

## Marijuana interaction with methamphetamine addiction

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### Background

The use of marijuana has long been recognized as an antecedent to the use of 'hard drugs' such as methamphetamine. This gateway hypothesis has been roundly debated for many years and attributed to social factors, 'peer pressure,' the availability of other drugs in settings in which marijuana is purchased and used. Twin studies have documented the strength of the association between early marijuana use (prior to age 17) and subsequent drug use. In twins discordant for early marijuana use, the marijuana using twin was more than four times more likely to use and become dependent on stimulants (Lynski 2003).

The sheer magnitude of marijuana use among adolescents should give us pause to consider the effects of this psychoactive drug on the future of our children. Nearly half of 12<sup>th</sup> graders have tried marijuana, and 6% admit to daily use (Johnson 2005), and these are the kids who stayed in school. The rate of marijuana use among high school drop outs is likely to be even higher. The marijuana they are using is also much more potent than the 'Iowa Ditch' that grew on the side of the road outside Des Moines in the late 60's. Marijuana now is grown in high tech growing labs, with TCH content as high as 15% (Mc Laren 2008).

This cannabis use is often occurring in adolescence, a time of significant neurologic maturation in areas of executive function, including decision making and impulse control. While multiple predisposing factors predict later drug use, including parental drug use, child abuse, conduct disorder, and novelty seeking as a personality trait, the use of cannabis in adolescence and early adulthood emerged as the strongest risk factor for later involvement in other illicit drugs (Fergusson 2008). Even a small increase in risk of addiction becomes socially significant when 50% of high school seniors are trying marijuana.

In addition, marijuana has effects on the brain in many of the same areas that methamphetamine changes, including the hippocampus and many areas of the frontal lobes so that injury to these areas caused by initial use of marijuana may be amplified by subsequent and concurrent use of methamphetamine. While scientists prefer to study isolated drug effects for the intellectual satisfaction of knowing precisely how various systems are affected, human behavior rarely cooperates. We are asked to predict the consequences of drug use based on single drug studies, when single drug use is the exception, rather than the norm.

Medication interactions have often been clinically significant in the context of prescription medications. These interactions are likely to be even more significant in the case of two very popular psychoactive drugs of unknown dose and purity used under conditions of concurrent exposure to alcohol, tobacco, and club drugs in people of

variable age and underlying health. This chapter will focus in the interaction between marijuana and methamphetamine on brain function and behavior, with an eye to the development and clinical course of dependence on methamphetamine.

### Biochemical interactions

Recent findings have revealed a vast neurotransmission system dubbed the endocannabinoid system due to its sensitivity to cannabinoid stimulation. The endocannabinoid system has been the subject of vigorous research for many years, not just for its interest as related to a drug of abuse, but also for its importance to understanding neurophysiology in general. The endocannabinoid system is in place not just so that people can get high on pot, but also for numerous neurologic processes of neuromodulation. It influences not only the reward system, but also appetite, learning and memory, and executive functions including impulse control and decision making. We can expect that use of marijuana, particularly at critical developmental stages, prenatal exposure and adolescent drug use, would exert changes in these functions, perhaps long lasting changes.

The endocannabinoid system has a complex relationship to the reward system of the brain, changing the sensitivity of the neural structures related to the sensation of pleasure. Interactions between cannabinoid receptors and responsiveness to alcohol (Lopez-Moreno 2008), heroin, (Solinas 2007) and methamphetamine (Landa 2006) have been delineated, with vast implications for the potential addictiveness of these substances. Since marijuana is often used in the context of concurrent use of other drugs, these interactions must be clearly understood in this time of increasing marijuana use.

Marijuana is also a common drug of abuse in the adolescent age range, from age 10-19, and so its impact on adolescent neurodevelopment must be taken into account as well. Functions such as judgment, impulse control, predicting the future consequences of an action, and delayed gratification, are being established. Such executive functions are processed in the frontal and temporal lobes, in areas that are maturing in adolescence. It is likely the psychoactive drugs have an impact on the maturation of these areas, with profound effects on the mature personality.

### Impact on the Reward Circuit

Marijuana has first and foremost effects on the reward circuit of the brain resulting in a sensation of euphoria and generalized well being. Rats treated with a cannabinoid CB1 agonist showed significant increases in dopamine release in the nucleus accumbens (Fadda 2006). Chronic exposure to TCH has been found to increase the length and number of dendritic branches in the shell of nucleus accumbens and also in the medial prefrontal cortex in rats (Kolb 2006). Cannabinoid exposure then seems to increase the sensitivity of the reward circuit to dopamine stimulation at a cellular level. This

heightened neural capacity for a dopamine response has its basis in changes in the neuroanatomy of the nucleus accumbens.

