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Intellectual, Neurocognitive, and Academic Achievement in Abstinent Adolescents with Cannabis Use Disorder

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Abstract

Rationale—The active component of cannabis, delta-9 tetrahydrocannabinol (THC), has a long half-life and widespread neurocognitive effects. There are inconsistent reports of neurocognitive deficits in adults and adolescents with cannabis use disorders (CUD), particularly after a period of abstinence.

Objectives—To examine neurocognitive measures (IQ, academic achievement, attention, memory, executive functions) in abstinent adolescents with CUD, while controlling for demographic, psychopathology, and poly-substance confounders.

Methods—We investigated neurocognitive performance in three groups: adolescents with CUD after successful first treatment and in full remission (n=33); controls with psychiatric disorders without substance use disorder history (n=37); and healthy adolescents (n=43).

Results—Adolescents with psychiatric disorders, regardless of CUD status, performed significantly worse than the healthy adolescents in academic achievement. No group differences were seen in IQ, attention, memory, or executive functions. Lower academic achievement was positively associated with younger age of CUD onset, regular cannabis use, and maximum daily use. In the CUD group, lifetime nicotine use episodes were negatively associated with IQ. Lower overall neurocognitive function was associated with younger age of onset of regular cannabis use and relapse within the one year follow-up.

Conclusions—Verifiably abstinent adolescents with CUD history did not differ from the two comparison groups, suggesting that previously reported neurocognitive deficits may be related to other factors, including residual drug effects, pre-existing cognitive deficits, concurrent use of other substances (e.g., nicotine), or psychopathology. Adolescents with CUD may not be vulnerable to THC neuropsychological deficits once they achieve remission from all drugs for at least 30 days.

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Keywords

Cannabis; Cannabis Use Disorder; Substance Use Disorder; Adolescence; Marijuana; Neurocognition; Executive Function; Academic Achievement; Memory; Psychopathology; Nicotine

Introduction

Adolescent cannabis use has increased in recent years, with approximately 25% of eighth grade students and nearly 40% of high school seniors reporting use (Johnston et al., 2012). The active component of cannabis, 9-tetrahydrocannabinol, or THC, is the most frequently used illicit drug (Substance Abuse and Mental Health Services Administration, 2010). THC acts as an exogenous agonist for endogenous cannabinoid pre-synaptic receptors. Endogenous cannabinoids play an important role in the control of the neural circuits and structures (e.g., the prefrontal cortex and hippocampus) involved in attention, executive function and memory. These brain structures and their circuits actively mature during adolescence. Animal studies demonstrate that adolescent cannabis use can affect the brain regions involved in these neurocognitive functions (Rubino et al., 2009) and may permanently impair adolescent neurocognitive functions (Crews et al., 2007; Schweinsburg et al., 2008a). Further, THC has a long half-life and is lipophilic. THC is distributed to adipose tissue, liver, lung, spleen, and the brain's myelin. THC is then slowly released back into the blood and metabolized, which can last from 5 to 95 days in heavy regular users (Musshoff & Madea, 2006). Thus, any toxic disruptions to these developing brain processes during adolescence may occur weeks to months after cannabis consumption and lead to a variety of neurocognitive difficulties in attention, memory, and executive functions.

Reports of neurocognitive deficits among individuals with cannabis use disorder (CUD) have been inconsistent. Previous findings of cognitive deficits in adolescents and adults with CUD had difficulty in separating residual effects of THC metabolites, the effects of alcohol and other drugs, pre-existing cognitive deficits that are common to the co-morbid psychopathology seen in adolescents with CUD, and/or pre-existing cognitive deficits that make one vulnerable to addictions and are present prior to drug misuse. Studies of adult cannabis users demonstrated deficits in verbal fluency, working memory, attention regulation, visual-spatial abilities, immediate and delayed memory functions, and executive functions (Ashton, 2001). However, in most studies the CUD subjects were abstinent for hours (Block & Ghoneim, 1993; Kanayama et al., 2004; Solowij et al., 2002), weeks (McHale & Hunt, 2008), and up to one month (Bolla et al., 2002; Lyons et al., 2004); so residual effects of THC metabolites may have confounded the results. Some adult studies have shown little or no difference in working memory and attention in cannabis users when compared to controls (Jager et al., 2006), leading some investigators to suggest that there are few long-term cognitive consequences of cannabis use (Gonzalez et al., 2002; Iversen, 2005; Pope et al., 2001; Pope & Yurgelun-Todd, 2001). One study reported that current cannabis use, particularly with increasing amounts, was related to declining IQ scores; however, no decline was reported in former users (Fried et al., 2002). These investigators later showed that cognitive deficits associated with the residual effects of THC were seen for up to 3-months post abstinence in young adults (Fried et al., 2005). In a study of adults recruited from the prospective longitudinal Dunedin Study, neuropsychological function was examined at age 13 (prior to the onset of cannabis use) and age 38 (Meier, et al., 2012). These investigators found that persistent cannabis use for over 20 years was associated with a decline of global, as opposed to specific, neurocognitive functions, which persisted after adjusting for education and a variety of alternative explanations (e.g., recent use, nicotine or other drug dependence including alcohol, schizophrenia). Furthermore, their findings were

associated with adolescent-onset cannabis use more than adult-onset use suggesting that the adolescent brain may be more vulnerable to cannabis related neuro-toxicity (Meier, et al., 2012). However, these authors did not obtain urine THC levels on their subjects so a direct pharmacological or residual effect of THC on global neurocognitive functions could not be determined.

