Published in final edited form as:

Psychopharmacology (Berl). 2013 April ; 226(3): 515–529. doi:10.1007/s00213-012-2924-5.

Pre-encoding administration of amphetamine or THC preferentially modulates emotional memory in humans

Michael E. Ballard¹, David A. Gallo², and Harriet de Wit^{1,*}

¹Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Ave., MC3077, Chicago, IL 60637, USA

²Department of Psychology, University of Chicago, 5848 S. University Ave., Chicago, IL 60637, USA

Abstract

Rationale—Many addictive drugs are known to have effects on learning and memory, and these effects could motivate future drug use. Specifically, addictive drugs may affect memory of emotional events and experiences in ways that are attractive to some users. However, few studies have investigated the effects of addictive drugs on emotional memory in humans.

Objectives—This study examined the effects of the memory-enhancing drug dextroamphetamine (AMP) and the memory-impairing drug Δ^9 -tetrahydrocannabinol (THC) on emotional memory in healthy volunteers.

Methods—Participants completed three experimental sessions across which they received capsules containing placebo and two doses of either AMP (10 and 20 mg; $N=25$) or THC (7.5 and 15 mg; $N=25$) before viewing pictures of positive (pleasant), neutral, and negative (unpleasant) scenes. Memory for the pictures was assessed two days later, under drug-free conditions.

Results—Relative to placebo, memory for emotional pictures was improved by AMP and impaired by THC, but neither drug significantly affected memory for unemotional pictures. Positive memory biases were not observed with either drug, and there was no indication that the drugs' memory effects were directly related to their subjective or physiological effects alone.

Conclusions—This study provides the first clear evidence that stimulant drugs can preferentially strengthen, and cannabinoids can preferentially impair, memory for emotional events in humans. Although addictive drugs do not appear to positively bias memory, the possibility remains that these drugs' effects on emotional memory could influence drug use among certain individuals.

Keywords

Drugs; memory; amphetamine; THC; human; mood; drug abuse; emotional; arousal

Introduction

Memories of emotional events exert a strong influence over behavior. Certainly it is often advantageous for survival to remember emotional events, as these memories can motivate harm avoidance and pursuit of biologically relevant rewards (e.g., food, sex) (Nairne et al.

*Corresponding author: Harriet de Wit, PhD, Dept of Psychiatry and Behavioral Neuroscience, University of Chicago, Tel: 773 702-1537, Fax: 773 834-7698, hdew@uchicago.edu.

Disclosures: Over the past 3 years HdW has received funding from Unilever for an unrelated research study. The authors have no other disclosures or conflicts of interest to report.

2007). However, memories of emotional events can also have pernicious consequences. For instance, post-traumatic stress disorder is associated with invasive memories of traumatic events (Steckler and Risbrough 2012), and clinically depressed patients often remember negative events over positive ones (Leppanen 2006). Overactive memories of positive events can also be detrimental, as they may lead to compulsive behavior. Indeed, drug addiction is increasingly viewed as a disorder of learning and memory, and recent theories posit potent memories of previous positive drug experiences promote compulsive drug use (Hyman 2005; Koob 2009; Robbins et al. 2008). But while anecdotal reports from drug users provide some support for this view, there are also reports of people using drugs to cope with, or 'to forget', painful life events (Bell 1996; Boys et al. 2001; Crowley 1972; Pandina and Johnson 1999), suggesting that addictive drugs may influence how emotional events are remembered in ways that are attractive to certain individuals. Nevertheless, only a handful of controlled laboratory studies have investigated the effects of addictive drugs on emotional memory in humans.

In the present study, we examined the effects of two different addictive drugs – dextroamphetamine (AMP) and Δ^9 -tetrahydrocannabinol (THC) – on emotional memory in healthy human volunteers. We chose to study these two drugs in part because both are widely used for their euphorogenic properties, but they have distinctly different behavioral, pharmacological, and cognitive effects. AMP is a prototypic stimulant drug that acts directly at vesicular monoamine transporters to increase synaptic concentrations of monoamines (primarily dopamine and norepinephrine) (Patrick and Markowitz 1997; Rothman et al. 2001). THC, on the other hand, has more sedative effects (Robson 2001), and acts as a partial agonist at cannabinoid receptors (Howlett et al. 2004; Tanda and Goldberg 2003). At moderate doses, AMP can enhance memory encoding by increasing alertness (Estrada et al. 2012), vigilance (Killgore et al. 2008), focused attention (Hamidovic et al. 2010), and motivation (Wardle et al. 2011), and by enhancing working memory (Tipper et al. 2005), associative learning (Breitenstein et al. 2006), and cognitive flexibility (Kempton et al. 1999), while THC adversely impacts many of these same processes (for a review, see Ranganathan and D'Souza 2006). Accordingly, several studies have shown people exhibit superior memory for lists of unemotional words studied under the influence of AMP (e.g., Breitenstein et al. 2004; Mintzer and Griffiths 2003; Zeeuws and Soetens 2007), whereas THC generally impairs memory under similar conditions (for a review, see Ranganathan and D'Souza 2006). AMP similarly improves memory when it is administered immediately after encoding (list studying) (Soetens et al. 1993), indicating it also enhances consolidation of recently encoded memories. Although clear evidence that THC impairs memory consolidation in humans has not been shown, cannabinoid agonists typically impair memory retention in rodents when administered immediately after training (Campolongo et al. 2009; Clarke et al. 2008; Costanzi et al. 2004; Ghiasvand et al. 2011). To our knowledge, neither AMP nor THC has been previously evaluated on measures of long-term declarative emotional memory in humans.

We hypothesized that AMP would preferentially enhance, and THC would preferentially impair, memory for emotional stimuli relative to neutral stimuli. This prediction was based primarily on functional neuroimaging studies showing that AMP potentiates (Hariri et al. 2002), while THC dampens (Bhattacharyya et al. 2010; Phan et al. 2008), amygdalar activation in response to emotional images in humans. The amygdala is highly sensitive to emotionally arousing stimuli (both positively and negatively valenced), and its activation may serve to strengthen memory consolidation (for a review, see Roozendaal and McGaugh 2011). Moreover, experimental procedures that increase amygdalar reactivity to emotional images (e.g., stress (van Marle et al. 2009), cortisol (Henckens et al. 2012)) preferentially enhance memory for emotional stimuli when administered prior to encoding in humans (Buchanan and Lovallo 2001; Payne et al. 2007). Evidence of selective emotional memory

impairments in humans also has been observed with pre-encoding administration of several drugs that dampen amygdalar reactivity to emotional images, including both addictive drugs (e.g., alcohol (Gilman et al. 2008; Knowles and Duka 2004), benzodiazepines (Buchanan et al. 2003; Del-Ben et al. 2010; Kamboj and Curran 2006; Paulus et al. 2005)) and non-addictive drugs (e.g., dopaminergic receptor antagonists (Gibbs et al. 2007; Mehta et al. 2005; Takahashi et al. 2005), β -adrenergic receptor antagonists (Cahill et al. 1994; van Stegeren et al. 1998; van Stegeren et al. 2005) – findings which additionally provide mechanistic support for our hypothesis. This hypothesis also appears to be consistent with research indicating that emotional memory consolidation varies directly with arousal state. In line with this view, both stress and cortisol similarly enhance emotional memory when administered immediately after encoding (Kuhlmann and Wolf 2006; Smeets et al. 2008), and an analogous effect has been observed following the viewing of either pleasant or aversive arousing videos immediately after encoding (Liu et al. 2008). On the other hand, listening to relaxing music during or immediately after encoding correspondingly preferentially impairs emotional memory in humans (Liu et al. 2008).

Our predictions regarding the emotional memory effects of AMP and THC in humans are also broadly congruent with the non-human animal literature. In particular in rodents, AMP typically enhances (Davies et al. 1974; Fulginiti and Cancela 1983; Janak and Martinez 1992; Lee and Ma 1995; Martinez et al. 1980; Wood and Anagnostaras 2009), whereas cannabinoid agonists typically impair (for reviews, see Akirav 2011; McLaughlin and Gobbi 2012) acquisition and retention of motivated conditioned behaviors. Still, direct comparisons of emotional and unemotional memory in non-human animals are lacking, which limits the conclusions that can be drawn regarding the importance of emotional task elements in mediating the effects of drugs on performance in preclinical models. The present study therefore builds on prior research concerning the factors that modulate emotional memory in humans, and it addresses gaps in the preclinical literature.

We separately hypothesized that AMP might preferentially enhance memory for positive relative to negative stimuli, while THC might preferentially impair memory for negative relative to positive stimuli. This prediction was based primarily on the drugs' capacity to induce positive mood states, as a sizeable literature indicates that information is more likely to be remembered if its valence matches the individual's mood state during encoding (for reviews, see Bower and Forgas 2000; Eich 2001). Along these lines, it stands to reason that addictive drugs may positively bias users' memories of the events surrounding drug use, resulting in users preferentially remembering subjectively positive aspects of the drug use experience over more negative ones. Such a positive memory bias would fit broadly with the above-noted anecdotal reports from drug users of the factors that motivate drug use, and there is evidence that drug users' memory of subjectively positive drug effects overshadows their memory of negative drug effects (McCusker 2001). Nevertheless, the possibility that addictive drugs may differentially modulate memory for positively and negatively valenced emotional stimuli has rarely been explored in controlled laboratory studies.