Specifically stimulation of the CB1 cannabinoid receptors primes the reward pathway and sensitizes the system to be more responsive to methamphetamine stimulation (Landa 2006) and to a moderate dose of alcohol (Lopez-Moreno 2008) in a persistent manner. The effect is not just a product of acute intoxication, but is rather a change in the neuroanatomy of the nucleus accumbens. This sensitization could result in a situation in which even low doses of lower purity methamphetamine would be potently rewarding in individuals who have smoked marijuana prior to, or concurrent with, their first experience with methamphetamine.

This finding alone could help explain the widely differing 'addiction rate' among methamphetamine users, depending on the social context of their drug use. Lower addiction rates are often seen in those who use methamphetamine occupationally to enhance their work performance, (ie, military personnel), or medically (ie for obesity) vs those using it recreationally (Eliyahu 2007). While still experiencing the alertness, endurance, or anorectic aspects of methamphetamine, these individuals may be much less sensitive to the euphoric effects of the drug in the absence of previous or concurrent marijuana use.

#### Executive Function

Marijuana has also been found to have significant effects on the functioning of the frontal lobe as it relates to executive function including decision making and impulse control. This is of concern as methamphetamine also directly impacts many of the same areas. The use of marijuana may set the anatomic stage for the behavioral and personality changes, including the occupational failure and interpersonal strife so often seen in methamphetamine addiction. These effects would likely be exaggerated in the case of adolescent users who are still in the process of maturing these brain structures. The combined forces of marijuana use and methamphetamine's effects could amplify the frontal lobe injury that so often complicates substance abuse treatment.

Impairment of the frontal lobe areas involved with executive function has been well documented in heavy marijuana users. Bolla in 2002 correlated marijuana use to poor performance in problem solving, learning, inhibition and reaction time in heavy users who were abstinent for 28 days. To delineate the neurologic basis for this finding, the same group compared abstinent marijuana users with controls under PET scanning (Bolla 2005) and found that the marijuana users showed less activation in the right lateral orbitofrontal cortex (OFC) and the right dorsolateral prefrontal cortex (DLPFC) than the Control group on the Iowa Gambling Task. Heavy marijuana users did not perform as well as non-users on this measurement of executive function and decision making skills.

More recent use of marijuana has far more significant effects on the functioning of these executive functions. **Current users have significantly reduced white matter volumes**

**in the parahippocampal gyrus and left parietal lobe on MRI scanning (Matochik 2005).** Yurgelun-Todd (1998) demonstrated anterior cingulate and prefrontal dysfunction in marijuana users at 24 hours abstinence that partially normalized after 28 days, though anterior cingulate function was still significantly impaired at 28 days abstinence. Exposure to marijuana, even remotely – after 28 days of abstinence- compromises inhibitory control and executive function. The degree of cognitive impairment is even greater in the presence of acute intoxication, which is the more common context of an individual's first use of methamphetamine.

In tests of inhibition processing, fMRI testing was done at 28 days abstinence during a Stroop task involving inhibition of the dominant process of reading words to instead give the colors of words printed in incongruent ink. The cortical activation pattern of the heavy marijuana users reflected reduced activation of the anterior cingulate and more widespread dorsolateral prefrontal lobe compensatory activity (Gruber 2005). Marijuana users are thus more dependent on dorsolateral prefrontal lobe activity to be successful in inhibitory processing.

Methamphetamine use significantly compromises these 'back-up' areas and further impairs decision making and impulse control. The anatomic basis for this reduced impulse control is demonstrated by several fMRI studies involving human methamphetamine users attempting inhibitory control tasks under fMRI monitoring. Anterior cingulate and dorsolateral prefrontal cortex activity has been shown to be essential in response inhibition and impulse control (Garavan 2002). Studies have demonstrated reduced task related activation of the anterior cingulate gyrus in methamphetamine users (Hwuang 2006). Paulus (2002) studied methamphetamine addicts in early recovery by fMRI as they did a two choice prediction task and a two choice response task. He demonstrated less activation of dorsolateral prefrontal cortex and failure to activate ventromedial prefrontal cortex during this decision making task.

