



# An exploratory study of the combined effects of orally administered methylphenidate and delta-9-tetrahydrocannabinol (THC) on cardiovascular function, subjective effects, and performance in healthy adults



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## ABSTRACT

Methylphenidate (MPH) is commonly prescribed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), and is often used illicitly by young adults. Illicit users often coadminister MPH with marijuana. Little is known about physiologic and subjective effects of these substances used in combination. In this double-blind, cross-over experiment, sixteen healthy adult subjects free from psychiatric illness (including ADHD) and reporting modest levels of marijuana use participated in 6 experimental sessions wherein all combinations of placebo or 10 mg oral doses of delta-9-tetrahydrocannabinol (THC); and 0 mg, 10 mg and 40 mg of MPH were administered. Sessions were separated by at least 48 hours. Vital signs, subjective effects, and performance measures were collected. THC and MPH showed additive effects on heart rate and rate pressure product (e.g., peak heart rate for 10 mg THC + 0 mg, 10 mg, and 40 mg MPH = 89.1, 95.9, 102.0 beats/min, respectively). Main effects of THC and MPH were also observed on a range of subjective measures of drug effects, and significant THC dose × MPH dose interactions were found on measures of "Feel Drug," "Good Effects," and "Take Drug Again." THC increased commission errors on a continuous performance test (CPT) and MPH reduced reaction time variability on this measure. Effects of THC, MPH, and their combination were variable on a measure of working memory (n-back task), though in general, MPH decreased reaction times and THC mitigated these effects. These results suggest that the combination of low to moderate doses of MPH and THC produces unique effects on cardiovascular function, subjective effects and performance measures.

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## 1. Introduction

Methylphenidate (MPH) is considered a front-line treatment for the clinical management of attention deficit hyperactivity disorder (ADHD) (Pliszka et al., 2006). Although hundreds of studies have documented the efficacy of MPH for treating ADHD (Faraone, Biederman, & Roe, 2002; Faraone & Buitelaar, 2010; Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004), significant increases in prescription rates of MPH over the last 15 years have led to controversy about abuse, misuse, and diversion of the drug (Robison, Sclar, Skaer, & Galin, 1999; Safer, Zito, & Fine, 1996; Sembower, Ertischek, Buchholtz, Dasgupta, & Schnoll, 2013; Visser, Blumberg, Danielson, Bitsko, & Kogan, 2013; Visser et al., 2014; Zito et al., 2000; Zosel, Bartelson, Bailey, Lowenstein, & Dart, 2013).

Prevalence of prescribed stimulant misuse is highest among individuals between 12 and 25 years of age, ranging from 0.9% to 10.0% across studies. A number of studies report that stimulant diversion is a common problem, even among children as young as 6th grade (Johnston, O'Malley, Bachman, & Schulenberg, 2006; Kroutil et al., 2006; McCabe, Boyd, & Young, 2007; McCabe, Knight, Teter, & Wechsler, 2005; McCabe, Teter, & Boyd, 2004; McCabe, Teter, & Boyd, 2006; McCabe & West, 2013; Poulin, 2001).

Illicit users of prescription stimulants, including MPH, have higher rates of other drug and alcohol use, including cannabis (Barrett, Darredeau, Bordy, & Pihl, 2005; Low & Gendaszek, 2002; McCabe, Cranford, & Boyd, 2006; McCabe, Cranford, Morales, & Young, 2006; McCabe & West, 2013; McCabe et al., 2004, 2005, 2007; Poulin, 2001; Teter, McCabe, Cranford, Boyd, & Guthrie, 2005; Wilens, Gignac, Swezey, Monuteaux, & Biederman, 2006; Williams, Goodale, Shay-Fiddler, Gloster, & Chang, 2004). Most studies, however, have not differentiated between *concurrent* use (use of more than one drug within some specified time period; e.g., past 12 months) and *simultaneous* use (co-ingestion of more than one drug at the same

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time) (Martin, Clifford, & Clapper, 1992; Massello & Carpenter, 1999; Schensul, Convey, & Burkholder, 2005). Those studies that have assessed simultaneous substance use among illicit prescription stimulant users, suggest that it is very common for these drugs to be used in combination with marijuana; one study found that 52% of undergraduate illicit MPH users reported simultaneous use with marijuana (Barrett, Darredeau, & Pihl, 2006).

Both MPH and oral formulations of delta-9-tetrahydrocannabinol (THC) – the primary psychoactive component of smoked marijuana – result in robust cardiovascular (Hart, Haney, Vosburg, Comer, & Foltin, 2005; Kollins & Rush, 1999; Rush, Essman, Simpson, & Baker, 2001; Rush, Kollins, & Pazzaglia, 1998), subjective (Hart et al., 2002, 2005; Rush et al., 1998, 2001), and performance effects (Coghill et al., 2013; Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Hammerness, Fried, Petty, Meller, & Biederman, 2013; Lane, Cherek, Tcheremissine, Lieving, & Pietras, 2005; Linssen, Sambeth, Vuurman, & Riedel, 2014; McDonald, Schleifer, Richards, & de Wit, 2003; Nandam et al., 2011; Ramaekers et al., 2006). Although several studies have examined the interactive effects of smoked marijuana administered in combination with other stimulant-like drugs (e.g., cocaine, nicotine) (Foltin & Fischman, 1990; Penetar et al., 2005), no studies to date have explicitly examined the effects of MPH and THC co-administration.

