

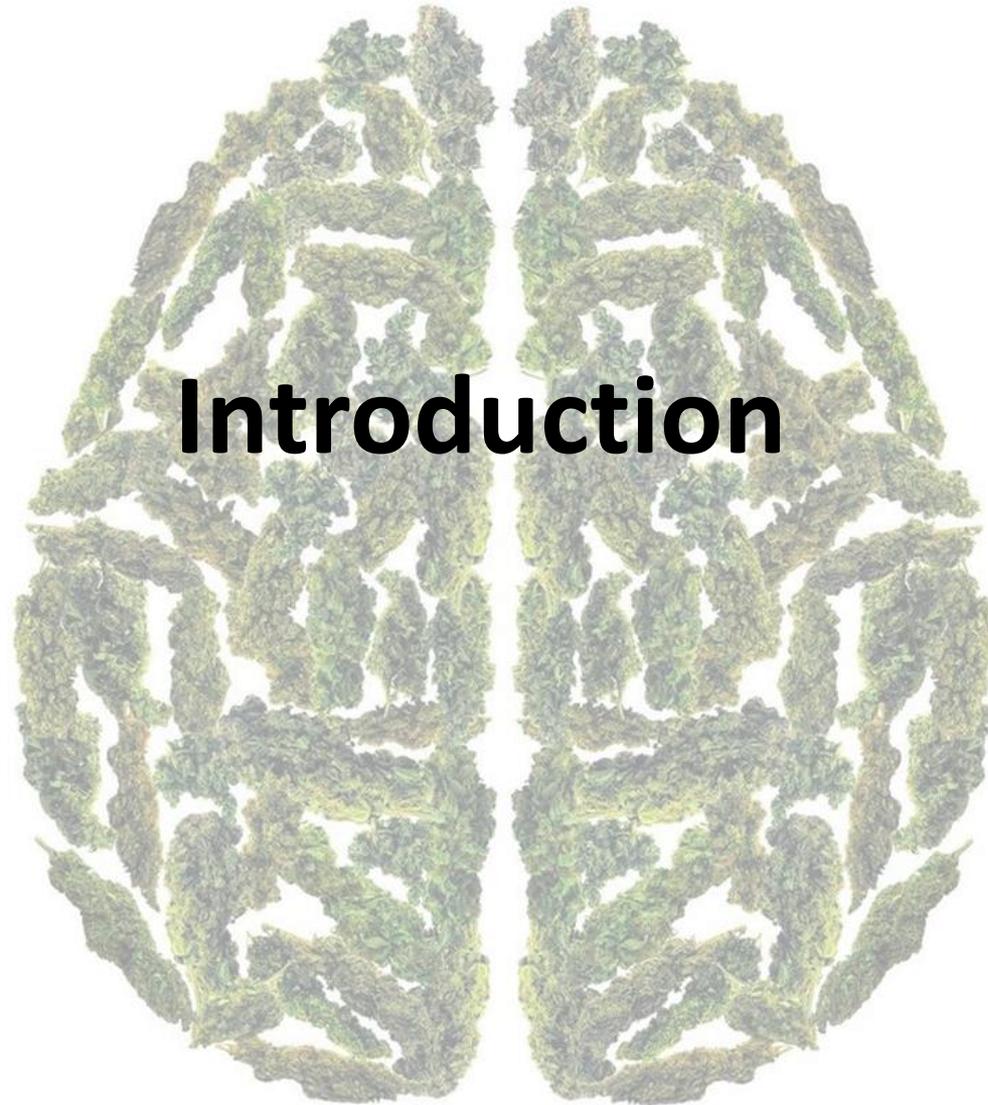
# Long-Term Effects of Cannabis on the Brain

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# Overview

- Introduction to the issue
- Neural pathways affected by long-term cannabis exposure
- Effects of intrauterine cannabis exposure
- Neuroimaging studies
- Summary

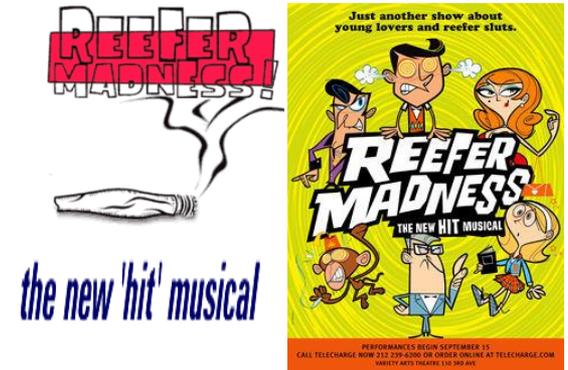


# Introduction

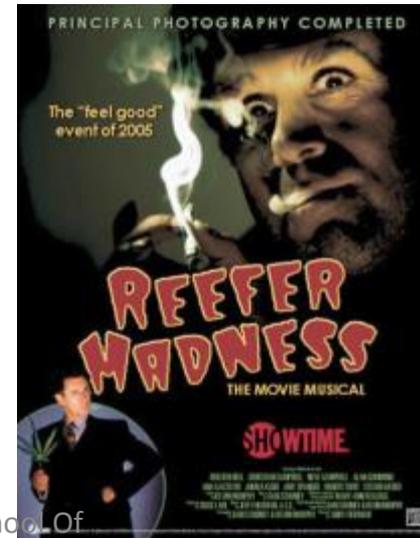
# 1936



# 1999-2001



# 2005



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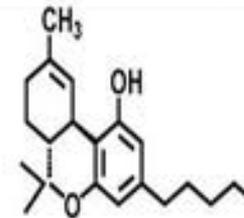
# Marijuana/Cannabis / Cannabinoids

Over 100 compounds ; over 70 phytocannabinoids

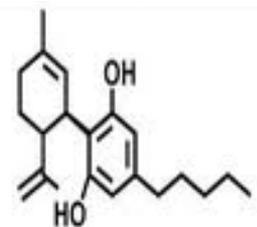
Delta-9 THC prominent psychoactive constituent

Dose related effects:

- High, euphoria, relaxation
- Cognitive impairment (memory, learning, attention, time perspective)
- Anxiety, Panic, Hallucinations, Psychosis?
- Abuse/Dependence



$\Delta^9$ -tetrahydrocannabinol  
(THC)



Cannabidiol  
(CBD)

# Marijuana

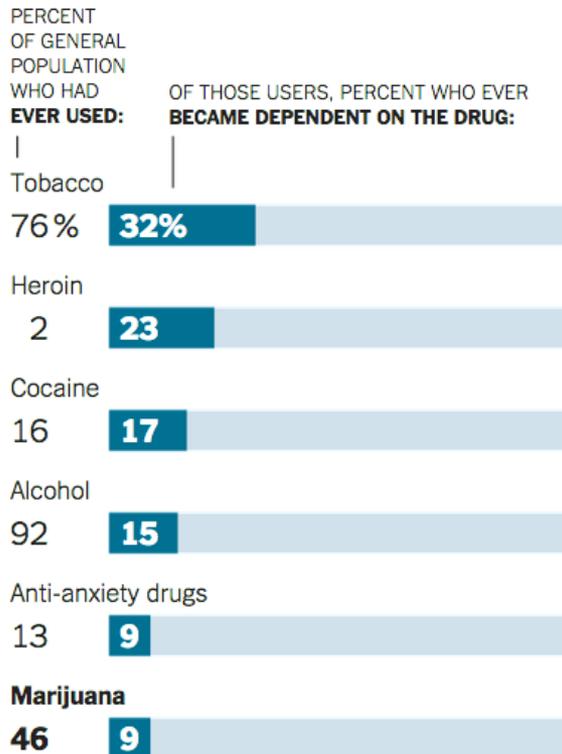




# Cannabis: is it really *THAT* bad?

## Who Got Hooked

An Institute of Medicine study found dependency rates for marijuana were far lower than those for other substances.



Source: Institute of Medicine, 1999

“An independent scientific committee in Britain compared 20 drugs in 2010 for the harms they caused to individual users and to society as a whole through crime, family breakdown, absenteeism, and other social ills. Adding up all the damage, the panel estimated that alcohol was the most harmful drug, followed by heroin and crack cocaine. Marijuana ranked eighth, having slightly more than one-fourth the harm of alcohol.”

Boffey (2014, July). What science says about marijuana. *New York Times*.

**Is there any reason for concern?**





# What has research over the past two decades revealed about the adverse health effects of recreational cannabis use?

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## ABSTRACT

**Aims** To examine changes in the evidence on the adverse health effects of cannabis since 1993. **Methods** A comparison of the evidence in 1993 with the evidence and interpretation of the same health outcomes in 2013. **Results** Research in the past 20 years has shown that driving while cannabis-impaired approximately doubles car crash risk and that around one in 10 regular cannabis users develop dependence. Regular cannabis use in adolescence approximately doubles the risks of early school-leaving and of cognitive impairment and psychoses in adulthood. Regular cannabis use in adolescence is also associated strongly with the use of other illicit drugs. These associations persist after controlling for plausible confounding variables in longitudinal studies. This suggests that cannabis use is a contributory cause of these outcomes but some researchers still argue that these relationships are explained by shared causes or risk factors. Cannabis smoking probably increases cardiovascular disease risk in middle-aged adults but its effects on respiratory function and respiratory cancer remain unclear, because most cannabis smokers have smoked or still smoke tobacco. **Conclusions** The epidemiological literature in the past 20 years shows that cannabis use increases the risk of accidents and can produce dependence, and that there are consistent associations between regular cannabis use and poor psychosocial outcomes and mental health in adulthood.

## Adverse effects of chronic use

### *Psychosocial outcomes*

- Regular cannabis users can develop a dependence syndrome, the risks of which are around 1 in 10 of all cannabis users and 1 in 6 among those who start in adolescence.
- Regular cannabis users double their risks of experiencing psychotic symptoms and disorders, especially if they have a personal or family history of psychotic disorders, and if they initiate cannabis use in their mid-teens.
- Regular adolescent cannabis users have lower educational attainment than non-using peers.
- Regular adolescent cannabis users are more likely to use other illicit drugs.



- Regular cannabis use that begins in adolescence and continues throughout young adulthood appears to produce cognitive impairment but the mechanism and reversibility of the impairment is unclear.
- Regular cannabis use in adolescence approximately doubles the risk of being diagnosed with schizophrenia or reporting psychotic symptoms in adulthood.
- All these relationships have persisted after controlling for plausible confounders in well-designed studies, but some researchers still question whether adverse effects are related causally to regular cannabis use or explained by shared risk factors.

### *Physical health outcomes*

- Regular cannabis smokers have higher risks of developing chronic bronchitis, but it is unclear if it impairs respiratory function.
- Cannabis smoking by middle-aged adults probably increases the risks of myocardial infarction.

## The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood

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### ABSTRACT

**Aims** Debate continues about whether the association between cannabis use in adolescence and common mental disorders is causal. Most reports have focused on associations in adolescence, with few studies extending into adulthood. We examine the association from adolescence until the age of 29 years in a representative prospective cohort of young Australians. **Design** Nine-wave, 15-year representative longitudinal cohort study, with six waves of data collection in adolescence (mean age 14.9–17.4 years) and three in young adulthood (mean age 20.7, 24.1 and 29.1 years). **Participants** Participants were a cohort of 1943 recruited in secondary school and surveyed at each wave when possible from mid-teen age to their late 20s. **Setting** Victoria, Australia. **Measurements** Psychiatric morbidity was assessed with the Revised Clinical Interview Schedule (CIS-R) at each adolescent wave, and as Composite International Diagnostic Interview (CIDI)-defined ICD-10 major depressive episode and anxiety disorder at 29 years. Frequency of cannabis use was measured in the past 6 months in adolescence. Cannabis use frequency in the last year and DSM-IV cannabis dependence were assessed at 29 years. Cross-sectional and prospective associations of these outcomes with cannabis use and dependence were estimated as odds ratios (OR), using multivariable logistic regression models, with the outcomes of interest, major depressive episode (MDE) and anxiety disorder (AD) at 29 years. **Findings** There were no consistent associations between adolescent cannabis use and depression at age 29 years. Daily cannabis use was associated with anxiety disorder at 29 years [adjusted OR 2.5, 95% confidence interval (CI):< 1.2–5.2], as was cannabis dependence (adjusted OR 2.2, 95% CI: 1.1–4.4). Among weekly+ adolescent cannabis users, those who continued to use cannabis use daily at 29 years remained at significantly increased odds of anxiety disorder (adjusted OR 3.2, 95% CI: 1.1–9.2). **Conclusions** Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.

**“Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety... in adolescence and late young adulthood, even among regular users who then cease using the drug.”**

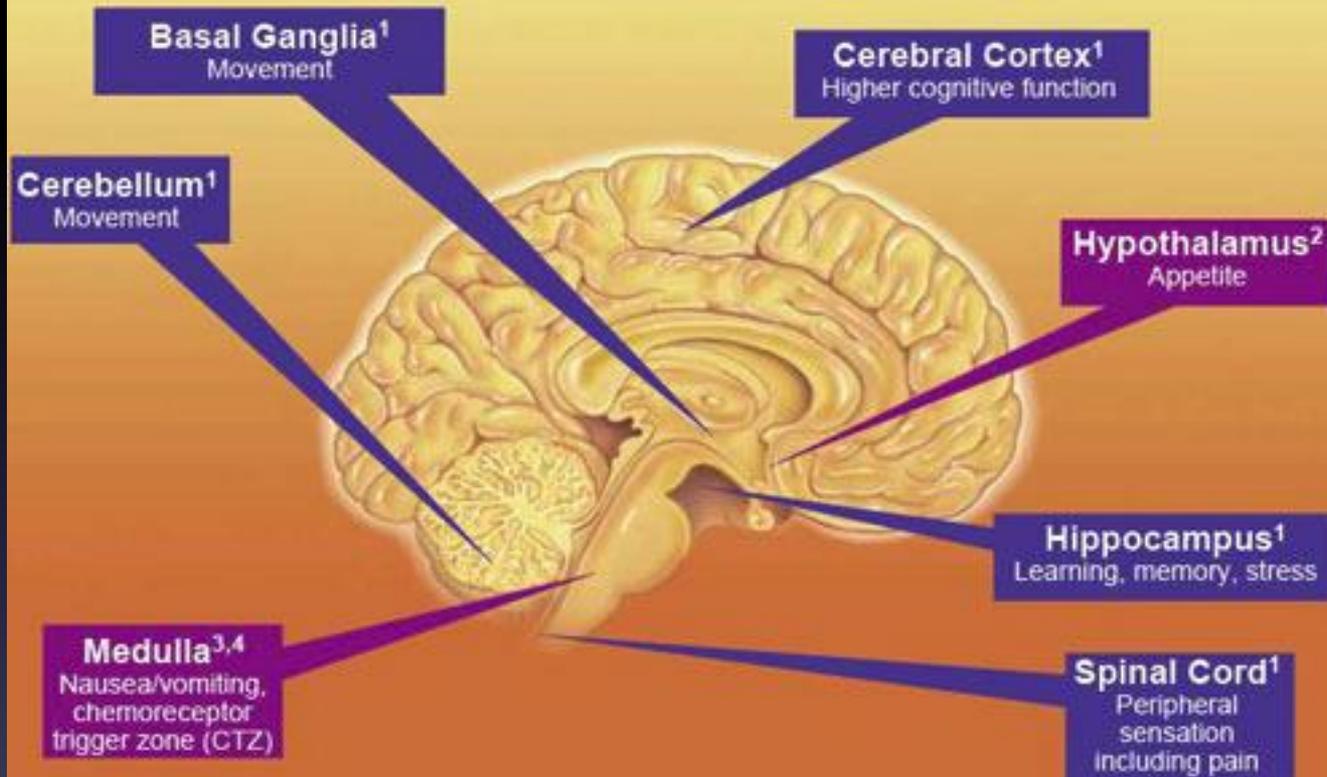
**“It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.”**

# Neurobiology

## Endogenous Cannabinoid System

- Receptors: CB1 and CB2
- Location: where the action is
  - Hippocampus
  - Basal ganglia
  - Cerebellum
- Endogenous cannabinoid: e.g., Anandamide

