisms of control of neuron survival by the endocannabinoid system." Curr Pharm Des **14**(23): 2279-2288.

Giedd, J. N. (2004). "Structural magnetic resonance imaging of the adolescent brain." Ann N Y Acad Sci **1021**: 77-85.

Magnetic resonance imaging (MRI) provides accurate anatomical brain images without the use of ionizing radiation, allowing longitudinal studies of brain morphometry during adolescent development. Results from an ongoing brain imaging project being conducted at the Child Psychiatry Branch of the National Institute of Mental Health indicate dynamic changes in brain anatomy throughout adolescence. White matter increases in a roughly linear pattern, with minor differences in slope in the four major lobes (frontal, parietal, temporal, occipital). Cortical gray matter follows an inverted U-shape developmental course with greater regional variation than white matter. For instance, frontal gray matter volume peaks at about age 11.0 years in girls and 12.1 years in boys, whereas temporal gray matter volume peaks at about age at 16.7 years in girls and 16.2 years in boys. The dorsal lateral prefrontal cortex, important for controlling impulses, is among the latest brain regions to mature without reaching adult dimensions until the early 20s. The details of the relationships between anatomical changes and behavioral changes, and the forces that influence brain development, have not been well established and remain a prominent goal of ongoing investigations.

Gogtay, N., et al. (2004). "Dynamic mapping of human cortical development during childhood through early adulthood." Proc Natl Acad Sci U S A **101**(21): 8174-8179.

We report the dynamic anatomical sequence of human cortical gray matter development between the age of 4-21 years using quantitative four-dimensional maps and time-lapse sequences. Thirteen healthy children for whom anatomic brain MRI scans were obtained every 2 years, for 8-10 years, were studied. By using models of the cortical surface and sulcal landmarks and a statistical model for gray matter density, human cortical development could be visualized across the age range in a spatiotemporally detailed time-lapse sequence. The resulting time-lapse "movies" reveal that (i) higher-order association cortices mature only after lower-order somatosensory and visual cortices, the functions of which they integrate, are developed, and (ii) phylogenetically older brain areas mature earlier than newer ones. Direct comparison with normal cortical development may help understanding of some neurodevelopmental disorders such as childhood-onset schizophrenia or autism.

Gonzalez, R. (2007). "Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance." Neuropsychol Rev **17**(3): 347-361.

Gonzalez, R. and J. M. Swanson (2012). "Long-term effects of adolescent-onset and persistent use of cannabis." Proc Natl Acad Sci U S A **109**(40): 15970-15971.

Grant, I., et al. (2003). "Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study." J Int Neuropsychol Soc **9**(5): 679-689.

The possible medicinal use of cannabinoids for chronic diseases emphasizes the need to understand the long-term effects of these compounds on the central nervous system. We provide a quantitative synthesis of empirical research pertaining to the non-acute (residual) effects of cannabis on the neurocognitive performance of adult human subjects. Out of 1,014 studies retrieved using a thorough search strategy, only 11 studies met essential a priori inclusion criteria, providing data for a total of 623 cannabis users and 409 non- or minimal users. Neuropsychological results were grouped into 8 ability domains, and effect sizes were calculated by domain for each study individually, and combined for the full set of studies. Using slightly liberalized criteria, an additional four studies were included in a second analysis, bringing the total number of subjects to 1,188 (i.e., 704 cannabis users and 484 non-users). With the exception of both the learning and forgetting domains, effect size confidence intervals for the remaining 6 domains included zero, suggesting a lack of effect. Few studies on the non-acute neurocognitive effects of cannabis meet current research standards; nevertheless, our results indicate that there might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected. However, from a neurocognitive standpoint, the small magnitude of these effect sizes suggests that if cannabis compounds are found to have therapeutic value, they may have an acceptable margin of safety under the more limited conditions of exposure that would likely obtain in a medical setting.

Green, B., et al. (2005). "Cannabis use and misuse prevalence among people with psychosis." Br J Psychiatry **187**: 306-313.

Gruber, S. A., et al. (2009). "Altered affective response in marijuana smokers: an FMRI study." Drug Alcohol Depend **105**(1-2): 139-153.