Although the neurocognitive effects of adolescent CUD are understudied, these studies also show deficits in psychomotor speed, verbal fluency, working memory, attention, visual-spatial abilities, immediate and delayed memory functions, and executive functions, in adolescents who were abstinent hours (Harvey et al., 2007; Lane et al., 2007), days (Fontes et al., 2011; Grant et al., 2012), weeks (Hanson et al., 2010; Lisdahl & Price, 2012; Medina et al., 2007), and up to one month (Millsaps et al., 1994); so residual effects of THC metabolites may have also confounded the results.

Adolescent onset CUD commonly occurs with co-morbid DSM Axis I disorders including: alcohol use disorder and nicotine dependence (Clark, 2004; Lynskey et al., 2003); disruptive behavior disorders (Armstrong & Costello, 2002; Costello et al., 2003); and affective disorders (Degenhardt et al., 2003; Dembo et al., 1988). Similar psychiatric co-morbidity is common in adult CUD (Stinson et al., 2006). Individuals who use cannabis often use other substances such as alcohol and nicotine which may affect their neurocognitive function. Abstinent cannabis users who were also smokers, performed worse on tests of sustained attention and working memory than controls (Jacobsen et al., 2004), and delayed recall of verbal memory deteriorated significantly during nicotine withdrawal compared with controls (Jacobsen et al., 2007). Some investigators have argued that psychiatric and other drug co-morbidity may actually account for more of the variance than cannabis use itself in the rates of addiction and drug recidivism in adolescents (Kaminer & Bukstein, 2008; Spear et al., 1999). To date, most of the available adolescent cannabis studies (Fontes, et al., 2011; Grant, et al., 2012; Hanson, et al., 2010; Harvey, et al., 2007; Medina, et al., 2007) have controlled for the presence of mood, anxiety, and psychotic disorders but have not controlled for the presence of disruptive disorders or trauma such as child protective services history, all of which are commonly seen in adolescent substance use disorder (SUD)(Clark, 2004; Clark et al., 1997). Many previous studies that controlled for co-morbidity did not control for the residual effects of THC on brain function (Fontes, et al., 2011; Grant, et al., 2012; Hanson, et al., 2010; Harvey, et al., 2007) or the presence of disruptive disorders (Lisdahl & Price, 2012). Furthermore, studies that controlled for psychiatric co-morbidity were only able to control for co-morbid heavy alcohol and nicotine use statistically (Medina, et al., 2007). Also, most of the above studies did not control for prenatal exposure to drugs, psychiatric disorders, residual effects of THC (e.g., verifiable abstinence for at least 30 days with negative urine THC levels), or other substance use.

To address these limitations, we designed a study that controlled for these factors while examining the neurocognitive effects of CUD in adolescents. We cross-sectionally investigated neuropsychological performance in three groups of medically healthy adolescents: Group 1: adolescents without any lifetime DSM-IV or DSM-5 axis I disorders including substance use disorders and binge behaviors; Group 2: adolescents with psychiatric disorders (psychopathology), but no lifetime DSM-IV or DSM-5 substance use disorders including binge behaviors; and Group 3: adolescents with a primary diagnosis of DSM-IV and DSM-5 CUD in full remission without current nicotine dependence and or history of regular drinking. We hypothesized that abstinent adolescents with CUD would perform worse on standardized neuropsychological measures of executive function and memory than the two comparison groups. We further hypothesized that neurocognitive performance would be related to cannabis consumption variables (e.g., age of onset of CUD,

duration of CUD). We also explored the relationship between neuropsychological measures obtained at abstinence and relapse during the post-assessment one-year follow-up.

Method

Subjects

Thirty-three adolescents with current outpatient treatment for CUD who were in full remission; 37 adolescent control outpatients with psychopathology commonly observed among adolescents with CUD (Clark, 2004; Stinson, et al., 2006), but without any SUD history (Group 2); and 33 healthy control adolescents participated (Table 1). The adolescent controls with psychopathology and CUD groups were group-matched to have a similar number of biological parents with lifetime SUD and were recruited through the same outpatient university clinics, where core treatment is cognitive behavioral therapy with family therapy. Healthy adolescents were recruited through local advertisements in the surrounding community. The study was approved by the University Medical Center Institutional Review Board. Adolescents provided written assent and legal guardians provided written informed consent before participation.

