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One Month of Cannabis Abstinence in Adolescents and Young Adults is Associated with Improved Memory

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Abstract

Objective: Associations between adolescent cannabis use and poor neurocognitive functioning have been reported from cross-sectional studies that cannot determine causality. Prospective designs can assess whether extended cannabis abstinence has a beneficial effect on cognition.

Methods: Eighty-eight older adolescents who used cannabis regularly were enrolled in the hospital laboratory and a local high school between July 2015 and December 2016. Participants were randomly assigned to four weeks of cannabis abstinence, verified by decreasing 11-nor-9-carboxy-9-tetrahydrocannabinol urine concentration (MJ-Abst; n=62), or a monitoring control condition with no abstinence requirement (MJ-Mon; n=26). Attention and memory were assessed at baseline and weekly for four weeks with the Cambridge Neuropsychological Test Automated Battery.

Results: Among MJ-Abst, 55 (88.7%) met *a priori* criteria for biochemically-confirmed 30-day continuous abstinence. There was an effect of abstinence on verbal memory, $p=0.002$, that was consistent across four weeks of abstinence, with no time by abstinence interaction, driven by improved verbal learning in the first week of abstinence. MJ-Abst had better memory on average and at weeks 1, 2, 3 than MJ-Mon, and only MJ-Abst improved in memory from baseline to week 1. There was no effect of abstinence on attention: both groups improved similarly, consistent with a practice effect.

Conclusions: This study suggests that cannabis abstinence is associated with improvements in verbal learning that appear to occur largely in the first week following last use. Future studies are needed to determine whether the improvement in cognition with abstinence is associated with improvement in academic and other functional outcomes.

Keywords

Marijuana; Cannabis; Abstinence; Cognition; Adolescents; Contingency Management

Introduction

Cannabis use in adolescence is widespread, and rates of use are likely to increase further as more states move toward legalization. Lifetime, annual, past month and daily cannabis use among middle and high school-aged students was respectively 28.6%, 22.6%, 13.7% and 3.0% in 2016, with rates of daily use doubling between 8th and 12th grade.¹ Students report very easy accessibility to cannabis and attitudes of harm perception in 2016 were at or near historic lows, with only one in three 12th grade students perceiving great risk in regular cannabis use.¹

Regular cannabis exposure during adolescence may cause greater adverse effects than later exposure due to ongoing neuromaturation occurring well into the third decade of life.^{2,3} Gray matter in areas underlying higher order cognition is last to mature,⁴ and increased myelination contributing to white matter development continues through at least the late 20s.⁵⁻⁹ Cannabis use is thought to affect normal neuromaturation¹⁰ via effects of tetrahydrocannabinol (THC) on endocannabinoid-guided neuromaturation and selective synaptic pruning during adolescence.¹¹ Exposure to synthetic cannabinoids or THC during adolescence but not later in life is associated with cognitive impairments¹²⁻¹⁵ that are linked with biomarkers of aberrant neurodevelopment, including shorter dendrites and reduced spine densities in the hippocampus.¹⁵ Epidemiologic studies have also reported associations between earlier cannabis onset and poor neurocognition^{16, 17} as well as abnormalities in brain activation patterns.¹⁸ for a review see 19

We sought to determine whether neurocognition improves with extended cannabis abstinence. To our knowledge, only two studies have prospectively examined patterns of adolescent neurocognitive recovery with cannabis abstinence, one in comparison to non-using controls²⁰ and one in comparison to cannabis users who continue to smoke.²¹ In a non-randomized trial, Hanson and colleagues²⁰ found remittance of memory deficits after three weeks of abstinence among adolescent cannabis users compared to non-users. The second study, which was designed to evaluate changes in cognitive performance among adolescents enrolled in a randomized, placebo-controlled trial of *N*-acetylcysteine for cannabis cessation, showed improvement in verbal memory and psychomotor speed in those who were abstinent for four or eight weeks compared to those who continued to smoke.²¹ These studies provide preliminary evidence that abstinence is associated with improved neurocognitive function. However, no study to date has employed an experimental design in which adolescent participants are randomized to stop using cannabis to control for group differences that might influence performance (e.g., learning, baseline neurocognition, amotivation), and assessed neurocognition regularly during abstinence to determine the course of neurocognitive recovery.

We aimed to determine whether cognition improved to a greater degree in adolescent and young adult regular cannabis users randomized to an abstinence condition than those

randomized to a monitoring control condition, and the timing of any improvement. We focused our cognitive assessment on attention and memory, processes critical to academic performance and implicated in early cannabis exposure.

