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Response perseveration and adaptation in heavy marijuana-smoking adolescents

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Abstract

The present study examined two behavioral processes – response perseveration and response adaptation – in adolescents who were heavy marijuana smokers and control adolescents. Testing took place in a controlled laboratory setting, using customized software and either a computer keyboard or a custom built response panel for response input. Adolescents age 14–18 were recruited into a heavy smoking (near daily) group ($N=22$) or a control group ($N=31$) with <15 lifetime uses of marijuana and no history of substance abuse or dependence. Marijuana use was verified by daily quantification of urinary cannabinoids and self-reports. Participants completed laboratory tasks designed to measure response perseveration (Wisconsin Card Sort Task, WCST) and response adaptation (concurrent variable-ratio reinforcement schedule with changing contingencies). Data were analyzed via ANOVA, controlling for multiple factors including: gender, age, nicotine use, presence of conduct disorder, and subscales of the Youth Self Report. After controlling for these compared to controls marijuana-using participants made significantly more perseverative and total errors on the WCST and showed significantly impaired (e.g., less adaptive) response allocation to the changing reinforcement contingencies on the concurrent-reinforcement task. Within the constraints of the study's limitations in controlling for alternative sources of between-subject variability, the data suggest that individuals who regularly smoke marijuana during adolescence show measurable perturbations in important basic behavioral processes. The data are also consistent with a previous laboratory study demonstrating reduced motivation in marijuana-smoking adolescents versus controls [Lane, S.D., Cherek, D.R., Pietras, C.J., and

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1. Introduction

There is now strong evidence to suggest that marijuana smoking produces both acute and lasting detrimental effects on human behavioral and brain functions (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Chait & Pierri, 1992; Gruber & Yurgelun-Todd, 2005; Kalant, 2004; Lane & Cherek, 2002; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Pope et al., 2003; Solowij et al., 2002; Volkow et al., 1996; Wilson et al., 2000). The extent and duration of these effects have been difficult to characterize, owing in part to limitations in control over experimental conditions (e.g., duration and amount of use) and proper matching control groups (see Kalant, 2004; Pope, 2002; Solowij et al., 2002).

Despite a considerable amount of recent work focused on characterizing neural and behavioral consequences of persistent, heavy marijuana use, relatively little attention has been devoted to the consequences of marijuana use during adolescence (Crowley, Macdonald, Whitmore, & Mikulich, 1998; Fergusson, Horwood, & Swain-Campbell, 2002; Kamon, Budney, & Stanger, 2005; Lane, Cherek, Pietras, & Steinberg, 2005; Schwartz, Gruenewald, Klitzner, & Fedio, 1989; Vandrey, Budney, Kamon, & Stanger, 2005; Young et al., 2002). The limited effort devoted to adolescent populations represents a shortcoming in research efforts. Approximately 30% of all marijuana users in the US are adolescents, and use rates among adolescents have increased over the past 12 years (Johnston, O'Malley, & Bachman, 2005; NIDA, 2004). Equally compelling is epidemiological evidence showing that peak risk for marijuana dependence occurs at age 17 (Wagner & Anthony, 2002). These data suggest that adolescence may be a period of heightened exposure to marijuana, increased risk for heavy marijuana use, and perhaps a period of peak vulnerability to deleterious drug effects (Fergusson, Horwood, Lynskey, & Madden, 2003; Kelley, Schochet, & Landry, 2004; Spear, 2000). The present study focused on a group of adolescents between the age of 14 and 18, who were currently smoking marijuana on a regular basis (4 to 7 days per week), often multiple times per day. Thus, this represented a group of individuals who may show deficits in cognitive and behavioral performances related, in part, to heavy marijuana use.

Studies to date have commonly employed neuropsychological test batteries and/or brain imaging techniques to measure marijuana effects related to heavy use. These studies suggest that chronic marijuana users show impairments relative to controls on tests that measure behavioral and cognitive processes such as response perseveration, adaptation, and flexibility decision making, using laboratory tests such as the Wisconsin Card Sort Task (WCST), the Stroop Test, and the Iowa Gambling Task (Bolla et al., 2002; Pope et al., 2003; Solowij et al., 2002; Whitlow et al., 2004). These deficits appear to be related to atypical patterns of brain activation in mesolimbic and prefrontal regions.