# Concentrations of CB<sub>1</sub> receptors



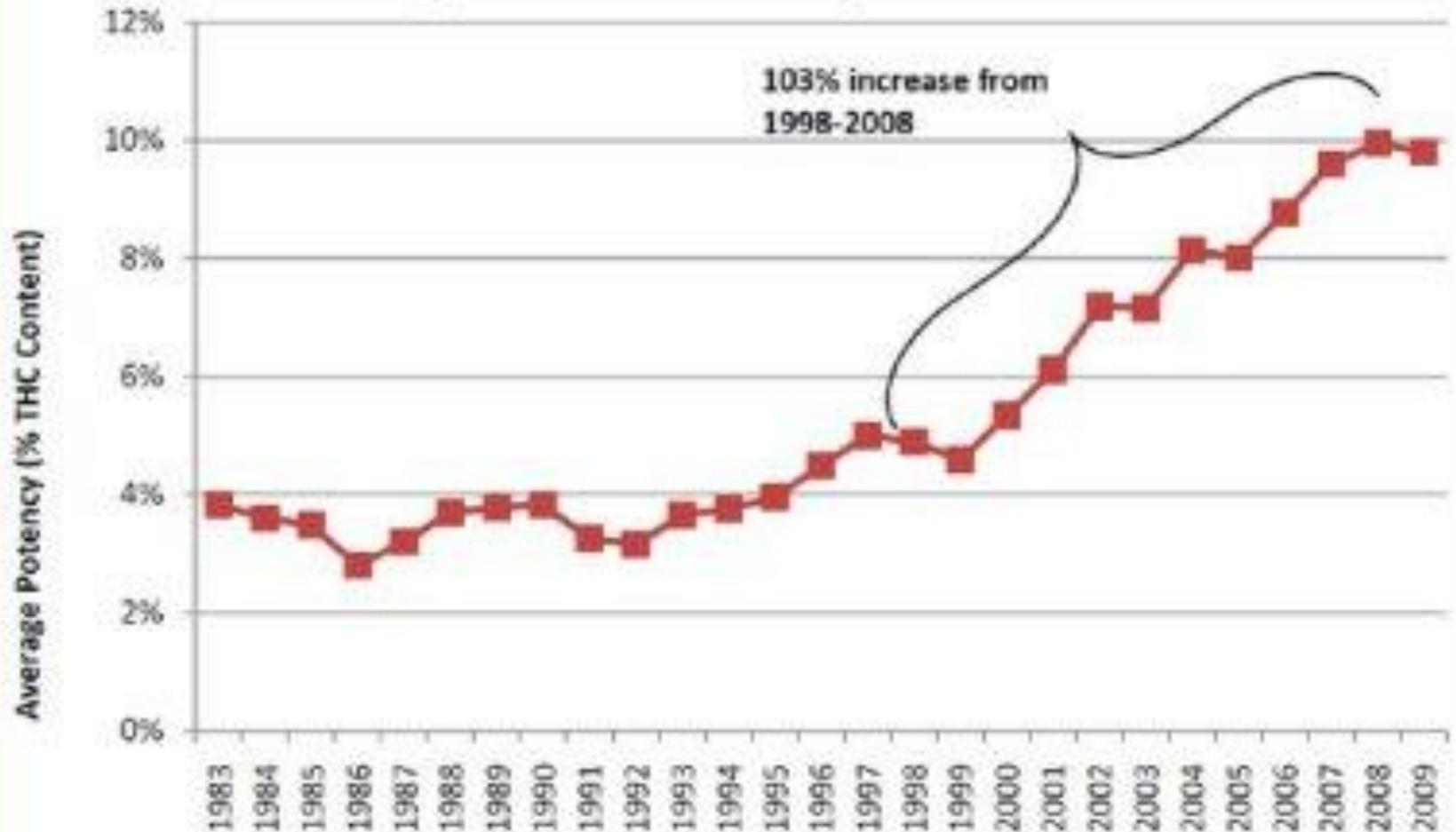
1. Joy JE, et al, eds. *Marjuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-81. 2. Martin BR, et al. *J Support Oncol*. 2004;2(4):305-318. 3. Grotenhemmen F. *Curr Drug Targets CNS Neurol Disord*. 2005;4(5):507-530. 4. Navari RM, et al. *Expert Opin Emerg Drugs*. 2006;11(1):137-151.

# Cannabinoid System

## Receptor Location and Function

- Cerebellum - movement/coordination
- Hippocampus - learning, memory
- Cerebral Cortex - executive function
- Nucleus Accumbens - reward (dopamine system)
- Basal Ganglia - movement
- Hypothalamus - body regulation
- Amygdala - emotional responses
- Spinal Cord - sensation (pain)
- Brain Stem - sleep, arousal, motor
- Central Gray Matter - analgesia
- Nucleus solitary tract - visceral sensation, nausea/vomiting

## Potency of Seized Marijuana in the U.S.



Source: University of Mississippi, National Center for Natural Products Research, *Potency Monitoring Project Quarterly Report 107 (January 2010)*

AFTER HOURS OF THOUGHT ...  
OR MINUTES OF THOUGHT,  
WHICHEVER JUST OCCURRED,  
I THINK MARIJUANA IS  
NATURE'S WAY OF SAYING,  
"FORGET IT."



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# Addiction?

Is it cannabis / marijuana addictive?

Factors impacting its addictive potential?

Persons with mental illnesses?

- What do we mean by self-medication?

# ADDICTION / ADDICTIVE POTENTIAL

- = **Pharmacology (only one part)**
- = **Availability**
- = **Cost**
- = **Genetics**
- = **Intrapersonal Factors (emotional/behavioral)**
- = **Environmental Factors / Alternatives**
- = **Societal Norms and Attitudes**

# Clinical Consequences

Dose Dependent / Frequency / Acute vs. Chronic

Medical / physical

- respiratory, cardiac, reproductive system

Behavioral / cognitive

- memory, attention, executive function, judgment/decision-making, driving, sleep, brain structure/function,
  - **addiction/excessive use and its functional consequences**
    - **difficult to treat (stop); same types of problems as other substance use disorders**

**Psychiatric / mental illness**

- anxiety, depression, SMI (bipolar, schizophrenia)?

# Impact on Mental Illness

- Psychotic Disorders
- Affective Disorders
- Anxiety Disorders / PTSD
- ADHD
  
- Causal Factor and/or Impact on Existing Illness

# Cannabis and Psychosis

Acute effects

Chronic Effects

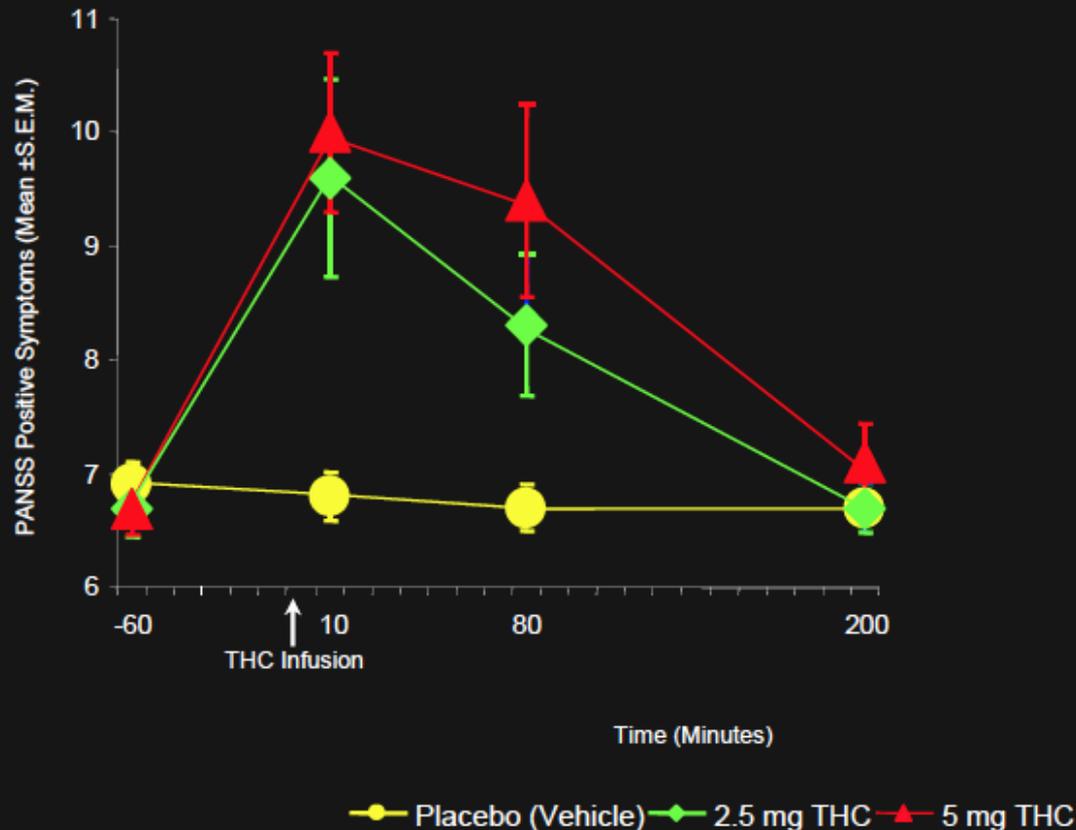
Causal Influences

Impact on existing illness and its course

The data...

# $\Delta$ -9-THC Induced Psychotic-like Symptoms In Healthy Subjects in the Laboratory

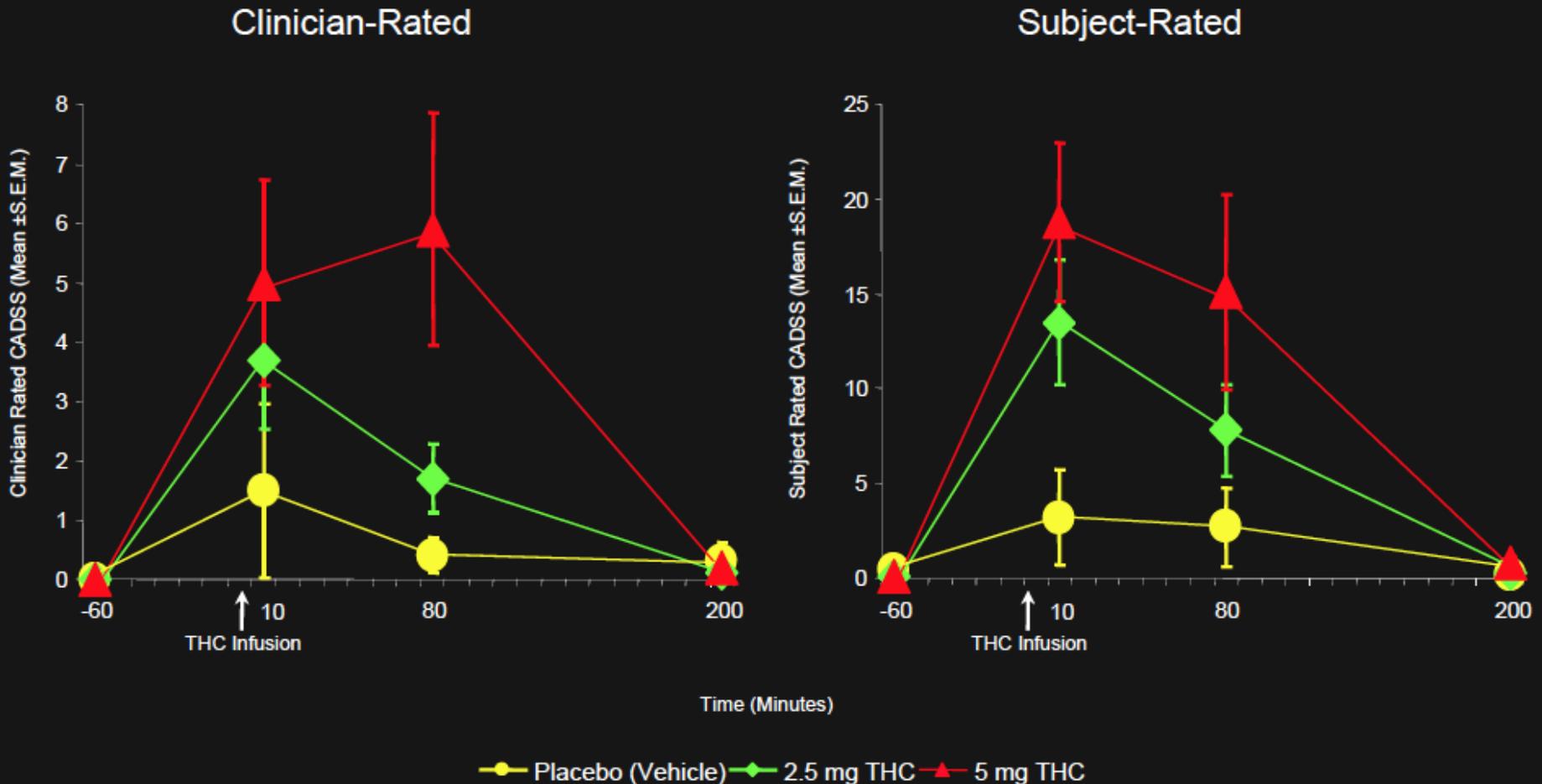
## Positive Symptoms

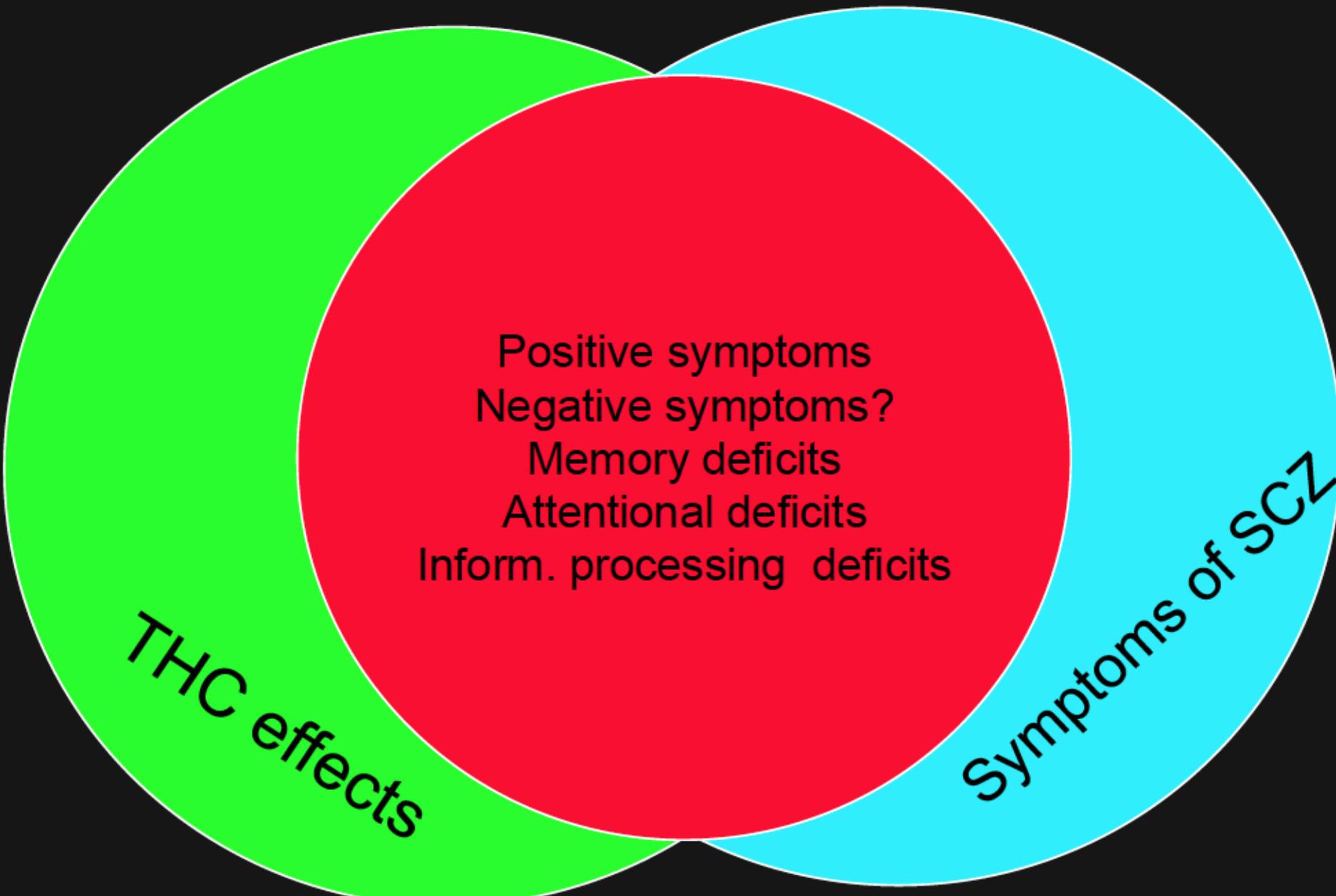


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(D'Souza et al., *Neuropsychopharmacology* 2004)

# $\Delta$ -9-THC Induced Perceptual Alterations In Healthy Subjects





Positive symptoms  
Negative symptoms?  
Memory deficits  
Attentional deficits  
Inform. processing deficits

THC effects

Symptoms of SCZ

# Cannabis Use Doubles the risk of psychosis

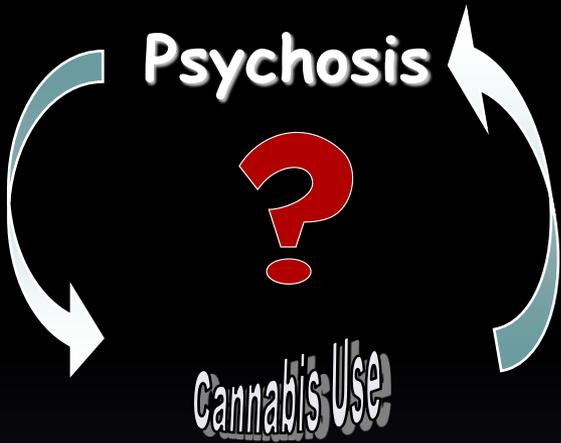
Table 1 | **General population studies of the effect of cannabis use on the risk of psychosis**

