Impact of Marijuana on Children and Adolescents

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Research into how marijuana produces its effects led scientists to discover that the brain has a huge, delicately balanced cannabinoid system of its own. Oily resin found in the leaves and flowers of the cannabis plant contains several chemicals called "cannabinoids" (e.g., THC, or delta-9-tetrahydrocannabinol). THC closely resembles the natural chemistry in our brain, effectively mimicking some of the brain's neurotransmitters. Smoking marijuana produces its characteristic "high" by flooding our brain with molecules that cannot be distinguished from its own internally produced neurochemistry, throwing the brain far from its natural chemical balance.

While many people put a negative moral value and judgment on the experience of intoxication, and others put a positive value and judgment on the experience, medicine does neither. Medicine restricts its focus to relieving suffering and investigating events that cause suffering. Currently, considerable research is now focusing on the unique impacts of marijuana on children and adolescents.

Five reasons exist for focusing on the impact that marijuana has on children and adolescents:

1. The brain continues to undergo important development up until the age of 25(Giedd 2004).
2. Children and adolescents are at far greater risk of becoming dependent on marijuana, and dependence happens far more quickly.
3. Children and adolescents are more significantly affected by marijuana, even before dependence occurs.
4. Structural changes have been found in the brains of young marijuana users.
5. Subtle effects from marijuana on emotions and reasoning are increasingly being demonstrated in all marijuana users.

1. Brain Development in Children and Adolescents

Unlike computers, which are finished products before being turned on, human brains begin functioning long before they are fully developed. We begin experiencing the world and developing our sense of identity with very immature brains, unable to understand abstract reasoning or to calculate realistic

consequences of our actions. Fortunately, at puberty the brain undergoes a sudden and stunning growth of new connections among its 50-100 billion nerve cells, permitting a new, and higher level of comprehension of self and the world to emerge(Gagtay 2004) (Yurgelun-Todd and Killgore 2006). A gradual maturation of this new brain growth occurs throughout adolescence, including in regions that contain heavy concentrations of the brain's intrinsic cannabinoid system. One of the questions under active research today is whether the normal course of brain development during adolescence is altered by heavy use of marijuana during this period of active neural reorganization. We are currently aware of significant ebbing and flowing in the level of cannabinoid receptors and cannabinoid neurotransmitters throughout adolescent brain development(Fernandez-Ruiz, Berrendero et al. 2000).

Not only does the brain's natural endocannabinoid neural system undergo development throughout adolescence, but it also helps guide the development of the rest of the brain. The proper laying down of nerve tracts within the brain is facilitated by our natural cannabinoids(Romero, Garcia-Palomero et al. 1997). Even the maturation of other neurotransmitter systems is influenced by our endogenous cannabinoid system(Trezza, Cuomo et al. 2008). Exposure to excessive cannabinoid stimulation from the outside during early phases of development has been shown to alter the normal development of endorphin, glutamate, GABA, serotonin and catecholamine (e.g., adrenaline and dopamine) neural systems.

The impact of marijuana on brain development is like a large unfinished puzzle. Research has uncovered thousands of pieces to the puzzle, but the final picture still remains in flux. Science does have most of the borders pieced together at this point, however, and we are certain that **critical periods occur when the excessive cannabinoid stimulation produced by marijuana have significant impact on the course of brain development**.

2. Marijuana Addiction in Children and Adolescents

There are four separate lines of research that prove marijuana has all the characteristics of an addictive drug.

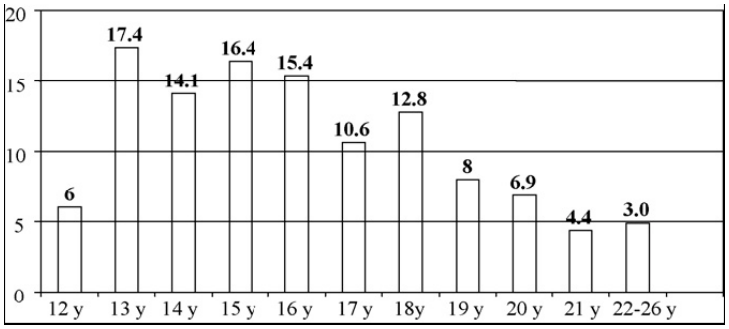
1. Neuroscientists have demonstrated that marijuana affects the brain's reward centers in similar ways as all other known drugs of addiction(Kolb, Gorny et al. 2006).
2. Animal studies have demonstrated consistent withdrawal patterns of behavior when THC, the main active ingredient, is given twice a day for one week and then suddenly withdrawn(Tanda and Goldberg 2003).
3. Clinical reports in humans reveal a similar pattern of withdrawal symptoms during the first weeks of abstinence(Budney and Hughes 2006). Common symptoms of marijuana withdrawal (reported by > 70% of abstinent individuals) include anger or aggression, decreased appetite or weight

loss, irritability, nervousness/anxiety, restlessness, and sleep difficulties including strange dreams(Budney, Hughes et al. 2004; Hasin, Keyes et al. 2008).

4. Epidemiologists have found that approximately 9% of people who begin smoking marijuana at 18 years or older satisfy the criteria for dependence(Budney, Roffman et al. 2007). This number triples at ages under 18. For near-daily users, the risk for dependence some time later in life is estimated to be 35-40%(Kandel 1992).

The epidemiology of marijuana dependence appears to be relatively predictable. While approximately 9% of all individuals who begin using marijuana after age 18 eventually satisfy the criteria for dependence at some time in their lives, much higher rates hold for individuals who initiate use before 18, with the highest rates being shown by the youngest initiates.

Children and adolescents brains and personalities are under rapid development. As a result, they can become addicted more often and more rapidly than adults. For example, only 4.4% of individuals who start smoking marijuana after age 21 become addicted within the first two years of use, while 17.4% of thirteen-year-olds become addicted within the first two years (similar percentages also hold for the risk of developing alcohol dependence).



Percentages of past year cannabis use disorder by age among recent cannabis onset users (prior 2 years)(Winters and Lee 2008)

3. Impact of Marijuana on Brain Function in Children and Adolescents

Addiction represents only one impact that marijuana can have on youth. Marijuana has a range of impacts that occur before full addiction is established. Research is rapidly accumulating proof that marijuana can affect the functioning of developing brains leading to greater cognitive deficits in children and adolescents than in adults. Recent studies have found that, while adolescent marijuana users may score as

well as nonusers on cognitive tests, they recruit more areas of the brain to accomplish the task, a sign of inefficient brain function(Tapert, Schweinsburg et al. 2007).

Not only are functional differences found in adolescent marijuana smokers, but also cognitive differences exist even after 28 days of documented abstinence(Medina, Hanson et al. 2007; Hanson, Winward et al. 2010). Whereas adults recover cognitively more quickly, adolescent marijuana users demonstrate more prolonged decreased psychomotor speed and diminishment in several higher functions, including sequencing ability, story learning, and complex attention.

It is likely that these cognitive deficits in regular smokers share responsibility for decreased academic performance. Adolescents who have smoked more than 100 times (easily achieved by weekend smoking for two years) leave school 5.8 times more often, enter college 3.3 times less often and earn a college degree 4.5 times less often(Fergusson, Horwood et al. 2003).

Studies of the impact of cannabis exposure during adolescence on emotional development have focused primarily on subsequent anxiety and depressive disorders. Both animal and human studies find significant gender differences, with females showing more vulnerability(Patton, Coffey et al. 2002). Further studies are needed to understand the gender differences in marijuana's effects. It is clear, however, that marijuana decreases scores on Affective Sensitivity Scales and ratings of interpersonal skills and affective resonance(Clopton, Janowsky et al. 1979; Janowsky, Clopton et al. 1979; Limonero, Tomas-Sabado et al. 2006).

There is little doubt about the existence of an association between marijuana use and psychotic illness(Moore, Zammit et al. 2007; Kuepper, van Os et al. 2011; Large 2011). Six longitudinal studies in five countries show that regular cannabis use confers a twofold increase in the risk for later schizophrenia(Zammit, Allebeck et al. 2002). Cannabis use is also associated with an earlier age at onset of psychotic disorders, particularly schizophrenia(Veen, Selten et al. 2004; Semple, McIntosh et al. 2005).