There is also evidence that marijuana smoking may disrupt behavioral processes involving learning and motivation (Lane, Cherek, Pietras, & Tcheremissine, 2004; Lane et al., 2005; Paule et al., 1992; Stiglick & Kalant, 1983). Studies with human participants have demonstrated that reinforced behavior patterns can be altered by acute Δ^9 THC administration (Foltin et al., 1989; Kamien, Bickel, Higgins, & Hughes, 1994; Lane & Cherek, 2002; Lane et al., 2004). Previously, we demonstrated that acute administration of marijuana altered response adaptation, using a choice-based laboratory task designed to measure sensitivity to continually changing reinforcement contingencies (Lane & Cherek, 2002). At high doses (3.89% Δ^9 THC), subjects tended to perseverate on a preferred response option, despite the fact that the reinforcement density (rate of monetary reward) on that option systematically decreased throughout the session, and thus produced reduced earnings.

In the present study, we employed both the WCST and a variation of the response adaptation procedure used in Lane and Cherek (2002) to study a group of adolescents who were current, regular marijuana smokers and a group of control adolescents with little drug use history. We previously demonstrated diminished performance on a laboratory task of motivation in a similar group of adolescent heavy marijuana smokers (Lane et al., 2005). Based on previous results of both acute and chronic marijuana smoking, we expected to find impaired performance on the WCST and diminished sensitivity to changes in reinforcement contingencies in marijuana-smoking adolescents, particularly with regard to response flexibility and adaptation.

2. Methods

2.1. Participants

Male and female adolescent participants (14–18 years old) responded to local newspaper advertisements. All participants were recruited via ads seeking individuals for behavioral research. No specific details were provided regarding desired participant characteristics or the nature of the study. Based on information obtained during initial telephone interviews, potential participants were brought to the laboratory for more extensive interviews covering physical and mental health status, and drug and alcohol use history.

Exclusionary criteria included: (a) current medical problems (e.g., seizures, diabetes, history of head injury); (b) current use of any medications; (c) current drug use other than marijuana, defined by drug positive urine samples (see below); (d) past history of substance dependence other than marijuana, as measured by the Structured Clinical Interview module for drug and alcohol dependence (SCID-I, version 2.0, First, Spitzer, Gibbon, & Williams, 1996) for the DSM-IV (American Psychiatric Association, 1994); and (e) no diagnosis of any other lifetime Axis I disorder as measured by the Children's Interview for Psychiatric Syndromes (Weller, Weller, Fristad, & Rooney, 1999). Importantly, this meant the exclusion of any adolescent who met criteria for attention-deficit hyperactivity disorder (ADHD). Four adolescents, three marijuana smokers and one control, were excluded for ADHD. The ChIPS is a structured diagnostic interview, similar in modular format to the SCID, designed for children and adolescents aged 6–18 years. A ChIPS diagnosis of conduct disorder was supplemented by the relevant module of the SCID-II, version 1.0 for Axis II disorders (Spitzer, Williams, Gibbon, & First, 1990).

Prior to entering the study, participants read and signed a detailed consent form and a parent or legal guardian signed a parental consent form. The final sample included 53 participants. One group ($N = 22$) constituted regular marijuana smokers, and included fifteen males and six females; hereafter referred to as the MJ+ group. Participants in this group had to meet the following criteria: (a) report current marijuana smoking of at least 4 days per week (most reported daily use); and (b) provide cannabinoid-positive urine samples during participation in the experiment. All participants in this group met DSM-IV criteria for current marijuana abuse or dependence. A post-experimental questionnaire provided a list of substances including nicotine, alcohol, and classes of illicit substances, and asked participants to check off any days in the last seven in which they had used any of these substances. Two participants who reported chronic marijuana smoking provided cannabinoid-negative urines during the experiment. Their data were not included in the final sample of 22 participants. No participants in the MJ+ group met current criteria for abuse or dependence on any drug other than marijuana. Alcohol use in the MJ+ group had the following characteristics: past alcohol use = 17; current drinking = 12 (average 4.1/week); >50 drinking episodes in lifetime = 12; met DSM-IV/SCID criteria for past alcohol abuse = 6. Those 6 who met abuse criteria were classified based on (a) driving under the influence at least twice within 12 months, or (b) public intoxication. Importantly, all subjects were required to provide a negative (000) breath alcohol level each morning of testing (details below).

Urine drug screen analysis for all major classes of drugs was carried out using enzyme multiple immunoassay (EMIT d.a.u ®-SYVA Corp). Cannabinoid-positive urine samples were subjected to creatinine-corrected quantitative estimation using an Olympus AU400 automated analyzer to obtain a numerical value on cannabinoid levels (nanograms per milliliter, ng/ml). Each day residual urinary cannabinoid levels were documented in all participants in the MJ+ group. Levels averaged 893.98 ± 158.28 ng/ml (see Table 1) and ranged from approximately 90 to >3000 ng/ml.