Method

Participants

Participants (N=88) were adolescents and young adults, aged 16 to 25, recruited via peer referral and community advertisements and in a public high school in a northwest Boston suburb. Inclusion criteria were assessed via telephone screen and included cannabis use at least weekly, use in the week prior to screening, English fluency, and willingness to be randomized to 30 days of abstinence. Participants were randomized 2:1 to four weeks of cannabis abstinence achieved with a contingency management (CM) intervention (MJ-Abst; n=62) or non-contingent monitoring, matched for contact time, with no abstinence requirement (MJ-Mon; n=26).

Procedures

Enrollment occurred between July 2015 and December 2016. A detailed description of procedures has been described previously.²² Procedures were approved by the Partners Healthcare Human Subjects Committee. Written informed consent was obtained for participants over the age of 18, and written parental consent and participant assent were obtained for individuals under the age of 18.

Participants completed seven visits in a private office in the hospital laboratory or on the high school campus. There were five cognitive assessments administered at baseline (prior to any change in cannabis use), and weekly for four consecutive weeks. Participants also met with study staff twice between baseline and the week one visit to provide urine samples.

Randomization occurred at the end of the baseline visit. After baseline, those assigned to MJ-Abst were asked to stop using cannabis for one month and completed a behavioral contract²³ that listed behaviors to be monitored, schedule of monitoring, and contingencies to be imposed. MJ-Mon were not asked to abstain from cannabis and provided urine samples for toxicology on the same schedule as those assigned to MJ-Abst.

MJ-Abst earned incentives on a two-track system for attendance and abstinence, with static denominations for attendance and escalating denominations for abstinence. The first 35 participants earned \$585 for 30 days of abstinence with full attendance (\$405 for abstinence and \$180 for full attendance). Due to the success of the CM paradigm at eliciting 30 days of cannabis abstinence,²² the payment schedule was reduced by approximately 30% for the final 27 participants (\$315 for 30 days of abstinence and \$105 for full attendance). MJ-Mon received escalating payments for attendance, totaling \$220 for full attendance. Incentives were distributed via reloadable credit cards through Clinical Trials Payer (CT Payer) on the day of the visit for attendance and upon receipt of the quantitative urinalysis results confirming abstinence (for MJ-Abst; described below).

For MJ-Abst, abstinence was indexed by self-reported non-use and progressively decreasing urine concentrations of 11-nor-9-carboxy-9-tetrahydrocannabinol (THCCOOH), the main secondary THC metabolite and a widely accepted cannabis biomarker. Samples were shipped overnight to Dominion Diagnostics (Kingstown, RI) where THCCOOH levels were assayed using liquid chromatography/tandem mass spectrometry, normalized to creatinine.²⁴ New use was established using a statistical model developed by Schwilke and colleagues.²⁵

Assessments

Demographic and background information were assessed at baseline. Full-scale IQ was estimated at baseline using the two-subtest Wechsler Abbreviated Scale of Intelligence²⁶ for those recruited through the school and Wechsler Test of Adult Reading (WTAR²⁷) for participants recruited at the hospital. Cannabis and alcohol dependence were assessed at baseline with the Cannabis Use Disorder Identification Test – Revised (CUDIT-R²⁸) and Alcohol Use Disorders Identification Test (AUDIT²⁹), respectively. A modified Timeline Followback interview³⁰ was conducted at baseline to approximate quantity and frequency of past 90-day cannabis and alcohol use. Current and lifetime Axis I diagnoses were assessed with the Structured Clinical Interview for DSM-IV (SCID-IV³¹) for participants recruited at the hospital.

Cognition was assessed at baseline and weekly for four consecutive weeks with the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition). Attention was indexed with the Attention Switching Task (AST), a measure of cued attentional set-shifting, and the Rapid Visual Information Processing Task (RVP), a measure of visual sustained attention. For the AST, an arrow appeared on one side of the screen, and a cue was presented indicating whether the participant should respond according to the direction of the arrow, or the side of the screen on which the arrow appeared. AST outcome variables included total errors, response latency (ms), switching cost (difference between response latencies when the rule was switching versus when the rule remained constant; ms), and congruency cost (difference between response latency of congruent versus incongruent trials; ms). For the RVP, digits from two to nine randomly appeared at the rate of 100 digits per minute in the center of the screen for six-minutes and 30 seconds. Participants registered responses using the press pad every time the last digit in one of three target sequences (2-4-6, 3-5-7, and 4-6-8) was observed. Sixteen target sequences occurred every two minutes, with a total of 27 targets presented. RVP outcome measures included total hits, total false alarms, A' (i.e., signal detection measure of sensitivity to the target), mean response latency (ms), and mean response speed variability (ms).

