Review

Biological Psychiatry

# Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review

Samantha J. Broyd, Hendrika H. van Hell, Camilla Beale, Murat Yücel, and Nadia Solowij

**ABSTRACT**

Cannabis use has been associated with impaired cognition during acute intoxication as well as in the unintoxicated state in long-term users. However, the evidence has been mixed and contested, and no systematic reviews of the literature on neuropsychological task-based measures of cognition have been conducted in an attempt to synthesize the findings. We systematically review the empirical research published in the past decade (from January 2004 to February 2015) on acute and chronic effects of cannabis and cannabinoids and on persistence or recovery after abstinence. We summarize the findings into the major categories of the cognitive domains investigated, considering sample characteristics and associations with various cannabis use parameters. Verbal learning and memory and attention are most consistently impaired by acute and chronic exposure to cannabis. Psychomotor function is most affected during acute intoxication, with some evidence for persistence in chronic users and after cessation of use. Impaired verbal memory, attention, and some executive functions may persist after prolonged abstinence, but persistence or recovery across all cognitive domains remains underresearched. Associations between poorer performance and a range of cannabis use parameters, including a younger age of onset, are frequently reported. Little further evidence has emerged for the development of tolerance to the acutely impairing effects of cannabis. Evidence for potential protection from harmful effects by cannabidiol continues to increase but is not definitive. In light of increasing trends toward legalization of cannabis, the knowledge gained from this body of research needs to be incorporated into strategies to minimize harm.

*Keywords:* Attention, Brain, Cannabis, Cognition, Executive function, Memory

http://dx.doi.org/10.1016/j.biopsych.2015.12.002

Shifts in public opinion and policies toward legalization of cannabis are poised to result in an increase in the prevalence of cannabis use beyond the 178 million users estimated to exist today (1–3). Although most individuals who try cannabis do not go on to use it regularly (1,2), individuals who do so risk adverse effects to physical and mental health (4). Negative sequelae that have been attributed to regular and prolonged cannabis use include alterations to brain morphology (5–7) and function (8–11); psychosis risk (12,13); poor psychosocial outcomes (4,14–17); and impaired cognition, especially deficits in attention, learning and memory (18–21), and executive functions (9,22). Morphological and connectivity changes in brain structures with high amounts of cannabinoid receptors (e.g., hippocampus, prefrontal cortex, cerebellum) (23) may mediate observed cognitive deficits in cannabis users (5–7, 9–11,24), although direct structure/function relationships are not readily demonstrated.

A substantial number of studies have been published in recent years, prompted by renewed interest in understanding the effects of cannabis on the brain partly as a result of mounting evidence for links between cannabis use and psychosis (25–28) and recognition of similarities between cognitive impairment in cannabis users and deficits observed in patients with schizophrenia (19). Interest has emerged in examining the effects of different compounds within cannabis plant matter, specifically (−)-*trans*-$\Delta^9$-tetrahydrocannabinol (THC), the primary psychoactive constituent considered to be psychotogenic, and cannabidiol (CBD), the second most abundant cannabinoid, shown to have antipsychotic properties (29) and to attenuate the psychotogenic effects of THC, with opposite effects on brain function (30). Recent critical reviews have focused on neuroimaging outcomes from acute cannabinoid challenge (9,31) and on brain morphology in chronic users (5,7,32). However, to date, the literature on neuropsychological task-based measures of cognition has not been examined in the form of a systematic review. We systematically review the empirical research published in the past decade. We identify core themes that have emerged from the recent literature or continue to plague this field and study limitations and future directions for this research area.

## METHOD

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1) (33). The search strategy and

ISSN: 0006-3223

Drug and Alcohol Dependence 162 (2016) 137–145

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

# Marijuana use trajectories and academic outcomes among college students

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ARTICLE INFO

*Article history:*
Received 15 October 2015
Received in revised form 26 February 2016
Accepted 28 February 2016
Available online 19 March 2016

*Keywords:*
Marijuana
College students
Early intervention
Academic performance
Longitudinal study
Trajectory modeling

ABSTRACT

*Background:* Marijuana is the most commonly used illicit drug by college students. Prior studies have established an association between marijuana use and poor academic performance in college, but research on the frequency of marijuana use over the entire college career is limited. The study objective was to examine the association of marijuana use trajectories on academic outcomes, including senior year enrollment, plans to graduate on time, and GPA.
*Methods:* Data were collected from a cohort of 3146 students from 11 colleges in North Carolina and Virginia at six time points across the college career. Group-based trajectory models were used to characterize longitudinal marijuana use patterns during college. Associations between marijuana trajectory groups and academic outcomes were modeled using random-effects linear and logistic regressions.
*Results:* Five marijuana trajectory groups were identified: non-users (69.0%), infrequent users (16.6%), decreasing users (4.7%), increasing users (5.8%), and frequent users (3.9%). Decreasing users and frequent users were more likely to drop out of college and plan to delay graduation when compared to non-users. All marijuana user groups reported lower GPAs, on average, than non-users.
*Conclusion:* These results identify marijuana use patterns that put students at risk for poor academic performance in college. Students who use marijuana frequently at the beginning of the college career are especially at risk for lower academic achievement than non-users, suggesting that early intervention is critical.



## 1. Introduction

Marijuana is the most commonly used illicit substance among college students, with 48.5% reporting lifetime use, 20.8% past month use, and 5.9% reporting daily use in 2013 (Johnston et al., 2015). Daily and past 30 day marijuana use among college students has risen steadily since 2007. Daily marijuana users exhibit more characteristics of dependence than less frequent users (Hammersley and Leon, 2006), which makes the increase in daily use particularly concerning. At the same time that daily use is increasing, perceptions of harm associated with regular marijuana use are declining; only 35.1% of young adults think smoking marijuana regularly places the user at great risk compared to 57.2% a decade ago (Johnston et al., 2015).

Prior research has found that college student marijuana users are more likely to be white, male, single, members of fraternities or sororities, non-athletes, not religious, cigarette smokers, and heavy episodic drinkers (Bell et al., 1997; Johnston et al., 2015; Buckman et al., 2011; Wechsler et al. 1997; Yusko et al., 2008; McCabe et al., 2005; Mohler-Kuo et al., 2003). Students who initiate marijuana prior to age 16 are more likely to continue to use marijuana in college and be regular users (Mohler-Kuo et al., 2003), and early age of initiation has been shown to be associated with problems later in life such as depression and drug dependence (Green and Ritter, 2000; Ellickson et al., 2005; Chen et al., 2009). In one study, initiation of marijuana use during freshman year was found to be associated with living on campus, using cigarettes or alcohol, and Hispanic ethnicity (Suerken et al., 2014).

Acute effects of marijuana use among college students include impaired driving (Whitehill et al., 2014) and engaging in risky sex-

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http://dx.doi.org/10.1016/j.drugalcdep.2016.02.041
0376-8716/

*Psychological Medicine* (2016), **46**, 841–854. © Cambridge University Press 2015
doi:10.1017/S0033291715002342

ORIGINAL ARTICLE

# Effect of high-potency cannabis on corpus callosum microstructure

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**Background.** The use of cannabis with higher Δ9-tetrahydrocannabinol content has been associated with greater risk, and earlier onset, of psychosis. However, the effect of cannabis potency on brain morphology has never been explored. Here, we investigated whether cannabis potency and pattern of use are associated with changes in corpus callosum (CC) microstructural organization, in patients with first-episode psychosis (FEP) and individuals without psychosis, cannabis users and non-users.

**Method.** The CC of 56 FEP (37 cannabis users) and 43 individuals without psychosis (22 cannabis users) was virtually dissected and segmented using diffusion tensor imaging tractography. The diffusion index of fractional anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity was calculated for each segment.

**Results.** Across the whole sample, users of high-potency cannabis had higher total CC MD and higher total CC AD than both low-potency users and those who never used ($p = 0.005$ and $p = 0.004$, respectively). Daily users also had higher total CC MD and higher total CC AD than both occasional users and those who never used ($p = 0.001$ and $p < 0.001$, respectively). However, there was no effect of group (patient/individuals without psychosis) or group x potency interaction for either potency or frequency of use. The within-group analysis showed in fact that the effects of potency and frequency were similar in FEP users and in users without psychosis.

**Conclusions.** Frequent use of high-potency cannabis is associated with disturbed callosal microstructural organization in individuals with and without psychosis. Since high-potency preparations are now replacing traditional herbal drugs in many European countries, raising awareness about the risks of high-potency cannabis is crucial.

*Received 4 March 2015; Revised 30 September 2015; Accepted 2 October 2015; First published online 27 November 2015*

**Key words**: Cannabis, corpus callosum, first-episode psychosis, tractography, white matter.

## Introduction

Cannabis use has been associated with an increased risk of subsequent psychosis (Henquet *et al.* 2008; Casadio *et al.* 2011). Our group has previously shown that this risk is greater, and onset occurs earlier, in those individuals who use more frequently and those who use cannabis with higher Δ9-tetrahydrocannabinol (THC) content (high-potency types such as 'skunk') (Di Forti *et al.* 2009, 2014). Exploring the role of potency in increasing the risk of psychosis has become particularly important since, over the last decade, modern 'high-potency' products (sinsemilla or 'skunk') in 'street cannabis' have been found to have higher THC (16–22%) and lower cannabidiol (CBD) (<0.1%) content (Potter *et al.* 2008). Interestingly, the THC component of cannabis has been proposed to have a neurotoxic effect on the brain (Gilman *et al.* 2014), while the CBD component has been proposed to be actually neuroprotective (Pertwee, 2008). While the long-term use of cannabis has been associated with alterations in both brain function and morphology (Lorenzetti *et al.* 2010; Schacht *et al.* 2012; Battistella *et al.* 2014), the effect of potency on the brain has never been explored.

THC acts on cannabinoid-1 (CB1) receptors, which, among other effects, modulate a variety of glial cell functions, including oligodendrocytes, and may induce

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Drug and Alcohol Dependence 156 (2015) 90–96

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Adolescent substance use and educational attainment: An integrative data analysis comparing cannabis and alcohol from three Australasian cohorts

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ARTICLE INFO

*Article history:*
Received 5 June 2015
Received in revised form 31 July 2015
Accepted 28 August 2015
Available online 12 September 2015

*Keywords:*
Cannabis
Alcohol
Adolescence
Educational outcomes

ABSTRACT

*Background:* The relative contributions of cannabis and alcohol use to educational outcomes are unclear. We examined the extent to which adolescent cannabis or alcohol use predicts educational attainment in emerging adulthood.

*Methods:* Participant-level data were integrated from three longitudinal studies from Australia and New Zealand (Australian Temperament Project, Christchurch Health and Development Study, and Victorian Adolescent Health Cohort Study). The number of participants varied by analysis ($N$ = 2179–3678) and were assessed on multiple occasions between ages 13 and 25. We described the association between frequency of cannabis or alcohol use prior to age 17 and high school non-completion, university non-enrolment, and degree non-attainment by age 25. Two other measures of alcohol use in adolescence were also examined.

*Results:* After covariate adjustment using a propensity score approach, adolescent cannabis use (weekly+) was associated with 1½ to two-fold increases in the odds of high school non-completion (OR = 1.60, 95% CI = 1.09–2.35), university non-enrolment (OR = 1.51, 95% CI = 1.06–2.13), and degree non-attainment (OR = 1.96, 95% CI = 1.36–2.81). In contrast, adjusted associations for all measures of adolescent alcohol use were inconsistent and weaker. Attributable risk estimates indicated adolescent cannabis use accounted for a greater proportion of the overall rate of non-progression with formal education than adolescent alcohol use.

*Conclusions:* Findings are important to the debate about the relative harms of cannabis and alcohol use. Adolescent cannabis use is a better marker of lower educational attainment than adolescent alcohol use and identifies an important target population for preventive intervention.



## 1. Introduction

Successfully completing high school and attaining a university degree are critical developmental milestones linked to better health (Cutler and Lleras-Muney, 2010) and greater economic productivity (US Bureau of Labor Statistics, 2014). Alcohol and cannabis are commonly used by young people in the school-age years.

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http://dx.doi.org/10.1016/j.drugalcdep.2015.08.034
0376-8716/

# Marijuana Use Predicts Cognitive Performance on Tasks of Executive Function

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**ABSTRACT. Objective:** Despite growing evidence that chronic marijuana use is associated with cognitive impairment, particularly when use is initiated at an early age, national trends demonstrate significant decreases in the perceived risk of marijuana corresponding with increased use, especially among youth. The current study assessed the impact of marijuana use on executive function and whether patterns of marijuana use, including earlier age at onset, higher frequency, and increased magnitude of use, predict impairment. **Method:** Forty-four chronic, heavy marijuana smokers (37 male, 7 female) and 32 healthy, nonsmoking control participants (20 male, 12 female) recruited from the Greater Boston area completed two assessments of executive function: the Stroop Color Word Test and Wisconsin Card Sorting Test (WCST). **Results:** Marijuana smokers had poorer executive function relative to control participants, a between-group difference that was primarily driven by individuals with early onset of marijuana use (before age 16; $n = 21$); significance remained even when controlling for frequency and magnitude of use. Further, earlier age at marijuana onset and increased marijuana use predicted poorer neurocognitive performance, and perseverative errors on the WCST significantly predicted marijuana group membership. **Conclusions:** These findings underscore the impact of early onset of marijuana use on executive function impairment independent of increased frequency and magnitude of use. In addition, poorer performance on the WCST may serve as a neuropsychological marker for heavy marijuana users. These results highlight the need for additional research to identify predictors associated with early marijuana use, as exposure to marijuana during a period of developmental vulnerability may result in negative cognitive consequences. (*J. Stud. Alcohol Drugs, 77*, 298–308, 2016)

MARIJUANA REMAINS THE MOST commonly used drug other than alcohol in the United States. Results from the Substance Abuse and Mental Health Services Administration (SAMHSA, 2014) national survey reported that between 2007 and 2013, the number of Americans reporting marijuana use within the past month increased from 14.5 million to 19.8 million. Similarly, heavy marijuana use (marijuana use on 20 or more days in the past month) increased from 5.1 million to 8.1 million people (SAMHSA, 2014). According to the Monitoring the Future study, which surveys drug use among high school students and young adults, 21.2% of high school seniors used marijuana within the past 30 days, and more than a quarter of these—5.8% of seniors overall—reported daily marijuana use (Johnston et al., 2015).

Results from the Monitoring the Future survey also suggest that perceived risk related to marijuana use may be a leading indicator of marijuana use patterns. For the past two decades, perceived risk of marijuana use has substantially declined among 12th graders, dovetailing with increased use in this population. In 2014, 36% of high school seniors viewed regular marijuana use as harmful, compared with 52% of seniors surveyed 5 years earlier (Johnston et al., 2015). Together, these data indicate a trend of decreased perception of risk related to marijuana use coinciding with increased marijuana use among the nation's most vulnerable population, those who are not yet neurodevelopmentally mature.

Increasing national media coverage and ongoing debates regarding the legalization of medical marijuana often highlight potential benefits, and it is therefore not surprising that national trends demonstrate a strong relationship between decreased perception of risk and increased marijuana use. In light of these shifts in attitude, it is important to examine the impact of chronic marijuana use and to determine if assessing such factors as age at onset, frequency, and magnitude of marijuana use provides an opportunity to predict neurocognitive outcomes.

Numerous studies have reported marijuana-associated impairments in frontal function, most notably during tasks that require executive control, inhibition, and decision making (for review, see Crane et al., 2013; Crean et al., 2011). Further, several investigations have specifically examined the role of age at marijuana onset, with results suggesting that earlier age at marijuana onset is related to impairment on measures of visual scanning (Ehrenreich et al., 1999), verbal IQ (Pope et al., 2003; Solowij et al., 2011), and executive function (Battisti et al., 2010; Fontes et al., 2011; Gruber et al., 2012b). Gruber and colleagues (2012b) found that mari-

Received: May 29, 2015. Revision: August 19, 2015.

Support for this project was provided by National Institute on Drug Abuse grants 5R21-DA021241 and 1R01-DA032646 (awarded to Staci A. Gruber). The authors have no conflicts of interest.

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Addiction
RESEARCH REPORT
SSA SOCIETY FOR THE STUDY OF ADDICTION
doi:10.1111/add.13042

# Cannabis use among Swedish men in adolescence and the risk of adverse life course outcomes: results from a 20 year-follow-up study

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## ABSTRACT

**Aims** To examine associations between cannabis use in adolescence (at age 18) and unemployment and social welfare assistance in adulthood (at age 40) among Swedish men. **Design** Longitudinal cohort study. **Setting and Participants** A total of 49 321 Swedish men born in 1949–51, who were conscripted to compulsory military service at 18–20 years of age. **Measurements** All men answered two detailed questionnaires at conscription and were subject to examinations of physical aptitude psychological functioning and medical status. By follow-up in national databases, information on unemployment and social welfare assistance was obtained. **Findings** Individuals who used cannabis at high levels in adolescence had increased risk of future unemployment and of receiving social welfare assistance. Adjusted for all confounders (social background, psychological functioning, health behaviours, educational level, psychiatric diagnoses), an increased relative risk (RR) of unemployment remained in the group reporting cannabis use > 50 times [RR = 1.26, 95% confidence interval (CI) = 1.04–1.53] only. For social welfare assistance, RR in the group reporting cannabis use 1–10 times was 1.15 (95% CI = 1.06–1.26), RR for 11–50 times was 1.21 (95% CI = 1.04–1.42) and RR for > 50 times was 1.38 (95% CI = 1.19–1.62). **Conclusions** Heavy cannabis use among Swedish men in late adolescence appears to be associated with unemployment and being in need of social welfare assistance in adulthood. These associations are not explained fully by other health-related, social or behavioural problems.

