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MARIJUANA EFFECTS ON HUMAN FORGETTING FUNCTIONS

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It has long been known that acute marijuana administration impairs working memory (e.g., the discrimination of stimuli separated by a delay). The determination of which of the individual components of memory are altered by marijuana is an unresolved problem. Previous human studies did not use test protocols that allowed for the determination of delay-independent (initial discrimination) from delay-dependent (forgetting or retrieval) components of memory. Using methods developed in the experimental analysis of behavior and signal detection theory, we tested the acute effects of smoked marijuana on forgetting functions in 5 humans. Immediately after smoking placebo, a low dose, or a high dose of marijuana (varying in Δ^9-THC content), subjects completed delayed match-to-sample testing that included a range of retention intervals within each test session (0.5, 4, 12, and 24 s). Performances (discriminability) at each dose were plotted as forgetting functions, as described and developed by White and colleagues (White, 1985; White & Ruske, 2002). For all 5 subjects, both Δ^9-THC doses impaired delay-dependent discrimination but not delay-independent discrimination. The outcome is consistent with current nonhuman studies examining the role of the cannabinoid system on delayed matching procedures, and the data help illuminate one behavioral mechanism through which marijuana alters memory performance.

Key words: marijuana, delayed match-to-sample, memory, human

For nearly 30 years, it has been well documented that acute marijuana smoking impairs working memory in humans (Heishman, Arasteh, & Stitzer, 1997; Miller, Cornett, Brightwell, McFarland, Drew, et al., 1977; Tinklenberg, Melges, Hollister, & Gillespie, 1970), as well as in nonhuman animals (Castellano, Rossi-Arnaud, Cestari, & Costanzi, 2003; Heyser, Hampson, & Deadwyler, 1993; Schulze et al., 1989). In human experiments, the methods used to evaluate these effects have provided information about global impairment, for example, impaired accuracy on tests such as word recall, digit recall, and paired-associate word memory (Chait & Pierri, 1992; Earleywine, 2002).

Procedures in the experimental analysis of behavior used to measure memory typically employ delayed matching-to-sample (DMTS) testing in which two or more comparison stimuli are presented following the presentation of a sample stimulus. The sample and comparison stimuli are separated by some delay period, and a correct response is operationally defined as responding to the comparison that was identical to the sample (White, 1985; White & Ruske, 2002). Thus remembering may be defined as stimulus control at a temporal distance. Current behavioral accounts of remembering describe a two-component system. One component entails an initial discrimination, in which correct performance is independent of the delay between sample and comparison. Other areas in the behavioral sciences, notably cognitive psychology and neuroscience, generally refer to this component as attention or encoding of information. A second component requires correct discrimination of the comparison stimulus at a point in time after the sample has been removed, and thus is influenced by the length of the delay (White, 1985, 2001; White & Wixted, 1999). In the other areas, the delay-dependent component of discrimination is referred to as recall or retrieval.

Because accurate remembering involves both delay-independent (initial) and delay-dependent discriminations, disruption of either (or both) may occur when performance is impaired on memory tasks. Therefore, it has been emphasized that accurate characterization of memory performance requires test procedures that allow measurement of both components (White, 1985; White & Ruske, 2002; White & Wixted, 1999). To experimentally meet this requirement, a range of retention (delay) intervals must be used such that rates of forgetting can be assessed via a rate parameter from a function fitted to the performance data, for example, a forgetting function (Rubin & Wenzel, 1996; White & Ruske, 2002). Analyzing forget-

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ting functions across a range of retention intervals allows delineation of delay-independent from delay-dependent components of stimulus discrimination. To quantify performance on DMTS procedures, signal detection measures of discriminability such as log *d* or logit *p* (Luce, 1963; Macmillan & Creelman, 1991) may be calculated and plotted across a range of retention intervals. Forgetting functions may then be generated by fitting a negative exponential function to the data (see Method section for details). From the equation parameters, the *y*-intercept and the slope are then interpreted as representing initial discrimination and delay-dependent discrimination (or rate of forgetting), respectively. White and colleagues (Parkes & White, 2000; Ruske, Fisher, & White, 1997) used this approach to measure acute effects of cholinergic drugs in pigeons and showed that memory impairment or enhancement was associated almost entirely with changes in initial discrimination; rates of forgetting were not affected.

