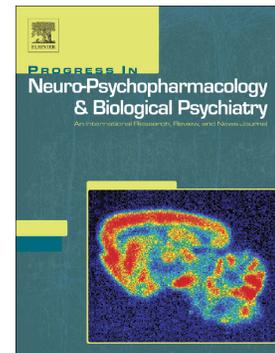


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Tetrahydrocannabinol (THC) impairs encoding but not retrieval of verbal information.

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Abstract

Introduction: Cannabis and agonists of the brain cannabinoid receptor (CB₁R) produce acute memory impairments in humans. However, the extent to which cannabinoids impair encoding and retrieval in humans has not been established. The objective of this analysis was to determine whether the administration of Δ^9 -Tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, impairs encoding and/or retrieval of verbal information.

Materials and Methods: Healthy subjects were recruited from the community. Subjects were administered the Rey-Auditory Verbal Learning Test (RAVLT) either before administration of THC (experiment #1) (n=38) or while under the influence of THC (experiment #2) (n=57). Immediate and delayed recall on the RAVLT was compared. Subjects received intravenous THC, in a placebo-controlled, double-blind, randomized manner at doses known to produce behavioral and subjective effects consistent with cannabis intoxication.

Results: Total immediate recall, short delayed recall, and long delayed recall were reduced in a statistically significant manner *only* when the RAVLT was administered to subjects while they were under the influence of THC (experiment #2) and not when the RAVLT was administered prior.

Conclusions: THC acutely interferes with encoding of verbal memory without interfering with retrieval. These data suggest that learning information prior to the use of cannabis or cannabinoids is not likely to disrupt recall of that information. Future studies will be necessary to determine whether THC impairs encoding of non-verbal information, to what extent THC impairs memory consolidation, and the role of other cannabinoids in the memory-impairing effects of cannabis.

Clinical Trial Information:

Cannabinoids, Neural Synchrony, and Information Processing (THC-Gamma)

<http://clinicaltrials.gov/ct2/show/study/NCT00708994>

NCT00708994

Pharmacogenetics of Cannabinoid Response

<http://clinicaltrials.gov/ct2/show/NCT00678730>

NCT00678730

ACCEPTED MANUSCRIPT

1. Introduction

Cannabis is the most commonly used drug used worldwide, with an estimated 183 million people having used the drug in 2014 (UNODC, 2016). In 2010, an estimated 13 million people were cannabis dependent accounting for global burden of disease of 2 million disease-adjusted life years (Degenhardt et al., 2013). The age at initiation of cannabis use has been progressively getting younger. In 2014, a total of 2.5 million persons 12 years or older in the US had used cannabis for the first time during the preceding 12 months, an average of approximately 7,000 new users each day (CBHSQ, 2015). The emerging trend of legalization of “medical” cannabis in the US, Canada, Europe and other parts of the world, for both medical and psychiatric indications (Wilkinson et al., 2016a, Wilkinson et al., 2016b), the legalization of recreational cannabis use (Bly, 2012), the earlier onset of cannabis use (Ernst et al., 2012), the increasing potency of cannabis (Mehmedic et al., 2010) and the recreational use of highly potent synthetic cannabinoid receptor agonists such as Spice and K-2 (Johnson et al., 2011, Vardakou et al., 2010), underscores the need to further understand the acute effects of these compounds.

In particular, we need to understand the acute effects of these drugs in young people who represent the overwhelming majority of cannabis users. Cannabis use is most prevalent among people aged 18 to 25 (with 19.8% using it in the past month) 7.0% of people aged 12 to 17 reported marijuana use in the past month (Johnston, 2016). Among people aged 12 or older, past month cannabis use increased from 6.2% in 2002 to 8.3% (~22.2 million people) in 2015 (CBHSQ, 2015) Importantly, a significant number of people in this demographic are likely to be in high school and college during which they have to learn new information related to their academic demands. Cannabis and cannabinoid receptor (CB1R) agonists such as tetrahydrocannabinol (THC) have been shown to acutely impair learning and

memory in humans ^{reviewed in} (Ranganathan and D'Souza, 2006). Furthermore, cannabis use during adolescence has been reported to be associated with a higher probability of dropping out from high school, university non-enrolment, and failure to obtain (Silins et al., 2015). Thus, understanding to what extent and precisely how recreational use of cannabis and cannabinoids interfere with learning and memory in this population is of significant public health importance.

The most well-studied acute cognitive effects of CB1R agonists are on declarative verbal memory (Ranganathan and D'Souza, 2006).

Verbal memory is typically measured with verbal learning tasks that require subjects to learn a supraspan list of words and recall it several times immediately and after a delay. Declarative learning and memory involves the processes of encoding, consolidation, and retrieval. These processes may not be entirely dissociable, but nevertheless remain important constructs in understanding learning and memory (Bernard et al., 2001, Nyberg et al., 2002). *Encoding* refers to the initial stage of processing during which the acquisition of information occurs. Encoding is followed by a series of changes that *consolidate* the new information in order to protect against disruption and decay. *Retrieval* refers to the access or recall of previously encoded memories. The effects of a drug on verbal learning and recall may be a consequence of the drug affecting encoding, consolidation, retrieval, or all three.

A number of laboratory studies in humans have demonstrated that THC results in an impairment in immediate- and delayed-recall among infrequent users. (Curran et al., 2002, D'Souza et al., 2004, Hart et al., 2010, Hart et al., 2001, Solowij and Battisti, 2008). The results from animal studies suggest that THC and other cannabinoid 1 (CB1R) receptor agonists disrupt memory (Goonawardena et al., 2011, Hampson and Deadwyler, 1998, Kruk-Slomka et al., 2016, Shiri et al., 2016) (Kruk-Slomka and Biala, 2016, Wise et al., 2012). . However, to what extent cannabinoids affect different memory subprocesses is still under

study. Cannabinoid agonists have been shown to disrupt encoding (Hampson and Deadwyler, 2000, Hampson et al. , 2011) and when administered post training (i.e after encoding) caused an impairment in retrieval (Mackowiak et al. , 2009, Yim et al. , 2008).

Whether THC differentially effects encoding, consolidation, or retrieval of verbal memory has however, not been studied in humans. Although not specifically related to verbal memory, a few studies have attempted to examine the effects of THC on encoding. Ballard et al. (Ballard et al. , 2013) found that administration of THC prior to encoding on an emotional memory task resulted in impairment in encoding. In another study, Bossong et al (Bossong et al. , 2012a) showed that THC disrupted encoding and recall on a pictorial memory task (Bossong, Jager, 2012a). However, the design of the studies did not make it possible to disentangle the effects on the different phases i.e. encoding, consolidation and retrieval.