**Keywords** Cannabis, cohort study, education, longitudinal, social welfare assistance, unemployment.

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Submitted 5 March 2015; initial review completed 6 May 2015; final version accepted 8 July 2015

## INTRODUCTION

Cannabis use, and especially heavy use, in adolescence has been associated with social and socio-economic consequences, such as impaired cognitive functioning [1], low educational attainment [2,3] and educational problems [4]. Cannabis use in late adolescence and early adulthood has also been associated with lower income and lower work commitment in early adulthood, i.e. before 30 years of age [5–7]. Cannabis users have been found less likely to work [8,9], and in a recent study we found adolescent heavy cannabis users to be at an increased risk of later receiving disability pension [10]. Moreover, cannabis users have been found to be at an increased risk for receiving social welfare assistance and to be less likely to leave the assistance system [11].

However, previous research on possible associations between cannabis use and later social outcomes is inconsistent, and above all fails to elucidate the causal direction and possible mechanisms behind these associations. For one thing, a recent Australian study combining three long-running longitudinal studies showed that adolescent cannabis users had an increased risk of dropping out of high school, but not of later welfare dependence [12]. In a recent American study, the importance of unobserved confounding in the relationship between cannabis use and labour market outcomes was examined, and the authors concluded that cannabis use may be less harmful with regard to employment and income than previous studies have reported [13].

Given that cognitive impairment may possibly result from heavy cannabis use [1,14], one would expect

 

Journal of Adolescent Health 57 (2015) 205–211

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

# Predicting Young Adult Degree Attainment by Late Adolescent Marijuana Use

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*Article history:* Received October 10, 2014; Accepted April 29, 2015
*Keywords:* Marijuana use; Marijuana use consequences; Drug use consequences; Educational attainment; Degree attainment; Propensity score methods; Adolescents; Young adults

ABSTRACT

**Purpose:** The purpose of this study was to assess whether infrequent and frequent marijuana use at age 19/20 years predicts receipt of educational degrees by the mid-20s, independent of confounding age 18 adolescent risk factors.

**Methods:** Data were from the Monitoring the Future study, an annual nationally representative survey of high school seniors followed into adulthood. Thirteen cohorts (1990–2002) of high school seniors were followed longitudinally to their mid-20s (n = 4,925; 54% female). We used logistic regression and propensity score matching with successive inclusion of age 18 risk factors and substance use to compare age 19/20 frequent marijuana users (six or more occasions in past 30 days) to nonusers, frequent users to infrequent users (1–6 occasions), and infrequent users to nonusers on their likelihood of degree attainment by the mid-20s.

**Results:** Frequent marijuana users were less likely than infrequent users and nonusers to earn bachelor's degrees, even after controlling for a host of age 18 risk factors (e.g., family socioeconomic background, academic performance, educational expectations, truancy). However, these differences were reduced in magnitude to statistical nonsignificance when we controlled for age 18 substance use. Across analyses, the proportion reaching this educational milestone did not differ significantly between infrequent users and nonusers.

**Conclusions:** Results support a growing body of work suggesting that frequent marijuana use predicts a lower likelihood of postsecondary educational attainment, and this difference may originate during secondary school.



**IMPLICATIONS AND CONTRIBUTION**

In a national sample, late adolescent frequent marijuana users were less likely to attain bachelor's degrees by their mid-20s compared with infrequent and nonusers, independent of adolescent risk factors but not of adolescent substance use. Infrequent users and nonusers did not differ in degree attainment.

Marijuana is the most widely used illegal drug among adolescents [1]. Marijuana use during adolescence is clearly associated with many deleterious social and psychological correlates, with evidence of a link to lower educational attainment, especially among early and frequent users [2–6]. However, significant methodological challenges have led some scholars to question the evidence for marijuana's detrimental *causal* impact [4,7,8]. Notably, ethical and legal constraints against randomized trials

**Conflicts of Interest:** The authors have no conflicts of interest or financial relationships relevant to this article to disclose. All authors receive support from the U.S. National Institutes of Health; D.D.K., P.M.O., and J.S. receive support from the Robert Wood Johnson Foundation; and John Schulenberg receives support from the U.S. National Science Foundation.

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1054-139X/
http://dx.doi.org/10.1016/j.jadohealth.2015.04.028

# Cannabis-Related Episodic Memory Deficits and Hippocampal Morphological Differences in Healthy Individuals and Schizophrenia Subjects

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**ABSTRACT:** Cannabis use has been associated with episodic memory (EM) impairments and abnormal hippocampus morphology among both healthy individuals and schizophrenia subjects. Considering the hippocampus' role in EM, research is needed to evaluate the relationship between cannabis-related hippocampal morphology and EM among healthy and clinical groups. We examined differences in hippocampus morphology between control and schizophrenia subjects with and without a past (not current) cannabis use disorder (CUD). Subjects group-matched on demographics included 44 healthy controls (CON), 10 subjects with a CUD history (CON-CUD), 28 schizophrenia subjects with no history of substance use disorders (SCZ), and 15 schizophrenia subjects with a CUD history (SCZ-CUD). Large-deformation, high-dimensional brain mapping with MRI produced surface-based representations of the hippocampus that were compared across all four groups and correlated with EM and CUD history. Surface maps of the hippocampus were generated to visualize morphological differences. CON-CUD and SCZ-CUD were characterized by distinct cannabis-related hippocampal shape differences and parametric deficits in EM performance. Shape differences observed in CON-CUD were associated with poorer EM performance, while shape differences observed in SCZ-CUD were associated with a longer duration of CUD and shorter duration of CUD remission. A past history of CUD may be associated with notable differences in hippocampal morphology and EM impairments among adults with and without schizophrenia. Although the results may be compatible with a causal hypothesis, we must consider that the observed cannabis-related shape differences in the hippocampus could also be explained as biomarkers of a neurobiological susceptibility to poor memory or the effects of cannabis. © 2015 Wiley Periodicals, Inc.

**KEY WORDS:** hippocampus; Marijuana; neuroimaging; morphology; shape analysis

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Grant sponsor: National Institute of Mental Health; Grant number: R01 MH056584 and P50 MH071616; Grant sponsor: National Institute on Drug Abuse; Grant number: DA026002, DA026104, DA027804.

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Accepted for publication 22 January 2015.
DOI 10.1002/hipo.22427
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).



## INTRODUCTION

Over the past decade, policy makers have redefined state laws surrounding cannabis use in the United States, including the decriminalization or legalization of cannabis possession for medical and recreational purposes. In 2010, the National Survey on Drug Use and Health (SAMHSA, 2011) identified cannabis as the most commonly used illicit drug in the United States and recent policy changes regarding cannabis in Colorado resulted in an increased prevalence of cannabis abuse and a decrease in perceived risk of cannabis use among adolescents (Schuermeyer et al., 2014). Based on recent evidence that cannabis use beginning in adolescence has been linked to cognitive deficits Meier et al., 2012, it is important to evaluate the relationship between cannabis use and the morphology of brain structures underlying specific cognitive functions.

Cannabis use and the acute administration of delta-9-tetrahydrocannabinol ($\Delta_9$-THC) (a CB1 receptor agonist and main psychoactive compound in cannabis) have been associated with impairments in episodic memory (EM) (see Ranganathan and D'Souza, 2006; Crane et al., 2013) for review), the type of memory associated with autobiographical events (Stark, 2007). Limbic structures, in particular the hippocampus, play an integral role in memory formation and are characterized by a high density of cannabinoid type 1 (CB1) receptors (Svizenska et al., 2008). Cannabis use disrupts memory by overactivating CB1 receptor expression in the hippocampus which inhibits glutamateric and GABAergic neurotransmission and suppresses LTP and LTD (Navakkode and Korte, 2014).

Recent evidence suggests that heavy cannabis users had altered hippocampal morphology (Medina et al., 2014; Yucel et al., 2008; Ashtari et al., 2011; Solowij et al., 2013) that was related to cannabis use history (e.g., age of onset, duration of use). Specifically, reduced hippocampal volume and shape differences were correlated with recent and overall duration of cannabis use (Ashtari et al., 2011; Solowij et al., 2013). However, these recent findings differ from older studies looking at hippocampal volume

Neurobiology of Disease

# 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 Δ9-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

## Introduction

Marijuana (cannabis) is the most commonly used illicit drug in the United States (15.2 million past-month users; US Department of Health and Human Services, 2008). It is also the most widely used illicit drug on college campuses (Mohler-Kuo et al., 2003). Moreover, its use is increasing among adolescents and young adults (Henry et al., 2003), partially due to society's changing beliefs about cannabis use and its legal status.

Cannabis use is associated with impairments of cognitive functions, including learning and memory, attention, and decision-making. Animal studies show structural changes in brain regions underlying these functions after exposure to Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis (Lawston et al., 2000; Downer et al., 2001). In the nucleus accumbens, the length of the dendrites and number of dendritic spines increases with THC exposure in rats (Kolb et al., 2006). Less is known about the relationship between cannabis use and brain structure in humans. Although some studies have shown volume reductions in the hippocampus, amygdala, and cerebellum, others have not shown such effects (see Lorenzetti et al., 2010 for review). Differences in methodology may have contributed to these mixed results, suggesting that using a variety of structural methods together to quantify brain morphology may be important.

In the present study, we collected high-resolution T1 MRI scans on young adult (age 18–25 years) cannabis/marijuana users and matched nonusing controls. We conducted three blinded, automated, and independent analyses of brain structure and their

Received Nov. 6, 2013; revised March 9, 2014; accepted March 11, 2014.

Author contributions: J.M.G., M.J.L., B.K., N.M., A.J.v.d.K., A.B., and H.C.B. designed research; J.M.G., J.K.K., S.L., and A.J.v.d.K. performed research; M.J.L., B.K., A.B., and H.C.B. contributed unpublished reagents/analytic tools; J.M.G., J.K.K., S.L., M.J.L., N.M., A.B., and H.C.B. analyzed data; J.M.G., A.B., and H.C.B. wrote the paper.

This work was supported by the National Institute on Drug Abuse (Grants 14118, 026002, 026104, and 027804 to H.C.B. and Grant 034093 to J.M.G.), the Office of National Drug Control Policy, Counterdrug Technology Assessment Center (Grants DABK39-03-0098 and DABK39-03-C-0098), and the National Institute of Neurological Disorders and Stroke, National Institutes of Health (Grant 052368 to A.J.B.). H.C.B. was also supported by the Warren Wright Adolescent Center at Northwestern Memorial Hospital and Northwestern University, Chicago. J.M.G. was supported by a Harvard Medical School Norman E. Zinberg Fellowship in Addiction Psychiatry Research.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.4745-13.2014

 0270-6474/14/345529-10$15.00/0

OPEN

Neuropsychopharmacology (2014) 39, 2041–2048

www.neuropsychopharmacology.org

# 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.
*Neuropsychopharmacology* (2014) **39,** 2041–2048; doi:10.1038/npp.2014.67; published online 16 April 2014

## INTRODUCTION

Cannabis is one of the most widely used recreational drugs, taking third place among drugs of concern in addiction treatment services (Degenhardt *et al*, 2008). Despite these statistics pointing to the potential harms associated with long-term cannabis use, little is known about the progression from recreational to regular use and its effects on brain structure.

Current knowledge is mostly inferred from animal studies; it has been demonstrated that the main psychoactive component of cannabis (Δ9-Tetrahydrocannabinol, THC) induces dose-dependent toxicity and structural changes in brain regions rich in cannabinoid CB1 receptors. These are mainly located in the hippocampus, amygdala, cerebellum, prefrontal cortex, and striatum (Burns *et al*, 2007; Downer *et al*, 2001; Lawston *et al*, 2000).

In contrast to the animal literature, the investigation of the structural effects of long-term cannabis use on the human brain has brought less consistent findings. Changes in gray or white matter density have been reported in different locations in frontal and parietal lobes without overlapping findings across studies (Churchwell *et al*, 2010; Gruber *et al*, 2011; Matochik *et al*, 2005). The discrepancy in the results might be due to heterogeneity in sample characteristics, inter-individual differences linked to past history of drug use, amount of consumption, related psychological problems (temperament, level of anxiety or arousal), and/or methodological differences in data processing (Batalla *et al*, 2013; Lorenzetti *et al*, 2010). However, changes in the hippocampus/parahippocampal complex and in the amygdala have often been reported (Demirakca *et al*, 2011; Matochik *et al*, 2005; Yücel *et al*, 2008; Zalesky *et al*, 2012). These findings suggest that long-term cannabis use is associated with brain morphology alterations in regions linked to memory and executive and affective processing (Yücel *et al*, 2008).

Decrease in hippocampal volume in regular cannabis smokers has been correlated with lifetime consumption (Ashtari *et al*, 2011; Yücel *et al*, 2008) and psychotic symptoms (Yücel *et al*, 2008). In Cousijn *et al* (2012), volume reduction in the amygdala and the hippocampus does not differ significantly between regular cannabis users and controls but still correlates with the amount of cannabis used and the severity of cannabis dependence, respectively.

In addition to the several issues characterizing the literature so far, most of the studies examine only predefined regions of interest (i.e., the hippocampus and

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Received 5 December 2013; revised 22 February 2014; accepted 6 March 2014; accepted article preview online 17 March 2014

Salud Mental 2013;36:335-342

# Effects of marijuana consumption in students on brain functions demonstrated by means of neuropsychological tests and neuro-SPECT imaging

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**Original article**


## SUMMARY

Comparative study based on 565 school adolescents coming from four schools in the metropolitan area of Santiago, Chile. All were interviewed in order to select a sample that was stratified by sex, class and condition of users or non users. The variables of intelligence quotient and socioeconomic status were maintained constant. Two groups were made: 40 marijuana-only users and 40 non users. We compared the results obtained in both groups in the neuropsychological tests while the neuroSPECT studies of users were compared against a normal database for the same age group.

Adolescent marijuana users demonstrate less cognitive capacity related to the process of learning such as attention, concentration, ranking, visuo-spatial integration, immediate retention and visual memory. The differences between both groups are statistically significant.

The findings of neuroSPECT show subgenual bilateral hypoperfusion, more marked on the left side (Brodmann's area 25), frontal bilateral hypoperfusion (Brodmann's areas 10 and 32), front cingulate *gyrus* hypoperfusion (Brodmann's area 24) and hypoperfusion of Brodmann's area 36 that projects over the hippocampus.

Students that were only-marijuana users demonstrate coincident abnormal findings of neuroimages and neuropsychological tests in brain learning-related areas and also significant differences between users with non users in the neuropsychological tests.


**Key words:** Cannabis, marijuana, adolescents, NeuroSPECT, HMPAO, neuropsychological tests.


## RESUMEN

Estudio comparativo basado en 565 escolares adolescentes pertenecientes a cuatro colegios de Santiago, Chile. Fueron encuestados todos para seleccionar una muestra estratificada por sexo, curso y condición de consumidores o no consumidores, manteniendo constante las variables coeficiente intelectual y nivel socioeconómico. Se conforman dos grupos: 40 consumidores exclusivos de marihuana y 40 no consumidores. Se comparan los resultados obtenidos en ambos grupos en los Test Neuropsicológios y del NeuroSPECT de consumidores con una base de datos considerados normales para el mismo grupo etario.

Los adolescentes consumidores de marihuana evidencian menores habilidades cognitivas asociadas al proceso de aprendizaje, tales como atención, concentración, jerarquización, integración visoespacial, retención inmediata y memoria visual. Las diferencias entre ambos grupos son estadísticamente significativas.

Los hallazgos del NeuroSPECT muestran hipoperfusión subgenual bilateral, más marcada en el hemisferio izquierdo (área 25 de Brodmann), hipoperfusión frontal bilateral (areas 10 y 32 de Brodmann), hipoperfusión del *gyrus* cingulado anterior (área 24 de Brodmann) e hipoperfusión del área 36 de Brodmann que proyecta sobre el hipocampo.

Los estudiantes consumidores exclusivamente de marihuana muestran compromiso coincidente en neuroimágenes y test neuropsicológicos en áreas del cerebro relacionadas con el aprendizaje y se diferencian significativamente de los no-consumidores en las pruebas neuropsicológicas.


**Palabras claves:** *Cannabis*, marihuana, adolescentes, NeuroSPECT, HMPAO, pruebas neuropsicológicas.


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Received: August 5, 2013. Accepted: August 30, 2013.

BJPsych | The British Journal of Psychiatry (2011) 198, 442–447. doi: 10.1192/bjp.bp.110.077479

# Cannabis use before age 15 and subsequent executive functioning

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**Background**
Many studies have suggested that adolescence is a period of particular vulnerability to neurocognitive effects associated with substance misuse. However, few large studies have measured differences in cognitive performance between chronic cannabis users who started in early adolescence (before age 15) with those who started later.

**Aims**
To examine the executive functioning of individuals who started chronic cannabis use before age 15 compared with those who started chronic cannabis use after 15 and controls.

**Method**
We evaluated the performance of 104 chronic cannabis users (49 early-onset users and 55 late-onset users) and 44 controls who undertook neuropsychological tasks, with a focus on executive functioning. Comparisons involving neuropsychological measures were performed using generalised linear model analysis of variance (ANOVA).

**Results**
The early-onset group showed significantly poorer performance compared with the controls and the late-onset group on tasks assessing sustained attention, impulse control and executive functioning.

**Conclusions**
Early-onset chronic cannabis users exhibited poorer cognitive performance than controls and late-onset users in executive functioning. Chronic cannabis use, when started before age 15, may have more deleterious effects on neurocognitive functioning.