4. The Impact of Marijuana on Brain Structure in Children and Adolescents

Our brain's natural cannabinoid chemistry gradually develops from fetal life until adulthood, hand in hand with the rest of the brain's development(Fernandez-Ruiz, Berrendero et al. 2000). Multiple studies now show that our cannabinoid chemistry is also instrumental in guiding the development of other brain structures as well(Romero, Garcia-Palomero et al. 1997).

At puberty, the brain undergoes explosive growth, particularly in the rich branching of connections among brain cells. Much of this growth occurs in the outer layer of the brain, the cortex. After this profusion of growth, nature has a way of trimming away the connections that do not get used and strengthening those

connections that contribute to learning. This pruning process lasts until the mid-twenties. As pruning occurs, the cortex becomes thinner, much as proper pruning of shrubbery in the spring reduces its volume.

Researchers have now begun finding differences in the volume of brain tissue in young marijuana users, compared to non-using adolescents, in areas with a high density of cannabinoid receptors. Scientists believe that excessive stimulation of these receptors by the THC in marijuana interferes with the normal pruning process. For example, marijuana use during adolescence has been found to contribute to asymmetrical increases in the size of the hippocampi, structures that are critical for learning and memory(Scallet, Uemura et al. 1987; Medina, Schweinsburg et al. 2007). The cerebellum, important for concentration and fine motor control, is enlarged in young marijuana users(Medina, Nagel et al.). The amygdalae, important for emotionality, have been found to be asymmetrically enlarged in female marijuana users(McQueeny, Padula et al. 2011). And the frontal cortex has been shown to be thinner in adolescent marijuana users, particularly in those who began smoking at earlier ages(Churchwell, Lopez-Larson et al. 2010). Measures of impulsivity were also higher the thinner the cortex, indicating that structural changes have functional consequences.

Finally, long-term heavy marijuana use, which most often begins during early adolescence, has been shown to eventually decrease the size of the hippocampus by 12% and the amygdala by 7%(Yucel, Solowij et al. 2008). In addition, studies have demonstrated up to 44% fewer synapses in the hippocampi of animals chronically exposed to THC.

Chronic exposure to excessive cannabinoid stimulation can alter the size and internal structure of multiple areas of the brain, with greater impact when exposure occurs during early life.

5. Subtle Effects on Emotions and Reasoning Occur in all Marijuana Users

Multiple subtle, but important, impacts of marijuana on the brain occur at all ages, but have greater impact on children and adolescents. This greater impact is due both to the less mature development of the young brain and the fact that youth are still in the process of developing a sense of identity, a set of values, and the basic education required to launch successfully into independent adulthood.

A host of subtle effects, both acute and chronic (i.e., both during the experience of being “high” and effects that linger long afterward), stem from the amygdala’s reactivity to marijuana. The dense concentration of cannabinoid receptors in the amygdala(Katona, Rancz et al. 2001) respond to THC by quickly

being reduced in number. Within 14 days of daily marijuana use, 24% of the receptors have disappeared(Romero, Berrendero et al. 1998).

This reduction in cannabinoid receptors (CB1) in the amygdala can have pervasive consequences. For example, human temperament is defined as the biological set point for a variety of emotions, cognitions and behaviors every individual inherits. One important facet of temperament is an individual's response to novelty. Uninhibited individuals approach novelty, while inhibited individuals tend to avoid novelty. The level of cannabinoid receptors in the amygdala is directly (inversely) related to whether an individual is inhibited or uninhibited(Van Laere, Goffin et al. 2009). A high level of CB1 creates an amygdala that is highly reactive to novelty, leading individuals to be novelty avoidant and thus inhibited. On the other hand, lower CB1 levels lead to a less reactive amygdala, and thus to novelty seeking individuals. As noted previously, heavy marijuana use substantially alters the concentration of CB1 receptors in the amygdala and thus is likely to modify an individual's response to novelty and alter the degree of inhibition.

Activity in the amygdala is associated with more than our response to novelty. A full range of emotional responsivity is related to activity within the amygdala. For example, studies show that the amygdala reacts to fearful facial expressions viewed so briefly that we are unconscious of seeing them(Gruber, Rogowska et al. 2009). Marijuana smokers, however, have less of a response. In fact, the amygdala's response to threat related stimuli is inversely related to the amount of marijuana an individual smokes(Cornelius, Aizenstein et al. 2010).

It now appears that our natural cannabinoid system is an integral part of the brain's mechanism for forgetting, especially forgetting painful memories(Marsicano, Wotjak et al. 2002; Chhatwal, Davis et al. 2005). Decreasing cannabinoid tone prevents extinction of aversive learning and increasing cannabinoid tone promotes forgetting of aversive experiences. Measurements of activity in the amygdala of individuals suffering from PTSD (characterized by the inability to quell reactions to traumatic events) reveal extreme reactivity to fearful faces(Shin, Wright et al. 2005). This may explain why marijuana is frequently the drug of choice for PTSD sufferers, since the THC reduces activity in the amygdala and temporarily extinguishes the aversive memories. While this appears to suggest that marijuana is useful "medicine" for PTSD, this would fail to recognize that our natural cannabinoid system produces the extinction of aversive memories by interacting with a specific subset of CB1 receptors while THC from the outside interacts with all CB1 receptors(Trezza, Cuomo et al. 2008). The role of our cannabinoid system in aiding the forgetting of aversive memories is important because young marijuana users become less likely to learn from negative experiences when they are chronically suppressing their amygdala response to threat. As a result, euphoric recall (the good times while "high") will predominate over any negative aspects of their marijuana experience.

If this suppressed reaction to negative experiences seems merely hypothetical, it is useful to review studies using the Iowa Gambling Task, which assesses reactions to losses and gains(Bolla, Eldreth et al. 2005; Wesley, Hanlon et al. 2011). Heavy marijuana use decreases the brain's response to losses, leading individuals to make choices based more on gains than on the size of any losses. Aversive experiences are reduced in their influence. The result is the development of inefficient strategies for solving problems – a bad foundation for psychological development during childhood and adolescence.

Recent studies have demonstrated that the subtle impact of marijuana cannot always be demonstrated during structured laboratory testing of cognitive tasks. However, even when no impairments are measured on standardized tests, brain imaging often reveals the recruitment of larger than normal areas of the brain to accomplish the task, presumably a means of compensating for subtle deficits(Jager, Van Hell et al. 2007; Tapert, Schweinsburg et al. 2007; Becker, Wagner et al. 2010; Jager, Block et al. 2010). And measures of real-world functioning reveal significantly reduced everyday memory, prospective memory (which requires planning and sequencing) and cognitive abilities(Fisk and Montgomery 2008) in marijuana users.

CONCLUSION

Five reasons have been documented for focusing on the impact that marijuana has on children and adolescents. The human brain continues to undergo important development up until the age of 25. As a result of their brains still undergoing growth and development, children and adolescents are at far greater risk of becoming dependent on marijuana, and dependence happens far more quickly. Apart from addiction itself, children and adolescents are more significantly affected by marijuana in other ways. Structural changes have been found in the brains of young marijuana users that lead to functional impairments, including cognitive deficits that can result in educational under-achievement. Subtle effects of marijuana on emotions are increasingly being demonstrated in all marijuana users that would be more profoundly disruptive to individuals still developing psychologically.

While the majority of children and adolescents who use marijuana do not become dependent and are not grossly harmed, the fact remains that their brains' are modified. This is the reason people smoke marijuana, to change their brains, and thus to change their experience. Altered brain function alters a person's subjective experience of themselves and the world. However, altering brain function by introducing excessive cannabinoid stimulation also physically alters the brain well beyond the period of initial intoxication. When marijuana use becomes daily, or nearly daily, this alteration to the brain can become chronic, and structural. In very many cases, children and adolescents who reach this point in their marijuana use do

not perceive the ongoing impact of marijuana on their experience, nor do they often connect any negative changes in their lives with marijuana use.