The effect of a drug on encoding, consolidation, retrieval during a verbal memory task can be studied by adjusting the timing of drug administration relative to the different phases of the task: learning list, immediate recall, delayed -recall and delayed recognition recall. The accuracy of immediate-recall following, or the rate of learning during, the learning trials of the word-list is considered to be a measure of “encoding” of verbal memory. Intact immediate recall with impairments in delayed recall suggests deficits in consolidation and/or retrieval. Impairments in delayed recall with intact delayed recognition recall suggest deficits in retrieval but not consolidation.

Administering a drug before encoding but terminating its effects before retrieval would help isolate drug-induced encoding deficits. However, this is not feasible in the case of cannabinoids, given the long half-life of THC. An alternative strategy is to administer THC before and after encoding in separate experiments using the verbal learning task and then compare the effects on immediate recall, delayed recall and delayed recognition recall. There are no human studies to date, that have employed a standardized and controlled dose and

method of THC administration to determine the extent to which cannabis, THC, and other CB₁R agonists interfere with encoding, consolidation, or retrieval of verbal information.

The current study examined the effects of intravenous (i.v.) THC on verbal memory in human volunteers using a standardized drug administration method to address this gap in the literature. Because CB₁R agonists are known to impair long-term potentiation (Ievlevskiy et al.), a putative neural substrate of memory encoding and consolidation, we hypothesized that the administration of THC would impair the encoding of verbal information while sparing retrieval.

2. Materials and Methods

The study were approved by the institutional review boards at Yale University and Veterans Connecticut Healthcare System (VACHS), West Haven, CT. THC was administered with approval from the US Food and Drug Administration through an Investigational New Drug application (IND # 51,671 [D'Souza]). Informed consent was obtained from subjects prior to study participation.

2.1. Study design:

The experiments were double-blind, randomized placebo-controlled by design (figure 1). In experiment #1 subjects received THC or placebo after the learning trials of a word list (post-encoding THC condition). In experiment #2 subjects received THC or placebo before the learning trials of the word list (pre-encoding THC condition). The effects of THC induced “altered state” was measured on the item “high” on a 0-100 visual analog scale (VAS). Verbal memory was measured using the *Rey Auditory Verbal Learning Test* (RAVLT), a task

sensitive to hippocampal function that has five alternate versions (Rosenberg et al. , 1984, Ryan et al. , 1986), none of which are semantically organized.

2.2. Screening

Psychiatrically and physically healthy subjects were recruited from the local community using advertisements and word of mouth. After completing a brief phone screening, eligible healthy subjects underwent an in-person screening that included a medical history, physical exam, laboratory tests including EKG, psychiatric interview using the Structured Clinical Interview for DSM-IV Diagnoses (SCID), intelligence tests, and cannabis use history.

2.3. Inclusion and exclusion criteria:

Inclusion criteria were: (1) 18-55 years old; (2) able to provide informed consent; (3) good physical and mental health as determined by history, the Structured Clinical Interview for DSM-IV TR (SCID-NP) and collateral information, physical and laboratory examinations, and ECG and vital signs recordings; and (4) cannabis use at least once in their lifetime.

Exclusion criteria were: (1) diagnosis of DSM-5 alcohol or substance dependence (including cannabis) except nicotine dependence in the past year; (2) current or lifetime major Axis I or Axis II diagnoses; (3) positive pregnancy test; (4) recent (<6 weeks) major stressors (including problems with the primary support group, problems related to the social environment, educational problems, occupational problems, housing problems, economic problems, problems with access to health care services, and problems related to interaction with the legal system or criminal behavior); (5) history of counseling, except for a life circumstance disorder (e.g., bereavement, divorce); (6) history of any psychotropic medication use except sleep medication for > 1 month; (7) major Axis I diagnosis in first degree relative (assessed through subject's self-report); (8) IQ less than 80; (9) less than high

school education; and (10) positive urine toxicology (other than cannabis) on test day mornings.

A collateral informant identified by the subject was contacted to corroborate the subject's psychiatric and medical history. Subjects were instructed to refrain from using illicit drugs (except cannabis) for two weeks, consuming caffeinated beverages and alcohol for 1 week, and to refrain from cannabis use for a minimum of 24 hours prior to each test day until study completion. The subjects recruited were not regular cannabis users (i.e. were not daily users) to avoid the possibility that a subject would be experiencing symptoms of withdrawal prior to a THC challenge. Frequency of cannabis use was measured at screening by self-report of number of days used in the past 30 days.

2.4. Study medication:

Subjects received THC or placebo (in ethanol vehicle) infused over 15 minutes into a rapidly flowing normal saline infusion.

2.4.1. Justification of THC dose and route of administration:

The i.v. route of administration was chosen to reduce inter- and intra-individual variability in plasma THC levels observed with the inhaled route and to mimic the time course of plasma THC levels associated with the "high" as discussed in (D'Souza, Perry, 2004). Even with standardized paced smoking procedures, subjects are able to titrate the dose of cannabinoids they receive and in doing so, negate attempts to deliver a uniform dose (Ilan et al. , 2005). The choice of THC rather than cannabis is to address the confounding effects of other cannabinoids, and flavonoids present in cannabis.

Subjects received THC (0.03 mg/kg in experiment #1- 0.05mg/kg in experiment #2) or placebo, given intravenously into a rapidly flowing i.v. infusion of normal saline. The

formulation of THC and placebo were as described previously in (D'Souza, Perry, 2004). This dose range been shown in previous studies at our center to produce behavioral, subjective, cognitive and physiological effects consistent with the effects of cannabis (D'Souza et al. , 2005, D'Souza et al. , 2012, D'Souza, Perry, 2004). THC induced “altered state” was measured as “high” on a VAS for subjective effects in both experiments and are reported below (figure 3). Expectancy effects were minimized as described elsewhere, by informing subjects that they may receive one of many possible doses on each test day (D'Souza, Fridberg, 2012).

2.5. Test Days

Subjects reported to the test facility at 8 am after an overnight fast. Negative urine toxicology and pregnancy tests were confirmed on each test morning. They were provided a standardized breakfast, after which i.v. lines were inserted. Baseline ratings were completed followed by the THC or placebo infusion. Subjects completed two test days over a two- to three-week period, separated by at least 72 hours in order to limit residual effects of THC.