**Declaration of interest**
None.

Studies have demonstrated neuropsychological deficits associated with acute exposure to cannabis.[1,2] However, results from studies examining persistent cognitive impairments associated with chronic cannabis use are contradictory, with some studies,[3,4] but not all,[5,6] showing significant neuropsychological deficits even after some weeks of abstinence. One possible explanation for these inconsistent findings is that cannabis is more neurotoxic for some populations than for others. Individuals who are exposed to potentially neurotoxic substances before age 15, while the brain is still developing,[7] may be at higher risk of developing persistent neuropsychological deficits compared with older individuals. One model of genetic control postulates that species with delayed brain development have a larger relative volume of later-developing structures (for example cortical areas, particularly the prefrontal cortex). Consequently, later-developing structures interact with environmental factors for prolonged postnatal periods, which can importantly contribute to the tuning and shaping of circuitry. Prefrontal cortex anatomical development continues after birth with full maturation being achieved only around the early 20s.[8] In addition, different areas within the prefrontal cortex mature at different times. This area of the brain encompasses a number of distinct cognitive processes with different developmental trajectories, including planning, verbal fluency, complex problem-solving and impulse control.[9]

Studies have suggested that adolescence is a period of particular vulnerability to development of neurocognitive effects associated with substance use.[10–12] Findings from animal studies have suggested that cannabinoid 1 ($CB_1$) receptor levels peak in early adolescence[13] and animals exposed to cannabis in adolescence are more vulnerable to learning impairments compared with animals exposed in adult life. Medina *et al* demonstrated that after a month of abstinence, adolescent cannabis users showed slower psychomotor speed, poorer complex attention and memory skills, and degraded planning/sequencing abilities compared with 34 non-users.[14] Furthermore, there was an inverse correlation between lifetime marijuana exposure and cognitive performance in the same cognitive domains, suggesting a dose-dependent effect. The authors conclude that frequent marijuana use during adolescence may negatively influence neuromaturation and cognitive development. Wilson *et al* evaluated the possible role of age on first use of cannabis interfering with brain and body development.[15] Brain volume measurements (whole brain, grey matter, white matter and lateral ventricle volumes) and global cerebral blood flow were evaluated in 57 chronic cannabis users. Participants who started using cannabis before age 17 had smaller total brain and cortical grey matter volumes with larger white matter volumes. Both males and females who started regular early use were physically smaller in height and weight, with greater effects in males.

Executive functioning is a term that refers to complex mental control processes reflected in future-oriented behaviour that includes cognitive flexibility in problem-solving, focused attention, inhibition of impulsive responses, monitoring, evaluating and adjusting self-directed perception and working memory. From a neurophysiological point of view, executive functions mainly rely on circuits involving prefrontal areas.[16] According to DSM-IV,[17] compulsive use and intense, persistent desire to use a substance, despite the presence of physical and psychological consequences related to the substance use, is a core symptom of dependence syndrome. In this sense, executive deficits might play a central role in the development of addictive behaviours and, consequently, in substance use disorder treatment issues.[18]

Undoubtedly, adolescents are vulnerable to impaired cognitive effects associated with cannabis misuse.[19] The results suggest that chronic cannabis users process complex information more slowly and performance worsens in cognitive overload tasks as lifetime consumption increases.[20] With this in mind, we examined the

Psychology of Addictive Behaviors


0893-164X/11/$12.00 DOI: 10.1037/a0026269

# Age of Onset of Marijuana Use and Executive Function

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Marijuana (MJ) remains the most widely abused illicit substance in the United States, and in recent years, a decline in perceived risk of MJ use has been accompanied by a simultaneous increase in rates of use among adolescents. In this study, the authors hypothesized that chronic MJ smokers would perform cognitive tasks, specifically those that require executive function, more poorly than control subjects and that individuals who started smoking MJ regularly *prior to age 16* (early onset) would have more difficulty than those who started *after age 16* (late onset). Thirty-four chronic, heavy MJ smokers separated into early and late onset groups, and 28 non-MJ smoking controls completed a battery of neurocognitive measures. As hypothesized, MJ smokers performed more poorly than controls on several measures of executive function. Age of onset analyses revealed that these between-group differences were largely attributed to the early onset group, who were also shown to smoke twice as often and nearly 3 times as much MJ per week relative to the late onset smokers. Age of onset, frequency, and magnitude of MJ use were all shown to impact cognitive performance. Findings suggest that earlier MJ onset is related to poorer cognitive function and increased frequency and magnitude of MJ use relative to later MJ onset. Exposure to MJ during a period of neurodevelopmental vulnerability, such as adolescence, may result in altered brain development and enduring neuropsychological changes.

*Keywords:* cognitive function, marijuana, adolescence, early onset

Within the United States, marijuana (MJ) remains the most widely used illicit substance. In 2009, 16.7 million Americans aged 12 and older reported at least one instance of use in the past month, and MJ use within youths aged 12–17 rose to 7.3%, a significant increase from 2008 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2010). Relatively few studies have examined the direct relationship between age of onset of MJ use and cognitive performance, despite the alarming number of adolescent consumers. National survey data suggest that attentional problems exist in young smokers, with 71.7% of adolescents who used MJ at least once a week reporting trouble concentrating compared to 50.8% of nonsmokers (SAMHSA, 1998). Additionally, surveys have shown that perceived risk and perceived disapproval are linked to increased rates of MJ use among adolescents, with current MJ use much less prevalent among youths who perceived strong parental disapproval for trying MJ than for those who did not (4.8% vs. 31.3%; SAMHSA, 2010). In recent years, a decline in perceived risk of MJ has been accompanied by a simultaneous increase in rates of use among adolescents (Johnston, O'Malley, Bachman, & Schulenberg, 2011). As rates of perceived risk decline and MJ use among adolescents increases, age of onset of first regular MJ use has also dropped significantly (Copeland & Swift, 2009; Degenhardt et al., 2008; SAMHSA, 2010). Adolescence is a time of neuromaturation, with increasing evidence that the adolescent brain may be more vulnerable to the effects of drugs and alcohol than the adult brain (Monti et al., 2005), and those who are at the greatest risk for adverse consequences appear to represent a growing population of consumers of MJ (Schneider, 2008).

Previous studies focused on neurocognitive function have reported significantly altered frontal–executive function in MJ smokers. Pope and Yurgelun-Todd (1996) reported lower performance scores on tests designed to measure frontal–executive function in MJ smokers relative to control subjects, and Solowij et al. (2002) reported significantly worse performance on a battery of neurocognitive measures that included attention, memory, and executive function in heavy MJ smokers relative to both lighter smokers and non-smoking controls. Studies of the cognitive effects of MJ following a brief abstinence period have also reported that heavy MJ use is associated with deficits in cognitive tasks mediated by the frontal system (Fletcher et al., 1996; Harvey, Sellman,

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We declare that there is no conflict of interest. This project was supported by National Institute of Drug Abuse Grant No. 5 R21 DA021241.

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Published in final edited form as:
*J Addict Med*. 2011 March 1; 5(1): 1–8. doi:10.1097/ADM.0b013e31820c23fa.

# An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions

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## Abstract

Cannabis use has been shown to impair cognitive functions on a number of levels—from basic motor coordination to more complex executive function tasks, such as the ability to plan, organize, solve problems, make decisions, remember, and control emotions and behavior. These deficits differ in severity depending on the quantity, recency, age of onset and duration of marijuana use. Understanding how cannabis use impairs executive function is important. Individuals with cannabis-related impairment in executive functions have been found to have trouble learning and applying the skills required for successful recovery, putting them at increased risk for relapse to cannabis use. Here we review the research on the acute, residual, and long-term effects of cannabis use on executive functions, and discuss the implications for treatment.

### Keywords

cannabis; marijuana; cognition; executive functions; treatment

## OVERVIEW

Consumption of cannabis for medical purposes is legal with a prescription in 15 states, and many states are in the process of decriminalizing non-medical marijuana use. More than 97.5 million Americans over the age of 12 have used illicit marijuana, and it is considered by many to be a benign recreational drug. However, evidence exists of significant harm for some individuals, with 1 in 10 users developing cannabis dependence (SAMHSA, 2007). Furthermore, sixteen percent (~300,000) of all substance abuse treatment admissions in the United States were for cannabis-related disorders; this is second only to alcohol-related disorders (SAMHSA, 2006). It is estimated that more than 4 million Americans meet Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; APA, 1994) diagnostic criteria for cannabis dependence (SAMHSA, 2007). This figure has doubled from 2001, and will likely continue to grow. Thus, an understanding of the effects of cannabis on executive functions is likely to be of widespread clinical relevance.

Delta 9-tetrahydrocannabinol (THC) is the primary psychoactive constituent of the cannabis sativa plant and is believed to be primarily responsible for the cognitive effects and the addictive potential of smoked cannabis. THC intoxication has been shown to impair cognitive function on a number of levels—from basic motor coordination to more complex

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The authors have no relevant financial interests to disclose.

Psychopharmacology (2011) 216:131–144
DOI 10.1007/s00213-011-2203-x

ORIGINAL INVESTIGATION

# Verbal learning and memory in adolescent cannabis users, alcohol users and non-users

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Received: 21 November 2010 / Accepted: 24 January 2011 / Published online: 17 February 2011


**Abstract**
*Rationale* Long-term heavy cannabis use can result in memory impairment. Adolescent users may be especially vulnerable to the adverse neurocognitive effects of cannabis.
*Objectives and methods* In a cross-sectional and prospective neuropsychological study of 181 adolescents aged 16–20 (mean 18.3 years), we compared performance indices from one of the most widely used measures of learning and memory—the Rey Auditory Verbal Learning Test—between cannabis users ($n$=52; mean 2.4 years of use, 14 days/month, median abstinence 20.3 h), alcohol users ($n$=67) and non-user controls ($n$=62) matched for age, education and premorbid intellectual ability (assessed prospectively), and alcohol consumption for cannabis and alcohol users.
*Results* Cannabis users performed significantly worse than alcohol users and non-users on all performance indices. They recalled significantly fewer words overall ($p$<0.001), demonstrating impaired learning ($p$<0.001), retention ($p$<0.001) and retrieval ($p$<0.05) (Cohen's $d$ 0.43–0.84). The degree of impairment was associated with the duration, quantity, frequency and age of onset of cannabis use, but was unrelated to alcohol exposure or other drug use. No gender effects were detected and the findings remained after controlling for premorbid intellectual ability. An earlier age of onset of regular cannabis use was associated with worse memory performance after controlling for extent of exposure to cannabis.
*Conclusions* Despite relatively brief exposure, adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy users. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00213-011-2203-x) contains supplementary material, which is available to authorized users.

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Experimental and Clinical Psychopharmacology
2010, Vol. 18, No. 2, 109–119


1064-1297/10/$12.00 DOI: 10.1037/a0019295

# Cognitive Function as an Emerging Treatment Target for Marijuana Addiction

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Cannabis is the most widely used illicit substance in the world, and demand for effective treatment is increasing. However, abstinence rates following behavioral therapies have been modest, and there are no effective pharmacotherapies for the treatment of cannabis addiction. We propose a novel research agenda and a potential treatment strategy, based on observations that both acute and chronic exposure to cannabis are associated with dose-related cognitive impairments, most consistently in attention, working memory, verbal learning, and memory functions. These impairments are not completely reversible upon cessation of marijuana use, and moreover may interfere with the treatment of marijuana addiction. Therefore, targeting cognitive impairment associated with chronic marijuana use may be a promising novel strategy for the treatment of marijuana addiction. Preclinical studies suggest that medications enhancing the cholinergic transmission may attenuate cannabis-induced cognitive impairments, but these cognitive enhancing medications have not been examined in controlled human studies. Preliminary evidence from individuals addicted to other drugs suggests that computerized cognitive rehabilitation may also have utility to improve cognitive function in marijuana users. Future clinical studies optimally designed to measure cognitive function as well as drug use behavior would be needed to test the efficacy of these treatments for marijuana addiction.

*Keywords:* marijuana, cannabis, cognitive function, acetylcholine, cholinesterase inhibitors

Marijuana (cannabis) is the most widely used illicit substance in the world. In the United States, there are approximately 2 to 3 million new users of marijuana every year, and significantly, two-thirds of them are between 12 and 17 years of age (Compton, Grant, Colliver, Glantz, & Stinson, 2004; ONDCP, 2008; SAMHSA, 2008). It is estimated that one out of 12 marijuana users will eventually become dependent on marijuana (Wagner & Anthony, 2002).

As with other addictions, cannabis-dependent individuals continue to use marijuana despite significant problems associated with its use. Marijuana use has been associated with low academic achievement, early school dropout, delinquency, legal problems, unemployment, cigarette smoking, and risk for the development of psychotic disorder (Ferdinand et al., 2005; Friedman, Glassman, & Terras, 2001; Hall & Degenhardt, 2009; Henquet et al., 2005), although there may be alternative explanations for these associations that need to be ruled out before a causal link can be established (Hall & Degenhardt, 2009; Sewell, Poling, & Sofuoglu, 2009). For example, the association between marijuana and nicotine addiction, could be because of common genetic vulnerability (Agrawal et al., 2008). However, reports from several countries (including the United States, United Kingdom, and the Netherlands) indicate that the average age of initiation of marijuana use is decreasing, while the average delta-9-tetrahydrocannabinol (THC; the main psychoactive ingredient of cannabis) content of cannabis is increasing (ElSohly et al., 2000; Pijlman, Rigter, Hoek, Goldschmidt, & Niesink, 2005; Potter, Clark, & Brown, 2008). This may result in greater addictive potential as well as increased negative consequences of marijuana use.

While individuals seeking treatment for marijuana use problems were once comparatively rare (Stephens, Babor, Kadden, Miller, & MTP Research Group, 2002), increased treatment-seeking has been observed among marijuana users, making marijuana one of the most common illicit drugs of use among admissions to treatment programs in the United States (SAMHSA, 2008). Currently, there are no effective medications for the treatment of marijuana addiction, and available behavioral treatments are modestly effective (Nordstrom & Levin, 2007). Thus, development of effective treatment strategies, specifically for cannabis use disorders (dependence or abuse), is urgently needed.

Many studies have demonstrated that chronic exposure to marijuana is associated with dose-related cognitive impairments, most consistently in attention, working memory,

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This study was supported by National Institute on Drug Abuse grants K02-DA-021304 (MS), K05-DA00457 (KMC), P50-DA09241, and the Department of Veterans Affairs VISN 1 MIRECC.

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frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 14 December 2010
doi: 10.3389/fpsyg.2010.00225

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

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**Reviewed by:**
Susan F. Tapert, University of California at San Diego, USA
Dick Veltman, Free University, Netherlands

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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**

## INTRODUCTION

Adolescence is a time during which a variety of factors may converge to increase the likelihood of substance use initiation, abuse, and dependence (Schepis et al., 2008). Adolescents may be particularly susceptible to cannabis use since it is the most commonly abused substance worldwide with North America ranking second for reported utilization (UN, 2008). Adolescence may also be a time of vulnerability to addiction, as it has been reported that early initiation increases the risk for cannabis dependence (Chen et al., 2005). A greater risk for dependence may be associated with an increased sensitivity to the rewarding properties of drugs during this developmental stage (Spear, 2000) and cannabis abuse may disrupt normal neuromaturation and reward sensitivity (Crews et al., 2007). Consistent with this perspective, preclinical models indicate that cannabinoid receptor type 1 ($CB_1$) significantly changes density in prefrontal cortex and other reward related brain regions during adolescence (Ellgren et al., 2008), suggesting a possible interval of neural vulnerability to cannabis exposure.

Preclinical models have provided further evidence that chronic or escalating doses of delta-9-tetrahydrocannabinol produce alterations in prefrontal and nucleus accumbens dendritic morphology 30 days following treatment (Kolb et al., 2006) and this cellular reorganization may be related to disruptions in the function of these structures which are normally involved in reward representation and goal-directed behavior (Robinson and Kolb, 2004; Kalivas and Volkow, 2005). In accordance with this view, animal models have shown that brain reward systems become hypersensitive to drugs of abuse such as heroin and cocaine following adolescent cannabis exposure (Ellgren et al., 2007; Higuera-Matas et al., 2008). Collectively, these studies indicate that the transition from childhood to adulthood involves a critical window during which cannabis use can impact normal remodeling of the prefrontal cortex (Egerton et al., 2006; Crews et al., 2007) and possibly alter the incentive salience of other drugs of abuse (Robinson and Berridge, 1993).

The neurocognitive impact of initiating cannabis use early in life is also of great concern (Medina et al., 2007; Jacobus et al., 2009). Studies employing neuroimaging techniques have shown that prefrontal cortical gray matter undergoes significant morphological change during adolescence and research investigating prefrontal functioning during this period suggests that delayed development of this region may be related to both cannabis use and risk for substance abuse. For example, Medina et al. (2007) demonstrated that adolescent cannabis users who were

THE AMERICAN JOURNAL ON ADDICTIONS

*The American Journal on Addictions*, 24: 499–506, 2015

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12201

# Frequent Marijuana Use, Binge Drinking and Mental Health Problems Among Undergraduates

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**Background and Objectives:** In light of the rapidly changing legal status of marijuana in the U.S., there has been increased interest in the potentially adverse outcomes of heavy marijuana use among young persons. The goal of this study was to investigate frequent marijuana use among undergraduates, and its association with the use of illicit substances, mental health problems, and stress.
**Methods:** Undergraduates from one university in the Northeast were surveyed using a questionnaire derived from the American College Health Association-National College Health Assessment ($N = 1,776$). Logistic regression analyses were used to examine relationships between frequency of marijuana use and other substance use, binge drinking, negative consequences of drinking, mental health problems, and perceived stress. Analyses were adjusted for demographics differences such as gender, race, year in school, and sorority/fraternity membership.
**Results:** Approximately 1 in 12 undergraduates (8.5%) reported using marijuana more than 10 days in the past month. Frequent marijuana use was associated with increased likelihood of other substance use and alcohol-related negative outcomes. Marijuana use was associated with increased reports of anxiety, and frequent use was associated with depression and substance use problems. Perceived stress was not associated with marijuana use.
**Conclusions and Scientific Significance:** These findings, indicating that frequent use is related to depression, other substance use and negative outcomes, contribute to our understanding of marijuana use among undergraduates. Given the relatively high prevalence of marijuana use among young persons, future studies should seek to uncover potentially causal relationships between frequent marijuana use and a variety of negative outcomes. (Am J Addict 2015;24:499–506)

Received September 4, 2014; revised December 17, 2014; accepted January 1, 2015.
Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.
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## INTRODUCTION

Marijuana is the most commonly used illicit drug in the United States.[1] Data indicate that the prevalence of marijuana use among college students has increased since 2000.[2] For example, in 2000, 13.6% of young adults reported past-month marijuana use[3]; by 2013, the percentage increased to 19.1%.[1] In addition, 23 states and the District of Columbia now allow the medical use of marijuana for certain conditions, and within the past two years, four states legalized the recreational use of marijuana for adults. These developments may increase the availability and use of marijuana by adults and there is some concern that use by young people might be increased as a result.[4,5] It is important to note that there are not yet any data to support or refute this concern.