We are aware of only two studies that have measured effects of addictive drugs on long-term declarative memory for both positive and negative emotional stimuli in humans. Those studies found little evidence that either alcohol (Knowles and Duka 2004) or the benzodiazepine triazolam (Buchanan et al. 2003) impaired memory more strongly for negative relative to positive images. Nevertheless, evidence that acute treatment with norepinephrine reuptake inhibitors prior to encoding preferentially increases delayed (15 min) recall of positive self-relevant adjectives in healthy humans in the absence of measurable acute changes in mood state (for a review, see Harmer et al. 2010) provides mechanistic support for an AMP-induced positive memory bias. As well, evidence that acute treatment with a cannabinoid inverse agonist prior to encoding preferentially increases

delayed (15 min) recall of negative self-relevant adjectives in healthy humans without altering mood state (Horder et al. 2009) provides indirect mechanistic support for a THC-induced positive memory bias. Thus, even though clear evidence that addictive drugs positively bias memory is currently lacking, it remains possible that positive memory biases might be detected with AMP and THC.

Our primary interest in this study was to investigate how AMP and THC affect long-term memory for emotional events encountered under the influence. Drugs were administered before participants viewed a range of emotionally positive, neutral, and negative pictures, and memory was tested under drug-free conditions two days later. As such, the drugs could potentially directly affect both memory encoding processes and early consolidation, but retrieval was assessed in the absence of any drug effects. Participants ingested placebo capsules and two different doses of either AMP (10, 20 mg) or THC (7.5, 15 mg) across separate sessions in counterbalanced order under double-blind conditions. Drug doses are within the range shown to affect memory for unemotional information when administered prior to encoding in humans (e.g., Ballard et al. 2012b; Curran et al. 2002; Mintzer and Griffiths 2003; Zeeuws and Soetens 2007). Measures of subjective drug response, mood state, and cardiovascular function were obtained and examined in relation to the drugs' memory effects.

Methods

Subjects

Healthy volunteers aged 18–35 years were recruited from the University of Chicago and the surrounding community via posters, advertisements, and word-of-mouth referrals, and participated either in the AMP study ($N=25$; 12 female) or the THC study ($N=25$; 11 female). The studies were conducted separately, but utilized the same inclusion criteria and procedure. All potential participants underwent a physician-supervised physical examination including an electrocardiogram, completed a health questionnaire with detailed information on current and lifetime drug use, and were interviewed by trained clinical psychologists using a semi-structured SCID interview. Exclusion criteria included current Axis I DSM-IV disorder including any Substance Dependence (American Psychiatric Association 1994) other than Tobacco Dependence. Tobacco Dependence does not appear to affect subjective response to the drugs used in this study (unpublished, in-house analyses, $N=400$ for AMP, $N=30$ for THC). Volunteers were excluded if they had a history of psychosis or mania, less than a high school education, lack of fluency in English, a body mass index outside of 19–26 kg/m², high blood pressure ($>140/90$), an abnormal electrocardiogram, reported daily use of any medication other than birth control, or were pregnant, lactating, or planning to become pregnant in the next three months. For ethical reasons, participants were only eligible if they reported using cannabis more than 10 times in their lifetime with no serious cannabis-related adverse events. Inclusion was limited to individuals not currently using cannabis more than three times per week, to reduce the likelihood of tolerance to THC's effects on memory (D'Souza et al. 2008). Women not taking hormonal contraceptives in the AMP group ($n=6$ of 12) were tested during their follicular phase only because hormonal fluctuations of the menstrual cycle can influence responses to the drug (White et al. 2002).

Design

Two parallel studies were carried out investigating the respective effects of AMP and THC on emotional memory encoding. Both studies utilized a three-session, double-blind, placebo-controlled, counterbalanced, cross-over design. Each of the three sessions consisted of two laboratory visits – a four-hour visit (encoding phase) followed two days later by a one-hour visit (retrieval phase). During the encoding phase visits, participants received capsules

containing placebo or AMP (10, 20 mg; AMP group) or THC (7.5, 15 mg; THC group) in random order, before viewing standardized pictures (see *Dependent measures*, below). Memory for the pictures viewed during the encoding phase visit was assessed at the subsequent retrieval phase visit, during which no drugs were administered. Additional procedures were included to assess the drugs' effects on processing of facial emotions and on associative false memory, but they will not be described here. These additional procedures were held constant with respect to the current procedure and have been reported previously (Ballard et al. 2012a; Ballard et al. 2012b). This study was approved by the University of Chicago Institutional Review Board.

Procedure

Qualifying participants attended a one-hour orientation session to be acquainted with the study procedures and risks, provide informed consent, and practice study tasks and questionnaires. They were informed that they would be participating in a study on the effects of drugs on mood and memory. To minimize drug-related expectancies, all participants were told that they might receive a placebo, stimulant (e.g., amphetamine), sedative/tranquilizer (e.g., Valium), or a marijuana-like drug. Participants were instructed to consume their normal amounts of caffeine and nicotine before sessions, but to abstain from using alcohol and prescription (other than birth control), over the counter, and illicit drugs for 24 hours before the sessions. They were notified that they would be tested for drug use before each session to verify abstinence. Participants were also advised to get their normal amounts of sleep, and not to eat solid food for two hours before the encoding phase visits to allow for proper drug absorption.

Participants were tested individually in comfortably furnished rooms with a television and VCR, magazines, and a computer for administering questionnaires and tasks. They were allowed to watch television, selected neutral movies, or read when no measures were being obtained, but they were not allowed to sleep, work, or study, and they had no access to cell phones or internet. Upon arrival for all six visits, participants first completed compliance measures including breath alcohol level (Alco-sensor III, Intoximeters, St. Louis, MO), and urine drug (ToxCup, Branan Medical Co. Irvine, CA) and pregnancy (women only, using an hCG assay; Aimstrip, Craig Medical, Vista, CA) tests. During the encoding phase visits, after completing pre-capsule subjective ratings and physiological measures (see *Dependent measures*, below), participants ingested capsules (0 minutes) containing placebo or active drug with 100 mL water. Every 30 minutes for the remainder of the encoding phase visits, participants completed subjective mood and drug effect ratings, and provided cardiovascular measurements. At 90 minutes after capsule ingestion, when peak drug effects were expected to be present (Wachtel et al. 2002; White et al. 2007), participants viewed the pictures for which their memory would be tested two days later. At the end of the encoding phase visits, participants completed an end-of-session questionnaire, and were allowed to leave when residual subjective and physiological drug effects had subsided. During the retrieval phase visits, participants returned to the laboratory for one hour to complete mood questionnaires and the recognition memory task. All participants were fully debriefed at study completion.

Dependent measures

Memory Task—Memory was measured using a common picture recognition procedure, which was designed to assess participants' ability to discriminate previously studied pictures from novel distractor pictures. The stimuli consisted of six sets of 60 pictures drawn from the International Affective Picture System (IAPS; Lang et al. 1999). Each set was comprised of photographs depicting a range of positive or pleasant, neutral, and negative or unpleasant scenes (20 each category), according to normative ratings, and all six picture sets were matched on extremity of valence and arousal. Normed valence ratings of IAPS pictures

range from 1 (very negative) to 9 (very positive), and arousal ratings range from 1 (not at all arousing) to 9 (very arousing). Positive pictures selected for this study had a mean valence of 7.05 (range: 6–8.34), and mean arousal of 5.58 (range: 4.51–7.35); Neutral pictures had a mean valence of 5.07 (range: 4.03–5.99), and a mean arousal of 3.35 (range: 1.72–4.36); Negative pictures had a mean valence of 2.73 (range: 1.46–3.92), and a mean arousal of 5.6 (range: 4.53–7.29) (Lang et al. 1999). Participants viewed a different picture set during each of the encoding phase visits after receiving active drug or placebo. Their memory for the pictures was then tested two days later, at the corresponding retrieval phase visit. There, participants performed a recognition test during which they were instructed to correctly identify the previously viewed pictures from a set containing an equal number of novel (unstudied) distractor pictures. The same two sets of pictures were always paired together during a single test. Set order was counterbalanced across participants, and sets were not re-used across sessions. IAPS pictures reliably elicit emotional responses and are commonly used as a tool for examining emotional memory in humans.

Encoding Phase: During each of the three encoding phase visits, participants viewed a single set of 60 pictures. Pictures were displayed individually on a computer screen for 3000 msec each, and were pseudorandomized such that no more than two pictures from the same valence category were presented consecutively. The participant initiated the presentation of each picture by pressing a key. To ensure that the studied pictures would meaningfully processed under each of the drug conditions, participants were required to rate each picture for perceived valence and arousal, using Likert scales from one to nine. Valence was defined as: 1) how positive, and 2) how negative the picture made them feel, and arousal was defined as how stimulated, excited, or awake they felt in response to the picture (Lang et al. 1993). Valence and arousal ratings were self-paced. Outcome measures included subjective ratings of positivity, negativity, and arousal response to pictures from individual valence categories.