More than 94 million Americans have tried marijuana, and it remains the most widely used illicit drug in the nation. Investigations of the cognitive effects of marijuana report alterations in brain function during tasks requiring executive control, including inhibition and decision-making. Endogenous cannabinoids regulate a variety of emotional responses, including anxiety, mood control, and aggression; nevertheless, little is known about smokers' responses to affective stimuli. The anterior cingulate and amygdala play key roles in the inhibition of impulsive behavior and affective regulation, and studies using PET and fMRI have demonstrated changes within these regions in marijuana smokers. Given alterations in mood and perception often observed in smokers, we hypothesized altered fMRI patterns of response in 15 chronic heavy marijuana smokers relative to 15 non-marijuana smoking control subjects during the viewing of masked happy and fearful faces. Despite no between-group differences on clinical or demographic measures, smokers demonstrated a relative decrease in both anterior cingulate and amygdalar activity during masked affective stimuli compared to controls, who showed relative increases in activation within these regions during the viewing of masked faces. Findings indicate that chronic heavy marijuana smokers demonstrate altered activation of frontal and limbic systems while viewing masked faces, consistent with autoradiographic studies reporting high CB-1 receptor density in these regions. These data suggest differences in affective processing in chronic smokers, even when stimuli are presented below the level of conscious processing, and underscore the likelihood that marijuana smokers process emotional information differently from those who do not smoke, which may result in negative consequences.

Harkany, T., et al. (2008). "Endocannabinoid functions controlling neuronal specification during brain development." Mol Cell Endocrinol **286**(1-2 Suppl 1): S84-90.

Heath, R. G., et al. (1980). "Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys." Biol Psychiatry **15**(5): 657-690.

Henquet, C., et al. (2005). "Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people." BMJ **330**(7481): 11.

Hirvonen, J., et al. (2012). "Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers." Mol Psychiatry **17**(6): 642-649.

Hoffman, A. F., et al. (2007). "Opposing actions of chronic Delta9-tetrahydrocannabinol and cannabinoid antagonists on hippocampal long-term potentiation." Learn Mem **14**(1-2): 63-74.

Huppi, P. S. and J. Dubois (2006). "Diffusion tensor imaging of brain development." Semin Fetal Neonatal Med **11**(6): 489-497.

Jacobus, J., et al. (2009). "Functional consequences of marijuana use in adolescents." Pharmacol Biochem Behav **92**(4): 559-565.

Lachenmeier, D. W. and J. Rehm (2015). "Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach." Sci Rep **5**: 8126.

A comparative risk assessment of drugs including alcohol and tobacco using the margin of exposure (MOE) approach was conducted. The MOE is defined as ratio between toxicological threshold (benchmark dose) and estimated human intake. Median lethal dose values from animal experiments were used to derive the benchmark dose. The human intake was calculated for individual scenarios and population-based scenarios. The MOE was calculated using probabilistic Monte Carlo simulations. The benchmark dose values ranged from 2 mg/kg bodyweight for heroin to 531 mg/kg bodyweight for alcohol (ethanol). For individual exposure the four substances alcohol, nicotine, cocaine and heroin fall into the "high risk" category with MOE < 10, the rest of the compounds except THC fall into the "risk" category with MOE < 100. On a population scale, only alcohol would fall into the "high risk" category, and cigarette smoking would fall into the "risk" category, while all other agents (opiates, cocaine, amphetamine-type

stimulants, ecstasy, and benzodiazepines) had MOEs > 100, and cannabis had a MOE > 10,000. The toxicological MOE approach validates epidemiological and social science-based drug ranking approaches especially in regard to the positions of alcohol and tobacco (high risk) and cannabis (low risk).

Landfield, P. W., et al. (1988). "Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems." Brain Res **443**(1-2): 47-62.

Lawston, J., et al. (2000). "Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2." Brain Res **877**(2): 407-410.

Luna, B. and J. A. Sweeney (2004). "The emergence of collaborative brain function: FMRI studies of the development of response inhibition." Ann N Y Acad Sci **1021**: 296-309.

Marsicano, G., et al. (2002). "The endogenous cannabinoid system controls extinction of aversive memories." Nature **418**(6897): 530-534.