Heavy, long-term use of smoked marijuana use has been shown to negatively affect lung function[6] and cardiovascular health.[7] In addition, it is estimated that approximately 9% of those who use marijuana will become dependent at some point in their lifetime.[8,9] Young adulthood is a particularly critical period for the development of drug use problems. It has been estimated that 20% of young adults meet criteria for substance abuse or dependence, and only 7% of these young adults receive treatment.[10] As the availability of marijuana becomes more widespread, it will be important to monitor the correlates of frequent marijuana use in young adults, a group that might

Published in final edited form as:
*Int J Drug Policy*. 2015 February ; 26(2): 135–142. doi:10.1016/j.drugpo.2014.07.011.

# Probability and predictors of the cannabis gateway effect: A national study

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## Abstract

**Background—**While several studies have shown a high association between cannabis use and use of other illicit drugs, the predictors of progression from cannabis to other illicit drugs remain largely unknown. This study aims to estimate the cumulative probability of progression to illicit drug use among individuals with lifetime history of cannabis use, and to identify predictors of progression from cannabis use to other illicit drugs use.

**Methods—**Analyses were conducted on the sub-sample of participants in Wave 1of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) who started cannabis use before using any other drug (n= 6,624). Estimated projections of the cumulative probability of progression from cannabis use to use of any other illegal drug use in the general population were obtained by the standard actuarial method. Univariate and multivariable survival analyses with time-varying covariates were implemented to identify predictors of progression to any drug use.

**Results—**Lifetime cumulative probability estimates indicated that 44.7% of individuals with lifetime cannabis use progressed to other illicit drug use at some time in their lives. Several sociodemographic characteristics, internalizing and externalizing psychiatric disorders and indicators of substance use severity predicted progression from cannabis use to other illicit drugs use.

**Conclusion—**A large proportion of individuals who use cannabis go on to use other illegal drugs. The increased risk of progression from cannabis use to other illicit drugs use among individuals with mental disorders underscores the importance of considering the benefits and adverse effects of changes in cannabis regulations and of developing prevention and treatment strategies directed at curtailing cannabis use in these populations.



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**Conflict of Interest** No conflict declared.

OPEN

Neuropsychopharmacology (2014) 39, 2041–2048

www.neuropsychopharmacology.org

# 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.
*Neuropsychopharmacology* (2014) **39,** 2041–2048; doi:10.1038/npp.2014.67; published online 16 April 2014

## INTRODUCTION

Cannabis is one of the most widely used recreational drugs, taking third place among drugs of concern in addiction treatment services (Degenhardt *et al*, 2008). Despite these statistics pointing to the potential harms associated with long-term cannabis use, little is known about the progression from recreational to regular use and its effects on brain structure.

Current knowledge is mostly inferred from animal studies; it has been demonstrated that the main psychoactive component of cannabis (Δ9-Tetrahydrocannabinol, THC) induces dose-dependent toxicity and structural changes in brain regions rich in cannabinoid CB1 receptors. These are mainly located in the hippocampus, amygdala, cerebellum, prefrontal cortex, and striatum (Burns *et al*, 2007; Downer *et al*, 2001; Lawston *et al*, 2000).

In contrast to the animal literature, the investigation of the structural effects of long-term cannabis use on the human brain has brought less consistent findings. Changes in gray or white matter density have been reported in different locations in frontal and parietal lobes without overlapping findings across studies (Churchwell *et al*, 2010; Gruber *et al*, 2011; Matochik *et al*, 2005). The discrepancy in the results might be due to heterogeneity in sample characteristics, inter-individual differences linked to past history of drug use, amount of consumption, related psychological problems (temperament, level of anxiety or arousal), and/or methodological differences in data processing (Batalla *et al*, 2013; Lorenzetti *et al*, 2010). However, changes in the hippocampus/parahippocampal complex and in the amygdala have often been reported (Demirakca *et al*, 2011; Matochik *et al*, 2005; Yücel *et al*, 2008; Zalesky *et al*, 2012). These findings suggest that long-term cannabis use is associated with brain morphology alterations in regions linked to memory and executive and affective processing (Yücel *et al*, 2008).

Decrease in hippocampal volume in regular cannabis smokers has been correlated with lifetime consumption (Ashtari *et al*, 2011; Yücel *et al*, 2008) and psychotic symptoms (Yücel *et al*, 2008). In Cousijn *et al* (2012), volume reduction in the amygdala and the hippocampus does not differ significantly between regular cannabis users and controls but still correlates with the amount of cannabis used and the severity of cannabis dependence, respectively.

In addition to the several issues characterizing the literature so far, most of the studies examine only predefined regions of interest (i.e., the hippocampus and

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Received 5 December 2013; revised 22 February 2014; accepted 6 March 2014; accepted article preview online 17 March 2014

PNAS PLUS

SEE COMMENTARY

# Persistent cannabis users show neuropsychological decline from childhood to midlife

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Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

**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.**

marijuana | longitudinal | cognition

Cannabis, the most widely used illicit drug in the world, is increasingly being recognized for both its toxic and its therapeutic properties (1). Research on the harmful and beneficial effects of cannabis use is important because it can inform decisions regarding the medicinal use and legalization of cannabis, and the results of these decisions will have major public-health consequences. As debate surrounding these issues continues in the United States and abroad, new findings concerning the harmful effects of cannabis on neuropsychological functioning are emerging.

Accumulating evidence suggests that long-term, heavy cannabis use may cause enduring neuropsychological impairment—impairment that persists beyond the period of acute intoxication (2). Studies of long-term, heavy cannabis users fairly consistently show that these individuals perform worse on neuropsychological tests (2–5), and some (6–8) but not all (9) studies suggest that impairment may remain even after extended periods of abstinence. The magnitude and persistence of impairment may depend on factors such as the quantity, frequency, duration, and age-of-onset of cannabis use (2), as more severe and enduring impairment is evident among individuals with more frequent and prolonged heavy use and a younger age-of-onset (3, 6, 8, 10–16).

The extant evidence base draws on case–control studies of recruited cannabis users and comparison subjects. These studies screen participants for potential confounding factors, such as alcohol and drug dependence, and compare them on neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and, in this study, the sample was small and the average duration of regular cannabis use was only 2 y.

In the present study, we investigated the association between persistent cannabis use—prospectively assessed over 20 y—and neuropsychological functioning in a birth cohort of 1,037 individuals. Study members underwent neuropsychological testing in 1985 and 1986 before the onset of cannabis use and again in 2010–2012, after some had developed a persistent pattern of cannabis use. We tested six hypotheses. First, we tested the "cognitive decline" hypothesis that persistent cannabis users evidence greater decline in test performance from childhood to adulthood than nonusers. By examining within-person change in neuropsychological functioning, any effect of premorbid deficits on later (postcannabis-initiation) test performance was nullified. Second, we tested the "specificity" hypothesis to address whether impairment is confined to specific neuropsychological domains or whether it is more global. To test this hypothesis, we administered multiple tests for each of five specific domains, as different tests may be differentially sensitive to cannabis-associated neuropsychological impairment. In conducting our analyses, we tested alternative explanations for the association between per-

Author contributions: M.H.M., A.C., and T.E.M. designed research; M.H.M., A.C., A.A., H.H., R.H., R.S.E.K., K.M., A.W., R.P., and T.E.M. performed research; M.H.M., A.C., R.H., and T.E.M. analyzed data; and M.H.M., A.C., and T.E.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

See Commentary on page 15970.

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See Author Summary on page 15980 (volume 109, number 40).

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1206820109/-/DCSupplemental.

PLOS ONE

RESEARCH ARTICLE

# Alcohol, tobacco and cannabis use are associated with job loss at follow-up: Findings from the CONSTANCES cohort

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**Citation:** Airagnes G, Lemogne C, Meneton P, Plessz M, Goldberg M, Hoertel N, et al. (2019) Alcohol, tobacco and cannabis use are associated with job loss at follow-up: Findings from the CONSTANCES cohort. PLoS ONE 14(9): e0222361. https://doi.org/10.1371/journal.pone.0222361

**Editor:** Raymond Niaura, Global Public Health, New York University, UNITED STATES

**Received:** March 22, 2019

**Accepted:** August 27, 2019

**Published:** September 9, 2019



**Data Availability Statement:** Personal health data underlying the findings of our study are not publicly available due to legal reasons related to data privacy protection. However, the data are available upon request to all interested researchers after authorization of the French "Commission nationale de l'informatique et des libertés". The persons to contact are Dr. Marie Zins (rf.mresni@sniz.eiram) or Pr. Marcel Goldberg (rf.mresni@grebdlog.lecram).

## Abstract

### Background

Substance use is more prevalent among unemployed subjects compared to employed ones. However, quantifying the risk subsequent of job loss at short-term according to substance use remains underexplored as well as examining if this association persist across various sociodemographic and occupational positions previously linked to job loss. We examined this issue prospectively for alcohol, tobacco, cannabis use and their combination, among a large population-based sample of men and women, while taking into account age, gender, overall health status and depressive symptoms.

### Methods

From the French population-based CONSTANCES cohort, 18,879 working participants were included between 2012 and 2016. At baseline, alcohol use disorder risk according to the Alcohol Use Disorders Identification Test (mild, dangerous, problematic or dependence), tobacco (non-smoker, former smoker, 1–9, 10–19, >19 cigarettes/day) and cannabis use (never, not in past year, less than once a month, once a month or more) were assessed. Employment status at one-year (working versus not working) was the dependent variable. Logistic regressions provided Odds Ratios(OR(95%CI)) of job loss at one-year, adjusting for age, gender, self-reported health and depressive state (measured with the Center of Epidemiologic Studies Depression scale). Stratified analyses were performed for education, occupational grade, household income, job stress (measured with the Effort-Reward Imbalance), type of job contract, type of work time and history of unemployment. In sensitivity analyses, employment status over a three-year follow-up was used as dependent variable.

doi:10.1111/add.14939

# Marijuana use trends among college students in states with and without legalization of recreational use: initial and longer-term changes from 2008 to 2018

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## ABSTRACT

**Background and aims** Young adult college students in the United States are likely to be affected by marijuana liberalization trends. However, changes in students' marijuana use following recreational marijuana legalization (RML) have not been examined in more than one RML state at a time, or beyond 1–2 years post-legalization. **Design** Cross-sectional National College Health Assessment survey administered twice yearly from 2008 to 2018. **Setting** A total of 587 4-year colleges and universities in 48 US states. **Participants** Undergraduates aged 18–26 years attending college in US states that did ($n$ = 234 669 in seven states) or did not ($n$ = 599 605 in 41 states) enact RML between 2008 and 2018. **Measurements** Self-reported marijuana use (past 30 days) and individual and contextual covariates, institution-provided institutional and community covariates and publicly available dates when states enacted RML. **Findings** Adjusting for covariates, state differences and state-specific linear time trends (accounting for pre-RML trends), prevalence of 30-day marijuana use increased more among students exposed to RML [odds ratio (OR) = 1.23, 95% confidence interval (CI) = 1.19–1.28, $P < 0.001$] than among non-RML state students throughout the same time-period; the results were similar for frequent use (≥ 20 days) (OR = 1.18, 95% CI = 1.10–1.27, $P < 0.001$). Interaction models supported stronger RML effects among students who were female, residing off-campus and aged 21 years and older; sexual orientation did not moderate RML effects. In the earliest states to enact RML (2012) there were increases in use prevalence in the second through the sixth year post-RML compared to pre-RML. In the second legalization group (2015) there were increases in the first and second year post-RML, and greater increases in the third year. In the later states (2016–17), increases were observed in both years after RML. **Conclusions** In US states that enacted recreational marijuana legislation from 2012 to 2017 there was evidence for a general trend towards greater increases in marijuana use by college students and differential impact by gender, legal using age and campus residence.

**Keywords** Adolescence, cannabis, college students, early adulthood, recreational marijuana legalization, substance use.

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Submitted 8 June 2019; initial review completed 14 August 2019; final version accepted 6 December 2019

## INTRODUCTION

Seven years after states first passed recreational marijuana legalization (RML) in the United States, the effects of these laws on the prevalence of marijuana use are not well understood. There is particular interest in how RML may be impacting adolescents and young adults. During this developmental period, experimentation, onset of regular use and escalation to problem use often occur and show peak prevalence [1–3]. Additionally, the negative academic and employment consequences of marijuana use can be observed in these age groups [4–6], perhaps because brain areas and functions sensitive to cannabis are still rapidly maturing [7]. Young people may be particularly susceptible to the policy environment, as genetic factors account for fewer than half of the variations in marijuana and other substance use in early adulthood [8] and are attenuated by legislative, institutional and interpersonal controls [9]. The impact of the marijuana policy context is evident, for example, in the observation that the prevalence of marijuana use among young people varies markedly by US region, is higher in states that

Pharmacology & Therapeutics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

# The neuropsychopharmacology of cannabis: A review of human imaging studies

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ARTICLE INFO

*Keywords:*
Addiction
Cannabis
Cognition
Development
Neuroimaging
Psychosis

ABSTRACT

The laws governing cannabis are evolving worldwide and associated with changing patterns of use. The main psychoactive drug in cannabis is $\Delta^9$-tetrahydrocannabinol (THC), a partial agonist at the endocannabinoid $CB_1$ receptor. Acutely, cannabis and THC produce a range of effects on several neurocognitive and pharmacological systems. These include effects on executive, emotional, reward and memory processing via direct interactions with the endocannabinoid system and indirect effects on the glutamatergic, GABAergic and dopaminergic systems. Cannabidiol, a non-intoxicating cannabinoid found in some forms of cannabis, may offset some of these acute effects. Heavy repeated cannabis use, particularly during adolescence, has been associated with adverse effects on these systems, which increase the risk of mental illnesses including addiction and psychosis. Here, we provide a comprehensive state of the art review on the acute and chronic neuropsychopharmacology of cannabis by synthesizing the available neuroimaging research in humans. We describe the effects of drug exposure during development, implications for understanding psychosis and cannabis use disorder, and methodological considerations. Greater understanding of the precise mechanisms underlying the effects of cannabis may also give rise to new treatment targets.



**Contents**



*Abbreviations:* ACC, Anterior cingulate cortex; ASL, Arterial spin labelling; BOLD, Blood-oxygen-level dependent; CBD, Cannabidiol; CBF, Cerebral blood flow; $CB_1R$, Endocannabinoid type 1 receptor; CT, Computed tomography; $D_2R$, Dopamine type 2 receptor; DLPFC, Dorsolateral prefrontal cortex; DTI, Diffusion tensor imaging; EEG, Electroencephalography; OFC, Orbitofrontal cortex; FDG, Fludeoxyglucose; fMRI, Functional magnetic resonance imaging; GABA, γ-Aminobutyric acid; MID, Monetary incentive delay; MRI, Magnetic resonance imaging; MRS, Magnetic resonance spectroscopy; NAA, N-Acetylaspartate; NAc, Nucleus accumbens; PCC, Posterior cingulate cortex; PET, Positron emission tomography; PFC, Prefrontal cortex; THC, $\Delta^9$-Tetrahydrocannabinol.

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https://doi.org/10.1016/j.pharmthera.2018.10.006


Please cite this article as: Bloomfield, M.A.P., et al., The neuropsychopharmacology of cannabis: A review of human imaging studies, *Pharmacology & Therapeutics* (2018), https://doi.org/10.1016/j.pharmthera.2018.10.006

# Changes in Healthcare Encounter Rates Possibly Related to Cannabis or Alcohol following Legalization of Recreational Marijuana in a Safety-Net Hospital

## An Interrupted Time Series Analysis

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Journal of Addiction Medicine: November 20, 2018 - Volume Publish Ahead of Print - Issue - p
doi: 10.1097/ADM.0000000000000480
Original Research: PDF Only



Objectives: Liberalization of marijuana laws in Colorado contributed to increases in cannabis-related adverse events over time. We examined characteristics of patients with healthcare encounters possibly related to cannabis and assessed the temporal association between legalization of recreational marijuana and healthcare encounters possibly attributed to cannabis.

Methods: Annual encounter rates possibly related to cannabis and alcohol were compared using negative binomial regression. Two-time intervals, pre/post-recreational marijuana legalization (January 2009 to December 2013 and January 2014 to December 2015, respectively) were used to examine changes in monthly rates of emergency encounters and hospitalizations possibly related to cannabis. Level and trend changes on encounter rates by legalization period were assessed using interrupted time series analyses. Encounters possibly related to alcohol were used as a comparator group.

Results: Most encounters identified during the study period had alcohol-related International Classification of Diseases Diagnosis and Procedural Codes (ICD-9/10-CM) codes (94.8% vs 5.2% for cannabis). Patients with encounters possibly related to cannabis were younger, more likely to be hospitalized and more likely to be admitted to the psychiatric unit than patients with encounters possibly related to alcohol. Initial and sustained effects of encounter rates possibly related to cannabis demonstrated an increased trend in slope before and after recreational marijuana legalization. The slope became more abrupt following legalization with a significant increase in trend during the post-legalization period ($\beta = 2.7$, standard error = 0.3, $\rho < 0.0001$). No significant change was noted for encounters possibly related to alcohol.

Conclusions: Additional research should identify patients at highest risk of an adverse health event related to cannabis and quantify costs associated with cannabis-related healthcare delivery.

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# Dopaminergic Function in Cannabis Users and Its Relationship to Cannabis-Induced Psychotic Symptoms

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**Background:** 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.