The overwhelming preponderance of scientific evidence provides adequate rationale for public policies that deter, delay and detect child and adolescent marijuana use. Our goal should be to limit access to marijuana for those under 21, to keep youth engaged in school, to provide schools with resources to identify and help students using marijuana, to construct a community-based intervention system to evaluate youth under 18 years of age who are using marijuana problematically and to provide them educational and constructive interventions, and to provide professional treatment to youth who have become dependent on marijuana. Deter, delay and detect.

REFERENCES

Becker, B., D. Wagner, et al. (2010). "Altered parahippocampal functioning in cannabis users is related to the frequency of use." Psychopharmacology (Berl) **209**(4): 361-374.

RATIONALE: Converging lines of evidence suggest an association between cannabis use and impaired episodic memory as well as related associative learning. These deficits have been associated with the duration, frequency, and age of onset of cannabis use. However, it remains unclear whether these parameters of use differently impact memory-related hippocampal functioning. METHODS: Forty-two cannabis users were examined by means of functional magnetic resonance imaging while they encoded and retrieved face-profession associations. Region of interest analysis was subsequently used to compare (para-)hippocampal functioning in users with (1) a longer and shorter duration of use, (2) a higher and lower frequency of use, and (3) an earlier and later onset. To further separate the effects of these parameters of use on performance and (para-)hippocampal activity, linear regression analysis was applied. RESULTS: Compared to low-frequency users, high-frequency users displayed stronger blood oxygenation level-dependent response during encoding in the left parahippocampal gyrus. No differences were obvious for the groups separated according to duration of use or an earlier and later onset of use. Linear regression analysis confirmed the association between a higher frequency of use and increased activity in the left parahippocampal gyrus. CONCLUSIONS: Our findings suggest that the frequency of use might have a particular critical impact on intact parahippocampal functioning in cannabis users. Increased activity within the encoding-related network might reflect functional compensation to maintain cognitive functioning.

Bolla, K. I., D. A. Eldreth, et al. (2005). "Neural substrates of faulty decision-making in abstinent marijuana users." Neuroimage **26**(2): 480-492.

Persistent dose-related cognitive decrements have been reported in 28-day abstinent heavy marijuana (MJ) users. However, the neural substrates of

these decrements in cognitive performance are not known. This study aimed to determine if 25-day abstinent MJ users show persistent dose-related alterations in performance and brain activity using PET H(2)(15)O during the Iowa Gambling Task-IGT (a decision-making task). Eleven heavy MJ users and 11 non-drug users participated. The MJ group resided in an inpatient research unit at the NIH/NIDA-IRP for 25 days prior to testing to ensure abstinence. A dose-related association was found between increased MJ use and lower IGT performance and alterations in brain activity. The MJ group showed greater activation in the left cerebellum and less activation in the right lateral orbitofrontal cortex (OFC) and the right dorsolateral prefrontal cortex (DLPFC) than the Control group. When the MJ group was divided into Moderate (8-35 joints/week) and Heavy users (53-84 joints/week), the Heavy MJ group showed less activation in the left medial OFC and greater activation in the left cerebellum than the Moderate group. However, brain activity and task performance were similar between the Moderate MJ users and the Control group, suggesting a "threshold effect". These preliminary findings indicate that very heavy users of MJ have persistent decision-making deficits and alterations in brain activity. Specifically, the Heavy MJ users may focus on only the immediate reinforcing aspects of a situation (i.e., getting high) while ignoring the negative consequences. Thus, faulty decision-making could make an individual more prone to addictive behavior and more resistant to treatment. Finally, it is unclear if these neurologic findings will become progressively worse with continued heavy MJ use or if they will resolve with abstinence from MJ use.

Budney, A. J. and J. R. Hughes (2006). "The cannabis withdrawal syndrome." Curr Opin Psychiatry **19**(3): 233-238.

PURPOSE OF REVIEW: The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter the treatment have difficulty in achieving and maintaining abstinence from cannabis. Understanding the impact of cannabis withdrawal syndrome on quit attempts is of obvious importance. Cannabis, however, has long been considered a 'soft' drug, and many continue to question whether one can truly become dependent on cannabis. Skepticism is typically focused on whether cannabis use can result in 'physiological' dependence or withdrawal, and whether withdrawal is of clinical importance. RECENT FINDINGS: The neurobiological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity, and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers. SUMMARY: A clinically important withdrawal syndrome associated with cannabis dependence has been

established. Additional research must determine how cannabis withdrawal affects cessation attempts and the best way to treat its symptoms.

Budney, A. J., J. R. Hughes, et al. (2004). "Review of the validity and significance of cannabis withdrawal syndrome." Am J Psychiatry **161**(11): 1967-1977.

The authors review the literature examining the validity and significance of cannabis withdrawal syndrome. Findings from animal laboratory research are briefly reviewed, and human laboratory and clinical studies are surveyed in more detail. Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance. Diagnostic criteria for cannabis withdrawal syndrome are proposed.

Budney, A. J., R. Roffman, et al. (2007). "Marijuana dependence and its treatment." Addict Sci Clin Pract **4**(1): 4-16.

The prevalence of marijuana abuse and dependence disorders has been increasing among adults and adolescents in the United States. This paper reviews the problems associated with marijuana use, including unique characteristics of marijuana dependence, and the results of laboratory research and treatment trials to date. It also discusses limitations of current knowledge and potential areas for advancing research and clinical intervention.

Chhatwal, J. P., M. Davis, et al. (2005). "Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear." Neuropsychopharmacology **30**(3): 516-524.

The endogenous cannabinoid (eCB) system represents a major therapeutic target for the treatment of a variety of anxiety-related disorders. A recent study has demonstrated that pharmacologic or genetic disruption of CB1-receptor-mediated neurotransmission decreases the extinction of conditioned fear in mice. Here, we examined whether CB1 blockade would similarly disrupt extinction in rats, using fear-potentiated startle as a measure of conditioned fear. We also examined whether pharmacologic enhancement of CB1 activation would lead to enhancements in extinction. Our results indicate that systemic administration of the CB1 antagonist rimonabant (SR141716A) prior to extinction training led to significant, dose-dependent decreases in extinction. While the administration of the CB1 agonist WIN 55,212-2 did not appear to affect extinction, administration of AM404, an inhibitor of eCB breakdown and reuptake, led to dose-dependent enhancements in extinction. In addition to showing decreased fear 1 and 24 h

after extinction training, AM404-treated animals showed decreased shock-induced reinstatement of fear. Control experiments demonstrated that the effects of AM404 could not be attributed to alterations in the expression of conditioned fear, locomotion, shock reactivity, or baseline startle, as these parameters seemed unchanged by AM404. Furthermore, coadministration of rimonabant with AM404 blocked this enhancement of extinction, suggesting that AM404 was acting to increase CB1 receptor activation during extinction training. These results demonstrate that the eCB system can be modulated to enhance emotional learning, and suggest that eCB modulators may be therapeutically useful as adjuncts for exposure-based psychotherapies such as those used to treat Post-Traumatic Stress Disorder and other anxiety disorders.

Churchwell, J. C., M. Lopez-Larson, et al. (2010). "Altered frontal cortical volume and decision making in adolescent cannabis users." Front Psychol **1**: 225.