Exclusion criteria for subjects were: (1) medical, neurological, or pervasive developmental or psychotic disorders and daily prescribed medication use; (2) head injury, loss of consciousness; (3) birth weight under 5 lbs. and/or postnatal compromise with neonatal intensive care stay; (4) morbid obesity or growth failure; (5) IQ<80; (6) maternal tobacco dependence, alcohol use greater than 4 drinks a month or use of illegal drugs during pregnancy with adolescent participant (these data were collected upon interview with the biological mother and subject birth/prenatal record review); (7) in all healthy controls, lifetime history of DSM-IV or DSM-5 Axis I disorders confirmed by KSADS-PL interview; (8) in healthy controls and controls with psychopathology, lifetime DSM-IV or DSM-5 SUD; (9) current SUD in the CUD group; and (10) all groups, positive urine or saliva toxicology test for any substances including cotinine on the day of assessment.

Measures

Diagnoses were made using the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997) which was administered to all adolescents and their legal guardians as previously described (De Bellis et al., 2009). Disorder onset, defined as the time at which diagnostic criteria were first met, was determined for each disorder. If diagnostic disagreements were not resolved with this method, consensus diagnoses were reached among a child psychiatrist (MDDB) and child psychologist (SRH) using the Best Estimate Method (Clark, 1999; Kosten & Rounsaville, 1992), where a date of onset, defined as the time at which diagnostic criteria were first met, was determined for each disorder (Clark et al., 2001). If disorders occurred within one month of each other, they were considered co-occurring. Substance use information was gathered by directly interviewing adolescents. For each symptom, ages of onset were estimated to the nearest month. Methods from the Lifetime History of Alcohol Use Interview (Skinner, 1982) were incorporated into the KSADS-PL to collect supplemental information on cannabis, alcohol and other abused substances, including nicotine, and seven other drug classes (stimulants, sedatives/anxiolytics, cocaine, opioids, hallucinogens, solvents/inhalants, and other). Additional information included average quantity and frequency of use, age of onset of regular use (defined as use at least twice a month for 2 months), maximum frequency and quantity of use, and age of maximum frequency and quantity of use. The unit of cannabis use was a standard joint (Chung et al., 2004).

CUD patients were in Full Remission to meet criteria for the study. CUD patients also had to be in remission of any cannabis use, alcohol use, nicotine use, or other SUD prior to study enrollment. Most CUD patients were in DSM-IV-TR Early Full Remission (i.e., no cannabis use for at least one month but less than 12 months) and only two patients were in Sustained Full Remission (i.e., no cannabis use for 12 months or longer) but were maintained in treatment secondary to cravings. However, all subjects met DSM-5 criteria for CUD in early remission. Only one patient with CUD had a history of heavy drinking (defined as greater than 200 lifetime episodes). The mean lifetime alcohol use episodes was significantly less in the 18 CUD patients without alcohol abuse compared to the 15 CUD patients with alcohol abuse ($t_{1,32}$=2.0, p=.05). The mean lifetime number of drinks consumed was significantly less in the 18 CUD patients without alcohol abuse compared to the 15 CUD patients with alcohol abuse ($t_{1,32}$=2.42, p=.02). The mean lifetime nicotine use episodes was significantly less in the 16 CUD patients without nicotine dependence compared to the 17 CUD patients with nicotine dependence ($t_{1,32}$=3.65, p=.001). The mean lifetime number of cigarettes consumed was less in the 16 CUD patients without nicotine dependence compared to the 17 CUD patients with nicotine dependence ($t_{1,32}$=1.93, p=.06). Note the CUD patient's primary drug of choice and primary addiction was cannabis; they did not have significant history of misuse of other illicit drugs, which was an exclusion for this study (Table 2).

One year after the assessment, CUD subjects and their guardians underwent a telephone interview to determine CUD relapse.

No subjects were taking psychotropic or other daily medications at the time of the study. Note that, as commonly seen in adolescent subjects with Axis I disorders, who may have benefited from medications, these adolescents had chosen to refuse medications prior to being informed of this study. No subjects were asked to stop prescribed medications to be in this study. All adolescents received saliva and urine toxicology screens prior to neurocognitive testing to confirm the absence of THC, alcohol, tobacco, or other drug use. Any participants with a positive screen were excluded from this investigation and not reported here.

Neurocognitive Outcomes—Intelligence (IQ) was determined using the *Wechsler Abbreviated Scale of Intelligence* (WASI,Wechsler, 1997). For this study, we used two subtests (Vocabulary and Matrix Reasoning) to generate an estimated Full Scale IQ.

Academic achievement was assessed using the reading and math subtests of *Woodcock-Johnson-III Tests of Academic Achievement* (WJ-IIIWoodcock et al., 2001) to generate overall scores for each academic domain.