Country in which the study was conducted	Number of participants	Follow up	Odds ratio (95% confidence interval)	Study design
United States	4,494	NA	2.4 (1.2, 7.1)	Population based
Sweden	50,053	25 years	2.1 (1.2, 3.7)	Conscript cohort
The Netherlands	4,045	3 years	2.8 (1.2,6.5)	Population based
Israel	9,724	4–15 years	2.0 (1.3, 3.1)	Population based
New Zealand (Christchurch)	1,265	3 years	1.8 (1.2, 2.6)	Birth cohort
New Zealand (Dunedin)	1,253	15 years	3.1 (0.7,13.3)	Birth cohort
The Netherlands	1,580	14 years	2.8 (1.79,4.43)	Population based
Germany	2,436	4 years	1.7 (1.1, 1.5)	Population based
United Kingdom	8,580	18 months	1.5 (0.55,3.94)	Population based

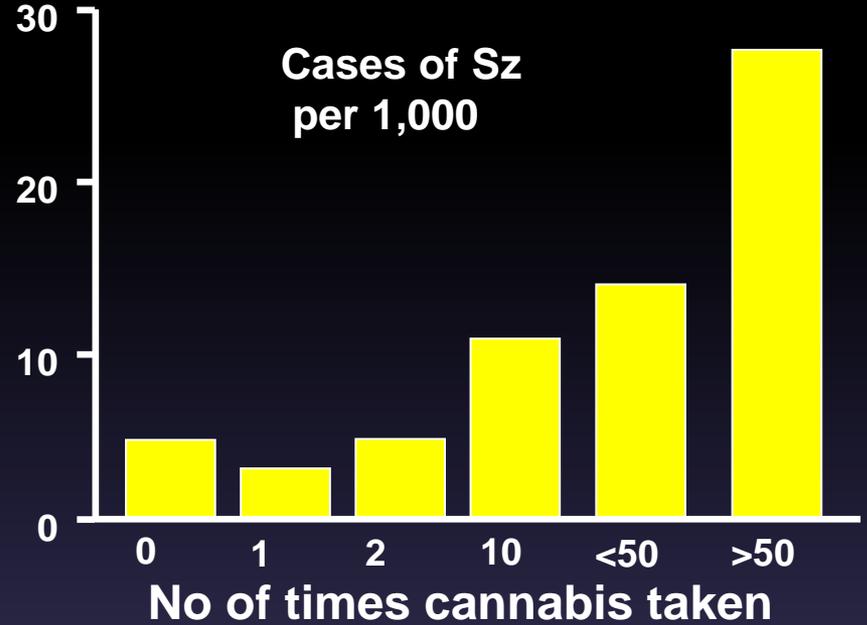
NA, not applicable.

**2-fold increase**

Morrison, Murray et al., Nature Neuroscience, 2008

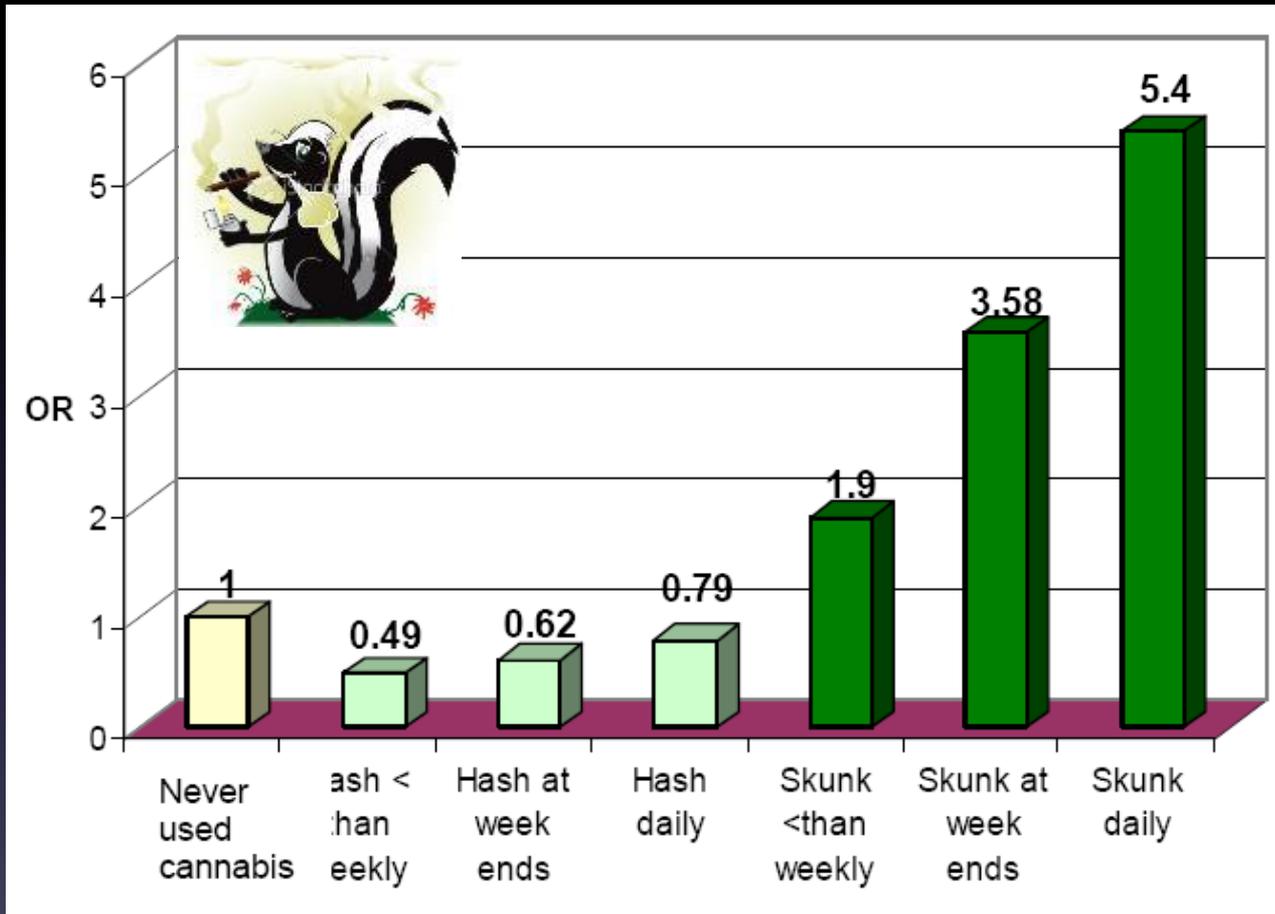


**Swedish Army Study of  
Andréasson et al 1987**



# Risk of being a Psychotic Case

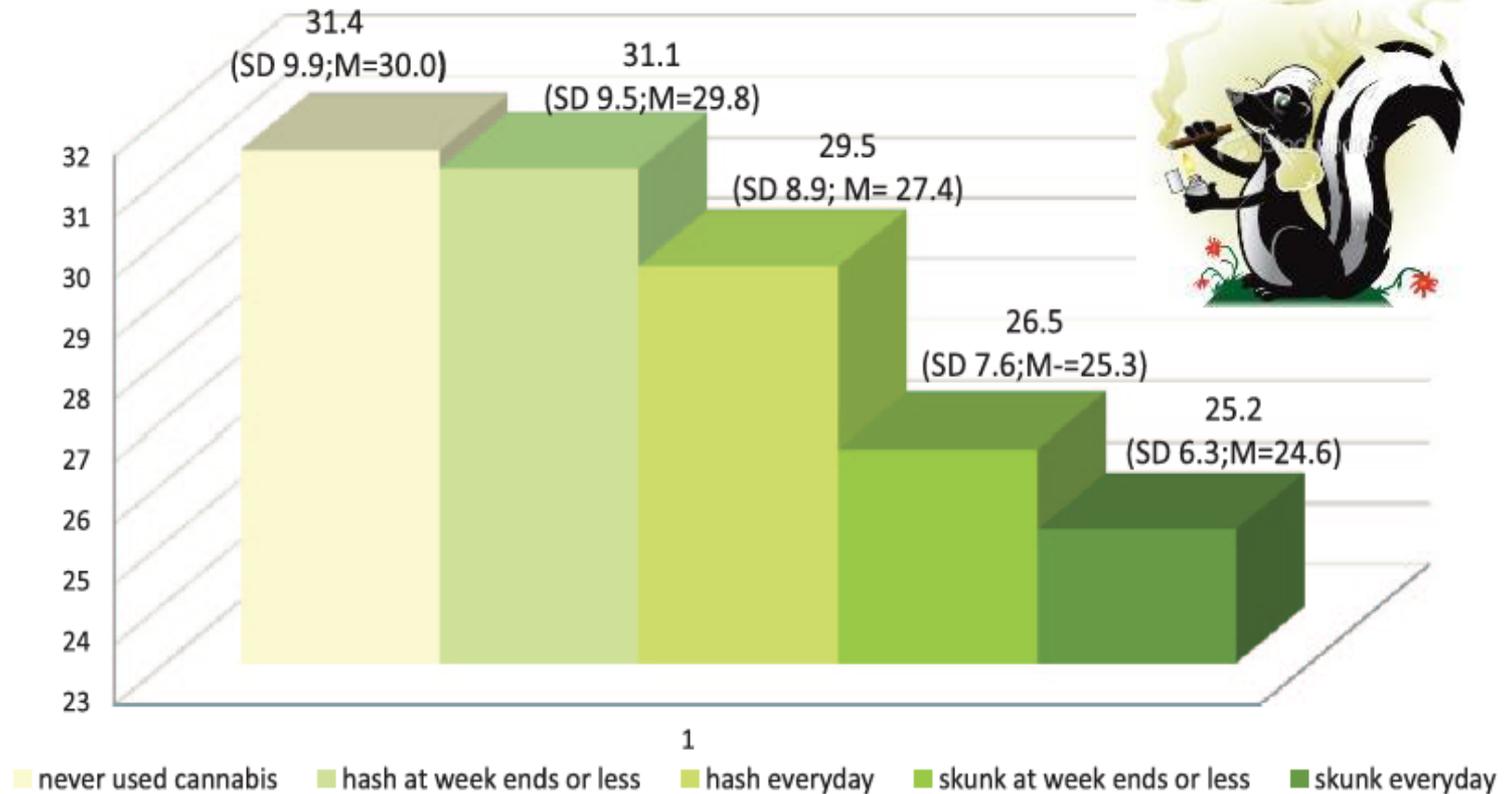
(OR adjusted for gender, age, ethnicity, Stimulants, level of Ed)



Frequent Use of High-Potency Cannabis, Drives the Increased Probability of Psychosis in Cannabis Users (Di Forti et al, 2014)

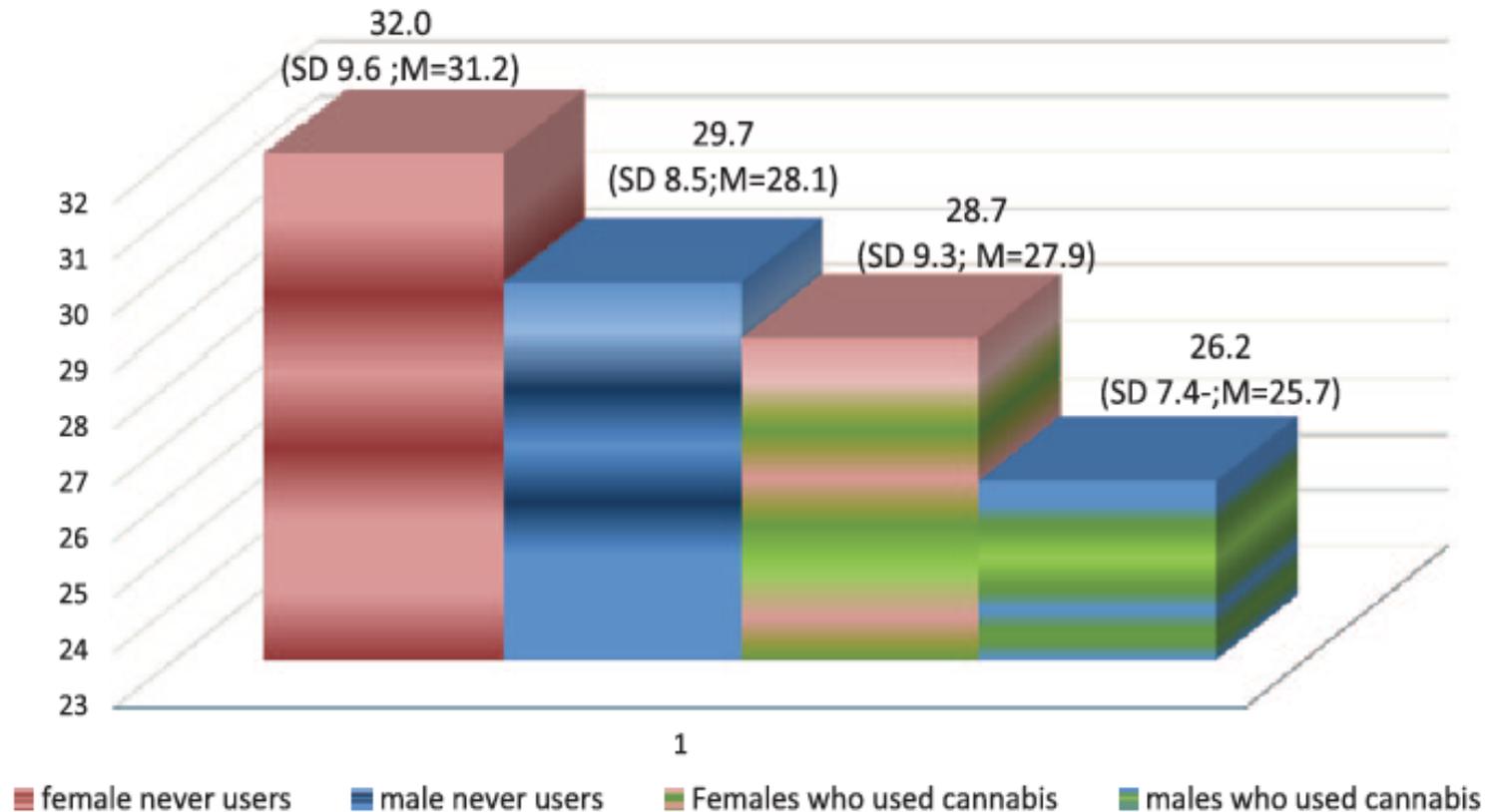
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## Mean age (yrs) of onset of psychosis by degree of exposure to cannabis



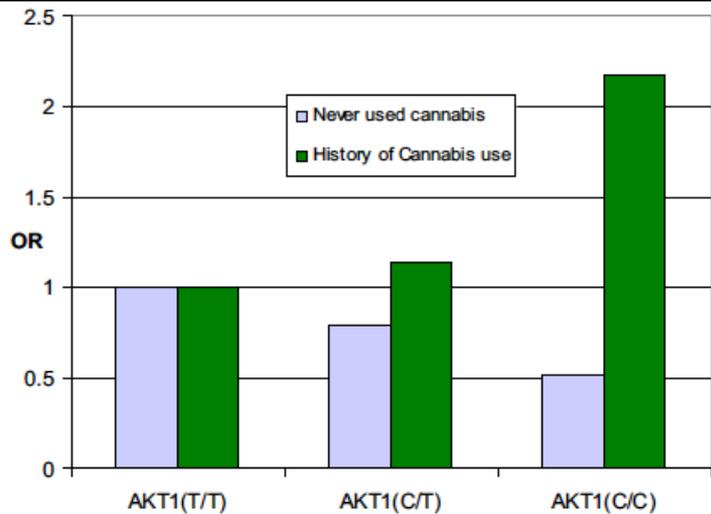
**Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users (Di Forti et al., 2014)**

## Mean age (yrs) of onset of psychosis by history of cannabis and gender

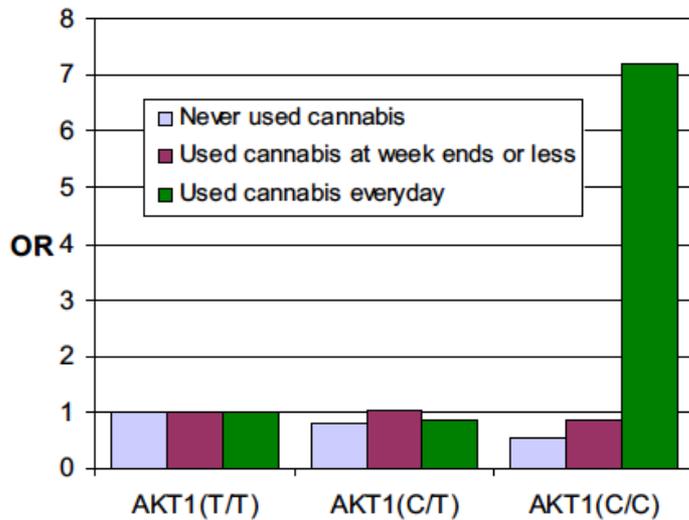


**Males at higher risk, but doesn't account for potency and frequency effects (Di Forti et al., 2014)**

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**Figure 2.** Odds ratio (OR) of psychosis for subjects with *AKT1* rs 2494732 C/T or C/C genotype compared to T/T, according to their cannabis use.



