Does Marijuana Affect the Brain Reading Recommendations:

Reading 1 Title:

Potency Trends of D9 -THC and Other Cannabinoids in Confiscated Cannabis Preparations from 1993 to 2008*

Abstract:

The University of Mississippi has a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with cannabis, including the Potency Monitoring (PM) program, which provides analytical potency data on cannabis preparations confiscated in the United States. This report provides data on 46,211 samples seized and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993–2008. The data showed an upward trend in the mean D9 -tetrahydrocannabinol (D9 -THC) content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. Hashish potencies did not increase consistently during this period; however, the mean yearly potency varied from 2.5–9.2% (1993–2003) to 12.0–29.3% (2004–2008). Hash oil potencies also varied considerably during this period (16.8 € 16.3%). The increase in cannabis preparation potency is mainly due to the increase in the potency of nondomestic versus domestic samples.

Reference:


Reading 2 Title:

Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings

Abstract:

Monitoring the Future (MTF) is a long-term study of American adolescents, college students, and adults through age 50. It has been conducted annually by the University of Michigan’s Institute for Social Research since its inception in 1975 and is supported under a series of investigator-initiated, competing research grants from the National Institute on Drug Abuse.

Reference:


Reading 3 Title:

Elevated brain cannabinoid CB₁ receptor availability in post-traumatic stress disorder: a positron emission tomography study
Abstract:

Endocannabinoids and their attending cannabinoid type 1 (CB₁) receptor have been implicated in animal models of post-traumatic stress disorder (PTSD). However, their specific role has not been studied in people with PTSD. Herein, we present an in vivo imaging study using positron emission tomography (PET) and the CB₁-selective radioligand [¹¹C]OMAR in individuals with PTSD, and healthy controls with lifetime histories of trauma (trauma-exposed controls (TC)) and those without such histories (healthy controls (HC)). Untreated individuals with PTSD (N=25) with non-combat trauma histories, and TC (N=12) and HC (N=23) participated in a magnetic resonance imaging scan and a resting PET scan with the CB₁ receptor antagonist radiotracer [¹¹C]OMAR, which measures the volume of distribution (Vₜ) linearly related to CB₁ receptor availability. Peripheral levels of anandamide, 2-arachidonoylglycerol, oleylethanolamide, palmitolethanolamide and cortisol were also assessed. In the PTSD group, relative to the HC and TC groups, we found elevated brain-wide [¹¹C]OMAR Vₜ values (F(2,53)=7.96, P=0.001; 19.5% and 14.5% higher, respectively), which were most pronounced in women (F(1,53)=5.52, P=0.023). Anandamide concentrations were reduced in the PTSD relative to the TC (53.1% lower) and HC (58.2% lower) groups. Cortisol levels were lower in the PTSD and TC groups relative to the HC group. Three biomarkers examined collectively—OMAR Vₜ, anandamide and cortisol—correctly classified nearly 85% of PTSD cases. These results suggest that abnormal CB₁ receptor-mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder.

Reference:


Reading 4 Title:

Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms.

Abstract:

Cannabis is the most widely used illicit drug globally, and users are at increased risk of mental illnesses including psychotic disorders such as schizophrenia. Substance dependence and schizophrenia are both associated with dopaminergic dysfunction. It has been proposed, although never directly tested, that the link between cannabis use and schizophrenia is mediated by altered dopaminergic function. We compared dopamine synthesis capacity in 19 regular cannabis users who experienced psychotic-like symptoms when they consumed cannabis with 19 nonuser sex- and age-matched control subjects. Dopamine synthesis capacity (indexed as the influx rate constant [Formula: see text] ) was measured with positron emission tomography and 3,4-dihydroxy-6-[(18)F]-fluoro-l-phenylalanine ([(18)F]-DOPA). Cannabis users had reduced dopamine synthesis capacity in the striatum (effect size: .85; t36 = 2.54, p = .016) and its associative (effect size: .85; t36 = 2.54, p = .015) and limbic subdivisions (effect size: .74; t36 = 2.23, p = .032) compared with control subjects. The group difference in dopamine synthesis capacity in cannabis users compared with control subjects was driven by those users meeting cannabis abuse or
dependence criteria. Dopamine synthesis capacity was negatively associated with higher levels of cannabis use ($r = -0.77$, $p < 0.001$) and positively associated with age of onset of cannabis use ($r = 0.51$, $p = 0.027$) but was not associated with cannabis-induced psychotic-like symptoms ($r = 0.32$, $p = 0.19$). These findings indicate that chronic cannabis use is associated with reduced dopamine synthesis capacity and question the hypothesis that cannabis increases the risk of psychotic disorders by inducing the same dopaminergic alterations seen in schizophrenia.