2.6. Details of RAVLT administration and Measures

The RAVLT was administered following a standardized method. First, a list of 15 words (list A) was read aloud to subjects five times. At the end of each reading (trial), subjects were asked to recall as many words as they could (trials 1-5). After five trials of list A, a second list of 15 words (list B: interference list) was read to the subjects and they were then asked to recall words from this list, (interference; trial 6). Following this, subjects were asked to recall words they had learned from List A without cues (short delayed recall; trial 7). Finally, after 30 min, subjects were asked to again recall words from list A without cues (long delayed recall; trial 8). The following outcomes were assessed:

1. Total Immediate Recall (the sum of total words correctly recalled in trials 1 to 5).
2. Rate of Learning (increase in recall across learning trials: trial 5 minus trial 1).
3. Short Delayed Recall (trial 7) 5 minutes after trial 5.
4. Long Delayed Recall (trial 8) 30 minutes after trial 5

Alternate versions of the RAVLT were administered on each test day and counterbalanced across subjects in order to avoid practice effects. The test-day administration of the RAVLT relative to THC infusion is depicted in Figure 1.

Experiment #1: All five trials of list A, list B recall, and short delayed recall (trials 1 to 7) trials of the RAVLT were administered 35 minutes *before* infusion of THC. The long delayed recall (trial 8) was administered two hours *after* THC infusion.

Experiment #2: All five trials of list A, list B recall, and short delayed recall (trials 1 to 7) trials of the RAVLT were administered 25 minutes *after* infusion of THC. The long delayed recall (trial 8) was administered 95 min after short delayed recall trials, in order to standardize the experiments such that, in both experiments, delayed recall was tested two hours (120 minutes) after the start of THC infusion.

Measurement of “high” on the visual analog scale (VAS): The VAS was administered at -120, -30, +15, +60, +300 minutes. The peak change was taken as the highest value at any time point.

2.7.Data Analysis

Initially, data were examined descriptively using means, standard deviations, and graphs. Based on examination of normal probability and residual plots and Kolmogorov-Smirnov test statistics, each outcome appeared sufficiently normal for parametric analyses. Outcomes were assessed using linear mixed models with drug (active vs. placebo) included as a within-

subject factor and experiment (#1 vs. #2) as a between-subjects factor. The best-fitting variance-covariance structure was selected based on information criteria. Post-hoc tests were performed to determine the nature of any significant study by THC dose interaction effect by constructing linear contrasts where THC effects were tested within each study. Contrasts were constructed using the CONTRAST statement in SAS PROC MIXED and tested with F-tests. In the above models, age, gender, education, IQ, and cannabis use in the past 30 days were considered as covariates but did not change results and dropped for parsimony. Order effects were tested; none were present. All tests were two-sided and considered significant at the $\alpha=0.05$ threshold. All analyses were conducted using SAS, version 9.3 (Cary,NC).

3. Results

3.1. Subject characteristics:

A total of 38 subjects participated in experiment #1 (i.e. THC administered after encoding) and 57 in experiment #2 (i.e. THC administered before encoding). Additionally, 16 subjects who participated in experiment #1 also participated in experiment #2. There were no significant differences between experiment #1 and #2 on demographic variables (Table 1).

3.2. Performance on RRAVLT:

Immediate Recall [sum of trials 1 to 5] (Figure 2A)

In experiment #1, subjects recalled 59.17 ± 10.08 words on the THC condition and 59.40 ± 9.41 words on the placebo condition ($p=0.99$). In experiment #2, subjects recalled 44.86 ± 13.09 words on the THC condition and 55.50 ± 9.64 words on the placebo condition ($p < 0.0001$). There were significant main effects of drug [$F(1,93) = 26.5, p < 0.0001$] and experiment [$F(1,93) = 17.8, p < 0.0001$], and a significant drug x experiment interactive effect [$F(1,113)$

= 26.7, $p < 0.0001$]. *Post hoc* analyses revealed that immediate recall was impaired by THC condition only in experiment #2 ($p < 0.0001$), but not in experiment #1 ($p = 0.99$) (Table 2).

Rate of Learning [trial 5 minus 1] (Figure 2B)

In experiment #1, the learning rate was 6.03 ± 2.08 word/trial on the THC condition and 5.37 ± 1.77 word/trial on the placebo condition ($p = 0.18$). In experiment #2 the learning rate was 5.91 ± 2.88 word/trial on the THC condition and 5.52 ± 1.85 word/trial on the placebo condition ($p = 0.31$). There were no significant main effects of drug [$F(1,93) = 2.8$, $p = 0.09$] or experiment [$F(1,93) = 0$, $p = 0.9$], or significant drug x experiment interactive effects [$F(1,93) = 0.1$, $p = 0.68$], indicating that THC did not affect the rate of learning across the five trials (Tables 2).

Short Delayed Recall [trial 7] (Figure 2C)

In experiment #1, on the short delayed recall, subjects recalled 13.14 ± 2.24 words on the THC condition and 12.80 ± 2.62 words on the placebo condition ($p = 0.54$). In experiment #2, subjects recalled 9.33 ± 4.22 words on the THC condition and 11.69 ± 2.72 words on the placebo condition ($p < 0.0001$). There were significant main effects of drug [$F(1,93) = 10.1$, $p = 0.001$] and experiment [$F(1,93) = 16.53$, $p < 0.0001$], and a significant drug x experiment interaction effect [$F(1,93) = 17.19$, $p < 0.0001$]. *Post hoc* analyses revealed that short delayed recall was impaired by THC only in experiment #2 (< 0.0001).

Long Delayed Recall [trial 8] (Figure 2D)

In experiment #1, on the long delayed recall, subjects recalled 10.79 ± 3.61 words on the THC condition and 11.00 ± 3.79 words on the placebo condition ($p = 0.67$). In experiment #2, subjects recalled 9.04 ± 4.29 words on the THC condition and 11.45 ± 2.90 words on the

placebo condition ($p < 0.0001$). There was no significant main effect of experiment [$F(1,92) = 1, p = 0.32$] observed. However, there was a significant main effect of drug [$F(1,92) = 13.9, p = 0.0003$] and a significant drug x experiment interactive effect [$F(1,92) = 9.32, p = 0.003$]. *Post hoc* analyses revealed that long delayed recall was impaired by THC only in experiment #2 (< 0.0001).

3.3. Subjective effects (Figure 3):

Both experiments produced similar THC induced subjective effects as measured by “high” on the VAS. The VAS “high” mean \pm SD were 61.21 ± 28.64 with THC vs 9.97 ± 21.05 with placebo in experiment #1; and 58.44 ± 28.37 with THC vs 8.58 ± 15.34 with placebo in experiment #2. As expected there was a significant effect of dose (active THC versus placebo) [$F(1,92) = 204.9, p < 0.0001$] indicating that THC produces an altered state compared to placebo. There were no significant main effects of experiment [$F(1,92) = 0.86, p = 0.35$] on peak change from baseline on VAS “high” and no experiment X drug interaction [$F(1,92) = 0.04, p = 0.83$].