**Methods:** 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 $K_i^{cer}$) was measured with positron emission tomography and 3,4-dihydroxy-6-[$^{18}$F]-fluoro-*l*-phenylalanine ([$^{18}$F]-DOPA).

**Results:** Cannabis users had reduced dopamine synthesis capacity in the striatum (effect size: .85; $t_{36} = 2.54$, $p = .016$) and its associative (effect size: .85; $t_{36} = 2.54$, $p = .015$) and limbic subdivisions (effect size: .74; $t_{36} = 2.23$, $p = .032$) 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 ($r = -.77$, $p < .001$) and positively associated with age of onset of cannabis use ($r = .51$, $p = .027$) but was not associated with cannabis-induced psychotic-like symptoms ($r = .32$, $p = .19$).

**Conclusions:** 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.

**Key Words:** Addiction, dependence, dopamine, drugs, imaging, psychosis

Cannabis is the most widely used illicit drug globally (1), and the prevalence of cannabis abuse or dependence in the United States is 4.4% (2). Cannabis can induce transient psychotic symptoms in healthy individuals (3,4), and there is consistent epidemiologic evidence that cannabis dose-dependently increases the risk of psychotic disorders (5,6).

Dopaminergic dysfunction is linked to drug dependence (7–11) and psychosis (12–17). Increased dopamine synthesis capacity and release have been reported in psychotic patients (18–26), drugs that increase dopamine release can induce or worsen psychosis (15,27,28), and elevated dopamine synthesis capacity has been reported in people who subsequently develop a frank psychotic disorder (29–32). Patients with cannabis-induced psychosis have elevated peripheral dopamine metabolites (33), and a case report found striatal dopamine release and symptom exacerbation in a schizophrenic patient following cannabis use (34). Thus, cannabis has been proposed to increase psychosis risk by causing striatal hyperdopaminergia (32).

Supporting this, preclinical studies indicate acute administration of Δ9-tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis (35), increases mesolimbic dopaminergic neuron firing rates via endocannabinoid $CB_1$ receptor agonism (36). $CB_1$ agonists inhibit striatal dopamine reuptake (37), selectively increase tyrosine hydroxylase expression (38), and increase dopamine release (39) and synthesis (40) in the majority of, although not all, studies (41).

Dopaminergic sensitisation to THC occurs in animals (42), suggesting that dopaminergic effects are greater with regular cannabis exposures. Studies in recently abstinent and ex-cannabis users have not found abnormal striatal dopamine release (43) or $D_{2/3}$ receptor availability (44,45), but this may be due to normalization of dopaminergic function with abstinence, as has been observed with alcohol (46). One study reported reduced dopamine transporter availability in cannabis users (47), although this was related to concurrent tobacco use, rather than cannabis. However, to our knowledge, no study has examined dopamine synthesis capacity in cannabis users or whether acute psychotic response to cannabis is related to dopaminergic function.

We therefore sought to study presynaptic dopaminergic function in active cannabis users who experienced cannabis-induced psychotic-like symptoms because these individuals are most at risk of psychosis (48). We hypothesized that regular cannabis users sensitive to cannabis' psychotogenic effects would exhibit elevated dopamine synthesis capacity compared with nonuser control subjects, and this would be directly related to cannabis-induced psychotic-like symptom severity.

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Received Nov 15, 2012; revised May 17, 2013; accepted May 23, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.05.027

Pharmacology, Biochemistry and Behavior 96 (2010) 67–74

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

# Cannabis with high $\Delta^9$-THC contents affects perception and visual selective attention acutely: An event-related potential study

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ARTICLE INFO

*Article history:*
Received 18 November 2008
Received in revised form 29 March 2010
Accepted 12 April 2010
Available online 24 April 2010

*Keywords:*
$\Delta^9$-Tetrahydrocannabinol (THC)
(Acute) dose–response relationship
(Selective) attention
Event-Related Potentials (ERPs)

ABSTRACT

Objective: Cannabis intake has been reported to affect cognitive functions such as selective attention. This study addressed the effects of exposure to cannabis with up to 69.4 mg $\Delta^9$-tetrahydrocannabinol (THC) on Event-Related Potentials (ERPs) recorded during a visual selective attention task. Methods: Twenty-four participants smoked cannabis cigarettes with four doses of THC on four test days in a randomized, double blind, placebo-controlled, crossover study. Two hours after THC exposure the participants performed a visual selective attention task and concomitant ERPs were recorded. Results: Accuracy decreased linearly and reaction times increased linearly with THC dose. However, performance measures and most of the ERP components related specifically to selective attention did not show significant dose effects. Only in relatively light cannabis users the Occipital Selection Negativity decreased linearly with dose. Furthermore, ERP components reflecting perceptual processing, as well as the P300 component, decreased in amplitude after THC exposure. Only the former effect showed a linear dose–response relation. Conclusions: The decrements in performance and ERP amplitudes induced by exposure to cannabis with high THC content resulted from a non-selective decrease in attentional or processing resources. Significance: Performance requiring attentional resources, such as vehicle control, may be compromised several hours after smoking cannabis cigarettes containing high doses of THC, as presently available in Europe and Northern America.



## 1. Introduction

Cannabis, also known as marijuana, is the plant material of the *Cannabis sativa* L. It is one of the most commonly used recreational drugs in the Western world. The main reasons for its abuse are its reinforcing (Justinova et al., 2005), relaxing, euphoric and psychedelic effects. Cannabis exerts its psychoactive effects mainly through $\Delta^9$-tetrahydrocannabinol (THC). THC is an agonist of Cannabinoid type 1 (CB1) receptors. These receptors are vastly present all over the cortex (Herkenham et al., 1990; Eggan and Lewis, 2007). They typically reside on presynaptic neurons and are inhibited by retrograde transmission of endogenous cannabinoids (Wilson and Nicoll, 2001).

Numerous studies have shown that acute exposure to cannabinoids has detrimental effects on cognitive functioning, including psychomotor and memory performance (for reviews, see Ameri, 1999; Lichtman et al., 2002; Iversen, 2003; Ramaekers et al., 2004; Lundqvist, 2005; Ranganathan and D'Souza, 2006). Acute exposure to THC and cannabis also affects selective attention (Hooker and Jones, 1987; for a review Pope et al., 1995; more recently Curran et al., 2002) and executive functions such as planning, psychomotor inhibition and performance monitoring (Ramaekers et al., 2006).

In recent years the average THC content of (sinsemilla or "skunk") cannabis cigarettes has increased to about 50 mg in Western Europe (61 mg cf. Niesink et al., 2004; 42 mg cf. Potter et al., 2008) and to 63 mg in the United States of America (El Sohly, 2004). In contrast acute effects in laboratory tests have been studied up to doses of about 40 mg THC (Hart et al., 2001; Ramaekers et al., 2006). The present study assessed the effects of exposure to cannabis cigarettes containing doses up to 69.4 mg THC in regular non-daily cannabis users. Intermediate doses studied were 29.3 and 49.1 mg, next to placebo. The present article focuses on the effects of these doses on non-spatial visual attention and concurrent ERP recordings. Elsewhere we reported that these high doses of THC are detrimental to processing speed and accuracy on a number of psychomotor tasks (Hunault et al., 2009) that were dependent on sustained attention, working memory and motor control.

Six ERP components were recorded at various latencies and scalp positions in the present non-spatial visual attention task. These included manifestations of 1) perception of the stimulus features that defined relevant and irrelevant stimuli (the exogenous Spatial-

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0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.04.008

Addiction

RESEARCH REPORT

doi:10.1111/j.1360-0443.2008.02221.x

# Cannabis use and later life outcomes

**David M. Fergusson & Joseph M. Boden**

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## ABSTRACT

**Aim** 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. **Design** A longitudinal study of a New Zealand birth cohort studied to age 25 years. **Measurements** 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 behavioural adjustment and cognitive ability and adolescent and young adult mental health and substance use. **Findings** 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 ($P < 0.05$). **Conclusions** 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.

**Keywords** Cannabis use, education, life satisfaction, longitudinal study, mental health, unemployment, welfare.

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Submitted 2 November 2007; initial review completed 4 February 2008; final version accepted 27 February 2008

## INTRODUCTION

In recent years, there have been growing concerns and debates about the effects of cannabis use on the health and wellbeing of young people. These concerns have been motivated by evidence of growing cannabis use in young people [1,2], changes in the nature and strength of cannabis [3,4] and by growing evidence linking cannabis to mental health and other problems [1,5–9]. While the role of cannabis in encouraging psychosocial problems in young people remains controversial, there is growing evidence from both epidemiology and neuroscience that cannabis may be more harmful than believed previously [10,11].

An aspect of these concerns that requires further attention is the extent to which the use, and in particular heavy use, of cannabis may have adverse consequences for a number of important life-course outcomes, including educational achievement, income, welfare dependence, unemployment, relationship satisfaction and life satisfaction. Specifically, there have been frequent references in the literature on cannabis to suggest that cannabis use may reduce educational achievement [12–14], increase welfare dependence [15], reduce income [16] and lead to impaired interpersonal relationships [17]. While there is some evidence of statistical linkage with these outcomes, it may be suggested that the apparent associations between cannabis use and these life-course outcomes may reflect the presence of uncontrolled sources of confounding [18].

In this study, we use data gathered over the course of a 25-year longitudinal study to examine the linkages

Soc Psychiatry Psychiatr Epidemiol (2015) 50:1317–1326
DOI 10.1007/s00127-015-1070-x

INVITED REVIEWS

# Psychosocial sequelae of cannabis use and implications for policy: findings from the Christchurch Health and Development Study

**David M. Fergusson[1] · Joseph M. Boden[1] · L. John Horwood[1]**

Received: 4 March 2015 / Accepted: 13 May 2015 / Published online: 26 May 2015


**Abstract**
*Background* The Christchurch Health and Development Study is a longitudinal study of a birth cohort of 1265 children who were born in Christchurch, New Zealand, in 1977. This cohort has now been studied from birth to the age of 35.
*Scope of this review* This article examines a series of findings from the CHDS that address a range of issues relating to the use of cannabis amongst the cohort. These issues include: (a) patterns of cannabis use and cannabis dependence; (b) linkages between cannabis use and adverse educational and economic outcomes; (c) cannabis and other illicit drug use; (d) cannabis and psychotic symptoms; (e) other CHDS findings related to cannabis; and (f) the consequences of cannabis use for adults using cannabis regularly.
*Findings* In general, the findings of the CHDS suggest that individuals who use cannabis regularly, or who begin using cannabis at earlier ages, are at increased risk of a range of adverse outcomes, including: lower levels of educational attainment; welfare dependence and unemployment; using other, more dangerous illicit drugs; and psychotic symptomatology. It should also be noted, however, that there is a substantial proportion of regular adult users who do not experience harmful consequences as a result of cannabis use.
*Conclusions* Collectively, these findings suggest that cannabis policy needs to be further developed and evaluated in order to find the best way to regulate a widely-used, and increasingly legal substance.

**Keywords** Cannabis · Cannabis dependence · Education · Unemployment · Welfare dependence · Gateway theory · Psychosis

## Introduction

Over the last two decades there have been ongoing debates about the extent to which the use of cannabis/marijuana has harmful effects upon users [1–4]. These debates have tended to polarize into two groups; first, those who tend of minimize the potential harmful effects of cannabis and argue strongly for the liberalization of cannabis laws and permitting access to legal cannabis [5–7]; and second, those who view cannabis as a harmful drug for which continued prohibition is the correct approach [8, 9].

One of the inevitable features of research into the harmful effects of cannabis is that research has been conducted in different settings, using different research designs and measurement methods. While this heterogeneity has benefits for examining the generality of findings about cannabis, it also has some limitations, as the results from different studies may make it difficult to provide a clear picture of the ways in which cannabis use may influence the health and wellbeing of a particular population.

Against this background the aims of this paper are to provide an overview of the findings of a large longitudinal study in which the use of cannabis has been studied from mid-adolescence (age 14) to mature adulthood (age 35). This study is the Christchurch Heath and Development Study, which is a longitudinal study of a birth 1265 cohort of children born in the Christchurch (New Zealand) area in

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Published in final edited form as:
*J Subst Abuse Treat*. 2013 ; 45(5): 426–432. doi:10.1016/j.jsat.2013.05.011.

# Concurrent Life-course Trajectories of Employment and Marijuana-use: Exploring Interdependence of Longitudinal Outcomes

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## Abstract

This study analyzes data on 7,661 individuals who participated in the 1979 National Longitudinal Survey of Youth (NLSY79) to estimate trajectories of employment and marijuana-use over a 17-year period. Bivariate random intercept and slope modeling is applied to examine concurrently the cross-correlation between the two concurrent longitudinal trajectories from age 23 to 39. Parameter estimates indicate baseline level (at age 23) of employment to be negatively correlated with marijuana, suggesting marijuana-use is associated with lower workforce productivity at age 23. The longitudinal employment slope is positively correlated with employment intercept for both males and females, indicating that survey participants with higher levels of employment at age 23 are more likely to have a positive impact on employment trajectory over time. For males, however, the employment slope is also significantly correlated with marijuana intercept ($r = -0.07$), indicating marijuana-use in early adulthood may uniquely lower workforce productivity over age.

### Keywords

employment; marijuana-use; gender differences; life-course; multivariate longitudinal outcomes

## 1 Introduction

The adverse consequences of illicit drug use on users' physical (Mokdad et al., 2004) and psychological health (Brook et al., 2002) have been examined extensively. Substance abuse has been found to be associated with reduced cognitive abilities (Pope & Yurgelun-Todd,

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**Author Disclosures**
This study is supported in part by the UCLA Center for Advancing Longitudinal Drug Abuse Research (P30DA016383 from the National Institute on Drug Abuse or NIDA) (PI: Hser). David Y.C. Huang is also supported by a grant (R03HD064619) from the National Institute of Child Health and Human Development. Yih-Ing Hser is also supported by a Senior Scientist award from NIDA (K05DA017648). All authors declare that they have no conflict of interest.

HHS Public Access

Author manuscript

*Neuropsychopharmacology*. Author manuscript; available in PMC 2010 April 01.

Published in final edited form as:

*Neuropsychopharmacology*. 2009 October ; 34(11): 2450–2458. doi:10.1038/npp.2009.67.

# Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users

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## Abstract

Drug abuse and other psychiatric conditions (e.g., schizophrenia) have been associated with a diminished neural response to errors, particularly in the anterior cingulate cortex (ACC) thought critical to error processing. A diminished capacity for detecting errors has been linked to clinical symptoms including the loss of insight, delusions and perseverative behaviour. Sixteen active chronic cannabis users and 16 control participants were administered a Go/No-go response inhibition task during event-related fMRI data collection. The task provides measures of inhibitory control and error awareness. Cannabis users' inhibitory control performance was equivalent to that of the control group, but the former demonstrated a significant deficit in awareness of commission errors. Cannabis users demonstrated a diminished capacity for monitoring their behaviour that was associated with hypoactivity in the ACC and right insula. In addition, increased levels of hypoactivity in both the ACC and right insula regions were significantly correlated with error awareness rates in the cannabis group (but not controls). These difficulties are consistent with previous reports of hypoactivity in the neural systems underlying cognitive control and the monitoring of interoceptive awareness in chronic drug users, and highlight the potential relationship between cognitive dysfunction and behavioural deficits that have the potential to contribute to the maintenance of drug abuse.

### Keywords

Performance monitoring; error-related; drug addiction; marijuana; insula; cognitive control

## INTRODUCTION

Healthy adults are very good at detecting cognitive failures, whereas a common feature of many psychiatric and neurological conditions is a diminished capacity for performance monitoring (Ullsperger, 2006). Deficits in error detection have also been found to relate to



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Disclosures

Drs Hester, Nestor and Garavan reported no biomedical financial interests or potential conflicts of interest.

Drug and Alcohol Dependence 110 (2010) 247–253

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Cannabis use and educational achievement: Findings from three Australasian cohort studies

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ARTICLE INFO

*Article history:*
Received 30 November 2009
Received in revised form 22 March 2010
Accepted 23 March 2010
Available online 24 April 2010

*Keywords:*
Cannabis
Educational achievement
Meta-analysis
Longitudinal study

ABSTRACT

*Background:* The associations between age of onset of cannabis use and educational achievement were examined using data from three Australasian cohort studies involving over 6000 participants. The research aims were to compare findings across studies and obtain pooled estimates of association using meta-analytic methods.
*Methods:* Data on age of onset of cannabis use (<15, 15–17, never before age 18) and three educational outcomes (high school completion, university enrolment, degree attainment) were common to all studies. Each study also assessed a broad range of confounding factors.
*Results:* There were significant ($p < .001$) associations between age of onset of cannabis use and all outcomes such that rates of attainment were highest for those who had not used cannabis by age 18 and lowest for those who first used cannabis before age 15. These findings were evident for each study and for the pooled data, and persisted after control for confounding. There was no consistent trend for cannabis use to have greater effect on the academic achievement of males but there was a significant gender by age of onset interaction for university enrolment. This interaction suggested that cannabis use by males had a greater detrimental effect on university participation than for females. Pooled estimates suggested that early use of cannabis may contribute up to 17% of the rate of failure to obtain the educational milestones of high school completion, university enrolment and degree attainment.
*Conclusions:* Findings suggest the presence of a robust association between age of onset of cannabis use and subsequent educational achievement.



## 1. Introduction

There has been increasing research into the relationships between cannabis use by young people and educational achievement. Findings suggests that young people who use cannabis early or heavily are at increased risks of educational under-achievement including: school dropout (Brook et al., 1999; Ellickson et al., 1998; Fergusson and Boden, 2008; Fergusson et al., 2003, 1996; Lynskey et al., 2003; Tanner et al., 1999; van Ours and Williams, 2009); failure to attend tertiary education (Fergusson and Boden, 2008; Fergusson et al., 2003; Newcomb and Bentler, 1988b; Tanner et al., 1999); and failure to attain university degrees (Fergusson and Boden, 2008; van Ours and Williams, 2009). These associations have been found to persist following control for confounding social, personal and related factors (Fergusson et al., 1996; Lynskey and Hall, 2000; Townsend et al., 2007; van Ours and Williams, 2009).