The second group of participants (N = 31, 19 males and 12 females) served as a control group. None met criteria for abuse or dependence on any drug. Thirteen participants in this group reported past cigarette smoking. Eight control participants reported past marijuana use, with two reporting ≈ 15 lifetime

Table 1
Demographic, substance use, and psychometric data for marijuana smoking and control adolescent groups.

Variable	Marijuana	Control	t^a or χ^2 value	p value
Gender (male/female)	15/6	19/12	–	–
Age	16.86 ± 0.32	15.93 ± 0.24	2.24	0.027
Education (years completed)	9.64 ± 0.34	9.61 ± 0.26	0.06	0.961
Number of years of MJ use	3.27 ± 0.33	–	–	–
History of nicotine use	18	13	5.72	0.017
History of illicit drug use[b]	19	27	<1.0	0.943
Urine cannabinoid level (ng/ml)	893.98 ± 158.28 0	–		
Conduct disorder	13	6	6.45	0.011
Shipley (Intelligence test)[c]	48.09 ± 1.60	53.10 ± 1.41	2.33	0.024
Youth Self Report:[d]				
Withdrawn	5.11 ± 0.62	2.68 ± 0.35	3.21	0.022
Somatic complaints	2.42 ± 0.46	1.39 ± 0.73	1.78	0.662
Anxious/depressed	6.05 ± 0.94	3.54 ± 0.40	2.12	0.325
Social problems	3.21 ± 0.53	1.86 ± 0.28	2.05	0.382
Thought problem	2.47 ± 0.33	1.453 ± 0.45	2.41	0.165
Attention problems	4.63 ± 0.60	3.54 ± 0.54	1.45	0.990
Delinquent behavior	6.95 ± 0.70	3.25 ± 0.93	4.20	0.001
Aggressive behavior	9.63 ± 1.09	8.68 ± 0.43	0.66	1.00

Values represent the mean ± SEM.
[a] t-scores presented as absolute values.
[b] Includes alcohol, cocaine, codeine, hallucinogens, benzodiazepines, marijuana (for controls only), and MDMA.
[c] Age-equivalent t-score.
[d] Bonferroni adjusted p values.

uses and the remainder reporting <10. No control participants reported current illicit drug use, none tested positive during the study, and none met criteria for past substance dependence. Alcohol use in the control group had the following characteristics: past alcohol use = 18; current drinking = 4 (average 5.0/week); >50 drinking episodes in lifetime = 5; met DSM-IV/SCID criteria for past alcohol abuse = 1.

To measure aspects of social and cognitive function, participants were administered the Youth Self Report (Achenbach, 1991) and the Shipley Institute of Living Scale (Shipley-Boyle, 1967). These tests were administered on the final day to prevent bias or interpretation on the part of the participants as to the purpose of the study. The Achenbach Youth Self Report (YSR) was used to assess behavior characteristics and social functioning. This instrument has been used in previous studies to provide profiles of psychiatric syndromes in both high-risk and low-risk/typically developing adolescents (Achenbach, 1991; Bender & Loesel, 1997). The Shipley Institute of Living Scale is a test of general intellectual aptitude that includes a 40-item vocabulary test and a 20-item abstraction test. The Shipley scale has been age-normed for adolescents and adults and provides an age-adjusted *t*-score. In young adult populations, Shipley score estimates of WAIS IQ correlate highly (0.76–0.87) with actual WAIS IQ scores (Zachary, Crumpton, & Spiegel, 1985). It is considered appropriate for adults and adolescents age 14 and older (Zachary, Paulson, & Gorsuch, 1985).

Participant demographics including age, gender, education level, marijuana-smoking characteristics, other drug use, and psychometric outcomes are summarized in Table 1. There were no statistically significant differences between the two groups with regard to education level, past use of substances other than marijuana, or most subscales of the Youth Self Report. However, the groups differed on age (the MJ+ group was about 10 months older on average), history of nicotine use, the number meeting criteria for conduct disorder, the withdrawn and delinquency subscales of the YSR, and on general cognitive ability (Shipley). These differences were factored into the data analyses, described below.