The effects of simultaneous MPH and marijuana use may differ from the effects of either drug alone. Both MPH and marijuana, for instance, increase heart rate and blood pressure when administered acutely, even with oral formulations of delta-9-tetrahydrocannabinol (THC) (Hart et al., 2005; Kollins & Rush, 1999; Rush et al., 1998, 2001). With respect to subjective drug effects, both MPH and oral THC acutely increase ratings of “good effects,” “like drug,” and “like to take again” (Hart et al., 2002, 2005; Rush et al., 1998, 2001). In addition to physiological and subjective effects, MPH-THC co-administration may result in unique behavioral effects compared with the acute effects of each drug. THC administered alone either orally or in smoked form has been shown to disrupt a range of neurocognitive endpoints, including decision making (Lane et al., 2005), inhibitory control (McDonald et al., 2003; Ramaekers et al., 2006), and memory (Curran et al., 2002); though these effects have not been categorically replicated (Vadhan et al., 2007). By contrast, MPH has been shown to *improve* a range of neurocognitive endpoints, including inhibitory control and memory in individuals with and without ADHD (Coghill et al., 2013; Hammerness et al., 2013; Linssen et al., 2014; Nandam et al., 2011). It is not known whether the simultaneous use of THC and MPH results in additive effects on cardiovascular function and/or subjective effects; or whether MPH would serve to mitigate the performance impairing effects of marijuana.

Given the reported rates of simultaneous use of MPH and marijuana (Barrett et al., 2005, 2006), characterizing the effects of these specific drugs in combination is important to more fully evaluate the potential risks of co-administration. The primary objective of the present study therefore was to assess the effects of orally administered THC (dronabinol) alone (0 mg vs. 10 mg) and in combination with two doses of immediate release methylphenidate (0 mg, 10 mg, 40 mg) in a blinded fashion on measures of cardiovascular function (heart rate, blood pressure), subjective drug effects, and cognitive function (inhibitory control, attention, and working memory).

Given the exploratory nature of this study, we elected to use orally administered THC since it was more practical to administer in the context of a human laboratory study. Orally administered THC has been shown to have similar subjective and cardiovascular effects as smoked marijuana; and produces dose-dependent increases in plasma THC levels (Chait & Zacny, 1992; Hart et al., 2002; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002) and we therefore reasoned that an oral THC would be a safe and practical approach for an initial investigation of the combined effects of MPH and THC.

## 2. Methods

### 2.1. Subjects

Sixteen subjects (10 males, 6 females) with a history of recreational marijuana use participated in the study after providing informed consent approved by the local Institutional Review Board. All subjects underwent a physical examination by a licensed physician, and medical and developmental histories were obtained. Current and previous drug use, including alcohol and cigarettes, were also measured at screening. To participate in the study, subjects were required to be between the ages of 18–45 years (mean age = 24.6 years), inclusive; have a body mass index >18 but <35; and report at least 10 lifetime uses of marijuana, including at least once in the past 2 months. All participants reported more than 40 lifetime uses of marijuana, smoked for the first time at age 16.6 years, and reported smoking an average of 4 times in the past 30 days. A total of 12/16 participants report lifetime cigarette smoking, with 8/16 reporting cigarette smoking in the past 30 days. Participants reported an average of 7 times using alcohol in the past 30 days. Other than marijuana, the majority of participants reported no other illicit drug use in their lifetime, although several reported using inhalants ( $n = 2$ ); cocaine ( $n = 3$ ); ecstasy ( $n = 1$ ); prescription stimulants ( $n = 2$ ); and prescription pain medicine ( $n = 2$ ).

Subjects were excluded if they met criteria for any *DSM-IV* diagnosis [assessed using the Structured Clinical Interview for *DSM-IV* (First, Gibbon, Williams, & Spitzer, 1997)]; reported a history of adverse reaction to stimulant medication; had a resting heart rate of >100 beats/minute or a systolic blood pressure >150 mm/Hg; reported a history of any significant medical problems (e.g., seizures, cardiac abnormalities, etc.); were currently prescribed any psychoactive medications; had an estimated IQ of <80 [assessed using the Kauffmann Brief Intelligence Scale (Kaufman & Kaufman, 2004)]; scored  $\geq 6$  on the Marijuana Screening Inventory [MSI-X; (Alexander & Leung, 2006)]; or scored  $\geq 8$  on the Alcohol Use Disorders Identification Test [AUDIT; (Bohn, Babor, & Kranzler, 1995)].

### 2.2. General procedures

All study procedures were reviewed and approved by the local institutional review board. All subjects provided informed consent for the study and, following a Screening session, completed 6 experimental sessions. Subjects were told that the purpose of the study was to measure the effects of stimulant drugs (methylphenidate and/or amphetamine) alone and/or in combination with THC (dronabinol) on mood, cardiovascular functioning, and behavior. Subjects were told that they could receive methylphenidate, amphetamine, dronabinol, and placebo in any combination. Other than receiving this general information, participants were unaware of the type of drug administered. Following the study, subjects were informed specifically which drugs they had received.

