



Published in final edited form as:

Drug Alcohol Depend. 2013 December 1; 133(2): . doi:10.1016/j.drugalcdep.2013.08.001.

Impact of ADHD and Cannabis Use on Executive Functioning in Young Adults

Leanne Tamm,

Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. ML 10006, Cincinnati, OH 45229

Jeffery N. Epstein,

Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. ML 10006, Cincinnati, OH 45229

Krista M. Lisdahl,

University of Wisconsin-Milwaukee, Psychology Department, Garland Hall Rm 224, 2441 East Hartford Ave, Milwaukee, WI 53211. Brooke Molina University of Pittsburgh, 3811 O'Hara St., Pittsburgh, PA 15213

Susan Tapert,

University of California, San Diego, 3350 La Jolla Village Drive (116B), San Diego, CA 92161

Stephen P. Hinshaw,

Department of Psychology, Tolman Hall #1650, University of California Berkeley, CA 94720-1650

L. Eugene Arnold,

Ohio State University 479 S. Galena Rd., Sunbury, OH 43074

Katerina Velanova,

Western Psychiatric Institute and Clinic University of Pittsburgh Loeffler Building - Room 120, 121 Meyran Avenue, Pittsburgh, PA 15213

Howard Abikoff,

NYU Child Study Center / Dept. of Child and Adolescent Psychiatry, One Park Avenue, 7th Fl. / New York, NY 10016

James M. Swanson, and

University of California, Irvine Child Development Center, 19722 MacArthur Blvd, Irvine, CA 92612

© 2013 Elsevier Ireland Ltd. All rights reserved.

Corresponding Author: Leanne Tamm, Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. MLC 10006, Cincinnati OH 45229-3039, Phone: 513-803-3176, FAX: 513-636-0755, leanne.tamm@cchmc.org.

¹The Multimodal Treatment Study of Children with ADHD (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial, continued under an NIMH contract as a follow-up study and finally under a National Institute on Drug Abuse (NIDA) contract. Collaborators from NIMH: L. Eugene Arnold (currently at Ohio State University). Principal investigators and co-investigators from the sites are: University of California, Berkeley/San Francisco: Stephen P. Hinshaw (Berkeley), Glen R. Elliott (San Francisco); Duke University: Karen C. Wells, Jeffery N. Epstein (currently at Cincinnati Children's Hospital Medical Center), Desiree W. Murray; University of California, Irvine: James Swanson, Timothy Wigal; New York University: Howard B. Abikoff; New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill (Columbia). University of Pittsburgh: Brooke Molina. Additional investigators for Neuroimaging Study: Leanne Tamm, PI (Cincinnati Children's Hospital Medical Center), James Bjork (Division of Clinical Neuroscience and Behavioral Research, NIDA), Daniel Mathalon (UC San Francisco), Allen Song (Duke), Bradley Peterson (Columbia), Steven Potkin and Claudia Buss (UC Irvine), Katerina Velanova (Pittsburgh), Neuroimaging Consultants: Susan Tapert and Joshua Kuperman (UC San Diego), BJ Casey and Leah Somerville, (Sackler Institute, Cornell), Krista Lisdahl (University of Wisconsin-Milwaukee). Neuroimaging Analysis and Interpretation: Terry Jernigan and Anders Dale (UC San Diego), F. Xavier Castellanos and Clare Kelly (New York University).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

MTA Neuroimaging Group¹

Abstract

Background—Attention-deficit/hyperactivity disorder (ADHD) and cannabis use are each associated with specific cognitive deficits. Few studies have investigated the neurocognitive profile of individuals with both an ADHD history and regular cannabis use. The greatest cognitive impairment is expected among ADHD Cannabis Users compared to those with ADHD-only, Cannabis use-only, or neither.

Methods—Young adults (24.2±1.2 years) with a childhood ADHD diagnosis who did (n=42) and did not (n=45) report past year monthly cannabis use were compared on neuropsychological measures to a local normative comparison group (LNCG) who did (n=20) and did not (n=21) report past year regular cannabis use. Age, gender, IQ, socioeconomic status, and past year alcohol and smoking were statistical covariates.

Results—The ADHD group performed worse than LNCG on verbal memory, processing speed, cognitive interference, decision-making, working memory, and response inhibition. No significant effects for cannabis use emerged. Interactions between ADHD and cannabis were non-significant. Exploratory analyses revealed that individuals who began using cannabis regularly before age 16 (n=27) may have poorer executive functioning (i.e., decision-making, working memory, and response inhibition), than users who began later (n=32); replication is warranted with a larger sample.

Conclusions—A childhood diagnosis of ADHD, but not cannabis use in adulthood, was associated with executive dysfunction. Earlier initiation of cannabis use may be linked to poor cognitive outcomes and a significantly greater proportion of the ADHD group began using cannabis before age 16. Regular cannabis use starting after age 16 may not be sufficient to aggravate longstanding cognitive deficits characteristic of ADHD.

Keywords

ADHD; cannabis; executive functioning; early onset

1. INTRODUCTION

Executive functioning (EF) plays a role in the development and maintenance of substance use disorders (SUD; Almeida et al., 2008). EF includes processes such as planning, organization, decision-making, set shifting and maintenance, working memory, and the like (Lezak et al., 2004). Individuals with poor EF have difficulty engaging in future goal-oriented behavior and incorporating experience to modify behavior. A defining characteristic of SUD is intense desire to use substance(s) regardless of short and long term consequences. Significant substance use can dramatically affect how an individual handles the reinforcing properties of substances as well as influence control mechanisms and quality of responses to decisions (Almeida et al., 2008). It is not surprising both that (a) regular substance use is associated with deficits in EF (Grant et al., 2012; Piechatek et al., 2009) and (b) etiological models include cognitive dysfunction as a risk factor for developing SUD (Chassin et al., 2004).

A population with inherent EF difficulties includes individuals with attention-deficit/hyperactivity disorder (ADHD; Hervey et al., 2004; Willcutt et al., 2005). Patients with ADHD have particular deficits in the domains of attention and response inhibition (Malloy-Diniz et al., 2007), working memory (Andersen et al., 2012; Schweitzer et al., 2006), risky decision-making (Malloy-Diniz et al., 2007; Toplak et al., 2005), and planning and shifting (Rohlf et al., 2012; van Mourik et al., 2005). Not surprisingly, childhood ADHD is

associated with increased risk of later substance use, abuse, or dependence in adolescence and adulthood (Charach et al., 2011; Lee et al., 2011). In addition, individuals with SUD frequently have comorbid ADHD (Wilens, 2007). It is not clear whether individuals with ADHD are at risk for more adverse cognitive consequences of substance use than individuals without ADHD. The minimal research on this topic is mixed. Some studies do not find a relationship between substance use and EF in individuals with ADHD (Wilens et al., 2011a, 2011b). Others suggest substance use uniquely predicts EF deficits even after controlling for Diagnostic and Statistical Manual (DSM) disorders, including ADHD (Fried et al., 2005).

In the current study, we evaluated EF performance for young adults with and without ADHD histories crossed with cannabis use. We aimed to ascertain whether any aspects of EF deficits are specific to ADHD or to cannabis use, and whether co-occurring ADHD and cannabis use have an additive effect on EF deficits. Our focus on cannabis is relevant because it is the most commonly used illicit drug in individuals with ADHD (Lee et al., 2011; Molina et al., 2013) and cannabinoids significantly impact on EF (Pattij et al., 2008). We anticipated individuals with a history of ADHD would perform more poorly than demographically similar age-mates without ADHD histories on response inhibition, decision-making, working memory, verbal memory including acquisition, recall, and recognition, and processing speed. The cognitive functioning literature is mixed for cannabis use, but we predicted that cannabis users would perform more poorly than non-users on decision-making (Fridberg et al., 2010; Whitlow et al., 2004), verbal memory (Gonzalez et al., 2012; McHale and Hunt, 2008), and cognitive interference (Battisti et al., 2010). Although no studies to our knowledge have specifically examined the interaction of ADHD and cannabis use, we anticipated the most severe cognitive deficits for cannabis users with ADHD.

It is also possible that early onset of cannabis use may disrupt healthy neurodevelopment, which is of concern in cases of ADHD given reports of developmental lags in brain maturation among individuals with this disorder (Shaw et al., 2007). Adolescence is a dynamic time when brain regions associated with EF (e.g., prefrontal cortex, parietal cortex, and cerebellum) undergo gray matter synaptic pruning which continues into the mid-20s (Lenroot and Giedd, 2006; Sowell et al., 2004). Maturation of white matter tracts, yielding more efficient neural conductivity, also continues into the early-30s (Barnea-Goraly et al., 2005; Nagel et al., 2006). During adolescence, the limbic system develops earlier than the prefrontal cortex (Casey et al., 2008); development of top-down control of the limbic system (resulting in improved inhibitory control and affective processing) is therefore a gradual process (Casey et al., 2008; Liston et al., 2006; Monk et al., 2003). Adolescence may be a sensitive period associated with increased neurocognitive deficits resulting from substance use. Indeed, research has shown an association between initiation of cannabis use prior to the age of 16 and enduring deficits on attention (Ehrenreich et al., 1999) and short-term memory (Schwartz et al., 1989) even after 28 days of monitored abstinence (Pope et al., 2003). Therefore, we also conducted exploratory analyses investigating whether regular cannabis use prior to age 16 was a stronger predictor of EF deficits than contemporaneous use. We anticipated that cannabis users who engaged earlier in cannabis use would demonstrate poorer EF performance.

2. METHOD

The study was approved by each site's Institutional Review Board and informed consent was obtained from all participants prior to any procedures.

2.1 Participants

Participants were recruited from the longitudinal follow-up of the Multimodal Treatment Study of ADHD (MTA) to participate in the current study. Recruitment took place at either the 14- or 16-year follow-up assessments (i.e., 14 or 16 years after study enrollment in childhood). Original MTA participants included 579 children aged 7.0 to 9.9 years diagnosed in childhood with ADHD Combined Type. The MTA procedures for diagnosis, treatment specifics, and sample demographics have been described elsewhere (MTA Cooperative Group, 1999). A local normative comparison group (LNCG, n=289) was recruited 24 months after baseline assessment to reflect the local populations from which the ADHD sample was drawn. ADHD and LNCG participants have been followed longitudinally with visits at 36-months, and 6, 8, 10, 12, 14, and 16 years after baseline assessment of the ADHD group.

Participants in the current study included 87 ADHD (42 Cannabis Users and 45 Non-users) and 41 LNCG (20 Cannabis Users and 21 Non-users; i.e., 128 participants total; mean age 24.2 ± 1.4 ; 80.5% male; see Table 1) based on their self-report of cannabis in the past year. A participant was classified as a Cannabis User if he or she reported using cannabis monthly or more frequently during the previous year, and as a Cannabis Non-user if they had used cannabis <4 times during the previous year. It should be noted that the majority of participants in the Cannabis User group reported weekly or daily use in the past year. Participants were excluded if they self-reported binge drinking (drinking ≥ 5 drinks in a single session ≥ 1 time/week) as well as monthly or greater recreational use of other substances (e.g., cocaine, narcotics, hallucinogens, etc.). Other exclusionary criteria included any characteristic that would contraindicate magnetic resonance imaging (MRI) exposure (e.g., orthodontic braces), or a history of traumatic brain injury with loss of consciousness or that occurred in the past year. Participants taking psychotropic medications other than for ADHD were also excluded. It should be noted that few participants reported currently taking stimulant medication to manage their ADHD (see Table 1) which is generally consistent with longitudinal studies reporting that young adults who were medicated in childhood often discontinue treatment with stimulant medication in early adulthood (Barkley et al., 2008).

2.2 Design and Procedure

Coordinators reviewed participant responses to the Substance Use Questionnaire (Molina et al., 2013; Molina and Pelham, 2003) obtained at the year 14 or 16 MTA follow-up visit and approached potential participants about the current study. Those interested were presented with the study description and additional screening questionnaires (e.g., brain injury screen (Bogner and Corrigan, 2009)). Eligible participants returned for a single session during which neuropsychological measures were completed, followed by an MRI scan (results to be presented elsewhere). All participants observed a 36-hour washout period for illicit drugs and alcohol, and a 1-hour washout period for nicotine and caffeine prior to the neuropsychological battery. All participants also observed a 24-hour washout for any other prescribed or over-the-counter medications. Neuropsychological assessment instruments were administered in the following order: Hopkins Verbal Learning Task (HVLT), Iowa Gambling Task, Trail Making Test, HVLT Recall, Go/NoGo, Delis-Kaplan Color-Word Interference Task, and Paced Auditory Serial Addition Test.

2.3 Measures

Substance Use Questionnaire (SUQ) (Molina et al., 2013; Molina and Pelham, 2003)—The SUQ assesses past 12-month use of alcohol, tobacco products, cannabis, and other drugs. The measure was modeled after similar substance use measures that rely on confidential youth self-report (Molina et al., 2013). An NIH Certificate of Confidentiality

strengthened assurance of privacy. For purposes of this study, participants also completed an adapted version reporting on their substance use in the past month.

Hopkins Verbal Learning Task (HVLT) (Brandt, 1991)—The HVLT, a measure of verbal learning and memory, involves learning 12 words that represent 3 semantic categories. The list is presented 3 times and then, after a 20-minute delay, participants recall as many words as they can remember. Finally, the participant is provided cues and asked to recall if the word was on the original list. For this study, we utilized the score for trial 1 (immediate recall), total recall, and delayed recall as dependent variables.

Go/NoGo Response Inhibition Task (GNG)—The GNG assesses response inhibition. The computerized GNG task requires participants to press the spacebar in response to a variety of non-target stimuli (i.e., letters) while inhibiting their response to a specific target stimulus (i.e., “X”). Stimuli appear individually for 250 msec. followed by a fixation cross for the duration of the interstimulus interval. Participants completed 360 trials. A ratio of 10% target and 90% non-target stimuli was maintained. For the current study, the dependent variables were percent commission errors and tau, an ex-Gaussian estimate of response variability (Leth-Steenson et al., 2000). Because reaction time (RT) distributions are typically skewed we utilized RTSYS (<http://www.newcl.org>) to separate the normal curve component of the RT distribution from the exponential component. Tau is the statistic that describes the exponential component. Greater tau represents more skew and more extreme RTs scattered throughout task performance. Tau is the indicator of RT variability that seems to be most sensitive to ADHD-related patterns of increased variability in RTs (Epstein et al., 2011).

Iowa Gambling Task (IGT) (Bechara et al., 1994)—The 100-trial computerized IGT assesses decision-making. Participants were provided a “loan” of \$2,000 and directed to win as much money as possible by choosing cards from any of 4 decks one at a time. All of the cards carried an immediate reward, but some also carried a penalty. Two decks were disadvantageous resulting in net losses. Two decks were advantageous resulting in net gains. For the current study, a net score was calculated by subtracting disadvantageous card choices from the advantageous card choices.

Delis-Kaplan Executive Function System Color Word Interference Task (D-KEFS-CWI) (Delis et al., 2001)—The D-KEFS-CWI, a measure of cognitive interference, includes 4 conditions: Color Naming, Word Reading, Inhibition, and Inhibition/Switching. The Color Naming task is a test of how quickly the participant can name colors. The Word Reading task evaluates how quickly the participant can read words (e.g., red, green). The Inhibition Task requires the participant to name the color ink a word is printed in, sometimes the same and sometimes different. The Inhibition/Switching Task requires the participant to switch back and forth between naming and reading. For the current study, the time it took the participant to complete the Inhibition condition was the dependent variable.

Paced Auditory Serial Addition Test (PASAT)—The PASAT was included to assess working memory (Spren and Strauss, 1998). Individuals are presented with single-digit numbers one at a time every 3000 msec. and are asked to add the most recent number to the previously presented number and so on. Percent accuracy was the dependent variable.

Trail Making Task (TMT)—The TMT was included to assess processing speed (Lezak et al., 2004). The test includes 2 conditions, both with 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1–25, and the participant draws lines to connect

the numbers in ascending order. In Part B, the circles include both numbers and letters; the participant draws lines to connect the circles in an ascending pattern but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The participant is instructed to connect the circles as quickly as possible. For the current study, time to complete Part B was the dependent variable.

2.4 Statistical Approach

Before computing our statistical analyses we compared the 4 groups on demographic and baseline characteristic variables using one-way ANOVAs for the continuous variables and the χ^2 test for categorical variables. Associations between the dependent variables and age, gender, IQ, race, alcohol use in the past year, smoking use in the past year, maternal education (proxy for socioeconomic status (Abramson et al., 1982)), and nicotine withdrawal were conducted to determine whether they should be included as covariates. If *any* covariate was significantly associated ($p < .05$) with *any* neuropsychological variable, that covariate was included. We did not include current medication status as a potential covariate because no participants took medication on the day of assessment so we did not anticipate immediate pharmacological effects from stimulant medication.

A 2 (Diagnosis: ADHD, LNCG) x 2 (use status: Cannabis User, Non-user) MANCOVA (two-tailed), controlling for age, gender, IQ, socioeconomic status, and frequency of alcohol use and tobacco use in the past year was conducted for the dependent variables. Significant findings were followed up by investigating univariate effects. Effect sizes were also calculated. Exploratory analyses were conducted to investigate whether age of onset of cannabis use moderated the neuropsychological findings. Cannabis Users were divided into those who initiated use prior to age 16 and those who initiated after age 15 because research shows that cannabis use prior to the age of 16 leads to enduring EF deficits (Ehrenreich et al., 1999; Pope et al., 2003; Schwartz et al., 1989). We selected the youngest age a participant reported using cannabis monthly or more from the SUQ reports at each MTA assessment beginning at the 6-year follow-up. A 2 (Diagnosis: ADHD, LNCG) x 2 (Cannabis Use Age of Onset: Early, Late) MANCOVA, controlling for age, IQ, race, and frequency of alcohol use and tobacco use in the past year was conducted for the dependent variables. Effect sizes (Cohen's d ; Cohen, 1992) were also calculated; effect sizes from .20 to .49 were considered small, from .50 to .79 moderate, and $> .80$ large.

3. RESULTS

The LNCG were younger than the ADHD participants, and Cannabis Users were more likely to be male and smokers than Non-users (see Table 1). Groups did not differ significantly with respect to ethnicity/race, IQ, or medication status. Individuals with ADHD reported first using cannabis regularly at an earlier age ($M=15.2$, $SD=2.9$) than LNCG participants [$M=17.1$, $SD=2.6$; $F(1,62)=5.6$, $p=.021$]. It should be noted that 5 individuals in the ADHD Non-user group reported prior cannabis use (reported age of onset $M=15.6$, $SD=2.4$) but reported no use in the past year.

Age, gender, socioeconomic status, IQ, frequency of tobacco use in the past year, and frequency of alcohol use in the past year correlated significantly ($p < .05$) with one or more of the neuropsychological variables and, thus, were included in the models as covariates. Race/ethnicity was not significantly associated with any neuropsychological variable.

The 2 (Diagnosis: ADHD, LNCG) x 2 (Cannabis user status: User, Non-user) MANCOVA controlling for the aforementioned covariates revealed a main effect for diagnosis [$F(9,120)=3.37$, $p=.001$] but not User status [$F(9,120)=1.22$, $p=.288$] or their interaction [$F(9,120)=.80$, $p=.620$]. Univariate analyses following up the main effect of diagnosis

revealed statistically significant ADHD main effects for HVLТ Immediate ($d=.46$) and Total Recall ($d=.52$) variables, D-KEFS Inhibition Time ($d=.47$), IGT Net Score ($d=.48$), PASAT Accuracy ($d=.66$), and GNG commission errors ($d=.68$) (see Table 2). The ADHD group performed more poorly than the LNCG with near-medium to medium effect sizes across these measures. No main effects were observed for ADHD diagnosis on the HVLТ Delayed Recall ($d=.56$), TMT ($d=.54$), or GNG tau ($d=.22$) variables. There was also a significant effect of cannabis use for the IGT Net Score ($d=.22$) with the cannabis users performing more poorly than non-cannabis users.

The exploratory 2 (Diagnosis: ADHD, LNCG) x 2 (Cannabis Use Age of Onset: Early [<16], Late [16]) MANCOVA controlling for the aforementioned covariates was not significant for diagnosis [$F(9,59)=2.08$, $p=.054$], cannabis use age of onset [$F(9,59)=.89$, $p=.539$], or their interaction [$F(9,59)=.38$, $p=.939$]. Because some cell sizes for this exploratory analysis were exceedingly small ($n=6$ for LNCG early onset cannabis use), we opted to review effects sizes for cannabis age of onset. These were of medium size for GNG percent commission ($d=.67$) and IGT net score ($d=.52$), and small for HVLТ immediate recall ($d=.20$), HVLТ total recall ($d=.24$), TMT Part B time ($d=.39$), D-KEFS inhibition time ($d=.33$), PASAT percent accuracy ($d=.43$), and GNG tau ($d=.44$). In all cases, early onset cannabis users performed more poorly than late onset cannabis users.

4. DISCUSSION

To our knowledge, this is the first study investigating the combined effects of ADHD and cannabis use on EF. We predicted childhood-diagnosed ADHD and cannabis use would be related to worse EF. Instead, for almost all tasks we observed a clear effect for ADHD but not for cannabis use, either contemporaneous or historical. The strongest negative effects of ADHD were on impulsivity, working memory, and verbal memory. Although we also expected individuals with a childhood history of ADHD who used cannabis regularly would demonstrate particularly poor EF performance, we found no significant ADHD by cannabis use interactions.

As expected, the ADHD group made significantly more errors of commission and demonstrated worse working memory, verbal memory, decision making, and cognitive interference than the LNCG. We also observed non-significant impacts on delayed recall and processing speed with medium effect sizes ($d=.5$). Interestingly, we did not observe the expected effect of ADHD on tau. Since reaction time variability is particularly characteristic of ADHD (Tamm et al., 2012), at least in children, we were surprised no effect was observed. Some literature suggests reaction time variability is less evident as individuals with ADHD develop (Drechsler et al., 2005) so the non-significant finding may be due to maturation.

We did not have information to investigate whether participants in the current study still met diagnostic criteria for ADHD. However, at the 8-year follow-up, the original ADHD group in the larger MTA sample demonstrated greater impairment even though only 30% met current ADHD diagnostic criteria (Molina et al., 2009) suggesting a childhood diagnosis of ADHD is risk factor for continued EF deficits, which is consistent with other studies (Fischer et al., 2005; Halperin et al., 2008; Hinshaw et al., 2012). We did not observe significant effects of cannabis use except for a small significant effect of cannabis use on decision-making, which should be interpreted with caution given the overall MANCOVA did not indicate a significant main effect for cannabis use. However, the direction of the finding is consistent with the literature (Fridberg et al., 2010; Grant et al., 2012; Whitlow et al., 2004) and provides modest support suggesting that cannabis use is associated with poorer performance on decision making tasks. Cannabis users may have deficits in the

ability to balance rewards and punishments that contribute to drug-taking behavior. This could be cause or effect. Interestingly, this task assesses a ‘hot’ executive function, i.e., one that involves incentives and motivation (Zelazo and Muller, 2002), which may play a more critical role in the process of addiction than ‘cool’ or more abstract executive functions (Moreno-Lopez et al., 2012). It should be noted that studies suggest that dose, persistence, and chronicity of use may impact the effect of cannabis on EF (Almeida et al., 2008; Meier et al., 2012). Cannabis use in our study ranged from monthly to daily over the past year and all were abstinent on the day of testing, which may have affected our ability to detect effects of cannabis use on EF due to recovery of function.

Our exploratory analyses investigating age of onset of cannabis use were not significant, potentially because of the much smaller sample size for these analyses. However, review of effect sizes revealed that earlier use of cannabis was associated with poorer performance on cognitive tasks assessing decision-making, working memory, impulsive errors, and response variability than late onset of use. These tasks involve visual attention, which is negatively influenced by early-onset cannabis use (Ehrenreich et al., 1999). Individuals who initiate use of cannabis before age 16 may be at higher risk for developing persistent neuropsychological deficits because their brain is still developing (Fontes et al., 2011), especially the prefrontal cortex (Ellgren et al., 2008) which is associated with several executive functions including planning, verbal fluency, complex problem-solving, and impulse control, each with its own developmental trajectory (Fuster, 2006). Thus, adolescence is a particularly vulnerable time for neurocognitive effects of substance use (Monti et al., 2005). Still, we clearly found that ADHD diagnosis had a much larger impact on EF than cannabis use. Because ADHD is associated with developmental delays, particularly in the prefrontal cortex (Shaw et al., 2007), it is possible that the cognitive consequences of ADHD were sufficient that additional impact on EF from cannabis use was difficult to detect. It should be noted that a higher proportion of individuals with ADHD initiated cannabis use early, which may make it difficult to disentangle the independent impact of cannabis on cognition, given larger effect sizes of ADHD. Furthermore, there may be an interaction whereby early onset cannabis use exacerbates ADHD symptomatology through negatively impacting EF. Further investigation is clearly warranted.

Our findings must be interpreted in light of several limitations. Sample sizes were small, particularly for the exploratory age of onset analyses. The cross-sectional design makes it difficult to determine causality although the ADHD diagnosis did precede cannabis use for all participants (Molina et al., 2007). The measure of cannabis use was based on self-report, which is not the most objective method compared to biological measures. Our results may not generalize to more persistent chronic cannabis users. Excluding regular binge drinkers may also limit generalizability given the high co-occurrence of alcohol and cannabis use (e.g., McCurley and Snyder, 2008). Although we requested participants abstain from prescribed medication and illicit drug and alcohol use prior to the assessment, we did not verify their compliance with this directive. The concern about participants not complying with this directive for cannabis use is somewhat mitigated by the fact that we did not observe an effect of cannabis; if participants indeed did not comply with the requested washout period, we may have observed a false-positive finding based on the negative effects of cannabis on cognitive functioning (Azorlosa et al., 1992). It is also possible that discontinuation of stimulant medication may have impaired performance on the cognitive tasks (Wang et al., 2013); however, with such a small proportion (<7%) of our ADHD sample taking stimulant medication “sometimes” or “always”, it is unlikely that such discontinuation effects would have led to the ADHD group differences..

There are a number of issues needing further investigation. It will be imperative to investigate the effects of regular cannabis use in young adults who continue to meet

diagnostic criteria for ADHD, particularly because some studies suggest persistent ADHD is associated with poorer EF (Halperin et al., 2008) and higher rates of comorbid SUD (Sullivan and Rudnik-Levin, 2001). It will also be important to investigate whether having a diagnosed cannabis SUD results in more dramatic impact on EF than the regular use defining this sample of users. Another issue that may impact EF outcomes is the age of onset of cannabis use. Future research will need to examine whether there is a critical developmental window when cannabis use more severely affects neuropsychological functioning. Other areas of investigation might include an analysis of whether EF deficits in childhood predict poorer cognitive outcomes, and whether early deficits interact with cannabis use with and without ADHD. Our results should not be taken to indicate that cannabis use carries no risk for cognitive function, only that further investigation is needed.

Acknowledgments

Role of Funding Source:

Data collection and sharing for this project was funded by the National Institute on Drug Abuse (NIDA) Multimodal Treatment Study of Children with ADHD (MTA) Neuroimaging Study (NIDA Contract #: HHSN271200800009C). Members of NIDA participated in monthly steering committee calls where study design, data collection, and data interpretation issues were discussed.

Data collection and sharing for this project was funded by the National Institute on Drug Abuse (NIDA) Multimodal Treatment Study of Children with ADHD (MTA) Neuroimaging Study (NIDA Contract #: HHSN271200800009C).

Contributors

Drs. Tamm, Epstein, Hinshaw, Molina, Arnold, Swanson, and Abikoff designed the study and wrote the protocol. Drs. Lisdahl and Tapert consulted regarding the selection and interpretation of the neuropsychological measures as well as inclusion/exclusion criteria. Dr. Tamm managed the literature searches and summaries of previous related work, with contributions by Drs. Molina and Lisdahl. Drs. Tamm and Epstein undertook the statistical analysis and received consultation from Drs. Molina, Arnold, Abikoff, Swanson, and Lisdahl on selection of covariates and analytic plan. Dr. Tamm wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Tamm reports no biomedical financial interests or potential conflicts of interest. She receives research grant funding from NIH/NIMH & NICHD.

Dr. Epstein reports no biomedical financial interests or potential conflicts of interest. He receives research grant funding from NIH/NIMH & NICHD.

Dr. Lisdahl reports no biomedical financial interests or potential conflicts of interest. She receives research grant funding from NIH/NIDA.

Dr. Tapert reports no biomedical financial interests or potential conflicts of interest.

Dr. Hinshaw reports no biomedical financial interests or potential conflicts of interest

Dr. Arnold has received research funding from CureMark, Forest, Lilly, and Shire, advisory board honoraria from Biomarin, Novartis, Noven, Roche, Seaside Therapeutics, and Shire, consulting fees from Tris Pharma, and travel support from Noven.

Dr. Velanova reports no biomedical financial interests or potential conflicts of interest

Over the last two years Dr. Abikoff has received grant funding from NIMH, NIDA and the Lemberg Foundation, and royalties from Multi-Health Systems, School Specialty Inc., and Guilford Press.

Dr. Swanson has received research support from Alza, Richwood, Shire, Celgene, Novartis, Celltech, Gliatech, Cephalon, Watson, CIBA, Janssen, and McNeil; has been on the advisory board for Alza, Richwood, Shire, Celgene, Novartis, Celltech, UCB, Gliatech, Cephalon, McNeil, and Lilly; has been on speaker's bureau for Alza, Shire, Novartis, Celltech, UCB, Cephalon, CIBA, Janssen, and McNeil; and has consulted to Alza, Richwood, Shire, Celgene, Novartis, Celltech, UCB, Gliatech, Cephalon, Watson, CIBA, Janssen, McNeil, and Lilly.

Dr. Molina reports no biomedical financial interests or potential conflicts of interest.

References

- Abramson JH, Gofin R, Habib J, Pridan H, Gofin J. Indicators of social class. A comparative appraisal of measures for use in epidemiological studies. *Soc Sci Med*. 1982; 16:1739–1746. [PubMed: 7178920]
- Almeida PP, Novaes MA, Bressan RA, Lacerda AL. Review: executive functioning and cannabis use. *Rev Bras Psiquiatr*. 2008; 30:69–76. [PubMed: 18373021]
- Andersen PN, Egeland J, Oie M. Learning and memory impairments in children and adolescents with attention-deficit/hyperactivity disorder. *J Learn Disabil*. 2012 Epub ahead of print.
- Azorlosa JL, Heishman SJ, Stitzer ML, Mahaffey JM. Marijuana smoking: effect of varying 9-tetrahydrocannabinol content and number of puffs. *J Pharm Exp Thera*. 1992; 261:114–122.
- Barkley, RA.; Murphy, KR.; Fischer, M. *ADHD: What the Science Says*. Guilford Press; New York: 2008.
- Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, Dant CC, Reiss AL. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex*. 2005; 15:1848–1854. [PubMed: 15758200]
- Battisti RA, Roodenrys S, Johnstone SJ, Pesa N, Hermens DF, Solowij N. Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. *Psychopharmacology*. 2010; 212:613–624. [PubMed: 20721538]
- Bechara A, Damasio A, Damasio H, Anderson S. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. 1994; 50:7–15. [PubMed: 8039375]
- Bogner J, Corrigan JD. Reliability and predictive validity of the Ohio State University TBI identification method with prisoners. *J Head Trauma Rehabil*. 2009; 24:279–291. [PubMed: 19625867]
- Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neuropsychol*. 1991; 5:125–142.
- Casey BJ, Getz S, Galvan A. The adolescent brain. *Dev Rev*. 2008; 28:62–77. [PubMed: 18688292]
- Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry*. 2011; 50:9–21. [PubMed: 21156266]
- Chassin, L.; Hussong, A.; Barrera, JM.; Molina, BSG.; Trim, R.; Ritter, J. Adolescent substance use. In: Lerner, RM.; Steinberg, L., editors. *Handbook of Adolescent Psychology*. John Wiley & Sons, Inc; Hoboken: 2004. p. 665–696.
- Cohen J. A power primer. *Psychol Bull*. 1992; 112:155–159. [PubMed: 19565683]
- Delis, DC.; Kaplan, E.; Kramer, JH. *Delis Kaplan Executive Function System: Examiner's manual*. Psychological Corporation; San Antonio: 2001.
- Drechsler R, Brandeis D, Foldenyi M, Imhof K, Steinhausen HC. The course of neuropsychological functions in children with attention deficit hyperactivity disorder from late childhood to early adolescence. *J Child Psychol Psychiatry*. 2005; 46:824–836. [PubMed: 16033631]

- Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe MR. Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*. 1999; 142:295–301. [PubMed: 10208322]
- Ellgren M, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, Devi LA, Hurd YL. Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur Neuropsychopharmacol*. 2008; 18:826–834. [PubMed: 18674887]
- Epstein JN, Langberg JM, Rosen PJ, Graham A, Narad ME, Antonini TN, Brinkman WB, Froehlich T, Simon JO, Altaye M. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. *Neuropsychology*. 2011; 25:427–441. [PubMed: 21463041]
- Fischer M, Barkley RA, Smallish L, Fletcher K. Executive functioning in hyperactive children as young adults: attention, inhibition, response perseveration, and the impact of comorbidity. *Dev Neuropsychol*. 2005; 27:107–133. [PubMed: 15737944]
- Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, Bressan RA, Lacerda AL. Cannabis use before age 15 and subsequent executive functioning. *Br J Psychiatry*. 2011; 198:442–447. [PubMed: 21628706]
- Fridberg DJ, Queller S, Ahn WY, Kim W, Bishara AJ, Busemeyer JR, Porrino L, Stout JC. Cognitive mechanisms underlying risky decision-making in chronic cannabis users. *J Math Psychol*. 2010; 54:28–38. [PubMed: 20419064]
- Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marijuana—a comparison with pre-drug performance. *Neurotoxicol Teratol*. 2005; 27:231–239. [PubMed: 15734274]
- Fuster JM. The cognit: a network model of cortical representation. *Int J Psychophysiol*. 2006; 60:125–132. [PubMed: 16626831]
- Gonzalez R, Schuster RM, Mermelstein RJ, Vassileva J, Martin EM, Diviak KR. Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. *J Clin Exp Neuropsychol*. 2012; 34:962–976. [PubMed: 22882144]
- Grant JE, Chamberlain SR, Schreiber L, Odlaug BL. Neuropsychological deficits associated with cannabis use in young adults. *Drug Alcohol Depend*. 2012; 121:159–162. [PubMed: 21920674]
- Halperin JM, Trampush JW, Miller CJ, Marks DJ, Newcorn JH. Neuropsychological outcome in adolescents/young adults with childhood ADHD: profiles of persisters, remitters and controls. *J Child Psychol Psychiatry*. 2008; 49:958–966. [PubMed: 18573145]
- Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. *Neuropsychology*. 2004; 18:485–503. [PubMed: 15291727]
- Hinshaw SP, Owens EB, Zalecki C, Huggins SP, Montenegro-Nevado AJ, Schrodek E, Swanson EN. Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *J Consult Clin Psychol*. 2012; 80:1041–1051. [PubMed: 22889337]
- Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev*. 2011; 31:328–341. [PubMed: 21382538]
- Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neurosci Biobehav Rev*. 2006; 30:718–729. [PubMed: 16887188]
- Leth-Steenson C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. *Acta Psychol (Amst)*. 2000; 104:167–190. [PubMed: 10900704]
- Lezak, MD.; Howieson, DB.; Loring, DW. *Neuropsychological Assessment*. Oxford University Press; New York: 2004.
- Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, Casey BJ. Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cereb Cortex*. 2006; 16:553–560. [PubMed: 16033925]
- Malloy-Diniz L, Fuentes D, Leite WB, Correa H, Bechara A. Impulsive behavior in adults with attention deficit/ hyperactivity disorder: characterization of attentional, motor and cognitive impulsiveness. *J Int Neuropsychol Soc*. 2007; 13:693–698. [PubMed: 17521490]

- McCurley, C.; Snyder, HN. Juvenile Justice Bulletin. U.S. Department of Justice: Office of Juvenile Justice and Delinquency Prevention; 2008. Co-occurrence of Substance Use Behaviors in Youth; p. 1-8.
- McHale S, Hunt N. Executive function deficits in short-term abstinent cannabis users. *Hum Psychopharmacol.* 2008; 23:409–415. [PubMed: 18421794]
- Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A.* 2012; 109:E2657–2664. [PubMed: 22927402]
- Molina BS, Flory K, Hinshaw SP, Greiner AR, Arnold LE, Swanson JM, Hechtman L, Jensen PS, Vitiello B, Hoza B, Pelham WE, Elliott GR, Wells KC, Abikoff HB, Gibbons RD, Marcus S, Conners CK, Epstein JN, Greenhill LL, March JS, Newcorn JH, Severe JB, Wigal T. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry.* 2007; 46:1028–1040. [PubMed: 17667481]
- Molina BS, Hinshaw SP, Arnold LE, Swanson JM, Pelham W, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff H, Greenhill L, Jensen P, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S. MTA Cooperative Group. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *J Am Acad Child Adolesc Psychiatry.* 2013 in press.
- Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry.* 2009; 48:484–500. [PubMed: 19318991]
- Molina BS, Pelham WE Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *J Abnorm Psychol.* 2003; 112:497–507. [PubMed: 12943028]
- Monk CS, McClure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, Charney DS, Ernst M, Pine DS. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage.* 2003; 20:420–428. [PubMed: 14527602]
- Monti PM, Miranda R Jr, Nixon K, Sher KJ, Swartzwelder HS, Tapert SF, White A, Crews FT. Adolescence: booze, brains, and behavior. *Alcohol Clin Exp Res.* 2005; 29:207–220. [PubMed: 15714044]
- Moreno-Lopez L, Stamatakis EA, Fernandez-Serrano MJ, Gomez-Rio M, Rodriguez-Fernandez A, Perez-Garcia M, Verdejo-Garcia A. Neural correlates of hot and cold executive functions in polysubstance addiction: association between neuropsychological performance and resting brain metabolism as measured by positron emission tomography. *Psychiatry Res.* 2012; 203:214–221. [PubMed: 22959812]
- MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry.* 1999; 56:1073–1086. [PubMed: 10591283]
- Nagel BJ, Medina KL, Yoshii J, Schweinsburg AD, Moadab I, Tapert SF. Age-related changes in prefrontal white matter volume across adolescence. *Neuroreport.* 2006; 17:1427–1431. [PubMed: 16932152]
- Pattij T, Wiskerke J, Schoffelmeer AN. Cannabinoid modulation of executive functions. *Eur J Pharmacol.* 2008; 585:458–463. [PubMed: 18423599]
- Piechatek M, Indlekofer F, Daamen M, Glasmacher C, Lieb R, Pfister H, Tucha O, Lange KW, Wittchen HU, Schutz CG. Is moderate substance use associated with altered executive functioning in a population-based sample of young adults? *Hum Psychopharmacol.* 2009; 24:650–665. [PubMed: 19946940]
- Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend.* 2003; 69:303–310. [PubMed: 12633916]
- Rohlf H, Jucksch V, Gawrilow C, Huss M, Hein J, Lehmkuhl U, Salbach-Andrae H. Set shifting and working memory in adults with attention-deficit/hyperactivity disorder. *J Neural Transm.* 2012; 119:95–106. [PubMed: 21626411]

- Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. *Am J Dis Child*. 1989; 143:1214–1219. [PubMed: 2801665]
- Schweitzer JB, Hanford RB, Medoff DR. Working memory deficits in adults with ADHD: is there evidence for subtype differences? *Behav Brain Funct*. 2006; 2:43. [PubMed: 17173676]
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A*. 2007; 104:19649–19654. [PubMed: 18024590]
- Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci*. 2004; 24:8223–8231. [PubMed: 15385605]
- Spreen, O.; Strauss, E. *A Compendium of Neuropsychological Tests*. Oxford University Press; New York: 1998.
- Sullivan MA, Rudnik-Levin F. Attention deficit/hyperactivity disorder and substance abuse. Diagnostic and therapeutic considerations. *Ann N Y Acad Sci*. 2001; 931:251–270. [PubMed: 11462745]
- Tamm L, Narad ME, Antonini TN, O'Brien KM, Hawk LW Jr, Epstein JN. Reaction time variability in ADHD: a review. *Neurotherapeutics*. 2012; 9:500–508. [PubMed: 22930417]
- Toplak ME, Jain U, Tannock R. Executive and motivational processes in adolescents with Attention-Deficit-Hyperactivity Disorder (ADHD). *Behav Brain Funct*. 2005; 1:8. [PubMed: 15982413]
- van Mourik R, Oosterlaan J, Sergeant JA. The Stroop revisited: a meta-analysis of interference control in AD/HD. *J Child Psychol Psychiatry*. 2005; 46:150–165. [PubMed: 15679524]
- Wang GJ, Volkow ND, Wigal T, Kollins SH, Newcorn JH, Telang F, Logan J, Jayne M, Wong CT, Han H, Fowler JS, Zhu W, Swanson JM. Long-term stimulant treatment affects brain dopamine transporter level in patients with attention deficit hyperactive disorder. *PLoS One*. 2013; 8:e63023. [PubMed: 23696790]
- Whitlow CT, Liguori A, Livengood LB, Hart SL, Mussat-Whitlow BJ, Lamborn CM, Laurienti PJ, Porrino LJ. Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend*. 2004; 76:107–111. [PubMed: 15380295]
- Wilens TE. The nature of the relationship between attention-deficit/hyperactivity disorder and substance use. *J Clin Psychiatry*. 2007; 68(Suppl 11):4–8. [PubMed: 18307375]
- Wilens TE, Martelon M, Fried R, Petty C, Bateman C, Biederman J. Do executive function deficits predict later substance use disorders among adolescents and young adults? *J Am Acad Child Adolesc Psychiatry*. 2011a; 50:141–149. [PubMed: 21241951]
- Wilens TE, Martelon M, Joshi G, Bateman C, Fried R, Petty C, Biederman J. Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2011b; 50:543–553. [PubMed: 21621138]
- Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry*. 2005; 57:1336–1346. [PubMed: 15950006]
- Zelazo, PD.; Muller, U. Executive function in typical and atypical development. In: Goswami, U., editor. *Handbook of Childhood Cognitive Development*. Blackwell Publishing; Oxford: 2002. p. 445-469.

Table 1

Participant Characteristics

	ADHD Non User (n=45)	ADHD User (n=42)	LNCG Non User (n=21)	LNCG User (n=20)	Statistical Test
Age	24.6 (1.4)	24.4 (1.3)	23.4 (1.5)	23.7 (1.4)	F (3,126) = 4.97 *
Male	73.3%	92.9%	66.7%	85.0%	2 (3) = 8.37 *
Smoker	24.4%	52.4%	14.3%	30.0%	2 (3) = 12.07 *
Race					
Caucasian	60.0%	57.1%	57.1%	70.0%	2 (18) = 14.57
African American	15.6%	26.2%	9.5%	15.0%	
Hispanic	6.7%	4.8%	14.3%	15.0%	
Hispanic (black)	0%	2.4%	0%	0%	
Asian	6.7%	0%	4.8%	0%	
Biracial	8.9%	7.1%	9.5%	0%	
Other	2.2%	2.4%	4.8%	0%	
IQ	102.7 (16.6)	101.9 (13.0)	105.6 (23.4)	110.5 (21.6)	F (3,126) = 1.21
Medication Status ^a					2 (6) = 5.01
Use sometimes	0%	2%	0%	0%	
Use always	4%	7%	0%	0%	
Cannabis Use Past Year					
< 4 times	100%	0%	100%	0%	
Monthly	0%	7.1%	0%	10.0%	
Weekly	0%	31.0%	0%	35.0%	
Daily	0%	61.9%	0%	55.0%	
Days Cannabis Use in Last 30	.09 (.4)	14.6 (11.5)	.10 (.3)	19.4 (9.0)	t (60) = 1.61 b

* p<.05;

^a Participants were un-medicated during neuropsychological testing;

^b Comparison between ADHD (n=42) and LNCG (n=20) users only.

ADHD = Attention-Deficit/Hyperactivity Disorder, LNCG = Local Normative Comparison Group

Table 2

Results of 2 (ADHD, LNCG) X 2 (User, Non User) MANCOVA

Dependent Variable	ADHD Non User n=43	ADHD User n=40	LNCG Non User n=19	LNCG User n=19	Main Effect Diagnosis	Main Effect User Status	Interaction
HVLT Immediate Recall	6.38 (.27)	6.68 (.29)	7.25 (.42)	7.36 (.42)	F(9,120)=4.40* d=.46	F(9,120)=.30 d=.01	F(9,120)=.07
HVLT Total Recall	39.86 (1.56)	39.86 (1.68)	45.52 (2.41)	45.47 (2.41)	F(9,120)=6.98** d=.52	F(9,120)<.01 d=.08	F(9,120)<.01
HVLT Delayed Recall	39.01 (1.76)	40.67 (1.89)	43.64 (2.71)	44.87 (2.70)	F(9,120)=3.38 T d=.56	F(9,120)=.36 d=.04	F(9,120)=.01
TMT Trial B Time	56.58 (5.17)	60.35 (5.57)	46.56 (7.98)	44.50 (7.96)	F(9,120)=3.36 T d=.54	F(9,120)=.02 d=.04	F(9,120)=.20
D-KEFS Inhibition Time	50.23 (2.28)	55.94 (2.46)	47.76 (3.52)	43.26 (3.52)	F(9,120)=5.95* d=.47	F(9,120)=.04 d=.13	F(9,120)=3.20 T
IGT Net Score	12.71 (3.49)	6.21 (3.76)	32.47 (5.38)	10.11 (5.37)	F(9,120)=6.17* d=.48	F(9,120)=9.08** d=.22	F(9,120)=3.28 T
PASAT Percent Accuracy	37.03 (2.60)	36.08 (2.80)	46.78 (4.01)	48.56 (4.01)	F(9,120)=9.79** d=.66	F(9,120)=.01 d=.07	F(9,120)=.18
GNG Percent Commission	46.15 (2.97)	48.97 (3.20)	30.54 (4.58)	29.18 (4.57)	F(9,120)=19.06** d=.68	F(9,120)=.03 d=.11	F(9,120)=.31
GNG Tau	79.29 (7.00)	88.76 (7.54)	83.95 (10.80)	77.24 (10.78)	F(9,120)=.13 d=.22	F(9,120)=.02 d=.18	F(9,120)=.85

Means are estimated marginal means adjusted for covariates (standard errors);

* p<.05,

** p<.01,

T p<.10,

d=Cohen's Effect Size generated from unadjusted means and standard deviations, ADHD=Attention-Deficit/Hyperactivity Disorder, LNCG=Local Normative Comparison Group; HVLT=Hopkins Verbal Learning Test; TMT=Trail Making Test; D-KEFS=Delis Kaplan Executive Function System; IGT=Iowa Gambling Test; PASAT=Paced Auditory Serial Addition Test; GNG=Go/NoGo