Memory was measured with the Delayed-Matching-To-Sample Task (DMS), Spatial Span Task (SSP), and Verbal Recognition Memory Task (VRM). The DMS is a test of simultaneous and delayed matching to sample. Participants were shown a complex pattern (the sample) followed by four choice patterns. Participants selected the choice pattern identical to the sample as quickly as possible. Latency between presentation of the choice stimuli varied between 0, 4, or 12-second delays. Participants were administered 24 counterbalanced trials including eight trials at each delay. DMS outcome variables included number of correct responses and latency to correct response, each at all three delay intervals.

SSP measures visual span capacity. A pattern of white boxes was shown, and the boxes changed color one at a time in variable sequence. Once the sequence presentation was complete, participants touched the boxes in the order as was originally presented. Each task level was comprised of three possible sequences, and the sequence length at each level increased from two to nine boxes. The task terminated when all three sequences at a given level were completed unsuccessfully. Outcome variables included the longest sequence successfully recalled and mean time to last response (ms). VRM is a measure of immediate and delayed verbal memory. Participants were shown a list of 18 words twice. After each presentation and a 20–30 minute delay, they were asked to recall as many of the words as possible. Outcome variables included initial encoding (number of words recalled after trial one), total encoding (sum of words recalled in trial one and trial two), and delayed recall.

Alternate forms of CANTAB tasks were administered when available to minimize practice effects. Outcome variables were converted to z scores based on the overall group means and standard deviations at baseline, when all participants were non-abstinent. Z scores within each test were averaged at each time point separately by abstinence group to create test score composites, and averaged within domain at each time point separately by abstinence group to create attention and memory composites. Primary outcomes were the attention and memory domain composite scores, and secondary analyses focused on test score composites.

Analytic Approach

Data were analyzed using Stata 13.1 and SAS 9.4. At baseline, participants were all considered non-abstinent. At subsequent time points, participants were analyzed per randomized group. Cognitive data from MJ-Abst who did not attain four weeks of abstinence were only included in analyses from visits with biochemically confirmed abstinence. MJ-Abst who dropped out of the study were considered non-abstinent at all visits with missing data. Repeated measures analyses of variance (ANOVA) were conducted to study longitudinal change in cognition from baseline through week 4. Separate models were conducted for attention and memory domain composite scores, and test composite scores when appropriate. Significant group effects were followed-up with pairwise group comparisons at each time point. Significant time effects were followed-up by comparing differences in slopes between consecutive time points, separately by group. Alpha was set at 0.05 for all statistical tests.

Results

Participant Characteristics

MJ-Mon and MJ-Abst groups were comparable across demographic, mood, alcohol and cannabis use indices, including frequency and amount of cannabis consumed in the 90 days prior to the intervention (Table 1), and across measures of cognition at baseline (supplementary eTable 1).

Verification of Cannabis Abstinence

Creatinine-adjusted THCCOOH levels declined across the 4-weeks for MJ-Abst and not MJ-Mon (Figure 1). Fifty-five of the 62 (88.7%) participants assigned to MJ-Abst met pre-

specified criteria for 30-day biochemically-confirmed continuous abstinence. Comparison of baseline characteristics of MJ-Abst, divided by 30-day continuous abstinence status, is provided in Supplementary eTable 2. All participants in MJ-Mon used cannabis during the study period, averaging 4.87 days ($SD = 3.15$) of use between visits.

Attention

There was a main effect of time (study week) [$F(4,88) = 13.80, p < 0.0001$] on attention, and no main effect of abstinence status [$F(1,88) = 0.37, p = 0.55$] or abstinence status by time interaction [$F(3,88) = 0.34, p = 0.79$]. This indicates that attention improved similarly in MJ-Abst and MJ-Mon over the 4-week assessment period (Figure 2a).

Memory

There was a main effect of abstinence status on memory [$F(1,88) = 10.75, p = 0.002$], such that MJ-Abst had better memory than MJ-Mon overall, and at weeks 1, 2, 3 and 4 (trend). There was no main effect of time [$F(4,88) = 0.27, p = 0.89$] or group by time interaction [$F(3,88) = 0.38, p = 0.77$]. Memory improved in MJ-Abst from baseline to week 1 (Figure 2b).