3.4. Subgroup analyses:

To eliminate the possibility that the differences in learning and memory could have been related to differences in characteristics of the samples, we reanalyzed the data collected in 16 subjects who participated in both experiments. The findings persist that recall was impaired only in experiment #2 when the RAVLT was administered to subjects under the influence of THC.

4. Discussion

These experiments may be amongst the first attempts in humans to investigate the effects of i.v. THC on encoding, consolidation and retrieval of verbal memory. Both the immediate and delayed recall of verbal information that was presented prior to the administration of THC (i.e., encoding prior to THC administration) were unimpaired, even when delayed recall occurred under the influence of THC (long delayed recall in experiment #1). However, when verbal information was presented under the influence of THC (i.e., encoding after THC administration), immediate and delayed recall were impaired. These results support the hypothesis that THC specifically impairs encoding but not retrieval of verbal information.

The dose range of THC used in these experiments have been shown in previous studies at our center to impair performance on verbal memory tasks when administered prior to the encoding of information (D'Souza, Abi-Saab, 2005, D'Souza, Fridberg, 2012, D'Souza, Perry, 2004). Furthermore, the dose range also produces subjective and other effects consistent with the known effects of cannabis. Thus the relative lack of effects of THC on recall cannot be explained by dose, but rather by the timing of administration in relation to encoding.

Of note, the impairments in immediate as well as delayed recall in experiment #2 were statistically as well as clinically significant. Using a criterion of > 1 SD below the mean (Solowij, 1998), 47.8% of subjects in experiment #2 showed clinically significant THC-induced impairments on total immediate recall and 39.1% showed impairments on long delayed recall. This compares to 14.3% of subjects in experiment #1 who scored > 1 SD below the mean on immediate and 14.7% on delayed recall. Using this approach, a greater proportion of subjects in experiment #2 showed clinically significant impairments.

Previous studies on the effects of CB₁R agonists on memory in humans have used THC or cannabis. These studies had designs that did not permit differentiating effects of

cannabinoids on encoding and retrieval. The results of the current study provide evidence that THC impairs encoding but not retrieval of verbal information. These results are consistent with preclinical studies demonstrating that hippocampal firing during encoding is impaired both by THC and by the synthetic CB₁R agonist WIN 55,212-2 during a delayed non-match-to-sample task (Hampson and Deadwyler, 1999), such that rats fail to learn under the influence of CB₁R agonists. Two human neuroimaging studies have examined the effects of THC on brain activation during an associative memory task (Bhattacharyya et al., 2009a, Bossong et al., 2012b). In both studies, THC *selectively reduced brain activation during encoding* of pictures, supporting impaired brain activity during encoding associated with THC despite the fact that neither of the studies detected any impairment in performance when THC was present.

Our findings should be interpreted in the context of neurobiological processes involved in encoding, consolidation and retrieval of verbal memory. Brain regions involved in verbal memory encoding include medial temporal lobe (MTL) structures such as hippocampus (specifically, the posterior hippocampus (Fernandez et al., 1998)); and prefrontal cortex (PFC) (specifically, the ventrolateral PFC (involved in selecting and maintaining incoming information) and dorsolateral PFC (involved in organizing and forming associations between items during encoding)) (Blumenfeld and Ranganath, 2007, Kim, 2011, Spaniol et al., 2009, Wagner et al., 2016). Brain regions involved in retrieval include left superior parietal and dorsolateral and anterior PFC regions (Kim, 2011, Spaniol, Davidson, 2009). Of note, the hippocampus is less involved in retrieval, than in encoding (Spaniol, Davidson, 2009). Phase synchronization of neural oscillations in the theta and gamma frequency is known to play an important role in encoding and retrieval (Babiloni et al., 2009, Shaikhouni et al., 2016, Watrous et al., 2013).

An integrative model of memory encoding, storage and retrieval of declarative information posits that encoding is primarily dependent on the hippocampus, related MTL structures, and PFC. Information is subsequently sparsely distributed to non-hippocampal sites such as the PFC and parietal cortex where different aspects of the memory is stored. This is accomplished through phase synchronization in reverberating neural circuits involving hippocampus and PFC, parietal regions (Daumas et al. , 2005, Watrous, Tandon, 2013). As consolidation of memory in extra-hippocampal sites, the hippocampal memory decays, but retains a “memory-trace” that can be activated during retrieval (Kandel et al. , 2014, Nadel and Bohbot, 2001, Ryan et al. , 2010) . Consistent with this model, a functional imaging study that examined the effects of oral THC on memory on a paired association learning task, found that THC (Bhattacharyya et al. , 2009b) impaired MTL function during encoding, and disrupted left dorsoanterior cingulate and medial PFC function during recall (Bhattacharyya, Fusar-Poli, 2009b). Another functional imaging study that used a pictorial memory task, noted similar disrupted right MTL and inferior frontal activity during encoding, and increase in activation in bilateral precuneus and cuneus during recall (Bossong, Jager, 2012a). These two studies however did not show impairment on test-performance on memory tasks. So it is unclear if similar findings are seen when there is significant impairment in encoding or retrieval of verbal memory.

Animal studies suggest that the impairment in encoding may be related to THC interference with the endocannabinoid-mediated modulation of synaptic neurotransmission and long term depression, which is critical for learning and memory (Heifets and Castillo). An additional mechanism is suggested by the critical role of, the endocannabinoid system to the formation of long-term potentiation in the lateral perforant path (LPP), one of two cortical inputs to the hippocampus, that is also implicated in the formation of episodic memory in humans (Reagh and Yassa, 2014, Wang et al. , 2016)

CB1 receptors are expressed in high density in the hippocampus, PFC and parietal regions (Eggan and Lewis, 2007). In the hippocampus, CB1 receptors are predominantly located on GABAergic interneurons and on glutamatergic axon terminals (Kruk-Slomka, Dzik, 2016) THC has also been shown to disrupt phase synchronization of theta (Stone et al., 2012) and gamma oscillations (Cortes-Briones et al., 2015), Given this, it is likely that THC impairs encoding through actions in the left PFC and hippocampus, areas that are known to be rich in CB₁ receptors (Mackie, 2005) and caused by abnormal neural synchrony. An additional consideration is the difference between effects of THC from that of endocannabinoids (eCBs). eCBs are produced on demand, actions typically in response to neurotransmitter release, and after producing effects, are quickly inactivated via a retrograde mechanism. In contrast, THC an exocannabinoid, unlike eCBs, is not inactivated immediately and its effects are non-physiological.