Anticipating future outcomes is central to decision making and a failure to consider long-term consequences may lead to impulsive choices. Adolescence is a vulnerable period during which underdeveloped prefrontal cortical systems may contribute to poor judgment, impulsive choices, and substance abuse. Conversely, substance abuse during this period may alter neural systems involved in decision making and lead to greater impulsivity. Although a broad neural network which supports decision making undergoes extensive change during adolescent development, one region that may be critical is the medial prefrontal cortex. Altered functional integrity of this region may be specifically related to reward perception, substance abuse, and dependence. In the present investigation, we acquired structural magnetic resonance images (MRI), using a 3T Siemens Trio scanner, from 18 cannabis abusing adolescents (CA; 2 female and 16 male subjects; mean age, 17.7 years; range 16-19 years), and 18 healthy controls (HC; 6 female and 12 male subjects; mean age, 17.2 years; range 16-19 years). In order to measure medial orbital prefrontal cortex (moPFC) morphology related to substance abuse and impulsivity, semi-automated cortical reconstruction and volumetric segmentation of MRIs was performed with FreeSurfer. Impulsivity was evaluated with the Barratt Impulsiveness Scale (BIS). Our results indicate that cannabis abusing adolescents have decreased right moPFC volume compared to controls, $p = 0.01$, $d = 0.92$, $CI(0.95) = 0.21, 1.59$. Cannabis abusing adolescents also show decreased future orientation, as indexed by the BIS non-planning subscale, when compared to controls, $p = 0.01$, $d = 0.89$, $CI(0.95) = 0.23, 1.55$. Moreover, total moPFC volume was positively correlated with age of first use $r(18) = 0.49$, $p < 0.03$, suggesting that alterations in this region may be related to initiation of cannabis use or that early initiation may lead to reduced moPFC volume.

Clopton, P. L., D. S. Janowsky, et al. (1979). "Marijuana and the perception of affect." Psychopharmacology (Berl) **61**(2): 203-206.

The influence of marijuana on the ability to perceive emotions in others was studied in 30 male volunteers who were experienced marijuana users. Subjects smoked either placebo or active marijuana containing 6 mg delta 9-THC. The Affective Sensitivity Scale, a test developed to measure the ability to perceive emotions in others, was divided at midpoint and the two halves were administered before and after smoking, respectively. Analysis of variance demonstrated a decline in test scores following active marijuana administration, while changes following the placebo treatment were not significant.

Cornelius, J. R., H. J. Aizenstein, et al. (2010). "Amygdala reactivity is inversely related to level of cannabis use in individuals with comorbid cannabis dependence and major depression." Addict Behav **35**(6): 644-646.

Phan et al. (2008) recently reported that an acute dose of oral THC is associated with a decrease in threat-related amygdala reactivity during a social threat stimulus task. However, to date, those findings have not been replicated, and have not been extended to clinical studies involving smoked rather than oral cannabis. In this study, we hypothesized that level of cannabis smoked by participants in our treatment study would be inversely related to the level of threat-related amygdala reactivity. Subjects were recruited from among participants in our double-blind, placebo-controlled trial of fluoxetine in comorbid youth with cannabis dependence/major depression. The threat-related amygdala reactivity task used by Hariri et al. (2009) was completed during BOLD fMRI scans at study baseline and then again 12 weeks later at the end of the trial. Data are available from six subjects with pre-and post-treatment fMRI data. During the course of the study, five of the six subjects demonstrated a decrease in their level of cannabis use, with a mean decrease of 64%, and those persons all demonstrated an increase in their level of amygdala reactivity. One subject demonstrated an increase in their level of cannabis use (a 79% increase) during the treatment trial, and that person demonstrated a decrease in their level of amygdala reactivity. Thus, a higher level of cannabis use was consistently associated with a lower level of amygdala reactivity across all subjects (matched pairs $t = 2.70$, $df = 5$, $p < 0.05$, two-tailed). These findings are consistent with the reports by Phan et al. (2008) and Hariri et al. (2009) suggesting that cannabinoids have an inhibitory effect on threat-related amygdala reactivity.

Fergusson, D. M., L. J. Horwood, et al. (2003). "Cannabis and educational achievement." Addiction **98**(12): 1681-1692.

AIMS: To examine the relationship between cannabis use in adolescence/young adulthood and levels of educational attainment. DESIGN: Data were gathered over the course of a 25-year longitudinal study of a birth cohort of 1265 New Zealand children. MEASUREMENTS: Measures analysed included (a) frequency of cannabis use in adolescence and young adulthood (15-25 years); (b) levels of educational achievement to age 25 years; and (c)

social, family and individual characteristics assessed prior to age 16. FINDINGS: Increasing cannabis use was associated with increasing risks of leaving school without qualifications, failure to enter university and failure to obtain a university degree. The association between cannabis use and leaving school without qualifications persisted after control for confounding factors. When due allowance was made for pre-existing levels of cannabis use there was no evidence to suggest the presence of reverse causal pathways in which lower educational achievement led to increased cannabis use. CONCLUSIONS: Findings support the view that cannabis use may act to decrease educational achievement in young people. It is likely that this reflects the effects of the social context within which cannabis is used rather than any direct effect of cannabis on cognitive ability or motivation.

Fernandez-Ruiz, J., F. Berrendero, et al. (2000). "The endogenous cannabinoid system and brain development." Trends Neurosci **23**(1): 14-20.

Cannabinoid receptors and their endogenous ligands constitute a novel modulatory system that is involved in specific brain functions, such as nociception, control of movement, memory and neuroendocrine regulation. Recently, it has also been suggested that this system is involved in brain development. Studies have used a variety of techniques to elucidate the effects of cannabinoids during development, as well as to characterize the presence of elements of the endogenous cannabinoid system (receptors and ligands) in the developing brain. Collectively, they suggest that endocannabinoids participate in brain development through the activation of second-messenger-coupled cannabinoid receptors.

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.

Gagtay (2004). "Dynamic mapping of human cortical development during childhood through early adulthood." PNAS **101**(21): 8174-8179.

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.

Gruber, S. A., J. Rogowska, 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.

Hanson, K. L., J. L. Winward, et al. (2010). "Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence." Addict Behav.

BACKGROUND: Cognitive deficits that persist up to a month have been detected among adult marijuana users, but decrements and their pattern of recovery are less known in adolescent users. Previously, we reported cognitive deficits among adolescent marijuana users after one month of abstinence (Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007). In this longitudinal study, we characterized neurocognitive changes among marijuana-using adolescents across the first three weeks of abstinence. METHOD: Participants were adolescent marijuana users with limited alcohol and other drug use (n=19) and demographically similar non-using controls (n=21) ages 15-19. Participants completed a brief neuropsychological battery on three occasions, after 3days, 2weeks, and 3weeks of stopping substance use. Abstinence was ascertained by decreasing tetrahydrocannabinol metabolite values on serial urine drug screens. Verbal learning, verbal working memory, attention and vigilance, and time estimation were evaluated. RESULTS: Marijuana users demonstrated poorer verbal learning ($p<.01$), verbal working memory ($p<.05$), and attention accuracy ($p<.01$) compared to controls. Improvements in users were seen on word list learning after 2weeks of abstinence and on verbal working memory after 3weeks. While attention processing speed was similar between groups, attention accuracy remained deficient in users throughout the 3-week abstinence period. CONCLUSIONS: This preliminary study detected poorer verbal learning and verbal working memory among adolescent marijuana users that improved during three weeks of abstinence, while attention deficits persisted. These results implicate possible hippocampal, subcortical, and prefrontal cortex abnormalities.

Hasin, D. S., K. M. Keyes, et al. (2008). "Cannabis withdrawal in the United States: results from NESARC." J Clin Psychiatry **69**(9): 1354-1363.