Retrieval Phase: Two days after each encoding phase visit, participants returned to the laboratory for a retrieval phase visit, to test their memory for the pictures viewed during the previous encoding phase visit. At each retrieval phase visit, memory was assessed using all 60 of the pictures from the set studied at the previous encoding phase visit, interspersed with 60 novel pictures, presented in the same manner as during the encoding phase. Participants were instructed to identify pictures they had seen two days earlier during the encoding phase visit (yes/no), and to rate their current positivity, negativity, and arousal responses to each. Raw outcome measures included hit rate (the proportion of studied pictures correctly recognized as studied at test), false alarm rate (the proportion of unstudied pictures incorrectly recognized as studied at test), and valence and arousal ratings. The main outcome measure was a calculated score of memory accuracy derived from subtracting false alarm rate from hit rate. This method of subtracting false alarms from hits is widely used in order to control for changes in base rate responding (Snodgrass and Corwin 1988).

Subjective Effects Measures—Participants completed several subjective mood and drug effect rating scales as described previously (Ballard et al. 2012a). Briefly, these included the Drug Effects Questionnaire (DEQ; Fischman and Foltin 1991), Visual Analog Scales (VAS; Folstein and Luria 1973), and Positive Affect and Negative Affect Schedule (PANAS; Watson et al. 1988), which were administered at baseline and every 30 minutes after capsule ingestion, the Addiction Research Center Inventory (ARCI; Martin et al. 1971), which was administered at baseline, and 90 and 180 minutes post-capsule, and an end-of-session questionnaire administered at 180 minutes post-capsule. The DEQ includes five questions that measure how much participants feel a drug effect, dislike the drug effect, like the drug effect, feel high, and want more of the drug. The VAS includes the adjectives

‘anxious’, ‘stimulated’, ‘confused’, ‘sedated’, ‘excited’, ‘angry’, and ‘elated’. The PANAS consists of 10 negative and 10 positive mood terms designed to measure positive and negative affect. The ARCI measures drug-specific effects on a true-false questionnaire. The ESQ measures overall perception of drug effects, including: i) desire to take the drug again “yes/no”, and ii) best guess of drug received (stimulant, sedative/anxiolytic, marijuana-like drug, or placebo).

For the purpose of this study we focused on four ratings: subjective stimulation and sedation (VAS scales; range: 0 to 10), a composite measure of drug preference (calculated as DEQ ratings of ‘like drug’ minus DEQ ratings of ‘dislike drug’; range: –10 to +10), and overall drug effect (DEQ ratings of ‘feel drug’ (range: 0 to 10). We calculated mean change from pre-capsule baseline scores acquired immediately before and after encoding phase picture set viewing (+90 and +120 minutes post-capsule) to estimate drug effects at the time the pictures were viewed. Subjective stimulation and sedation were selected because changes in arousal may preferentially influence memory for emotionally salient stimuli, and drug preference was selected because positive and negative subjective drug responses may correspond to positive and negative memory biases, respectively. Drug ‘feel’ was selected to investigate the importance of overall awareness of drug effects to their memory effects.

Physiologic Effects Measures—Blood pressure and heart rate were measured at baseline, and every 30 min post-capsule, using a portable digital blood pressure monitor (AND Medical/Life Source, San Jose, CA). Mean change from pre-capsule baseline scores acquired immediately before and after encoding phase picture set viewing (+90 and +120 minutes post-capsule) were calculated and examined in relation to effects of the study drugs on memory. These measures were selected because, like subjective stimulation, physiological arousal changes may similarly accompany preferential emotional memory changes.

Drugs

AMP (Barr Laboratories, Pomona, New York) and THC (Marinol® [dronabinol]; Solvay Pharmaceuticals, Marietta, Georgia) were placed in opaque size 00 capsules in doses of 10 or 20 mg (AMP) or 7.5 or 15 mg (THC), with dextrose filler. Placebo capsules contained only dextrose. Capsules were administered in counterbalanced order under double-blind conditions. These doses of AMP and THC are within the range shown to affect memory in previous studies (e.g., Ballard et al. 2012b; Curran et al. 2002; Mintzer and Griffiths 2003; Zeeuw and Soetens 2007), and the oral route ensures a steady time course of response throughout the study session (Wachtel et al. 2002; White et al. 2002).

Statistical Analyses

Memory Task—Memory task data were analyzed to determine the drugs’ overall effects on emotional evaluation and memory accuracy using two-way repeated-measures ANOVA with drug dose (placebo, low, moderate) and picture valence (positive, neutral, negative) as the within-subjects factors. Further, in order to fully explore our two non-competing hypotheses that the drugs would more strongly affect memory for pictures of certain valence, we also examined the size of the effect each drug had on responses to items from each valence category using individual one-way repeated-measures ANOVA. Because we expected dose-dependent increases in drug effects, linear main effects of drug dose are reported, unless otherwise specified (i.e., when the lower dose was found to exert a stronger effect than the higher dose). Quadratic valence effects are reported because we were interested in investigating the extent to which each drug affected emotional pictures (both positive- and negative valence) more strongly than unemotional pictures (neutral valence). Alpha was set at $p=.05$ for all analyses, and trend-level main effects of drug dose ($p<.1$)

were followed up by post hoc paired *t*-tests, to examine dose-dependency. One-tailed tests were used because we had specific predictions about the direction of the drugs' effects on memory (i.e., that AMP would enhance, whereas THC would impair, memory performance relative to placebo). All data reported related to the memory task (i.e., both picture ratings and memory performance) reflect an $n=24$ in both groups. One participant in the AMP group received the wrong picture set during one of the encoding visits, and one participant in the THC group did not adhere to the memory task instructions during the high dose condition, and these participants were therefore excluded from these analyses.

Emotional Processing Data: Participants' subjective ratings of their positive, negative, and arousal responses to the pictures were analyzed for: 1) the studied pictures at encoding, 2) the studied pictures at retrieval, and 3) the distractor pictures at retrieval. These analyses were chosen to provide information on the drugs' effects on perception, which may influence memory. Neither drug influenced the ratings at retrieval when administered on the study day, so these results are not discussed.

Memory Data: Memory accuracy, hit rate, and false alarm rate data were first analyzed using predetermined valence categories according to normed ratings, but were also reanalyzed using individualized valence and arousal categories according to each individual participant's valence and arousal ratings of the pictures. For the subjective rating analyses, pictures were sorted in descending order of subjective positivity minus negativity into three valence categories (positive, neutral, and negative). Reanalysis of each participant's memory data according to valence categories determined by their own subjective ratings of picture valence yielded analogous results to those obtained using normatively determined valence categories. Thus, only analyses of the former are provided for ease of interpretation with respect to effects of the drugs on subjective picture ratings.

Subjective and physiologic effects of AMP and THC at encoding, and relation to memory performance—Drug effects on subjective and physiologic state were analyzed using one-way repeated-measures ANOVA, with drug dose (placebo, lower, higher) as the within-subject factor. Significant main effects of drug dose were followed by paired *t*-tests. We also performed exploratory analyses to examine relationships between the drugs' effects on memory and their effects on subjective and physiologic state. Bivariate correlational analyses of drug effect (drug minus placebo) were conducted on these measures for each dose of each drug separately. We looked for relationships between memory performance (memory accuracy, hit rate, and false alarm rate for positive and negative vs. neutral pictures separately) and the drugs' effects on subjective measures (drug preference, 'feel drug', 'stimulated', 'sedated') and cardiovascular measures (systolic and diastolic blood pressure and heart rate). Alpha was set liberally at $p=.05$ for correlational analyses, given the exploratory nature of these analyses and to facilitate generation of novel hypotheses for future investigation.

Results

Participant characteristics

Demographic characteristics and past-month drug use of the participants in the AMP ($N=25$; 12 female) and THC ($N=25$; 11 female) groups are summarized in Tables 1 and 2, respectively. Lifetime recreational drug use histories are summarized in Supplementary Tables 1 (AMP group) and 2 (THC group). All participants were healthy current or past occasional recreational cannabis users. Most were in their early twenties, self-identified as 'white', and reported light to moderate use of alcohol and other drugs. The groups did not

differ on any of the demographic characteristics or on memory task performance under placebo conditions.

Emotional processing

Participants' subjective ratings were appropriate to the pictures' designated valence categories (AMP group: Table 3; THC group: Table 4), and positive and negative pictures were rated as significantly more arousing than neutral pictures, regardless of dose ($p < .001$). Despite positive and negative pictures being equated on arousal according to normative ratings, participants in both the AMP and THC groups rated negative pictures as slightly, but significantly, more arousing than positive pictures in the placebo condition ($p < .001$).

AMP—AMP dose-dependently increased positivity and arousal ratings of the pictures during encoding. Accordingly, AMP (20 mg) significantly increased positivity ($F_{1,23}=5.83$, $p=.024$, $MSE=0.3$, $\eta_p^2=.2$) and arousal ($F_{1,23}=4.69$, $p=.041$, $MSE=0.13$, $\eta_p^2=.16$) ratings of the pictures overall, and these effects did not depend on picture valence (i.e., no Dose x Valence interactions). AMP did not alter negativity ratings.