Subjects arrived at the laboratory between 0700 and 0900 on the morning of each scheduled experimental session. Subjects were transported to and from the laboratory by taxi. Subjects provided urine samples each day that were screened for excluded drugs using InstaCup Drug Screens (Columbia Laboratory Supplies). Breath alcohol levels were assessed each morning with a handheld breathalyzer (ALERT model; Columbia Laboratory Supplies) and participants were required to record a BAL of 0.0. No subjects were excluded for noncompliance with drug and alcohol requirements. Subjects also had to pass a field sobriety test to participate in the session for that day. Following arrival, subjective effects measures and vital signs were assessed. Approximately 30 minutes after arrival, THC capsules were administered (0 mg or 10 mg). Ninety minutes later, MPH capsules were administered (0 mg, 10 mg, or 40 mg). The timing of dosing was designed such that peak effects of methylphenidate occurred at comparable times as peak effects of THC – peak effects of oral

THC occur approximately 3 hours post-dose, whereas MPH peak effects occur approximately 1.5 hours after dosing.

Throughout the session, vital signs and subjective effects were assessed every 30 minutes. Performance measures were administered 4 hours following THC administration (2.5 hours following MPH administration). The last assessment point was 6.5 hours following THC administration, after which a field sobriety test was conducted and subjects were dismissed from the laboratory. Transportation was again provided via taxi for all subjects. When behavioral or physiological testing was not ongoing, subjects were allowed to participate in a variety of sedentary activities, such as reading/studying, watching television, playing video or card games or solving puzzles.

Behavioral testing was conducted in a separated sound-attenuated room located adjacent to the general laboratory area. The testing rooms consisted of a desk and chair, a PC computer and monitor, keyboard, computer mouse, and physiological monitoring equipment. The PC was used to record responses to all subject-rated measures using the mouse as the primary input device. Subjects were able to earn up to \$800 for completing all experimental sessions.

### 2.3. Dependent measures – vital signs

Heart rate and blood pressure were recorded using a Vital Check 4200 digital monitor (Ivac Corp., San Diego, CA). Physiological measures were recorded upon arrival to the laboratory, and every thirty minutes thereafter. Subjects who exhibited sustained (at 2 or more consecutive assessments) heart rate or systolic blood pressure above 100 beats/minute or 160 mm/Hg, respectively were evaluated by a physician to ensure safety. In addition to the measured heart rate and blood pressure parameters, rate-pressure product was calculated as the product of heart rate and systolic blood pressure. Rate-pressure product is considered to be an indicator of the oxygen requirements of the heart and is a measure of overall cardiac exertion. Vital signs and other adverse reactions were monitored throughout each session and a study physician (RD or AC) were available in the event of untoward events.

### 2.4. Dependent Measures – subject-rated effects

The Adjective Rating Scale (ARS) (Oliveto et al., 1992), the Addiction Research Center Inventory (ARCI) (Martin, Sloan, Sapira, & Jasinski, 1971), and the Drug-Effect Questionnaire (DEQ) (Rush et al., 2001; Stoops, Glaser, Fillmore, & Rush, 2004) were used to assess subjective effects. The ARS consists of 32 items and contains two 16-item subscales: Sedative and Stimulant. The Stimulant scale from the ARS has been shown to be sensitive to the effects of MPH in the dose range used in the present study (Rush et al., 2001). The ARCI is commonly used to assess abuse liability of a variety of drug classes and contains five major subscales: Morphine-Benzedrine Group (MBG; a measure of euphoria); Pentobarbital, Chlorpromazine, Alcohol Group (PCAG; a measure of sedation); Lysergic Acid Diethylamide (LSD; a measure of dysphoria); and Benzedrine Group and Amphetamine scales (BG, A; empirically derived stimulant sensitive scales). The DEQ consists of eleven 100 mm visual analog scales presented on the computer screen one at a time. Subjects are instructed to rate each item on the basis of how they feel at the present time. Each visual analog scale was anchored with the descriptors “not at all,” “some,” and “an awful lot.” The DEQ items were: “I feel the medicine’s effect,” “I feel good effects of the medicine,” “I feel bad effects from the medicine,” “I like the medicine,” “I feel friendly,” “I feel confused,” “I can concentrate right now,” “I feel excited,” “I feel alert,” “I feel relaxed,” and “I would like to take this medicine again.” Subjects used the mouse to position a cross-line on the analog scale to indicate their response.

### 2.5. Dependent measures – performance measures

#### 2.5.1. Conners Continuous Performance Test (CPT; (Conners, 1994))

The Conners Continuous Performance Test was completed on an IBM-compatible desktop computer. During this task, 360 total letters appeared on the computer screen, one at a time, each for approximately 250 milliseconds. The 360 trials were presented in 18 blocks of 20 trials each. The blocks differed only in the interstimulus intervals (ISI) between letter presentations, which lasted 1-, 2-, or 4-seconds. Subjects were instructed to press the spacebar when any letter except the letter “X” appeared on the screen. The event rate, or percentage of trials when letters other than “X” appeared, was 90% across all ISI blocks. Reaction time was measured from the point at which any letter other than “X” appeared on the screen until the spacebar was depressed. The Conners’ CPT task takes approximately 14 minutes to complete. Four primary outcome measures were used or data analysis: 1) omission errors (failure to respond to non-“X” targets; a measure of vigilance); 2) commission errors (responding to “X” targets; a measure of inhibitory control); 3) reaction time (time from presentation of a non-“X” target to response; a measure of psychomotor function; and 4) reaction time standard error (the variability of reaction time; a measure of attentional lapses).