Reference:

**Reading 5 Title:**

Deficits in striatal dopamine release in cannabis dependence

**Abstract:**

Most drugs of abuse lead to a general blunting of dopamine release in the chronic phase of dependence, which contributes to poor outcome. To test whether cannabis dependence is associated with a similar dopaminergic deficit, we examined striatal and extrastriatal dopamine release in severely cannabis-dependent participants (CD), free of any comorbid conditions, including nicotine use. Eleven CD and 12 healthy controls (HC) completed two positron emission tomography scans with $[^{11}\text{C}]$-PHNO, before and after oral administration of d-amphetamine. CD stayed inpatient for 5–7 days prior to the scans to standardize abstinence. Magnetic resonance spectroscopy (MRS) measures of glutamate in the striatum and hippocampus were obtained in the same subjects. Percent change in $[^{11}\text{C}]$-PHNO-binding potential ($\Delta BP_{\text{ND}}$) was compared between groups and correlations with MRS glutamate, subclinical psychopathological and neurocognitive parameters were examined. CD had significantly lower $\Delta BP_{\text{ND}}$ in the striatum ($P=0.002$, effect size (ES)=1.48), including the associative striatum ($P=0.003$, ES=1.39), sensorimotor striatum ($P=0.003$, ES=1.41) and the pallidus ($P=0.012$, ES=1.16). Lower dopamine release in the associative striatum correlated with inattention and negative symptoms in CD, and with poorer working memory and probabilistic category learning performance in both CD and HC. No relationships to MRS glutamate and amphetamine-induced subclinical positive symptoms were detected. In conclusion, this study provides evidence that severe cannabis dependence—without the confounds of any comorbidity—is associated with a deficit in striatal dopamine release. This deficit extends to other extrastriatal areas and predicts subclinical psychopathology.

Reference:

**Reading 6 Title:**
Balanced modulation of striatal activation from D2 /D3 receptors in caudate and ventral striatum: Disruption in cannabis abusers.

Abstract:

Proper communication between dorsal caudate (CD) and ventral striatum (VS) is likely to be crucial for on-time responses and its disruption might result in impulsivity. Here, we used functional magnetic resonance imaging (fMRI) with a sensorimotor reaction time task and positron emission tomography (PET) with [(11)C]raclopride in 14 healthy controls and 18 cannabis abusers to contrast the modulation of striatal fMRI responses by dopamine receptors (D2 /D3 R) in CD and VS. In controls, we show that the fMRI signals in VS that occurs concomitantly with on-time responses showed opposite modulation from D2 /D3 R in CD (inhibitory) and D2 /D3 R in VS (stimulatory). In contrast, this modulation was not significant in cannabis abusers. Findings suggest that action speed requires balanced VS-inhibition from D2 /D3 R in CD and VS-facilitation from D2 /D3 R in VS.

Reference:

Reading 7 Title:
Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity.

Abstract:

Moves to legalize marijuana highlight the urgency to investigate effects of chronic marijuana in the human brain. Here, we challenged 48 participants (24 controls and 24 marijuana abusers) with methylphenidate (MP), a drug that elevates extracellular dopamine (DA) as a surrogate for probing the reactivity of the brain to DA stimulation. We compared the subjective, cardiovascular, and brain DA responses (measured with PET and [11C]raclopride) to MP between controls and marijuana abusers. Although baseline (placebo) measures of striatal DA D2 receptor availability did not differ between groups, the marijuana abusers showed markedly blunted responses when challenged with MP. Specifically, compared with controls, marijuana abusers had significantly attenuated behavioral (“self-reports” for high, drug effects, anxiety, and restlessness), cardiovascular (pulse rate and diastolic blood pressure), and brain DA responses (measured with PET and [11C]raclopride) to MP between controls and marijuana abusers. Although baseline (placebo) measures of striatal DA D2 receptor availability did not differ between groups, the marijuana abusers showed markedly blunted responses when challenged with MP. Specifically, compared with controls, marijuana abusers had significantly attenuated behavioral (“self-reports” for high, drug effects, anxiety, and restlessness), cardiovascular (pulse rate and diastolic blood pressure), and brain DA responses (measured with PET and [11C]raclopride, although normal reductions in striatal nondisplaceable binding potential (BPND)) responses to MP. In ventral striatum (key brain reward region), MP-induced reductions in DVs and BPND (reflecting DA increases) were inversely correlated with scores of negative emotionality, which were significantly higher for marijuana abusers than controls. In marijuana abusers, DA responses in ventral striatum were also inversely correlated with addiction severity and craving. The attenuated responses to MP, including reduced decreases in striatal DVs, are consistent with decreased brain reactivity to the DA stimulation in
marijuana abusers that might contribute to their negative emotionality (increased stress reactivity and irritability) and addictive behaviors.

Reference:

http://dx.doi.org/10.1073/pnas.1411228111

**Reading 8 Title:**

Functional connectivity disruption in neonates with prenatal marijuana exposure

**Abstract:**

Prenatal marijuana exposure (PME) is linked to neurobehavioral and cognitive impairments; however, findings in childhood and adolescence are inconsistent. Type-1 cannabinoid receptors (CB1R) modulate fetal neurodevelopment, mediating PME effects on growth of functional circuitry sub-serving behaviors critical for academic and social success. The purpose of this study was to investigate the effects of prenatal marijuana on development of early brain functional circuitry prior to prolonged postnatal environmental influences. We measured resting state functional connectivity during unsedated sleep in infants at 2–6 weeks (+MJ: 20 with PME in combination with nicotine, alcohol, opiates, and/or selective serotonin reuptake inhibitors; −MJ: 23 exposed to the same other drugs without marijuana, CTR: 20 drug-free controls). Connectivity of subcortical seed regions with high fetal CB1R expression was examined. Marijuana-specific differences were observed in insula and three striatal connections: anterior insula–cerebellum, right caudate–cerebellum, right caudate–right fusiform gyrus/inferior occipital, left caudate–cerebellum. +MJ neonates had hypo-connectivity in all clusters compared with −MJ and CTR groups. Altered striatal connectivity to areas involved in visual spatial and motor learning, attention, and in fine-tuning of motor outputs involved in movement and language production may contribute to neurobehavioral deficits reported in this at-risk group. Disrupted anterior insula connectivity may contribute to altered integration of interoceptive signals with salience estimates, motivation, decision-making, and later drug use. Compared with CTRs, both +MJ and −MJ groups demonstrated hyper-connectivity of left amygdala seed with orbital frontal cortex and hypo-connectivity of posterior thalamus seed with hippocampus, suggesting vulnerability to multiple drugs in these circuits.

Reference:

http://dx.doi.org/10.3389/fnhum.2015.00601

**Reading 9 Title:**
Effect of long-term cannabis use on axonal fibre connectivity.

Abstract:

Cannabis use typically begins during adolescence and early adulthood, a period when cannabinoid receptors are still abundant in white matter pathways across the brain. However, few studies to date have explored the impact of regular cannabis use on white matter structure, with no previous studies examining its impact on axonal connectivity. The aim of this study was to examine axonal fibre pathways across the brain for evidence of microstructural alterations associated with long-term cannabis use and to test whether age of regular cannabis use is associated with severity of any microstructural change. To this end, diffusion-weighted magnetic resonance imaging and brain connectivity mapping techniques were performed in 59 cannabis users with longstanding histories of heavy use and 33 matched controls. Axonal connectivity was found to be impaired in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum and commissural fibres. Radial and axial diffusivity in these pathways were associated with the age at which regular cannabis use commenced. Our findings indicate long-term cannabis use is hazardous to the white matter of the developing brain. Delaying the age at which regular use begins may minimize the severity of microstructural impairment.