THC—The effects of THC on picture ratings have been previously reported elsewhere (Ballard et al. 2012a). THC did not affect positivity ratings of the pictures overall. There was some indication that it increased arousal ratings, but only at the lower dose (quadratic Dose: $F_{1,23}=6.56$, $p=.017$, $MSE=0.46$, $\eta_p^2=.22$; linear Dose: $p=.33$). This effect was mainly due to increased arousal ratings of neutral pictures (quadratic Dose: $F_{1,23}=6.23$, $p=.02$, $MSE=0.72$, $\eta_p^2=.21$), and positive pictures (quadratic Dose: $F_{1,23}=4.03$, $p=.057$, $MSE=0.7$, $\eta_p^2=.15$). The lower dose of THC also tended to increase negativity ratings of the pictures overall (quadratic Dose: $F_{1,23}=4.27$, $p=.05$, $MSE=0.43$, $\eta_p^2=.16$; linear Dose: $p=.54$). Again, this effect was primarily limited to neutral pictures (quadratic Dose: $F_{1,23}=3.07$, $p=.027$, $MSE=0.55$, $\eta_p^2=.2$).

Memory results

Raw hit rates and false alarm rates for pictures from each valence category are presented in Tables 5 (AMP group) and 6 (THC group). In general, hit rates were high and false alarm rates were low for all conditions, demonstrating good overall memory performance. There were no sex differences in memory performance under placebo conditions. Participants' memory did not vary depending on picture valence in the placebo conditions, and there were no significant differences between the two groups of participants in their memory for pictures of positive, neutral, or negative valence under placebo conditions. Although amygdala-hippocampal interactions can sometimes enhance memory for emotionally arousing information in a drug-free state (Kensinger 2004), the high degree of conceptual overlap for emotional images also can increase memory confusions relative to unemotional images, thereby countering these otherwise beneficial effects of emotion (Gallo et al. 2009; see also Brainerd et al. 2008; D'Argembeau and Van der Linden 2004; Dougal and Rotello 2007; Howe 2007; Talmi et al. 2007). For this reason, our focus was on each drug's potential effects on memory accuracy within a given emotional valence category, as opposed to the effects of emotional valence on memory accuracy within a given drug condition.

AMP—As expected, AMP significantly improved memory performance overall ($F_{1,23}=6.27$, $p=.02$, $MSE=32.13$, $\eta_p^2=.21$), with both doses of AMP significantly increasing accuracy relative to placebo ($t_{23} > 3.01$, $p < .01$). Although the Dose x Valence interaction was not significant, because of our *a priori* interest, we examined the drug's effect on memory for pictures from each valence category separately. These analyses indicated that, as shown in Figure 1, AMP significantly improved memory for positive pictures ($F_{1,23}=5.69$, $p=.026$, $MSE=61.87$, $\eta_p^2=.2$), and it also tended to improve memory for negative pictures

($F_{1,23}=4.19$, $p=.052$, $MSE=65.74$, $\eta_p^2=.15$), but memory for neutral pictures was not altered by AMP.

Further analyses revealed that the AMP-induced memory enhancement was mainly due to increased hit rates for studied pictures ($F_{1,23}=7.27$, $p=.013$, $MSE=14.04$, $\eta_p^2=.24$) at both doses ($t_{23}s>2.02$, $ps<.028$). There was no Dose x Valence interaction on hit rate, but consistent with its effects on memory accuracy, AMP significantly increased hit rates for both positive pictures ($F_{1,23}=6.93$, $p=.015$, $MSE=27.15$, $\eta_p^2=.23$) and negative pictures ($F_{1,23}=8.85$, $p=.007$, $MSE=23.55$, $\eta_p^2=.28$), without affecting neutral picture hits. Participants also made fewer false alarms in the AMP conditions (quadratic Dose: $F_{1,23}=5.25$, $p=.031$, $MSE=5.58$, $\eta_p^2=.19$); although in general, false alarm rates were very low.

THC—Also in line with predictions, THC significantly impaired memory performance overall ($F_{1,23}=6.37$, $p=.019$, $MSE=31.64$, $\eta_p^2=.22$), with both doses of THC significantly reducing accuracy relative to placebo ($t_{23}s>2.18$, $ps<.02$). Although the Dose x Valence interaction was not significant, there was evidence that THC preferentially impaired memory for emotional pictures. Indeed, as shown in Figure 2, THC significantly impaired memory for positive pictures ($F_{1,23}=5.81$, $p=.024$, $MSE=97.62$, $\eta_p^2=.2$), and it also tended to impair memory for negative pictures ($F_{1,23}=3.32$, $p=.081$, $MSE=62.68$, $\eta_p^2=.13$), but did not affect memory for neutral pictures.

Further analyses revealed that THC reduced hit rates for studied pictures ($F_{1,23}=8.61$, $p=.007$, $MSE=29.26$, $\eta_p^2=.27$) at both doses ($t_{23}s>2.52$, $ps<.006$). Consistent with its effects on memory accuracy, THC primarily reduced hit rates for emotional pictures. The Dose x Valence interaction on hit rate narrowly missed significance ($F_{1,23}=4.15$, $p=.053$, $MSE=22.79$, $\eta_p^2=.15$). Still, THC significantly reduced hit rates for positive pictures ($F_{1,23}=12.38$, $p=.002$, $MSE=57.59$, $\eta_p^2=.35$), and a similar trend was seen for negative pictures ($F_{1,23}=3.43$, $p=.077$, $MSE=49.19$, $\eta_p^2=.13$), whereas it did not robustly alter hit rates for neutral pictures. THC administration did not affect false alarm rates, and false alarms were very low across conditions.

Subjective and physiologic effects of AMP and THC at encoding, and relation to memory performance

The drugs' effects on select subjective drug response and mood measures and physiology at the time pictures were encoded are summarized in Tables 7 (AMP group) & 8 (THC group). Mean change from pre-capsule scores for all measures are detailed in Supplementary Tables 3 (AMP group) and 4 (THC group), and those for THC have been previously reported elsewhere (Ballard et al. 2012a).

AMP—AMP produced subjective and cardiovascular effects expected for a stimulant drug of abuse. Participants reported feeling the effects of only the higher dose of AMP (20 mg). Based on preference scores calculated as 'dislike drug effects' scores subtracted from 'like drug effects' scores, participants clearly preferred both doses of AMP to placebo, with ratings being roundly positive (range: -1.9 to 8.6 and -1.3 to 10 , for the 10 and 20 mg dose, respectively). However, consistent with the finding that participants did not report feeling the 10 mg dose of AMP, only 12 out of the 25 study participants indicated a desire to take the 10 mg dose of AMP again, whereas 24 out of the 25 reported a desire to take the 20 mg dose again. AMP increased subjective ratings of stimulation (both doses) and reduced ratings of sedation (significant at 10 mg only). AMP also increased physiological arousal measures, including systolic and diastolic blood pressure, and heart rate. The majority of participants failed to correctly identify the 10 mg dose of AMP as a stimulant drug, but over

half correctly identified the 20 mg dose of AMP as being stimulant-like (10 mg: 24%; 20 mg: 64%). Although AMP both enhanced memory and increased subjective drug effect and mood scale ratings and cardiovascular measures relative to placebo, exploratory correlational analyses did not suggest that AMP-induced memory changes were directly related to its subjective or cardiovascular effects across doses.

THC—THC also produced expected subjective and cardiovascular effects. Participants reported feeling the effects of both doses of THC. However, they did not roundly prefer THC to placebo: There was wide inter-individual variability in preference for THC's effects (range: -4.0 to 4.7 and -7 to 6.2, for the 7.5 and 15 mg dose, respectively). Accordingly, only 15 of the 25 study participants indicated a desire to take the 7.5 mg dose of THC again, and 11 of the 25 reported a desire to take the 15 mg dose again. THC increased ratings of both subjective stimulation and sedation at both doses, sometimes concomitantly. THC also increased physiological arousal measures. Just over half of the participants correctly identified THC as a marijuana-like drug (7.5 mg: 56%; 15 mg: 52%). Although THC both impaired memory and increased subjective drug effect and mood scale ratings and cardiovascular measures relative to the placebo condition, exploratory correlational analyses did not suggest that THC-induced memory changes were directly related to its subjective or cardiovascular effects across doses. [Insert Table 8 near here]

Discussion

This study investigated the acute effects of AMP and THC on emotional memory formation in human volunteers. We had two independent primary hypotheses. The first hypothesis was that both drugs would predominantly influence memory for emotional relative to neutral pictures. This hypothesis was supported: AMP enhanced, and THC impaired memory for both positive and negative pictures, but neither drug affected memory for neutral pictures. The second hypothesis was that both drugs would positively bias participants' memory of the emotional pictures. This hypothesis was not supported: neither AMP nor THC increased participants' tendency to endorse positive over negative studied or unstudied pictures as studied during memory testing.

That AMP preferentially improved memory for emotional pictures is consistent with Hariri et al.'s (2002) report that AMP potentiates amygdalar reactivity to emotionally arousing images in humans. Together, these observations fit with data indicating that other experimental manipulations that similarly increase amygdalar reactivity (e.g., stress (van Marle et al. 2009), cortisol (Henckens et al. 2012)) also preferentially enhance emotional memory when administered prior to encoding in humans (Buchanan and Lovaglio 2001; Payne et al. 2007), but see also (Henckens et al. 2009; Henckens et al. 2012). AMP increases dopamine (DA) and norepinephrine (NE) release in the amygdala (Rothman et al. 2001), and it indirectly increases circulating levels of cortisol (White et al. 2006) – all of which may enhance amygdalar reactivity in humans (Henckens et al. 2012; Onur et al. 2009; Tessitore et al. 2002). Moreover in humans, both DA antagonists and β -adrenergic antagonists dampen amygdalar reactivity (Takahashi et al. 2005; van Stegeren et al. 2005), and pre-encoding administration of either preferentially impairs emotional memory (Cahill et al. 1994; Gibbs et al. 2007; Mehta et al. 2005; van Stegeren et al. 1998). Thus, AMP may have enhanced emotional memory in the present study by increasing the perceived salience of emotional stimuli by the amygdala during encoding.