For attention, the *Conner's Continuous Performance Test* (CPT-II, Conners & MHS Staff, 2000) provided age-based standard scores for Errors of Omission, Variability, and Reaction Time. The Errors of Commission variable was included as a measure of inhibitory control under the domain of executive functions. Other measures of executive function included the *Delis-Kaplan Executive Function System* (D-KEFS, Delis et al., 2001) subtests of Tower, Color-Word Interference, and Trail-Making, *Wisconsin Card Sorting Test (Heaton, 1981)*; *WJ-III Tests of Cognitive Abilities* Auditory Working Memory Cluster (Woodcock, et al., 2001); and the age-appropriate version of the *California Verbal Learning Test* (CVLT-C or CVLT-II) (Delis et al., 1994, 2000) perseverations score. For memory, we used the age-appropriate version of the CVLT, the *Rey-Osterrieth Complex Figure* Delay (Duley et al., 1993), and the *Wide Range Assessment of Memory and Learning* (WRAML) (Sheslow & Adams 1990) indices of verbal memory, verbal recognition, visual memory, and visual recognition.

Data Analyses

Preliminary data analyses showed group differences on the sociodemographic variables, child protective services history, and the presence of psychiatric disorders. ANOVA with follow-up pairwise comparisons were used for continuous variables, or Chi Square for the categorical variables. Since the CUD group differed from the controls with psychopathology in ADHD Combined Type and Conduct Disorder, we controlled for these disorders. To address the first hypothesis, we employed ANCOVA and four MANCOVAs, controlling for any sociodemographic variables and the presence of ADHD Combined Type and Conduct Disorder, to determine the presence of group differences across the three groups on IQ, the academic achievement, attention, memory, and executive function domains, respectively. Follow-up pair-wise comparisons were done using Tukey-Kramer HSD or Post-hoc Analysis of Means of Proportion for categorical data. Effect sizes, using Partial Eta Square (η^2) were calculated for significant group differences (Small = .06–.12; Medium = .13–.16; Large > .16)(Cohen, 1988). To address the second hypothesis, we conducted Spearman's Rho Correlations with only the CUD participants to examine the degree of the relationship between targeted CUD-related and other substance consumption variables (e.g., age of onset of CUD, CUD duration) and summary indices for IQ, achievement, and neurocognitive functioning. For data reduction purposes, the standard scores for the academic variables and neurocognitive measures, respectively, were averaged to generate a single achievement and a single neurocognitive summary variable.

Results

Preliminary Analyses

The three groups did not differ in age, sex, height, weight, head circumference, caregiver IQ, socioeconomic status, race/ethnicity, handedness, and parental family history of SUD. Because our treatment center had a majority of male adolescents with CUD, there was a nonsignificant trend ($p < .09$) for more males in the CUD group.

The Adolescent Controls with Comorbid Psychopathology (Mean 2.38±1.1) without Substance Abuse and CUD (2.76 ±1.15) groups were similar on number of Axis I disorders in past 12 months, presence of any mood and anxiety disorders, presence of oppositional defiant disorder, and history of child protective services involvement (Supplemental Table 1). The CUD group was significantly greater than the Adolescent Controls with Psychopathology without Substance Abuse in disruptive behavior psychopathology on ADHD Combined Type and Conduct Disorder; as stated, these latter variables were used as covariates in our group comparisons. It should be noted that the diagnosis of conduct disorder in the CUD sample was directly related to cannabis use and co-occurred with their initial cannabis abuse diagnosis. For example, these CUD subjects made conduct disorder criteria because they lied, skipped school, were out past curfew or overnight to use cannabis.

Group Differences

Group comparison data and effect sizes are shown in Table 3. Specifically, after controlling for ADHD Combined Type and Conduct Disorder, the three groups were not significantly different on IQ, attention, memory, or executive functions. There were no group differences in these cognitive domains when we ran the analyses with 1) only the 25 CUD patients who had greater than 200 lifetime cannabis consumption episodes or controlling for lifetime cannabis use or consumption variables; 2) controlling for alcohol abuse history, lifetime drinking episodes, or lifetime number of drinks; or 3) controlling for nicotine dependence history, lifetime smoking episodes, or lifetime number of cigarettes.

Adolescents with psychiatric disorders, regardless of CUD status performed significantly worse than controls in academic achievement, (F (16, 202) = 2.18, $p < .007$). Follow-up univariate analyses revealed that Groups 2 and 3 preformed lower in reading (F (2, 108) = 4.96, $p < .009$), and the associated subtests of reading fluency and reading comprehension, with small effect sizes ($\eta^2 = .06$ to .098). For nearly all of the reading tasks, the two clinical groups performed below the healthy control group. Follow-up univariate analyses revealed that Groups 2 and 3 performed lower in the math domain (F (2, 108) = 5.62, $p < .005$), with all math subtests showing the two clinical groups below the healthy control group. Effect sizes were small ($\eta^2 = .063$ to .097). There were no significant differences between the CUD group in remission and Adolescent Controls with Psychopathology without SUD history groups on any of the academic achievement comparisons.