**Figure 3.** Odds ratio (OR) of psychosis for *AKT1* rs 2494732 C/T or C/C carriers compared to subjects with the T/T genotype depending on lifetime frequency of cannabis use.

Findings provide support that genetic variation at rs2494732 of *AKT1* influences the risk of developing a psychotic disorder in cannabis users

DiForti et al. (2012)

# Causality

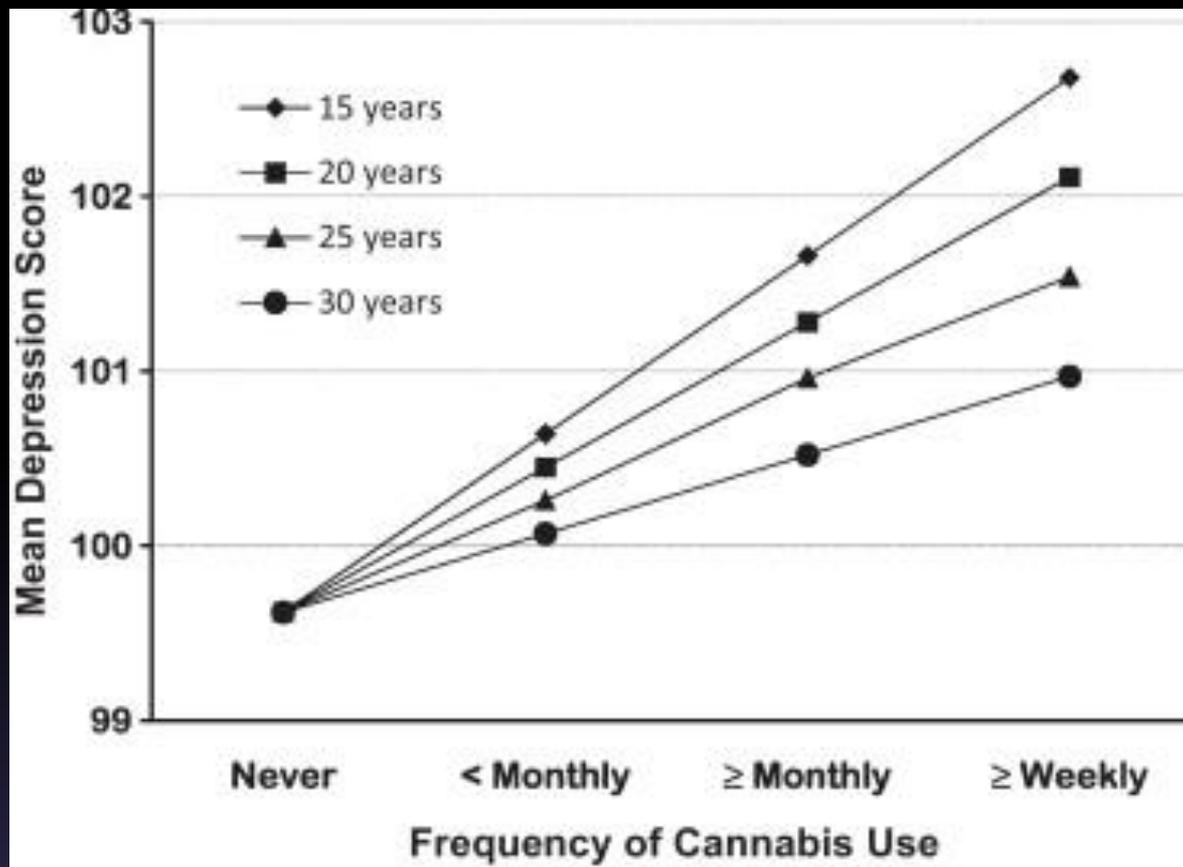
- Biological Plausibility
- Dose-response
- Strength of the association
- Direction of the effect
- Temporality
- Specificity
- Experimental Evidence
- Consistency

# Summary: Cannabis → Psychotic Disorder

- Dose and Frequency Important Factors
  - Age of onset (maybe onset) , use of high potency
- Gender influence on early onset is offset by cannabis use

# Cannabis and Depression (and BiPolar?)

- Co-morbidity is high
- Positive associations between marijuana use and depression in adolescent (suicide rates?)
- Data on cannabis use causing depression is not strong
- No data suggesting that cannabis is helpful for depression



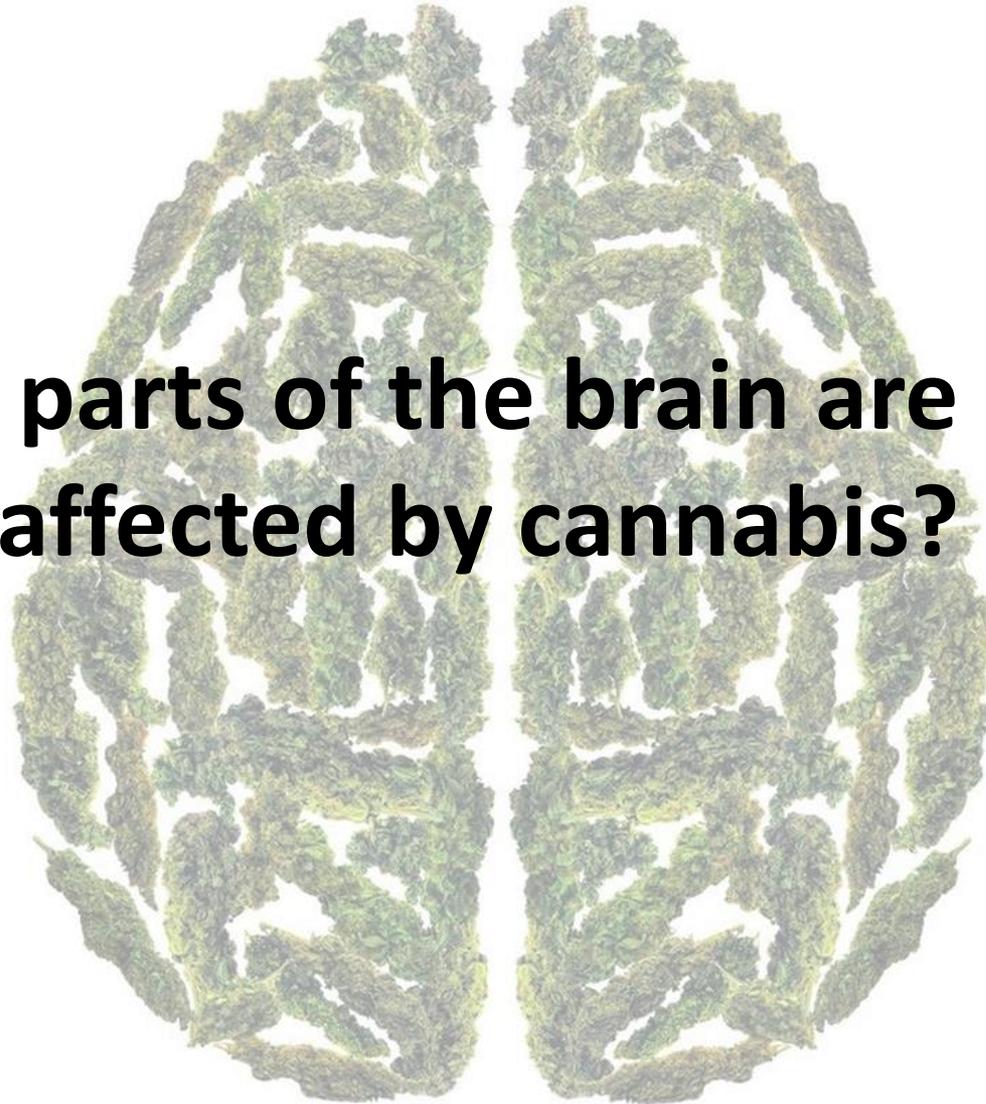
Estimated associations between frequency of cannabis use and mean depression scores at selected ages (15, 20, 25, 30 years) after adjustment for fixed sources of confounding.

Horwood , et al., 2012: **An integrative data analysis of four Australasian cohorts**

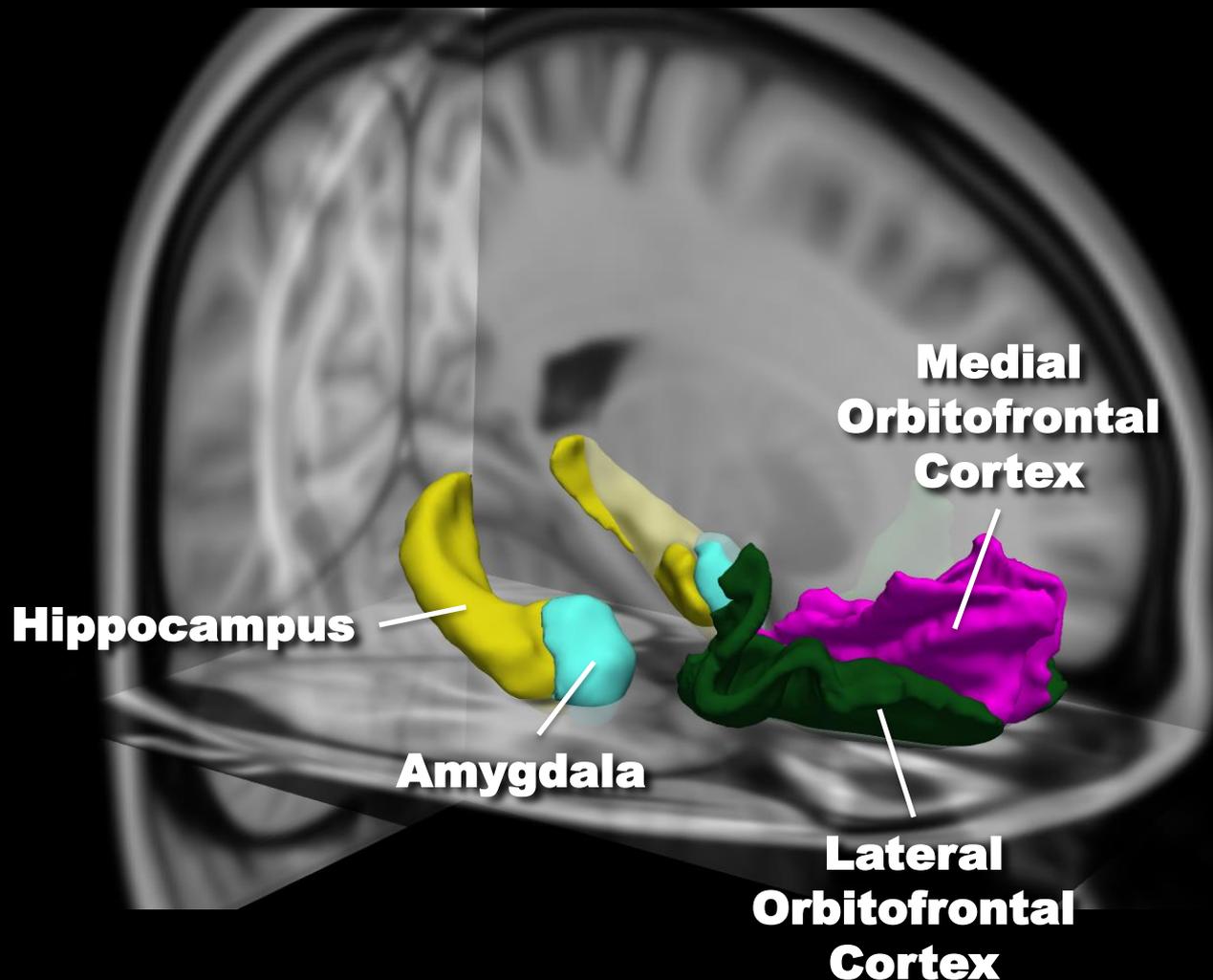
# Cannabis Use and Anxiety

- Co-morbidity is high
- Positive associations between marijuana use and anxiety in adolescent
- Data on cannabis use leading to anxiety is not equivocal, but is worrisome
- Heavy cannabis use during adolescent predicts AD at 29 yrs, even if stopped using
- No data suggesting that cannabis is helpful for anxiety