4.1.Strengths and Limitations

Strengths of this study include the design (randomized, double-blind, and placebo-controlled), the standardized delivery of THC, the use of alternative and equivalent versions of the RAVLT in order to avoid practice effects, the inclusion of similar groups, characterization and inclusion of potential confounding variables in the analyses, and the large sample size. Measurement of recent cannabis exposure (over the last 30 days) permitted controlling for tolerance to the effects of THC.

Several limitations need to be considered. The between subject design is not a powerful as a within subject design. However, in the 16 subjects who participated in both experiments i.e., within subjects, the findings prevailed. There were differences in the timing of some of the tasks. The differences in testing delayed recall across experiments was

necessitated by a need to minimize confounding due to THC's effects on attention and other psychotomimetic effects. If the same time period was kept between learning and delayed recall across the two studies, delayed recall in experiment #1 would have been measured at the peak of THC's effects on attention and psychotomimesis, while in experiment #2 delayed recall would be tested well after the acute effects of THC had worn off. That is, subjects had to retain information and recall for a longer period of time (155 minutes) in experiment #1 in contrast to 95 minutes in experiment #2 would predict worse performance in experiment #1 unlike what we observed. While the used across experiments were similar, they were not identical. It should be noted that at a dose of 0.028 mg/kg (D'Souza et al. , 2008), a dose lower than the one used in experiment #1 (0.03 mg/kg), THC produced robust effects on immediate and delayed recall. Thus, in that study (D'Souza, Braley, 2008), learning occurred under the influence of THC in contrast to experiment #1. That a similar dose of THC produced robust impairments suggest that the lack of impairments in experiment #1 is likely a result of the timing of learning in relation to THC. Plasma THC levels were not measured in this study. However, that in both experiments VAS "high" scores were similar suggest that the level of exposure (dose) was similar across studies. Some subjects studied had been exposed to cannabis in the past 30 days. Thus, one cannot completely rule out the possibility that residual effects of cannabis use influenced memory performance. However, this is unlikely to explain the effects of THC on memory encoding since there were no group differences in cannabis exposure between the two experiments. Measurement of other types of memory (e.g. visual, spatial, emotional) would have further strengthened our results.

5. Conclusions, implications and future directions

THC impairs recall of information encoded during drug effects. These results suggest people should avoid learning new information under the influence of CB₁R agonists. This is

especially relevant to high school and college-age students who have to learn new information related to their academic demands. Young adults consistently have a higher prevalence of cannabis use than other age groups and represent the overwhelming majority of the cannabis-using population (CBHSQ, 2015, Ernst, Kruger, 2012). For example, in the Monitoring the Future survey, 19.8% of young adults aged 18-25 years and 7.0% of adolescents aged 12-17 years reported cannabis use in the past month (Johnston, 2016). Deficits in learning related to cannabinoids may contribute to the reported reductions in academic performance (Silins, Fergusson, 2015).

Future studies should include ecologically valid measures of learning new information. Some evidence suggests a correlation between chronic use of cannabis and poor academic performance (Fergusson et al. , 2003, Macleod et al. , 2004, Windle and Wiesner, 2004) and also intelligence quotient (Meier et al. , 2012). However, whether the effects of cannabis on academic performance are related to THC-induced deficits in the encoding of verbal information needs to be further studied. Future studies should also be designed to examine the dose related effects of THC on the encoding of non-verbal information and to determine the effects of THC on the consolidation of memory.

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References

- Babiloni C, Vecchio F, Mirabella G, Buttiglione M, Sebastiano F, Picardi A, et al. Hippocampal, amygdala, and neocortical synchronization of theta rhythms is related to an immediate recall during rey auditory verbal learning test. *Hum Brain Mapp.* 2009;30:2077-89.
- Ballard ME, Gallo DA, de Wit H. Pre-encoding administration of amphetamine or THC preferentially modulates emotional memory in humans. *Psychopharmacology (Berl).* 2013;226:515-29.
- Bernard F, Desgranges B, Platel H, Baron JC, Eustache F. Contributions of frontal and medial temporal regions to verbal episodic memory: a PET study. *Neuroreport.* 2001;12:1737-41.
- Bhattacharyya S, Crippa JA, Martin-Santos R, Winton-Brown T, Fusar-Poli P. Imaging the neural effects of cannabinoids: current status and future opportunities for psychopharmacology. *Curr Pharm Des.* 2009a;15:2603-14.
- Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, et al. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. *Arch Gen Psychiatry.* 2009b;66:442-51.
- Blumenfeld RS, Ranganath C. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist.* 2007;13:280-91.
- Bly LS. Colorado, Washington OK recreational marijuana use. *USA Today*2012.
- Bosson MG, Jager G, van Hell HH, Zuurman L, Jansma JM, Mehta MA, et al. Effects of Delta9-tetrahydrocannabinol administration on human encoding and recall memory function: a pharmacological fMRI study. *J Cogn Neurosci.* 2012a;24:588-99.
- Bosson MG, Jager G, van Hell HH, Zuurman L, Jansma JM, Mehta MA, et al. Effects of Delta9-tetrahydrocannabinol administration on human encoding and recall memory function: a pharmacological fMRI study. *J Cogn Neurosci.* 2012b;24:588-99.
- CBHSQ. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. In: Administration SAaMHS, editor. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015.
- Cortes-Briones J, Skosnik PD, Mathalon D, Cahill J, Pittman B, Williams A, et al. Delta9-THC Disrupts Gamma (gamma)-Band Neural Oscillations in Humans. *Neuropsychopharmacology.* 2015;40:2124-34.
- Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl).* 2002;164:61-70.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry*. 2005;57:594-608.

D'Souza DC, Braley G, Blaise R, Vendetti M, Oliver S, Pittman B, et al. Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Delta-9-tetrahydrocannabinol in humans. *Psychopharmacology (Berl)*. 2008;198:587-603.

D'Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, et al. Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Delta(9)-THC in humans. *Neuropsychopharmacology*. 2012;37:1632-46.

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29:1558-72.

Daumas S, Halley H, Frances B, Lassalle JM. Encoding, consolidation, and retrieval of contextual memory: differential involvement of dorsal CA3 and CA1 hippocampal subregions. *Learn Mem*. 2005;12:375-82.

Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J, et al. The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. *PLoS One*. 2013;8:e76635.

Eggan SM, Lewis DA. Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. *Cereb Cortex*. 2007;17:175-91.

Ernst L, Kruger K, Lindigkeit R, Schiebel HM, Beuerle T. Synthetic cannabinoids in "spice-like" herbal blends: First appearance of JWH-307 and recurrence of JWH-018 on the German market. *Forensic science international*. 2012;222:216-22.