In addition to potentially enhancing emotional memory encoding, AMP may also have enhanced initial consolidation of emotional memories. Glucocorticoids, NE, and DA can further indirectly enhance hippocampal-dependent consolidation via actions on the amygdala (for a review, see McGaugh and Roozendaal 2009), and glucocorticoids can also

strengthen consolidation directly at the hippocampus (Micheau et al. 1984; Roozendaal and McGaugh 1997). Consistent with the role of these hormones and transmitters in modulating arousal state, post-encoding stress, viewing of pleasant or aversive arousing videos, and cortisol all preferentially enhance emotional memory consolidation in healthy humans (Kuhlmann and Wolf 2006; Liu et al. 2008; Smeets et al. 2008). Our finding with AMP, taken together with these other data, suggest emotional memory consolidation may be preferentially enhanced during periods of heightened arousal, and multiple neurochemical systems could play roles mediating this effect. While we did not find evidence that AMP enhanced emotional memory most strongly in those participants who displayed the greatest AMP-induced increases in arousal, cortisol was not measured here. Therefore, AMP may have enhanced emotional memory encoding, early consolidation, or both. This enhancement may have been mediated by a potentiation of amygdalar facilitation of hippocampal binding resulting from increased release of glucocorticoids, NE, and DA.

That AMP preferentially enhanced emotional memory formation is important because it is the first demonstration of such a profile with a stimulant drug in humans. Previous studies have observed only a marginal emotional memory enhancement in humans with pre-encoding administration of yohimbine – an α -adrenergic antagonist that indirectly promotes norepinephrine release (O'Carroll et al. 1999; van Stegeren et al. 2010). Further, Brignell et al. (2007) found that pre-encoding administration of the amphetamine-like drug methylphenidate tended to improve neutral but not emotional memory. Precise reasons for the apparent discrepancies across these studies remain to be elucidated. They may be related to drug differences, but differences in the nature of the stimuli used may also be a significant factor. O'Carroll et al. (1999) and Brignell et al. (2007) employed the emotional slide story task developed by Cahill and McGaugh (1995). That task includes only 11 stimuli (4 negatively valenced arousing slides buffered by 7 neutral slides; positively valenced emotional material is not included). Because the emotional and neutral images are presented as part of a single story, this may limit the task's ability to differentiate the effects of drugs on emotional events from neutral events. Although van Stegeren et al. (2010) employed IAPS pictures in their study, they too included only those with neutral and negative valence. In the present study, we employed 20 positively valenced and 20 negatively valenced emotionally arousing images along with 20 neutrally valenced, low-arousal images spanning a range of topics. This picture task allowed us to more clearly differentiate the effects of drugs on the different kinds of emotional materials with varying content, thereby eliciting a broader range of emotional and cognitive associations. Also importantly contrasting with AMP, yohimbine did not potentiate amygdalar responses to emotional images during encoding in van Stegeren et al.'s (2010) study – consistent with the drug's inability to enhance emotional memory. Future studies employing functional neuroimaging techniques, wider dose ranges of these and other stimulant drugs, and memory tasks with a wider range of emotional stimuli will shed more light on these potential issues.

That THC preferentially impaired emotional memory is also consistent with its capacity to dampen amygdalar reactivity to emotionally arousing images in humans (Bhattacharyya et al. 2010; Phan et al. 2008). Together, these observations fit with data indicating that other drugs that similarly dampen amygdalar reactivity, including the addictive drugs alcohol (Gilman et al. 2008) and benzodiazepines (Del-Ben et al. 2010; Paulus et al. 2005), also preferentially impair emotional memory when administered prior to encoding in humans (Buchanan et al. 2003; Knowles and Duka 2004). As was the case in the current study, those other memory studies employed IAPS pictures of varying valence. Type-1 cannabinoid receptors densely populate the amygdala (Katona et al. 2001; Mackie 2005), and their activation can inhibit excitatory input to this area of the brain (Azad et al. 2003). Still, THC also has indirect effects on multiple hormonal and neurotransmitter systems that could have contributed to the observed performance effects (e.g., reduced DA and NE release in the

amygdala (Szabo and Schlicker 2005), increased cortisol release (Ranganathan et al. 2009)). Therefore, while the precise neurochemical mechanisms underlying the effects of THC on emotional memory remain to be resolved, it seems likely THC may have reduced the perceived salience of emotional stimuli by the amygdala during encoding.

To the extent that THC induced feelings of sedation, our finding that it preferentially impaired emotional memory formation is also broadly consistent with research showing listening to relaxing music during or immediately after encoding preferentially impairs emotional memory in healthy humans (Liu et al. 2008). Together, these data fit with the idea that emotional memory consolidation typically varies directly as a function of arousal state. Still, as with AMP, there was no evidence that the THC-induced emotional memory impairment was directly related to its sedative effects in this sample. Notably too, THC also increased subjective stimulation in some individuals and it increased physiological arousal – these effects were also not directly related to emotional memory changes. Evidence that cannabinoid agonists often impair retention of motivated conditioned behaviors in rodents (for reviews, see Akirav 2011; McLaughlin and Gobbi 2012) suggests that THC may have also impaired emotional memory consolidation in the present study, but there are presently few data regarding the effects of THC on memory consolidation in humans.

Contrary to our hypothesis that AMP and THC would positively bias memory, neither drug increased participants' tendency to remember positive pictures over negative pictures, even among those who most enjoyed the drugs' effects. We postulated that addictive drugs' reinforcing properties might derive in part from their tendency to induce a positive memory bias for drug-related events or experiences. This hypothesis was based on literature indicating that events are more likely to be remembered if their valence matches with the individual's mood state at the time they are perceived (for a review, see Eich 2001). Still, the present data fit broadly with evidence suggesting that neither alcohol (Knowles and Duka 2004) nor benzodiazepines (Buchanan et al. 2003) appear to bias memory in favor of positive over negative stimuli viewed under the influence. Thus, while users' memory of prior positive drug experiences may drive subsequent drug taking, despite their euphorogenic properties addictive drugs do not seem to positively bias memory for the events experienced while under the influence.

Both AMP and THC affected participants' subjective ratings of the pictures during encoding, although these effects were not obviously related to the drugs' effects on memory. Replicating our previous finding (Wardle and de Wit 2012), participants rated all pictures as more arousing and positive after AMP, regardless of valence. On the other hand, AMP preferentially enhanced memory for emotional pictures. After THC (7.5 mg), participants rated positive pictures as more arousing, while the drug dose-dependently impaired memory for positive pictures. Participants also rated neutral pictures as more arousing after this dose of THC, but THC did not affect memory for neutral pictures. These findings are intriguing because they suggest that drugs' effects on emotional memory are not solely due to their effects on users' subjective evaluation of stimulus arousal during encoding.

The present study has several strengths, including the use of two doses of two pharmacologically distinct addictive drugs, a double-blind cross-over design with placebo controls, and memory testing occurred under drug-free conditions allowing us to isolate the effects of the drugs on memory formation (i.e., encoding and initial consolidation) from their potential effects on retrieval. It is important to point out, though, that it is possible that these findings would not generalize to higher doses (Baldi and Bucherelli 2005; Husain and Mehta 2011), related drugs, or other routes of administration (Wachtel et al. 2002). With respect to THC, it also is possible that whole plant cannabis, which contains other chemical compounds in addition to THC, would produce different effects (Zuardi et al. 1982, but see

Ilan et al. 2005; Karschner et al. 2011). Further, that studied pictures were discriminated with high accuracy under placebo conditions could have limited our ability to detect more robust memory changes. As such, studies including longer retention intervals, free recall memory assessments, and confidence ratings may be even more sensitive to the drug effects found here. Perhaps most importantly, it remains to be determined whether the drug effects observed here generalize to real-life situations (e.g., personally relevant emotional events, stressful conditions) and other populations (e.g., drug-naïve individuals, regular users (D'Souza et al. 2008), patients with psychiatric disorders). These considerations suggest several interesting directions for future research.

In conclusion, our results add to a small but growing literature indicating that several addictive drugs have particularly strong effects on memory for emotional events in humans. We propose that these emotional memory effects are due to drug-induced changes in the functioning of brain regions involved in processing and storing emotional information, such as the amygdala. Future drug studies employing functional neuroimaging techniques could provide additional tests of this hypothesis. Finally, the results of the present study provide further evidence addictive drugs are not likely to positively bias users' subsequent memory of emotional events experienced under the influence – even among individuals who most enjoy their effects. Nevertheless, it remains a possibility that certain addictive drugs' memory effects may influence their appeal to certain users, or in certain situations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported by NIDA DA02812 and DA031796, and MEB was supported by T32 DA007255 and F31 DA030863.