Change in Components of Memory with Abstinence: Exploratory Analysis

To examine the components of memory most impacted by cannabis abstinence, each test that comprised the memory composite was evaluated separately (Table 2). Main effects of abstinence and time on VRM appeared to drive the overall effect of abstinence on memory. The main effect of time on VRM was driven by improvement from baseline to week 1 in MJ-Abst only. The main effect of abstinence was such that the MJ-Abst performed better than MJ-Mon overall, and at weeks 1, 2 (trend), 3 (trend), and 4 (trend). For SSP and DMS, there were main effects for time, but the effect of abstinence status and the abstinence status by time interactions were not significant.

To better understand the aspect(s) of declarative memory most impacted by cannabis abstinence, analyses were repeated considering each of the three comprising VRM variables separately (Table 3). There was a main effect of abstinence status for initial and total encoding. MJ-Abst learned more words on average after trial one and altogether, and this effect was significant overall, and at weeks 1, 2 (trend for initial encoding only), 3 (initial encoding only), and 4 (trend for initial and total encoding). The main effect of time and the abstinence status by time interactions were not significant for either initial or total encoding. For delayed recall, there was a main effect of time. Abstinence status and the group by time interaction were not significant, indicating that MJ-Abst and MJ-Mon's overall abilities to recall words after a delay were comparable and they changed in their ability to perform this task similarly over time.

Discussion

Memory, but not attention, improved more among adolescents and young adults who abstained from cannabis compared to those who continued to use. This is consistent with prior studies that indicated neurocognitive dysfunction persists after several days of

abstinence,^{32–35} particularly in the domain of memory,^{for reviews see 36–38} and with findings that verbal memory improved after four or eight weeks of abstinence.²¹ The current study extends this finding by demonstrating that improvement in memory appears to occur with one week of continuous cannabis abstinence.

Declarative memory, particularly encoding of novel information, was the aspect of memory most impacted by cannabis abstinence. Those who maintained abstinence learned more words than those who continued to use cannabis. This is consistent with other studies that suggest a specific effect of cannabis on learning, including recent findings that THC acutely interferes with encoding of verbal memory without interfering with retrieval³⁹ and that an effect of cannabis on learning accounts for effects on delayed recall.¹⁷ Cannabis use may impede learning via disruption in the prefrontal, parietal and temporal cortices that are implicated in the memory learning network.^{40, 41} This is supported by findings of dense localization of CB1 receptors in the prefrontal cortex, as well as frontal grey^{42, 43} and white matter disruptions in cannabis-using adolescents.^{44–47} In contrast, this study found abstinent and non-abstinent individuals to have comparable visual span capacity, short-term visual recognition memory, and verbal recall of information after a delay, and these abilities improved comparably across groups over the four-week assessment period.

Attention improved over time in both abstinent and non-abstinent groups, a finding that could be consistent with a pilot report that while attention processing speed was similar between abstinent cannabis users and non-users, attention accuracy remained lower among users throughout three-weeks of abstinence.²⁰ A non-cannabis exposed control group is needed to understand whether young cannabis users experience subcortically-mediated attention dysfunction that persists even after 30 days of abstinence.

The primary limitation of this study was the absence of a control group of non-users. Without comparison to a non-using sample or knowledge of performance prior to the initiation of cannabis use, it is difficult to interpret the role of cannabis in affecting domains that did not improve more among abstainers compared to non-abstainers, such as tasks of attention, visual span capacity, short-term visual recognition memory, and verbal delayed recall. There are several possible explanations: 1) deficits predate cannabis use, 2) deficits from cannabis exposure are permanent or long-lasting, 3) substantial practice effects in the control group wash out the ability to detect subtle between-group differences, or 4) cannabis does not adversely impact attention or these other domains, thus no improvement over practice effects would be evident with abstinence. Without non-users, normative score comparisons, and/or knowledge of pre-use cognitive functioning, it is difficult to determine whether the extent of improvement in the abstinent group represents a return-to-baseline. A larger trial currently underway (1K23DA042946, PI: Schuster) includes a non-user comparator group, which will be essential in determining whether the extent of memory change in the first week of abstinence represents a full return-to-baseline.