Acquisition and storage of aversive memories is one of the basic principles of central nervous systems throughout the animal kingdom. In the absence of reinforcement, the resulting behavioural response will gradually diminish to be finally extinct. Despite the importance of extinction, its cellular mechanisms are largely unknown. The cannabinoid receptor 1 (CB1) and endocannabinoids are present in memory-related brain areas and modulate memory. Here we show that the endogenous cannabinoid system has a central function in extinction of aversive memories. CB1-deficient mice showed strongly impaired short-term and long-term extinction in auditory fear-conditioning tests, with unaffected memory acquisition and consolidation. Treatment of wild-type mice with the CB1 antagonist SR141716A mimicked the phenotype of CB1-deficient mice, revealing that CB1 is required at the moment of memory extinction. Consistently, tone presentation during extinction trials resulted in elevated levels of endocannabinoids in the basolateral amygdala complex, a region known to control extinction of aversive memories. In the basolateral amygdala, endocannabinoids and CB1 were crucially involved in long-term depression of GABA (gamma-aminobutyric acid)-mediated inhibitory currents. We propose that endocannabinoids facilitate extinction of aversive memories through their selective inhibitory effects on local inhibitory networks in the amygdala.

McGrath, J., et al. (2010). "Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults." Arch Gen Psychiatry **67**(5): 440-447.

Medina, K. L., et al. (2007). "Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence." J Int Neuropsychol Soc **13**(5): 807-820.

In adults, studies examining the long-lasting cognitive effects of marijuana use demonstrate subtle deficits in attention, executive function, and memory. Because neuromaturation continues through adolescence, these results cannot necessarily generalize to adolescent marijuana users. The goal of this study was to examine neuropsychological functioning in abstinent marijuana using and demographically similar control adolescents. Data were collected from 65 adolescent marijuana users (n=31, 26% females) and controls (n=34, 26% females) 16-18 years of age. Extensive exclusionary criteria included independent psychiatric, medical, and neurologic disorders. Neuropsychological assessments were conducted after>23 days of monitored abstinence. After controlling for lifetime alcohol use and depressive symptoms, adolescent marijuana users demonstrated slower psychomotor speed ($p<.05$), and poorer complex attention ($p<.04$), story memory ($p<.04$), and planning and sequencing ability ($p<.001$) compared with controls. Post hoc analysis revealed that the number of lifetime marijuana use episodes was associated with poorer cognitive function, even after controlling for lifetime alcohol use. The general pattern of results suggested that, even after a month of monitored abstinence, adolescent marijuana users demonstrate subtle neuropsychological deficits compared with nonusers. It is possible that frequent marijuana use during adolescence may negatively influence neuromaturation and cognitive development.

Meier, M. H., et al. (2012). "Persistent cannabis users show neuropsychological decline from childhood to midlife." Proc Natl Acad Sci U S A **109**(40): E2657-2664.

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

Moore, T. H., et al. (2007). "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review." Lancet **370**(9584): 319-328.

BACKGROUND: Whether cannabis can cause psychotic or affective symptoms that persist beyond transient intoxication is unclear. We systematically reviewed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes. METHODS: We searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from their inception to September, 2006, searched reference lists of studies selected for inclusion, and contacted experts. Studies were included if longitudinal and population based. 35 studies from 4804 references were included. Data extraction and quality assessment were done independently and in duplicate. FINDINGS: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 1.54-2.84). Results of analyses restricted to studies of more clinically relevant psychotic disorders were similar. Depression, suicidal thoughts, and anxiety outcomes were examined separately. Findings for these outcomes were less consistent, and fewer attempts were made to address non-causal explanations, than for psychosis. A substantial confounding effect was present for both psychotic and affective outcomes. INTERPRETATION: The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

Mulder, J., et al. (2008). "Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning." Proc Natl Acad Sci U S A **105**(25): 8760-8765.

Nutt, D. J., et al. (2010). "Drug harms in the UK: a multicriteria decision analysis." Lancet **376**(9752): 1558-1565.

BACKGROUND: Proper assessment of the harms caused by the misuse of drugs can inform policy makers in health, policing, and social care. We aimed to apply multicriteria decision analysis (MCDA) modelling to a range of drug harms in the UK. METHODS: Members of the Independent Scientific Committee on Drugs, including two invited specialists, met in a 1-day interactive workshop to score 20 drugs on 16 criteria: nine related to the harms that a drug produces in the individual and seven to the harms to others. Drugs were scored out of 100 points, and the criteria were weighted to indicate their relative importance. FINDINGS: MCDA modelling showed that heroin, crack cocaine, and metamfetamine were the most harmful drugs to individuals (part scores 34, 37, and 32, respectively), whereas alcohol, heroin, and crack cocaine were the most harmful to others (46, 21, and 17, respectively). Overall, alcohol was the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places. INTERPRETATION: These findings lend support to previous work assessing drug harms, and show how the improved scoring and weighting approach of MCDA increases the differentiation between the most and least harmful drugs. However, the findings correlate poorly with present UK drug classification, which is not based simply on considerations of harm. FUNDING: Centre for Crime and Justice Studies (UK).