2.2. Participant payment and daily schedule

Participants were paid daily for performance during experimental sessions, non-contingent bonus payments for urine samples, alcohol-free breath samples, attendance, and a completion bonus on the last day. Breath alcohol samples were collected each morning upon arrival at the laboratory and measured by an Alco-sensor III (Intoximeters, Inc., St. Louis, Mo). Each day of the study, participants arrived at approximately 8:00 AM and provided breath and urine samples by approximately 8:15 AM. After collection of breath and urine samples, participants began experimental testing. On day 1, participants completed the Wisconsin Cart Sort Task, WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1983) at approximately 9:00 AM, and three additional laboratory-based test sessions across the morning and afternoon (these additional data are not reported here). On Day 2, participants completed phase 1 of the response adaptation task, with five sessions at 8:30 AM, 9:30 AM, 10:30 AM; 1:00 PM, and 2:00 PM. On Day 3, participants completed phase 2 of the response adaptation task, with four sessions at 8:30 AM, 10:00 AM; 1:00 PM, and 2:00 PM. Additional details on the WCST and concurrent VR task are provided below. Between test sessions, participants stayed in a waiting room with magazines, books, and a TV. Lunch was provided at 12:00 pm. Participants arrived at the laboratory either by bus or car, and travel time from home to the laboratory ranged from 30 to 90 min. Many participants indicated smoking marijuana on the evening preceding experimental testing. None reported smoking on the morning of testing.

2.3. Apparatus and instructions

During WCST testing participants worked alone in a small room ≈3×3 m equipped with a MS Windows-based PC and used the computer keyboard to provide response input. During the response adaptation test sessions, participants worked alone in 1.2×1.8 m, sound-attenuating test chamber equipped with a VGA color monitor, and a 10.0×43.0×25.0 cm response panel with three Microswitch buttons labeled A, B, and C. Experimental events and data collection were handled by a remote © MS Windows-based PC and a Med Associates model 750 interface card, using custom software written in © Microsoft Visual Basic.

Prior to the WCST testing session, participants were read a standardized set of instructions (Heaton et al., 1983). Participants were also told that they would be paid based on the accuracy of their performance during the test, but no information regarding payment amounts was provided. At the end of the day, participants were paid based on their percentile score ($0.10×age-corrected percentile on total errors). Prior to phases 1 and 2 of the response adaptation testing session, participants were read a set of instructions describing how money could be earned by responding on the response panel buttons, the requirements for switching between alternatives, and which stimuli were associated with responding and monetary earnings (see below). No information regarding payment amounts was provided, and instructions were purposely limited to the technical requirements of button pressing and switching. Participants were presented with minimal information to decrease the probability that the instructions would influence their behavior on the task. If participants raised questions, the instructions were repeated.

2.4. Wisconsin Cart Sort Task

The WCST is a well-known, standardized assessment of problem-solving and cognitive flexibility that requires matching cards based on rules (shape, color, number) that change periodically. Poor performance can indicate problems with frontal lobe and executive functions. A computerized version was used, which provided age-adjusted percentiles on several different dependent measures. Because participant's ages ranged between 14 and 18, and normed WCST performance improves over this age range, age-adjusted percentile scores were used to correct for any age related differences within and between groups. The present analyses focused on total errors and perseverative errors, the latter reflect repeated choosing of a criterion (i.e., shape) that was recently but no longer correct.

2.5. Response adaptation task

Two subjects in the MJ+ group and three subjects in the control group dropped out of the study after the first day, and thus the final N for this task was 20 MJ+ and 28 control participants. The task was modified from a previous version developed in our laboratory to study acute marijuana effects on sensitivity to changing reinforcement conditions (Lane and Cherek, 2002). In phase 1, the procedure presented two mutually exclusive response options, represented by the letter C or A shown on the monitor screen, corresponding to the respective buttons on the response panel. Only one option was available at a time. Each option had a variable-ratio 35 (VR 35) response requirement, meaning that on average a reinforcer ($0.03) was added to the monetary total after every 35 responses. Ratio values were generated and selected according to the Fleshler–Hoffman progression (Fleshler & Hoffman, 1962), an algorithm which produces a constant probability of reinforcement on any given response and responding that is generally rapid and consistent. Reinforcers were monetary amounts, shown in dollars and cents, represented by a cumulative counter located near the top of the on-screen display. Every 5 min of a 25 min session, the available response option (C or A) changed and participants simply had to switch to the other response button and continue responding to earn money. The order in which the response options were presented was counterbalanced across subjects. The purpose of phase 1/Day 2 was to establish equivalent response and reinforcement histories on both response options, thereby preventing bias for one alternative over the other prior to phase 2.