#### 2.5.2. n-Back task

A modified version of the n-back task was used (Mendrek et al., 2006). The task is a computer-administered test of working memory that takes approximately 10 minutes to complete. During the n-back task, participants see a series of letters of the alphabet presented on a screen at a rate of one letter per second. Participants are required to identify whether the current stimulus being presented on the screen is the same as the stimulus presented n-back. In the 1-back condition, participants identify whether the current letter is the same as the letter that preceded it (i.e., 1 letter back). In the 2-back condition, participants identify whether the current letter is the same as the letter presented 2 letters back. Similarly, in the 3-back condition, participants identify whether the current letter is the same as the letter presented 3 letters back. A ‘0-back’ condition in which subjects press a button whenever they see the letter ‘X’ presented is also administered. Each letter is presented for 400 ms followed by a 1600 ms inter-stimulus interval. Each n-back condition was presented in a 42-s block, followed by a 15-s fixation period and a 3-s instruction screen. In each block, 7 targets were presented (33%) and 14 non-targets (67%), for a total of 21 trials. Two blocks of each n-back condition were presented, making 8 blocks total. Primary outcomes from this task included the percentage of correct responses in each n-back condition (0, 1, 2, or 3), and reaction time for each condition.

### 2.6. Drug dose and administration

Across the 6 experimental sessions, subjects received, in random order, all combinations of 2 doses of THC (0 mg, 10 mg) and 3 doses of MPH (0 mg, 10 mg, 40 mg). Experimental sessions were scheduled a minimum of 48 hours apart. All drugs were administered under double-blind conditions and were prepared by a research pharmacy. Doses were prepared by encapsulating commercially available MPH hydrochloride or dronabinol and lactose filler. Placebo capsules contained only lactose. Medical oversight for the protocol was the responsibility of the study physicians. During each session, participants orally ingested capsules with 150 ml water. THC capsules were administered approximately 30 minutes following arrival at the laboratory and MPH capsules were administered 90 minutes following THC administration. Drug administration procedures were designed to ensure that participants swallowed the capsules and did not open them in their mouths and taste the contents (Abreu & Griffiths, 1996).

## 2.7. Data analysis

Analyses were conducted using Stata SE for Macintosh (Stata Corp., College Station, TX, USA). All data were analyzed using 2 (THC dose: 0 mg, 10 mg)  $\times$  3 (MPH dose: 0 mg, 10 mg, 40 mg) repeated measures ANOVA. When main effects or interactions were observed, planned pairwise comparisons were conducted to test the additive effects of THC administration following MPH administration across doses. Specifically, 0 mg THC was compared to 10 mg THC across MPH dose levels and 0, 10, and 40 mg MPH were compared across the two THC dose levels. These comparisons were conducted using the Tukey HSD test. CPT and n-back data were analyzed with the outcome measures noted. For subjective effects and vital sign data, analyses were conducted in two ways. First, peak effects were analyzed, which were the highest values reported following drug administration for each day. Second, area-under-the-time-course-curve (AUC) analyses were conducted using the trapezoid method (Kollins & Rush, 2002). Since AUC and peak effects results were virtually identical with respect to the pattern of findings, only peak effects data are described in the results.

## 3. Results

### 3.1. Vital signs

In general, both drugs and their combination were well-tolerated across participants. One adverse event required the attention of the study physician – a male study participant experienced extended tachycardia (>100 bpm) following the combination of 40 mg MPH and 10 mg THC. The study physician monitored the participant and performed an ECG. The participant remained in the lab for several extra hours to ensure safety. Since this event occurred on his last study visit, he did not have to be return for any additional study visits.

#### 3.1.1. Heart Rate

Table 1 shows peak effects results for heart rate, systolic and diastolic blood pressure, and rate-pressure product. Both MPH and THC resulted in significant main effects on heart rate. In the absence of MPH (i.e., MPH placebo condition), there was no difference between the placebo and 10 mg THC conditions (84.3 vs. 89.1 bpm, respectively). In the absence of THC, 40 mg MPH resulted in significantly greater heart rate compared to both the 10 mg MPH and 0 mg MPH conditions. The combination of 10 mg THC and both the 10 mg and 40 mg MPH doses resulted in significantly higher heart rate than either of these MPH conditions in combination with 0 mg THC. Finally, when administered in combination with 10 mg THC, 40 mg MPH resulted in significantly higher heart rate than 0 mg MPH.

#### 3.1.2. Systolic and diastolic blood pressure

There was a significant main effect of MPH on both systolic and diastolic blood pressure characterized by an increase under the 40 mg dose of MPH. No other significant main effects or interactions were observed.