Fergusson DM, Horwood LJ, Beutrais AL. Cannabis and educational achievement. *Addiction*. 2003;98:1681-92.

Fernandez G, Weyerts H, Schrader-Bolsche M, Tendolkar I, Smid HG, Tempelmann C, et al. Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. *J Neurosci*. 1998;18:1841-7.

Goonawardena AV, Sesay J, Sexton CA, Riedel G, Hampson RE. Pharmacological elevation of anandamide impairs short-term memory by altering the neurophysiology in the hippocampus. *Neuropharmacology*. 2011;61:1016-25.

Hampson RE, Deadwyler SA. Role of cannabinoid receptors in memory storage. *Neurobiol Dis*. 1998;5:474-82.

Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci*. 1999;65:715-23.

Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. *J Neurosci*. 2000;20:8932-42.

- Hampson RE, Sweatt AJ, Goonawardena AV, Song D, Chan RH, Marmarelis VZ, et al. Memory encoding in hippocampal ensembles is negatively influenced by cannabinoid CB1 receptors. *Behav Pharmacol.* 2011;22:335-46.
- Hart CL, Ilan AB, Gevins A, Gunderson EW, Role K, Colley J, et al. Neurophysiological and cognitive effects of smoked marijuana in frequent users. *Pharmacol Biochem Behav.* 2010;96:333-41.
- Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology.* 2001;25:757-65.
- Heifets BD, Castillo PE. Endocannabinoid signaling and long-term synaptic plasticity. *Annual review of physiology.* 2009;71:283-306.
- Ievglevskiy O, Palygin O, Kondratskaya E, Grebenyuk S, Krishtal O. Modulation of ATP-induced LTP by cannabinoid receptors in rat hippocampus. *Purinergic signalling.* 2012;8:705-13.
- Ilan AB, Gevins A, Coleman M, Elsohly MA, de Wit H. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behav Pharmacol.* 2005;16:487-96.
- Johnson LA, Johnson RL, Alfonzo C. Spice: a legal marijuana equivalent. *Military medicine.* 2011;176:718-20.
- Johnston LD, O'Malley, P. M., Miech, R. A., Bachman, J. G., & Schulenberg, J. E. Monitoring the Future national survey results on drug use, 1975-2015: Overview, key findings on adolescent drug use. In: Institute for Social Research TUoM, editor. *Ann Arbor* 2016.
- Kandel ER, Dudai Y, Mayford MR. The molecular and systems biology of memory. *Cell.* 2014;157:163-86.
- Kim H. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuroimage.* 2011;54:2446-61.
- Kruk-Slomka M, Biala G. CB1 receptors in the formation of the different phases of memory-related processes in the inhibitory avoidance test in mice. *Behav Brain Res.* 2016;301:84-95.
- Kruk-Slomka M, Dzik A, Budzynska B, Biala G. Endocannabinoid System: the Direct and Indirect Involvement in the Memory and Learning Processes-a Short Review. *Mol Neurobiol.* 2016.
- Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handbook of experimental pharmacology.* 2005:299-325.
- Mackowiak M, Chocyk A, Dudys D, Wedzony K. Activation of CB1 cannabinoid receptors impairs memory consolidation and hippocampal polysialylated neural cell adhesion molecule expression in contextual fear conditioning. *Neuroscience.* 2009;158:1708-16.

Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet*. 2004;363:1579-88.

Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, et al. Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *J Forensic Sci*. 2010;55:1209-17.

Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012;109:E2657-64.

Nadel L, Bohbot V. Consolidation of memory. *Hippocampus*. 2001;11:56-60.

Nyberg L, Forkstam C, Petersson KM, Cabeza R, Ingvar M. Brain imaging of human memory systems: between-systems similarities and within-system differences. *Brain research Cognitive brain research*. 2002;13:281-92.

Ranganathan M, D'Souza D. The Acute Effects of Cannabinoids on Memory in Humans: A review. *Psychopharmacology*. 2006.

Reagh ZM, Yassa MA. Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. *Proc Natl Acad Sci U S A*. 2014;111:E4264-73.

Rosenberg SJ, Ryan JJ, Prifitera A. Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. *Journal of Clinical Psychology*. 1984;40:785-7.

Ryan JJ, Geisser ME, Randall DM, Georgemiller RJ. Alternate form reliability and equivalency of the Rey Auditory Verbal Learning Test. *Journal of Clinical & Experimental Neuropsychology*. 1986;8:611-6.

Ryan L, Lin CY, Ketcham K, Nadel L. The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus*. 2010;20:11-8.

Shaikhouni A, Yaffe R, Inati S, Zaghoul KA. 211 Cortical Oscillations During Memory Encoding Are Reinstated on a Faster Time Scale During Memory Recall. *Neurosurgery*. 2016;63 Suppl 1:182-3.

Shiri M, Komaki A, Oryan S, Taheri M, Komaki H, Etaee F. Effects of cannabinoid and vanilloid receptor agonists and their interaction on learning and memory in rats. *Can J Physiol Pharmacol*. 2016:1-6.

Silins E, Fergusson DM, Patton GC, Horwood LJ, Olsson CA, Hutchinson DM, et al. Adolescent substance use and educational attainment: An integrative data analysis comparing cannabis and alcohol from three Australasian cohorts. *Drug Alcohol Depend*. 2015;156:90-6.

Solowij N. *Cannabis and Cognitive Functioning*. Cambridge: Cambridge University Press; 1998.

Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev*. 2008;1:81-98.

Spaniol J, Davidson PS, Kim AS, Han H, Moscovitch M, Grady CL. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia*. 2009;47:1765-79.

Stone JM, Morrison PD, Brugger S, Nottage J, Bhattacharyya S, Sumich A, et al. Communication breakdown: delta-9 tetrahydrocannabinol effects on pre-speech neural coherence. *Mol Psychiatry*. 2012;17:568-9.

UNODC. World Drug Report 2016. United Nations publication; 2016.

Vardakou I, Pistos C, Spiliopoulou C. Spice drugs as a new trend: mode of action, identification and legislation. *Toxicol Lett*. 2010;197:157-62.

Wagner IC, van Buuren M, Bovy L, Fernandez G. Parallel Engagement of Regions Associated with Encoding and Later Retrieval Forms Durable Memories. *J Neurosci*. 2016;36:7985-95.

Wang W, Trieu BH, Palmer LC, Jia Y, Pham DT, Jung KM, et al. A Primary Cortical Input to Hippocampus Expresses a Pathway-Specific and Endocannabinoid-Dependent Form of Long-Term Potentiation. *eNeuro*. 2016;3.

Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD. Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. *Nat Neurosci*. 2013;16:349-56.