In phase 2 (Day 3), session 1 was identical to Day 2. On session 2, a concurrent VR reinforcement schedule was introduced. In this arrangement, the VR 35 schedules (on both options) functioned identically as described above. However, instead of a single response option, both options (C and A) were available at any time during the session. To switch between options, subjects were required to press the middle (B) button 10 times (e.g., a changeover response requirement). Once a response was made, the other letter disappeared and only the letter corresponding to the selected option was shown on the screen. During the first 10 min of the session, the two VR schedule values were identical on each option (VR 35) — meaning money could be earned at the same rate on either option. Thereafter, every 10 min one of the concurrently available response options changed in schedule value, and as a result decreased in reinforcement frequency. Response proportions during minutes 0–10 determined the decreasing option; whichever option was preferred (>0.50 response allocation) became the option that decreased in reinforcer frequency. The decreasing option changed every 10 min by 3, 4, 5, and 6 times its original value, and thus changed according to the following progression: min 11–20 = VR 105; min 21–30 = VR 140; min 31–40 = VR 175; min 41–50 = VR 210. The option that was selected <0.50 remained at VR 35 throughout the 50-min session. Thus, by the last 10 min of the session, responding on the decreasing option would produce earnings at 1/6 the rate of the other option.

The selected range of interval values was purposely restricted so that discriminations could be made and an appropriate behavioral transition could be observed within a single 50-min session. Subjects were read a modified set of instructions prior to session 2 that indicated that (a) both options would be concurrently available during the session, (b) the session would be twice as long, and (c) how to switch over the other response option. Responding adaptively (i.e., maximizing monetary earnings) during session 2 required first discriminating that one option had changed in reward frequency, and subsequently allocating a greater proportion of responses to the non-decreasing option. Importantly, the schedule arrangement was a non-independent concurrent VR arrangement in which responses on one option count towards the completion of the other option. For example, if 35 responses are scheduled on option A and 50 responses on option C, then after 35 responses have been completed on option A, only 15 responses are required to earn the $0.03 reinforcer on option C. This non-independent schedule arrangement promotes responding on both options and prevents exclusive responding on a single option, because the longer one has been responding on one option, the higher the probability that money has become available on the other alternative (see MacDonall, 1988; Meisch & Spiga, 1998).

2.6. Dependent measures and data analyses

For the WCST, the two primary dependent measures were the age-corrected percentiles for total errors and perseverative errors. For the response adaptation task, the primary dependent measure was a calculation of response efficiency across the five 10-min time blocks, across which the schedule values changed. Response efficiency was measured as the [number of responses]/[reinforcers earned] on the decreasing option. Higher values at latter stages in the 50-min session indicate worse response efficiency and decreased sensitivity to the reinforcement contingencies (e.g., greater response effort allocated to the decreasing key despite fewer reinforcers earned).

Data from all dependent measures were analyzed by analysis of variance (ANOVA) using SAS Proc GLM (©SAS, Cary, NC) to assess the main effects of the group, with repeated measures over the five 10-min time blocks in the response adaptation task. For all ANOVAs, potentially significant between-group factors were entered as covariates (see Table 1). While lifetime use of drugs other than marijuana was not different between the groups, we coded amount of drug use in the following manner: 0 = no use; 1 = 0–10 uses; 2 = 11–50 uses; 3 => 50 uses. Though no subjects met DSM criteria for history of dependence on other drugs, these data were also included as a covariate to control for the potential influence of use of other drugs.

3. Results

Table 1 provides demographic and psychometric data for the MJ+ and control groups. The groups were statistically different in age (MJ+ subjects were about 10.5 months older), history of nicotine use (more smokers in the MJ+ group), number meeting DSM criteria for conduct disorder (more CD in the MJ+ group), cognitive aptitude as measured by the Shipley (controls scored higher, but both were close to the age-adjusted mean of 50), and the Youth Self Report (YSR) withdrawn and delinquency subscales (MJ+ scored higher on both). Though several of these outcomes could well be the result of heavy marijuana smoking, all factors that were either significantly different or deemed potentially important were entered as covariates in the primary analyses.

Fig. 1 shows the average age-adjusted performances, expressed as percentile scores, for total errors and perseverative errors on the WCST. Higher scores indicate better performances. On both dependent measures, controls scored near the 60th percentile, while the MJ+ group scored below the 40th percentile. An ANOVA comparing the groups on the WCST total errors percentile score was conducted with the following covariates: nicotine use, history of other drug use, age, gender, Shipley score, CD status, YSR withdrawn, and YSR delinquency. Controlling for all these factors, there was a highly significant main effect of Group, F (1, 43) = 18.95, p = 0.0001. The YSR delinquency scale revealed a trend, F (1, 43) =