**Table 1**

Mean peak effects (SD) for vital signs across dose levels of MPH and THC.

| Peak Effects          | MPH Dose         |                  |                  |                  |                  |                  | THC F   | MPH F   | THC x MPH F |
|-----------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------|---------|-------------|
|                       | 0 mg             |                  | 10 mg            |                  | 40 mg            |                  |         |         |             |
|                       | 0 mg THC         | 10 mg THC        | 0 mg THC         | 10 mg THC        | 0 mg THC         | 10 mg THC        |         |         |             |
| Heart Rate            | 84.3 (10.6)      | 89.1 (8.3)       | 83.6 (11.8)      | 95.9 (10.1)      | 95.3 (15.4)      | 102.0 (18.1)     | 26.73** | 14.39** | 1.32        |
| Systolic BP           | 136.1 (13.2)     | 139.1 (16.9)     | 137.3 (9.8)      | 136.1 (15.8)     | 142.3 (15.3)     | 145.1 (17.1)     | 0.41    | 4.79*   | 0.91        |
| Diastolic BP          | 83 (5.9)         | 85.9 (11.8)      | 83.5 (8.0)       | 83.1 (5.6)       | 87.5 (11.2)      | 88.1 (9.7)       | 0.4     | 4.49*   | 0.5         |
| Rate pressure product | 11441.8 (1584.1) | 12352.0 (1610.5) | 11425.5 (1478.6) | 13031.1 (1847.0) | 13461.1 (2025.5) | 14845.8 (3429.0) | 10.7**  | 16.45** | 0.19        |

Right columns indicate F-values for 2 factor repeated measures ANOVA. \*p < 0.05, \*\*p < 0.01.

### 3.1.3. Rate pressure product

Significant main effects of both THC and MPH were observed for RPP. There was no difference between 10 mg THC and 0 mg THC in the absence of MPH. By contrast, the 40 mg dose of MPH resulted in significantly higher RPP compared to both the 10 mg MPH dose and the 0 mg MPH dose in the absence of THC. The 10 mg dose of THC resulted in significantly higher RPP than the 0 mg THC dose when administered in combination with both 10 and 40 mg MPH. When 40 mg MPH was administered in combination with 10 mg THC, RPP was higher than 10 mg.

## 3.2. Subjective effects

Table 2 illustrates peak effects for the ARS, ARCI, and DEQ. There were main effects for MPH on the following subscales: ARS Stimulant scale, ARCI MBG and A scales, DEQ Feel Drug, Good Effect, Bad Effect, Like Drug, Confused, Excited, and Take Again Scales. In general, the main effects of MPH across subjective effect scales were characterized by higher ratings for the 40 mg dose compared to the 10 mg or 0 mg doses. For example, on the ARS Stimulant subscale in the both THC conditions, the 40 mg MPH dose resulted in significantly higher ratings than the 10 mg or 0 mg MPH dose.

There were significant main effects of THC dose on the following subscales: ARS Sedative scale, ARCI PCAG and LSD scales, DEQ Feel Drug, Good Effects, Bad Effects, Like Drug, Confused, and Alert subscales. The main effects of THC were characterized in general by a pattern of elevated ratings under the 10 mg condition compared to the 0 mg condition, regardless of MPH dose.

Significant MPH  $\times$  THC interactions were observed on 3 of the DEQ scales: Feel Drug, Good Effects, and Take Drug Again (Fig. 2, Panels C–E). The interaction was characterized by dose-dependent increases in ratings of MPH effects under the THC 0 mg condition combined with comparatively higher and consistent ratings of 10 mg THC effects across doses of MPH.

## 3.3. Performance measures

Table 3 shows results from the CPT and n-back across drug conditions. For the CPT, no drug effects were observed for omission errors. There was a significant main effect of THC on commission errors that was generally characterized by a greater number of errors in the 10 mg condition compared to the 0 mg condition across MPH doses, although these specific contrasts were not significantly different. There was also a significant main effect of MPH on RT SE characterized by a general MPH-dose-dependent decrease in RT SE across both doses of THC.

On the n-back task, there were no main effects or interactions for correct responding under any of the conditions. There were main effects of MPH dose on RT in both the 0-back and 2-back conditions. Both of these effects were characterized by faster reaction times on 40 mg MPH compared to 10 mg MPH under 0 mg THC conditions. There was also a significant main effect of THC in the 3-back condition.

**Table 2**

Mean peak effects(SD)for subjective effects measures across dose levels of MPH and THC.