These changes appear to be more than just a pharmacologic effect of methamphetamine. There appears to be some cellular destruction of a more permanent nature going on as well. The massive releases of neurotransmitter caused by methamphetamine use result in high levels of nitrogen and oxygen free radical formation (Acikgov 2000). These free radicals are formed by the metabolism of methamphetamine, and also by the breakdown of the huge amounts of mono-amine neurotransmitters that have been released both intra and extra cellularly. These mono-amine neurotransmitters must also be broken down, and MAO, the usual enzyme to do that is inhibited by methamphetamine. Alternative metabolic routes are used resulting in the generation of large amounts of hydroxyl free radicals nitric oxide and peroxy nitrite, which are extremely toxic to brain cells (Jeng 2006).

Free radical compounds denature proteins, damage DNA and generally wreak havoc in the areas of the brain in which they are concentrated (Cubbels 1994). Because most of the neurotransmitters are released in the midbrain, nucleus accumbens, and striatum, and in the prefrontal cortex, those areas are disproportionately affected by methamphetamine abuse with progressively worsening cognitive and executive function. (Li 2008) Nordhal

(2005) did MRS (magnetic resonance spectroscopy) measures of N-acetylaspartate-creatine and phosphocreatine (NAA/Cr), choline-creatine and phosphocreatine (Cho/Cr), and choline-N-acetylaspartate (Cho/NAA) ratios in the anterior cingulate cortex of abstinent meth users and found evidence of cellular compromise that only partially corrected after prolonged periods (years) of abstinence.

These changes have implications for addiction recovery and relapse as function in crucial frontal lobe areas is compromised. Methamphetamine users had significantly impaired inhibitory control on a Stop Signal Test measuring latency to inhibit a motor response (Montorosso 2005). Impulsivity is also related to impaired perception of time intervals, with methamphetamine abusers consistently overestimating time intervals and accelerating fingertaps (Whittman 2007). This 'trigger fingered' impaired capacity for inhibitory processing would reduce the ability to resist impulses, delay gratification, and thus increase the likelihood of relapse. In a landmark study, Paulus (2005) showed that those addicts who eventually relapsed had markedly reduced activation of the dorsolateral prefrontal cortex and anterior cingulate gyrus compared to addicts who did not subsequently relapse. Subjects were followed for up to three years to observe for relapse, and the predictive power of this functional measure of brain activity in these areas was impressive.

### Memory and Learning

In addition to its direct effects on the reward circuit and executive function, marijuana has significant effects on the hippocampus and various areas of the frontal lobe that could also affect memory and learning, in a way that could increase the likelihood that a person would use and become dependent on methamphetamine, and increase the neurologic impact of their methamphetamine use. A hippocampus, for instance, that is already compromised by marijuana use might be more vulnerable to the neurotoxic effects of methamphetamine.

Long and short term heavy cannabis use leads to impaired verbal memory and fluency, attention and psychomotor speed at 24 hours after last use (in the absence of intoxication) which has implications for occupational performance and driving safety (Messinis 2006). Short term abstinent cannabis users had deficits in verbal fluency, visual recognition, delayed visual recall, and short- and long-interval prospective memory. There were no differences for immediate visual recall (McHale 2008) Recent users also demonstrated abnormal brain activation patterns during a working memory task, with recruitment of additional regions not typically used for this type of working memory (Kanayama 2004)

Even after 28 days of abstinence performance was significantly worse in both long and short term memory for heavy users. Nestor (2008) demonstrated that cannabis using adults had significantly lower activity in the superior temporal gyrus, and several areas of the frontal lobe compared to controls during learning in a name - face task. Results also showed that cannabis using adults had significantly lower activity in the frontal and

temporal lobes, and higher activity in the right parahippocampal gyrus during learning. These changes indicate functional deficits and compensatory processes in cannabis users.

Heavy use is defined as daily smoking of at least one joint per day, a condition met by about 6% of all high school seniors (Johnson 2005). While moderate recreational users of marijuana had normal performance on tests of working memory and selective attention, cannabis users displayed a significant alteration in brain activity in the left superior parietal cortex after 10 days of abstinence (Jager 2006) indicating that even moderate use has an effect on brain function. But again, those same frontal lobe structures compromised by marijuana use may be more susceptible to the more serious neurotoxic effects of methamphetamine when it is used after or concurrent with marijuana.