References

- Akirav I. The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus. *Front Behav Neurosci.* 2011; 5:34. [PubMed: 21734875]
- Azad SC, Eder M, Marsicano G, Lutz B, Zieglgansberger W, Rammes G. Activation of the cannabinoid receptor type 1 decreases glutamatergic and GABAergic synaptic transmission in the lateral amygdala of the mouse. *Learn Mem.* 2003; 10:116–28. [PubMed: 12663750]
- Baldi E, Bucherelli C. The inverted “u-shaped” dose-effect relationships in learning and memory: modulation of arousal and consolidation. *Nonlinearity Biol Toxicol Med.* 2005; 3:9–21. [PubMed: 19330154]
- Ballard ME, Bedi G, de Wit H. Effects of delta-9-tetrahydrocannabinol on evaluation of emotional images. *J Psychopharmacol.* 2012a in press.
- Ballard ME, Gallo DA, de Wit H. Psychoactive drugs and false memory: comparison of dextroamphetamine and delta-9-tetrahydrocannabinol on false recognition. *Psychopharmacology (Berl).* 2012b; 219:15–24. [PubMed: 21647577]
- Bell, I. Why do people use drugs?. In: Wilkinson, C.; Saunders, B., editors. *Perspectives on drug addiction.* Montgomery Press; Perth: 1996. p. 40-46.
- Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, CMOC, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology.* 2010; 35:764–74. [PubMed: 19924114]

- Bower, GH.; Forgas, JP. Affect, memory, and social cognition. In: Eich, E.; Kihlstrom, JF.; Bower, GH.; Forgas, JP.; Niedenthal, PM., editors. *Cognition and Emotion*. Oxford University Press; New York: 2000. p. 87-168.
- Boys A, Marsden J, Strang J. Understanding reasons for drug use amongst young people: a functional perspective. *Health Educ Res*. 2001; 16:457–69. [PubMed: 11525392]
- Brainerd CJ, Stein LM, Silveira RA, Rohenkohl G, Reyna VF. How does negative emotion cause false memories? *Psychol Sci*. 2008; 19:919–25. [PubMed: 18947358]
- Breitenstein C, Floel A, Korsukewitz C, Wailke S, Bushuven S, Knecht S. A shift of paradigm: from noradrenergic to dopaminergic modulation of learning? *J Neurol Sci*. 2006; 248:42–7. [PubMed: 16815467]
- Breitenstein C, Wailke S, Bushuven S, Kamping S, Zwitserlood P, Ringelstein EB, Knecht S. D-amphetamine boosts language learning independent of its cardiovascular and motor arousing effects. *Neuropsychopharmacology*. 2004; 29:1704–14. [PubMed: 15114342]
- Brignell CM, Rosenthal J, Curran HV. Pharmacological manipulations of arousal and memory for emotional material: effects of a single dose of methylphenidate or lorazepam. *J Psychopharmacol*. 2007; 21:673–83. [PubMed: 17606475]
- Buchanan TW, Karafin MS, Adolphs R. Selective effects of triazolam on memory for emotional, relative to neutral, stimuli: differential effects on gist versus detail. *Behav Neurosci*. 2003; 117:517–25. [PubMed: 12802880]
- Buchanan TW, Lovaglio WR. Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology*. 2001; 26:307–17. [PubMed: 11166493]
- Cahill L, McGaugh JL. A novel demonstration of enhanced memory associated with emotional arousal. *Conscious Cogn*. 1995; 4:410–21. [PubMed: 8750416]
- Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. *Nature*. 1994; 371:702–4. [PubMed: 7935815]
- Campolongo P, Roozendaal B, Trezza V, Hauer D, Schelling G, McGaugh JL, Cuomo V. Endocannabinoids in the rat basolateral amygdala enhance memory consolidation and enable glucocorticoid modulation of memory. *Proc Natl Acad Sci U S A*. 2009; 106:4888–93. [PubMed: 19255436]
- Clarke JR, Rossato JI, Monteiro S, Bevilacqua LR, Izquierdo I, Cammarota M. Posttraining activation of CB1 cannabinoid receptors in the CA1 region of the dorsal hippocampus impairs object recognition long-term memory. *Neurobiol Learn Mem*. 2008; 90:374–81. [PubMed: 18524639]
- Costanzi M, Battaglia M, Rossi-Arnaud C, Cestari V, Castellano C. Effects of anandamide and morphine combinations on memory consolidation in cd1 mice: involvement of dopaminergic mechanisms. *Neurobiol Learn Mem*. 2004; 81:144–9. [PubMed: 14990234]
- Crowley TJ. The reinforcers for drug abuse: why people take drugs. *Compr Psychiatry*. 1972; 13:51–62. [PubMed: 5059418]
- 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. [PubMed: 12373420]
- D'Argembeau A, Van der Linden M. Influence of affective meaning on memory for contextual information. *Emotion*. 2004; 4:173–88. [PubMed: 15222854]
- D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Cooper T, Perry E, Krystal J. Blunted psychotomimetic and amnesic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology*. 2008; 33:2505–16. [PubMed: 18185500]
- Davies JA, Jackson B, Redfern PH. The effect of amantadine, L-dopa, (plus)-amphetamine and apomorphine on the acquisition of the conditioned avoidance response. *Neuropharmacology*. 1974; 13:199–204. [PubMed: 4840843]
- Del-Ben CM, Ferreira CA, Sanchez TA, Alves-Neto WC, Guapo VG, de Araujo DB, Graeff FG. Effects of diazepam on BOLD activation during the processing of aversive faces. *J Psychopharmacol*. 2010
- Dougal S, Rotello CM. “Remembering” emotional words is based on response bias, not recollection. *Psychon Bull Rev*. 2007; 14:423–9. [PubMed: 17874582]

- Eich, E. Mood-dependent Memory International Encyclopedia of the Social & Behavioral Sciences. Pergamon; Oxford: 2001. p. 10014-10017.
- Estrada A, Kelley AM, Webb CM, Athy JR, Crowley JS. Modafinil as a replacement for dextroamphetamine for sustaining alertness in military helicopter pilots. *Aviat Space Environ Med.* 2012; 83:556–64. [PubMed: 22764609]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict.* 1991; 86:1563–70. [PubMed: 1786488]
- Folstein MF, Luria R. Reliability, validity, and clinical application of the visual analog mood scale. *Psychol Med.* 1973; 3:8.
- Fulginiti S, Cancela LM. Effect of naloxone and amphetamine on acquisition and memory consolidation of active avoidance responses in rats. *Psychopharmacology (Berl).* 1983; 79:45–8. [PubMed: 6403964]
- Gallo DA, Foster KT, Johnson EL. Elevated false recollection of emotional pictures in young and older adults. *Psychol Aging.* 2009; 24:981–8. [PubMed: 20025411]
- Ghiasvand M, Rezayof A, Zarrindast MR, Ahmadi S. Activation of cannabinoid CB1 receptors in the central amygdala impairs inhibitory avoidance memory consolidation via NMDA receptors. *Neurobiol Learn Mem.* 2011; 96:333–8. [PubMed: 21740975]
- Gibbs AA, Naudts KH, Spencer EP, David AS. The role of dopamine in attentional and memory biases for emotional information. *Am J Psychiatry.* 2007; 164:1603–9. quiz 1624. [PubMed: 17898353]
- Gilman JM, Ramchandani VA, Davis MB, Bjork JM, Hommer DW. Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. *J Neurosci.* 2008; 28:4583–91. [PubMed: 18448634]
- Hamidovic A, Dlugos A, Palmer AA, de Wit H. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. *Psychiatr Genet.* 2010; 20:85–92. [PubMed: 20414144]
- Hariri AR, Mattay VS, Tessitore A, Fera F, Smith WG, Weinberger DR. Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology.* 2002; 27:1036–40. [PubMed: 12464460]
- Harmer CJ, Cowen PJ, Goodwin GM. Efficacy markers in depression. *J Psychopharmacol.* 2010
- Henckens MJ, Hermans EJ, Pu Z, Joels M, Fernandez G. Stressed memories: how acute stress affects memory formation in humans. *J Neurosci.* 2009; 29:10111–9. [PubMed: 19675245]
- Henckens MJ, van Wingen GA, Joels M, Fernandez G. Time-dependent effects of cortisol on selective attention and emotional interference: a functional MRI study. *Front Integr Neurosci.* 2012; 6:66. [PubMed: 22973203]
- Horder J, Cowen PJ, Di Simplicio M, Browning M, Harmer CJ. Acute administration of the cannabinoid CB1 antagonist rimonabant impairs positive affective memory in healthy volunteers. *Psychopharmacology (Berl).* 2009; 205:85–91. [PubMed: 19337726]
- Howe ML. Children's emotional false memories. *Psychol Sci.* 2007; 18:856–60. [PubMed: 17894601]
- Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology.* 2004; 47(Suppl 1):345–58. [PubMed: 15464149]
- Husain M, Mehta MA. Cognitive enhancement by drugs in health and disease. *Trends Cogn Sci.* 2011; 15:28–36. [PubMed: 21146447]
- Hyman SE. Addiction: a disease of learning and memory. *Am J Psychiatry.* 2005; 162:1414–22. [PubMed: 16055762]
- 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. [PubMed: 16148455]
- Janak PH, Martinez JL Jr. Cocaine and amphetamine facilitate retention of jump-up responding in rats. *Pharmacol Biochem Behav.* 1992; 41:837–40. [PubMed: 1594652]
- Kamboj SK, Curran HV. Neutral and emotional episodic memory: global impairment after lorazepam or scopolamine. *Psychopharmacology (Berl).* 2006; 188:482–8. [PubMed: 17047934]