Power, R. A., et al. (2014). "Genetic predisposition to schizophrenia associated with increased use of cannabis." Mol Psychiatry **19**(11): 1201-1204.

Ranganathan, M. and D. C. D'Souza (2006). "The acute effects of cannabinoids on memory in humans: a review." Psychopharmacology (Berl) **188**(4): 425-444.

RATIONALE: Cannabis is one of the most frequently used substances. Cannabis and its constituent cannabinoids are known to impair several aspects of cognitive function, with the most robust effects on short-term episodic and working memory in humans. A large body of the work in this area occurred in the 1970s before the discovery of cannabinoid receptors. Recent advances in the knowledge of cannabinoid receptors' function have rekindled interest in examining effects of exogenous cannabinoids on memory and in understanding the mechanism of these effects. OBJECTIVE: The literature about the acute effects of cannabinoids on memory tasks in humans is reviewed. The limitations of the human literature including issues of dose, route of administration, small sample sizes, sample selection, effects of other drug use, tolerance and dependence to cannabinoids, and the timing and sensitivity of psychological tests are discussed. Finally, the human literature is discussed against the backdrop of preclinical findings. RESULTS: Acute administration of Delta-9-THC transiently impairs immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner. In particular, cannabinoids increase intrusion errors. These effects are more robust with the inhaled and intravenous route and correspond to peak drug levels. CONCLUSIONS: This profile of effects suggests that cannabinoids impair all stages of memory including encoding, consolidation, and retrieval. Several mechanisms, including effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter (GABA, glutamate, acetyl choline, dopamine) release, have been implicated in the amnestic effects of cannabinoids. Future research in humans is necessary to characterize the neuroanatomical and neurochemical basis of the memory impairing effects of cannabinoids, to dissect out their effects on the various stages of memory and to bridge the expanding gap between the humans and preclinical literature.

Robbe, D. and G. Buzsaki (2009). "Alteration of theta timescale dynamics of hippocampal place cells by a cannabinoid is associated with memory impairment." J Neurosci **29**(40): 12597-12605.

Rolles, S. and F. Measham (2011). "Questioning the method and utility of ranking drug harms in drug policy." Int J Drug Policy **22**(4): 243-246.

In a 2010 Lancet paper Nutt et al. propose a model for evaluating and ranking drug harms, building on earlier work by incorporating multi criteria decision analysis. It is argued that problems arise in modelling drug harms using rankable single figure indices when determinants of harm reflect pharmacology translated through a complex prism of social and behavioural variables, in turn influenced by a range of policy environments. The delphic methodolgy used is highly vulnerable to subjective judgements and even the more robust measures, such as drug related death and dependence, can be understood as socially constructed. The failure of the model to dissaggregate drug use harms from those related to the policy environment is also highlighted. Beyond these methodological challenges the utility of single figure index harm rankings is questioned, specifically their role in increasingly redundant legal frameworks utilising a harm-based hierarchy of punitive sanctions. If analysis is to include the capacity to capture the complexity relating to drug using behaviours and environments; specific personal and social risks for particular using populations; and the broader socio-cultural context to contemporary intoxication, there will need to be acceptance that analysis of the various harm vectors must remain separate - the complexity of such analysis is not something that can or should be over generalised to suit political discourse or outdated legal frameworks.

Romero, J., et al. (1998). "Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to delta9-tetrahydrocannabinol." Synapse **30**(3): 298-308.