**Conversely, concurrent marijuana use in methamphetamine users is associated with marked changes in brain activation patterns during a auditory continuous performance task with decreased activation of the orbitofrontal, parahippocampal and temporal lobes when compared to meth users who did not use marijuana (Voytek 2005).**

The toxicity of methamphetamine is profound, and the cognitive changes seen in methamphetamine addicts are far more pronounced than those associated with marijuana. Methamphetamine abusers have cognitive deficits, abnormal metabolic activity and structural deficits in frontal, temporal and para hippocampal cortices, and reduced hippocampal volume. The magnitude of disruption in these areas is correlated with cognitive deficits in attention, memory, and executive function in many domains (London 2005, Thompson 2004). Woods (2007) did a meta-analysis of available data on the neuropsychological effects of MA abuse/dependence. They revealed deficits in episodic memory, executive functions, information processing speed, motor skills, language, and visuoconstructional abilities in methamphetamine users that was far more prominent and easily measurable than those found in marijuana users. Primate studies of methamphetamine exposed animals have demonstrated profound impairment in cognitive function, particularly spatial working memory and long term associative memory that were related to dopamine deficiencies in the prefrontal cortex, cingulate cortex, and striatum (Castner 2005). These cognitive deficits greatly impair ability to participate in cognitive behavioral therapy as a component of rehabilitation. Memory, attention span, and information processing slowly improve over the course of 12-18 months, requiring prolonged treatment at great cost.

### Developmental Considerations

A large number of the people who are initiating methamphetamine use are in the adolescent age group, with an average age of 19 (Brecht 2006) and nearly all of them use alcohol, tobacco, and /or marijuana prior to first use of methamphetamine. Adolescents are more likely to smoke or snort meth than to inject it at their first use (Wood 2008) and to do so in the context of marijuana use. Youth and young adults are in a developmental phase in which the rate of maturation and development of the brain that is exceeded only by that of infancy and early childhood. In this extremely important developmental

window, our teenagers are exposing themselves to neurotoxic drugs that will affect their lives and opportunities significantly.

The vulnerability of the adolescent brain is just beginning to be understood. The endo-cannabinoid inhibition of synaptic function in the hippocampus was more pronounced in adolescent rats than adults, which may account for the increased sensitivity of adolescent animals to TCH induced memory impairment (Kang-Park 2007). Adolescent THC exposure resulted in CB1/G protein uncoupling in the hippocampus that persisted into adulthood (Rubino 2008) suggesting that a cannabinoid related disconnection can be expressed in adulthood as a developmental deficit. These animal studies support the conclusion that the neurologic changes seen with human marijuana use do not likely precede drug use (as predisposing factors), but are in fact consequences of adolescent marijuana use in normal teens.

Normal adolescent neuro-development includes extensive remodeling of the frontal lobes occurring between the ages of 12 and 21 (Gogtay 2004, Shaw 2008). This process involves myelination of white matter tracts and synaptic pruning in areas of the frontal lobes involved in executive function, including judgment, prediction of future consequences, inhibitory processes, and impulse control. All of these functions are important when resisting peer pressure and controlling alcohol and drug intake.

Tapert(2007) measured brain function by an fMRI technique during a go/no-go task indicating inhibitory control in adolescent marijuana users compared to controls (controlled for alcohol intake). Marijuana users performed as well as non-users, but recruited additional cortical areas in the frontal and parietal lobes, in order to perform the task. These changes were noted after 28 days of abstinence and thus reflect a persistent finding. These findings suggest that a key capability of executive function, inhibition of impulses is impaired not just when an individual is intoxicated, as classical gate-way theories have posited, but for weeks afterward, during a developmental period in which forebrain maturation is taking place.

The effects of marijuana on other cognitive functions have also been found to be more significant in adolescents than in adults. Memory and learning are critical functions for academic and occupational success and have been found to be distorted in adolescent marijuana users. Schweinsburg (2008) showed that marijuana using adolescents, after one month of abstinence, performed normally on a spatial working memory assessment, but had markedly different cortical activation patterns reflecting different attention mental strategies used to achieve the same end result. In another fMRI study of marijuana using adolescents studied in a spatial working memory task, users showed changes in recruitment of the anterior cingulate gyrus, temporal cortex, and hippocampal gyrus, again at 28 days abstinence (Padula 2007).

Not all of the studies have shown equivalent performance for marijuana using adolescents. Medina and Tapert's group has done extensive research into the state of the hippocampus in adolescents who use marijuana, alcohol, and both, and found significant differences in hippocampal volumes. They also demonstrated, after a month of monitored

abstinence, marijuana users had slower psychomotor speed, poorer complex attention, poorer story memory, and reduced planning and sequencing ability, all correlated with lifetime marijuana exposure and controlling for alcohol use (Medina and Hanson 2007). Smaller hippocampal volumes in the marijuana using youth were also associated with more depressive symptoms on the Beck Depression Inventory (Medina and Nagel 2007).