- Karschner EL, Darwin WD, McMahon RP, Liu F, Wright S, Goodwin RS, Huestis MA. Subjective and physiological effects after controlled sativex and oral THC administration. *Clin Pharmacol Ther.* 2011
- Katona I, Rancz EA, Acsady L, Ledent C, Mackie K, Hajos N, Freund TF. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. *J Neurosci.* 2001; 21:9506–18. [PubMed: 11717385]
- Kempton S, Vance A, Maruff P, Luk E, Costin J, Pantelis C. Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychol Med.* 1999; 29:527–38. [PubMed: 10405075]
- Kensinger EA. Remembering emotional experiences: the contribution of valence and arousal. *Rev Neurosci.* 2004; 15:241–51. [PubMed: 15526549]
- Killgore WD, Rupp TL, Grugle NL, Reichardt RM, Lipizzi EL, Balkin TJ. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. *J Sleep Res.* 2008; 17:309–21. [PubMed: 18522689]
- Knowles SK, Duka T. Does alcohol affect memory for emotional and non-emotional experiences in different ways? *Behav Pharmacol.* 2004; 15:111–21. [PubMed: 15096911]
- Koob GF. Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry.* 2009; 42(Suppl 1):S32–41. [PubMed: 19434554]
- Kuhlmann S, Wolf OT. Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behav Neurosci.* 2006; 120:217–23. [PubMed: 16492134]
- Lang, PJ.; Bradley, MM.; Cuthbert, BN. International Affective Picture System (IAPS): Technical Manual and Affective Ratings. Gainesville, FL: NIMH Center for the study of emotion and attention, University of Florida; 1999.
- Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology.* 1993; 30:261–73. [PubMed: 8497555]
- Lee EH, Ma YL. Amphetamine enhances memory retention and facilitates norepinephrine release from the hippocampus in rats. *Brain Res Bull.* 1995; 37:411–6. [PubMed: 7620915]
- Leppanen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry.* 2006; 19:34–9. [PubMed: 16612176]
- Liu DL, Graham S, Zorawski M. Enhanced selective memory consolidation following post-learning pleasant and aversive arousal. *Neurobiol Learn Mem.* 2008; 89:36–46. [PubMed: 17951081]
- Mackie, K. Distribution of cannabinoid receptors in the central and peripheral nervous system. In: Pertwee, RG., editor. *Cannabinoids. Handbook of Experimental Pharmacology.* Springer-Verlag; Heidelberg: 2005. p. 299-325.
- Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther.* 1971; 12:245–58. [PubMed: 5554941]
- Martinez JL Jr, Jensen RA, Messing RB, Vasquez BJ, Soumireu-Mourat B, Geddes D, Liang KC, McGaugh JL. Central and peripheral actions of amphetamine on memory storage. *Brain Res.* 1980; 182:157–66. [PubMed: 7350983]
- McCusker CG. Cognitive biases and addiction: an evolution in theory and method. *Addiction.* 2001; 96:47–56. [PubMed: 11177519]
- McGaugh JL, Roozendaal B. Drug enhancement of memory consolidation: historical perspective and neurobiological implications. *Psychopharmacology (Berl).* 2009; 202:3–14. [PubMed: 18704369]
- McLaughlin RJ, Gobbi G. Cannabinoids and emotionality: a neuroanatomical perspective. *Neuroscience.* 2012; 204:134–44. [PubMed: 21827834]
- Mehta MA, Hinton EC, Montgomery AJ, Bantick RA, Grasby PM. Sulpiride and mnemonic function: effects of a dopamine D2 receptor antagonist on working memory, emotional memory and long-term memory in healthy volunteers. *J Psychopharmacol.* 2005; 19:29–38. [PubMed: 15671126]
- Micheau J, Destrade C, Soumireu-Mourat B. Time-dependent effects of posttraining intrahippocampal injections of corticosterone on retention of appetitive learning tasks in mice. *Eur J Pharmacol.* 1984; 106:39–46. [PubMed: 6529972]
- Mintzer MZ, Griffiths RR. Triazolam-amphetamine interaction: dissociation of effects on memory versus arousal. *J Psychopharmacol.* 2003; 17:17–29. [PubMed: 12680736]

- Nairne JS, Thompson SR, Pandeirada JN. Adaptive memory: survival processing enhances retention. *J Exp Psychol Learn Mem Cogn*. 2007; 33:263–73. [PubMed: 17352610]
- O'Carroll RE, Drysdale E, Cahill L, Shajahan P, Ebmeier KP. Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. *Psychol Med*. 1999; 29:1083–8. [PubMed: 10576300]
- Onur OA, Walter H, Schlaepfer TE, Rehme AK, Schmidt C, Keyser C, Maier W, Hurlmann R. Noradrenergic enhancement of amygdala responses to fear. *Soc Cogn Affect Neurosci*. 2009; 4:119–26. [PubMed: 19246474]
- Pandina, RJ.; Johnson, VL. Why people use, abuse, and become dependent on drugs: Progress toward a heuristic model. In: Glantz, MD.; Hartel, CR., editors. *Drug abuse: Origins & interventions*. American Psychological Association; Washington, DC: 1999. p. 119-147.
- Patrick KS, Markowitz JS. Pharmacology of methylphenidate, amphetamine enantiomers and pemoline in attention-deficit hyperactivity disorder. *Hum Psychopharmacol Clin Exp*. 1997; 12:527–46.
- Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Arch Gen Psychiatry*. 2005; 62:282–8. [PubMed: 15753241]
- Payne JD, Jackson ED, Hoscheidt S, Ryan L, Jacobs WJ, Nadel L. Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. *Learn Mem*. 2007; 14:861–8. [PubMed: 18086830]
- Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de Wit H. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *J Neurosci*. 2008; 28:2313–9. [PubMed: 18322078]
- Ranganathan M, Braley G, Pittman B, Cooper T, Perry E, Krystal J, D'Souza DC. The effects of cannabinoids on serum cortisol and prolactin in humans. *Psychopharmacology (Berl)*. 2009; 203:737–44. [PubMed: 19083209]
- Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology (Berl)*. 2006; 188:425–44. [PubMed: 17019571]
- Robbins TW, Ersche KD, Everitt BJ. Drug addiction and the memory systems of the brain. *Ann N Y Acad Sci*. 2008; 1141:1–21. [PubMed: 18991949]
- Robson P. Therapeutic aspects of cannabis and cannabinoids. *Br J Psychiatry*. 2001; 178:107–15. [PubMed: 11157423]
- Roozendaal B, McGaugh JL. Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. *Eur J Neurosci*. 1997; 9:76–83. [PubMed: 9042571]
- Roozendaal B, McGaugh JL. Memory modulation. *Behav Neurosci*. 2011; 125:797–824. [PubMed: 22122145]
- Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001; 39:32–41. [PubMed: 11071707]
- Smeets T, Otgaar H, Candel I, Wolf OT. True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. *Psychoneuroendocrinology*. 2008; 33:1378–86. [PubMed: 18790572]
- Snodgrass JG, Corwin J. Pragmatics of measuring recognition memory: applications to dementia and amnesia. *J Exp Psychol Gen*. 1988; 117:34–50. [PubMed: 2966230]
- Soetens E, D'Hooge R, Hueting JE. Amphetamine enhances human-memory consolidation. *Neurosci Lett*. 1993; 161:9–12. [PubMed: 8255556]
- Steckler T, Risbrough V. Pharmacological treatment of PTSD - established and new approaches. *Neuropharmacology*. 2012; 62:617–27. [PubMed: 21736888]
- Szabo B, Schlicker E. Effects of cannabinoids on neurotransmission. *Handb Exp Pharmacol*. 2005:327–565. [PubMed: 16596780]
- Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. *Neuroimage*. 2005; 27:991–1001. [PubMed: 15978846]