An additional limitation of the study is the inability to determine a more precise time point of when memory improvement occurred during the first week of abstinence. The current study cannot determine whether improvement represented a reversal of the acute effects of THC, or resolution of more persistent cognitive effects. Future studies are warranted which

examine cognitive change at more frequent intervals within the first week of abstinence. However, regardless of whether the change observed is a reversal of the early residual effects or recovery from cannabis' persistent effects, findings are still of high clinical significance, as the difference in performance between groups persisted across the entire one month assessment period. Finally, an additional limitation is the possibility that a ceiling effect may have impeded our ability to detect further improvement in memory after the first week of abstinence. The non-abstinent group evidenced no improvement from baseline to week 1, suggesting that they did not benefit at all from practice. Practice effects across the one month testing period were more detectable in the attention domain, and therefore less prone to a ceiling effect.

The functional significance of the observed memory improvement in abstinent cannabis users is also not known. The larger follow-up trial will determine whether cognitive improvement with cannabis abstinence translates to self-perceived cognitive enhancements, collateral-reported cognitive enhancements, and objective markers of improved academic performance. By design, this study also recruited a more heterogeneous group of cannabis users (in terms of cannabis use severity and co-morbidities), enhancing generalizability to the more typical adolescent user. However, this may have resulted in greater within-group cognitive variability, particularly the MJ-Mon group which had fewer participants. We were also not powered to examine risk factors for poor neurocognitive recovery with abstinence (e.g., baseline cognitive reserve, psychiatric co-morbidity). Finally, this study focused on changes in memory and attention as they were hypothesized to be most impacted by cannabis abstinence. Future studies will employ a more comprehensive cognitive battery to determine the specificity of the abstinence impact on memory.

This study provides convincing evidence that adolescents and young adults may experience improvements in their ability to learn new information when they stop using cannabis. Attention does not appear to be impacted by one month of cannabis abstinence. It is essential that we develop a better understanding of whether cannabis exposure in adolescence is associated with cognitive deficits, and if so, whether and over what period such deficits improve with abstinence. This knowledge has a potential for high public health impact, including physician advice to adolescents and their parents, and local, statewide, and national policymaking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

- It is not known whether adolescents continue to experience cognitive deficits even after they stop using cannabis.
- Your patient will likely experience an improvement in his/her thinking abilities, particularly his/her memory for new information, when he/she stops using cannabis.

Figure 1.

A total of 592 valid urine specimens were collected during the study period, and 93.2% ($n = 552$) of the specimens had THCCOOH levels that were quantifiable based on available laboratory methods (range of creatinine-unadjusted THCCOOH levels in quantifiable samples: 0 – 3920ng/ml; range of creatinine-adjusted THCCOOH levels in quantifiable samples: 0 – 1765.8ng/mg). Urine creatinine-adjusted THCCOOH concentrations declined during four weeks of monitored cannabis abstinence only among those randomized to 4 weeks of cannabis abstinence (MJ-Abst). Values are presented for specimens where quantifiable THCCOOH and creatinine were available. All values represent means and standard errors.

Omnibus Model Effects

Time (Study Week): $F(4,88) = 13.80, p < 0.0001$

Abstinence Status: $F(1,88) = 0.37, p = 0.55$

Abstinence Status X Time (Study Week): $F(3,88) = 0.34, p = 0.79$

Comparison of Slopes Between Weeks by Group

Baseline to Week 1:

MJ-Abst: $\beta = 0.29, t(88) = 5.42, p < 0.0001$

MJ-Mon: $\beta = 0.23, t(88) = 3.16, p = 0.002$

Week 1 to Week 2:

MJ-Abst: $\beta = 0.09, t(88) = 1.75, p = 0.08$

MJ-Mon: $\beta = 0.16, t(88) = 2.20, p = 0.03$

Week 2 to Week 3:

MJ-Abst: $\beta = 0.10, t(88) = 2.07, p = 0.04$

MJ-Mon: $\beta = 0.02, t(88) = 0.33, p = 0.74$

Week 3 to Week 4:

MJ-Abst: $\beta = 0.02, t(88) = 0.43, p = 0.67$

MJ-Mon: $\beta = 0.02, t(88) = 0.33, p = 0.74$

Pairwise Group Comparisons at Each Time Point

Week 1 (MJ-Abst vs MJ-Mon): $\beta = 0.06, t(88) = 0.77, p = 0.45$

Week 2 (MJ-Abst vs MJ-Mon): $\beta = -0.02, t(88) = -0.18, p = 0.86$

Week 3 (MJ-Abst vs MJ-Mon): $\beta = 0.06, t(88) = 0.77, p = 0.44$

Week 4 (MJ-Abst vs MJ-Mon): $\beta = 0.06, t(88) = 0.67, p = 0.51$

Omnibus Model Effects

Time (Study Week): $F(4,88) = 0.27, p = 0.89$

Abstinence Status: $F(1,88) = 10.75, p = 0.002$

Abstinence Status X Time (Study Week): $F(3,88) = 0.38, p = 0.77$

Comparison of Slopes Between Weeks by Group

Baseline to Week 1:

MJ-Abst: $\beta = 0.26, t(88) = 5.60, p < 0.0001$

MJ-Mon: $\beta = -0.004, t(88) = -0.05, p = 0.96$

Week 1 to Week 2:

MJ-Abst: $\beta = -0.01, t(88) = -0.20, p = 0.85$

MJ-Mon: $\beta = 0.06, t(88) = 0.81, p = 0.42$

Week 2 to Week 3:

MJ-Abst: $\beta = 0.01, t(88) = 0.13, p = 0.90$

MJ-Mon: $\beta = -0.05, t(88) = -0.68, p = 0.50$

Week 3 to Week 4:

MJ-Abst: $\beta = 0.002, t(88) = 0.03, p = 0.97$

MJ-Mon: $\beta = 0.07, t(88) = 0.92, p = 0.36$

Pairwise Group Comparisons at Each Time Point

Week 1 (MJ-Abst vs MJ-Mon): $\beta = 0.26, t(88) = 3.43, p = 0.0009$

Week 2 (MJ-Abst vs MJ-Mon): $\beta = 0.19, t(88) = 2.25, p = 0.03$

Week 3 (MJ-Abst vs MJ-Mon): $\beta = 0.25, t(88) = 2.83, p = 0.006$

Week 4 (MJ-Abst vs MJ-Mon): $\beta = 0.18, t(88) = 1.86, p = 0.07$

Figure 2.

A. Attention improved similarly in MJ-Abst and MJ-Mon across the 4-week assessment period. All values represent means and standard errors. B. Memory improved only in MJ-Abst, and this improvement occurred in the first week of cannabis abstinence. All values represent means and standard errors.

Table 1.**Participant Descriptives at Baseline**

	Monitoring (MJ-Mon; n=26)	Abstinent (MJ-Abst; n=62)	p-values
Demographics			
Gender (% Male)	53.8	58.1	0.72
Age	21.2 (2.3)	20.5 (2)	0.20
Education (in years)	13.9 (2)	14.0 (1.8)	0.95
Race (%)			0.29
White	57.7	71	
Black	19.2	11.3	
Asian	3.9	3.2	
More than One Race	7.7	12.9	
Other	7.7	1.6	
Ethnicity (% Hispanic)	7.7	9.7	0.77
Cognition and Achievement			
IQ	106.0 (10.7)	107.9 (8.6)	0.36
GPA	3.1 (0.6)	3.1 (0.5)	0.91
Baseline Alcohol Use			
Past 90 Day Alcohol Use			
Days Alcohol Consumed	25.3 (20.2)	22.1 (13.8)	0.39
Drinks Consumed (Mdn [IQR])	63 [31, 152]	81.8 [48, 147]	0.48
Days Since Last Alcohol Use	3 [2, 6]	2 [2, 5]	0.50
Dependence Symptoms (AUDIT)	7.1 (5.4)	8.6 (5.9)	0.27
Baseline Cannabis Use			
Past 90 Day MJ Use			
Days MJ Consumed	57.5 (27.3)	54.4 (25.1)	0.61
Times MJ Consumed (Mdn [IQR])	107.5 [46, 157]	103 [50, 172]	0.94
Grams of MJ Consumed (Mdn [IQR])	23.8 [10.9, 57.6]	29.6 [10.1, 77.5]	0.96
Age of Initiation (% Initiated <16 years)	26.9	45.2	0.11
Days Since Last MJ Use	1 [1, 3]	1 [1, 2]	0.33
Dependence Symptoms (CUDIT)	13.1 (4.8)	14.4 (5.8)	0.32
CN-THCCOOH	104.1 [77.6, 274.5]	88.8 [29, 212.8]	0.12
Current SCID-V Diagnoses*			
Major Depression	1 (4.5)	2 (3.7)	0.88
Bipolar Disorder	0 (0)	2 (3.7)	0.36
Panic Disorder	0 (0)	2 (3.7)	0.36
Agoraphobia	0 (0)	1 (1.9)	0.52
Social Phobia	0 (0)	0 (0)	--
Specific Phobia	0 (0)	0 (0)	--
OCD	0 (0)	0 (0)	--
PTSD	1 (4.5)	2 (3.7)	0.88
Generalized Anxiety Disorder	1 (4.5)	4 (7.4)	0.64