| ARS peak effects   | MPH Dose    |             |             |             |             |             | THC F   | MPH F   | THC x MPH F |
|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|---------|-------------|
|                    | 0 mg        |             | 10 mg       |             | 40 mg       |             |         |         |             |
|                    | 0 mg THC    | 10 mg THC   | 0 mg THC    | 10 mg THC   | 0 mg THC    | 10 mg THC   |         |         |             |
| Stimulant subscale | 26.3 (3.7)  | 27.1 (4.6)  | 27.4 (5.0)  | 27.4 (5.9)  | 32.0 (7.3)  | 32.2 (5.8)  | 0.00    | 7.61**  | 0.01        |
| Sedative subscale  | 27.3 (8.4)  | 30.5 (7.6)  | 23.8 (6.7)  | 30.9 (10.8) | 24.6 (5.2)  | 29.8 (8.7)  | 11.35** | 0.47    | 2.58        |
| ARCI peak effects  |             |             |             |             |             |             |         |         |             |
| PCAG               | 6.0 (3.6)   | 8.3 (3.8)   | 4.6 (2.6)   | 8.1 (3.9)   | 5.3 (2.9)   | 8.7 (3.8)   | 36.74** | 0.71    | 1.47        |
| BG                 | 5.1 (2.1)   | 5.9 (2.3)   | 6.3 (2.7)   | 6.1 (3.1)   | 7.4 (2.8)   | 6.6 (2.2)   | 0.00    | 5.12*   | 2.70        |
| LSD                | 4.9 (2.0)   | 5.8 (2.3)   | 4.2 (2.3)   | 5.8 (3.0)   | 5.1 (2.7)   | 6.8 (2.4)   | 22.18** | 2.47    | 1.00        |
| MBG                | 7.0 (4.5)   | 9.9 (5.6)   | 9.3 (6.4)   | 10.6 (6.9)  | 11.5 (6.2)  | 12.3 (4.9)  | 3.69    | 7.64**  | 0.74        |
| A                  | 3.3 (2.5)   | 4.5 (2.9)   | 4.3 (3.0)   | 4.6 (2.8)   | 5.5 (2.7)   | 5.6 (2.4)   | 2.07    | 6.51**  | 0.72        |
| DEQ peak effects   |             |             |             |             |             |             |         |         |             |
| Feel drug effect   | 35.9 (32.3) | 78.5 (17.3) | 47.9 (32.1) | 75.8 (21.3) | 75.3 (24.5) | 82.7 (16.5) | 35.44** | 10.71** | 5.87**      |
| Good effect        | 34.9 (28.6) | 68.9 (14.0) | 55.6 (28.6) | 68.3 (24.3) | 67.9 (21.9) | 78.8 (16.5) | 26.35** | 9.59**  | 4.62*       |
| Bad effect         | 19.6 (22.9) | 41.9 (22.2) | 22.3 (24.1) | 28.3 (25.7) | 36.1 (29.3) | 47.6 (29.9) | 9.10**  | 7.64**  | 2.68        |
| Like drug          | 55.6 (13.6) | 67.7 (15.2) | 58.1 (22.1) | 66.8 (20.5) | 68.4 (17.9) | 73.1 (15.9) | 8.94**  | 6.50**  | 0.87        |
| Friendly           | 72.8 (17.3) | 70.7 (16.3) | 68.8 (15.4) | 75.1 (18.5) | 76.5 (17.0) | 74.9 (16.6) | 0.04    | 1.40    | 1.61        |
| Confused           | 18.6 (22.8) | 34.7 (27.8) | 16.9 (22.6) | 32.6 (27.1) | 29.3 (31.0) | 41.7 (31.6) | 13.15** | 6.21**  | 0.05        |
| Concentrate        | 77.8 (17.9) | 74.8 (14.9) | 76.1 (18.1) | 73.9 (17.7) | 81.4 (17.5) | 77.4 (15.2) | 3.99    | 2.01    | 0.04        |
| Excited            | 51.6 (23.1) | 52.1 (21.6) | 51.6 (26.2) | 52.3 (25.7) | 63.8 (22.2) | 67.2 (22.2) | 0.33    | 7.15**  | 0.09        |
| Alert              | 71.5 (19.2) | 71.7 (14.6) | 79.2 (15.8) | 71.9 (19.3) | 81.9 (14.1) | 77.7 (13.8) | 5.04*   | 2.53    | 0.77        |
| Relaxed            | 76.4 (16.7) | 75.5 (13.0) | 73.6 (16.1) | 81.8 (15.3) | 76.1 (17.3) | 79.4 (16.5) | 1.15    | 0.38    | 1.35        |
| Take drug          | 57.6 (23.3) | 65.2 (19.4) | 54.8 (25.0) | 67.2 (21.0) | 71.9 (18.4) | 71.3 (19.0) | 3.92    | 4.72*   | 4.57*       |

Right columns indicate F-values for 2 factor repeated measures ANOVA. \*p &lt; 0.05, \*\*p &lt; 0.01.

In general, the 10 mg dose of THC resulted in slower reaction times than the 0 mg THC condition across doses of MPH.

#### 4. Discussion

The present study is the first to systematically measure the effects of MPH administered in combination with THC in human participants. Several findings are noteworthy. First, there were significant additive effects of THC and MPH on heart rate. When administered with either 10 mg or 40 mg MPH, THC significantly increased heart rate more than the MPH doses alone. Second, additive and interactive effects of THC and MPH were observed across a range of subjective effects; however, most of these effects were largely due to robust effects of THC. Finally, the effects of THC and MPH alone and in combination on performance measures were inconsistent,

a finding that is somewhat discrepant from previous studies of orally administered and smoked THC.