A limitation of this literature has been that different studies have used different samples, different methods of assessing cannabis use and differing assessments of educational outcomes, limiting the extent to which cross study comparisons can be made (Townsend et al., 2007). It has often been suggested that these limitations may be overcome by meta-analytic methods that combine findings from different studies (Curran and Hussong, 2009; Hofer and Piccinin, 2009; Mulrow, 1994). However, such analysis may be compromised by variations in study quality (Blettner et al., 1999; Egger et al., 1998). In this paper we attempt to overcome these limitations by conducting a meta-analysis of three Australasian longitudinal studies that have collected similar data on the development of cannabis use and educational achievement. Overlapping measures include: (a) the assessment of age of first use of cannabis; (b) the use of

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0376-8716/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2010.03.008

Psychopharm

*Journal of Psychopharmacology*
23(5) (2009) 495–509

ISSN 0269-8811
SAGE Publications Ltd, Los Angeles, London, New Delhi and Singapore
10.1177/0269881108091076

# Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol

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## Abstract

Regular use of illegal drugs is suspected to cause cognitive impairments. Two substances have received heightened attention: 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') and δ-9-tetrahydrocannabinol (THC or 'cannabis'). Preclinical evidence, as well as human studies examining regular ecstasy consumers, indicated that ecstasy use may have negative effects on learning, verbal memory and complex attentional functions. Cannabis has also been linked to symptoms of inattention and deficits in learning and memory. Most of the published studies in this field of research recruited participants by means of newspaper advertisements or by using word-of-mouth strategies. Because participants were usually aware that their drug use was critical to the research design, this awareness may have caused selection bias or created expectation effects. Focussing on attention and memory, this study aimed to assess cognitive functioning in a community-based representative sample that was derived from a large-scale epidemiological study. Available data concerning drug use history allowed sampling of subjects with varying degrees of lifetime drug experiences. Cognitive functioning was examined in 284 young participants, between 22 and 34 years. In general, their lifetime drug experience was moderate. Participants completed a neuropsychological test battery, including measures for verbal learning, memory and various attentional functions. Linear regression analysis was performed to investigate the relationship between cognitive functioning and lifetime experience of drug use. Ecstasy and cannabis use were significantly related to poorer episodic memory function in a dose-related manner. For attentional measures, decrements of small effect sizes were found. Error measures in tonic and phasic alertness tasks, selective attention task and vigilance showed small but significant effects, suggesting a stronger tendency to experience lapses of attention. No indication for differences in reaction time was found. The results are consistent with decrements of memory and attentional performance described in previous studies. These effects are relatively small; however, it must be kept in mind that this study focussed on assessing young adults with moderate drug use from a population-based study.

## Key words

alcohol; alertness; cannabis; divided attention; ecstasy; flexibility; learning; memory; selective attention; vigilance

This article has been prepared in the context of the project F2 "*Targeted early interventions in ecstasy, regular cannabis and harmful alcohol users: utilizing individual neurocognitive and psychosocial problem profiles*." (CG Schuetz) of the Addiction Research Network ASAT (Allocating Substance Abuse Treatments to Patient Heterogeneity). Contact information: Email: asatkoordination@mpipsykl.mpg.de (http://www.asat-verband.de). ASAT is sponsored by a federal grant of the Federal Ministry of Education and Research (01 EB 0440 – 0441, 01 EB 0142).

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Published in final edited form as:
*Curr Pharm Des*. 2014 ; 20(13): 2186–2193.

# Effects of Cannabis on the Adolescent Brain

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## Abstract

This article reviews neuroimaging, neurocognitive, and preclinical findings on the effects of cannabis on the adolescent brain. Marijuana is the second most widely used intoxicant in adolescence, and teens who engage in heavy marijuana use often show disadvantages in neurocognitive performance, macrostructural and microstructural brain development, and alterations in brain functioning. It remains unclear whether such disadvantages reflect pre-existing differences that lead to increased substances use and further changes in brain architecture and behavioral outcomes. Future work should focus on prospective investigations to help disentangle dose-dependent effects from pre-existing effects, and to better understand the interactive relationships with other commonly abused substances (e.g., alcohol) to better understand the role of regular cannabis use on neurodevelopmental trajectories.

## Introduction

According to the 2011 Monitoring the Future Study, marijuana remains the most commonly used illicit drug in adolescence in the United States, one of few increasing in prevalence. In fact, marijuana has been the most commonly used illicit substance for almost 40 years, and presently 23% of 12$^{th}$ graders in the U.S. report using marijuana in the past month [1]. Marijuana use in adolescence could have implications for academic functioning, as well as social and occupational functioning extending into later life. Maturational brain changes, particularly myelination and synaptic pruning, are occurring throughout adolescence, well into early adulthood [2]. These remodeling processes are purportedly linked to efficient neural processing, and believed to underlie specialized cognitive processing necessary for optimal neurocognitive performance.

Cannabinoid receptors (CB1) are widely distributed throughout the brain (e.g., hippocampus, prefrontal cortex), and play a role in neurotransmitter release and concentrations across neural systems (excitatory and inhibitory). It has been suggested that these receptors increase during adolescence, have a role in genetic expression of neural development, and that alteration of the endocannabinoid system during adolescence may

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Developmental Cognitive Neuroscience 16 (2015) 101–109

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

# Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood

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ARTICLE INFO

*Article history:*
Received 2 January 2015
Received in revised form 17 April 2015
Accepted 18 April 2015
Available online 27 April 2015

*Keywords:*
Adolescence
Brain
Alcohol
Marijuana
Imaging
Cortical thickness

ABSTRACT

Studies suggest marijuana impacts gray and white matter neural tissue development, however few prospective studies have determined the relationship between cortical thickness and cannabis use spanning adolescence to young adulthood. This study aimed to understand how heavy marijuana use influences cortical thickness trajectories across adolescence. Subjects were adolescents with heavy marijuana use and concomitant alcohol use (MJ + ALC, $n = 30$) and controls (CON, $n = 38$) with limited substance use histories. Participants underwent magnetic resonance imaging and comprehensive substance use assessment at three independent time points. Repeated measures analysis of covariance was used to look at main effects of group, time, and Group × Time interactions on cortical thickness. MJ + ALC showed thicker cortical estimates across the brain (23 regions), particularly in frontal and parietal lobes ($ps < .05$). More cumulative marijuana use was associated with increased thickness estimates by 3-year follow-up ($ps < .05$). Heavy marijuana use during adolescence and into young adulthood may be associated with altered neural tissue development and interference with neuromaturation that can have neurobehavioral consequences. Continued follow-up of adolescent marijuana users will help understand ongoing neural changes that are associated with development of problematic use into adulthood, as well as potential for neural recovery with cessation of use.



## 1. Introduction

Adolescence is a unique developmental period characterized by major physiological, psychological, and neurodevelopmental changes. These changes typically coincide with escalation of alcohol and marijuana use (Brown et al., 2008), which continues into early adulthood (Sartor et al., 2007). The comorbid use of alcohol and marijuana among teens continues to subtly rise as perception of harm declines. Fifty-eight percent of alcohol drinking adolescents report using alcohol and marijuana simultaneously, (Agosti et al., 2002), 45% of youth endorse a lifetime prevalence of marijuana use by the 12th grade, and 22% of these youth endorse use in the past 30 days (Johnston et al., 2015).

The adolescent brain undergoes considerable maturation, including changes in cortical volume and refinement of cortical connections (Huttenlocher and Dabholkar, 1997). These neural transformations (e.g., maturing neural circuitry, cortical thinning and fiber projections) leave the adolescent brain more susceptible to potential neurotoxic effects of substances (Brown et al., 2000; Spear, 2000; Spear and Varlinskaya, 2005; Squeglia et al., 2009; Tapert et al., 2002). Although overall brain volume remains largely unchanged after puberty, ongoing synaptic refinement and myelination results in reduced gray matter and increased white matter volume by late adolescence (Casey et al., 2008; Giedd, 2004; Sowell et al., 2003; Yakovlev and Lecours, 1967).

Cortical gray matter follows an inverted U-shaped developmental course, with cortical volume peaking around ages 12–14 (Giedd, 2004; Giedd et al., 2009; Gogtay et al., 2004; Sowell et al., 2003). The mechanisms underlying the decline in cortical volume and thickness are suggested to involve pruning and elimination of weaker synaptic connections, decreases in neuropil, increases in intra-cortical myelination, or changes in the cellular organization of the cerebral cortex (Huttenlocher and Dabholkar, 1997; Paus et al.,

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http://dx.doi.org/10.1016/j.dcn.2015.04.006

HHS Public Access

Author manuscript

*Addiction*. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

*Addiction*. 2015 April ; 110(4): 627–635. doi:10.1111/add.12829.

# A LONGITUDINAL STUDY OF THE ASSOCIATION OF ADOLESCENT POLYDRUG USE, ALCOHOL USE, AND HIGH SCHOOL NON-COMPLETION

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## Abstract

**Aims—**Failure to complete high school predicts substantial economic and social disadvantage in adult life. The aim was to determine the longitudinal association of mid-adolescent polydrug use and high school non-completion, relative to other drug use profiles.

**Design—**A longitudinal analysis of the relationship between polydrug use in three cohorts at Grade 9 (age 14–15) and school non-completion (reported post high school).

**Setting—**A State-representative sample of students across Victoria, Australia.

**Participants—**2287 secondary school students from 152 high schools. The retention rate was 85%.

**Measurements—**The primary outcome was noncompletion of Grade 12 (assessed at age 19–23 years). At Grade 9, predictors included 30 day use of eight drugs, school commitment, academic failure, and peer drug use. Other controls included socioeconomic status, family relationship quality, depressive symptoms, gender, age, and cohort.

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**DECLARATION**: The authors declare that the material has not been published in whole or in part elsewhere, the paper is not currently being considered for publication elsewhere, all authors have been personally and actively involved in substantive work leading to the report and will hold themselves jointly and individually responsible for its content, and all relevant ethical safeguards have been met in relation to patient or subject protection. The authors declare that there are no potential conflicts of interest in relation to this study.

Curr Addict Rep (2014) 1:144–156
DOI 10.1007/s40429-014-0019-6

STIMULANTS, CANNABIS, AND CLUB DRUGS (AJ BUDNEY, R VANDREY AND D LEE, SECTION EDITORS)

# Considering Cannabis: The Effects of Regular Cannabis Use on Neurocognition in Adolescents and Young Adults

**Krista M. Lisdahl · Natasha E. Wright · Christopher Medina-Kirchner · Kristin E. Maple · Skyler Shollenbarger**

Published online: 26 April 2014


**Abstract** Thirty-six percent of high-school seniors have used cannabis in the past year, and an alarming 6.5 % smoked cannabis daily, up from 2.4 % in 1993. Adolescents and emerging adults are undergoing significant neurodevelopment and animal studies suggest they may be particularly vulnerable to negative drug effects. In this review, we will provide a detailed overview of studies outlining the effects of regular (at least weekly) cannabis use on neurocognition, including studies outlining cognitive, structural, and functional findings. We will also explore the public health impact of this research.

**Keywords** Adolescence · Emerging Adult · Young Adult · Cannabis · Marijuana · MRI · fMRI · Diffusion Tensor Imaging · Neuropsychology · Cognition · Age of Onset · *FAAH* · *CNR1* · THC · Cannabidiol · Public health · Neurotoxic effects of cannabis

## Introduction

Cannabis is the second most used drug after alcohol, with 22.9 % of high-school seniors and 20 % of college students using in the past month, and perhaps most alarmingly, one in every 15 seniors report using daily [1]. Research outlining the neurocognitive effects of chronic, regular (defined here as at least weekly) cannabis use in adolescents and young adults is of great public health concern. This review will summarize current findings regarding the neurocognitive consequences of cannabis use during the teenage and emerging adult years (focusing on ages 15–25 years). Studies utilizing neuropsychological assessment and structural and functional neuroimaging will be reviewed. Further, we will identify potential 'at-risk' groups who may experience more severe neurocognitive consequences of chronic cannabis use, such as those with early age of cannabis use onset and those with certain genotypic profiles, and will discuss the clinical and policy implications of this research.

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## Adolescence: A Sensitive Period?

Worldwide, most people start experimenting with drugs during the teenage years [2]. Adolescence is also a dynamic time marked by significant neurodevelopmental changes; brain regions underlying higher-order thinking and executive functioning, especially the prefrontal (PFC) and parietal cortex, undergo synaptic pruning into the mid-20s (see [3–6]). Quality and volume of white matter increase into the early 30s, which are associated with increased neural efficiency [7, 8]. This period of ongoing neurodevelopment may be a sensitive period in which drugs can exert a greater impact on the brain compared with exposure during adulthood (see [9]).

## Impacts of Regular Cannabis Use on Neurocognition in Teens and Young Adults

### Cognition

Although controversy exists in the adult literature, evidence is building to suggest that regular cannabis use during the teenage or emerging adult years (typically ages 15–25 years) is associated with cognitive deficits [10•]. Two longitudinal studies that followed adolescents with substance use disorders over 8 years found that increased cannabis use during the follow-up period significantly predicted poorer attention

Biological Psychology 110 (2015) 115–125

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

# Chronic cannabis use and ERP correlates of visual selective attention during the performance of a flanker go/nogo task

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ARTICLE INFO

*Article history:*
Received 13 March 2014
Received in revised form 9 June 2015
Accepted 23 July 2015
Available online 29 July 2015

*Keywords:*
Cannabis use
Selective attention
ERPs
N1
N2
Flanker
Go/nogo

ABSTRACT

The aim of the study was to investigate the relationship between chronic cannabis use and visual selective attention by examining event-related potentials (ERPs) during the performance of a flanker go/nogo task. Male participants were 15 chronic cannabis users (minimum two years use, at least once per week) and 15 drug naive controls. Cannabis users showed longer reaction times compared to controls with equivalent accuracy. Cannabis users also showed a reduction in the N2 'nogo effect' at frontal sites, particularly for incongruent stimuli, and particularly in the right hemisphere. This suggests differences between chronic cannabis users and controls in terms of inhibitory processing within the executive control network, and may implicate the right inferior frontal cortex. There was also preliminary evidence for differences in early selective attention, with controls but not cannabis users showing modulation of N1 amplitude by flanker congruency. Further investigation is required to examine the potential reversibility of these residual effects after long-term abstinence and to examine the role of early selective attention mechanisms in more detail.



## 1. Introduction

The acute effects of cannabis on cognitive processes are well documented, and include decrements in working memory, inhibitory processing, planning and decision making (see Crean, Crane, & Mason, 2011; Gonzalez, 2007). Chronic cannabis use, or repeated use over an extended period of time, is associated with differences in cognitive processing that persist beyond the period of acute intoxication (Crean et al., 2011). In a recent meta-analysis (Schreiner & Dunn, 2012), there was a small residual (non-acute) effect of cannabis use on overall cognitive function ($d = -.46$ to $-.12$), with similar small effects found for most cognitive domains including memory, attention and executive function. However, given that the active metabolites of cannabis can be stored in and subsequently released from adipose tissue for up to months after use (Grotenhermen, 2003; Huestis, 2007), the residual effects of cannabis on the CNS may not necessarily represent long-term neuro-adaptive changes (Schreiner & Dunn, 2012). While some recent reviews suggest that there may be neurocognitive adaptations which last beyond these residual effects (Crean et al., 2011; Solowij & Battisti, 2008), other research suggests that some effects are reversible with prolonged abstinence (Schreiner & Dunn, 2012). There is also evidence that adolescents may be particularly vulnerable to the long-term effects of cannabis on cognitive function (see Pattij, Wiskerke, & Schoffelmeer, 2008).

It has been suggested that altered cognitive processing in cannabis users is associated with functional changes in brain regions rich with cannabinoid CB1 receptors (Pattij et al., 2008). THC (the main psychoactive component in cannabis) acts on CB1 receptors and these are particularly concentrated in brain regions known to be involved in executive functioning, reward processing, attention and memory. These areas include the prefrontal cortex, anterior cingulate cortex, basal ganglia, hippocampus, and cerebellum (Burns et al., 2007; Herkenham et al., 1990). In a recent PET study, down-regulation of CB1 receptors was found in cortical but not subcortical areas among long-term daily cannabis users and these effects were found to reverse in most cortical areas after approximately 4 weeks of abstinence (Hirvonen et al., 2012).

Of particular interest to the present study are the residual effects of chronic cannabis use on selective attention. According to the attentional network model, the attention system of the brain is composed of distinct networks responsible for alerting, orienting and executive control (Petersen & Posner, 2012; Posner & Peterson, 1990). While the alerting network is most important for vigilance and sustained attention, the latter two networks are most relevant to selective attention. The orienting network involves the interaction between frontal and parietal areas and is argued to

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http://dx.doi.org/10.1016/j.biopsycho.2015.07.013
0301-0511/

# Cannabis Use and Memory Brain Function in Adolescent Boys: A Cross-Sectional Multicenter Functional Magnetic Resonance Imaging Study

Gerry Jager, Ph.D., Robert I. Block, Ph.D., Maartje Luijten, M.Sc., Nick F. Ramsey, Ph.D.