Recent studies have demonstrated that the pharmacological tolerance observed after prolonged exposure to plant or synthetic cannabinoids in adult individuals seems to have a pharmacodynamic rather than pharmacokinetic basis, because down-regulation of cannabinoid receptors was assessed in the brain of cannabinoid-tolerant rats. In the present study, we have examined the time-course of cannabinoid receptor down-regulation by analyzing cannabinoid receptor binding, using autoradiography, and mRNA expression, using in situ hybridization, in several brain structures of male adult rats daily exposed to delta9-tetrahydrocannabinol (delta9-THC) for 1, 3, 7, or 14 days. With only the exception of a few number of areas, most of the brain regions exhibited a progressive decrease in cannabinoid receptor binding. Two facts deserve to be mentioned. First, the pattern of this down-regulation process presented significant regional differences in terms of onset of the decrease and magnitude reached. Second, the loss of cannabinoid receptor binding was usually accompanied by no changes in its mRNA expression. Thus, some structures, such as most of the subfields of the Ammon's horn and the dentate gyrus in the hippocampus, exhibited a rapid (it appeared after the first injection) and marked (it reached approximately 30% of decrease after 14 days) reduction of cannabinoid receptor binding as a consequence of the daily delta9-THC administration. However, no changes occurred in mRNA levels. Decreased binding was also found in most of the basal ganglia, but the onset of this reduction was slow in the lateral caudate-putamen and the substantia nigra (it needed at least three days of daily delta9-THC administration), and, in particular, in the globus pallidus (more than 3 days). The magnitude of the decrease in binding was also more moderate, with maximal reductions always less than 28%. No changes were seen in the entopeduncular nucleus and only a trend in the medial caudate-putamen. However, the decrease in binding in some basal ganglia was, in this case, accompanied by a decrease in mRNA levels in the lateral caudate-putamen, but this appeared after 7 days of daily delta9-THC administration and, hence, after the onset of binding decrease. In the limbic structures, cannabinoid receptor binding decreased in the septum nuclei (it needed at least 3 days of daily delta9-THC administration), tended to diminish in the nucleus accumbens and was unaltered in the basolateral amygdaloid nucleus, with no changes in mRNA levels in these last two regions. Binding also decreased in the superficial and deep layers of the cerebral cortex, but only accompanied by trends in mRNA expression. The decrease in binding was initiated promptly in the deep layer (after the first injection) and it reached more than 30% of reduction after 14 days of daily delta9-THC administration, whereas, in the superficial layer, it needed more than 3 days of daily delta9-THC administration and reached less than 30% of reduction. Finally, no changes in binding and mRNA levels were found in the ventromedial hypothalamic nucleus. In summary, the daily administration of delta9-THC resulted in a progressive decrease in cannabinoid receptor binding in most of the brain areas studied, and it was a fact that always occurred before the changes in mRNA expression in those areas where these existed. The onset of the decrease in binding exhibited regional differences with areas, such as most of the hippocampal structures and the deep layer of the cerebral cortex, where the decrease occurred after the first administration. Other structures, however, needed at least 3 days or more to initiate receptor binding decrease. Two structures, the entopeduncular nucleus and the ventromedial hypothalamic nucleus, were unresponsive to chronic delta9-THC administration, whereas others, the medial caudate-putamen and the basolateral amygdaloid nucleus, only exhibited trends.

Romero, J., et al. (1995). "Changes in rat brain cannabinoid binding sites after acute or chronic exposure to their endogenous agonist, anandamide, or to delta 9-tetrahydrocannabinol." Pharmacol Biochem Behav **51**(4): 731-737.

Romero, J., et al. (1997). "Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions." Brain Res Mol Brain Res **46**(1-2): 100-108.

Rubino, T. and D. Parolaro (2008). "Long lasting consequences of cannabis exposure in adolescence." Mol Cell Endocrinol **286**(1-2 Suppl 1): S108-113.

SAMHSA (2000). "National Household Survey on Drug Abuse, 2000 (ICPSR 3262)." National Survey on Drug Use and Health (NSDUH) Series. from http://www.icpsr.umich.edu/icpsrweb/SAMHDA/studies/3262.

SAMHSA Center for Behavioral Health Statistics and Quality (2014). "The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings." The NSDUH Report (Sept 4, 2014). from http://www.icpsr.umich.edu/icpsrweb/SAMHDA/studies/35509.

Scallet, A. C. (1991). "Neurotoxicology of cannabis and THC: a review of chronic exposure studies in animals." Pharmacol Biochem Behav **40**(3): 671-676.