**What parts of the brain are most affected by cannabis?**

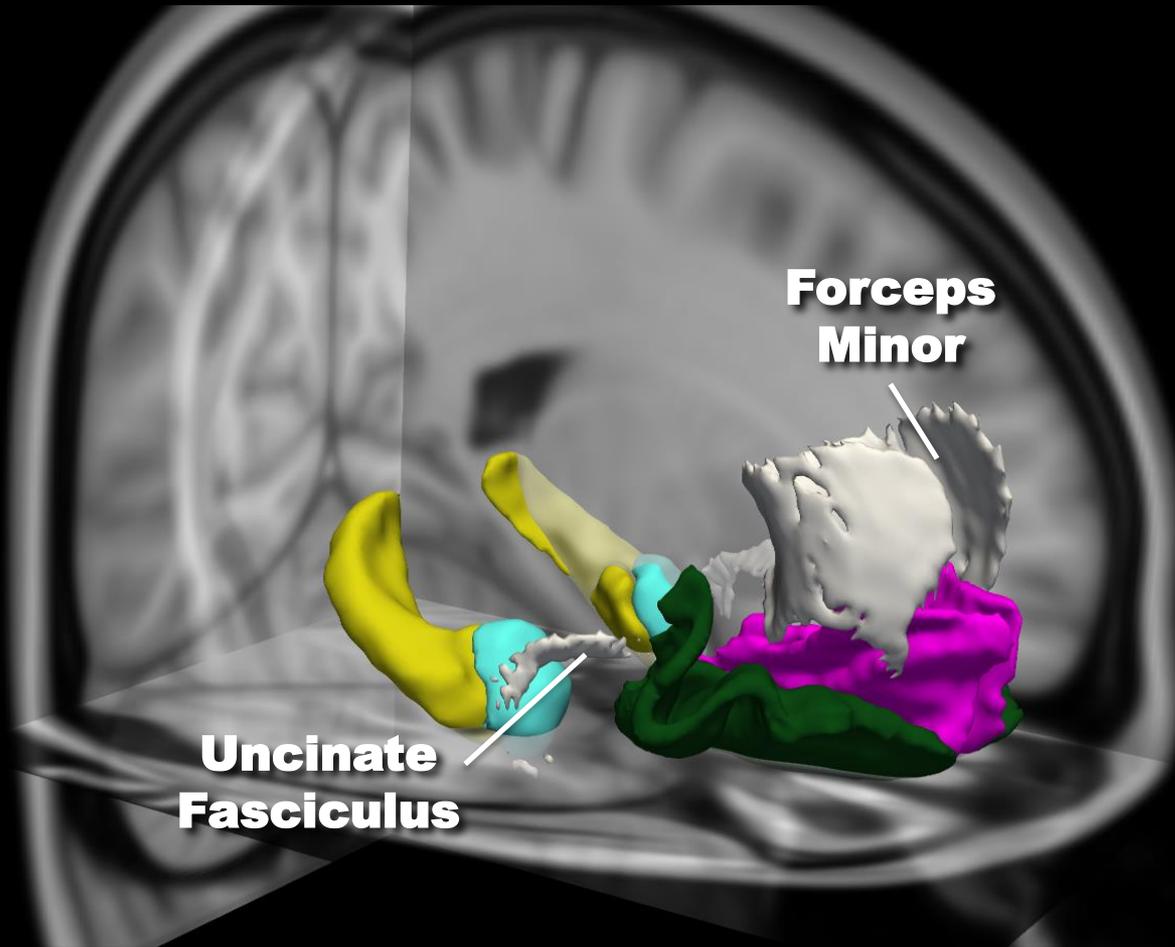


# Cannabis and the Brain



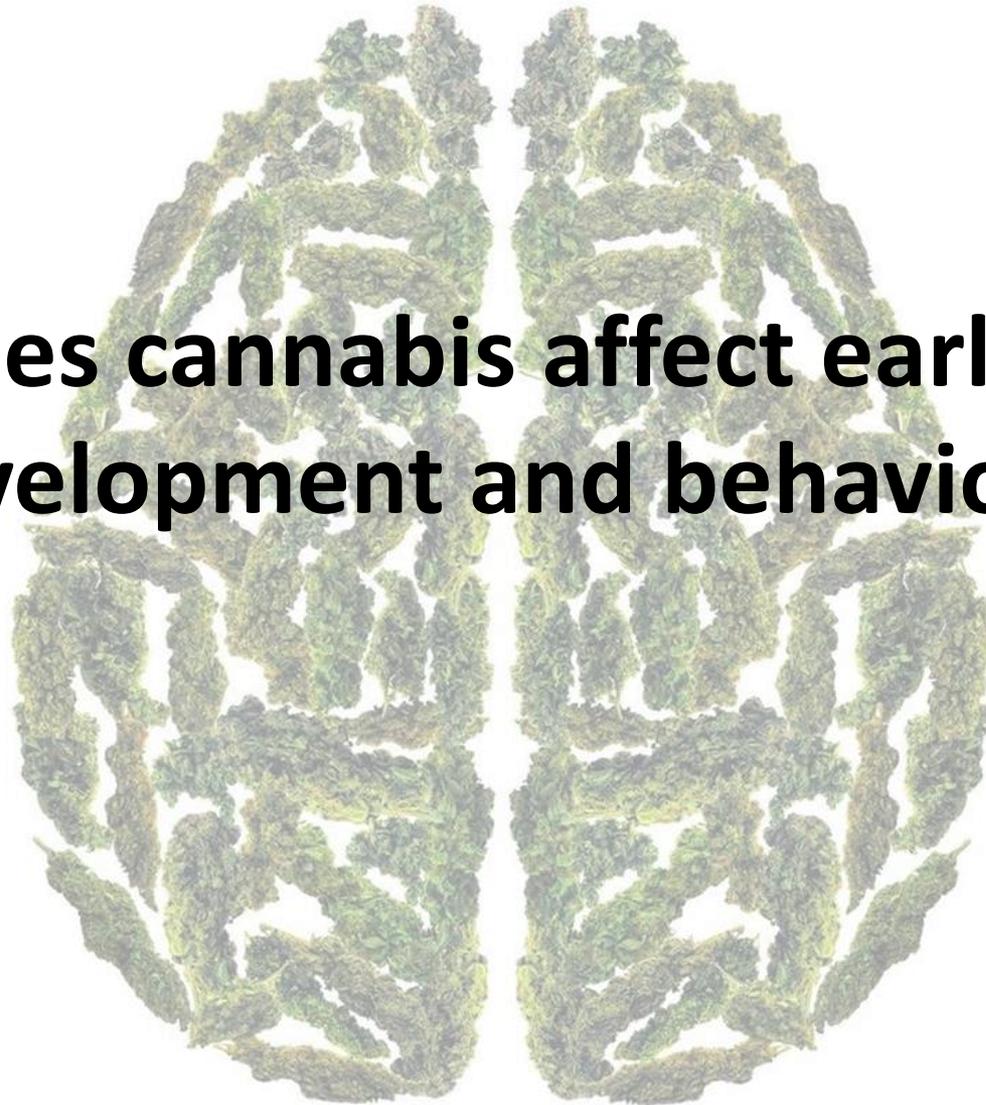
*Cannabis affects brain regions that are strongly implicated in emotion regulation, memory, and impulse control*

# Cannabis and the Brain



*Evidence suggests that cannabis affects the connections between these brain regions as well*

**How does cannabis affect early brain development and behavior?**



# Intrauterine Cannabis Exposure



# Intrauterine Cannabis Exposure

Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls<sup>☆</sup>

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## ABSTRACT

**Background:** The development of the fetal endocannabinoid receptor system may be vulnerable to maternal cannabis use during pregnancy and may produce long-term consequences in children. In this study, we aimed to determine the relationship between gestational cannabis use and childhood attention problems and aggressive behavior.

**Methods:** Using a large general population birth cohort, we examined the associations between parental prenatal cannabis and tobacco use and childhood behavior problems at 18 months measured using the Child Behavior Checklist in  $N = 4077$  children. Substance use was measured in early pregnancy.

**Results:** Linear regression analyses demonstrated that gestational exposure to cannabis is associated with behavioral problems in early childhood but only in girls and only in the area of increased aggressive behavior ( $B = 2.02$ ; 95% CI: 0.30–3.73;  $p = 0.02$ ) and attention problems ( $B = 1.04$ ; 95% CI: 0.46–1.62;  $p < 0.001$ ). Furthermore, this study showed that long-term (but not short term) tobacco exposure was associated with behavioral problems in girls ( $B = 1.16$ ; 95% CI: 0.20–2.12;  $p = 0.02$ ). There was no association between cannabis use of the father and child behavior problems.

**Conclusions:** Our results suggest that intrauterine exposure to cannabis is associated with an increased risk for aggressive behavior and attention problems as early as 18 months of age in girls, but not boys. Further research is needed to explore the association between prenatal cannabis exposure and child behavior at later ages. Our data support educating future mothers about the risk to their babies should they smoke cannabis during pregnancy.

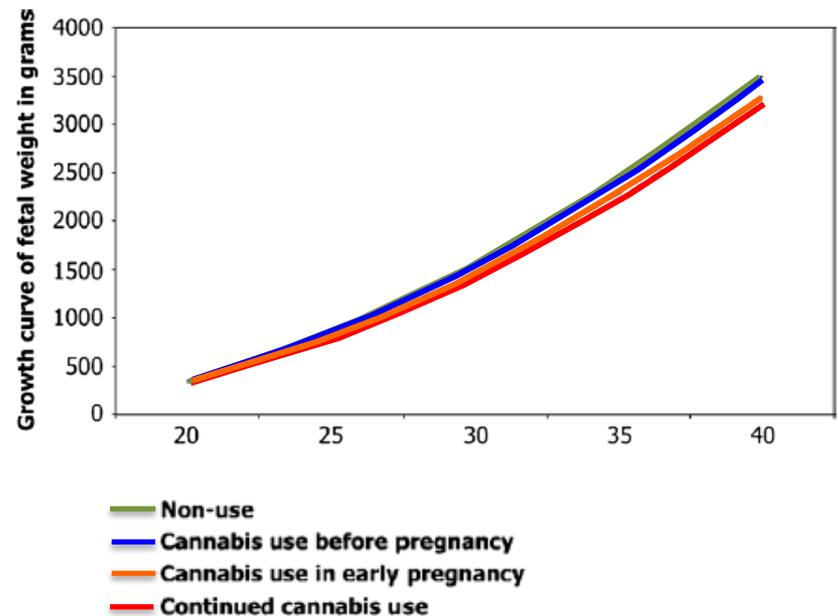
# Intrauterine Cannabis Exposure

## Intrauterine Cannabis Exposure Affects Fetal Growth Trajectories: The Generation R Study

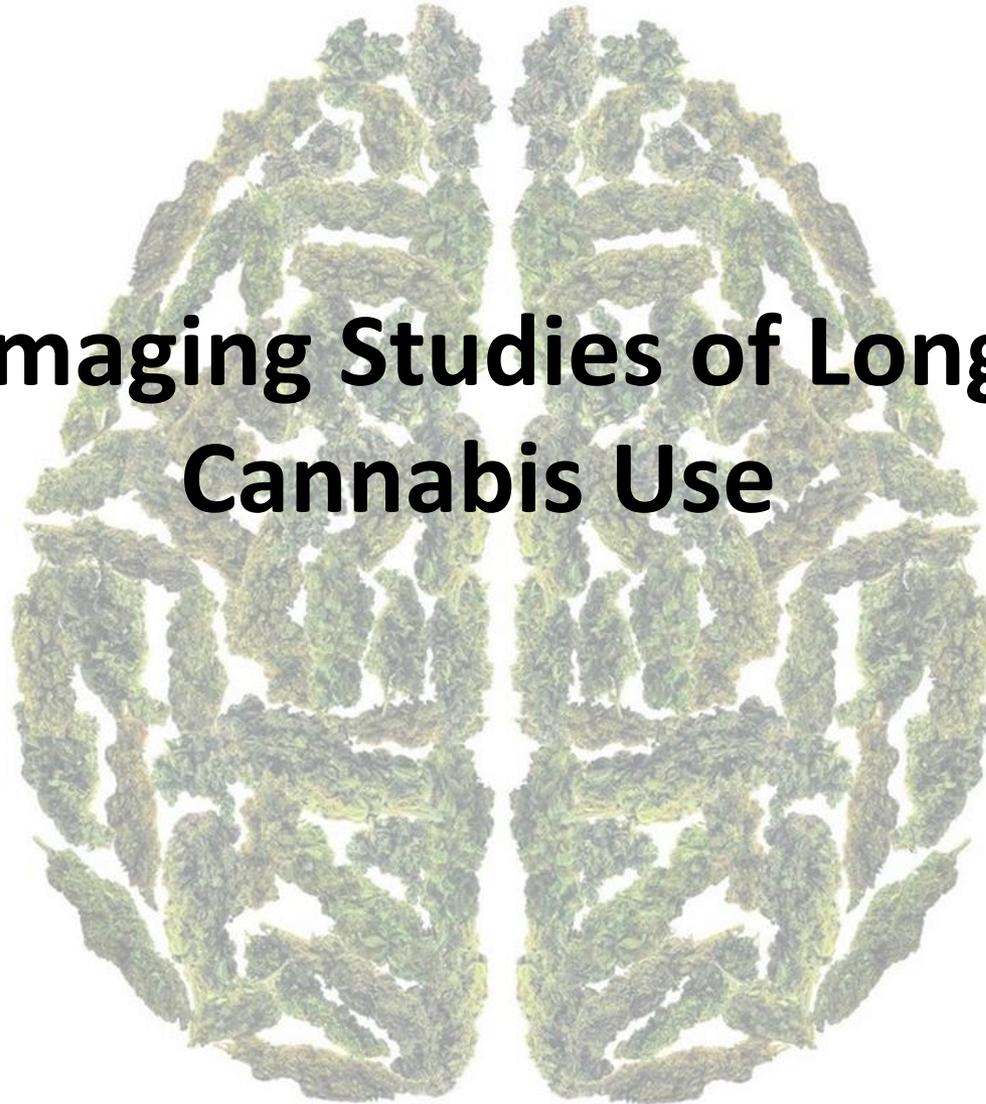
HANAN EL MARROUN, M.Sc., HENNING TIEMEIER, Ph.D., ERIC A.P. STEEGERS, Ph.D., M.D.,  
VINCENT W.V. JADDOE, Ph.D., M.D., ALBERT HOFMAN, Ph.D., M.D.,  
FRANK C. VERHULST, Ph.D., M.D., WIM VAN DEN BRINK, Ph.D., M.D.,  
AND ANJA C. HUIZINK, Ph.D.

### ABSTRACT

**Objective:** Cannabis is the most commonly consumed illicit drug among pregnant women. Intrauterine exposure to cannabis may result in risks for the developing fetus. The importance of intrauterine growth on subsequent psychological and behavioral child development has been demonstrated. This study examined the relation between maternal cannabis use and fetal growth until birth in a population-based sample. **Method:** Approximately 7,452 mothers enrolled during pregnancy and provided information on substance use and fetal growth. Fetal growth was determined using ultrasound measures in early, mid-, and late pregnancy. Additionally, birth weight was assessed. **Results:** Maternal cannabis use during pregnancy was associated with growth restriction in mid- and late pregnancy and with lower birth weight. This growth reduction was most pronounced for fetuses exposed to continued maternal cannabis use during pregnancy. Fetal weight in cannabis-exposed fetuses showed a growth reduction of  $-14.44$  g/week (95% confidence interval  $-22.94$  to  $-5.94$ ,  $p = .001$ ) and head circumference ( $-0.21$  mm/week, 95% confidence interval  $-0.42$  to  $0.02$ ,  $p = .07$ ), compared with nonexposed fetuses. Maternal cannabis use during pregnancy resulted in more pronounced growth restriction than maternal tobacco use. Paternal cannabis use was not associated with fetal growth restriction. **Conclusions:** Maternal cannabis use, even for a short period, may be associated with several adverse fetal growth trajectories. *J. Am. Acad. Child Adolesc. Psychiatry*, 2009;48(12):1173–1181. **Key Words:** intrauterine cannabis exposure, fetal growth, ultrasound measurements, longitudinal population cohort.



# Neuroimaging Studies of Long-Term Cannabis Use



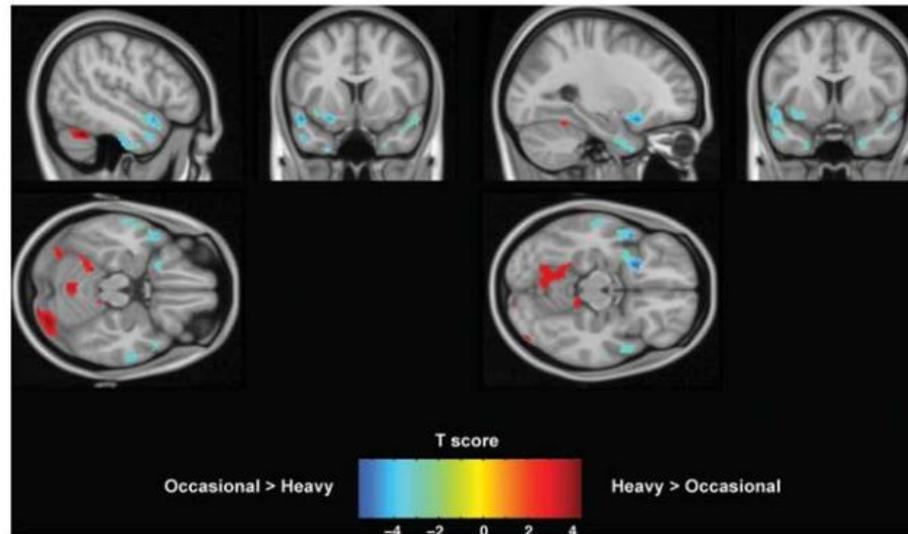
## Long-Term Effects of Cannabis on Brain Structure

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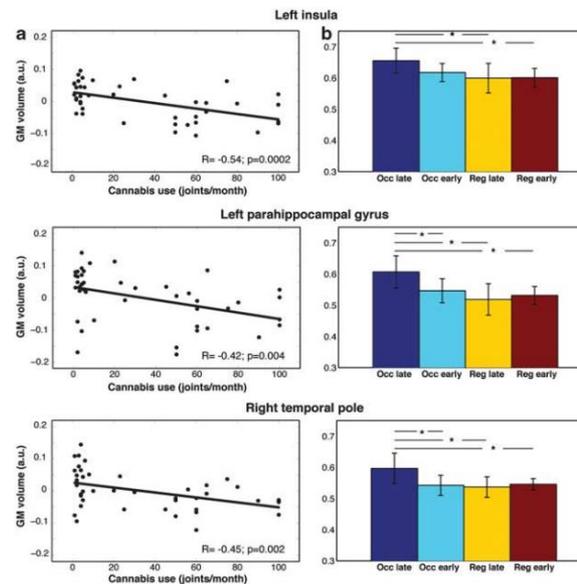
The dose-dependent toxicity of the main psychoactive component of cannabis in brain regions rich in cannabinoid CB1 receptors is well known in animal studies. However, research in humans does not show common findings across studies regarding the brain regions that are affected after long-term exposure to cannabis. In the present study, we investigate (using Voxel-based Morphometry) gray matter changes in a group of regular cannabis smokers in comparison with a group of occasional smokers matched by the years of cannabis use. We provide evidence that regular cannabis use is associated with gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex; these regions are rich in cannabinoid CB1 receptors and functionally associated with motivational, emotional, and affective processing. Furthermore, these changes correlate with the frequency of cannabis use in the 3 months before inclusion in the study. The age of onset of drug use also influences the magnitude of these changes. Significant gray matter volume reduction could result either from heavy consumption unrelated to the age of onset or instead from recreational cannabis use initiated at an adolescent age. In contrast, the larger gray matter volume detected in the cerebellum of regular smokers without any correlation with the monthly consumption of cannabis may be related to developmental (ontogenic) processes that occur in adolescence.

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**Blue areas indicate areas of reduced volume in regular cannabis users compared to occasional users**

**Figure 1** Voxel-Based Morphometry results on gray matter. Cold color bar shows regions where gray matter volume is lower in regular smokers compared with occasional ones. Hot color bar represents the opposite contrast. Maps are thresholded at  $P < 0.005$  and  $k > 60$  and superposed on a standard brain in the MNI space. Figure shows results in planes centered at  $-26, 7, 14$  mm and  $-48, 10, -19$  mm. Color bars represent T score.



**Figure 2** (a) Correlation between the modulated gray matter intensity at the center of gravity of the significant clusters and the monthly frequency of joints smoked during 3 months before inclusion in the study. Lines represent the fitting of the distribution of the values. Pearson's correlation coefficient and  $P$ -value are shown at the bottom of each plot. (b) Mean GM volume across the four subgroups (Occasional late, Occasional early, Regular late, Regular early). Whiskers represent 95% confidence interval, horizontal lines represent significant comparisons and stars the significance level ( $P < 0.05$ ).