Wilkinson ST, Radhakrishnan R, D'Souza DC. A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. *J Clin Psychiatry*. 2016a;77:1050-64.

Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana Legalization: Impact on Physicians and Public Health. *Annu Rev Med*. 2016b;67:453-66.

Windle M, Wiesner M. Trajectories of marijuana use from adolescence to young adulthood: predictors and outcomes. *Dev Psychopathol*. 2004;16:1007-27.

Wise LE, Long KA, Abdullah RA, Long JZ, Cravatt BF, Lichtman AH. Dual fatty acid amide hydrolase and monoacylglycerol lipase blockade produces THC-like Morris water maze deficits in mice. *ACS Chem Neurosci*. 2012;3:369-78.

Yim TT, Hong NS, Ejaredar M, McKenna JE, McDonald RJ. Post-training CB1 cannabinoid receptor agonist activation disrupts long-term consolidation of spatial memories in the hippocampus. *Neuroscience*. 2008;151:929-36.

Figure Caption

Figure 1: Experimental Design

Figure represents the designs of Experiment #1 (top panel) and Experiment #2 (bottom panel).

In Experiment #1 immediate recall was assessed prior to THC/placebo administration and long delayed free recall was assessed after THC/placebo administration.

In Experiment #2 immediate as well as delayed recall were assessed only after THC/placebo administration.

Figure 2: Effects of THC and Experiment on Learning

Effects of THC and Experiment on Rey-Auditory Verbal Learning Test outcomes:

A) Total immediate Recall, B) Learning Curves, C) Short Delayed Recall and D) Long Delayed Recall.

Error bars represent standard error.

Figure 3: Effect of THC and Experiment on “High”

Effects of THC and Experiment on Self-reported “High” measured by a Visual Analog Scale (0-100).