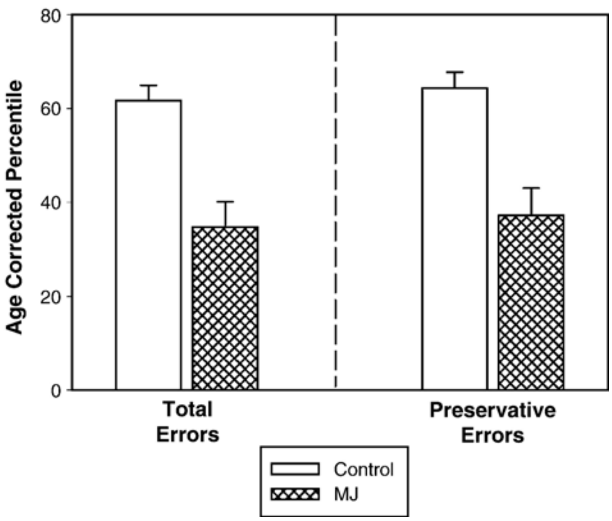

Fig. 1. Age-adjusted performances of the marijuana-using and control groups, in expressed as percentile scores, for total errors (left panel) and perseverative errors (right panel) on the Wisconsin Card Sort Task. The bars show the mean (±SEM) for each group.

3.17, $p=0.082$. There were no other significant effects (all p values >0.18). A similar finding was obtained comparing the groups on the perseverative errors percentile score, with a main effect of group, $F(1, 43)=12.73$, $p=0.0009$. No other significant effects were obtained (all p values >0.13). For total errors, the MJ+ group had a mean percentile of 34.64 (SEM ± 5.42) and the control group had a mean percentile of 61.74 (SEM ± 3.21). For perseverative errors, the MJ+ group had a mean percentile of 37.23 (SEM ± 5.78) and the control group had a mean percentile of 64.39 (SEM ± 3.36).

In order to determine if any combination of factors could better predict WCST performance better than marijuana use alone, stepwise multiple linear regression was conducted with group status (entered as categorical variable) and all the original covariates as predictor variables regressed against the WCST total and perseverative errors. The combination of group status and YSR delinquency score significantly predicted WCST total errors, overall $F=13.37$, $p<0.0001$, adjusted multiple $R^2=0.35$. The standardized regression coefficients were −0.68 and 0.28 for Group and YSR delinquency, respectively, indicating that MJ+ status and higher delinquency scores were related to lower total errors percentile scores. For WCST perseverative errors, no combination of variables better predicted performance than Group alone, overall $F=18.67$, $p=0.0001$, adjusted multiple $R^2=0.26$. The standardized regression coefficient was −0.52.

Fig. 2 shows response adaptation by the MJ+ and control groups across the five 10-min time blocks, centered on the response option in which reinforcement rates systematically decreased. Because response rate is positively correlated with earnings on ratio reinforcement schedules, we corrected for differences in response rate by dividing responses by reinforcers earned. This ratio provides a measure of efficiency and sensitivity to the contingencies. In theory, a participant responding primarily on the decreasing key could earn as much as a participant who had shifted the majority of responses to the non-decreasing key, but by the last 10-min block would have to complete up to six times more responses to do so. Thus, an efficient

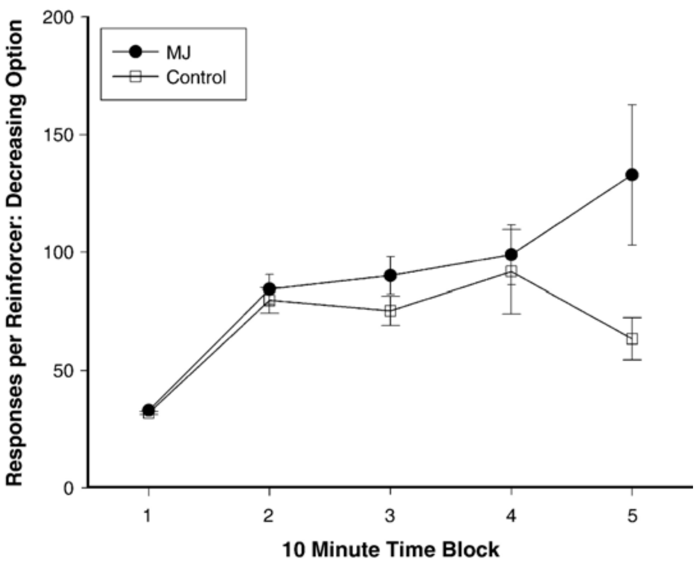

Fig. 2. Response adaptation by the marijuana-using and control groups across five 10-min time blocks on a 50-min concurrent variable-ratio task in which the initially-preferred response alternative decreased systematically every 10 min. The functions show mean (±SEM) responses per reinforcer on the decreasing response alternative. The response/reinforcer ratio provides a measure of efficiency and sensitivity to the contingencies, with lower values indicating greater efficiency. See text for further details.