- Talmi D, Schimmack U, Paterson T, Moscovitch M. The role of attention and relatedness in emotionally enhanced memory. *Emotion*. 2007; 7:89–102. [PubMed: 17352566]
- Tanda G, Goldberg SR. Cannabinoids: reward, dependence, and underlying neurochemical mechanisms - a review of recent preclinical data. *Psychopharmacology (Berl)*. 2003; 169:115–34. [PubMed: 12827346]
- Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, Weinberger DR, Mattay VS. Dopamine modulates the response of the human amygdala: a study in Parkinson's disease. *J Neurosci*. 2002; 22:9099–103. [PubMed: 12388617]
- Tipper CM, Cairo TA, Woodward TS, Phillips AG, Liddle PF, Ngan ET. Processing efficiency of a verbal working memory system is modulated by amphetamine: an fMRI investigation. *Psychopharmacology (Berl)*. 2005; 180:634–43. [PubMed: 15983790]
- van Marle HJ, Hermans EJ, Qin S, Fernandez G. From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. *Biol Psychiatry*. 2009; 66:649–55. [PubMed: 19596123]
- van Stegeren AH, Everaerd W, Cahill L, McGaugh JL, Gooren LJ. Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. *Psychopharmacology (Berl)*. 1998; 138:305–10. [PubMed: 9725752]
- van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijter JP, Rombouts SA. Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage*. 2005; 24:898–909. [PubMed: 15652324]
- van Stegeren AH, Roozendaal B, Kindt M, Wolf OT, Joels M. Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiol Learn Mem*. 2010; 93:56–65. [PubMed: 19695335]
- Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H. Comparison of the subjective effects of delta-9-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)*. 2002; 161:331–9. [PubMed: 12073159]
- Wardle MC, de Wit H. Effects of amphetamine on reactivity to emotional stimuli. *Psychopharmacology (Berl)*. 2012; 220:143–53. [PubMed: 21947316]
- Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. *J Neurosci*. 2011; 31:16597–602. [PubMed: 22090487]
- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988; 54:1063–70. [PubMed: 3397865]
- White TL, Grover VK, de Wit H. Cortisol effects of D-amphetamine relate to traits of fearlessness and aggression but not anxiety in healthy humans. *Pharmacol Biochem Behav*. 2006; 85:123–31. [PubMed: 16934318]
- White TL, Justice AJ, de Wit H. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase. *Pharmacol Biochem Behav*. 2002; 73:729–41. [PubMed: 12213517]
- White TL, Lejuez CW, de Wit H. Personality and gender differences in effects of d-amphetamine on risk taking. *Exp Clin Psychopharmacol*. 2007; 15:599–609. [PubMed: 18179313]
- Wood SC, Anagnostaras SG. Memory and psychostimulants: modulation of Pavlovian fear conditioning by amphetamine in C57BL/6 mice. *Psychopharmacology (Berl)*. 2009; 202:197–206. [PubMed: 18478205]
- Zeeuws I, Soetens E. Verbal memory performance improved via an acute administration of d-amphetamine. *Hum Psychopharmacol*. 2007; 22:279–87. [PubMed: 17599332]
- Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. *Psychopharmacology (Berl)*. 1982; 76:245–50. [PubMed: 6285406]

Fig. 1.

Effects of pre-encoding AMP on mean ($\pm$ SEM) recognition accuracy. 1 = perfect discrimination; 0 = no discrimination (chance responding).

* $p < .05$, # $p = .052$ compared to placebo.

Fig. 2.

Effects of pre-encoding THC on mean ($\pm$ SEM) recognition accuracy. 1 = perfect discrimination; 0 = no discrimination (chance responding).

* $p < .05$ compared to placebo.

Table 1

Participants' demographics and recent drug use (AMP group)

	Mean	SD	Range
Age (years)	24	3.65	18–33
Body Mass Index	23.02	1.93	19–26
Education (years)	15.36	1.5	12–18
Caffeine (cups/day)	1.43	0.98	0–4
Nicotine (cigarettes/week)	20.76	23.67	0–80
Alcohol (drinks/week)	10.1	7.93	2–30
Cannabis (times/month)	2.66	3.73	0–12

Table 2

Participants' demographics and recent drug use (THC group)

	Mean	SD	Range
Age (years)	24.36	4.56	18–35
Body Mass Index	22.45	2.04	19–26
Education (years)	15.48	1.45	12–18
Caffeine (cups/day)	1.64	1.08	0–5
Nicotine (cigarettes/week)	14.76	25.83	0–105
Alcohol (drinks/week)	7.12	4.2	0–14
Cannabis (times/month)	2.12	2.54	0–8

Table 3

Effects of AMP on subjective ratings of pictures during encoding

Subjective Rating		Picture Valence		
		Positive	Neutral	Negative
Positivity	Placebo	5.26 (0.26)	2.73 (0.23)	1.49 (0.08)
	10 mg	5.39 (0.25)	2.88 (0.19)	1.52 (0.09)
	20 mg *	5.53 (0.32)	3.03 (0.25)	1.66 (0.11)
Negativity	Placebo	1.63 (0.13)	1.85 (0.17)	6.05 (0.25)
	10 mg	1.62 (0.12)	1.97 (0.16)	6.2 (0.22)
	20 mg	1.75 (0.14)	2.03 (0.17)	6.28 (0.26)
Arousal	Placebo	4.04 (0.3)	2.43 (0.22)	4.68 (0.29)
	10 mg	4.21 (0.26)	2.53 (0.17)	5.18 (0.25)
	20 mg *	4.36 (0.3)	2.68 (0.22)	5.15 (0.3)

Data are means (SEM).

*
 $p < .05$ compared to placebo.

Table 4

Effects of THC on subjective ratings of pictures during encoding

Subjective Rating		Picture Valence		
		Positive	Neutral	Negative
Positivity	Placebo	5.7 (0.36)	3.55 (0.33)	1.72 (0.15)
	7.5 mg	5.63 (0.3)	3.7 (0.29)	1.96 (0.25)
	15 mg	5.81 (0.37)	4 (0.33)	1.9 (0.2)
Negativity	Placebo	1.83 (0.14)	1.93 (0.13)	6.67 (0.25)
	7.5 mg	2.28 (0.3)	2.61 (0.27)*	6.71 (0.3)
	15 mg	1.87 (0.17)	2.42 (0.22)	6.51 (0.27)
Arousal	Placebo	4.43 (0.29)	2.98 (0.25)	5.38 (0.32)
	7.5 mg *	4.98 (0.34)*	3.69 (0.35)*	5.67 (0.37)
	15 mg	4.7 (0.38)	3.34 (0.32)	5.26 (0.31)

Data are means (SEM).

*
 $p < .05$ compared to placebo.

Table 5

Effects of pre-encoding AMP on raw hit and false alarm rates

Dose	Hit Rate			False Alarm Rate		
	Positive Pictures	Neutral Pictures	Negative Pictures	Positive Pictures	Neutral Pictures	Negative Pictures
Placebo	.92 (.01)	.94 (.02)	.94 (.02)	.07 (.02)	.05 (.01)	.05 (.01)
10 mg	.95 (.02)	.93 (.02)	.99 (.01) *	.06 (.01)	.03 (.01) *	.03 (.01)
20 mg	.96 (.01) *	.95 (.01)	.98 (.01) *	.06 (.01)	.04 (.01)	.04 (.01)

Data are means (SEM).

* $p < .05$ compared to placebo.

Table 6

Effects of pre-encoding THC on raw hit and false alarm rates

Dose	Hit Rate			False Alarm Rate		
	Positive Pictures	Neutral Pictures	Negative Pictures	Positive Pictures	Neutral Pictures	Negative Pictures
Placebo	.93 (.02)	.93 (.02)	.96 (.01)	.08 (.02)	.06 (.02)	.04 (.01)
7.5 mg	.85 (.03) *	.9 (.03)	.94 (.02)	.06 (.01)	.05 (.01)	.06 (.01)
15 mg	.85 (.03) *	.9 (.02)	.92 (.02) *	.07 (.02)	.05 (.01)	.05 (.01)

Data are means (SEM).

* $p < .05$ compared to placebo.

Table 7

Effects of AMP on select subjective mood and cardiovascular measures at the time of encoding.

Measure	placebo	10 mg	20 mg	Dose ($F_{1,23}$)
Feel drug	0.95 (0.26)	1.52 (0.43)	3.49 (0.46) *	12.52
Drug preference	-0.12 (0.31)	1.77 (0.58) *	4.29 (0.7) *	19.08
Stimulated	-0.64 (0.29)	0.63 (0.42) *	2.84 (0.65) *	17.47 [†]
Sedated	1.03 (0.32)	-0.2 (0.31) *	0.5 (0.22)	4.58
Systolic blood pressure (mmHg)	-8.44 (1.43)	8.33 (1.2) *	17.73 (1.83) *	71.31
Diastolic blood pressure (mmHg)	-3.29 (1.25)	7.33 (1.46) *	16.27 (2) *	37.37
Heart rate (bpm)	-8.27 (1.38)	1.88 (2) *	0.81 (1.99) *	12.52

Data are change from baseline means (SEM) of ratings obtained immediately before and after pictures were studied (+90 and +120 min post-capsule), and corresponding F -values from one-way repeated measures ANOVA examining linear main effects of drug dose.

Bold values indicate a significant linear main effect of drug dose ($p < .05$).

[†] Greenhouse-Geisser adjusted value.

* $p < .05$ compared to placebo.

Table 8

Effects of THC on select subjective mood and cardiovascular measures at the time of encoding.

Measure	placebo	7.5 mg	15 mg	Dose ($F_{1,23}$)
Feel drug	0.34 (0.11)	4.15 (0.46) *	4.43 (0.69) *	29.55
Drug preference	-0.4 (0.28)	0.4 (0.51)	0.01 (0.8)	0.83
Stimulated	-0.3 (0.16)	1.46 (0.45) *	1.43 (0.62) *	6.26
Sedated	0.52 (0.16)	2.19 (0.41) *	2.35 (0.51) *	6.55
Systolic blood pressure (mmHg)	-3.54 (1.49)	-0.48 (2.08)	1.69 (1.7) *	2.76
Diastolic blood pressure (mmHg)	-2.31 (1.18)	-0.58 (1.58)	2.04 (1.23) *	4.01
Heart rate (bpm)	-6.15 (1.72)	0.13 (2.15) *	8.54 (3.57) *	10.55 [†]

Data are change from baseline means (SEM) of ratings obtained immediately before and after pictures were studied (+90 and +120 min post-capsule) and corresponding F -values from one-way repeated measures ANOVA examining linear main effects of drug dose.

Bold values indicate a significant linear main effect of drug dose ($p < .05$).

[†]Greenhouse-Geisser adjusted value.

* $p < .05$ compared to placebo.