	Monitoring (MJ-Mon; n=26)	Abstinent (MJ-Abst; n=62)	p-values
Anorexia	0 (0)	0 (0)	--
Bulimia	0 (0)	1 (1.9)	0.52
Psychosis	0 (0)	1 (1.9)	0.52

Note: All values are means, standard deviations, unless otherwise noted; AUDIT, Alcohol Use Disorders Identification Test; CN-THCCOOH, Creatinine-Adjusted 11-nor-9-carboxy-tetrahydrocannabinol in ng/mL; CUDIT, Cannabis Use Disorder Identification Test; IQR, Interquartile range; Mdn, Median; MJ, marijuana/cannabis; SCID-IV, Structured Clinical Interview for DSM-IV (*SCID-IV not administered to participants recruited in high schools; Monitoring n = 22 and Contingency Management n = 53); TLFB, 90-Day Timeline Followback.

Table 2.

Change in Tests of Memory by Abstinence Status Across 4-Week Study Period

<u>Omnibus Model Effects</u>		<u>Spatial Span</u>	<u>Delayed-Matching-To-Sample</u>	<u>Verbal Recognition Memory</u>
Time (Study Week)		$R(4,88) = 5.01, p = 0.001$	$R(4,88) = 4.54, p = 0.002$	$R(4,88) = 2.52, p = 0.047$
Abstinence Status		$R(1,88) = 2.95, p = 0.09$	$R(1,88) = 2.84, p = 0.10$	$R(1,88) = 8.65, p = 0.004$
Abstinence Status X Time		$R(3,88) = 1.74, p = 0.16$	$R(3,88) = 0.26, p = 0.85$	$R(3,88) = 0.58, p = 0.63$
<u>Comparison of Slopes Between Weeks by Group</u>				
<u>Baseline to Week 1</u>				
MJ-Abst		$\beta = 0.28, t(88) = 4.58, p < 0.0001$	$\beta = 0.31, t(88) = 4.81, p < 0.0001$	$\beta = 0.24, t(88) = 2.36, p = 0.02$
MJ-Mon		$\beta = 0.13, t(88) = 1.46, p = 0.15$	$\beta = 0.21, t(88) = 2.49, p = 0.01$	$\beta = -0.36, t(88) = -2.44, p = 0.02$
<u>Week 1 to Week 2</u>				
MJ-Abst		$\beta = 0.05, t(88) = 0.88, p = 0.38$	$\beta = 0.13, t(88) = 2.17, p = 0.03$	$\beta = -0.24, t(88) = -2.37, p = 0.02$
MJ-Mon		$\beta = 0.15, t(88) = 1.59, p = 0.12$	$\beta = 0.05, t(88) = 0.61, p = 0.55$	$\beta = -0.03, t(88) = -0.17, p = 0.87$
<u>Week 2 to Week 3</u>				
MJ-Abst		$\beta = 0.02, t(88) = 0.37, p = 0.71$	$\beta = -0.20, t(88) = -3.77, p = 0.0003$	$\beta = 0.19, t(88) = 1.53, p = 0.13$
MJ-Mon		$\beta = -0.17, t(88) = -2.07, p = 0.04$	$\beta = -0.13, t(88) = -1.67, p = 0.10$	$\beta = 0.16, t(88) = 0.82, p = 0.41$
<u>Week 3 to Week 4</u>				
MJ-Abst		$\beta = 0.08, t(88) = 1.32, p = 0.19$	$\beta = 0.10, t(88) = 1.91, p = 0.06$	$\beta = -0.16, t(88) = -1.15, p = 0.25$
MJ-Mon		$\beta = 0.25, t(88) = 3.02, p = 0.003$	$\beta = 0.11, t(88) = 1.39, p = 0.17$	$\beta = -0.16, t(88) = -0.80, p = 0.43$
<u>Pairwise Group Comparisons at Each Time Point</u>				
Week 1 (MJ-Abst vs MJ-Mon)		$\beta = 0.15, t(88) = 1.48, p = 0.14$	$\beta = 0.10, t(88) = 1.06, p = 0.29$	$\beta = 0.60, t(88) = 3.45, p = 0.0009$
Week 2 (MJ-Abst vs MJ-Mon)		$\beta = 0.05, t(88) = 0.57, p = 0.57$	$\beta = 0.17, t(88) = 1.70, p = 0.09$	$\beta = 0.38, t(88) = 1.93, p = 0.056$
Week 3 (MJ-Abst vs MJ-Mon)		$\beta = 0.25, t(88) = 2.69, p = 0.009$	$\beta = 0.11, t(88) = 1.26, p = 0.21$	$\beta = 0.42, t(88) = 1.95, p = 0.05$
Week 4 (MJ-Abst vs MJ-Mon)		$\beta = 0.07, t(88) = 0.62, p = 0.54$	$\beta = 0.10, t(88) = 1.05, p = 0.30$	$\beta = 0.42, t(88) = 1.83, p = 0.07$

Table 3.