Figure 1

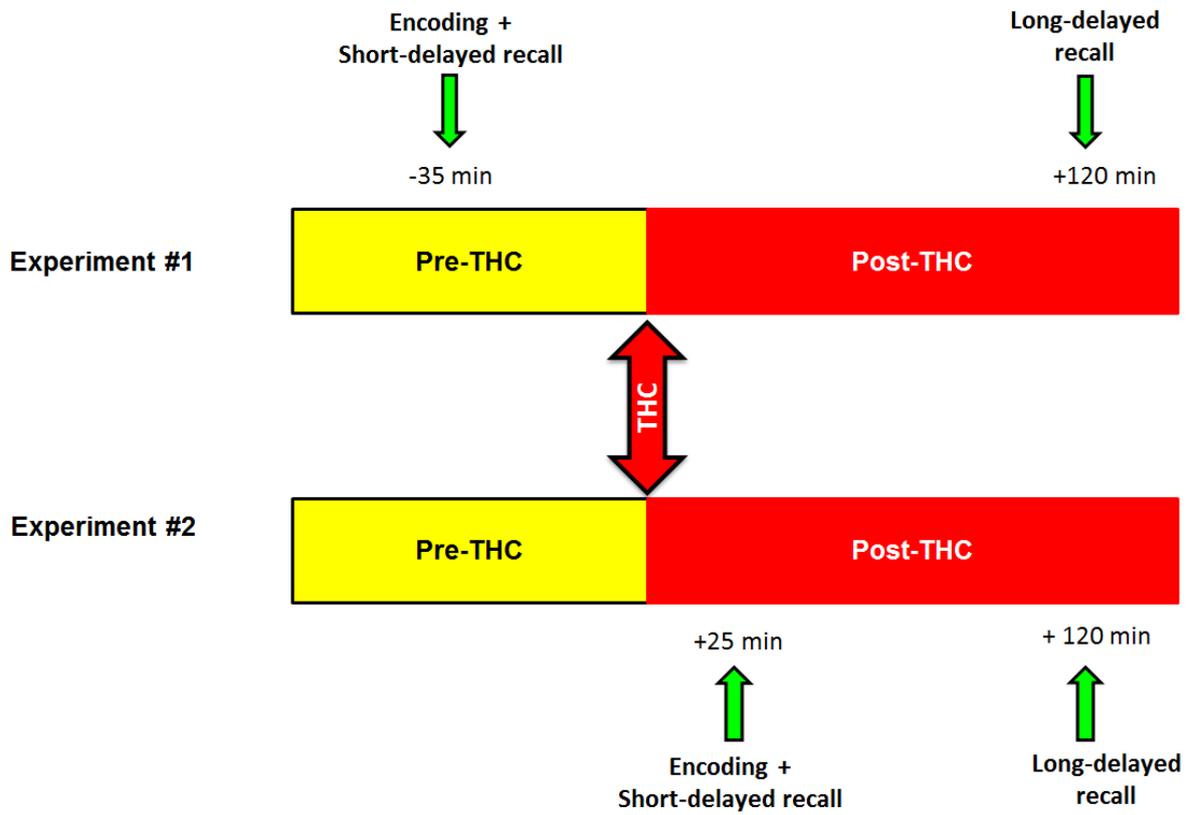


Figure 2

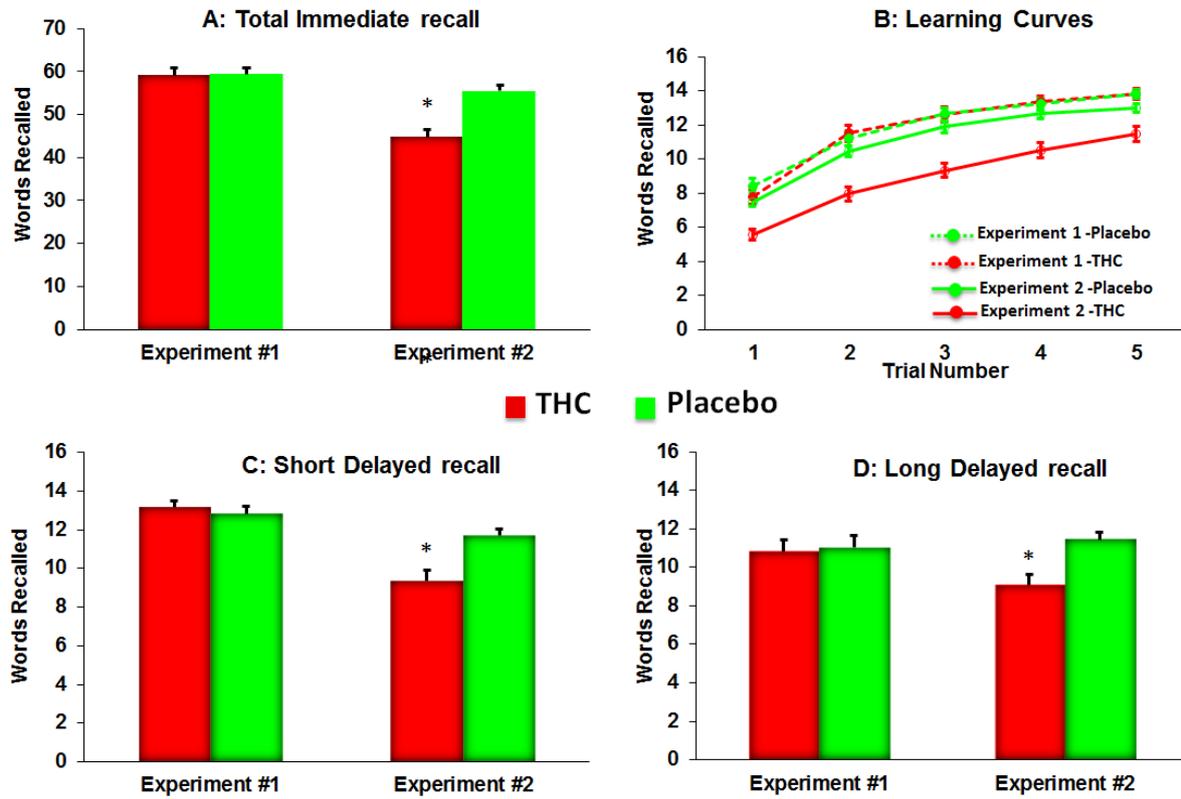
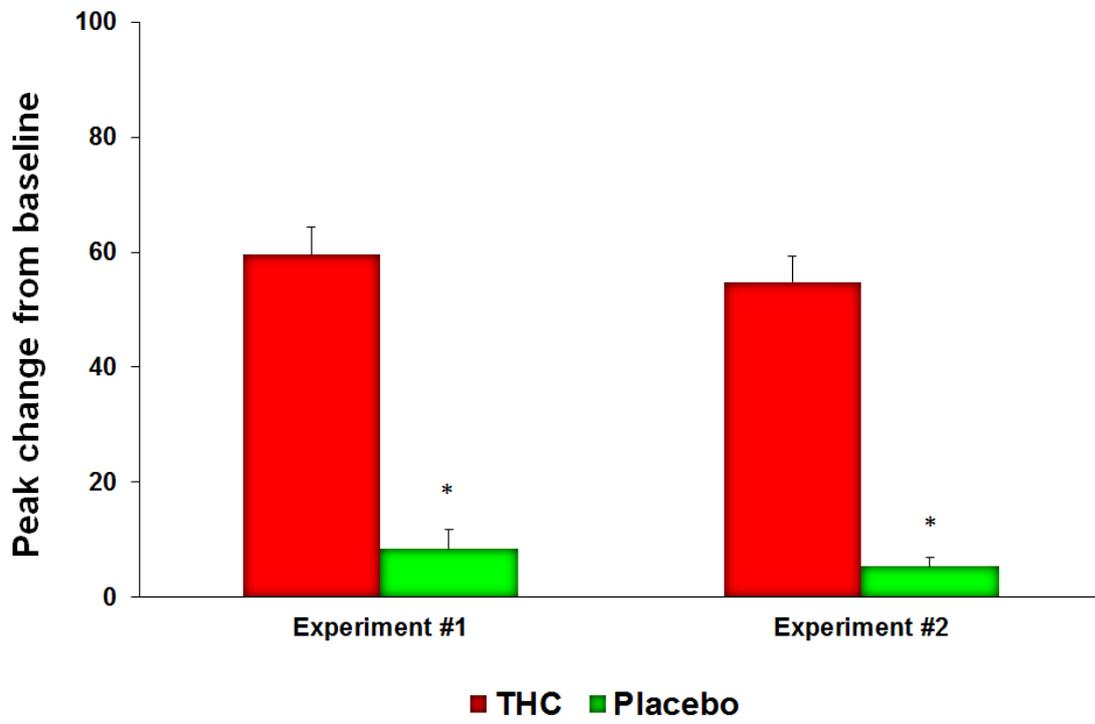


Figure 3



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Table 1: Subject Characteristics

	Experiment #1 Mean (SD)	Experiment #2 Mean (SD)	p-value
Age	25.7 (7.6)	24.8 (7.9)	0.61
IQ	115.5 (4.72)	115.9 (5.6)	0.67
Education (yrs)	15.2 (2.2)	14.7 (1.9)	0.29
Gender (%)			
Female	34.2	24.6	0.28
Male	65.8	75.4	
Cannabis Use in Past 30 Days:			
# of days	N (%)	N (%)	0.33
0	7 (18.4)	24 (42.1)	
1-3	5 (13.2)	12 (21.1)	
4-8	5 (13.2)	6 (10.5)	
9-15	6 (15.8)	8 (14)	
15-29	2 (5.3)	1 (1.8)	
Missing	13 (34.2)	6 (10.5)	
** $\chi^2(4)=0.3$			

Table 2: AVLT Scores

	THC Mean (SD)	Placebo Mean (SD)	P value
Experiment #1 (post-encoding THC condition)			
Total Immediate Recall	59.17 (10.08)	59.40 (9.41)	0.99
Short Delayed Recall (trial 7)	13.14 (2.24)	12.80 (2.62)	0.54
Long Delayed Recall (trial 8)	10.79 (3.61)	11.00 (3.79)	0.67
Rate of Learning (trial 5-1)	6.03 (2.08)	5.37 (1.77)	0.18
Experiment #2 (pre-encoding THC condition)			
Total Immediate Recall	44.86 (13.09)	55.50 (9.64)	<0.0001
Short Delayed Recall (trial 7)	9.33 (4.22)	11.69 (2.72)	<0.0001
Long Delayed Recall (trial 8)	9.04 (4.29)	11.45 (2.90)	<0.0001
Rate of Learning (trial 5-1)	5.91 (2.88)	5.52 (1.85)	0.31
AVLT: Rey Auditory Verbal Learning Test; THC: Delta-9-tetrahydrocannabinol			

Ethics statement

The authors declare that the manuscript is based on original research that has not been published. The research was approved by institutional ethics review board and all participants provided informed consent.

ACCEPTED MANUSCRIPT

Highlights

- The study examined the effects of intravenous delta-9 tetrahydrocannabinol (THC) on encoding and retrieval of verbal memory in a double-blind, placebo-controlled study design.
- When THC was administered following encoding of verbal information, delayed recall was not impaired.
- When encoding occurred in the presence of THC, delayed recall was impaired.
- Therefore, THC acutely interferes with encoding of verbal memory without interfering with retrieval.