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Cannabis use and neurocognitive functioning in a non-clinical sample of users

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Objective: With the recent debates over marijuana legalization and increases in use, it is critical to examine its role in cognition. While many studies generally support the adverse acute effects of cannabis on neurocognition, the non-acute effects remain less clear. The current study used a cross-sectional design to examine relationships between recent and past cannabis use on neurocognitive functioning in a non-clinical adult sample.

Method: One hundred and fifty-eight participants were recruited through fliers distributed around local college campuses and the community. All participants completed the Brief Drug Use History Form, the Structured Clinical Interview for DSM-IV Disorders, and neurocognitive assessment, and underwent urine toxicology screening. Participants consisted of recent users (n = 68), past users (n = 41), and non-users (n = 49).

Results: Recent users demonstrated significantly (p < .05) worse performance than non-users across cognitive domains of attention/working memory (M = 42.4, SD = 16.1 vs. M = 50.5, SD = 10.2), information processing speed (M = 44.3, SD = 7.3 vs. M = 52.1, SD = 11.0), and executive functioning (M = 43.6, SD = 13.4 vs. M = 48.6, SD = 7.2). There were no statistically significant differences between recent users and past users on neurocognitive performance. Frequency of cannabis use in the last 4 weeks was negatively associated with global neurocognitive performance and all individual cognitive domains. Similarly, amount of daily cannabis use was negatively associated with global neurocognitive performance and individual cognitive domains.

Conclusions: Our results support the widespread adverse effects of cannabis use on neurocognitive functioning. Although some of these adverse effects appear to attenuate with abstinence, past users' neurocognitive functioning was consistently lower than non-users.

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1. Introduction

Prevalence rates for cannabis use have steadily increased in recent years, with approximately 18.1 million individuals reporting marijuana use within the past month on a National Survey on Drug Use and Health (NSDUH) conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA, 2012). Over the past two decades, an extensive growing body of research has demonstrated that cannabis use adversely affects cognitive performance among measures that target attention (Abdullaev, Posner, Nunnally, & Dishion, 2010; Medina, Schweinsburg, Cohen-Zion, Nagel & Tapert, 2007; Solowij, Michie, & Fox, 1995; Solowij et al., 2002), working memory (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004), verbal learning and memory (Hanson et al., 2010; Harvey, Sellman, Porter, & Frampton, 2007; Lisdahl & Price, 2012; Mathias et al., 2011; McHale & Hunt, 2008; Medina et al., 2007; Tapert, Granholm, Leedy, & Brown, 2002), and executive functions (Battisti et al., 2010; Gonzalez et al., 2012; Grant, Chamberlain, Schreiber, & Odlaug, 2012; Lisdahl & Price, 2012; Pope & Yurgelun-Todd, 1996; Ranganathan & D’Souza, 2006; Schuster, Crane, Mermelstein, & Gonzalez, 2012; Solowij et al., 2012).
Delta 9-tetrahydrocannabinol (THC), the primary psychoactive agent of the cannabis sativa plant, is thought to be responsible for the cognitive effects of smoked cannabis (Bisogno, & Di Marzo, 2010; Grotenhermen, 2003). Briefly, THC acts by binding to CB1 receptors that are largely distributed through the central nervous system and aids in several important functional roles that modulate neural responses (GerdeMan, Ronesi, & Loving er, 2002; Heifets & Castillo, 2009; Yasuda, Huang, Tsumoto, 2008).

1.1. Effects of cannabis on cognition

Comprehensive reviews of the cannabis and cognition literature are available (see Gonzalez, 2007; Grant, Gonzalez, Carey, Natarajan, & Wolfons, 2003; Hart, van Gorp, Haney, Foltin, & Fischman, 2001; Lisdahl, Thayer, Squeglia, McQueeney, & Tapert, 2013; Schreiner & Dunn, 2012), which generally support the adverse acute effects of cannabis on cognition; however, non-acute effects remain less clear. Grant et al. (2003) reported that average effect sizes across studies of learning and forgetting among cannabis users were rather small in magnitude. In the same review, similar results were found across all domains of neurocognitive performance, suggestive of minimal adverse effects of cannabis use on neurocognitive performance. In a more recent meta-analysis, Schreiner and Dunn (2012) found that after at least 25 days of cannabis use, there were no residual effects on cognitive performance. Gonzalez (2007) highlighted some of the methodological limitations across studies examining the non-acute effects of cannabis that include heterogeneous participant samples that differ in factors such as severity of substance use, length of abstinence, and the presence of comorbid substance abuse and psychiatric disorders. More recent studies highlighted the moderating role of genetic polymorphisms such as the COMT val158met and 5-HTTLPR genes on the relationship between cannabis use and cognitive performance (Verdejo-García et al., 2013).

Researchers (i.e., Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001, 2002) have tested attention among current heavy cannabis users, former heavy cannabis users, and control subjects on days 0, 1, 7, and 28 of abstinence. On all four occasions, no significant between-group differences were found in attention performance despite impairments in other cognitive domains (i.e., learning and memory), which persisted up to 7 days of abstinence. After 28 days of abstinence, learning and memory impairments were no longer found. In a study that used a shorter abstinence period (i.e., 24 h), cannabis users showed longer reaction times and delayed processing speed compared with controls (Solowij et al., 1995, 2002). Using fMRI, Chang, Yakupov, Cloak, and Ernst (2006) found that marijuana users and controls demonstrated similar task performance on visual attention. However, both active and abstinent marijuana users showed activation differences across prefrontal, medial parietal, and occipital brain regions during the task, suggesting neural adaptation in chronic marijuana users.

A recent longitudinal study (Meier et al, 2012) that examined the effects of cannabis use on IQ and neuropsychological functioning suggested that the long-term effects of cannabis use may be more profound, as demonstrated by a drop from childhood average to adult low-average full-scale IQ among cannabis users. Frequency and amount of cannabis use have also been associated with neurocognitive performance in some studies. Studies have found that THC levels in urine are associated with the severity of cognitive impairment (Fried, Watkinson, James, & Gray, 2002; Pope et al., 2001). Using event-related potentials as a measure of brain function, Theunissen et al. (2012) found that THC significantly reduced P100 levels among heavy cannabis users. Similarly, Lane, Cherek, Theremissine, Lieving, and Petras (2005) found that subjects exposed to a high dose of THC (3.6%) demonstrated significantly greater risk-taking than subjects receiving lower doses of THC.

Together, these studies suggest that the magnitude of adverse effects of cannabis on cognition varies depending upon the frequency of use, and length of abstinence. However, findings have been mixed, calling attention to the need to further systematically examine how level and frequency of cannabis may affect neurocognition among diverse and representative samples.

1.2. Comorbid alcohol use

Considering that 51.8% of the population reports being current alcohol drinkers and 31.3% of heavy alcohol users also report using illicit drug (SAMHSA, 2012), it is difficult to ascertain whether the observed neuropsychological deficits among cannabis users are the direct results of cannabis use. Recent evidence suggests that heavy drinking during adolescence and young adulthood is associated with poorer neurocognitive functioning during the young adult years (Brown, Tapert, Granholm, & Delis, 2000; Giancola, Shoa, & Mezzich, 2001; Hanson, Medina, Padula, Tapert, & Brown, 2011; Sher, Martin, Wood, & Rutledge, 1997; Tapert & Brown, 1999). Therefore, consideration of comorbid alcohol may be an important area of examination in studies of the effects of cannabis on neurocognition.

1.3. Hypotheses

The purpose of the current study was to examine the effects of cannabis use in a non-clinical sample of adults. We recruited individuals who reported recent cannabis use (in the last 4 weeks), remote cannabis use (longer than 4 weeks), and no use. We chose 4 weeks as our abstinence cut-point based upon the work of Pope et al. (2001, 2002). Our study hypotheses were as follows: (H1) recent users (i.e., those who reported using cannabis in the last 4 weeks) will demonstrate poorer neurocognitive performance than non-users and past users; (H2) past users will demonstrate poorer performance than non-users, although to a lesser degree than recent users; (H3) among recent and past cannabis users, abstinence (of cannabis) will be associated with higher neurocognitive performance; and (H4) among recent users, frequency of cannabis use in the last 4 weeks and number of times used per day will be negatively associated with neurocognitive performance. Alcohol use variables (frequency and amount used) were included in statistical models as covariates to control for the effects of alcohol when examining the effects of cannabis on neurocognitive performance.

2. Method

2.1. Participants

Participants were recruited through fliers distributed around local college campuses and the community as part of a larger study examining psychosocial factors involved in neurocognitive test performance among African Americans and Caucasians. All participants were screened for neurological, psychiatric, and medical confounds using the Structured Clinical Interview (SCID) for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995), Mini-mental Status Exam (Folstein, Folstein, & McHugh, 1975), and questionnaires about neurological and medical history. Institutional Review Board approval was obtained prior to beginning study procedures. All participants provided written informed consent. Approximately 176 participants completed the study; however, 18 participants were excluded because they also reported use of stimulants or hallucinogens. One hundred and fifty-eight participants remained for testing study hypotheses. Participants were grouped as follows based on their reported cannabis use: recent users (n = 68), past users (i.e., more than 28 days; n = 41), and non-users (n = 49). Please see Table 1 for participant demographics.
Note: T-scores were calculated using the standardization methods of the respective tests. The T-scores were then used to calculate the effect size (η²), which is a measure of the proportion of variance explained by the independent variable in the model. The effect size is calculated as η² = SS_effect / SS_total, where SS_effect is the sum of squares for the effect and SS_total is the total sum of squares. The effect size is interpreted as small (η² = .01), medium (η² = .05), or large (η² = .15). The effect size is used to determine the practical significance of the findings, which is important in understanding the magnitude of the effect beyond statistical significance.

2.2. Measures

2.2.1. Structured Clinical Interview for DSM-IV Disorders (SCID)

Past and present substance abuse and psychiatric status was determined using the SCID for DSM-IV (First et al., 1995). The SCID is a semi-structured interview for making DSM-IV Axis I diagnoses.

2.2.2. Brief Drug Use History Form

The Brief Drug Use History Form (DHQ) is a questionnaire created by the University of California, Los Angeles’ Center for Advanced Longitudinal Drug Abuse Research to facilitate cross-project analysis. It collects information on inhalants, marijuana/hashish, hallucinogens, amphetamines, barbiturates, opiates, cocaine (crack/freebase and powder separately), tranquilizers, PCP, ecstasy, synthetic drugs, alcohol, and tobacco. Participants underwent urine toxicology screening, using Integrated E-Z Split Key (Innovacon, Inc., San Diego, CA), a test that utilizes monoclonal antibodies to selectively detect elevated levels of specific drugs in urine. The following drugs were tested: amphetamine, methamphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, marijuana (THC), MDMA, opiates, oxycodone, phencyclidine, propoxyphene, and norpropyline.

2.2.3. Neurocognitive assessment

Participants were administered a brief cognitive test battery that included measures with demonstrated validity, including tests of premotor intellectual ability (Wechsler Test of Adult Reading [WTAR]; Wechsler, 2001), attention/working memory (Trail Making Test — Part A; Reitan, 1958; Stroop Test [Color and Word conditions]; Golden, 1978; Wechsler Adult Intelligence Scale — IV [WAIS-IV; Wechsler, 2008] Letter–Number Sequencing subtest), speed of information processing (WAIS-IV Digit Symbol and Symbol Search subtests), learning and memory (Brief Visual Memory Test-Revised [BVMT-R]; Benedict, 1997; Hopkins Verbal Learning Test-Revised [HVLT-R] Immediate and Delayed subtests; Brandt & Benedict, 2001), and executive functioning (Trail Making Test — Part B; Reitan, 1958; Stroop Test [Color–Word condition]). All raw scores were converted to standardized t scores using published normative procedures (Heaton et al., 1995) and grouped by cognitive domain. Global neuropsychological performance was calculated by averaging t scores from individual cognitive tests, which is considered a standard approach to interpreting neurocognitive data (Heaton et al., 1991; Miller & Rohling, 2001). Cronbach’s alpha of the global neurocognitive performance scale was .92.

3. Statistical analyses

3.1. Tests of assumptions

Distributions for all measures were inspected for normality and linearity. Several of the drug frequency variables violated assumptions of normality. Logarithmic 10 transformations were applied to skewed variables, which resulted in normal distributions. Transformed variables were then used in Pearson correlational analyses with neurocognitive performance. Global neurocognitive performance and premorbid IQ were normally distributed (Shapiro–Wilk’s W = .97, df = 157, p = .34 & Shapiro–Wilk’s W = .91, df = 157, p = .32 respectively).

Analysis of variance and chi-square analysis were used to examine demographic differences between cannabis groups that are associated with neurocognitive performance. Correlational analyses between those demographic variables that differed between cannabis groups and neurocognitive test scores were conducted to determine whether they should be included in the models.

3.1.1. Group comparisons

Groups significantly differed in age, \( F(2, 155) = 22.1, p < .001 \), \( \eta^2 = .22 \). Post hoc tests revealed that past users were significantly older than recent users and non-users. Age was negatively associated with performance on measures of attention/working memory, \( \rho(156) = -.17, p = .03 \). Groups did not significantly differ on education, \( F(2, 155) = 2.56, p = .08, \eta^2 = .03 \) or ethnicity, \( \chi^2(2, n = 158) = 14.76, p = .14, \eta = .06 \). However, groups significantly differed in gender composition, \( \chi^2(2, n = 158) = 19.39, p < .001, \eta = .35 \). Specifically, males were more likely to report recent use of cannabis than females (57% vs. 24%, respectively). However, gender groups did not differ in neurocognitive performance, \( F(2, 155) = 0.94, p = .50, \eta^2 = .02 \) and...
was not included as a covariate in subsequent analyses. Groups also demonstrated significant differences in premorbid IQ scores (as measured by the WSTAR), $F(2, 155) = 5.78, p = .01, \eta^2 = .12$ with past users and recent users demonstrating higher premorbid IQ than non-users. WSTAR was significantly correlated with global neuropsychological performance, $r(157) = .47, p < .001$. Cannabis users (recent and past) reported significantly more alcohol use than non-users. No other drugs (e.g., opiates, hallucinogens, and stimulants) were reported or detected in urine (based upon toxicology testing).

Please see Table 1 for percentage of individuals who reported alcohol use, abuse, and dependence among cannabis use groups.

3.1.2. Statistical procedures
To test H1 and H2, analysis of covariance (ANCOVA) controlling for age, premorbid IQ (i.e., WSTAR), and frequency and amount of current alcohol use was conducted using cannabis group (i.e., recent users, past users, and non-users) as the independent variable and global neurocognitive $r$ score as the dependent variable. Follow-up analyses were conducted with individual cognitive domain scores. Finally, a series of post-hoc tests were conducted to isolate group differences following statistically significant omnibus $F$-tests. To test H3, time since last use was correlated with global neurocognitive performance and individual cognitive domains. In testing H4, cannabis drug use frequency variables were correlated with global neurocognitive performance and individual cognitive domain scores. Given the number of statistical comparisons, we adjusted our alpha level using false discovery rate (Benjamini & Hochberg, 2000) to control for Type I error. Power analysis was conducted using G Power 3.1 to determine the level of power based upon sample size, number of groups, and number of statistical covariates. With an alpha level of .05, we had 80% power for detecting medium effect sizes when performing ANCOVA.

4. Results
4.1. Hypothesis 1 & 2 (performed among all cannabis use groups)

ANCOVA revealed significant group difference in global neurocognitive performance, $F(5, 152) = 3.858, p = .02, \eta^2 = .09$, among the cannabis use groups. Tukey’s HSD post hoc tests revealed that recent users demonstrated poorer performance than past users and non-users. There were significant group differences in attention/working memory performance, $F(5, 152) = 5.29, p < .01, \eta^2 = .13$, with recent users performing more poorly than past users and non-users. There were significant group differences in speed of information processing, $F(5, 152) = 3.08, p = .05, \eta^2 = .06$, such that non-users performed better than recent users and past users. Recent users and past users demonstrated significantly poorer performance in executive functioning than non-users, $F(5, 152) = 6.09, p < .01, \eta^2 = .15$. See Table 1 for means and standard deviations on neurocognitive domains.

4.2. Hypothesis 3 (performed among recent and past users)

This hypothesis was not confirmed. Specifically, we did not find significant correlations between time since last use and global neurocognitive function, $r(107) = .05, p = .84$, or individual cognitive domains (all ps > .05).

4.3. Hypothesis 4 (performed among recent users)

Amount of times cannabis was used in the last 4 weeks was negatively associated with global neurocognitive performance, $r(66) = -.52, p < .001$, and cognitive domains of attention/working memory, $r(66) = -.50, p < .001$, learning/memory, $r(66) = -.42, p < .001$, information processing speed, $r(66) = -.42, p < .001$, and executive functioning, $r(66) = -.48, p = .004$. Similarly, amount of times cannabis was used per day was negatively associated with global neurocognitive performance, $r(66) = -.52, p = .01$, and cognitive domains of attention/working memory, $r(66) = -.46, p < .02$, learning/memory, $r(66) = -.45, p = .02$, information processing speed, $r(66) = -.50, p = .001$, and executive functioning, $r(66) = -.47, p < .01$.

5. Discussion

The purpose of the current study was to examine the relationship of cannabis use on neurocognitive performance among a non-clinical adult sample. A major strength of the current study was its comparison of the neurocognitive functioning of recent and past users while controlling for age, alcohol use, and premorbid IQ to better understand the effects of cannabis on neurocognition. Within our sample of cannabis users, we were interested in how abstinence and frequency of use contributed to cognitive performance. As expected, we found that recent users demonstrated worse neurocognitive functioning than past users and non-users in global neurocognitive performance and the domains of attention/working memory, information processing speed, and executive functioning. However, past users only differed from non-users in the domain of executive functioning. These findings are generally consistent with findings from Pope and colleagues (2001, 2002) and further support the contention that 28 days is a sufficient period during which cognitive functions seem to recover. This could be due to the reversible downregulation of CB1 receptors that have been found to occur in a variety of cortical regions (see Hirvonen et al., 2012). However, our sample of past users did not perform at the level of non-users across most domains, suggesting that cannabis use may ultimately interfere with optimal neurocognitive performance. Executive functioning represents a broad range of skills and abilities, such as planning, self-monitoring, inhibiting prepotent responses, and altering behavior in response to changing task demands. Neuroanatomical evidence suggests that the prefrontal cortex (PFC) and posterior association areas mediate a majority of these functions (Fegan & Lewis, 2006). Deficits in executive functions may persist long after use. Our findings pertaining to executive dysfunction are consistent with other studies (Bolla, Elderth, Matochik, and Cadet, 2005; Crean, Crane, and Mason (2011); Ramaekers, Kauert, van Ruitenbeek, Theunissen, Schneider & Moeller, 2006), suggesting that the long-term implications of impaired executive functions could result in problems with decision-making, impulsivity, and poor judgment.

Among our recent users, frequency of use was negatively associated with neurocognitive performance, demonstrating that severity of use is important when attempting to understand the neurocognitive effects of cannabis use among recent users. We were unable to precisely identify the independent and synergistic effects of alcohol since most of our cannabis use sample also reported recent alcohol use. Although this could be argued to be a limitation of the current study, we would like to highlight that the primary purpose of this study was to examine relationships between cannabis use and neurocognitive functioning. In our analyses, we learned that our sample, similar to the general population of substance abusers, also reported the use of alcohol. Therefore, we attempted to control for the frequency of alcohol use when testing study hypotheses. Nevertheless, the cannabis/alcohol comorbidity literature is limited with regard to neurocognitive functioning and we believe that this is an important avenue for further study.

While this study attempted to consider factors such as comorbid substance abuse, abstinence, and frequency of use that have been suggested to contribute to discrepant findings in the literature, we were unable to address all methodological issues. As with most studies that rely upon self-report, we are unable to be certain that our participants accurately recalled their cannabis use. Although our toxicology screen confirmed self-reported recent cannabis use, toxicology screening did not confirm frequency or amount used. Second, this study used a cross-sectional
design. As such, we are not able to make inferences about the long-term effects of cannabis use or changes in cognitive functioning that may result from chronic use over time. Third, although our past users and non-users did not differ on most of our neurocognitive measures, it is possible that our past users would demonstrate differential neural activation patterns had we employed a method such as neuroimaging to our current study design (as found by Chang et al., 2006). Future studies should consider the inclusion of neuroimaging modalities and longitudinal designs to identify the long-term effects of cannabis use on neural circuitry. Finally, we did not collect information on age of onset and cannabis use. Emerging evidence from the animal and human literature suggests that age of onset is an important factor when considering the long-term effects of cannabis (Dragt et al., 2010; Medina et al., 2007).

An unexpected yet interesting finding in the current study pertained to the higher premorbid IQ that was documented in our sample of cannabis users. Although other studies have found lower IQ among cannabis users (e.g., Meier et al., 2012), our sample demonstrated the opposite. Even more intriguing is that despite possessing higher premorbid IQ, which is largely associated with neurocognitive performance (Manly, Jacobs, Touradji, Small, & Stern, 2002), this factor did not change our findings that cannabis users performed worse than non-users on all domains of cognitive performance. However, it is possible that premorbid IQ protects against the adverse effects of cannabis, and may obscure the impact of cannabis on neurocognition. In other words, the adverse effects of cannabis on neurocognition may have been more pronounced in a sample of individuals with low premorbid intellectual functioning.

Based upon the current study results, one could suggest that because the relationships between cannabis use and cognition are relatively small in magnitude, it is questionable whether it is a drug that warrants further study. We believe that cannabis certainly merits further study because although the effects that have been reported in the neurobehavioral studies are relatively small, this does not necessarily translate to inferring that cannabis exerts small effects on the brain. Further, neurocognitive deficits in areas of working memory, attention and executive functions are associated with increased problems in drug use; therefore a reciprocal relationship between cognitive deficits and drug use problems may exist. The importance of these cognitive functions in predicting treatment outcomes remains to be determined.

Until more studies leverage in vivo, in vitro, and neurobehavioral measures longitudinally, the long-term effects of cannabis use remain unclear. As our population increases in age, a critical question pertains to the effects of cannabis use on neurocognitive functioning among older adults. Recent studies have begun to examine this question and have found that increasing cannabis use in late adolescence and early adulthood is associated with a range of adverse outcomes in later life that include poorer educational outcomes, lower income, greater welfare dependence and unemployment, and lower relationship and life satisfaction (Ferguson & Boden, 2008). Whether or not these adverse effects are related to cognitive dysfunction is unclear as there are a number of other psychosocial variables that may explain the relationship between cannabis use and adverse life-outcomes.

In the recent debate over legalization, many misperceptions about the safety of marijuana use have gained currency among young adults. Our results provide evidence that cannabis use is associated with cognitive impairments that persist after abstinence. Whether or not these impairments remain stable or decline to over time is still unclear. Nevertheless, we believe that the current findings extend the current cannabis literature by demonstrating distinct relationships between recent and past use of cannabis contributes on cognitive functioning while considering the role of premorbid IQ and comorbid alcohol use, which has received minimal attention in prior studies. Future studies should consider mediating and moderating variables such as genotype, personality, co-morbid conditions (e.g., psychiatric disorder) and age of onset to further delineate the impact of cannabis use on cognitive functioning.

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Contributors
Dr. April Thames designed the study, wrote the protocol, undertook the statistical analysis and wrote the first draft of the manuscript. Ms. Natalie Arbid managed the literature searches and summaries of previous related work and assisted with the write-up of the methods. Mr. Philip Sayegh contributed to the write-up of the discussion, production of tables, and provided edits. All authors contributed to and have approved the final manuscript.

Conflict of interest
The authors report no conflict of interest.

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