**Objective:** Early-onset cannabis use has been associated with later use/abuse, mental health problems (psychosis, depression), and abnormal development of cognition and brain function. During adolescence, ongoing neurodevelopmental maturation and experience shape the neural circuitry underlying complex cognitive functions such as memory and executive control. Prefrontal and temporal regions are critically involved in these functions. Maturational processes leave these brain areas prone to the potentially harmful effects of cannabis use. **Method:** We performed a two-site (United States and the Netherlands; pooled data) functional magnetic resonance imaging (MRI) study with a cross-sectional design, investigating the effects of adolescent cannabis use on working memory (WM) and associative memory (AM) brain function in 21 abstinent but frequent cannabis–using boys (13–19) years of age and compared them with 24 nonusing peers. Brain activity during WM was assessed before and after rule-based learning (automatization). AM was assessed using a pictorial hippocampal-dependent memory task. **Results:** Cannabis users performed normally on both memory tasks. During WM assessment, cannabis users showed excessive activity in prefrontal regions when a task was novel, whereas automatization of the task reduced activity to the same level in users and controls. No effect of cannabis use on AM-related brain function was found. **Conclusions:** In adolescent cannabis users, the WM system was overactive during a novel task, suggesting functional compensation. Inefficient WM recruitment was not related to a failure in automatization but became evident when processing continuously changing information. The results seem to confirm the vulnerability of still developing frontal lobe functioning for early-onset cannabis use. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(6):561–572. **Key Words:** cannabis, adolescence, early-onset, fMRI, memory

Early initiation of cannabis use increases the risk of later use/abuse of other drugs and drug dependence, and is associated with mental health problems such as psychosis and depression. The strength of this association appears to be dependent on the age when cannabis use begins.[1] A major concern that has only recently gained attention is the effect of early-onset cannabis use on adolescent brain function and neurodevelopment.

Supplemental material cited in this article is available online.

The still-developing adolescent brain differs anatomically and neurochemically from the adult brain[2,3] and is likely more susceptible to drug-induced adaptive neuronal plasticity.

Animal studies on the neural consequences of chronic cannabis exposure during the peri-adolescent period report changes in brain structure (predominantly limbic brain regions) and altered emotional and cognitive performance in later life.[4] However, these effects were mostly observed at relatively high doses of synthetic cannabinoids (Win 55,212-2; CP 55,940) and therefore may not be comparable to the human situation.

Studies in cannabis-using human adolescents

Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2011.03436.x

# Cannabis and social welfare assistance: a longitudinal study

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## ABSTRACT

**Aims** To investigate associations between cannabis use and subsequent receipt of social welfare assistance. **Design, setting and participants** The Young in Norway Longitudinal Study. A population-based Norwegian sample ($n = 2606$) was followed-up from adolescence to late 20s. Self-report data were merged with data from national registers. **Measurements** Data were extracted on the use of alcohol, tobacco and cannabis and other illegal substances. Information was also retrieved on socio-demographic and family factors, academic achievement, conduct problems and mental health. National registers provided data on social welfare assistance, educational level and crime statistics. **Findings** We observed prospective bivariate associations between increasing levels of cannabis use and subsequent social welfare assistance ($P < 0.0001$). The associations were reduced after adjusting for a range of potentially confounding factors, but remained significant. Frequent cannabis users were at highly increased risk for subsequently receiving social welfare assistance. At 28 years, those with 50+ times cannabis use during the previous 12 months and had an odds ratio of 9.3 (95% confidence interval: 4.3–20.1) for receiving social welfare assistance in the following 2-year span. Users of cannabis also had longer periods of receiving social welfare assistance than others ($P < 0.0001$) and were less likely to leave the welfare assistance system ($P < 0.0001$). **Conclusions** In Norway the use of cannabis is linked with subsequent receipt of social welfare assistance whether the consequences are related to use of the substance per se, or to cultural factors and the illegal status of the cannabis. Future research should attempt to understand the interactions of factors behind these associations.

**Keywords** Alcohol, cannabis, illegal drugs, longitudinal, marijuana, welfare assistance.

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Submitted 21 December 2010; initial review completed 1 March 2011; final version accepted 15 March 2011

## INTRODUCTION

A number of studies indicate that individuals with substance use-related problems are susceptible to repeat patterns of on-and-off welfare use, or 'welfare cycling' [1,2]. However, there are few population-based prospective studies in this area. At the same time, a growing body of evidence suggests that use of cannabis may have adverse social outcomes related to educational achievement [3,4], unemployment, reduced income and welfare dependency [5,6]. This study investigates the prospective associations between cannabis use and subsequent receipt of social welfare assistance in the context of a Nordic welfare state.

Many of the longitudinal reports on the consequences of cannabis use are based on populations with a high prevalence of cannabis use, such as the United States [5] and Australia [7]. The New Zealand Christchurch Study (CHDS) has formed the basis for the bulk of longitudinal reports [6,8,9]. However, in the CHDS, more than 70% of subjects had used cannabis before the age of 21, and many had a very high frequency of cannabis use [6]. In Norway, the prevalence of cannabis use is much lower, thereby making it an interesting case for contrast.

Furthermore, many studies of the consequences of substance use and abuse with regard to receipt of social welfare assistance have been conducted in areas with high levels of poverty and where welfare systems are not well developed [2,10]. By contrast, Norway is classified as a social democratic welfare regime, with currently the lowest unemployment rate in Europe [11], a high standard of living and a universal pension system [12]. The

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Contents lists available at ScienceDirect

Addictive Behaviors

# Marijuana use, craving, and academic motivation and performance among college students: An in-the-moment study

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## HIGHLIGHTS

- Craving predicted use in college students who frequently use marijuana.
- Craving was negatively associated with academic effort and motivation.
- Average minutes spent smoking marijuana was negatively related to GPA.
- Greater academic self-efficacy positively predicted GPA.

## ARTICLE INFO

Available online 27 March 2015

*Keywords:*
Marijuana
Craving
Ecological momentary assessment
Academics
Motivation
College students

## ABSTRACT

*Introduction:* Marijuana is the most commonly used illicit substance in the U.S., with high rates among young adults in the state of Colorado. Chronic, heavy marijuana use can impact cognitive functioning, which has the potential to influence academic performance of college students. It is possible that craving for marijuana may further contribute to diminished cognitive and affective functioning, thus leading to poor outcomes for students.
*Methods:* College student marijuana users ($n = 57$) were recruited based on heavy use and completed ecological momentary assessment (EMA) via text-messaging. The association between marijuana use and craving in a college setting was explored, as well as how these variables might relate to academic motivation, effort and success. The participants were sent text messages for two weeks, three times per day at random times.
*Results:* A temporal association between craving and marijuana use was found, where momentary craving positively predicted greater marijuana use. Similarly, as craving levels increased, the number of minutes spent studying decreased at the next assessment point. A negative association between momentary craving for marijuana and academic motivation was found in the same moment. Greater academic self-efficacy positively predicted cumulative GPA, while average minutes spent smoking marijuana was negatively related.
*Conclusions:* Using EMA, marijuana craving and use were significantly related. These findings provide further evidence that heavy marijuana use is negatively associated with academic outcomes.



## 1. Introduction

Marijuana is the most commonly used illicit drug in the U.S., with over 7% of the general population and 19% of 18–25 year olds reporting use of marijuana within the last month (Substance Abuse & Mental Health Services Administration [SAMHSA], 2014). In the state of Colorado, rates of marijuana use are among the highest in the nation, with 25% of 18–25 year olds reporting use within the last month (SAMHSA, 2012). Approximately one-third of college students report use of marijuana annually (Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2014; Mohler-Kuo, Lee, & Wechsler, 2003) and a significant portion (25%) of past-year cannabis users meet criteria for a cannabis disorder (Caldeira, Arria, O'Grady, Vincent, & Wish, 2008).

Chronic marijuana users experience significant consequences as a result of their use, including a range of cognitive deficits. Acute intoxication effects include deficits in psychomotor functioning (e.g., speed, accuracy), attention (including sustained selective, focused and divided attention problems), pre-attentive sensory memory, and short-term/working memory (problems in verbal learning/memory, immediate and delayed free recall; see Solowij & Pesa, 2010 for a review). When examining long-term deficits, studies have consistently shown problems with attention, inhibition, working memory, executive functioning, verbal memory, and time estimation in heavy, chronic users (Solowij & Pesa, 2010). Of

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http://dx.doi.org/10.1016/j.addbeh.2015.03.020
0306-4603/

HHS Public Access

Author manuscript

*Drug Alcohol Depend*. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

*Drug Alcohol Depend*. 2016 November 1; 168: 320–327. doi:10.1016/j.drugalcdep.2016.09.002.

# The Impact of Adolescent Exposure to Medical Marijuana Laws on High School Completion, College Enrollment and College Degree Completion*

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## Abstract

**Background—**There is concern that medical marijuana laws (MMLs) could negatively affect adolescents. To better understand these policies, we assess how adolescent exposure to MMLs is related to educational attainment.

**Methods—**Data from the 2000 Census and 2001–2014 American Community Surveys were restricted to individuals who were of high school age (14–18) between 1990 to 2012 ($n$ = 5,483,715). MML exposure was coded as: (i) a dichotomous “any MML” indicator, and (ii) number of years of high school age exposure. We used logistic regression to model whether MMLs affected: (a) completing high school by age 19; (b) beginning college, irrespective of completion; and (c) obtaining any degree after beginning college. A similar dataset based on the Youth Risk Behavior Survey (YRBS) was also constructed for confirmatory analyses assessing marijuana use.

**Results—**MMLs were associated with a 0.40 percentage point increase in the probability of not earning a high school diploma or GED after completing the 12th grade (from 3.99% to 4.39%). High school MML exposure was also associated with a 1.84 and 0.85 percentage point increase in the probability of college non-enrollment and degree non-completion, respectively (from 31.12% to 32.96% and 45.30% to 46.15%, respectively). Years of MML exposure exhibited a consistent

*Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

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**Contributors:** All authors listed have seen, approved and contributed to the manuscript. AP, AA, WT, JM and RA contributed to the development of the research questions. AP conducted all analyses and wrote the initial draft of the manuscript. All authors contributed to the interpretation of the findings, provided editorial comments and approved the final draft of the manuscript.

**Conflict of Interest:** No conflict declared.

Molecular and Cellular Endocrinology 286S (2008) S108–S113

Molecular and Cellular Endocrinology

www.elsevier.com/locate/mce

# Long lasting consequences of cannabis exposure in adolescence

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Received 10 January 2008; received in revised form 4 February 2008; accepted 4 February 2008

**Abstract**

Despite the increasing use of cannabis among adolescents, there are little and often contradictory studies on the long-term neurobiological consequences of cannabis consumption in juveniles. Adolescence is a critical phase for cerebral development, where the endocannabinoid system plays an important role influencing the release and action of different neurotransmitters. Therefore, a strong stimulation by the psychoactive component of marijuana, delta-9-tetrahydrocanabinol (THC), might lead to subtle but lasting neurobiological changes that can affect adult brain functions and behaviour.

The literature here summarized by use of experimental animal models, puts forward that heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse in selected individuals, and may represent a risk factor for developing schizophrenia in adulthood.

Therefore, the potential problems arising in relation to marijuana consumption in adolescence suggest that this developmental phase is a vulnerable period for persistent adverse effects of cannabinoids.



*Keywords:* Cannabinoids; Adolescence; Emotional profile; Cognition; Psychosis; Gateway hypothesis

## 1. Introduction

Cannabis is the most commonly used illicit substance among adolescents and young adults. In 2004, 46% of 12th graders in the USA reported having tried cannabis at some point in their lifetime, 34% reported having used within the past month, and 5.6% reported having smoked cannabis daily (Johnston et al., 2004). Initiation into cannabis use typically begins in adolescence, as youths aged 12–17 constitute about two thirds of the new cannabis users (SAMHSA, 2004). Approximately 14% of adolescent-onset cannabis users develops cannabis dependence, a rate roughly twice that reported for adult-onset users (Chen et al., 1997; Chen and Anthony, 2003). Cannabis dependence is defined in the Diagnostic and Statistical Manual of Mental Disorder (4th edition, text revision, DSM-IVTR) as having at least three out of seven symptoms within one year. Moreover, very recently, record numbers of teenagers were requiring drug treatment as a result of smoking skunk, the highly potent cannabis strain containing 25 times more delta-9-tetrahydrocannabinol (THC, the psychoactive ingredient) than the resin sold a decade ago.

Despite the constantly spreading use of cannabis among adolescents, there is little information about its neurobiological long-term consequences. The adolescent brain is particularly sensitive to internal and external variables such as drug exposure, environment and gonadal hormones, since in this period several active neural changes take place (Spear, 2000). In fact, adolescence is characterized by strong neuronal plasticity, with sprouting and pruning of synapses, myelinization of nerve fibers, changes in neurotransmitter concentrations and their receptor levels in brain areas essential for behavioural and cognitive functions (Rice and Barone, 2000). The receptor for cannabinoids (CB1) belongs to the Gi/Go-protein coupled receptor family, and, in mammalian brain, is densely diffused in regions involved in the processing of emotional inputs, rewarding stimuli, habit formation, and higher cognitive functions (Herkenham et al., 1990). Endogenous cannabinoids modulate neurotransmitter release in many brain regions via CB1 receptors (Morisset and Urban, 2001; Wilson and Nicoll, 2001, 2002; Wilson et al., 2001). Accumulating evidence indicates that their peculiar mechanism of action as retrograde messengers is able to strongly influence both short-term and long-term forms of

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doi:10.1016/j.mce.2008.02.003

# Young adult sequelae of adolescent cannabis use: an integrative analysis

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*Lancet Psychiatry* 2014; 1: 286–93

See Comment page 249

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## Summary

**Background** Debate continues about the consequences of adolescent cannabis use. Existing data are limited in statistical power to examine rarer outcomes and less common, heavier patterns of cannabis use than those already investigated; furthermore, evidence has a piecemeal approach to reporting of young adult sequelae. We aimed to provide a broad picture of the psychosocial sequelae of adolescent cannabis use.

**Methods** We integrated participant-level data from three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study. We investigated the association between the maximum frequency of cannabis use before age 17 years (never, less than monthly, monthly or more, weekly or more, or daily) and seven developmental outcomes assessed up to age 30 years (high-school completion, attainment of university degree, cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence). The number of participants varied by outcome (N=2537 to N=3765).

**Findings** We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of high-school completion (adjusted odds ratio 0·37, 95% CI 0·20–0·66) and degree attainment (0·38, 0·22–0·66), and substantially increased odds of later cannabis dependence (17·95, 9·44–34·12), use of other illicit drugs (7·80, 4·46–13·63), and suicide attempt (6·83, 2·04–22·90).

**Interpretation** Adverse sequelae of adolescent cannabis use are wide ranging and extend into young adulthood. Prevention or delay of cannabis use in adolescence is likely to have broad health and social benefits. Efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse developmental effects.

**Funding** Australian Government National Health and Medical Research Council.

## Introduction

Marked shifts have taken place in attitudes to cannabis use.[1] Moves to decriminalise or legalise cannabis use in several US states and Latin American countries are a sign of such changes in public opinion.[2] These shifts have happened while debate continues about the long-term health and social sequelae of adolescent cannabis use.[3,4] Additionally, in some countries adolescents are initiating cannabis use earlier than have those in previous years[5] and more adolescents are using cannabis heavily.[6–8] In England, 4% of 11–15 year olds are past-month cannabis users;[7] about 7% of US high-school seniors are daily or near-daily cannabis users;[8] and in Australia, less than 1% of 14–19 year olds use daily and 4% use weekly.[6] This prevalence is particularly concerning because adolescence seems to be a vulnerable developmental period for the consequences of cannabis exposure,[9] and evidence suggests that early use of cannabis is associated with increased risk of adverse developmental outcomes.[10–14]

Persisting questions about the long-term effects of adolescent cannabis use have clouded debate.[12,15,16] The existing evidence has limitations, including limited statistical power to examine rarer outcomes and less common, more regular patterns of cannabis use than those already assessed; insufficient control for confounding; and a tendency to examine only one outcome or domain. As such, the picture of adolescent cannabis use and its putative health consequences is fractured. We address this issue through the integration of data from three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project (ATP),[17] the Christchurch Health and Development Study (CHDS),[18] and the Victorian Adolescent Health Cohort Study (VAHCS).[19]

In this integrative meta-analysis, we examined the long-term sequelae of adolescent cannabis use on important domains of wellbeing during the transition to adulthood. Specifically, we aimed to develop similar measures of cannabis use and each outcome across all cohorts; examine the association between patterns of use before age 17 years and each outcome in combined data; and adjust the associations reported for a wide

Drug and Alcohol Dependence 156 (2015) 90–96

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Adolescent substance use and educational attainment: An integrative data analysis comparing cannabis and alcohol from three Australasian cohorts

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ARTICLE INFO

*Article history:*
Received 5 June 2015
Received in revised form 31 July 2015
Accepted 28 August 2015
Available online 12 September 2015

*Keywords:*
Cannabis
Alcohol
Adolescence
Educational outcomes

ABSTRACT

*Background:* The relative contributions of cannabis and alcohol use to educational outcomes are unclear. We examined the extent to which adolescent cannabis or alcohol use predicts educational attainment in emerging adulthood.

*Methods:* Participant-level data were integrated from three longitudinal studies from Australia and New Zealand (Australian Temperament Project, Christchurch Health and Development Study, and Victorian Adolescent Health Cohort Study). The number of participants varied by analysis ($N = 2179–3678$) and were assessed on multiple occasions between ages 13 and 25. We described the association between frequency of cannabis or alcohol use prior to age 17 and high school non-completion, university non-enrolment, and degree non-attainment by age 25. Two other measures of alcohol use in adolescence were also examined.

*Results:* After covariate adjustment using a propensity score approach, adolescent cannabis use (weekly+) was associated with 1½ to two-fold increases in the odds of high school non-completion (OR = 1.60, 95% CI = 1.09–2.35), university non-enrolment (OR = 1.51, 95% CI = 1.06–2.13), and degree non-attainment (OR = 1.96, 95% CI = 1.36–2.81). In contrast, adjusted associations for all measures of adolescent alcohol use were inconsistent and weaker. Attributable risk estimates indicated adolescent cannabis use accounted for a greater proportion of the overall rate of non-progression with formal education than adolescent alcohol use.

*Conclusions:* Findings are important to the debate about the relative harms of cannabis and alcohol use. Adolescent cannabis use is a better marker of lower educational attainment than adolescent alcohol use and identifies an important target population for preventive intervention.