responder would show a flat or decreasing function across the five 10-min time blocks, and an individual who perseverated on the (initially preferred) decreasing option would show an increasing function. Fig. 2 illustrates that both groups initially increased, but as the discrepancy in reinforcement rate between the two alternatives became greater, controls tended to adapt and return toward the efficiency level achieved in the first 10 min. Essentially, this means that most control subjects gradually shifted the majority of their responses over to the non-decreasing key. On the other hand, the MJ+ individuals showed a monotonically increasing function with the greatest discrepancy from controls in the last 10 min. In other words, MJ+ subjects continued to allocate a larger portion of their responses to the decreasing alternative, despite the fact it provided relatively little monetary return.

An ANOVA was conducted comparing the groups on response efficiency, with repeated measures across the five 10-min time periods, and included the same covariates described above. This analysis revealed no significant main effects of any variable. The three highest F scores were for YSR withdrawn 3.62, $p=0.064$, YSR delinquency 3.39, $p=0.071$, and Group $F=1.92$, $p=0.17$ (for all F scores, $df=1$, 37 and p values represent the Huynh–Feldt correction for repeated measures across time blocks). There was also a significant Time Period × Shipley score interaction, F (4, 148) = 3.39, $p=0.018$. In order to further examine these outcomes and regain statistical power, the ANOVA model was revised to include only the primary variable of interest (Group) and the covariates YSR withdrawn, YSR delinquency, and Shipley score. This model yielded a significant main effect of group $F=4.61$, $p=0.038$. There were no other main effects, but YSR withdrawn showed a trend, $F=3.15$, $p=0.083$. There was a significant Time Period × Group interaction, $F=2.92$, $p=0.042$, as well as a significant Time Period × Shipley score interaction, $F=3.45$, $p=0.022$. This result supports the data shown in Fig. 2; controlling for a range of alternative factors, compared to the control group the MJ+ group performed with less efficiency on the response adaptation task.

In order to determine if any combination of factors could better predict performance on the response adaptation task, stepwise multiple linear regression was conducted with group status and all the original covariates as predictor variables regressed against a summed response efficiency score (required to enter a single regression variable). This score was derived by determining the area under the curve (AUC) for each subject across the five 10 min time blocks shown in Fig. 2. Using the summary AUC value, no factor or combination of factors significantly accounted for response adaptation, overall $F=1.78$, $p=0.15$.

4. Discussion

Adolescents who smoked marijuana on a regular basis (four to seven days per week) and met abuse or dependence criteria were compared to a control group of adolescents with little drug use history on two experimental tasks measuring problem solving, response preseveration, and response adaptation — the WSCT and a task with concurrently available response options that changed over the course of a 50-min session. When controlling statistically for differences in nicotine use, history of other drug use, age, gender, Shipley score, CD status, and scores on the YSR, significant differences were found between the groups on both tasks. One interpretation of these data is that problem solving and/or response adaptation are impaired in the MJ+adolescents. Due to limitations, several explanations are possible for these outcomes. Below we discuss correspondences with previous data and limitations of the study.

The present data are consistent with several studies that examined the chronic effects of marijuana on neurocognitive performance (Bolla et al., 2002; Pope et al., 2003; Solowij et al., 2002), as well as the results of a previous experiment in our laboratory examining acute marijuana effects on response patterns under changing reinforcement schedules (Lane & Cherek, 2002; Lane et al., 2004). One consistent feature across these studies is the construct of response perseveration, e.g., failure to adaptively change behavior in the face of changing environmental contingencies. It is possible that response perseveration is one of the sequelae of regular or chronic marijuana use, and may be present in early-onset adolescent users. The data are also in line with the studies showing alteration of reinforced behavior following acute marijuana administration (Cherek, Lane, & Dougherty, 2002; Dougherty, Cherek, and Roache, 1994; Foltin et al., 1989; Lane & Cherek, 2002; Lane et al., 2004; Paule et al., 1992; Pihl & Sigal, 1978).

On the response adaptation task, the primary difference between marijuana-using adolescents and adolescent controls occurred in the last 10 min block of the 50-min session. This block represented the greatest differential in reinforcement density between the two response alternatives (a ratio of 6:1), and was thus the most easily discriminable. Fig. 2 reveals that when presented with this large discrepancy controls tended to return to more optimal responding, similar to the highly optimal response distributions when the rate of return on the two options was equal. On the other hand, the marijuana-using adolescents continued to perseverate on the less adaptive option during this block and subsequently produced exceedingly sub-optimal response patterns. This outcome is similar to the patterns of perseverative errors made on the WCST, and the data from the two tasks collectively suggest that failure to adapt to changing environmental consequences may be a marked characteristic of heavy marijuana use, or more conservatively, of individuals who engage in regular marijuana smoking. This idea is further supported by data from Whitlow et al. (2004), who showed that heavy marijuana users ($\geq$25 of 30 days for $\geq$5 years) demonstrated maladaptive perseveration on a risky (and disadvantageous) response option across 100 repeated trials on the Iowa gambling task.