These studies suggest long lasting changes in the neuroanatomy of important areas in the frontal lobes related to the acquisition of executive functions. If these areas do not mature properly during adolescence, a developmental window of opportunity is missed. We often find in the course of working with these young people that their emotional maturity matches the chronologic age at which they first began abusing substances. One of the challenges of addiction treatment is encouraging our clients to 'grow up'. Subsequent maturation can and does occur, but with a great deal more effort on the part of both client and therapist than would be the case with normal adolescence. We must seriously consider such neuroanatomic findings before we blithely accept the fact that 50% of our young people are using pot.

#### Prenatal exposure to Pot

Our final concern will be with the issue of prenatal exposure to marijuana and its effects on the unborn child. The young adults and adolescents we have been describing are predominantly of child-bearing age. In Barcelona Spain, 5.3% of newborns had a meconium screen positive for marijuana exposure, while only 1.7% of mothers admitted to using it during pregnancy (Lozano 2007). In the United States, 6% of newborns in four major cities were positive for marijuana in 2003, an increase from 3% in 1993 (Derauf 2007).

Parental substance abuse is a well known risk factor for the development of substance abuse in children. Children witnessing the substance abuse of a parent are much more likely to view substance abuse as normal and acceptable behavior. They are also likely to have experienced numerous adverse childhood events including abuse and neglect, which also predispose to addiction as they grow older (Dube 2003).

But there is a little more to it than that. Prenatal exposure to marijuana predicted early use of marijuana by offspring by the age of 14 even after controlling for the child's current alcohol and tobacco use, pubertal stage, sexual activity, delinquency, peer drug use, family history of drug abuse and characteristics of the home environment including parental depression, current drug use and strictness/supervision (Day 2006). Prenatal exposure to marijuana produces changes in the neurologic make-up of the child that independently predispose to later substance abuse.

The endocannabinoid system is key to the early development of the central nervous system, serving as a traffic cop directing the proliferation, migration, differentiation, and synapse formation of functional neural circuits throughout the developing brain (Harkany 2007). Rats exposed to THC prenatally had increased anxiety scores measure by peeps when removed from the nest, inhibited juvenile social interaction, and play among

adolescents, extending into adulthood with impaired elevated maze performance (Trezza 2008). Emotional development is impaired in humans also. Prenatal marijuana exposure in the first and third trimesters predicted significantly increased levels of depressive symptoms in 10 year old children (Gray 2005).

Prenatal marijuana exposure is also associated with cognitive deficits in children as measured by the Stanford- Binet verbal reasoning and short term memory scales at age 3, 4, and 6 (Fried 1990, Day 1994, Goldschmidt 2008) which is a non-environmental risk factor for substance abuse. More significantly, prenatal marijuana exposure is associated with impaired executive function and impulse control at age 9-12 (Fried 1998), with poorer Wide Range Achievement Test-Revised (WRAT-R) reading comprehension and spelling scores at age 10 (Goldschmidt 2004) and with higher order mental function, analysis and integration at age 13-16 (Fried 2003). These deficits are strong predisposing factors placing children at risk for substance abuse in those vulnerable adolescent years, even if their role models are drug free (Karacostas 1993).

## Conclusion

Marijuana use is a common antecedent to methamphetamine use, and both drugs affect similar structure in the brain. While methamphetamine is by far the more toxic of the two, causing significant functional disability that may take months or even years of therapy to reverse, marijuana may contribute more to this injury than has been previously acknowledged. Marijuana sensitizes the reward circuit to respond to methamphetamine more robustly, and predispose to addiction to methamphetamine. Marijuana also appears to aggravate the injury to cognitive structures by impairing the function of the key areas involved in memory and higher order thinking capacity. These effects are magnified even further when drug use occurs in adolescence, as the brain is going through a major remodeling in preparation for adulthood. When key maturation events fail to occur, there may not be an opportunity for a re-do.

Clearly the scientific findings related to marijuana need to be evaluated whenever the legalization of this drug is considered. The long term implications of the widespread use of any psychoactive drug should be carefully thought out. If alcohol were up for evaluation as a potential addition to our society, the data would probably argue for its exclusion. Alcohol causes untold social harm and personal tragedy. Do we really need another intoxicant in our already overly intoxicated society?

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