## Altered frontal cortical volume and decision making in adolescent cannabis users

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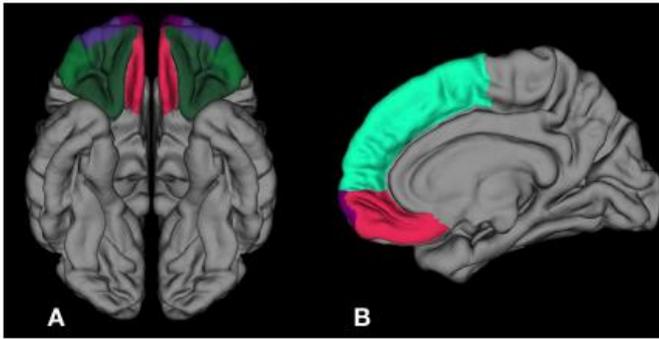
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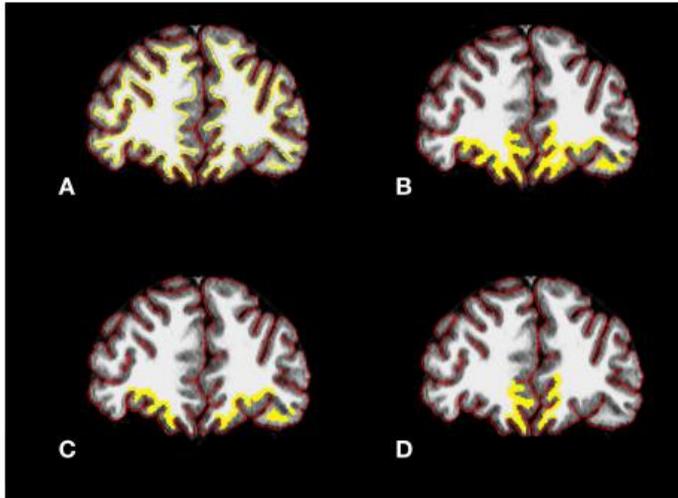
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Anticipating future outcomes is central to decision making and a failure to consider long-term consequences may lead to impulsive choices. Adolescence is a vulnerable period during which underdeveloped prefrontal cortical systems may contribute to 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.

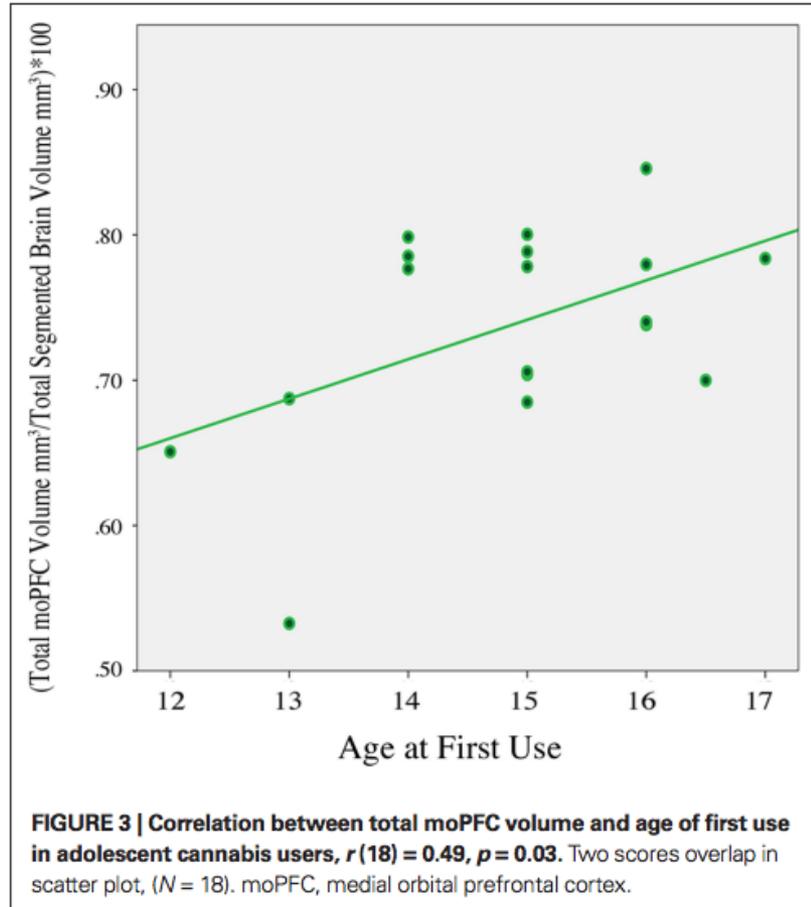
**Keywords:** adolescence, cannabis, prefrontal, orbitofrontal, decision making, impulsivity, marijuana, development



**FIGURE 1 | Inferior and sagittal 3-D representations with ROIs and reference regions employed in FreeSurfer including: (A)** moPFC in red, loPFC in dark green, and frontal pole in purple and **(B)** medial view showing superior PFC in light green, moPFC in red, and frontal pole in purple. ROI, region of interest; PFC, prefrontal cortex; loPFC, lateral orbital prefrontal cortex; moPFC, medial orbital prefrontal cortex.



**FIGURE 2 | Coronal sections from CA subject with (A)** cortical (red) and white matter (yellow) surfaces outlined, **(B)** ROI in entire orbital prefrontal cortical region, **(C)** ROI in loPFC, and **(D)** ROI in moPFC. CA, cannabis abusing; ROI, region of interest; loPFC, lateral orbital prefrontal cortex; moPFC, medial orbital prefrontal cortex. Yellow ROI line was thickened for visibility in **(B–D)**.



**FIGURE 3 | Correlation between total moPFC volume and age of first use in adolescent cannabis users,  $r(18) = 0.49, p = 0.03$ . Two scores overlap in scatter plot, ( $N = 18$ ). moPFC, medial orbital prefrontal cortex.**

***Earlier age of first use was associated with greater volumetric reductions in medial orbitofrontal cortex (mOFC)***

# Long-term effects of marijuana use on the brain

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Edited by Cameron Carter, University of California Davis Centre for Neuroscience, Sacramento, CA, and accepted by the Editorial Board October 13, 2014 (received for review August 8, 2014)

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.

MRI | orbitofrontal cortex | functional connectivity | resting state fMRI | diffusion tensor imaging

The rate of marijuana use has had a steady increase since 2007 (1). Among >400 chemical compounds, marijuana's effects are primarily attributed to  $\delta$ -9-tetrahydrocannabinol (THC), which is the main psychoactive ingredient in the cannabis plant. THC binds to cannabinoid receptors, which are ubiquitous in the brain. Consequently, exposure to THC leads to neural changes affecting diverse cognitive processes. These changes have been observed to be long-lasting, suggesting that neural changes due to marijuana use may affect neural architecture (2). However, to date, these brain changes as a result of marijuana use remains equivocal. Specifically, although functional changes have been widely reported across cognitive domains in both adult and adolescent cannabis users (3–6), structural changes associated with marijuana use have not been consistent. Although some have reported decreases in regional brain volume such as in the hippocampus, orbitofrontal cortex, amygdala, and striatum (7–12), others have reported increases in amygdala, nucleus accumbens, and cerebellar volumes in chronic marijuana users (13–15). However, others have reported no observable difference in global or regional gray or white matter volumes in chronic marijuana users (16, 17). These inconsistencies could be attributed to methodological differences across studies pertaining to study samples (e.g., severity of marijuana use, age, sex, comorbidity with other substance use or psychiatric disorders) and/or study design (e.g., study modality, regions of interest).

Because THC binds to cannabinoid 1 (CB1) receptors in the brain, when differences are observed, these morphological changes associated with marijuana use have been reported in

CB1 receptor-enriched areas such as the orbitofrontal cortex, anterior cingulate, striatum, amygdala, insula, hippocampus, and cerebellum (2, 11, 13, 18). CB1 receptors are widely distributed in the neocortex, but more restricted in the hindbrain and the spinal cord (19). For example, in a recent study by Battistella et al. (18), they found significant brain volume reductions in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex (OFC) in regular marijuana users compared with occasional users. Whether these reductions in brain volume lead to downstream changes in brain organization and function, however, is still unknown.

Nevertheless, emergent studies have demonstrated a link between brain structure and connectivity. For example, Van den Heuvel et al. and Greicius et al. demonstrated robust structural connections between white matter indexes and functional connectivity strength within the default mode network (20, 21). Similarly, others have reported correlated patterns of gray matter structure and connectivity that are in many ways reflective of the underlying intrinsic networks (22). Thus, given the literature suggesting a direct relationship between structural and functional connectivity, it is likely that connectivity changes would also be present where alterations in brain volume are observed as a result of marijuana use.

The goal of this study was to characterize alterations in brain morphometry and determine potential downstream effects in connectivity as a result of chronic marijuana use. To address the existing inconsistencies in the literature that may be in part due to methodological issues, we (i) used three different MRI techniques to investigate a large cohort of well-characterized chronic cannabis users with a wide age range (allowing for characterization without developmental or maturational biases) and compared them to age- and sex-matched nonusing controls; (ii) examined observable global (rather than select) gray matter

## Significance

The existing literature on the long-term effects of marijuana on the brain provides an inconsistent picture (i.e., presence or absence of structural changes) due to methodological differences across studies. We overcame these methodological issues by collecting multimodal measures in a large group of chronic marijuana using adults with a wide age range that allows for characterization of changes across lifespan without developmental or maturational biases as in other studies. Our findings suggest that chronic marijuana use is associated with complex neuroadaptive processes and that onset and duration of use have unique effects on these processes.

Author contributions: F.M.F. and V.D.C. designed research; F.M.F. and J.S. performed research; S.A., J.S.S., E.D., and A.C. analyzed data; and F.M.F. and S.A. wrote the paper.

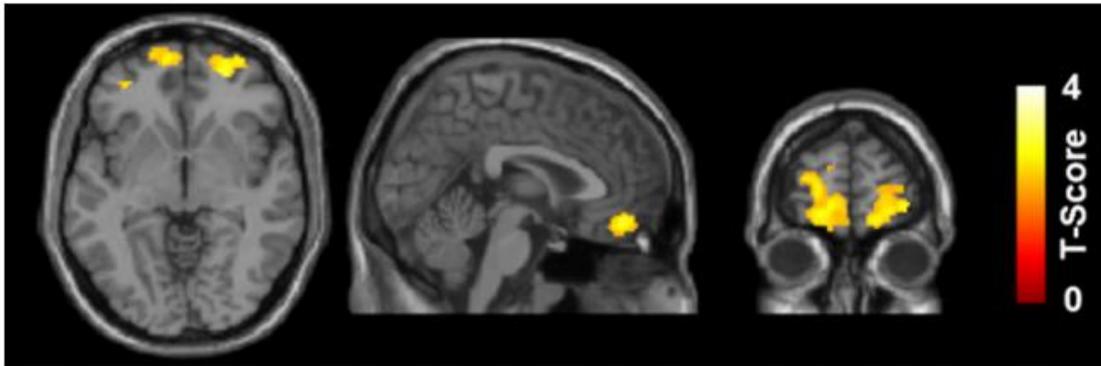
The authors declare no conflict of interest.

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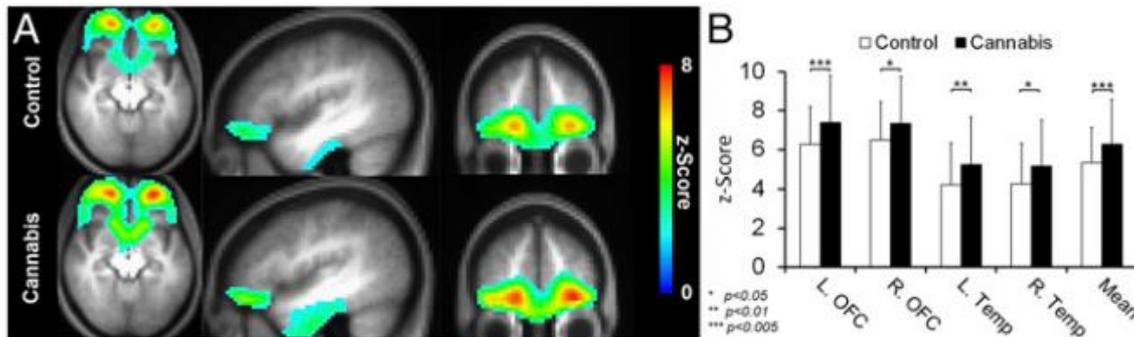
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**Fig. 1.** Group comparison of the gray matter volume by SPM8 plus DARTEL analysis demonstrates significant reduction of gray matter volume in bilateral orbitofrontal gyri (AAL atlas) in marijuana users compared with controls. Right side of the image represents the right hemisphere in axial view.

*Marijuana users linked to reduced bilateral orbitofrontal cortex volume...*



**Fig. 2.** (A) The average functional connectivity maps (i.e., OFC network; bilateral OFC and temporal gyri) of the control and cannabis groups are superimposed on their average T<sub>1</sub>-weighted image. For illustration purposes, the z-score maps were arbitrarily thresholded (z score  $\geq 2$ ,  $k \geq 50$ ) to qualitatively visualize the difference in the intensity and cluster size. (B) Mean fcMRI z scores are shown for the orbitofrontal network for cannabis and controls groups. The cannabis group showed higher resting activity in the bilateral OFC and temporal gyri compared with the control group.

*And, marijuana users exhibited higher resting activity in the bilateral orbitofrontal cortex and anterior temporal regions.*

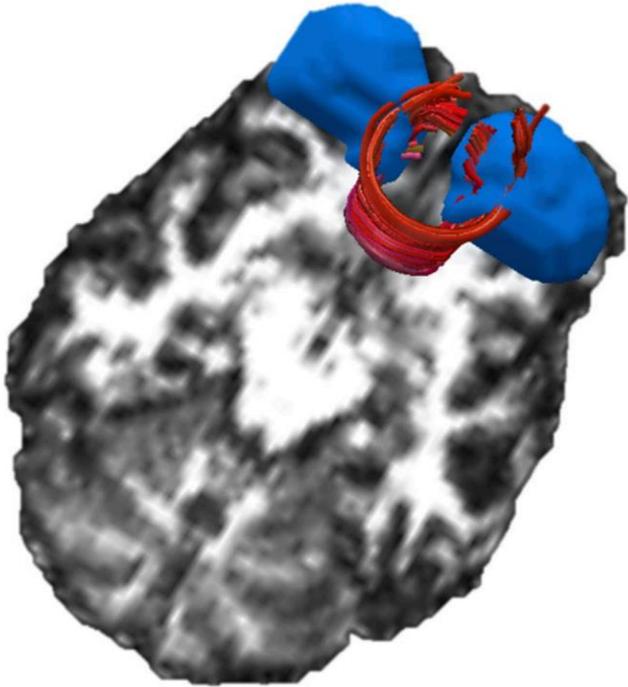


Fig. 3. A representative participant's forceps minor tract (in red) and gray matter nodes (in blue) is overlaid on its corresponding fractional anisotropy map.

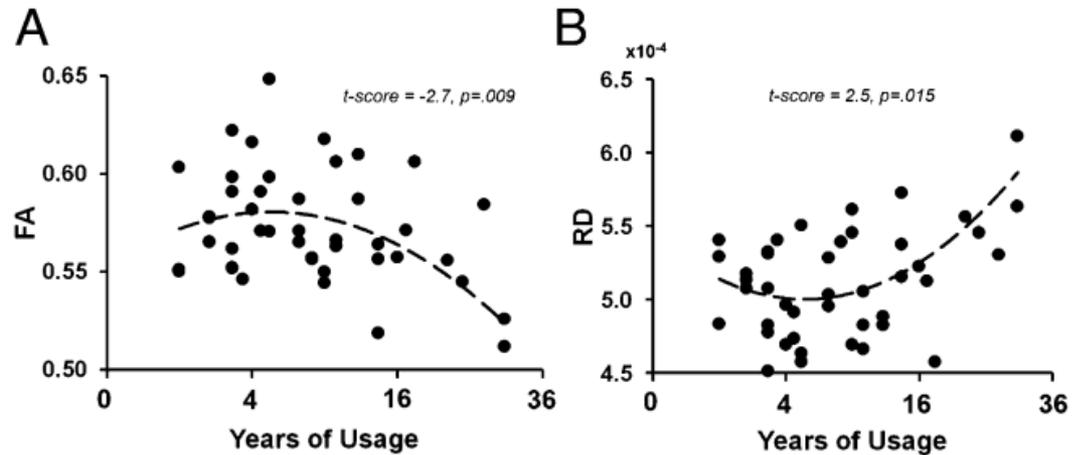


Fig. 4. The relationship between duration of marijuana use and forceps minor's FA (A) and RD (B). The quadratic curve showed the best fit per AIC. The x axis has been transformed to "square root of years of use" because of gap between participants' years of use.