CUD-Related Correlates of Intellectual, Achievement, and Neurocognitive Functions

The age of CUD onset (Spearman's rho =45, p<.01), age of onset of regular use (Spearman's rho =47, p<.01), and age of maximum daily use (Spearman's rho =40, p<.05) were positively correlated with Academic Achievement. The younger the age of CUD onset variables the lower the overall achievement score. Similarly, the age of onset of regular use correlated positively, and to a moderate degree, the Neurocognitive summary variable (Spearman's rho =40, p<.05). There were also trends showing that the age of CUD onset (Spearman's rho =.33, p<.1) and number of joints used per week (Spearman's rho =−.32, p<.1) were negatively associated with the neurocognitive summary variable, and that the longer the time since cannabis last use (Spearman's rho =.29 p<.1), the higher the IQ. Note there were no significant correlations with lifetime cannabis use or consumption variables and IQ, achievement, or neurocognitive functions. In the CUD group, lifetime nicotine use episodes were negatively associated with IQ (Spearman's rho =−.38, p<.01) and there was a trend that nicotine dependence history was negatively associated with IQ (Spearman's rho = −.31, p<.1). CUD patients with histories of alcohol abuse and their alcohol consumption variables did not influence the results.

Of the 33 CUD subjects, 5 were lost to follow-up at the one-year telephone assessment; while of the remaining 28, 20 (72%) relapsed while 8 remained drug-free. This rate is similar to the high rates of relapse previously described in adolescents treated for SUD (Williams et al., 2000). The Neurocognitive Summary score significantly correlated with relapse (Spearman's rho=−.39, p<.04) and the Achievement Summary suggested (Spearman's rho =−.35, p<.07) relapse during the one year follow-up, such that the lower the neurocognitive score, the greater the risk of cannabis relapse. Youth IQ did not correlate with relapse.

Discussion

This study examined neurocognitive deficits among verifiably abstinent adolescents with primary CUD who were in remission and not currently using alcohol or nicotine. These subjects were compared to healthy controls and to non-cannabis users with psychiatric disorders commonly observed in CUD patients. The abstinent CUD Group did not differ markedly from the two comparison groups, suggesting that previously reported neurocognitive deficits may be related to other factors, including residual THC effects, pre-existing cognitive deficits, concurrent use of other substances (e.g., nicotine), or psychiatric symptoms.

Previous studies of adolescent cannabis users found decreased attention, memory, and executive function (Harvey et al., 2007; Lane et al., 2007; Fontes et al., 2011; Grant et al., 2012; Hanson et al., 2010; Lisdahl & Price, 2012; Medina et al., 2007; Millsaps et al., 1994). In those studies, however, results may have been related to the residual effects of cannabis,

or cannabis or nicotine withdrawal. Similarly, our findings were not consistent with the few studies to date showing subtle impairment in memory and executive functions from cannabis use in adolescents with CUD who were abstinent for at least 3 weeks (Medina, et al., 2007; Schwartz et al., 1989). Our CUD subjects differed from those of Medina et al., 2007 in that our CUD subjects reported less mean lifetime alcohol use episodes, less mean lifetime cannabis use episodes, had no history of regular drinking, were abstinent for at least 30 days from all substances, had no alcohol withdrawal symptoms, and were appropriately 1.5 years younger than the subjects studied by Medina et al., 2007. These factors, particularly the greater age of subjects in the Medina et al., 2007 study, may have contributed to the differences in findings between our study and those of Medina et al., 2007.

Our data demonstrated that: 1) the younger the age of onset of CUD, regular cannabis use, and maximum daily use, the lower the overall achievement score; 2) the younger the age of regular cannabis use, the lower the neurocognitive summary variables; and suggested that 3) the age of CUD onset and number of joints used per week were negatively associated with the neurocognitive summary variable. This suggests that younger adolescents may be more sensitive to cognitive dysfunction. However, given our lack of clear group differences, we may speculate that the young adolescent brain may be able to recover once drug use stops.

It is interesting that we found that lifetime nicotine use episodes were negatively associated with IQ. Nicotine and cannabis dependences are frequently co-morbid (Clark, 2004; Lynskey, et al., 2003). In a large prospective study, which controlled for child IQ, educational attainment, occupation, and lung function, smoking history was a significant independent predictor of cognitive function at age 64 (Whalley et al., 2005). In adults, nicotine dependence was negatively associated with prefrontal grey matter and anterior cingulate volumes, brain structures that are important for intact cognitive function (Brody et al., 2004). Thus, adolescent nicotine dependence may be an underexplored co-morbid addiction that contributes to the cognitive dysfunction previously reported in adolescent cannabis users.

Our neurocognitive findings do align with the few available negative studies that have addressed this issue in abstinent adolescents and adults (Fried, et al., 2005; Fried, et al., 2002; Gonzalez, et al., 2002; Iversen, 2005; Pope, et al., 2001). Specifically, Fried and colleagues (Fried, et al., 2005; Fried, et al., 2002) reported that problems with learning, working memory, processing speed and memory abilities resolved once the adolescents with CUD discontinued use of cannabis, including heavy cannabis users (i.e., >5 joints per week). Interestingly, the mean abstinent time frame noted in our study (i.e., approximately three months) and average use of 17 joints per week were consistent with the findings of Fried and colleagues. This study strengthens this assertion in the debate by including additional methodological controls for the effects of residual THC and psychiatric and substance use co-morbidity.