Change in Measures of Verbal Declarative Memory By Abstinence Status Across 4-Week Study Period

	Initial Encoding	Total Encoding	Delayed Recall
Omnibus Model Effects			
Time (Study Week)	$F(4,88) = 1.13, p = 0.35$	$F(1,88) = 0.82, p = 0.51$	$F(4,88) = 5.56, p = 0.0005$
Abstinence Status	$F(1,88) = 10.00, p = 0.002$	$F(1,88) = 5.67, p = 0.02$	$F(1,88) = 2.91, p = 0.09$
Abstinence Status X Time	$F(3,88) = 0.21, p = 0.89$	$F(3,88) = 1.32, p = 0.27$	$F(3,88) = 1.49, p = 0.22$
Comparison of Slopes Between Weeks by Group			
Baseline to Week 1			
MJ-Abst	$\beta = 0.27, t(88) = 2.12, p = 0.04$	$\beta = 0.30, t(88) = 2.93, p = 0.004$	$\beta = 0.08, t(88) = 0.68, p = 0.50$
MJ-Mon	$\beta = -0.32, t(88) = 1.81, p = 0.07$	$\beta = -0.22, t(88) = -1.46, p = 0.15$	$\beta = -0.47, t(88) = -2.58, p = 0.01$
Week 1 to Week 2			
MJ-Abst	$\beta = -0.14, t(88) = -1.09, p = 0.28$	$\beta = -0.26, t(88) = -2.51, p = 0.01$	$\beta = -0.35, t(88) = -2.94, p = 0.004$
MJ-Mon	$\beta = 0.03, t(88) = 0.14, p = 0.89$	$\beta = 0.11, t(88) = 0.70, p = 0.49$	$\beta = -0.19, t(88) = -1.08, p = 0.28$
Week 2 to Week 3			
MJ-Abst	$\beta = 0.23, t(88) = 1.31, p = 0.19$	$\beta = 0.23, t(88) = 1.77, p = 0.08$	$\beta = 0.15, t(88) = 1.24, p = 0.22$
MJ-Mon	$\beta = 0.01, t(88) = 0.02, p = 0.98$	$\beta = 0.03, t(88) = 0.16, p = 0.87$	$\beta = 0.39, t(88) = 2.17, p = 0.03$
Week 3 to Week 4			
MJ-Abst	$\beta = -0.13, t(88) = -0.69, p = 0.49$	$\beta = -0.08, t(88) = -0.58, p = 0.57$	$\beta = -0.30, t(88) = -2.22, p = 0.03$
MJ-Mon	$\beta = -0.02, t(88) = -0.06, p = 0.96$	$\beta = -0.18, t(88) = -0.90, p = 0.37$	$\beta = -0.25, t(88) = -1.28, p = 0.20$
Pairwise Group Comparisons at Each Time Point			
Week 1 (MJ-Abst vs MJ-Mon)	$\beta = 0.59, t(88) = 2.95, p = 0.004$	$\beta = 0.52, t(88) = 3.06, p = 0.003$	$\beta = 0.60, t(88) = 3.45, p = 0.0009$
Week 2 (MJ-Abst vs MJ-Mon)	$\beta = 0.43, t(88) = 1.89, p = 0.06$	$\beta = 0.15, t(88) = 0.73, p = 0.47$	$[\beta = 0.38, t(88) = 1.93, p = 0.056]$
Week 3 (MJ-Abst vs MJ-Mon)	$\beta = 0.65, t(88) = 2.45, p = 0.02$	$\beta = 0.34, t(88) = 1.59, p = 0.12$	$\beta = 0.42, t(88) = 1.95, p = 0.05$
Week 4 (MJ-Abst vs MJ-Mon)	$\beta = 0.54, t(88) = 0.62, p = 0.06$	$\beta = 0.45, t(88) = 1.95, p = 0.05$	$\beta = 0.42, t(88) = 1.83, p = 0.07$