***Continued marijuana use is associated with reduced microstructural integrity (↓ fractional anisotropy, ↑ radial diffusivity) of white matter pathways connecting prefrontal areas.***

## Effect of long-term cannabis use on axonal fibre connectivity

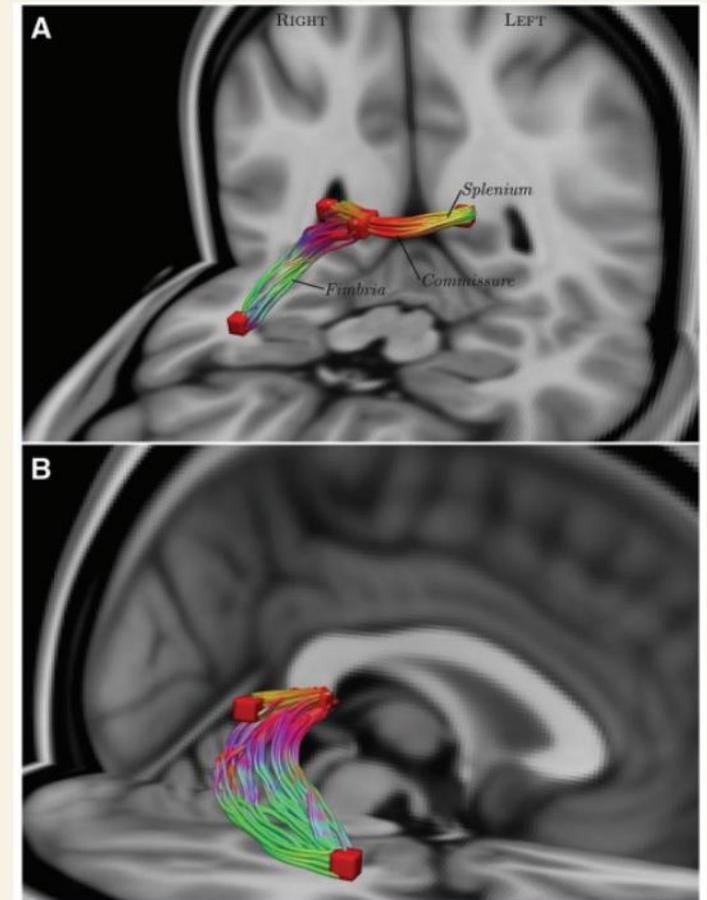
Andrew Zalesky,<sup>1</sup> Nadia Solowij,<sup>2</sup> Murat Yücel,<sup>1</sup> Dan I. Lubman,<sup>3</sup> Michael Takagi,<sup>1</sup> Ian H. Harding,<sup>1</sup> Valentina Lorenzetti,<sup>1</sup> Ruopeng Wang,<sup>4</sup> Karissa Searle,<sup>1</sup> Christos Pantelis<sup>1</sup> and Marc Seal<sup>5</sup>

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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.

***Reduced connectivity in the hippocampal commissure, posterior portion of the corpus callosum, and fimbria***



**Figure 3** The right fimbria of the hippocampus, hippocampal commissure and splenium comprised fewer streamlines in cannabis users compared to non-users ( $P < 0.05$ , corrected). Voxels interconnected by fewer streamlines are coloured red and the corresponding streamlines via which they are interconnected are coloured such that: left–right is red, superior–inferior is blue and anterior–posterior is green. **A** and **B** show different oblique views. The splenium and hippocampal commissure are obscured in **B** by the sagittal slice of the underlay image.

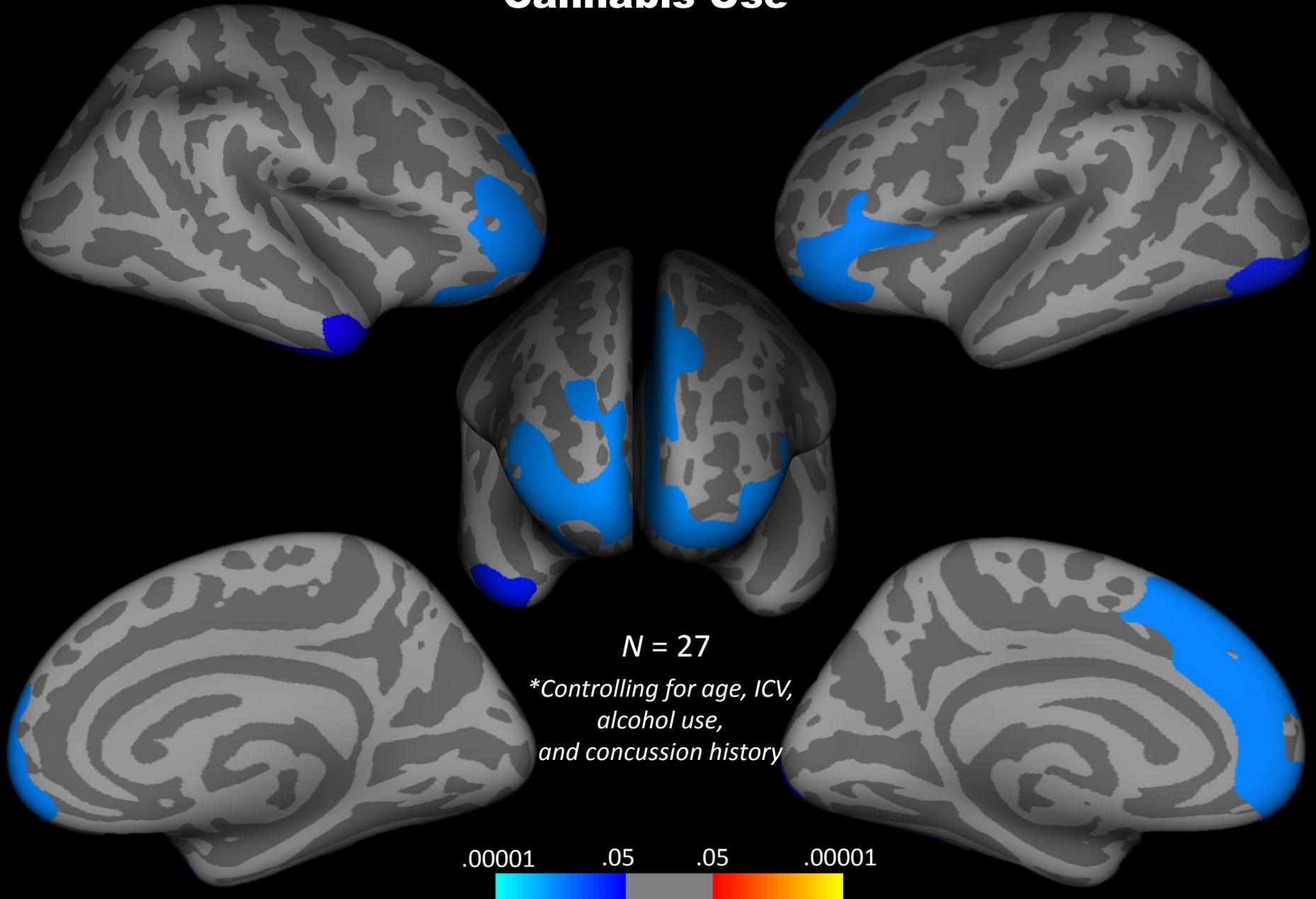
**Substance Use Research at  
the Vermont Center for  
Children, Youth, and Families**

# Brain Structural Correlates of Cannabis Use in Young, Healthy Ice Hockey Players

# Sample

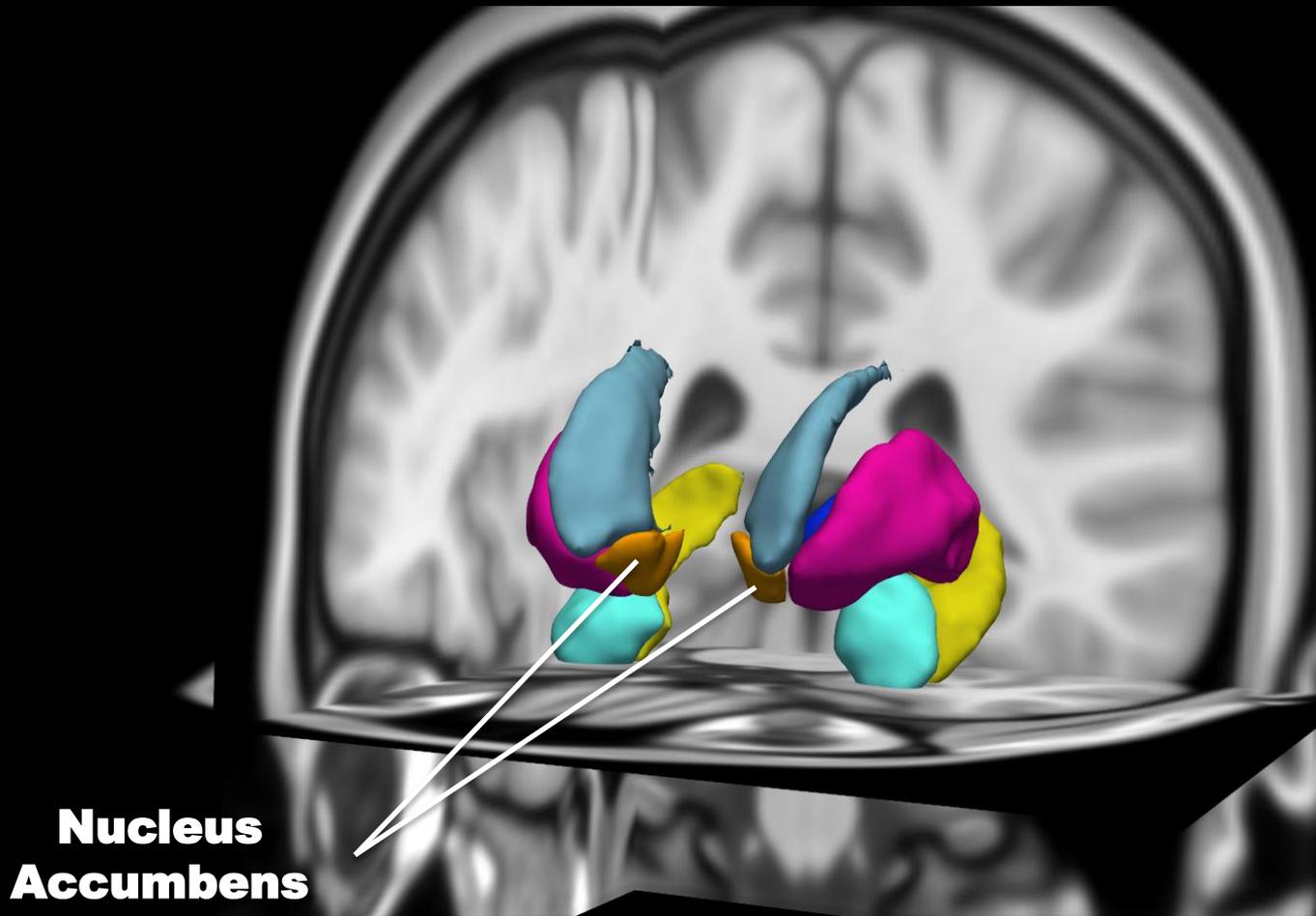
- Twenty-nine male subjects were recruited from preparatory school and collegiate ice hockey teams, and were between 14 and 23 years of age ( $M = 17.8$ ,  $SD = 2.2$ ).
- Of the 29 subjects that enrolled in the study, 27 underwent both neuroimaging and cognitive testing (2 subjects were unable to complete cognitive testing).

# Cortical Thinning Associated with Lifetime Cannabis Use



# **Cannabis Use and the Reward Pathway**

# Cannabis and the Reward Pathway



# Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users

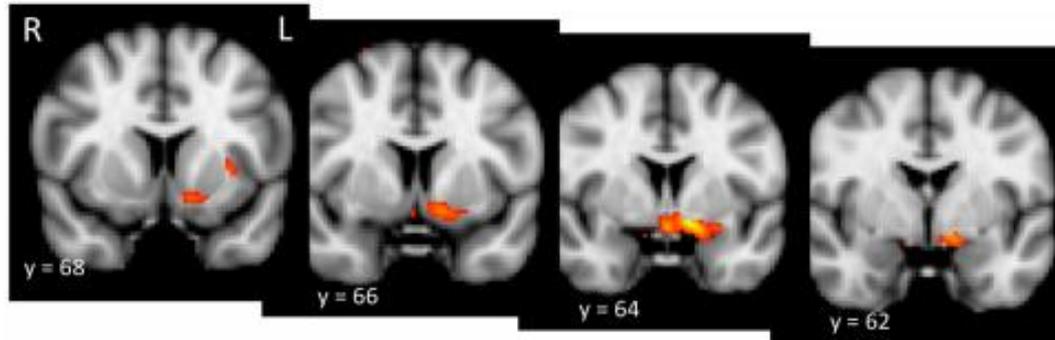
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Marijuana is the most commonly used illicit drug in the United States, but little is known about its effects on the human brain, particularly on reward/aversion regions implicated in addiction, such as the nucleus accumbens and amygdala. Animal studies show structural changes in brain regions such as the nucleus accumbens after exposure to  $\Delta 9$ -tetrahydrocannabinol, but less is known about cannabis use and brain morphometry in these regions in humans. We collected high-resolution MRI scans on young adult recreational marijuana users and nonusing controls and conducted three independent analyses of morphometry in these structures: (1) gray matter density using voxel-based morphometry, (2) volume (total brain and regional volumes), and (3) shape (surface morphometry). Gray matter density analyses revealed greater gray matter density in marijuana users than in control participants in the left nucleus accumbens extending to subcallosal cortex, hypothalamus, sublenticular extended amygdala, and left amygdala, even after controlling for age, sex, alcohol use, and cigarette smoking. Trend-level effects were observed for a volume increase in the left nucleus accumbens only. Significant shape differences were detected in the left nucleus accumbens and right amygdala. The left nucleus accumbens showed salient exposure-dependent alterations across all three measures and an altered multimodal relationship across measures in the marijuana group. These data suggest that marijuana exposure, even in young recreational users, is associated with exposure-dependent alterations of the neural matrix of core reward structures and is consistent with animal studies of changes in dendritic arborization.

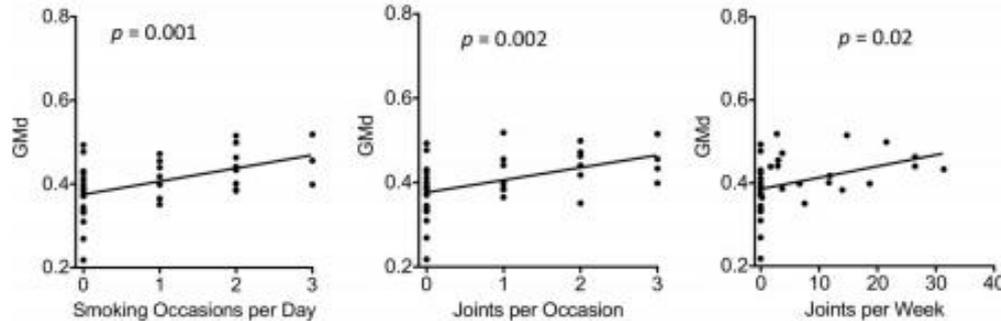
*Key words:* cannabis; gray matter density; marijuana; multimodal imaging; reward; topology/shape

**A** Gray Matter Density: Marijuana > Control Participants

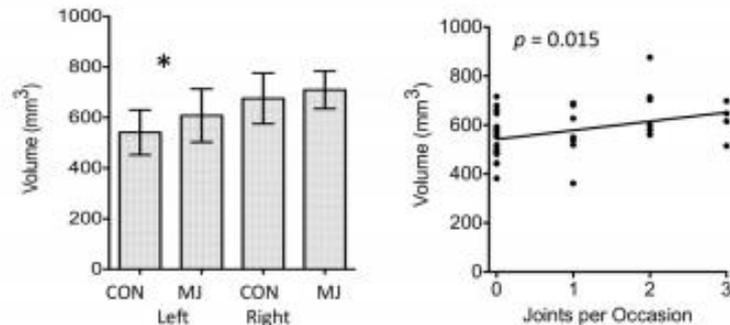


*More frequent cannabis use was associated with larger nucleus accumbens volumes—an area that has been termed the “pleasure center” of the brain and strongly tied to addictive behaviors*

**B** Associations Drug Use Behavior and Gray Matter Density in Left Nucleus Accumbens



**C** Volume and Associations with Drug Use in Left Nucleus Accumbens



# Weed or Wheel! fMRI, Behavioural, and Toxicological Investigations of How Cannabis Smoking Affects Skills Necessary for Driving

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## Abstract

Marijuana is the most widely used illicit drug, however its effects on cognitive functions underlying safe driving remain mostly unexplored. Our goal was to evaluate the impact of cannabis on the driving ability of occasional smokers, by investigating changes in the brain network involved in a tracking task. The subject characteristics, the percentage of  $\Delta^9$ -Tetrahydrocannabinol in the joint, and the inhaled dose were in accordance with real-life conditions. Thirty-one male volunteers were enrolled in this study that includes clinical and toxicological aspects together with functional magnetic resonance imaging of the brain and measurements of psychomotor skills. The fMRI paradigm was based on a visuo-motor tracking task, alternating active tracking blocks with passive tracking viewing and rest condition. We show that cannabis smoking, even at low  $\Delta^9$ -Tetrahydrocannabinol blood concentrations, decreases psychomotor skills and alters the activity of the brain networks involved in cognition. The relative decrease of Blood Oxygen Level Dependent response (BOLD) after cannabis smoking in the anterior insula, dorsomedial thalamus, and striatum compared to placebo smoking suggests an alteration of the network involved in saliency detection. In addition, the decrease of BOLD response in the right superior parietal cortex and in the dorsolateral prefrontal cortex indicates the involvement of the Control Executive network known to operate once the saliencies are identified. Furthermore, cannabis increases activity in the rostral anterior cingulate cortex and ventromedial prefrontal cortices, suggesting an increase in self-oriented mental activity. Subjects are more attracted by intrapersonal stimuli ("self") and fail to attend to task performance, leading to an insufficient allocation of task-oriented resources and to sub-optimal performance. These effects correlate with the subjective feeling of confusion rather than with the blood level of  $\Delta^9$ -Tetrahydrocannabinol. These findings bolster the zero-tolerance policy adopted in several countries that prohibits the presence of any amount of drugs in blood while driving.