The current study did not show the abstinent CUD Group to be significantly lower in IQ, attention, memory, or executive functions than either control group. However, in the area of academic achievement, the CUD group performed significantly lower than the Healthy Adolescent Group, but they were not lower than the adolescent controls with comorbid psychopathology without substance use disorder history. This was true for both reading and math skills. These findings continue to support the idea that once concomitant psychiatric disorders and other confounding factors are addressed, no unique academic effects are observed in the CUD Group. Lower academic achievement is a consistent finding in adolescents with non-psychotic psychiatric disorders (Nelson et al., 2004). However, our finding does raise the question of academic need in this sample, even if these needs may be

related more to lack of school attendance, academic self-esteem/involvement, and acute effects of cannabis misuse during school attendance on the developing adolescent brain.

We found no unique differences associated with adolescent CUD in remission. However, our correlational findings suggest that the younger the age of CUD onset and of maximum daily use, the poorer the academic achievement score; and that the younger the age of onset of regular cannabis use, the poorer the academic achievement and neurocognitive summary scores, suggesting that adolescents may be more vulnerable to the brain effects of THC. Thus, one may speculate that these findings imply that the adolescent brain may be more vulnerable to the effects of THC but able to recover once the drug use stops. Our finding that a younger age of CUD onset and more joints used per week was negatively associated with the neurocognitive summary variable supports this idea. It is possible that the adolescent brain may be able to recover from cannabis effects once a user becomes abstinent. Our finding that the longer the time since cannabis last use, the higher the IQ also supports this idea. Our correlational findings support previous data which suggest persistent cannabis use is indicative of global impairment in neurocognitive abilities, with adolescent use increasing the chances for long-term impairment (Meier et al., 2012). Given that the Neurocognitive Summary score significantly correlated with relapse and the Achievement Summary suggested relapse after clinic discharge and during the one year follow-up (such that the lower the scores the greater the risk of cannabis relapse), our study may also support that idea that cognitive deficits were present prior to drug misuse. Rigorously designed longitudinal studies are needed to test these alternative hypotheses.

It is possible that standard neurocognitive tests are not sensitive enough to uncover unique differences between adolescents with CUD and adolescents without any SUD but who suffer from psychiatric disorders. Indeed, in a subsample of the males from this study, we found that the CUD group differed from the controls with psychopathology and the healthy controls on fMRI blood oxygen level dependent (BOLD) signal measures of decision-making and reward evaluation, which correlated with relapse (De Bellis et al., 2013). Others have also found significant BOLD differences in imaging studies between abstinent adolescents with CUD and healthy controls in inhibitory processes (Tapert et al., 2007), verbal working memory (Jacobsen, et al., 2007), and spatial working memory tasks (Padula et al., 2007; Schweinsburg et al., 2008b).

Our study had several strengths. Our design insured that our results were not due to sociodemographic factors, prenatal exposure of substances, prenatal factors, outpatient clinic status, comorbid psychopathology, child maltreatment and trauma histories, greater familial risk in the CUD group, or other polysubstance use. Our study also has several limitations as our data were cross-sectional and had limited sample size. Given the small to moderate effect sizes seen between groups, we may not have had enough power to detect differences between the controls with psychopathology and the CUD group in remission; however, the means of most neurocognitive measures were similar between these two groups.

In summary, this is a well-controlled investigation examining the neurocognitive functions of abstinent adolescents with CUD. Few studies have examined this population with specific inclusion of key comparison samples and potential influential covariates. While adolescence is a sensitive period for ongoing development of the prefrontal cortex and hippocampus, and a vulnerable time for disruption of such functions as attention, memory, and executive capabilities, the adolescent brain may not be as vulnerable as previously believed to poor performance on standard neuropsychological assessments from the effects of cannabis once a user becomes abstinent from all drugs for at least 30 days. Previous findings of cognitive deficits in adolescents with CUD may be related to other factors, such as residual effects of THC metabolites, pre-existing cognitive deficits that were also common to co-morbid

psychopathology, or pre-existing cognitive deficits that may have been present prior to drug misuse. Given that our subjects' Neurocognitive Summary scores significantly correlated with relapse during the one year follow-up, our study suggests that subtle cognitive deficits may have been present prior to drug misuse. Additional more sensitive measures such as neuroimaging studies show further promise in the examination of the causes and consequences of cannabis consumption on neurocognitive functions in the adolescent brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical and Demographic Characteristics of Adolescent Groups: Healthy Controls (Group 1), Controls with Psychopathology (and without SUD history) (Group 2), and CUD in full remission (Group 3).

	Group, Mean (SD) Score					
Characteristics	**Healthy Controls (1)**	**Controls with Psychopathology (2)**	**CUD, in remission (3)**	**Test Statistic**	**p**	**Pairwise Group Differences**
N	43	37	33			
Sex (Females/Males)	21/22	13/24	8/25	$X^2 = 4.93$	.09	
Race (Caucasian/African American/Other)	32/6/5	21/10/6	22/6/5	$X^2 = 3.05$	.55	
Age, years (Mean ±SD)	16.24±1.03	15.9±1.08	16.37±0.98	$F_{2,110} = 2.01$	.14	
Age Range	14.7–17.2	12.9–17.4	13.5–17.1			
IQ	111.7 ±9.7	106.3±12.3	108.0±11.5	$F_{2,110} = 2.46$	.09	
Parent's IQ	112.6±15.7	109.9±11.9	110.5±15.7	$F_{2,110} = 0.36$	.70	
SES	46.3 ± 8.2	43.96±13.2	45.1±13.5	$F_{2,110} = 0.41$	.66	
Number of Biological Parents with SUD History (0,1,2)	26/8/0	21/9/4	11/15/2	$X^2 = 12.25$	.016	1<3*
Ever tried Cannabis? (no/yes)	37/6	31/6	0/33	$X^2 = 70.48$	.001	1,2<3*
Ever tried Tobacco? (no/yes)	34/9	30/7	0/33	$X^2 = 60.91$	.001	1,2<3*
Ever tried Alcohol? (no/yes)	13/30	13/24	1/32	$X^2 = 11.42$	.003	1,2<3*

Abbreviations: CUD, adolescents with cannabis use disorder in full early remission;

*Post-hoc Analysis of Means of Proportion

Table 2

Substance Use Characteristics of the Adolescent CUD group

		Mean±SD	Range
Number with History of DSM-IV-TR Cannabis Abuse Only	13		
Number with History of DSM-IV-TR Cannabis Dependence	20		
Number with History of DSM-IV-TR Cannabis Dependence with prior Cannabis Abuse	18		
Number with History of DSM-5 Cannabis Use Disorder (no/yes)	0/33		
Number of CUD subjects with heavy use (defined as greater than 200 lifetime cannabis consumption episodes)	25 of 33		
Age of CUD onset (years)		14.5±1.42	11–16.8
Age of CUD offset (years)		16.05±1.14	12.75–17.67
Time between the last cannabis use and testing (days)		110.7±110.0	30–480
Number of joints used per week during regular use		18.1±26.4	1–112
Age (years) of onset of regular cannabis use		14.19±1.53	10–16.4
Maximum Daily Cannabis Use (joints)		13.2 ±18.6	1–84
Age of Maximum Daily Cannabis Use		15.26±1.11	12–17
Lifetime Cannabis use episodes (days)		341.7±224.2	78–846
Lifetime cannabis consumption (number of joints)		2029±4339.1	39–24084
Number with History of Nicotine Dependence (no/yes)	16/17		
Lifetime nicotine use episodes (days)		440.9±754.9	1–2670
Lifetime number of cigarettes		1907.3±5741.8	1–30600
The mean lifetime nicotine use episodes and range (days) in the 16 CUD patients without nicotine dependence history.		28.7 ± 42.5	1–144
The mean lifetime number and range of cigarettes consumed in the 16 CUD patients without nicotine dependence.		31.9 ± 42.4	1–144
The mean lifetime nicotine use episodes and range (days) in the 17 CUD patients with nicotine dependence history.		853.1 ±901.9	60–2670
The mean lifetime number and range of cigarettes consumed in the 17 CUD patients with nicotine dependence.		3782.6 ± 7786.6	240–30600
Number with History of Alcohol Abuse without regular drinking (defined as alcohol use of at least 2 drinks a month for at least 2 months) (no/yes).	18/15		
Lifetime drinking episodes and range (days) in the CUD group		52.7±105.6	0–576
Lifetime number of drinks and range in the CUD group		272.8±508.5	0–2304
The mean and range of lifetime alcohol use episodes (days) in the 18 CUD patients without alcohol abuse.		20.8 ± 41.0	0–168
The mean lifetime number and range of drinks consumed in the 18 CUD patients without alcohol abuse		90.3 ± 202.3	0–840
The mean and range of lifetime alcohol use episodes in the 15 CUD patients with alcohol abuse.		91.0 ±143.5	10–576
The mean lifetime number and range of drinks consumed in the 15 CUD patients with alcohol abuse		491.8 ± 668.6	20–2304

Abbreviations: CUD, adolescents with cannabis use disorder in full early remission;

Table 3

Three group comparisons across the IQ, achievement, and neurocognitive measures controlling for the presence of ADHD Combined Type and Conduct Disorder.

Variable	Healthy Adolescents Control Group (1)	Controls with Comorbid Psychopathology (2)	CUD in Remission Group (3)	*F*-Value	*p*-Value	Group Comparisons[A]	Partial Eta Squared
IQ score	111.72 (9.71)	106.76 (12.47)	107.66 (11.51)	F(2,108)=2.12	.125	--	.038
Achievement				F(16,202)=2.18	.007	--	.147
WJ-III Reading	117.07 (15.98)	109.09 (12.77)	106.13 (14.41)	F(2,108)=4.96**	.009	2,3<1	.084
WJ-III Letter-Word	107.33 (10.95)	105.48 (9.79)	102.13 (11.87)	F(2,108)=0.72	.489	--	--
WJ-III Reading Fluency	119.23 (19.27)	110.03 (15.02)	106.09 (15.18)	F(2,108)=5.88**	.004	2,3<1	.098
WJ-III Passage Comprehension	110.14 (11.49)	103.52 (11.51)	104.34 (11.09)	F(2,108)=3.44*	.036	2<1	.060
WJ-III Mathematics	108.77 (13.85)	100.21 (15.73)	95.56 (12.07)	F(2,108)=5.62**	.005	2,3<1	.094
WJ-III Calculation	108.63 (14.94)	99.97 (17.36)	93.97 (13.89)	F(2,108)=5.78**	.004	2,3<1	.097
WJ-III Math Fluency	102.86 (10.83)	95.52 (16.92)	93.00 (12.42)	F(2,108)=4.35*	.015	2,3<1	.075
WJ-III Applied Prob	107.63 (12.80)	101.09 (12.97)	98.25 (9.72)	F(2,108)=3.61*	.03	2,3<1	.063
Attention				F(6,212)=1.28	.27	--	.035
CPT-II Errors of Omission	53.20 (4.89)	51.90 (5.34)	50.88 (8.20)	--	--	--	--
CPT-II Variability	55.69 (8.57)	49.74 (10.85)	47.52 (13.64)	--	--	--	--
CPT-II Errors of Commission	51.55 (8.71)	49.87 (11.19)	52.20 (8.35)	--	--	--	--
Memory				F(18,176)=0.61	.89	--	.058
WRAML-2 Verbal Memory	109.10 (12.22)	105.84 (16.99)	104.35 (11.30)	--	--	--	--
CVLT List A Total	50.64 (9.86)	50.00 (11.04)	50.38 (7.19)	--	--	--	--
WRAML-2 Verbal Recognition	106.13 (13.45)	103.39 (16.52)	102.88 (12.72)	--	--	--	--
CVLT Short-Delay Free Recall	49.10 (9.17)	46.61 (13.50)	51.35 (7.69)	--	--	--	--

Variable	Healthy Adolescents Control Group (1)	Controls with Comorbid Psychopathology (2)	CUD in Remission Group (3)	*F*-Value	*p*-Value	Group Comparisons[A]	Partial Eta Squared
CVLT Long-Delay Free Recall	50.90 (8.26)	49.03 (10.99)	51.15 (9.41)	--	--	--	--
WRAML-2 Visual Memory	101.38 (10.02)	98.06 (13.41)	100.69 (11.74)	--	--	--	--
WRAML-2 Visual Recognition	102.56 (15.64)	96.71 (14.87)	99.54 (15.50)	--	--	--	--
Rey-Osterrieth Complex Figure Delay	93.65 (16.02)	92.91 (14.27)	94.98 (17.82)	--	--	--	--
CVLT Learning Slope	45.90 (12.61)	47.74 (9.99)	50.19 (12.45)	--	--	--	--
Executive				F(20,148)=1.12	.33	--	.13
DKEFS Tower Total Achievement	10.50 (2.26)	10.30 (2.02)	9.58 (1.89)	--	--	--	--
DKEFS Tower Mean First-Move Time	11.11 (2.06)	10.70 (1.88)	10.74 (3.16)	--	--	--	--
WCST % Conceptual Level Responses	112.47 (15.04)	108.41 (13.82)	113.11 (9.69)	--	--	--	--
CVLT Perseverations	47.50 (9.71)	47.96 (8.58)	48.42 (8.67)	--	--	--	--
WCST Perseverative Reponses	115.37 (14.39)	111.15 (14.64)	117.53 (14.80)	--	--	--	--
DKEFS Trail-Making Condition 4	10.29 (1.92)	8.48 (2.99)	9.42 (1.80)	--	--	--	--
DKEFS Color-Word Interference-Inhibition/Switching	11.03 (1.99)	8.81 (2.94)	9.68 (1.63)	--	--	--	--
CPT-II Hit Reaction Time	51.87 (8.94)	50.00 (10.60)	51.42 (9.36)	--	--	--	--
CVLT Intrusions	50.66 (8.56)	48.33 (5.19)	50.26 (6.34)	--	--	--	--
WJ-III Auditory Working Memory	107.95 (10.68)	105.07 (17.16)	104.11 (13.63)	--	--	--	--

* p < .05;

** p < .01;

*** p < .001;

A Post-hoc LS Means Differences Tukey-Kramer HSD all pairwise comparison, p<.05