## 1. Introduction

Successfully completing high school and attaining a university degree are critical developmental milestones linked to better health (Cutler and Lleras-Muney, 2010) and greater economic productivity (US Bureau of Labor Statistics, 2014). Alcohol and cannabis are commonly used by young people in the school-age years.

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http://dx.doi.org/10.1016/j.drugalcdep.2015.08.034
0376-8716/

# Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment

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**Context** Cognitive impairments are associated with long-term cannabis use, but the parameters of use that contribute to impairments and the nature and endurance of cognitive dysfunction remain uncertain.

**Objective** To examine the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence.

**Design, Setting, and Participants** Multisite retrospective cross-sectional neuropsychological study conducted in the United States (Seattle, Wash; Farmington, Conn; and Miami, Fla) between 1997 and 2000 among 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use) compared with 33 nonuser controls.

**Main Outcome Measures** Measures from 9 standard neuropsychological tests that assessed attention, memory, and executive functioning, and were administered prior to entry to a treatment program and following a median 17-hour abstinence.

**Results** Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($P=.001$) or controls ($P=.005$); there was no difference between shorter-term users and controls. Long-term users showed impaired learning ($P=.007$), retention ($P=.003$), and retrieval ($P=.002$) compared with controls. Both user groups performed poorly on a time estimation task ($P<.001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use.

**Conclusions** These results confirm that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

*JAMA. 2002;287:1123-1131* www.jama.com

IN THE CURRENT CLIMATE OF DEBATE about marijuana laws and interest in marijuana as medicine,[1] one issue remains unresolved: Does heavy, frequent, or prolonged use of cannabis lead to a deterioration in cognitive function that persists well beyond any period of acute intoxication? Is the functioning of the brain altered in the long term? With over 7 million people using cannabis weekly or more often in the United States alone[2] and the potential for increased physician recommendations for select patients to use cannabis therapeutically,[1] answers to these questions are of significant public health concern.[3,4] Scientific evidence from past research clearly showed that gross impairment related to chronic cannabis use did not occur but was inconclusive with regard to the presence of more specific deficits.[5,6] Recent studies with improved methods have demonstrated changes in cognition and brain function associated with long-term or frequent use of cannabis. Specific impairments of attention, memory, and executive function have been found in cannabis users in the unintoxicated state (and in children exposed to cannabis in utero[7]) in controlled studies using brain event-related potential techniques[6,8-10] and neuropsychological assessments[11-15] including complex tasks.

Brain imaging studies of cannabis users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions.[16-19] Studies failing to detect cognitive decline associated with cannabis use[20] may reflect insufficient heavy or chronic use of cannabis in the sample or the use of insensitive assessment instruments. Impairments appear to increase with duration and frequency of cannabis use; however, the parameters of use that are associated with short- or long-lasting cognitive and brain dysfunction have not

**For editorial comment see p 1172.**

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Psychopharmacology (2011) 216:131–144
DOI 10.1007/s00213-011-2203-x

ORIGINAL INVESTIGATION

# Verbal learning and memory in adolescent cannabis users, alcohol users and non-users

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Received: 21 November 2010 / Accepted: 24 January 2011 / Published online: 17 February 2011


**Abstract**
*Rationale* Long-term heavy cannabis use can result in memory impairment. Adolescent users may be especially vulnerable to the adverse neurocognitive effects of cannabis.
*Objectives and methods* In a cross-sectional and prospective neuropsychological study of 181 adolescents aged 16–20 (mean 18.3 years), we compared performance indices from one of the most widely used measures of learning and memory—the Rey Auditory Verbal Learning Test—between cannabis users ($n$=52; mean 2.4 years of use, 14 days/month, median abstinence 20.3 h), alcohol users ($n$=67) and non-user controls ($n$=62) matched for age, education and premorbid intellectual ability (assessed prospectively), and alcohol consumption for cannabis and alcohol users.
*Results* Cannabis users performed significantly worse than alcohol users and non-users on all performance indices. They recalled significantly fewer words overall ($p$<0.001), demonstrating impaired learning ($p$<0.001), retention ($p$<0.001) and retrieval ($p$<0.05) (Cohen's $d$ 0.43–0.84). The degree of impairment was associated with the duration, quantity, frequency and age of onset of cannabis use, but was unrelated to alcohol exposure or other drug use. No gender effects were detected and the findings remained after controlling for premorbid intellectual ability. An earlier age of onset of regular cannabis use was associated with worse memory performance after controlling for extent of exposure to cannabis.
*Conclusions* Despite relatively brief exposure, adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy users. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00213-011-2203-x) contains supplementary material, which is available to authorized users.

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Addiction
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.12827

# Adolescent cannabis and tobacco use and educational outcomes at age 16: birth cohort study

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## ABSTRACT

**Aims** To investigate the relationship between cannabis and tobacco use by age 15 and subsequent educational outcomes. **Design** Birth cohort study. **Setting** England. **Participants** The sample was drawn from the Avon Longitudinal Study of Parents and Children; a core sample of 1155 individuals had complete information on all the variables. **Measurements** The main exposures were cannabis and tobacco use at age 15 assessed in clinic by computer-assisted questionnaire and serum cotinine. The main outcomes were performance in standardized assessments at 16 [Key Stage 4, General Certificate of Secondary Education (GCSE)] in English and mathematics (mean scores), completion of five or more assessments at grade C level or higher and leaving school having achieved no qualifications. Analyses were sequentially adjusted for multiple covariates using a hierarchical approach. Covariates considered were: maternal substance use (ever tobacco or cannabis use, alcohol use above recommended limits); life course socio-economic position (family occupational class, maternal education, family income); child sex; month and year of birth; child educational attainment prior to age 11 (Key Stage 2); child substance use (tobacco, alcohol and cannabis) prior to age 15 and child conduct disorder. **Findings** In fully adjusted models both cannabis and tobacco use at age 15 were associated with subsequent adverse educational outcomes. In general, the dose–response effect seen was consistent across all educational outcomes assessed. Weekly cannabis use was associated negatively with English GCSE results [grade point difference (GPD), −5.93, 95% confidence interval (CI) = −8.34, −3.53] and with mathematics GCSE results (GPD, −6.91, 95% CI = −9.92, −3.89). Daily tobacco smoking was associated negatively with English GCSE (GPD, −11.90, 95% CI = −13.47, −10.33) and with mathematics GCSE (GPD, −16.72, 95% CI = −18.57, −14.86). The greatest attenuation of these effects was seen on adjustment for other substance use and conduct disorder. Following adjustment, tobacco appeared to have a consistently stronger effect than cannabis. **Conclusions** Both cannabis and tobacco use in adolescence are associated strongly with subsequent adverse educational outcomes. Given the non-specific patterns of association seen and the attenuation of estimates on adjustment, it is possible that these effects arise through non-causal mechanisms, although a causal explanation cannot be discounted.

**Keywords** ALSPAC, cannabis use, cotinine, education, English, GCSE, mathematics, school dropout, smoking.

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Submitted 4 June 2014; initial review completed 5 August 2014; final version accepted 2 December 2014

## INTRODUCTION

Cannabis use, particularly among young people, is still relatively common [1–3]. UK cannabis use has been reportedly declining since its peak, although 2012/13 figures estimate that 30.9% of 16-24 year olds have ever used cannabis and 13.5% have smoked cannabis in the last year [4]. Various adverse psychosocial outcomes have been reported to be associated with cannabis use; however, the causal basis for these associations is often unclear. Lower educational attainment, for example, is associated consistently with higher use of cannabis. Evidence that this association is causal, such that preventing cannabis use among young people would increase their educational attainment, would have important implications for policy. A recent co-twin control study found that cannabis does not cause adverse education outcomes, but both traits are influenced by the same family environmental factors [5]. The available

*Journal of the International Neuropsychological Society* (2002), **8**, 873–883.

DOI: 10.1017/S1355617702870011

# Substance use and withdrawal: Neuropsychological functioning over 8 years in youth

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(RECEIVED September 5, 2001; REVISED December 6, 2001; ACCEPTED December 7, 2001)

**Abstract**

This study prospectively examined neuropsychological (NP) functioning associated with adolescent substance use and withdrawal. Participants were youths with histories of substance use disorders ($n = 47$) and demographically comparable youths with no such lifetime histories ($n = 26$). They were followed with NP testing and substance involvement interviews at 7 time points spanning 8 years, from ages 16 to 24, on average. After controlling for recent use, age, education, practice effects, and baseline NP functioning, substance use over the 8-year follow-up period significantly predicted performances on tests of memory and attention at Year 8. Additionally, withdrawal symptoms during the follow-up predicted visuospatial and attention scores at Year 8. Findings suggest that use and withdrawal may differentially impact neurocognitive functioning during youth, with heavy use leading to learning, retention, and attentional difficulties, and withdrawal leading to problems with visuospatial functioning. (*JINS*, 2002, *8*, 873–883.)

**Keywords:** Adolescence, Young adulthood, Youth, Substance use disorders, Withdrawal, Visuospatial functioning, Memory, Attention, Alcohol, Marijuana, Stimulants

## INTRODUCTION

In 2000, 32% of high school seniors reported getting drunk in the past month and 26% used another recreational drug (Johnston et al., 2001). An epidemiologic study reported that 9% of 14- to 18-year-old high school students met DSM–IV criteria for alcohol use disorders and 8% met criteria for abuse or dependence of other psychoactive substances (Rohde et al., 1996, 2001). Despite the high prevalence of substance use and related disorders, the long-term neurocognitive sequelae of alcohol and drug use during youth remain unclear.

Some studies have not found neuropsychological (NP) problems in adolescents with substance use disorders (SUD). For example, Brandt and Doyle (1983) studied adolescents in a psychiatric hospital. Half had used a variety of substances daily for the past year and half had rarely or never used alcohol or other drugs. Heavy users performed similarly to comparison youths on tests of cognitive flexibility (Trail Making Test) and concept formation (Category Test). In another study, no significant differences in cognitive performance were found between 38 adolescents with SUD and 321 adolescents without SUD, even though the substance involved youths were more likely to have repeated grades in school (Wilens et al., 1997). Similarly, 26 Colombian adolescents with SUD were compared to 38 controls, and no significant group differences were found in NP performance (Bernal et al., 1994).

Contrary to these results, other investigators have found significantly poorer NP functioning among adolescents with SUD relative to nonabusing youth. Giancola (Giancola et al., 1998) found poorer scores on visuospatial and inhibitory tasks among SUD girls than nonabusing controls. Moss et al. (1994) reported poorer language skills associated with alcohol use disorders in adolescents. Female adolescents with SUD performed worse than females without SUD on tests of intelligence, language skills, and sustained attention (Tarter et al., 1995). Another study reported that adolescents with SUD made more errors on an auditory continuous performance test and Paced Auditory Serial Addition Task than

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European Neuropsychopharmacology (2010) **20**, 153–163

www.elsevier.com/locate/euroneuro

# Chronic effects of cannabis use on the human reward system: An fMRI study

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Received 6 May 2009; received in revised form 11 November 2009; accepted 18 November 2009

**KEYWORDS**
Cannabis;
Reward;
Functional MRI;
Nicotine;
Nucleus accumbens

**Abstract**

Cannabis is one of the most used drugs of abuse. It affects the brain reward system in animals, and has proven rewarding and addictive potential in humans. We used functional MRI to measure brain activity during reward anticipation in a monetary reward task. Long-term cannabis users were compared to healthy controls. An additional control group consisting of nicotine users was included. Cannabis users showed attenuated brain activity during reward anticipation in the nucleus accumbens compared to non-smoking controls, but not compared to smoking controls. Cannabis users showed decreased reward anticipation activity in the caudate nucleus, compared to both non-smoking and smoking controls. These data suggest that nicotine may be responsible for attenuated reward anticipation activity in the accumbens, but that differences in the caudate are associated with the use of cannabis. Our findings imply that chronic cannabis use as well as nicotine, may cause an altered brain response to rewarding stimuli.


## 1. Introduction

Cannabis is one of the most widely used drugs since ancient times. Nowadays, it is commonly accepted that the drug has addictive potential. In the Dutch population cannabis use has increased in the past decade, and although daily use has become less frequent, a growing group of (daily) users seeks treatment to be able to deal with their heavy use (for a review see EMCDDA, 2007). This may be associated with the fact that the potency of cannabis has increased significantly in recent years (Pijlman et al., 2005; TNDM, 2006).

Cannabis has an effect on the reward system, as is clearly shown in animal studies (Gardner, 2002; Tanda and Goldberg, 2003; Wise, 1996). The rewarding effects of cannabis might be responsible for its addictive properties. Like most other drugs of abuse, prolonged cannabis exposure decreases

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doi:10.1016/j.euroneuro.2009.11.010

Journal of Health Economics 28 (2009) 132–142

Contents lists available at ScienceDirect

Journal of Health Economics

journal homepage: www.elsevier.com/locate/econbase

# Why parents worry: Initiation into cannabis use by youth and their educational attainment

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ARTICLE INFO

*Article history:*
Received 26 October 2006
Received in revised form 14 August 2008
Accepted 1 September 2008
Available online 11 September 2008

*JEL classification:*
C41
D12
I19

*Keywords:*
Cannabis use
Age of initiation
Educational attainment

ABSTRACT

In this paper we use individual level data from the Australian National Drug Strategy Household Survey to study the relationship between initiation into cannabis use and educational attainment. Using bivariate duration analysis we find that those initiating into cannabis use are much more likely to dropout of school, and that the reduction in years of education depends on the age at which initiation into cannabis occurs. We also find that the impact of cannabis uptake is larger for females than males.



## 1. Introduction

One of parents' greatest fears is that their child will become involved with drugs. Underlying this fear is the belief that drug use could lead to poor educational attainment, subsequent failure in the labor market, and without a good job to anchor their lives, an unhappy future. Viewed within a human capital framework, this scenario may find resonance. For example, drug use could lead teenagers to substitute time spent under the influence of drugs for time spent studying, resulting in poor academic achievement and an early exit from education. This is particularly a concern with cannabis because initiation into its use typically occurs during the teenage years, coinciding with the timing of critical decisions about investment in formal education, both at the extensive and intensive margins. There is, therefore, potential for youthful cannabis use to have a long lasting affect through its impact on the individual's stock of human capital. This paper investigates the extent to which this is the case by examining how the age of initiation into cannabis use effects subsequent educational attainment.

There is substantial evidence that early cannabis use is associated with lower levels of education (Macleod et al., 2004). What is less well understood is the extent to which this association reflects the causal impact of cannabis use on education outcomes. Associations will not reflect causal effects if, for example, those who self-select into cannabis use differ from those who do not use cannabis in ways that also impact on their academic achievement (selection on unobservables). For

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0167-6296/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jhealeco.2008.09.001

# Regional Brain Abnormalities Associated With Long-term Heavy Cannabis Use

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**Context:** Cannabis is the most widely used illicit drug in the developed world. Despite this, there is a paucity of research examining its long-term effect on the human brain.

**Objective:** To determine whether long-term heavy cannabis use is associated with gross anatomical abnormalities in 2 cannabinoid receptor–rich regions of the brain, the hippocampus and the amygdala.

**Design:** Cross-sectional design using high-resolution (3-T) structural magnetic resonance imaging.

**Setting:** Participants were recruited from the general community and underwent imaging at a hospital research facility.

**Participants:** Fifteen carefully selected long-term (>10 years) and heavy (>5 joints daily) cannabis-using men (mean age, 39.8 years; mean duration of regular use, 19.7 years) with no history of polydrug abuse or neurologic/mental disorder and 16 matched nonusing control subjects (mean age, 36.4 years).

**Main Outcome Measures:** Volumetric measures of the hippocampus and the amygdala combined with measures of cannabis use. Subthreshold psychotic symptoms and verbal learning ability were also measured.

**Results:** Cannabis users had bilaterally reduced hippocampal and amygdala volumes ($P=.001$), with a relatively (and significantly [$P=.02$]) greater magnitude of reduction in the former (12.0% vs 7.1%). Left hemisphere hippocampal volume was inversely associated with cumulative exposure to cannabis during the previous 10 years ($P=.01$) and subthreshold positive psychotic symptoms ($P<.001$). Positive symptom scores were also associated with cumulative exposure to cannabis ($P=.048$). Although cannabis users performed significantly worse than controls on verbal learning ($P<.001$), this did not correlate with regional brain volumes in either group.

**Conclusions:** These results provide new evidence of exposure-related structural abnormalities in the hippocampus and amygdala in long-term heavy cannabis users and corroborate similar findings in the animal literature. These findings indicate that heavy daily cannabis use across protracted periods exerts harmful effects on brain tissue and mental health.

*Arch Gen Psychiatry. 2008;65(6):694-701*

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THERE IS CONFLICTING evidence regarding the long-term effects of regular cannabis use. Although growing literature suggests that long-term cannabis use is associated with a wide range of adverse health consequences,[1-4] many people in the community, as well as cannabis users themselves, believe that cannabis is relatively harmless and should be legally available. With nearly 15 million Americans using cannabis in a given month, 3.4 million using cannabis daily for 12 months or more, and 2.1 million commencing use every year,[5] there is a clear need to conduct robust investigations that elucidate the long-term sequelae of long-term cannabis use.

The strongest evidence against the notion that cannabis is harmless comes from the animal literature[6-9] in which long-term cannabinoid administration has been shown to induce neurotoxic changes in the hippocampus, including decreases in neuronal volume, neuronal and synaptic density, and dendritic length of CA3 pyramidal neurons. Although such work suggests that exposure to cannabinoids may be neurotoxic in animals, much less is known about the neurobiologic consequences of long-term cannabis exposure in humans.

Only a handful of brain imaging studies have been conducted in human cannabis users, with inconsistent findings reported. Early cannabis research using pneumoencephalography[10] reported cerebral atrophy in a small sample (N=10) of cannabis users, but further studies using computed tomography[11-13] did not detect any abnormalities, despite the potential confounds of polydrug use, comorbid neurologic/psychiatric diagnoses, and a lack of appropriate comparison groups. More