> Several laboratories have reported that chronic exposure to delta-9-tetrahydrocannabinol (THC) or marijuana extracts persistently altered the structure and function of the rat hippocampus, a paleocortical brain region involved with learning and memory processes in both rats and humans. Certain choices must be made in designing experiments to evaluate cannabis neurotoxicity, such as dose, route of administration, duration of exposure, age at onset of exposure, species of subjects, whether or how long to allow withdrawal, and which endpoints or biomarkers of neurotoxicity to measure. A review of the literature suggests that both age during exposure and duration of exposure may be critical determinants of neurotoxicity. Cannabinoid administration for at least three months (8-10% of a rat's lifespan) was required to produce neurotoxic effects in peripubertal rodents, which would be comparable to about three years exposure in rhesus monkeys and seven to ten years in humans. Studies of monkeys after up to 12 months of daily exposure have not consistently reported neurotoxicity, and the results of longer exposures have not yet been studied.

Scallet, A. C., et al. (1987). "Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC)." Brain Res **436**(1): 193-198.

> Persistent behavioral effects resembling those of hippocampal brain lesions have been reported following chronic administration of marijuana or its major psychoactive constituent, delta-9-tetrahydrocannabinol (THC) to rats. We used morphometric techniques to investigate the effects of chronic THC on the anatomical integrity of the hippocampus. Rats dosed orally for 90 days with 10 to 60 mg/kg THC or vehicle were evaluated by light and electron microscopy up to 7 months after their last dose of drug. Electron micrographs revealed a striking ultrastructural appearance and statistically significant decreases in mean volume of neurons and their nuclei sampled from the hippocampal CA3 region of rats treated with the highest doses of THC. A 44% reduction in the number of synapses per unit volume was demonstrated in these same rats. Golgi impregnation studies of additional groups of rats treated with 10 or 20 mg/kg/day THC and sacrificed 2 months after their last treatment with THC revealed a reduction in the dendritic length of CA3 pyramidal neurons, despite normal appearing ultrastructure and no changes in synaptic density. The hippocampal changes reported here may constitute a morphological basis for behavioral effects after chronic exposure to marijuana.

Seager, M. A., et al. (2002). "Oscillatory brain states and learning: Impact of hippocampal theta-contingent training." Proc Natl Acad Sci U S A **99**(3): 1616-1620.

Silins, E. H., J.; Patton, G.C.; Fergusson, D,M.; Olsson, C.A.; Hutchinson, D.M.; Spry, E.; Tpumbourou, J.W.; Degenhardt, L.;Swift, W.; Coffey, C.; Tait, R.J.; Letcher, P.; Copeland, J.; Mattick, R.P. (2014). "Young adult sequelae of adolescent cannabis use: an integrative analysis." Lancet Psychiatry **1**(4): 286-293.

Solowij, N. and R. Battisti (2008). "The chronic effects of cannabis on memory in humans: a review." Curr Drug Abuse Rev **1**(1): 81-98.

> Memory problems are frequently associated with cannabis use, in both the short- and long-term. To date, reviews on the long-term cognitive sequelae of cannabis use have examined a broad range of cognitive functions, with none specifically focused on memory. Consequently, this review sought to examine the literature specific to memory function in cannabis users in the nontoxicated state with the aim of identifying the existence and nature of memory impairment in cannabis users and appraising potentially related mediators or moderators. Literature searches were conducted to extract well-controlled studies that investigated memory function in cannabis users outside of the acute intoxication period, with a focus on reviewing studies published within the past 10 years. Most recent studies have examined working memory and verbal episodic memory and cumulatively, the evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms in long-term or heavy cannabis users. These impairments are not dissimilar to those associated with acute intoxication and have been related to the duration, frequency, dose and age of onset of cannabis use. We consider the impact of not only specific parameters of cannabis use in the manifestation of memory dysfunction, but also such factors as age, neurodevelopmental stage, IQ, gender, various vulnerabilities and other substance-use interactions, in the context of neural efficiency and compensatory mechanisms. The precise nature of memory deficits in cannabis users, their neural substrates and manifestation requires much further exploration through a variety of behavioural, functional brain imaging, prospective and genetic studies.

Solowij, N. Y. c., M.; Lorenzetti, V.; Lubman, D. (2009). Structural Brain Alterations in Cannabis Users: Association with Cognitive Deficits and Psychiatric Symptoms. The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes. M. S. Ritsner, Springer Science**:** 215-225.