The present data are consonant with studies of adults who reported onset of marijuana use during adolescence and several thousand lifetime use episodes into adulthood. These adults scored significantly lower than late-onset, less frequent users and controls on a battery of laboratory cognitive and behavioral tests (Bolla et al., 2002; Pope et al., 2003; Solowij et al., 2002). However, despite clear similarity between the previous adult studies and the present report with adolescent users, several limitations of this study temper the conclusion that the observed differences between the groups were specifically related to marijuana use. Pope and colleagues have provided a thorough discourse on the host of potential confounding variables that may disturb studies of the effects of chronic marijuana smoking (and chronic use of other drugs), as well as the research designs that may aid in clarifying some of the unresolved questions that remain (see Kalant, 2004; Pope, 2002; Pope et al., 2003, also Halpern & Pope, 1999; Lyvers & Hasking, 2004). The design of the present experiment did not allow for examination (or control over) of many of these factors: age of first use, sociodemographic differences, graded levels of marijuana use in the control group, and documentation of functioning prior to marijuana exposure. Other unexamined factors that could have played a role include attention, and measurement error related to related to extra-experimental variables such as sleep deprivation, fatigue, and stress. It is even feasible that some of these variables may contribute to heavy marijuana use in adolescence.

Among adolescents with conduct disorder (CD), there is an uncommonly high prevalence of drug abuse and dependence (marijuana and alcohol in particular) (Crowley, Mikulich, Ehlers, Whitmore, & Macdonald, 2001; Fergusson & Horwood, 2000; Young et al., 1995). It is therefore difficult to obtain a control group, matched for the presence of CD, but with a limited drug-use history. However, the study would have been strengthened by the converse approach, e.g., enrollment of a greater number of participants without CD who were engaged in heavy MJ use, or perhaps even a comparison of groups in the absence of CD. Additionally, the study would have been strengthened by more closely matching groups on cognitive aptitude. Given no practical restrictions, the optimal experiment would require a within-subject, repeated measures design with control over age, onset, duration, abstinence, and frequency of marijuana use. Such an experiment would of course not be ethical or feasible with human adolescent participants, except perhaps under unique treatment settings in which adolescent smokers fell into distinct categories during the course of extended treatment. There are currently a limited number of treatment environments that can meet these conditions (see Kamon et al., 2005), but clarification of the present results will necessarily require additional experimentation outside our laboratory and implementation of creative research approaches.

As noted above, research with adolescent drug users has obvious limitations with regard to controlling important variables and covariates. Nonetheless, the hurdles present in conducting research on adolescent marijuana use should not deter the collection of data related to the potential sequelae of heavy marijuana use during adolescence. Despite the prevalence of marijuana abuse and dependence between the ages of 14 and 18, and the fact that it remains the most common illicit drug used by adolescents (Johnston et al., 2005; Wagner & Anthony, 2002; Wallace et al., 2003), laboratory studies of this group have been not been extensive. The period of adolescence may well constitute a time of unique sensitivity and vulnerability to drug exposure. Chronic use and abuse of drugs during this period may have considerable impact on behavioral, social, and cognitive functioning, and may alter ongoing neural/behavioral development (Fergusson, Horwood, & Beautrais, 2003; Iversen, 2005; Kelley et al., 2004; Paule, 2005; Spear, 2000). Indeed, the negative consequences that may follow heavy marijuana use have been documented in several research domains, including epidemiological (Fergusson et al., 2002; Wagner & Anthony, 2002; Young et al., 2002), clinical (Crowley et al., 1998; Vandrey et al., 2005; Young et al., 1995), cognitive/behavioral (Bolla et al., 2002; Lane et al., 2005; Pope et al., 2003;), and neurobiological studies (Gruber & Yurgelun-Todd, 2005; Matochik, Eldreth, Cadet, & Bolla, 2005). The contribution of the present laboratory-based results is restricted by limited generality, due to alternative variables that could not be fully controlled. However, the outcomes corroborate a growing literature in revealing potentially meaningful differences between adolescents who smoke marijuana heavily and those who do not smoke or do so infrequently.

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