Especially since the simultaneous use of these drugs is likely to occur in the context of smoked marijuana, which is itself associated with increased risk for a range of adverse cardiac events (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001; Sidney, 2002), the additive effects of THC and MPH on heart rate and RPP observed in the present study are noteworthy. Moreover, there is controversy regarding the occurrence of adverse cardiac events in patients prescribed MPH for clinical purposes (Biederman, Spencer, Wilens, Prince, & Faraone, 2006; Nissen, 2006; Winterstein et al., 2012), although in general data do not support the role of the drug in increasing risk in patients without significant predisposing factors (Cooper et al., 2011; Habel et al., 2011; Olsson et al., 2012; Westover & Halm, 2012; Winterstein et al., 2007, 2012). Whether the additive effects of MPH and THC observed in the present study would be observed following administration of

**Table 3**

CPT and n-Back performance measures [mean (SD)] across dose levels of MPH and THC.

| CPT                       | MPH dose      |               |               |               |               |               | THC F | MPH F  | THC x MPH F |
|---------------------------|---------------|---------------|---------------|---------------|---------------|---------------|-------|--------|-------------|
|                           | 0 mg          |               | 10 mg         |               | 40 mg         |               |       |        |             |
|                           | 0 mg THC      | 10 mg THC     | 0 mg THC      | 10 mg THC     | 0 mg THC      | 10 mg THC     |       |        |             |
| Omission errors (#)       | 3.2 (4.8)     | 5.3 (8.9)     | 1.4 (1.5)     | 1.9 (4.4)     | 1.3 (2.6)     | 3.9 (6.7)     | 2.11  | 2.61   | 0.6         |
| Commission errors (#)     | 10.0 (9.2)    | 14.0 (7.4)    | 10.5 (7.3)    | 11.0 (7.9)    | 10.3 (10.1)   | 12.5 (9.9)    | 5.37* | 0.52   | 0.58        |
| Reaction time (ms)        | 349.3 (109.1) | 335.6 (99.7)  | 338.7 (99.2)  | 330.2 (99.0)  | 354.0 (49.1)  | 332.5 (108.7) | 0.61  | 0.32   | 0.07        |
| Reaction time SE (ms)     | 6.2 (3.2)     | 8.6 (7.9)     | 5.8 (2.8)     | 4.9 (2.1)     | 4.5 (1.8)     | 5.8 (4.2)     | 1.03  | 7.18** | 1.34        |
| n-Back % correct          |               |               |               |               |               |               |       |        |             |
| 0-back                    | 0.99 (0.03)   | 0.98 (0.04)   | 0.98 (0.05)   | 1.0 (0.02)    | 0.99 (0.03)   | 1.0 (0.0)     | 0.03  | 1.46   | 2.03        |
| 1-back                    | 0.99 (0.02)   | 0.96 (0.11)   | 0.94 (0.13)   | 0.98 (0.04)   | 0.98 (0.04)   | 0.96 (0.11)   | 0.08  | 0.11   | 1.9         |
| 2-back                    | 0.88 (0.19)   | 0.87 (0.19)   | 0.82 (0.22)   | 0.85 (0.23)   | 0.86 (0.22)   | 0.95 (0.10)   | 0.04  | 1.64   | 0.92        |
| 3-back                    | 0.80 (0.25)   | 0.73 (0.27)   | 0.72 (0.26)   | 0.79 (0.27)   | 0.76 (0.25)   | 0.77 (0.26)   | 1.42  | 0.07   | 3.33        |
| n-Back reaction time (ms) |               |               |               |               |               |               |       |        |             |
| 0-back                    | 446.0 (57.6)  | 442.9 (61.8)  | 488.8 (84.4)  | 464.6 (65.1)  | 427.4 (65.7)  | 421.2 (36.4)  | 0.73  | 7.50** | 0.47        |
| 1-back                    | 457.7 (82.4)  | 493.3 (96.2)  | 465.5 (89.0)  | 460.8 (75.9)  | 424.5 (65.5)  | 451.6 (93.4)  | 3.51  | 2.46   | 0.86        |
| 2-back                    | 552.9 (155.8) | 577.6 (120.3) | 575.2 (150.5) | 552.8 (153.2) | 477.5 (90.4)  | 499.7 (116.3) | 0.23  | 4.40*  | 0.85        |
| 3-back                    | 611.0 (115.1) | 674.1 (180.5) | 596.4 (125.1) | 631.6 (178.7) | 526.5 (103.1) | 600.4 (127.4) | 5.98* | 2.62   | 0.33        |

Right columns indicate F-values for 2 factor repeated measures ANOVA. \*p &lt; 0.05, \*\*p &lt; 0.01.

smoked marijuana is unknown. However, for young adults using MPH illicitly, data from the present study and the extant literature suggest that there may be risk in combining oral MPH with smoked marijuana. Future work should more thoroughly characterize interactive cardiac effects of smoked marijuana taken in combination with orally administered MPH.

Consistent with previous research, in the present study, both MPH and THC significantly increased subjective ratings of drug effects compared to placebo conditions. There were also statistically significant interactions between THC and MPH for “Feel Drug Effect,” “Good Effects,” and “Take Again.” Given the pattern of findings, though, these interactions appear to be the result of 10 mg THC producing robust subjective effects across MPH doses. There was little evidence that any combination of MPH and THC doses produced effects different than THC alone. However, since both oral THC and MPH produce reinforcing effects in laboratory studies (Hart et al., 2002, 2005; Kollins, English, Robinson, Hallyburton, & Chrisman, 2009; Rush et al., 2001), future studies should explicitly examine the reinforcing effects of the combination of these drugs (including smoked marijuana) to more fully understand their synergistic abuse potential.