Sowell, E. R., et al. (1999). "In vivo evidence for post-adolescent brain maturation in frontal and striatal regions." Nat Neurosci **2**(10): 859-861.

Sowell, E. R., et al. (2004). "Longitudinal mapping of cortical thickness and brain growth in normal children." J Neurosci **24**(38): 8223-8231.

Taylor, M., et al. (2012). "Quantifying the RR of harm to self and others from substance misuse: results from a survey of clinical experts across Scotland." BMJ Open **2**(4).

OBJECTIVE: To produce an expert consensus hierarchy of harm to self and others from legal and illegal substance use. DESIGN: Structured questionnaire with nine scored categories of harm for 19 different commonly used substances. SETTING/PARTICIPANTS: 292 clinical experts from across Scotland. RESULTS: There was no stepped categorical distinction in harm between the different legal and illegal substances. Heroin was viewed as the most harmful, and cannabis the least harmful of the substances studied. Alcohol was ranked as the fourth most harmful substance, with alcohol, nicotine and volatile solvents being viewed as more harmful than some class A drugs. CONCLUSIONS: The harm rankings of 19 commonly used substances did not match the A, B, C classification under the Misuse of Drugs Act. The legality of a substance of misuse is not correlated with its perceived harm. These results could inform any legal review of drug misuse and help shape public health policy and practice.

Terranova, J. P., et al. (1996). "Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR 141716." Psychopharmacology (Berl) **126**(2): 165-172.

van Amsterdam, J., et al. (2010). "Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population." Eur Addict Res **16**(4): 202-207.

Drug policy makers continuously face a changing pattern of drug use, i.e. new drugs appear on the market, the popularity of certain drugs changes or drugs are used in another way or another combination. For legislative purposes, drugs have mostly been classified according to their addictive potency. Such classifications, however, lack a scientific basis. The present study describes the results of a risk assessment study where 19 recreational drugs (17 illicit drugs plus alcohol and tobacco) used in the Netherlands have been ranked by a Dutch expert panel according to their harm based on the scientific state of the art. The study applies a similar approach as recently applied by Nutt et al. [Lancet 2007;369:1047-1053], so that the results of both studies could be compared. The harm indicators scored are acute and chronic toxicity, addictive potency and social harm. The aim of this study is to evaluate whether the legal classification of drugs in the Netherlands corresponds with the ranking of the drugs according to their science-based ranking of harm. Based on the results, recommendations are formulated about the legal classification of recreational drugs at national and international level which serves a rational approach for drug control.

Van Laere, K., et al. (2009). "Relationship of type 1 cannabinoid receptor availability in the human brain to novelty-seeking temperament." Arch Gen Psychiatry **66**(2): 196-204.

CONTEXT: Brain neurochemistry can partially account for personality traits as a variance of normal human behavior, as has been demonstrated for monoamine neurotransmission. Positron emission tomography using fluorine 18-labeled MK-9470 now enables quantification of type 1 cannabinoid receptors (CB1R) in the brain. OBJECTIVE: To investigate whether there is a relationship between human temperament traits and regional cerebral CB1R availability. DESIGN: Forty-seven [(18)F]MK-9470 baseline scanning sessions were performed and correlated with the temperament dimensions and subdimensions of the 240-item Cloninger Temperament and Character Inventory. SETTING: Academic brain imaging center. PARTICIPANTS: Forty-seven nonsmoking, healthy volunteers (paid). Main Outcome Measure Voxel-based correlation of temperament variables of the inventory with regional CB1R availability. RESULTS: Novelty seeking was inversely correlated with global CB1R availability (r = -0.33, P = .02), with the most significant correlation in the left amygdala (r = -0.41, P = .005). In particular, the subdimension extravagance showed a highly significant inverse correlation to global CB1R availability (r = -0.53, P <.001), most pronounced in the amygdala, anterior cingulate, parietal cortex, and precuneus. Also, disorderliness was inversely correlated with global CB1R availability (r = -0.31, P = .04). CONCLUSIONS: Low baseline cerebral CB1R availability is related to a high novelty-seeking personality, in particular to extravagance, most pronounced in the amygdala. Further investigation of the functional role of the CB1R is warranted in pathological behavior known to be strongly related to novelty seeking, such as addiction and eating disorders.

van Os, J., et al. (2002). "Cannabis use and psychosis: a longitudinal population-based study." Am J Epidemiol **156**(4): 319-327.