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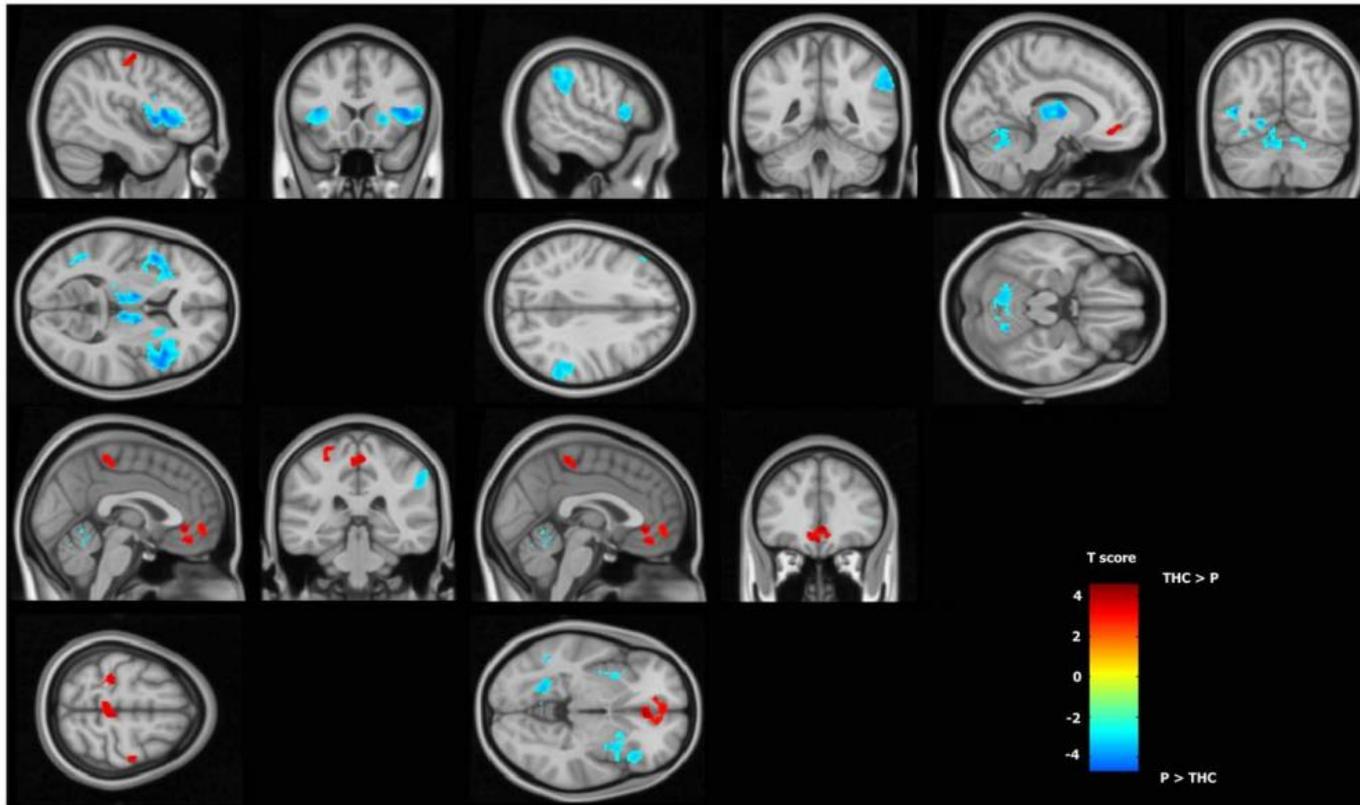
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**Competing Interests:** The authors have declared that no competing interests exist.

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These authors contributed equally to this work.



**Figure 6. Effect of THC smoking on brain function during the visuo-motor tracking task.** When comparing the THC and the Placebo sessions, fMRI BOLD response changes in the Active tracking task vs Passive condition reveal major alteration of brain networks. Hot colour bar represents regions showing an increase in BOLD signal after the cannabis smoking. Cold colour bar represents the opposite contrast. Maps are thresholded at  $p < 0.005$  and  $k > 40$  and superposed on a standard brain in the MNI (Montreal Neurological Institute) space.  
doi:10.1371/journal.pone.0052545.g006

***Decrease of BOLD response in the right superior parietal cortex and in the dorsolateral prefrontal cortex indicates the involvement of the Control Executive network. Furthermore, cannabis increases activity in the rostral anterior cingulate cortex and ventromedial prefrontal cortices, suggesting an increase in self-oriented mental activity. Subjects are more attracted by intrapersonal stimuli (“self”) and fail to attend to task performance, leading to an insufficient allocation of task-oriented resources and to sub-optimal performance.***

# Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings

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## Abstract

**Background:** The growing concern about cannabis use, the most commonly used illicit drug worldwide, has led to a significant increase in the number of human studies using neuroimaging techniques to determine the effect of cannabis on brain structure and function. We conducted a systematic review to assess the evidence of the impact of chronic cannabis use on brain structure and function in adults and adolescents.

**Methods:** Papers published until August 2012 were included from EMBASE, Medline, PubMed and LILACS databases following a comprehensive search strategy and pre-determined set of criteria for article selection. Only neuroimaging studies involving chronic cannabis users with a matched control group were considered.

**Results:** One hundred and forty-two studies were identified, of which 43 met the established criteria. Eight studies were in adolescent population. Neuroimaging studies provide evidence of morphological brain alterations in both population groups, particularly in the medial temporal and frontal cortices, as well as the cerebellum. These effects may be related to the amount of cannabis exposure. Functional neuroimaging studies suggest different patterns of resting global and brain activity during the performance of several cognitive tasks both in adolescents and adults, which may indicate compensatory effects in response to chronic cannabis exposure.

**Limitations:** However, the results pointed out methodological limitations of the work conducted to date and considerable heterogeneity in the findings.

**Conclusion:** Chronic cannabis use may alter brain structure and function in adult and adolescent population. Further studies should consider the use of convergent methodology, prospective large samples involving adolescent to adulthood subjects, and data-sharing initiatives.

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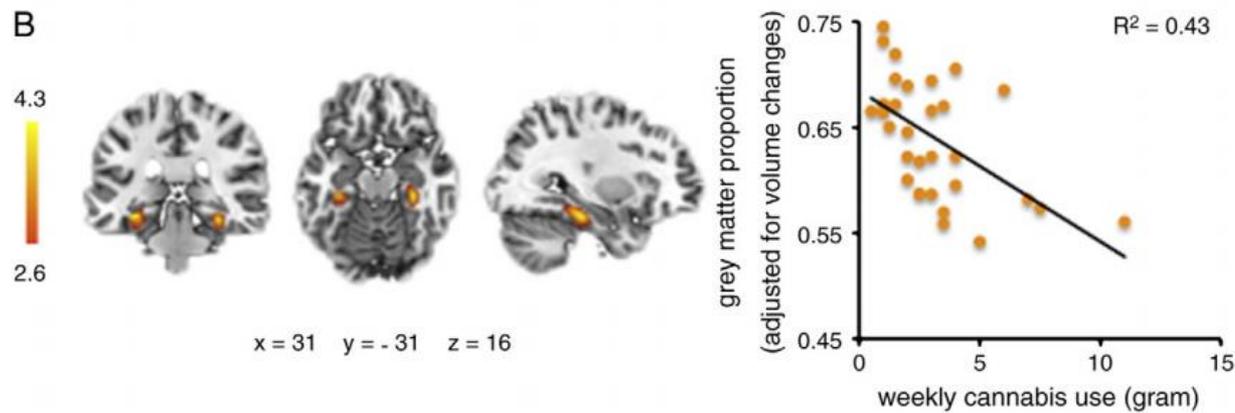
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# Review Findings

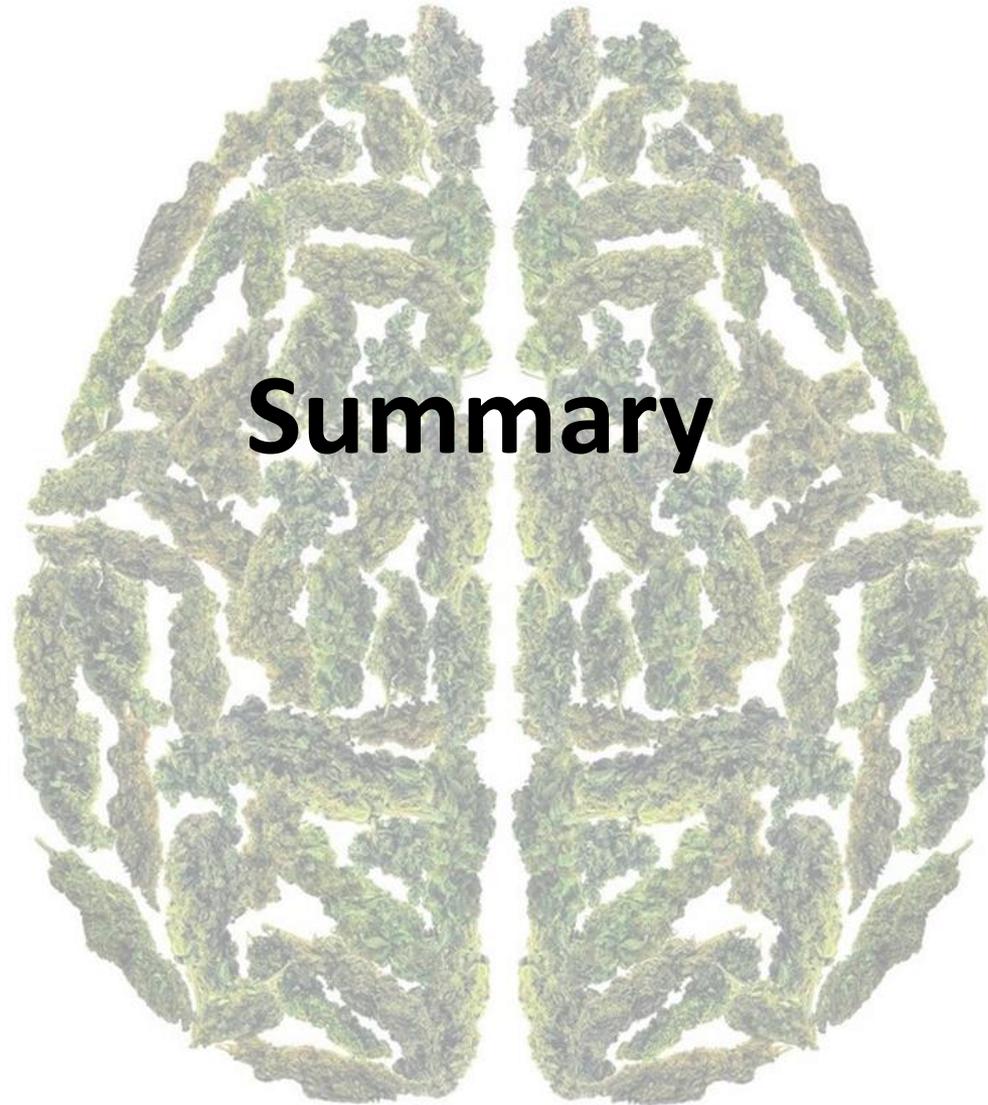
- In terms of structural findings, the most consistently reported brain alteration was *reduced hippocampal volume among adult cannabis users*—which was shown to persist even after several months of abstinence in one study and also to be related to amount of cannabis use (Ashtari et al., 2011; Cousijn et al., 2012; Matochik et al., 2005; Yücel et al., 2008).
- Diffusion imaging studies found *differences in the mean diffusivity or fractional anisotropy* in the corpus callosum and the frontal white matter (Barrick et al., 2008; Gruber et al., 2011)



**Fig. 2.** Relation between grey matter volume in Regions of Interest and individual characteristics of cannabis use and dependence in heavy cannabis users. (A) Right amygdala volume correlated negatively with severity of cannabis dependence (CUDIT score). (B) Bilateral hippocampus volume correlated negatively with weekly cannabis use (gram). Clusters of significant volume differences ( $p < .005$ , FWE cluster-corrected at  $p < .05$  adjusted for region of interest volume) are overlaid on a standard MNI brain. Right side of the brain is depicted at right side. Graphs show correlation of proportional volume in peak voxel with the dependent variable of interest.

Functional imaging studies of chronic cannabis users have demonstrated altered patterns of brain activity during a range of cognitive tasks—including tasks of attention, memory, and behavioral control.

- During a visual-attention task, both active and abstinent chronic cannabis users demonstrated ***decreased activation in the right prefrontal, medial and dorsal parietal cortices*** (Chang et al., 2006)
- Early age of onset and estimated cumulative cannabis lifetime exposure were both associated with ***reduced activation in the right prefrontal cortex*** (Chang et al., 2006)
- Block et al. (2002) found that cannabis users performed verbal memory tasks more poorly than controls, and their poorer performance was associated with ***reduced activation in the prefrontal cortex and greater activation in the posterior cerebellum***
- Jager et al. (2007) described ***attenuated activity in the right dorsolateral prefrontal cortex and bilateral parahippocampal gyri*** in cannabis users despite normal performance in an associative memory task



# Summary

# Summary

Epidemiology studies indicate that cannabis use increases the risk of accidents and can produce dependence, and that there are consistent associations between regular cannabis use and poor psychosocial outcomes and mental health in adulthood

Structural neuroimaging studies of long-term cannabis use consistently reveal volumetric reductions in key emotion regulatory regions of the brain—which may account for associations between anxiety and cannabis use.

Structural neuroimaging studies of long-term cannabis use also consistently reveal volumetric reductions in the hippocampus—a region of the brain strongly implicated in learning and memory. Such findings may explain epidemiological reports of cannabis use being associated with cognitive impairment and lower educational attainment.

# Summary (continued)

Functional imaging studies of chronic cannabis users have demonstrated altered patterns of brain activity during a range of cognitive tasks—including tasks of attention, memory, and behavioral control.

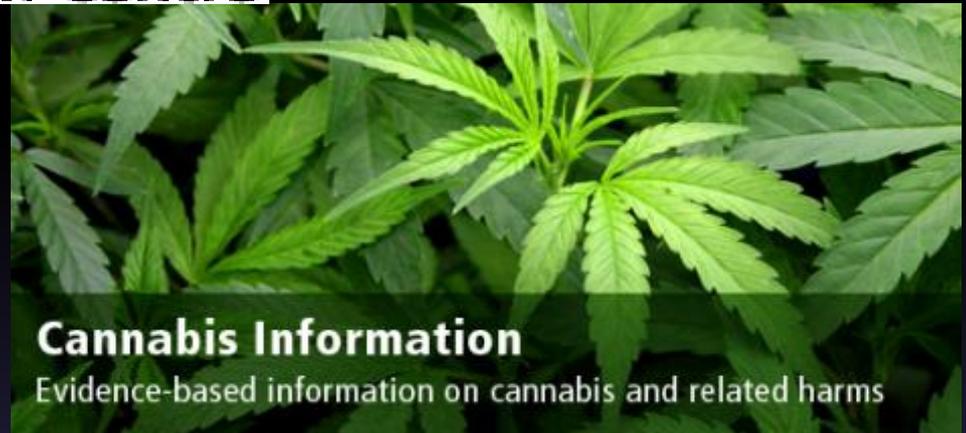
# Summary

- Cannabis use is associated with increased levels of mental illness; this relationship appears to be moderated by frequency of use and potency of the substance.
- Growing evidence that cannabis use may have causal impact on lowering of the age of onset of Psychotic Disorders; related to age of onset of cannabis use, frequency and potency.
  - Probability of occurrence is “low” in low risk samples
- Cannabis use can probably be considered a risk factor for poor outcomes in functioning across mental illnesses.
- Data do not support the use of cannabis to treat any type of mental illness

**ncpic**

national cannabis  
prevention and  
information centre

[ncpic.org.au](http://ncpic.org.au)



<http://www.drugabuse.gov/drugs-abuse/marijuana>

Alan Budney PHD Giesel School Of  
Medicine, Dartmouth

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