OBJECTIVE: Although cannabis is the most widely abused illicit drug, little is known about the prevalence of cannabis withdrawal and its factor structure, clinical validity, and psychiatric correlates in the general population. METHOD: National Epidemiologic Survey on Alcohol and Related Conditions participants were assessed, in 2001-2002, with structured in-person interviews covering substance history, DSM-IV Axis I and II disorders, and withdrawal symptoms after cessation of use. Of these, 2613 had been frequent cannabis users (> or = 3 times/week), and a "cannabis-only" subset (N = 1119) never binge-drank or used other drugs > or = 3 times/week. RESULTS: In the full sample and subset, 44.3% (SE = 1.19) and 44.2% (SE = 1.75), respectively, experienced > or = 2 cannabis withdrawal symptoms, while 34.4% (SE = 1.21) and 34.1% (SE = 1.76), respectively, experienced >

or = 3 symptoms. The symptoms formed 2 factors, one characterized by weakness, hypersomnia, and psychomotor retardation and the second by anxiety, restlessness, depression, and insomnia. Both symptom types were associated with significant distress/impairment ($p < .01$), substance use to relieve/avoid cannabis withdrawal symptoms ($p < .01$), and quantity of cannabis use (among the cannabis-only users $p < .05$). Panic ($p < .01$) and personality ($p > .01$) disorders were associated with anxiety symptoms in both samples, family history of drug problems was associated with weakness symptoms in the subset ($p = .01$), and depression was associated with both sets of symptoms in the subset ($p < \text{or} = .05$). CONCLUSION: Cannabis withdrawal was prevalent and clinically significant among a representative sample of frequent cannabis users. Similar results in the subset without polysubstance abuse confirmed the specificity of symptoms to cannabis. Cannabis withdrawal should be added to DSM-V, and the etiology and treatment implications of cannabis withdrawal symptoms should be investigated.

Jager, G., R. I. Block, et al. (2010). "Cannabis use and memory brain function in adolescent boys: a cross-sectional multicenter functional magnetic resonance imaging study." J Am Acad Child Adolesc Psychiatry **49**(6): 561-572, 572 e561-563.

OBJECTIVE: Early-onset cannabis use has been associated with later use/abuse, mental health problems (psychosis, depression), and abnormal development of cognition and brain function. During adolescence, ongoing neurodevelopmental maturation and experience shape the neural circuitry underlying complex cognitive functions such as memory and executive control. Prefrontal and temporal regions are critically involved in these functions. Maturational processes leave these brain areas prone to the potentially harmful effects of cannabis use. METHOD: We performed a two-site (United States and The Netherlands; pooled data) functional magnetic resonance imaging (MRI) study with a cross-sectional design, investigating the effects of adolescent cannabis use on working memory (WM) and associative memory (AM) brain function in 21 abstinent but frequent cannabis-using boys (13-19) years of age and compared them with 24 nonusing peers. Brain activity during WM was assessed before and after rule-based learning (automatization). AM was assessed using a pictorial hippocampal-dependent memory task. RESULTS: Cannabis users performed normally on both memory tasks. During WM assessment, cannabis users showed excessive activity in prefrontal regions when a task was novel, whereas automatization of the task reduced activity to the same level in users and controls. No effect of cannabis use on AM-related brain function was found. CONCLUSIONS: In adolescent cannabis users, the WM system was overactive during a novel task, suggesting functional compensation. Inefficient WM recruitment was not related to a failure in automatization but became evident when processing continuously changing information. The results seem to confirm the vulnerability of still developing frontal lobe functioning for early-onset cannabis use.

Jager, G., H. H. Van Hell, et al. (2007). "Effects of frequent cannabis use on hippocampal activity during an associative memory task." Eur Neuropsychopharmacol **17**(4): 289-297.

Interest is growing in the neurotoxic potential of cannabis on human brain function. We studied non-acute effects of frequent cannabis use on hippocampus-dependent associative memory, investigated with functional Magnetic Resonance Imaging (fMRI) in 20 frequent cannabis users and 20 non-users matched for age, gender and IQ. Structural changes in the (para)hippocampal region were measured using voxel-based morphometry (VBM). Cannabis users displayed lower activation than non-users in brain regions involved in associative learning, particularly in the (para)hippocampal regions and the right dorsolateral prefrontal cortex, despite normal performance. VBM-analysis of the (para)hippocampal regions revealed no differences in brain tissue composition between cannabis users and non-users. No relation was found between (para)hippocampal tissue composition and the magnitude of brain activity in the (para)hippocampal area. Therefore, lower brain activation may not signify neurocognitive impairment, but could be the expression of a non-cognitive variable related to frequent cannabis use, for example changes in cerebral perfusion or differences in vigilance.

Janowsky, D. S., P. L. Clopton, et al. (1979). "Interpersonal effects of marijuana. A model for the study of interpersonal psychopharmacology." Arch Gen Psychiatry **36**(7): 781-785.

The effect of marijuana on affective changes and interpersonal skills, including empathy, acceptance, warmth, and genuineness, was studied in 20 dyadic relationships in which the experimental subject smoking marijuana containing 6 mg of delta-9-tetrahydrocannabinol and a placebo in separate trials. Marijuana caused a relative decrease in the ratings of the interpersonal skills of the experimental subjects and decreased affective resonance between the experimental subjects and their partners.

Kandel (1992). "Progression to regular marijuana involvement: phenomenology and risk factors of near daily use." 221-253.

Katona, I., E. A. Rancz, et al. (2001). "Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission." J Neurosci **21**(23): 9506-9518.

Cannabinoids are the most popular illicit drugs used for recreational purposes worldwide. However, the neurobiological substrate of their mood-altering capacity has not been elucidated so far. Here we report that CB1 cannabinoid receptors are expressed at high levels in certain amygdala nuclei, especially in the lateral and basal nuclei, but are absent in other nuclei (e.g., in the central nucleus and in the medial nucleus). Expression of the CB1 protein was restricted to a distinct subpopulation of GABAergic interneurons

corresponding to large cholecystokinin-positive cells. Detailed electron microscopic investigation revealed that CB1 receptors are located presynaptically on cholecystokinin-positive axon terminals, which establish symmetrical GABAergic synapses with their postsynaptic targets. The physiological consequence of this particular anatomical localization was investigated by whole-cell patch-clamp recordings in principal cells of the lateral and basal nuclei. CB1 receptor agonists WIN 55,212-2 and CP 55,940 reduced the amplitude of GABA(A) receptor-mediated evoked and spontaneous IPSCs, whereas the action potential-independent miniature IPSCs were not significantly affected. In contrast, CB1 receptor agonists were ineffective in changing the amplitude of IPSCs in the rat central nucleus and in the basal nucleus of CB1 knock-out mice. These results suggest that cannabinoids target specific elements in neuronal networks of given amygdala nuclei, where they presynaptically modulate GABAergic synaptic transmission. We propose that these anatomical and physiological features, characteristic of CB1 receptors in several forebrain regions, represent the neuronal substrate for endocannabinoids involved in retrograde synaptic signaling and may explain some of the emotionally relevant behavioral effects of cannabinoid exposure.

Kolb, B., G. Gorny, et al. (2006). "Chronic treatment with Delta-9-tetrahydrocannabinol alters the structure of neurons in the nucleus accumbens shell and medial prefrontal cortex of rats." Synapse **60**(6): 429-436.

The potential of repeated exposure to Delta(9)-tetrahydrocannabinol (Delta(9)-THC) to produce long-lasting changes in synaptic connections in a manner similar to other drugs of abuse was evaluated in Sprague-Dawley rats. For 12 days, rats received two i.p. injections per day (8 h apart) of vehicle, a low dose of Delta(9)-THC (0.5 mg/kg), or escalating doses of Delta(9)-THC (0.5-4.0 mg/kg). Thirty days later, they were evaluated for sensitized locomotor activity (during the night cycle) for 60 min on each of three trials. Using a within-groups design, rats were tested following an injection of vehicle, 0.5 mg/kg Delta(9)-THC or 2.0 mg/kg Delta(9)-THC. The rats showed no evidence of sensitized locomotor activity in any group. Twenty-four hours after the final sensitization test, their brains were removed and then processed for Golgi-Cox staining. Prior exposure to Delta(9)-THC (both the low dose and the escalating doses) increased the length of the dendrites as well as the number of dendritic branches in the shell of the nucleus accumbens and in the medial prefrontal cortex, but not in the hippocampus, striatum, orbital frontal cortex, parietal cortex, or occipital cortex. These results are similar to those evident in brains of rats sensitized to amphetamine, and support previous findings that cannabinoids promote DA activity in the mesolimbic DA system.

Kuepper, R., J. van Os, et al. (2011). "Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study." BMJ **342**: d738.

OBJECTIVE: To determine whether use of cannabis in adolescence increases the risk for psychotic outcomes by affecting the incidence and persistence of subclinical expression of psychosis in the general population (that is, expression of psychosis below the level required for a clinical diagnosis). DESIGN: Analysis of data from a prospective population based cohort study in Germany (early developmental stages of psychopathology study). SETTING: Population based cohort study in Germany. PARTICIPANTS: 1923 individuals from the general population, aged 14-24 at baseline. MAIN OUTCOME MEASURE: Incidence and persistence of subthreshold psychotic symptoms after use of cannabis in adolescence. Cannabis use and psychotic symptoms were assessed at three time points (baseline, T2 (3.5 years), T3 (8.4 years)) over a 10 year follow-up period with the Munich version of the composite international diagnostic interview (M-CIDI). RESULTS: In individuals who had no reported lifetime psychotic symptoms and no reported lifetime cannabis use at baseline, incident cannabis use over the period from baseline to T2 increased the risk of later incident psychotic symptoms over the period from T2 to T3 (adjusted odds ratio 1.9, 95% confidence interval 1.1 to 3.1; P=0.021). Furthermore, continued use of cannabis increased the risk of persistent psychotic symptoms over the period from T2 to T3 (2.2, 1.2 to 4.2; P=0.016). The incidence rate of psychotic symptoms over the period from baseline to T2 was 31% (152) in exposed individuals versus 20% (284) in non-exposed individuals; over the period from T2 to T3 these rates were 14% (108) and 8% (49), respectively. CONCLUSION: Cannabis use is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder by impacting on the persistence of symptoms.

Large (2011). "Cannabis Use and Earlier Onset of Psychosis." Arch Gen Psychiatry.

Limonero, J. T., J. Tomas-Sabado, et al. (2006). "Perceived emotional intelligence and its relation to tobacco and cannabis use among university students." Psicothema **18 Suppl**: 95-100.

The aim of this work has been to analyse the role of Perceived Emotional Intelligence (PEI) in the use of tobacco and cannabis in 133 psychology undergraduates (114 women and 19 men), all aged between 18 and 27, with a mean age of 21.52 yr. (SD= 5.42). PEI was assessed using an abbreviated version of the Trait Meta-Mood Scale (TMMS), developed by Salovey, Mayer, Goldman, Turvey and Palfai (1995) and adapted into Spanish by Fernandez-Berrocal, Extremera, and Ramos (2004). The TMMS assesses an individual's ability to perceive, understand and manage emotion. The principal results obtained point to the fact that the students who consume tobacco or cannabis present lower levels of the Repair component of the TMMS and are those who started consuming tobacco or cannabis at an earlier age. On the other hand, Emotional Clarity appears to be related to the occasional consumption of cannabis, in that the students attaining high scores were those who consumed less. The Emotional Attention component of the TMMS

is not involved in the consumption of these substances. These preliminary findings indicate the existing relationship between some components of the TMMS and the consumption of tobacco or cannabis. Nevertheless, we need to further investigate the differing implications of each one of the PEI components in the use of these substances.

Marsicano, G., C. T. Wotjak, 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.

McQueeny, T., C. B. Padula, et al. (2011). "Gender effects on amygdala morphometry in adolescent marijuana users." Behav Brain Res **224**(1): 128-134.

Adolescent developments in limbic structures and the endogenous cannabinoid system suggest that teenagers may be more vulnerable to the negative consequences of marijuana use. This study examined the relationships between amygdala volume and internalizing symptoms in teenaged chronic marijuana users. Participants were 35 marijuana users and 47 controls ages 16-19 years. Exclusions included psychiatric (e.g., mood and anxiety) or neurologic disorders. Substance use, internalizing (anxiety/depression) symptoms and brain scans were collected after 28 days of monitored abstinence. Reliable raters manually traced amygdala and intracranial volumes on high-resolution magnetic resonance images. Female marijuana users had larger right amygdala volumes and more internalizing symptoms than female controls, after covarying head size, alcohol, nicotine and other substance use ($p<0.05$), while male users had similar volumes as male controls. For female controls and males, worse mood/anxiety was

linked to smaller right amygdala volume ($p<0.05$), whereas more internalizing problems was associated with bigger right amygdala in female marijuana users. Gender interactions may reflect marijuana-related interruptions to sex-specific neuromaturational processes and staging. Subtle amygdala development abnormalities may underlie particular vulnerabilities to sub-diagnostic depression and anxiety in teenage female marijuana users.

Medina, K. L., K. L. Hanson, 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.

Medina, K. L., B. J. Nagel, et al. "Abnormal cerebellar morphometry in abstinent adolescent marijuana users." Psychiatry Res **182**(2): 152-159.

Functional neuroimaging data from adults have, in general, revealed frontocerebellar dysfunction associated with acute and chronic marijuana (MJ) use. The goal of this study was to characterize cerebellar volume in adolescent chronic MJ users following 1 month of monitored abstinence. Participants were MJ users (n=16) and controls (n=16) aged 16-18 years. Extensive exclusionary criteria included history of psychiatric or neurologic disorders. Drug use history, neuropsychological data, and structural brain scans were collected after 28 days of monitored abstinence. Trained research staff defined cerebellar volumes (including three cerebellar vermis lobes and both cerebellar hemispheres) on high-resolution T1-weighted magnetic resonance images. Adolescent MJ users demonstrated significantly larger inferior posterior (lobules VIII-X) vermis volume than controls, above and

beyond effects of lifetime alcohol and other drug use, gender, and intracranial volume. Larger vermis volumes were associated with poorer executive functioning. Following 1 month of abstinence, adolescent MJ users had significantly larger posterior cerebellar vermis volumes than non-using controls. These greater volumes are suggested to be pathological based on linkage to poorer executive functioning. Longitudinal studies are needed to examine typical cerebellar development during adolescence and the influence of marijuana use.

Medina, K. L., A. D. Schweinsburg, et al. (2007). "Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry." Neurotoxicol Teratol **29**(1): 141-152.

BACKGROUND: Converging lines of evidence suggest that the hippocampus may be particularly vulnerable to deleterious effects of alcohol and marijuana use, especially during adolescence. The goal of this study was to examine hippocampal volume and asymmetry in adolescent users of alcohol and marijuana. METHODS: Participants were adolescent (aged 15-18) alcohol (ALC) users (n=16), marijuana and alcohol (MJ+ALC) users (n=26), and demographically similar controls (n=21). Extensive exclusionary criteria included prenatal toxic exposure, left handedness, and psychiatric and neurologic disorders. Substance use, cognitive, and anatomical measures were collected after at least 2 days of abstinence from all substances. RESULTS: Adolescent ALC users demonstrated a significantly different pattern of hippocampal asymmetry ($p<.05$) and reduced left hippocampal volume ($p<.05$) compared to MJ+ALC users and non-using controls. Increased alcohol abuse/dependence severity was associated with increased right>left (R>L) asymmetry and smaller left hippocampal volumes while marijuana abuse/dependence was associated with increased L>R asymmetry and larger left hippocampal volumes. Although MJ+ALC users did not differ from controls in asymmetry, functional relationships with verbal learning were found only among controls, among whom greater right than left hippocampal volume was associated with superior performance ($p<.05$). CONCLUSIONS: Aberrations in hippocampal asymmetry and left hippocampal volumes were found for adolescent heavy drinkers. Further, the functional relationship between hippocampal asymmetry and verbal learning was abnormal among adolescent substance users compared to healthy controls. These findings suggest differential effects of alcohol and combined marijuana and alcohol use on hippocampal morphometry and the relationship between hippocampal asymmetry and verbal learning performance among adolescents.

Moore, T. H., S. Zammit, 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.

Patton, G. C., C. Coffey, et al. (2002). "Cannabis use and mental health in young people: cohort study." Bmj **325**(7374): 1195-1198.

OBJECTIVE: To determine whether cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood. DESIGN: Seven wave cohort study over six years. SETTING: 44 schools in the Australian state of Victoria. PARTICIPANTS: A statewide secondary school sample of 1601 students aged 14-15 followed for seven years. MAIN OUTCOME MEASURE: Interview measure of depression and anxiety (revised clinical interview schedule) at wave 7. RESULTS: Some 60% of participants had used cannabis by the age of 20; 7% were daily users at that point. Daily use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (1.9, 1.1 to 3.3) after adjustment for potential baseline confounders. In contrast, depression and anxiety in teenagers predicted neither later weekly nor daily cannabis use. CONCLUSIONS: Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk. Given recent increasing levels of cannabis use, measures to reduce frequent and heavy recreational use seem warranted.

Romero, J., F. Berrendero, 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., E. Garcia-Palomero, et al. (1997). "Atypical location of cannabinoid receptors in white matter areas during rat brain development." Synapse **26**(3): 317-323.

Previous evidence suggests that the endogenous cannabinoid system could emerge and be operative early during brain development. In the present study, we have explored the distribution of specific binding for cannabinoid receptors in rat brain at gestational day 21 (GD21), postnatal days 5 (PND5) and 30 (PND30), and at adult age (> 70 days after birth) by using autoradiography with [3H]CP-55,940. Our results indicated that specific binding for cannabinoid receptors can be detected in the brain of rat fetuses at GD21 in the classic areas that contain these receptors in adulthood-in particular, in the cerebellum and the hippocampus and, to a lesser extent, in the basal ganglia, several limbic structures, and cerebral cortex. The density of cannabinoid receptors in all these structures increased progressively at all postnatal ages studied until reaching the classical adult values in 70-day-old animals. Interestingly, cannabinoid receptor binding can also be detected at GD21 in regions, in which they are scarcely distributed or not located in the adult brain and that have the particularity of all being enriched in neuronal fibers. Among these were the corpus callosum, anterior commissure, stria terminalis, fornix, white matter areas of brainstem, and others. This atypical location was quantitatively high at GD21, tended to wane at PND5, and practically disappeared at PND30 and in adulthood, with the only exception being the anterior commissure, which exhibited a moderate density for cannabinoid receptors. Moreover, the binding of [3H]CP-55,940 to cannabinoid receptors in the white matter regions at GD21 seems to be functional and involves a GTP-binding protein-mediated mechanism. Thus, the activation of these receptors with an agonist such as WIN-55,212-2 increased the binding of [35S]-guanylyl-5'-O-(gamma-thio)-triphosphate, measured by autoradiography, in the corpus callosum and white matter areas of brainstem of fetuses at GD21. This increase was reversed by coincubation of WIN-55,212-2 with SR141716, a cannabinoid receptor antagonist. As this antagonist is specific for the cerebral cannabinoid receptor subtype, called CB1, we can assert that the signal found for

cannabinoid receptor binding in the fetal and early postnatal brain likely corresponds to this receptor subtype. Collectively, all these data suggest the existence of a transient period of the brain development in the rat, around the last days of the fetal period and the first days of postnatal life, in which CB1 receptors appear located in neuronal fiber-enriched areas. During this period, CB1 receptors would be already functional acting through a GTP-binding protein-mediated mechanism. After this transient period, they progressively acquire the pattern of adult distribution. All this accounts for a specific role of the endogenous cannabinoid system in brain development.

Scallet, A. C., E. Uemura, 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.

Semple, D. M., A. M. McIntosh, et al. (2005). "Cannabis as a risk factor for psychosis: systematic review." J Psychopharmacol **19**(2): 187-194.

Various lines of evidence suggest an association between cannabis and psychosis. Five years ago, the only significant case-control study addressing this question was the Swedish Conscript Cohort. Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and assessed. Using specific search criteria on Embase, PsychINFO and Medline, all studies examining cannabis as an independent risk factor for schizophrenia, psychosis or psychotic symptoms, published between January 1966 and January 2004, were examined. Additional studies were also reviewed from references found in retrieved articles, reviews, and a cited reference search (ISI-Web of Science). Studies selected for meta-analysis included: (i) case-control studies where exposure to cannabis preceded the onset of schizophrenia or schizophrenia-like psychosis and (ii) cohort studies of healthy individuals recruited before

the median age of illness onset, with cannabis exposure determined prospectively and blind to eventual diagnosis. Studies of psychotic symptoms were also tabulated for further discussion. Eleven studies were identified examining the relationship between cannabis use and psychosis. Seven were included in the meta-analysis, with a derived odds ratio (fixed effects) of 2-9 (95 % confidence interval = 2.4-3.6). No evidence of publication bias or heterogeneity was found. Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia. In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.

Shin, L. M., C. I. Wright, et al. (2005). "A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder." Arch Gen Psychiatry **62**(3): 273-281.

BACKGROUND: Previous functional neuroimaging studies have demonstrated exaggerated amygdala responses and diminished medial prefrontal cortex responses during the symptomatic state in posttraumatic stress disorder (PTSD). OBJECTIVES: To determine whether these abnormalities also occur in response to overtly presented affective stimuli unrelated to trauma; to examine the functional relationship between the amygdala and medial prefrontal cortex and their relationship to PTSD symptom severity in response to these stimuli; and to determine whether responsivity of these regions habituates normally across repeated stimulus presentations in PTSD. DESIGN: Case-control study. SETTING: Academic medical center. PARTICIPANTS: Volunteer sample of 13 men with PTSD (PTSD group) and 13 trauma-exposed men without PTSD (control group). MAIN OUTCOME MEASURES: We used functional magnetic resonance imaging (fMRI) to study blood oxygenation level-dependent signal during the presentation of emotional facial expressions. RESULTS: The PTSD group exhibited exaggerated amygdala responses and diminished medial prefrontal cortex responses to fearful vs happy facial expressions. In addition, in the PTSD group, blood oxygenation level-dependent signal changes in the amygdala were negatively correlated with signal changes in the medial prefrontal cortex, and symptom severity was negatively related to blood oxygenation level-dependent signal changes in the medial prefrontal cortex. Finally, relative to the control group, the PTSD group tended to exhibit diminished habituation of fearful vs happy responses in the right amygdala across functional runs, although this effect did not exceed our a priori statistical threshold. CONCLUSIONS: These results provide evidence for exaggerated amygdala responsivity, diminished medial prefrontal cortex

responsivity, and a reciprocal relationship between these 2 regions during passive viewing of overtly presented affective stimuli unrelated to trauma in PTSD.

Tanda, G. and S. R. Goldberg (2003). "Cannabinoids: reward, dependence, and underlying neurochemical mechanisms--a review of recent preclinical data." Psychopharmacology (Berl) **169**(2): 115-134.

BACKGROUND AND RATIONALE: Starting with the discovery of an endogenous brain cannabinoid system with specific receptors and endogenous ligands, research in the cannabinoid field has accelerated dramatically over the last 15 years. Cannabis is the most used illicit psychotropic substance in the world but only recently have reliable preclinical models become available for investigating the rewarding and dependence-producing actions of its psychoactive constituent, delta9-tetrahydrocannabinol (THC). OBJECTIVES: The goal of this review is to examine the various animal models currently available that are being used to facilitate our understanding of the rewarding and dependence-producing actions of cannabinoids, which are central to their abuse liability, and of the neurochemical mechanisms that may underlie these actions of cannabinoids. RESULTS AND CONCLUSIONS: Recent demonstrations that strong and persistent intravenous self-administration behavior can be obtained in squirrel monkeys using a range of THC doses that are in agreement with the total intake and the single doses of THC normally self-administered by humans smoking marijuana cigarettes provides a reliable and direct tool for assessing the reinforcing effects of THC that are central to its abuse liability. In addition, recent demonstrations of persistent intravenous self-administration of synthetic cannabinoid CB1 receptor agonists by rats and mice and the development of genetically modified mice lacking specific cannabinoid receptors provide convenient rodent models for exploring underlying neurochemical mechanisms. Repeated demonstrations in rats that THC and synthetic CB1 agonists can induce conditioned place preferences or aversions, depending on details of dose and spacing, can reduce the threshold for intracranial self-stimulation behavior under certain conditions, and can serve as effective discriminative stimuli for operant behavior provide less direct, but more rapidly established, measures for investigating the rewarding effects of cannabinoids. Finally, there have been numerous recent reports of major functional interactions between endogenous cannabinoid, opioid, and dopaminergic neurotransmitter systems in areas such as analgesia, physical dependence and tolerance development, and drug reinforcement or reward. This provides an opportunity to search for drugs with the beneficial therapeutic effects of currently available cannabinoids or opioids but without undesirable adverse effects such as abuse liability.

Tapert, S. F., A. D. Schweinsburg, et al. (2007). "Functional MRI of inhibitory processing in abstinent adolescent marijuana users." Psychopharmacology (Berl) **194**(2): 173-183.

BACKGROUND: Marijuana intoxication appears to impair response inhibition, but it is unclear if impaired inhibition and associated brain abnormalities persist after prolonged abstinence among adolescent users. We hypothesized that brain activation during a go/no-go task would show persistent abnormalities in adolescent marijuana users after 28 days of abstinence. METHODS: Adolescents with (n = 16) and without (n = 17) histories of marijuana use were compared on blood oxygen level dependent (BOLD) response to a go/no-go task during functional magnetic resonance imaging (fMRI) after 28 days of monitored abstinence. Participants had no neurological problems or Axis I diagnoses other than cannabis abuse/dependence. RESULTS: Marijuana users did not differ from non-users on task performance but showed more BOLD response than non-users during inhibition trials in right dorsolateral prefrontal, bilateral medial frontal, bilateral inferior and superior parietal lobules, and right occipital gyri, as well as during "go" trials in right prefrontal, insular, and parietal cortices ($p < 0.05$, clusters > 943 microl). Differences remained significant even after controlling for lifetime and recent alcohol use. CONCLUSIONS: Adolescent marijuana users relative to non-users showed increased brain processing effort during an inhibition task in the presence of similar task performance, even after 28 days of abstinence. Thus, increased brain processing effort to achieve inhibition may predate the onset of regular use or result from it. Future investigations will need to determine whether increased brain processing effort is associated with risk to use.

Trezza, V., V. Cuomo, et al. (2008). "Cannabis and the developing brain: insights from behavior." Eur J Pharmacol **585**(2-3): 441-452.

The isolation and identification, in 1964, of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, opened the door to a whole new field of medical research. The exploration of the therapeutic potential of THC and other natural and synthetic cannabinoid compounds was paralleled by the discovery of the endocannabinoid system, comprising cannabinoid receptors and their endogenous ligands, which offered exciting new insights into brain function. Besides its well-known involvement in specific brain functions, such as control of movement, memory and emotions, the endocannabinoid system plays an important role in fundamental developmental processes such as cell proliferation, migration and differentiation. For this reason, changes in its activity during stages of high neuronal plasticity, such as the perinatal and the adolescent period, can have long-lasting neurobehavioral consequences. Here, we summarize human and animal studies examining the behavioral and neurobiological effects of in utero and adolescent exposure to cannabis. Since cannabis preparations are widely used and abused by young people, including pregnant women, understanding how cannabinoid compounds affect the developing brain,

leading to neurobehavioral alterations or neuropsychiatric disorders later in life, is a serious health issue. In addition, since the endocannabinoid system is emerging as a novel therapeutic target for the treatment of several neuropsychiatric diseases, a detailed investigation of possible adverse effects of cannabinoid compounds on the central nervous system (CNS) of immature individuals is warranted.

Van Laere, K., K. Goffin, 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.

Veen, N. D., J. P. Selten, et al. (2004). "Cannabis use and age at onset of schizophrenia." Am J Psychiatry **161**(3): 501-506.

OBJECTIVE: The purpose of the study was to assess the independent influences of gender and cannabis use on milestones of early course in schizophrenia. METHOD: In this population-based, first-contact incidence study conducted in The Hague, the Netherlands, patients (N=133) were interviewed with the Comprehensive Assessment of Symptoms and History, and key informants were interviewed with the Instrument for the Retrospective Assessment of the Onset of Schizophrenia. Milestones of early course were 1) first social and/or occupational dysfunction, 2) first psychotic

episode, and 3) first negative symptoms. RESULTS: Male patients were significantly younger than female patients at first social and/or occupational dysfunction, first psychotic episode, and first negative symptoms. Cannabis-using patients were significantly younger at these milestones than were patients who did not use cannabis. Multivariate analyses showed that cannabis use, but not gender, made an independent contribution to the prediction of age at first psychotic episode: male cannabis users were a mean of 6.9 years younger at illness onset than male nonusers. In contrast, age at first social and/or occupational dysfunction and the risk of developing negative symptoms before the first contact with a physician for treatment of possible psychotic disorder were predicted by gender, but not by cannabis use. CONCLUSIONS: The results indicate a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenia patients. Additional studies examining this possibly causal relationship are needed.

Wesley, M. J., C. A. Hanlon, 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.

Winters, K. C. and C. Y. Lee (2008). "Likelihood of developing an alcohol and cannabis use disorder during youth: association with recent use and age." Drug Alcohol Depend **92**(1-3): 239-247.

AIM: We extend the literature on the association of early onset of drug use and estimated risk for developing a substance use disorder (SUD) by investigating the risk that recent onset of alcohol and cannabis use confers for developing a substance use disorder at each chronological age of

adolescence and young adulthood (12-21-years-old). DESIGN: Using 2003 data from the National Survey on Drug Use and Health [Substance Abuse Mental Health Service Administration (SAMHSA), 2004. Overview of Findings from the 2003 National Survey on Drug Use and Health. Office of Applied Studies, NSDUH Series H-24, DHHS Publication No. SMA-04-3963, Rockville, MD], we computed separate risk indices for developing an alcohol and cannabis use disorder for recent (prior 2 years) alcohol and cannabis users, respectively, at each age from 12 to 21 years of age, and compared estimated risk to recent onsets users among respondents aged 22-26. FINDINGS: The results indicated that the teenage years were strongly linked to an elevated risk status. The odds ratio (OR) of having a prior year alcohol use disorder (AUD) among recent onset alcohol users was significantly elevated for youth at ages 14, 16, 17 and 18 (range of ORs=2.0-2.1) compared to the estimated risk for AUD among recent onset users aged 22-26. For cannabis, we obtained significantly elevated ORs for a cannabis use disorder (CUD) at each of teenage years (ages 12-18; range of ORs=3.9-7.2), when compared to older recent onset users (aged 22-26). CONCLUSIONS: These data provide further epidemiological support that adolescence is a particularly vulnerable period for developing a SUD.

Yucel, M., N. Solowij, 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.

Yurgelun-Todd, D. A. and W. D. Killgore (2006). "Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study." Neurosci Lett **406**(3): 194-199.

An emerging theory of adolescent development suggests that brain maturation involves a progressive "frontalization" of function whereby the prefrontal cortex gradually assumes primary responsibility for many of the cognitive processes initially performed by more primitive subcortical and limbic structures. To test the hypothesis of developmental frontalization in emotional processing, we analyzed the correlation between age and prefrontal cortex activity in a sample of 16 healthy adolescents (nine boys; seven girls), ranging in age from 8 to 15 years, as they viewed images of fearful and happy faces while undergoing functional magnetic resonance imaging (fMRI). During fear perception, age was significantly positively correlated with greater functional activity within the prefrontal cortex, whereas no significant relationship was evident between age and activity in the amygdala. Consistent with previous gender-related findings, age was significantly correlated with bilateral prefrontal activity for the sample of females, but was only significantly related to right prefrontal activity for the males. In contrast, similar age-related correlations were not evident during the perception of happy faces. These results suggest that the maturation of threat-related emotional processing during adolescence is related to the progressive acquisition of greater functional activity within the prefrontal cortex. The hypothesis of age related decreases in amygdala activity was not supported, but may have been due to low signal-to-noise and inadequate power in the present sample to resolve subtle changes in this small structure.

Zammit, S., P. Allebeck, et al. (2002). "Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study." Bmj **325**(7374): 1199.

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.