In the present study, oral THC increased commission errors on the CPT and MPH decreased reaction time variability. Effects of both drugs on n-back performance was inconsistent. Previous studies have reported that both oral THC and smoked marijuana decrease inhibitory control and increase risky decision-making. In one laboratory study, smoking a high concentration marijuana cigarette (3.58% THC), compared to a lower concentration marijuana cigarette or placebo, resulted in significantly more risky choices and less sensitivity to consequences (Lane et al., 2005; McDonald et al., 2003). Another study found that orally administered THC (7.5 mg and 15 mg), compared to placebo, produced significantly slower stop-signal reaction times, a putative measure of inhibitory control (McDonald et al., 2003). In the current study, although there were significant main effects of THC on CPT commission errors, there was significant variability on this particular measure, raising the possibility that there may be important individual differences that moderate THC effects on impulsive responding. THC-induced increases in commission errors were somewhat mitigated with administration of both 10 mg and 40 mg MPH. It is possible then, that the dose of MPH used in the present study were high enough to counteract the effects of a relatively low dose of THC. Future research should assess whether this same pattern of findings is observed across a broader range of THC and MPH doses. The effects of MPH on reaction time variability in the present study are consistent with a number of studies that have reported beneficial effects of stimulants on measures of this construct (Coghill et al., 2013).

The present study found no effects of MPH, THC, or their combination on accuracy on the n-back, a measure of working memory performance, although there were transient effects on reaction time during this task. Previous studies have documented the deleterious effects of THC/marijuana on working memory and other related processes (Ranganathan & D'Souza, 2006; Vadhan et al., 2007). However, most studies have examined only the effects of smoked or intravenous THC, and studies administering oral THC have failed to find effects on working memory (Curran et al., 2002).

The present findings need to be considered in light of several important limitations. First, the size and nature of the sample should be considered when generalizing outcomes. The number of participants precluded important subanalyses, such as differences by sex or race/ethnicity. Indeed previous studies have found differential effects of sex following co-administration of smoked marijuana and nicotine on cardiovascular outcomes (Penetar et al., 2005). Also, participants were screened for any Axis I psychopathology and, as such, individuals with ADHD were excluded. Given that some studies have shown differential patterns of stimulant drug effects in ADHD versus non-ADHD samples (Kollins et al., 2009), future work should evaluate whether co-administration of stimulants and THC results in

similar effects in individuals with and without ADHD. This is particularly important given that adolescents and adults with ADHD are at increased risk for problematic cannabis use (Charach, Yeung, Climans, & Lillie, 2011; Lee, Humphreys, Flory, Liu, & Glass, 2011; Molina et al., 2013) and information about the interactive effects of stimulant treatment with marijuana use is not well understood. Second, the dose ranges of both THC and MPH were relatively limited. Although the decision to evaluate the doses in the present study were guided based on safety considerations, assessment of a broader range of doses will help to more fully characterize the effects of MPH and THC co-administration. Third, since we only evaluated the performance measures at a single time point approximately 4 hours after THC administration and 2.5 hours after MPH administration, we may have missed the peak effects of one or both drugs across participants. This timing could have contributed to the relative lack/inconsistency of findings on performance measures. Future studies investigating the combination of these drugs would be well served to assess the time course of effects at multiple points. Fourth, participants were not explicitly instructed to refrain from food/caffeine on the mornings of sessions. Variability in food or caffeine intake across participants could have influenced the outcomes, and future work should standardize meals and caffeine intake prior to dosing. Finally, the generalizability of findings is limited by our use of the oral formulation of THC rather than smoked marijuana. Given the substantial pharmacokinetic differences between these two routes of administration, our findings should be interpreted cautiously, especially with respect to the potential cardiovascular effects of co-administration. For example, compared to oral administration, the maximum plasma concentrations of THC following smoked marijuana in occasional users has been shown to be 6–18 times higher (Bossong et al., 2009; Toennes, Ramaekers, Theunissen, Moeller, & Kauert, 2008) (Marinol package insert). Given the similarity in behavioral and subjective effects of oral THC vs. smoked marijuana, however (Chait & Zacny, 1992; Hart et al., 2002, 2005; Wachtel et al., 2002), the effects of oral THC and MPH are still of interest and provide an important first step in evaluating this often used drug combination. Still, future studies would be well served to evaluate the effects of smoked marijuana in combination with MPH, or other prescription stimulants, such as amphetamine.

In spite of these limitations, several conclusions can be drawn from the present study. First, co-administration of MPH and THC results in additive effects on heart rate and rate-pressure product. These increases in cardiovascular stress occur in combination with a slight, though statistically non-significant attenuation of THC-induced changes in inhibitory control (CPT commission errors). In addition, 10 mg THC produced robust subjective effects associated with drug liking. These data raise the possibility that the combination of prescription stimulants, such as MPH, and THC, especially in smoked form, may be a desirable “cocktail” for young adults seeking euphorogenic effects of marijuana without adversely impacting cognitive performance. However, this combination may come at the cost of increasing cardiovascular strain, which could increase risk.

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