Viveros, M. P., et al. (2012). "The endocannabinoid system in critical neurodevelopmental periods: sex differences and neuropsychiatric implications." J Psychopharmacol **26**(1): 164-176.

Vo, H. T., et al. (2014). "Working memory impairment in cannabis- and opioid-dependent adolescents." Subst Abus **35**(4): 387-390.

Volkow, N. D., et al. (2014). "Adverse health effects of marijuana use." N Engl J Med **370**(23): 2219-2227.

Weinstein, A., et al. (2008). "A study investigating the acute dose-response effects of 13 mg and 17 mg Delta 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana." J Psychopharmacol **22**(4): 441-451.

Wesley, M. J., et al. (2011). "Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences." Psychiatry Res **191**(1): 51-59.

Chronic marijuana users (MJ Users) perform poorly on the Iowa Gambling Task (IGT), a complex decision-making task in which monetary wins and losses guide strategy development. This functional magnetic resonance imaging (MRI) study sought to determine if the poor performance of MJ Users was related to differences in brain activity while evaluating wins and losses during the strategy development phase of the IGT. MJ Users (16) and Controls (16) performed a modified IGT in an MRI scanner.

Performance was tracked and functional activity in response to early wins and losses was examined. While the MJ Users continued to perform poorly at the end of the task, there was no difference in group performance during the initial strategy development phase. During this phase, before the emergence of behavioral differences, Controls exhibited significantly greater activity in response to losses in the anterior cingulate cortex, medial frontal cortex, precuneus, superior parietal lobe, occipital lobe and cerebellum as compared to MJ Users. Furthermore, in Controls, but not MJ Users, the functional response to losses in the anterior cingulate cortex, ventral medial prefrontal cortex and rostral prefrontal cortex positively correlated with performance over time. These data suggest MJ Users are less sensitive to negative feedback during strategy development.

Yakovlev, P. I. L., A.R. (1967). The myelogenetic cycles of regional maturation of the brain. Boston, MA, Blackwell Scientific.

Yucel, M., et al. (2008). "Regional brain abnormalities associated with long-term heavy cannabis use." Arch Gen Psychiatry **65**(6): 694-701.

CONTEXT: Cannabis is the most widely used illicit drug in the developed world. Despite this, there is a paucity of research examining its long-term effect on the human brain. OBJECTIVE: To determine whether long-term heavy cannabis use is associated with gross anatomical abnormalities in 2 cannabinoid receptor-rich regions of the brain, the hippocampus and the amygdala. DESIGN: Cross-sectional design using high-resolution (3-T) structural magnetic resonance imaging. SETTING: Participants were recruited from the general community and underwent imaging at a hospital research facility. PARTICIPANTS: Fifteen carefully selected long-term (>10 years) and heavy (>5 joints daily) cannabis-using men (mean age, 39.8 years; mean duration of regular use, 19.7 years) with no history of polydrug abuse or neurologic/mental disorder and 16 matched nonusing control subjects (mean age, 36.4 years). MAIN OUTCOME MEASURES: Volumetric measures of the hippocampus and the amygdala combined with measures of cannabis use. Subthreshold psychotic symptoms and verbal learning ability were also measured. RESULTS: Cannabis users had bilaterally reduced hippocampal and amygdala volumes (P = .001), with a relatively (and significantly [P = .02]) greater magnitude of reduction in the former (12.0% vs 7.1%). Left hemisphere hippocampal volume was inversely associated with cumulative exposure to cannabis during the previous 10 years (P = .01) and subthreshold positive psychotic symptoms (P < .001). Positive symptom scores were also associated with cumulative exposure to cannabis (P = .048). Although cannabis users performed significantly worse than controls on verbal learning (P < .001), this did not correlate with regional brain volumes in either group. CONCLUSIONS: These results provide new evidence of exposure-related structural abnormalities in the hippocampus and amygdala in long-term heavy cannabis users and corroborate similar findings in the animal literature. These findings indicate that heavy daily cannabis use across protracted periods exerts harmful effects on brain tissue and mental health.

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OBJECTIVES: An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases. DESIGN: Historical cohort study. SETTING: 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20). PARTICIPANTS: 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics. MAIN OUTCOME MEASURES: Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage. RESULTS: Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, P<0.001), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, P<0.015). The adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases. CONCLUSIONS: Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.