Reference:


Reading 10 Title:

Regional Brain Abnormalities Associated With Long-term Heavy Cannabis Use

Abstract:

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. 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. Cross-sectional design using high-resolution (3-T) structural magnetic resonance imaging. Participants were recruited from the general community and underwent imaging at a hospital research facility. 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). Volumetric measures of the hippocampus and the amygdala combined with measures of cannabis use. Subthreshold psychotic symptoms and verbal learning ability were also measured. 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. 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.

Reference:

Reading 11 Title:
Long-term effects of marijuana use on the brain
Abstract:
Questions surrounding the effects of chronic marijuana use on brain structure continue to increase. To date, however, findings remain inconclusive. In this comprehensive study that aimed to characterize brain alterations associated with chronic marijuana use, we measured gray matter (GM) volume via structural MRI across the whole brain by using voxel-based morphology, synchrony among abnormal GM regions during resting state via functional connectivity MRI, and white matter integrity (i.e., structural connectivity) between the abnormal GM regions via diffusion tensor imaging in 48 marijuana users and 62 age- and sex-matched nonusing controls. The results showed that compared with controls, marijuana users had significantly less bilateral orbitofrontal gyri volume, higher functional connectivity in the orbitofrontal cortex (OFC) network, and higher structural connectivity in tracts that innervate the OFC (forceps minor) as measured by fractional anisotropy (FA). Increased OFC functional connectivity in marijuana users was associated with earlier age of onset. Lastly, a quadratic trend was observed suggesting that the FA of the forceps minor tract initially increased following regular marijuana use but decreased with protracted regular use. This pattern may indicate differential effects of initial and chronic marijuana use that may reflect complex neuroadaptive processes in response to marijuana use. Despite the observed age of onset effects, longitudinal studies are needed to determine causality of these effects.

Reference:

Reading 12 Title:
Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults
Abstract:
Recent research has suggested that marijuana use is associated with volumetric and shape differences in subcortical structures, including the nucleus accumbens and amygdala, in a dose-dependent fashion. Replication of such results in well controlled studies is essential to clarify the effects of marijuana. To that end, this retrospective study examined brain morphology in a sample of adult daily marijuana users (n 29) versus nonusers (n 29) and a sample of adolescent daily users (n 50) versus nonusers (n 50). Groups were matched on a critical confounding variable, alcohol use, to a far greater degree than in previously published studies. We acquired high-resolution MRI scans, and investigated group differences in gray matter using voxel-based morphometry, surface-based morphometry, and shape analysis in structures suggested to be associated with marijuana use, as follows: the nucleus accumbens, amygdala, hippocampus, and cerebellum. No statistically significant differences were found between daily users and nonusers on volume or shape in the regions of interest. Effect sizes suggest that the failure to find differences was not due to a lack of statistical power, but rather was due to the lack of even a modest effect. In sum, the results indicate that, when carefully controlling for alcohol use, gender, age, and other variables, there is no association between marijuana use and standard volumetric or shape measurements of subcortical structures.

Reference:


Reading 13 Title:

Shared Predisposition in the Association Between Cannabis Use and Subcortical Brain Structure

Abstract:

Prior neuroimaging studies have suggested that alterations in brain structure may be a consequence of cannabis use. Siblings discordant for cannabis use offer an opportunity to use cross-sectional data to disentangle such causal hypotheses from shared effects of genetics and familial environment on brain structure and cannabis use. To determine whether cannabis use is associated with differences in brain structure in a large sample of twins/siblings and to examine sibling pairs discordant for cannabis use to separate potential causal and predispositional factors linking lifetime cannabis exposure to volumetric alterations. Cross-sectional diagnostic interview, behavioral, and neuroimaging data were collected from community sampling and established family registries from August 2012 to September 2014. This study included data from 483 participants (22-35 years old) enrolled in the ongoing Human Connectome Project, with 262 participants reporting cannabis exposure (ie, ever used cannabis in their lifetime). Cannabis exposure was measured with the Semi-Structured Assessment for the Genetics of Alcoholism. Whole-brain, hippocampus, amygdala, ventral striatum, and orbitofrontal cortex volumes were related to lifetime cannabis use (ever used, age at onset, and frequency of use) using linear regressions. Genetic ($\rho_g$) and environmental ($\rho_e$) correlations between cannabis use and brain volumes were estimated. Linear mixed models were used to examine volume differences in sex-matched concordant unexposed (n = 71 pairs), exposed (n = 81 pairs), or exposure discordant (n = 89 pairs) sibling
Among 483 study participants, cannabis exposure was related to smaller left amygdala (approximately 2.3%; $P = .007$) and right ventral striatum (approximately 3.5%; $P < .005$) volumes. These volumetric differences were within the range of normal variation. The association between left amygdala volume and cannabis use was largely owing to shared genetic factors ($\rho_g = -0.43; P = .004$), while the origin of the association with right ventral striatum volumes was unclear. Importantly, brain volumes did not differ between sex-matched siblings discordant for use (fixed effect $= -7.43; t = -0.93, P = .35$). Both the exposed and unexposed siblings in pairs discordant for cannabis exposure showed reduced amygdala volumes relative to members of concordant unexposed pairs (fixed effect $= 12.56; t = 2.97; P = .003$). In this study, differences in amygdala volume in cannabis users were attributable to common predispositional factors, genetic or environmental in origin, with little support for causal influences. Causal influences, in isolation or in conjunction with predispositional factors, may exist for other brain regions (e.g., ventral striatum) or at more severe levels of cannabis involvement and deserve further study.

Reference:

**Reading 14 Title:**
Persistent cannabis users show neuropsychological decline from childhood to midlife

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

Reference:
Reading 15 Title:
Cannabis use and later life outcomes

Abstract:
To examine the associations between the extent of cannabis use during adolescence and young adulthood and later education, economic, employment, relationship satisfaction and life satisfaction outcomes. A longitudinal study of a New Zealand birth cohort studied to age 25 years. Measures of: cannabis use at ages 14-25; university degree attainment to age 25; income at age 25; welfare dependence during the period 21-25 years; unemployment 21-25 years; relationship quality; life satisfaction. Also, measures of childhood socio-economic disadvantage, family adversity, childhood and early adolescent behavioral adjustment and cognitive ability and adolescent and young adult mental health and substance use. There were statistically significant bivariate associations between increasing levels of cannabis use at ages 14-21 and: lower levels of degree attainment by age 25 (P < 0.0001); lower income at age 25 (P < 0.01); higher levels of welfare dependence (P < 0.0001); higher unemployment (P < 0.0001); lower levels of relationship satisfaction (P < 0.001); and lower levels of life satisfaction (P < 0.0001). These associations were adjusted for a range of potentially confounding factors including: family socio-economic background; family functioning; exposure to child abuse; childhood and adolescent adjustment; early adolescent academic achievement; and comorbid mental disorders and substance use. After adjustment, the associations between increasing cannabis use and all outcome measures remained statistically significant (P < 0.05). The results of the present study suggest that increasing cannabis use in late adolescence and early adulthood is associated with a range of adverse outcomes in later life. High levels of cannabis use are related to poorer educational outcomes, lower income, greater welfare dependence and unemployment and lower relationship and life satisfaction. The findings add to a growing body of knowledge regarding the adverse consequences of heavy cannabis use.

Reference:

Reading 16 Title:
“High”-School: The Relationship between Early Marijuana Use and Educational Outcomes

Abstract:
We use unique survey data linked to nearly a decade of administrative welfare data to examine the relationship between early marijuana use (at age 14 or younger) and young people’s educational outcomes. We find evidence that early marijuana use is related to educational penalties that are compounded by high-intensity use and are larger for young people living in families with a history of welfare receipt. The relationships between marijuana use and both high school completion and achieving a university entrance score appear to stem from selectivity into the use of marijuana. In contrast, early marijuana use is associated with significantly lower university entrance score for those...
who obtain one and we provide evidence that this effect is unlikely to be driven by selection. Collectively, these findings point to a more nuanced view of the relationship between adolescent marijuana use and educational outcomes than is suggested by the existing literature.

Reference: