HHS Public Access

Author manuscript

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

J Clin Exp Neuropsychol. 2018 August ; 40(6): 529–543. doi:10.1080/13803395.2017.1385729.

Longitudinal Changes in Cognition in Young Adult Cannabis Users

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Abstract

Introduction: Adolescent cannabis use (CU) is associated with impaired attention, executive function, and verbal learning/memory. These associations are generally observed in cross-sectional studies. Longitudinal studies of cannabis users are lacking.

Method: The present study examines associations between CU and cognition over time in chronic daily adolescent-onset CUs, as compared to non-using controls. Both groups completed a neuropsychological battery at study intake and again two years later.

Results: Baseline group differences have been published (Becker, Collins, & Luciana, 2014) and indicated deficits in verbal learning and memory, motivated decision-making, planning and working memory in CUs. In this follow-up report, the longitudinal performance of users is compared to that of sustained non-users using the same battery. At follow-up, the majority of CUs continued to report regular and heavy cannabis use. Relative impairments in the domains of working memory, planning and verbal memory remained stable, suggesting that these are enduring vulnerabilities associated with continued CU during young adulthood. Improvements in motivated decision-making were evident in both groups. In addition, CUs demonstrated relatively better performance on short-duration speeded tasks. An earlier age of CU onset was associated with poorer verbal learning and memory and planning performance over time.

Conclusions: Verbal learning and memory and planning processes, as well as their neural correlates, merit further scrutiny within etiological models of cannabis-induced cognitive impairments.

Keywords

Cannabis; adolescence; neurocognition; memory; executive function

1.1 Introduction

Adolescent cannabis use (CU) is associated with cognitive disruptions based on cross-sectional research. Longitudinal studies are rare but permit consideration of dose-response

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associations, whether impairments exist before use onset, and whether they persist with continued use. This study follows a college-aged sample of adolescent-onset cannabis users (CUs) and comprehensively examines neurocognition over time.

It is well established that adolescent and young adult CUs demonstrate cognitive deficits that cut across domains of function. Among these are deficits in sustained attention (Dougherty et al., 2013; Jacobsen, Mencl, Westerveld, & Pugh, 2004), processing speed (Fried, Watkinson, & Gray, 2005; Lisdahl & Price, 2012; Medina et al., 2007) and complex attention (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Fontes et al., 2011; Lisdahl & Price, 2012). Relative deficits in executive functions have been reported across a number of paradigms and processes. For instance, inhibitory control is impaired in CU adolescents (Lisdahl & Price, 2012), adults (Bolla et al., 2002; Gruber & Yurgelun-Todd, 2012; Pope & Yurgelun-Todd, 1996), and early-onset users (Battisti, Roodenrys, Johnstone, Pesa et al., 2010; Fontes et al., 2011; Gruber et al., 2012). In addition, CUs demonstrate poor set-shifting performance (Gruber, Dahlgren, Sagar, Gonenc, & Killgore 2012; Lane, Cherek, Tcheremissine, Steinberg, & Sharon, 2007), which is worse with early onset use (Fontes et al., 2011; Gruber et al., 2012).

Studies that have focused on executive functions in the context of motivations to attain rewards have shown that adult CUs show decision-making deficits (Ernst et al., 2003; Verdejo-García, Rivas-Pérez, Vilar-López, & Pérez-García, 2007; Whitlow et al., 2004), which have been linked to increased CU disorder symptoms (Gonzalez, Schuster, Mermelstein, & Diviak, 2015). Younger CUs, as well as those with longer CU durations, are prone to impulsive choices (Clark, Roiser, Robbins, & Sahakian, 2009; Dougherty et al., 2013; Solowij et al., 2012).

Mnemonic function is variable depending on the domain of memory that is assessed. Consistent with deficits in executive function, prospective memory appears to be impaired in CUs (Bartholomew, Holroyd, & Heffernan, 2010; McHale & Hunt, 2008; Montgomery, Seddon, Fisk, Murphy, & Jansari, 2012). Findings for spatial memory are inconsistent, depending on the task. For instance, studies have found no evidence for deficits in spatial span (Harvey, Sellman, Porter, & Frampton, 2007) or visual n-back performance (Ehrenreich et al., 1999). In contrast, it was found in one study that CUs were impaired on a complex spatial self-ordered search task that involved both spatial memory and spatial monitoring (Harvey et al., 2007). In one study, male young adult heavy CUs demonstrated poorer delayed visuospatial memory as a function of amounts used (Pope & Yurgelun-Todd, 1996). Many labs have examined spatial memory performance and report no deficits (Bolla et al., 2002; Macher & Earleywine, 2012; Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010; McHale & Hunt, 2008; Medina et al., 2007).

A more robust finding is that performance during the encoding stage of verbal list-learning tasks is deficient in CU adolescents and adults (Gonzalez et al., 2012; Hanson et al., 2010; Harvey et al., 2007; Solowij et al., 2011) and that this deficit persists after abstinence (Bolla et al., 2002; Cuttler, McLaughlin, & Graf, 2012; Gonzalez et al., 2012; Hanson et al., 2010; Pope & Yurgelun-Todd, 1996; Solowij et al., 2011; Takagi et al., 2011). Similarly, CUs demonstrate impaired story learning following brief abstinence periods (Medina et al., 2007;

Schwartz, Gruenewald, Klitzner, & Fedio, 1989). A meta-analysis that focused on cognitive disruptions in the context of cannabis use (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003) reported a reliable impairment across studies in verbal learning and recall. Motivation may play an important role in CU's verbal learning performance given that motivational interventions have been shown to improve performance in CU but not in controls (Macher & Earleywine, 2012).

Most of these neurocognitive findings stem from cross-sectional research. Four studies have assessed CUs at multiple time points over years (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Jackson et al., 2016; Meier et al., 2012; Tait, Mackinnon, & Christensen, 2011). Meier et al. (2012) utilized a large birth cohort to prospectively assess cognition beginning before use initiation and extending into adulthood. Those who abstained from cannabis use had stable IQs over time, while decreases were observed among those who developed cannabis dependence. Adolescent-onset use was specifically associated with IQ declines. Jackson et al. (2016) used a behavior genetics approach to examine a large sample of adolescent twins as they transitioned into substance use. A major finding from this study was that CU twins failed to show significantly greater IQ declines over time relative to their abstinent siblings, suggesting that the cognitive changes observed by Meier et al. (2012) might be attributable to premorbid factors.

Tait et al. (2011) followed young adult CUs at four-year intervals for two assessments of cognition. Persistent heavy CUs demonstrated poorer immediate verbal recall while former users were unimpaired. The groups were otherwise equivalent, suggesting that verbal memory is selectively diminished with regular use but with potential for recovery after abstinence.

Another longitudinal study followed 16–19 year old alcohol+cannabis users over 3 years (Jacobus et al., 2015). Participants were assessed at baseline, after 18 months, and after 3 years. A global neuropsychological composite derived from numerous measures of cognition was equivalent between users and non- using controls at the first and third assessments, but it was lower among users at the second assessment. Verbal memory deficits were consistently found.

Overall, while this latter group of studies is informative, there is a relative dearth of information from longitudinal studies regarding the persistence of cognitive impairments in regular cannabis users as they reach adulthood. In this study, chronic daily adolescent-onset CUs were longitudinally assessed on a comprehensive battery and compared to demographically-matched non-using controls. Baseline group differences have been published (Becker et al., 2014) and indicated deficits in verbal learning and memory, motivated decision-making, planning and working memory. Longitudinal assessment using the same battery allows us to consider three questions: first, our primary aim is to determine whether relative deficits observed at baseline persist over time, which we expected to be the case. Examination of the areas where impairment was observed at baseline permits us to also ascertain whether there is recovery of function over time in any domains. Second, an exploratory aim is to determine whether new areas of impairment emerge in the context of persistent marijuana use. Finally, earlier onset cannabis use was expected to be associated

with more pronounced cognitive impairments, since an earlier onset of use would imply not only a greater lifetime exposure to cannabis but, in particular, a greater exposure during critical periods of adolescent brain development (Lisdahl, Gilbart, Wright, & Shollenbarger, 2013).

2.1 Methods

2.1.1 Sample

Thirty-eight CUs, ages 19–20 who initiated use before age 17, were recruited at baseline. Regular use (multiple times weekly) was required for baseline entry into the study. Most CUs (90%) reported using at least 5×/week; two reported using 3–4×/week. CUs were excluded if they reported current daily cigarette use or excessive alcohol use (4 drinks for females and 5 drinks for males more than twice weekly). All were college students. The current sample very slightly expands upon our prior report (Becker et al., 2014), including 1 additional CU.

All possible age-and sex-matched non-drug using controls (n=35) were selected from a concurrent longitudinal study. At recruitment, controls were excluded for lifetime Axis I (American Psychiatric Association, 2000) psychopathology, for more than minimal alcohol and cannabis use (although most were abstinent) and for any other illicit substance use. All participants were native English speakers, right-handed, with normal sensory function. Exclusions for all participants included MRI contraindications, neurological problems, head injury, intellectual disability, or current pregnancy. Participants responded to advertisements posted throughout the University. All were monetarily compensated and provided informed consent. The local Institutional Review Board approved the protocol.

As reported in our prior publications (Becker et al., 2014; Becker, Collins, Lim, Muetzel, & Luciana, 2015), CUs exhibited minimal psychopathology other than CU dependence. Specifically, one CU participant met DSM-IV criteria at baseline for current Bipolar Disorder Not-Otherwise-Specified (NOS). Another met criteria for past Bipolar NOS. Both were due to episodic hypomania, consistent with the reported comorbidity between SUDs and bipolar disorder (Perlis et al., 2004; Wilens et al., 2008). Other psychological disorders evident in the CU sample included past Oppositional Defiant Disorder (n = 2) and past Specific Phobia (n = 1). Findings remained unchanged when those with these disorders were excluded, so these participants were retained in all analyses. With respect to substance-related pathology, CUs exhibited more symptoms related to problematic cannabis use than to problematic alcohol use. Cannabis was their drug of choice. Because of this relative absence of psychopathology and because CUs were attending college full-time, had high IQs, and were from middle class backgrounds, we have considered them to be a relatively advantaged sample.

Of 71 fully completed baseline cases, 27 CUs and 31 controls completed follow-up assessments. This retention rate coheres with similar longitudinal studies (89%: Tait et al., 2011; 64%: Jacobus et al., 2015, personal communication, August 5, 2015). One cannabis user and 2 control participants were excluded from follow-up analyses due to missing data, yielding a follow-up sample of 26 CUs and 29 controls (see Table 1). Retest intervals were

equivalent between groups (cannabis users $M = 2.35$ years, $SD = 0.31$; control $M = 2.22$ years, $SD = 0.49$; see Table 1). These 55 individuals are the focus of analysis.

Participants were asked to refrain from substance use for at least 24 hours before testing. Longer abstinence periods were not required to avoid complications of withdrawal and because a goal was to capture functional capacities in the context of active use. Accordingly, drug testing was not implemented, which we acknowledge as a weakness of the study design.

2.1.2 Procedure

Interested participants completed phone screenings then in-person diagnostic interviews using the Kiddie-SADS-Present-and-Lifetime version (K-SADS-PL: Kaufman et al., 1997), demographic assessments, and the Edinburgh handedness inventory (Oldfield, 1971). Intelligence was estimated using two subtests (Vocabulary, Matrix Reasoning) from the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999). A second session included neuroimaging, self-report questionnaires and neurocognitive assessments. The same measures were repeated at follow-up. No willing participants were excluded from follow-up assessment after initial enrollment.

2.1.3 Neurocognitive Battery

Neurocognitive measures included tests of (1) Motor function: Finger Tapping Test (Lezak, Howieson, & Loring, 2004) and Grooved Pegboard (Lafayette Instruments, 1989); (2) Speeded attention: WAIS-III Digit Symbol (Wechsler, 1997), Letter Cancellation Test (Lezak et al., 2004); (3) Verbal fluency: Controlled Oral Word Association Test (COWAT: Delis, Kramer, Kaplan, & Ober, 2000); (4) Verbal working memory: WAIS-III Digit Span (Wechsler, 1997); (5) Verbal learning and memory: Rey Auditory Verbal Learning Test (RAVLT: Rey, 1993); (6) Spatial memory: CANTAB Spatial Working Memory (SWM: Owen, Downes, Sahakian, Polkey, & Robbins, 1990), Spatial Delayed Response (DRT: Luciana & Collins, 1997); (7) planning: CANTAB Tower of London (TOL: Owen et al., 1990); and (8) Motivated decision-making: Iowa Gambling Task (IGT: Bechara, Damasio, Damasio, & Anderson, 1994). These measures are summarized in Table 2 and repeat what was administered at the baseline assessment. Detailed descriptions of tasks and methods can be found in Becker et al., 2014.

2.1.4 Substance Use

Substance use amounts and frequencies were assessed with the K-SADS-PL. Controls reported minimal CU (≤ once monthly on average) and no illicit drug use. Multiple measures characterized use in CUs. A substance use questionnaire guided by NIAAA recommendations assessed daily use frequency, number of drinks/hits per occasion, and the largest number of drinks and hits consumed in 24 hours, each of which was assessed for the prior five years, the prior 12 months and prior 30 days. The total ingested hits for the last year was calculated. All participants completed Achenbach's Adult Self-Report (ASR; Achenbach & Rescorla, 2003), yielding daily tobacco use, days drunk, and days using drugs (other than alcohol or tobacco) for the previous 6 months.

2.2 Statistical Approach

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 20. Distributions were statistically examined for normality, and variables that did not meet the assumptions for parametric analysis were square root transformed, including error variables for Letter Cancellation, substance use variables from the ASR, and total number of hits within the past year for CUs. There were no statistical outliers.

To characterize longitudinal trends in cognitive performance, tasks were examined in parallel with our approach to analyzing the baseline data (Becker et al., 2014).

2.2.1 Group Differences

Demographic variables were examined between groups using ANOVA or the Chi-square test (e.g., for gender distributions) as appropriate for the task variable. Alcohol and nicotine use characteristics were examined between groups using oneway ANOVAs or the Mann Whitney U test (see Table 1).

Repeated measures analyses of covariance (ANCOVA) assessed for longitudinal group differences in cognitive performance, covarying sex, IQ, interval between assessments, and alcohol use (Hanson et al., 2010; Jacobus et al., 2015; Tait et al., 2011).While mean IQ did not vary between groups (see Table 1), IQ was included as a continuous covariate due to its associations with the dependent measures under investigation (Miller & Chapman, 2001) and to maintain consistency with our prior analyses of baseline data (Becker et al., 2014) which included IQ as a covariate. The alcohol use covariate was a composite variable averaged across the two time points. Specifically, alcohol use first was quantified within each time point as an average of two variables that were z-scored using the full sample. The first variable was calculated by multiplying self-reported typical drinking occasions per week with typical number of drinks per occasion, as assessed in the K-SADS-PL for the previous 6-month period; responses were coded for occasions per week (1 = 0 occasions, 2 = 1–2 occasions, 3 = 3+ occasions) and number of drinks (1 = 0 drinks, 2 = 1–2 drinks, 3 = 3+ drinks). The second variable was the ASR-reported number of days drunk in the last 6 months. Z-scores for the measures derived from the K-SADS-PL and ASR were averaged within time point. The averaged z-score across time points was calculated and used as a covariate in subsequent analyses. Given the stringent inclusion criteria adopted for controls, alcohol use was the only substance-related variable that could be used as a continuous covariate in between group analyses. Although the groups differed in self-reported nicotine use, there was insufficient variance in scores within controls for this variable to be used as a covariate. As reported below, the influence of alcohol and nicotine use on observed outcomes was assessed post-hoc within the CU group.

As reported below, group differences emerged for several cognitive domains. Within CUs, partial correlations explored whether cannabis use patterns and age of use onset were associated with these domains at follow-up, controlling for baseline performance, sex, IQ, interval between assessments, and alcohol use. Additionally, the influence of comorbid substance use was examined within the CU group to address whether use of alcohol and

nicotine, in addition to cannabis, was associated with more pronounced cognitive impairment.

For our primary family of comparisons of cognitive functions in CUs versus controls, i.e., contrasts based on the tasks that showed significant group differences in our prior report of the complete baseline data (Becker et al., 2014), alpha levels ≤ 0.01 are reported as statistically significant, to control for multiple comparisons and in parallel with our conservative approach to reporting the baseline data (Becker et al., 2014). Alpha levels below 0.05 are reported as marginally significant. Effect sizes (η_p^2) are provided given the limited interpretive value of significance testing and in light of the small sample. η_p^2 values of .01, .06, and .14 represent small, medium, and large effects (Cohen, 1988).

For exploratory correlational analyses that associate these areas of impairment with substance use characteristics within CUs, we report effect sizes (e.g., the correlation coefficients) as well as p-values for associations significant at $p < .05$. Correlation coefficients of .1, .3, and .5 represent small, medium, and large effects, respectively (Cohen, 1988).

Both p-values and effect sizes are provided to permit the reader to balance considerations related to Type I error (multiple comparisons) and Type II error (small sample sizes, where conventional statistical testing might obscure meaningful effects).

3.1 Results

3.1.1 Equivalence of the Baseline and Longitudinal Samples

Participants who did versus did not return for follow-up were equivalent in age, ethnicity, IQ, alcohol, tobacco use, ages of cannabis use initiation and use amounts within the last 3 and 12 months (measured at baseline). They were also equivalent in baseline cognition. In CUs, those who returned for follow-up assessment endorsed fewer occasions of non-cannabis illicit drug use during the past 6 months (at baseline).

3.1.2 Longitudinal Differences between Groups

3.1.2a Substance Use Characteristics—Because of the stringent recruitment criteria used for control participants to limit lifetime substance use, substance use varied considerably between groups at the study baseline as previously described (Becker et al., 2014).

At follow-up, CUs continued to report significantly higher alcohol and nicotine use than controls (Table 1). In terms of other drug use, CUs reported experimentation with other drugs in the year prior to follow-up, including psychedelics (n=17), cocaine (n=9), amphetamine (n=6) and barbiturates (n=1) with most reporting that their frequency of other drug use was less than 5 times per substance. Controls reported alcohol use at follow up (Table 1). They reported no nicotine use and relatively little illicit drug use (e.g., one control participant had tried psychedelics one time; 5 controls had tried cannabis less than five times; 4 controls had used cannabis in the range of 6–20 times).

The multiplicative alcohol-use variable, alcohol occasions per week × quantity used, was examined between groups, yielding main effects of Time ($F(1,53)= 29.89$, $p<.001$, $\eta_p^2= .36$: Follow-up > baseline) and Group ($F(1,53)=34.01$, $p<.001$, $\eta_p^2= .39$: CU > control) but no significant Group x Time interaction ($F(1,53)=1.49$, $p=.228$, $\eta_p^2= .027$).

With respect to cannabis use over time, CUs reported a *decreased* number of days using cannabis in the past year, $t(25) = 3.266$, $p = .003$, at follow-up versus baseline. Despite the decline, use remained heavy (past year median reported use occasions = 287.90 [range: 0–365]; mean =245.02; SD=134.92). The reported number of hits per day of use was unchanged over time.

3.1.2b Longitudinal Group Differences in Neurocognition (Table 3)—Repeated measures ANCOVAs, with cognitive variables across time as within subjects factors, group status as a between-subjects factor, and the four covariates of IQ, sex, time interval to follow-up, and average alcohol use over time, were used to measure change between baseline and follow-up. Significant Group or Group by Time interactions are emphasized in this presentation. Significant Group x Time interactions were followed-up with ANCOVAs to isolate group differences.

3.2 Deficits that Persist Over Time in CUs

In our prior report of the complete baseline data (Becker et al., 2014), the following test scores were noted to be reduced in CUs using an alpha level of 0.01: Letter Cancellation completion times, Verbal fluency total words generated, RAVLT interference trial total correct, RAVLT immediate recall, RAVLT delayed recall, spatial delayed response reaction times for the 500 millisecond and 8-second delay intervals, Tower of London number of moves used to complete three-move problems, and Iowa Gambling Task performance during the final two task blocks (e.g., last forty trials). In addition, the total IGT score, delayed response task errors on 8-second trials, as well as Tower of London number of perfect solutions, distinguished the groups at the $p<.05$ level of significance (Becker et al., 2014). These results cohere within the domains of speeded attention, verbal learning/memory, working memory, and motivated decision-making.

As indicated in Table 3, when these cognitive tests were re-examined in the context of repeated measures analyses of covariance, the following findings were obtained:

3.2.1 Speeded Attention

Repeated measures ANCOVAs incorporating both time points revealed a significant effect of Group for letter cancellation times (Table 3). CUs demonstrated significantly faster Letter Cancellation completion times at both time points, despite equivalent error scores. There were no significant Group or Group x Time effects for verbal fluency total scores.

3.2.2 Verbal Learning and Memory

Repeated measures analysis revealed a marginally significant ($p=.027$, $\eta_p^2 =.096$) main effect of Group for RAVLT delayed recall (Table 3). CU's performed worse regardless of time point. To assist in the interpretation of this finding, loss after consolidation was

calculated as the proportion of total words recalled after the 30-minute delay relative to words recalled during the final learning trial (Takagi et al., 2011) and then examined between groups across time. This analysis yielded a marginally significant main effect of Group ($F(149)=6.31$, $p=.015$, $\eta_p^2=.11$) but no significant Group x Time interaction (Table 3). Controls retained 92% (SE=.03) of information across the delay interval while cannabis users retained an average of 80% (SE = .03). The groups did not differ significantly in their rates of learning or in their immediate recall performance.

3.2.3 Working Memory and Planning

Spatial delayed response performance was examined through the use of efficiency scores (error scores x reaction times) for each of the three delay levels (no delay; 500 ms delay; 8-second delay). High efficiency scores indicate performance that is relatively slow and error-prone and have been associated in prior studies with clinical impairment (Luciana, Hanson & Whitley, 2004). When efficiency scores were examined over time, no significant group differences emerged for the no-delay condition. For the 500 ms delay condition, there was a significant Group x Time interaction ($F(1,50)= 7.07$, $p=.01$, $\eta_p^2 =.126$). Relative to controls, CUs demonstrated higher efficiency scores (poorer performance) at baseline ($F(1,49)=9.99$, $p=.003$, $\eta_p^2 =.169$) but not follow-up ($F(1,49) = 0.688$, $p=.411$, $\eta_p^2=.014$).

For the 8 sec delay condition, there was a significant main effect of Group ($F(1,50) = 8.87$, $p=.004$, $\eta_p^2 =.154$) as well as a marginally significant Group x Time interaction ($F(1,50)= 4.39$, $p=.041$, $\eta_p^2 =.082$. The main effect of Group was due to higher (poorer) scores by CUs relative to controls regardless of time point. The Group x Time interaction clarifies this finding by showing significantly worse performance by CUs relative to controls at baseline ($p<.001$, $\eta_p^2=.260$), but not follow-up ($p=.285$, $\eta_p^2= .023$).

In contrast, CUs performed worse across time points for the percentage of TOL perfect solutions (main effect of Group: $F(1, 50) = 7.43$, $p=.009$, $\eta_p^2=.14$). A posthoc examination of specific difficulty levels indicated a main effect of Group for performance on 3-move trials ($p=.001$, $\eta_p^2= .197$) with a marginal Group x Time interaction ($p=.02$; $\eta_p^2=.10$). The main effect of Group reflects poorer performance (higher average moves) by CUs relative to controls at both time points. The Group X Time interaction is due to significantly worse performance by CUs at baseline ($p = .001$, $\eta_p^2= .206$) and marginally worse performance at follow-up ($p = .042$, $\eta_p^2= .08$). Average TOL planning times and other aspects of working memory were not significantly different between groups.

3.2.4 Motivated Decision-Making (Iowa Gambling Task)

A repeated measures ANCOVA examined total good relative to bad choices on blocks 4 and 5 across time, together with the covariates described above. Blocks 4 and 5 were selected for examination, because they yielded group differences at baseline. A marginally significant main effect of Group was observed ($p=.04$, $\eta_p^2=.09$ Table 3) as well as a significant Group x Time interaction ($p=.007$, $\eta_p^2= .15$). To explore the Group x Time interaction, performance was examined within each time point. At baseline, there was a significant group difference favoring controls ($p<.001$, $\eta_p^2=.230$), while at follow-up, the groups were equivalent ($p=.99$, $\eta_p^2= .001$). Thus, baseline, but not follow-up, differences accounted for the interaction.

Performance on blocks 1–3 indicated no significant main effect of Group (p=.862, η_p^2= .001) but showed a marginal Group x Time interaction (p=.03, η_p^2= .097). Post-hoc examination of the interaction indicated a non-significant group difference at baseline (p=.085, η_p^2= .062) as well as a non-significant effect of Group at follow-up (p=.361, η_p^2= .019).

3.3 New deficits in Cannabis Users

There were no areas of function that were observed to be intact in CUs at baseline that were impaired at follow-up.

3.4 Impacts of Reduced Cannabis Use

While most CUs reported continuing to engage in heavy use over time, two reported declines (< 20 hits in past year). One reported abstinence. Findings remained as described above after exclusion of these three cases.

3.5 Associations with Cannabis Use Characteristics

Exploratory partial correlations assessed associations between longitudinal cognitive task performance and cannabis use characteristics within CUs, focusing on variables that indexed cumulative exposure. Baseline cognitive performance, time between assessments, sex, IQ, and average alcohol use were covaried. Predictors included total hits within the last 12 months (at follow-up) and age of cannabis use initiation. We focused this analysis on the variables that showed significant or marginally significant group differences in our longitudinal analyses (Letter Cancellation Times; Perfect Solutions on the TOL task; DRT efficiency scores for the 500 ms and 8 sec delays; RAVLT delayed recall, RAVLT retention after consolidation; IGT performance on Blocks 4 and 5).

There were no significant associations between these cognitive indices and follow-up numbers of reported hits in the past 12 months. A later age of CU onset was associated with better RAVLT delayed recall performance (partial r=.427, p=.05) as well as a greater proportion of information recalled after learning (partial r=..483, p=.027; see Figure 1, panels A and B). A later age of CU onset was also associated with a higher percentage of Tower of London perfect solutions (partial r=.439, p=.05; see Figure 1, Panel C). No other associations were significant.

3.6 Associations with other substance use

Alcohol use and past six months' nicotine use were examined within CUs for associations with these task variables controlling for sex, IQ, interval between assessments, and baseline values of the cognitive variable to determine the impact of comorbid substance use within CUs on cognitive functions that showed group differences. No significant associations were found.

4.0 Discussion

This study assessed neuropsychological performance among non-treatment-seeking young adult heavy cannabis users across two years of assessment. Cannabis users all initiated use prior to the age of 17. At baseline (Becker et al., 2014), CUs were aged 18–19 and demonstrated weaknesses in verbal learning and memory, spatial working memory, planning, and decision-making relative to non-using demographically-matched controls, consistent with cross-sectional studies (Bossong, Jager, Bhattacharyya, & Allen, 2014; Crean, Crane, & Mason, 2011; Lisdahl et al., 2013). They also demonstrated relative strengths in short-term speeded tasks as determined by measures of verbal fluency and letter cancellation speed. This longitudinal assessment of the sample examined these same functions in the context of a comprehensive neurocognitive assessment to determine areas of continued impairment versus recovery over time.

Two years later, CUs demonstrated similar patterns of cognitive strength and weakness. They unexpectedly exhibited an enduring strength on the letter cancellation task, showing rapid but accurate response execution when asked to attend and respond to relevant stimuli within a brief time interval. This finding is puzzling given that processing speed (Fried et al., 2005; Lisdahl & Price, 2012; Medina et al., 2007; Winward, Hanson, Tapert, & Brown, 2014) and occasionally fluency (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011) have been reported as diminished among CUs. Given that CUs have been shown to demonstrate impulsivity in the context of cognitive performance (Gruber et al., 2012), it may be that the enhanced psychomotor speed shown during our speeded tasks reflected this tendency. However, the profile exhibited by CUs is not consistent with impulsive responding given that we did not observe speed-accuracy trade-offs. Performance was faster but without costs given that error rates were similar between groups. CUs in this study demonstrated high average IQs, high levels of educational attainment, and low levels of comorbid psychopathology, which are atypical characteristics in drug-dependent individuals (Fernández-Serrano et al., 2011; Lisdahl & Price, 2012; Medina et al., 2007). Nonetheless, while these many advantages could account for why speeded attentional processing is intact, it remains unclear why this aspect of performance emerged as a strength, particularly given that controls were demographically matched, and performance was not associated with CU dose characteristics or with the comorbid use of other substances. This finding merits further scrutiny to assess whether cannabis might facilitate speeded processing under some conditions and if so, which neural mechanisms or behavioral variables contribute to this effect.

Despite this notable strength, relative impairments in other vital domains of cognition persisted over time. The relative deficits in planning and delayed verbal memory, observed at baseline, remained stable after two years, suggesting that these are enduring vulnerabilities, particularly in those who maintain heavy use. Similar impairments have been reported by others (Bolla et al., 2002; Cuttler et al., 2012; Gonzalez et al., 2012; Grant et al., 2003; Hanson et al., 2010; Harvey et al., 2007; Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007; Schwartz et al., 1989; Solowij et al., 2011; Tait et al., 2011; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010). The observed deficits in verbal memory are particularly compelling given that this finding is robust in the literature. While impaired

verbal memory might be explained by focal impairments involving hippocampally-based circuits that regulate explicit learning or by cannabis-induced changes in structural connectivity in cortical circuits as our work has suggested (Becker et al., 2015), the RAVLT is a complex task that might also require internal motivation and focused effort for successful performance. Self-organization that emerges through coordinated frontal and medial temporal mechanisms is required for successful encoding and retrieval (Long, Oztekin, & Badre, 2010). Retrieval processes, in turn, depend on the recruitment of efficient strategies to guide recall. The greater loss of information after learning that we observed in CUs relative to controls suggests disruptions in the circuitry that links explicit memory with executive control processes. A neurotoxic effect is supported by the observation that earlier ages of initiation were associated with less retention of information over time.

In addition to deficits in verbal memory, cannabis users showed relatively poor planning skills (Epstein & Kumra, 2015; McHale & Hunt, 2008; Montgomery et al., 2012) as evidenced by relatively fewer perfect Tower of London task solutions. This finding encompasses the full Tower of London task. However, posthoc analyses revealed that CUs were most obviously impaired on 3-move problems consistent with our baseline data (Becker et al., 2014). These problems are considered easy, because the solution is immediately visible without the need to recruit working memory or look-ahead skills (Luciana & Nelson, 2002). Perceptual difficulties seem unlikely given that more complex trials were accurately completed. In clinical neuropsychological settings, the observation of deficient performance on relatively easy task trials of a given task with normal performance on challenging trials suggests motivational difficulties (Lezak et al., 2004). In the context of amotivation, the stakes must be high or there must be a compelling challenge before effort-based resources are strongly recruited. Thus, CUs may not have found these trials challenging enough to warrant sufficient effort. In daily life, this dynamic might manifest as lack of engagement when chronic users of cannabis are confronted by mundane activities.

While these patterns for verbal memory and planning suggest enduring deficits, there were some functions that improved over time, notably feedback-based decision-making. The baseline deficits that we observed in IGT-based decision-making skills coheres with other reports (Fridberg et al., 2010; Yechiam, Busemeyer, Stout, & Bechara, 2005), and we expected this area of impairment to persist over time. Instead, we observed an improvement in decision-making skills that was marked in CUs. With reduced cannabis use, some cognitive deficits in young adults have been shown to resolve (Fried et al., 2005; Jacobus et al., 2015; Medina et al., 2007), potentially due to developmental delay. An alternative possible mechanism for recovery could be behavioral tolerance as demonstrated by regular versus occasional users on measures of attention (Desrosiers, Ramaekers, Chauchard, Gorelick, & Huestis, 2015; Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2009; Theunissen et al., 2012), and driving-based control (Bosker et al., 2012). Behavioral tolerance most strongly impacts performance of relatively simple or rote tasks, while complex tasks remain vulnerable (Ramaekers et al., 2009; Theunissen et al., 2012). Importantly, the Iowa Gambling Task is not a simple task, although its complexity may decrease after repeated administration. Thus, the idea that behavioral tolerance accounts for recovery of decision-making function is speculative. Moreover, although we shuffled deck

contingencies at follow-up, differential practice effects may have obscured group differences, accounting for the observed improvement over time in CUs.

Overall, we expected that continued heavy cannabis use would confer cognitive *declines* over time, which was not observed. Jacobus et al. (2015) also longitudinally examined a group of adolescent alcohol+cannabis users and failed to find evidence of worsening cognition over time. Neither Jacobus et al. (2015) nor this study indicate that new cognitive impairments develop over a 2–3 year period with sustained use in young adulthood. Instead, select impairments in verbal memory and executive functioning, both noted at baseline, appear to persist. An unresolved question concerns when such deficits are first apparent in relation to use onset.

Because these deficits were initially observed during heavy use, cause-effect associations are unclear. While neurotoxicity is one potential mechanism for the observed effects, it may be that premorbid function is impaired in individuals who show externalizing tendencies, such as drug use, before use onset, contributing to early initiation and continued difficulties (Iacono, Malone, & McGue, 2008). Alternatively, deficits may have emerged in our CU sample within the first years of cannabis use, coinciding with our baseline assessment. The latter explanation is supported by associations between poor verbal memory, planning, and age of use onset. Since the sample is relatively homogeneous in age and since they have reported continued heavy use over time, an earlier age of onset implies a greater length of cannabis exposure.

Accordingly, we provide evidence to support the idea that adolescent cannabis use may impact the expected trajectories of neural and cognitive development, irrespective of adult use patterns (Lisdahl et al., 2013). This theory is supported by longitudinal evidence linking earlier cannabis use with young adults' poorer processing speed and sequencing ability (Jacobus et al., 2015) and their greater IQ declines (Meier et al., 2012), as well as cross-sectional evidence that earlier use is associated with poorer IQ (Pope et al., 2003), attention (Ehrenreich et al., 1999), visual search (Huestegge, Radach, & Kunert, 2002), verbal fluency (Gruber et al., 2012), and executive functioning (Battisti et al., 2010; Fontes et al., 2011; Gruber et al., 2012). This is the first documentation of this pattern longitudinally in relation to verbal memory.

Important limitations must be mentioned. It is a challenge to balance risks of Type I and Type II error given that this study utilized a comprehensive neurocognitive battery in the assessment of a relatively small sample. To provide a comprehensive presentation and to replicate reported findings, we have presented our full set of findings but used an alpha level of 0.01 to interpret group-based differences in cognition as a means of controlling for multiple comparisons. This strategy may have increased our risk of Type II error given that several moderately-sized effects (see Table 3) failed to reach statistical significance. Our provision of p-values as well as effect sizes allow the reader to balance these various considerations related to Type I versus Type 2 error given that conventional statistical testing might obscure meaningful effects).

Also, males are overrepresented among CUs in this study. While this distribution coheres with national norms in the U.S. (Substance Abuse and Mental Health Services Administration, 2014), findings may not generalize to larger samples of female users.

Furthermore, drug testing was not employed to quantify exposure or confirm absolute levels of use. While we acknowledge the lack of drug testing as a significant limitation, we nonetheless recognize the value of these data and the likely validity of our findings. First, participants' self-reports convincingly described use-related symptoms and behaviors, and self-described users were consistent across measures in their endorsements. One might worry that the observed cognitive differences may have been influenced by residual cannabis effects. While we are confident that CUs were not acutely high during testing, we cannot rule out this possibility given that we studied chronic users. On the other hand, the possibility that users were in acute withdrawal appears unlikely given intact psychomotor performance (e.g., finger tapping; grooved pegboard) and the relative strength in speeded attention, neither of which is consistent with withdrawal syndromes (Haney et al., 2001). Finally, while we asked participants to report on the number of hits per day that they ingested (an admittedly crude measure), we did not attempt to obtain detailed information on the grams of cannabis used given that this information is likely to be unreliable across participants and particularly so in the context of retrospective reporting. Finally, we cannot statistically distinguish magnitude of exposure (e.g., lifetime dose) from timing of exposure given the homogeneity of age and use patterns in the current sample.

4.1 Conclusion

Findings from this longitudinal study suggest that individuals who begin heavy cannabis use during adolescence are vulnerable to persistent deficits in verbal memory and visual planning. While we cannot disentangle cause-effect associations, an earlier age of cannabis use onset is associated with greater impairment in adulthood. Future studies, such as the Adolescent Brain and Cognitive Development (ABCD) project, might fruitfully extend this work by quantifying the emergence of cognitive problems in substance-naive adolescents as they transition into cannabis use and by more comprehensively linking such problems to deviations in neural functions and motivational behavior.

Acknowledgments

This work was supported by the National Institute on Drug Abuse under grant R01DA017843 awarded to M. Luciana and by the National Institute on Alcohol Abuse and Alcoholism under grant R01AA020033 awarded to M. Luciana. Support from the University of Minnesota's Center for Neurobehavioral Development is also gratefully acknowledged.

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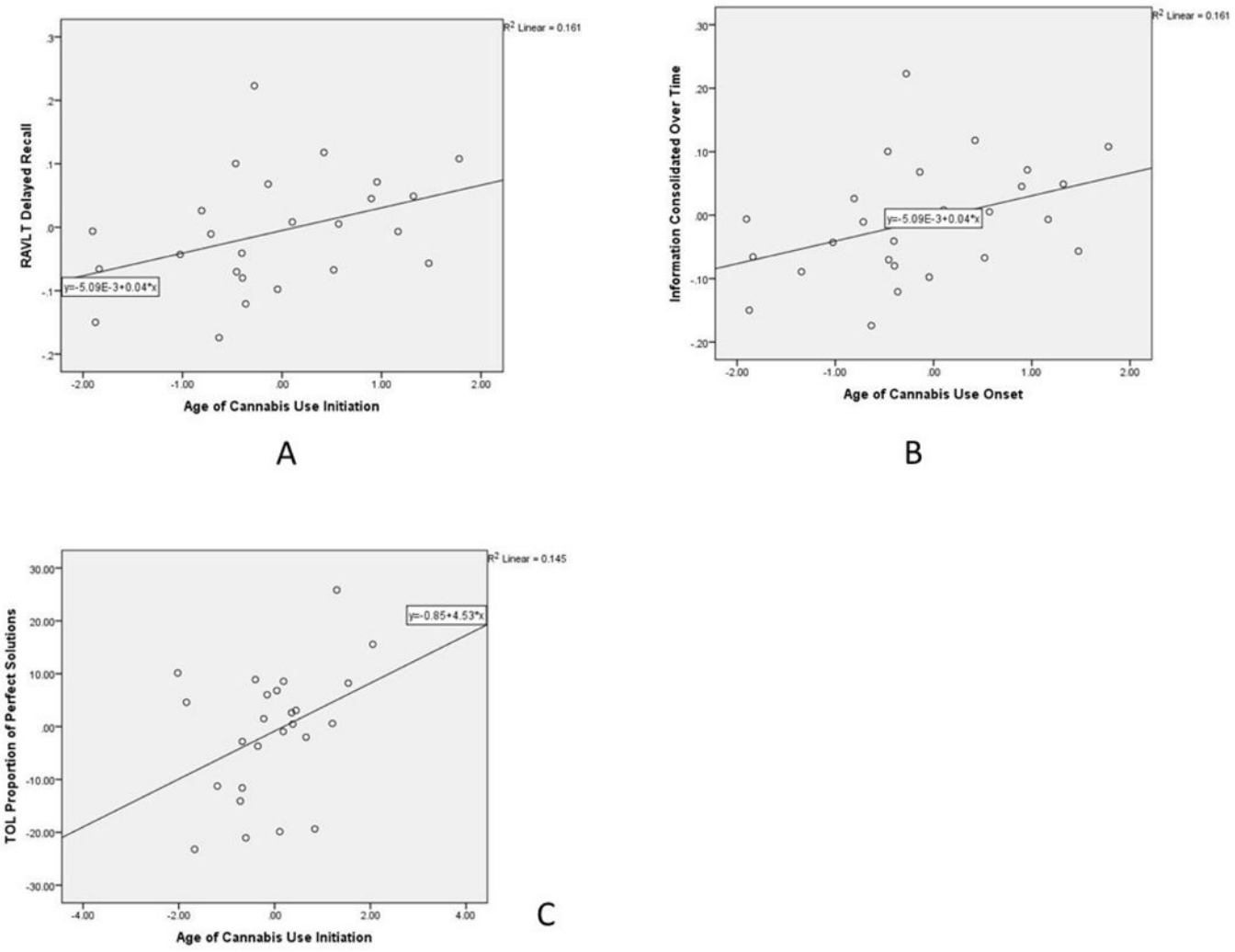

Figure 1.

Scatterplots of follow-up performance by age of cannabis use onset. Partial regression plot controlling for baseline delayed recall performance, sex, interval between assessments, IQ, and average alcohol use across time points. Panel A = RAVLT delayed recall; Panel B= RAVLT Information Retained After Consolidation; Panel C = Tower of London Proportion of Perfect Solutions.

Table 1.

Study 1 Demographic and substance use characteristics of cannabis users and controls at baseline and follow-up

Variable	Control	Cannabis User	*F, U,* χ^2	*p*
Baseline characteristics				
n	29	26		
Age	19.29 (0.93)	19.45 (0.63)	0.57	0.46
#Male/#Female	10/19	19/7	$\chi^2 = 8.19$	<0.01 *
#Caucasian/#Other Ethnicity	23/6	22/4	$\chi^2 = 0.26$	0.61
Years of education	13.00 (1.19)	13.28 (0.98)	0.865	0.36
Estimated Full Scale IQ[a]	114.58(1.84)	115.50 (1.95)	0.108	0.743
Vocabulary T-Score	61.76 (1.29)	62.12 (1.45)	0.34	0.85
Matrix reasoning T-Score	54.52 (1.13)	55.62 (1.08)	0.49	0.49
Alcohol use average composite score	−0.58 (0.71)	0.50 (0.73)	30.37 *	< 0.01 **
ASR substance use				
Past 6 months: Tobacco use per day	0.00 (0.00)	1.00 (1.62)	*U* = 232.0	< 0.01 **
Past 6 months: Days drunk	5.00 (9.51)	25.88 (17.92)	*U* = 76.0	< 0.01 **
Cannabis use[b]				
Age first used (years)	–	15.24 (1.23)		
Past year: Days used	–	327.90 (48.44)		
Past 30 days: Days used	–	26.70 (4.34)		
Past year: Total # hits	–	3180.00 (2522.51)		
Past 30 days: Total # hits	–	254.56 (213.39)		
Follow-up characteristics				
Years between assessments	2.22 (0.49)	2.36 (0.31)	1.60	0.21
Age at follow-up	21.52 (0.90)	21.82 (0.76)	1.77	0.19
Years of education	15.14 (1.13)	15.16 (2.72)	< 0.00	0.97
Estimated Full Scale IQ[a]	118.84 (1.54)	117.11 (1.63)	0.55	0.46
Vocabulary T-Score	62.25 (1.25)	61.38 (1.33)	0.21	0.65
Matrix reasoning T-Score	58.83 (0.90)	58.11 (0.96)	0.28	0.60
Alcohol use average composite score	–0.51 (0.52)	0.58 (0.76)	39.57	< 0.01 **

Variable	Control	Cannabis User	*F, U,* χ^2	*p*
ASR substance use				
Past 6 months: Tobacco use per day	0.00 (0.00)	2.03 (3.10)	$U = 130.5$	$< 0.01^{**}$
Past 6 months: Days drunk	6.90 (9.84)	27.65 (22.56)	$U = 110.5$	$< 0.01^{**}$
Cannabis use[b,c]				
Past year: Days used	–	245.02 (134.92)		
Past 30 days: Days used	–	18.28 (11.96)		
Past year: Total # hits	–	2561.90 (2396.39)		
Past 30 days: Total # hits	–	184.41 (204.75)		

Notes. Values represent means and standard deviation units, unless otherwise specified. Group comparisons using chi-square, Mann-Whitney U, or one-way analysis of variance are reported. ASR = Adult Self-Report.

[a] Marginal means and standard errors are presented, controlling for sex.

[b] Variables only included for cannabis users.

[c] Data unavailable for 1 cannabis user ($n = 25$).

$^{*}p \leq .05$.

$^{**}p \leq .01$.

Table 2.

Neurocognitive Measures

Domain	Measure	Variables	References
Basic Motor Function	Finger Tapping Test Grooved Pegboard	Number of taps across three trials for each hand Completion time for each hand	Lezak, Howieson, & Loring, 2004) Lafayette Instruments, 1989
Processing Speed	Digit Symbol: matching symbols to numbers under speeded directions	Number correct based on standardized administration	Lezak et al., 2004; Wechsler, 1997
	COWAT (Verbal Fluency): generate as many words as possible for each of three letters (F, A, S) in 60 seconds	Number of correct words generated	Delis, Kramer, Kaplan, & Ober, 2000; Lezak et al., 2004
	Letter Cancellation Task: Cross out occurrences of letters E and C as quickly as possible	Completion time; total errors (omission and commission)	Lezak et al., 2004
Verbal Learning and Memory	Rey Auditory Verbal Learning Test: Learn a list of 15 words across 5 trials then recall the list under immediate and delayed conditions	Total correct on learning trials (1–5); Immediate Recall (total correct); 30-minute Delayed Recall (total correct)	Rey, 1993
Planning	CANTAB Tower of London Task: Solve spatial planning problems in a pre-determined number of moves	Proportion of perfectly solved problems Average planning time	Owen, Downes, Sahakian, Polkey, & Robbins, 1990
Spatial Working Memory	Delayed Response Task (DRT): View a dot presented on-screen and recall its location after a specified delay CANTAB spatial working memory task Digit Span	Error scores and reaction times for No-delay trials 500 millisecond delay trials 8 second delay trials	Luciana & Collins, 1997; Luciana, Collins & Depue, 1998; Luciana, Hanson & Whitley, 2004
Motivated Decision-Making	Iowa Gambling Task (IGT): Select cards from four decks, using feedback to maximize winnings	Number of advantageous – disadvantageous choices for each of five 20-trial blocks	Bechara, Damasio, Damasio, & Anderson, 1994; Hooper, Luciana, Conklin, & Yarger, 2004

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2019 August 01.

Table 3.

Baseline and Follow-up neuropsychological battery scores for participants who completed the follow-up assessment (controls n = 29) and (cannabis users n = 26). Means reported are estimated marginal means, controlling for sex, IQ, interval between assessments, and average alcohol use across time points.

Cognitive Measure	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (*n* = 29) *M (SE)*	**Cannabis user (*n* = 26) *M (SE)***	**Control (*n* = 29) *M (SE)***	**Cannabis user (*n* = 26) *M (SE)***	**Group *F (p)/ η_p^2***	**Group × Time *F (p)/ η_p^2***
Finger Tapping Test	42.08 (1.83)	45.00 (1,97)	44.30 (1.36)	45.37 (1.47)	0.67 (.416)/.014	0.48 (.49)/0.01
Grooved Pegboard	66.88 (1.93)	68.84 (2.08)	65.12 (1.65)	66.73 (1.78)	0.079 (.780)/.002	0.39 (.534)/.008
Digit Symbol	86.05 (3.03)	91.82 (3.27)	91.46 (2.98)	95.64 (3.22)	1.15 (.289)/.023	0.118 (.733)/.002
Letter Cancellation						
Time (s)	114.38 (3.86)	93.08 (4.16)	109.23 (4.13)	95.79 (4.45)	**7.72 (.008)/.136**	1.85 (.180)/.036
Total Errors	1.69 (.60)	2.30 (.65)	2.46 (.66)	1.60 (.71)	0.250/.261/.026	1.29/.261/.026
COWAT						
Total correct words generated	43.35 (2.29)	49.35 (2.30)	45.70 (2.40)	50.26 (2.54)	2.03 (.161)/0.04	0.28 (.597)/.006
Digit Span[c]	6.66 (1.95)	6.06 (2.05)	6.06 (2.05)	6.51 (2.35)	1.11 (.298)/.023	2.12 (.153)/.042
Digits forward (# recalled)	7.57 (0.21)	7.04 (0.22)	7.46 (0.24)	7.20 (0.25)		
Digits backward (# recalled)	5.75 (0.27)	5.08 (0.29)	5.63 (0.30)	5.82 (0.31)		
RAVLT						
Total words: Trial 1–5	55.13 (1.8)	52.81 (1.9)	57.37 (1.5)	54.21 (1.6)	1.20 (.278)/.024	0.11 (.744)/.002
Total words: Interference trial	7.36(0.39)	6.02(0.43)	6.73 (0.38)	6.46 (0.41)	2.67 (.109)/.052	1.43 (.238)/.028
Total words: Immediate recall	12.27 (0.49)	10.51 (0.52)	11.82 (0.51)	11.09 (0.55)	3.17 (.081)/.061	1.11 (.298)/.022
Total words: Delayed recall	12.10 (0.55)	9.66 (0.59)	11.93 (0.53)	10.72 (0.56)	**5.22 (.027)/.096**	1.85 (.180)/.036
Proportion Consolidated	0.91 (.03)	0.77 (.04)	0.92 (.03)	0.83 (.04)	**6.31 (.015)/.114**	0.49 (.49)/.010
Spatial Working Memory[b c]						
Total between search errors[a]	12.20 (2.28)	14.73 (2.26)	9.44 (2.54)	11.91 (2.75)	0.46 (.502)/.010	< 0.00 (.988)/ <.000
Strategy Score: 6–8	30.18 (1.19)	30.39 (1.32)	27.57 (1.23)	27.42 (1.36)	< 0.00 (.989)/ <.000	0.03 (.855)/.001
Spatial Delayed Response Task						
Efficiency (No delay)	4301.49(328.05)	4737.49 (353.63)	3976.51 (517.03)	5091.07 (557.34)	1.69 (.200)/.033	.572 (.453)/.012
Efficiency (500 ms delay)	10333.08 (1033.60)	15960.24 (1114.18)	12804.65 (1633.72)	10469.40 (1761.08)	0.82/(.370)/.016	**7.07 (.011)/.126**
Efficiency (8000 ms delay)	16056.54 (1701.72)	28218.63 (1834.38)	21462.51 (2146.65)	25459.26 (2314.00)	**8.87 (.004)/.154**	**4.39 (.041)/.082**

Cognitive Measure	Baseline		Follow-up		Repeated Measures ANCOVA	
	Control (*n* = 29) *M (SE)*	**Cannabis user (*n* = 26) *M (SE)***	**Control (*n* = 29) *M (SE)***	**Cannabis user (*n* = 26) *M (SE)***	**Group *F (p)/* η_p^2**	**Group × Time *F (p)/* η_p^2**
Tower of London[b]						
% Perfect Solutions[d]	87.3 (3.09)	71.38 (3.26)	86.80 (3.23)	79.92 (3.40)	**7.43 (.009**)/.139**	1.72 (.197)/.036
First move initiation time: Average[d]	6962.46 (584.97)	7027.49 (644.84)	8845.35 (777.26)	6942.01 (797.47)	1.24 (.272)/.026	1.30 (.260)/.028
Iowa Gambling Task[e]						
Good-Bad Choices: Blocks 1–3 summed	4.42 (4.95)	−8.04 (5.08)	5.23 (6.16)	14.88 (6.33)	.031 (.862)/.001	**4.84 (.033)/.097**
Good-Bad Choices: Blocks 4–5 summed	19.37 (4.56)	−8.01 (4.69)	14.31 (5.14)	14.40 (5.28)	**4.47 (.040)/.090**	**8.02 (.007)/.151**

Notes. Baseline and follow-up statistics for the follow-up sample (control $n = 29$, cannabis user $n = 26$). Marginal means and standard errors are presented for the, controlling for time to follow-up interval, sex, IQ, and average alcohol use during baseline and follow-up.

[a] Square root transformed

[b] Data unavailable for 1 cannabis user ($n = 25$) at baseline.

[c] Data unavailable for 1 control at follow-up ($n = 28$).

[d] Data unavailable for 2 controls ($n = 27$) at follow-up.

[e] Data unavailable for 1 cannabis user ($n = 25$) and 3 controls ($n = 26$) at follow-up. Omnibus analyses are reported for the Finger-Tapping task (average taps per trial per hand per time point), for the Grooved Pegboard task (completion times per hand per time point), and Digit Span Task (digits forward; digits backward for each time point). No interactions between the reported group effects and hand (tapping; pegboard) or task phase (digit span) were observed. Comparisons where p-values are statistically significant (p<.01) or at trend level (p<.05) are bolded.