Current research on the neurobiology of marijuana and the cannabinoid receptor system suggests—based on both the function and the density of cannabinoid receptors in the hippocampus (Hampson & Deadwyler, 1999, 2000; Iversen, 2003; Wilson & Nicoll, 2001) and the importance of the hippocampal structure in memory function (Baxter & Murray, 2001; Deadwyler, Bunn, & Hampson, 1996)—that marijuana should impair memory by disrupting delay-dependent discrimination. Nonhuman studies have shown that modulation of cannabinoid receptors in the hippocampus by cannabinoid agonists (including Δ^9-THC) significantly disrupts performance during DMTS and (nonmatching) DNMTS procedures, and does so as a function of delay-interval value (Hampson & Deadwyler, 1998, 2000; Heyser et al., 1993; Iversen, 2003). However, other data suggest that Δ^9-THC disrupts initial (delay-independent) discrimination, for example, by degrading performance on tasks purported to measure attention processes (Chait & Pierri, 1992; Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Earleywine, 2002). The importance of hippocampal cannabinoid receptors in memory formation suggests that the delay-dependent components (e.g., rates of forgetting) should be most disrupted by marijuana administration. The possibility that both delay-dependent and delay-independent components could be altered provided the impetus for the present investigation.

METHOD

Subjects

Seven subjects were entered into the study after providing informed consent approved by the local Institutional Review Board. Two subjects were removed for noncompliance with study requirements (see below). The remaining 5 subjects, 3 males and 2 females (ages 21 to 34 years), all completed the study; subsequent demographics are based on these 5 subjects. All 5 reported occasional marijuana use defined as 2 to 10 times per month, as well as past use of at least one other drug, including alcohol, cocaine, opiates, and benzodiazepines. Past use of other drugs was intermittent and did not occur during the study, verified by daily urinalysis (see below). Subjects were recruited via local newspaper advertisements for "behavioral research." Based on information obtained during initial telephone interviews, potential subjects were brought to the laboratory for more extensive interviews covering physical and mental health status, and drug and alcohol use history. Exclusion criteria included: (a) current or past medical problems (e.g., traumatic head injury, asthma); (b) current use of any medications; (c) current illicit drug use (except marijuana); and (d) current or past history of an Axis I disorder other than substance dependence, as defined by the Structured Clinical Interview for the DSM-IV (SCID-I, version 2.0, First, Spitzer, Gibbon, & Williams, 1996).

Although subjects reporting marijuana use 2 to 10 times per month were recruited into the study, they were required to provide a clean urine sample prior to any testing. Following each active dose, a clean urine sample was required before the next active dose was administered. This typically took 3 to 4 days following an active dose, and active doses were separated by at least 5 calendar days. After beginning the study, participation was discontinued following three drug-positive urine samples (confirmed by daily urinalysis) or breath-alcohol samples. This requirement was used to rule out a potential interaction of acute marijuana and residual effects from extraexperimental drug use, including outside marijuana use. Urine drug screen analysis was

carried out using enzyme multiple immunoassay (EMIT® d.a.u.™, SYVA/DadeBehring Corp). Temperature monitoring and creatinine determinations were performed to detect attempts to alter urine samples. Two subjects were removed from the study for repeated positive drug tests (both for THC) at the beginning of the study, prior to active dosing. After several days of baseline testing, these individuals had not discontinued marijuana use.

Apparatus

During marijuana administration, subjects sat in a 1-m by 1-m chamber with two Plexiglas sides and an exhaust fan mounted at the top to ventilate smoke from the chamber. Inside the chamber were an ashtray, a pair of tweezers to hold the cigarette near the bottom, a cuff connecting to an oscillometric digital blood pressure and pulse monitor (Critikon Dynamap, Tampa, FL), and a carbon monoxide indicator (Vitalograph, Inc., Lenexa, KS). One Plexiglas wall faced a computer video monitor used to cue events during the smoking protocol.

During experimental test sessions, subjects worked alone in 1.2-m by 1.8-m sound-attenuating test chamber equipped with a 14-in. (36.5-cm) VGA color monitor and a mouse. Experimental events and data collection were handled by a remote Microsoft Windows® OS PC using custom software written in Microsoft Visual Basic®.

Subject Payment and Schedule

Subjects were paid daily for performance during experimental sessions (four sessions per day; earning approximately $6 to $10 per session; see below), attendance and clean urine samples ($10 per day for each), and were given a completion bonus at the end of the experiment ($10 for each day of participation). Excluding the completion bonus, subjects earned an average of $57.67 (± $4.40) per day during the experiment. The testing protocol lasted 4 to 6 weeks, with subjects participating either 2 or 3 days per week, dictated by their schedules. Subjects completed an average of 44.8 sessions (range 40 to 52) during the experiment. During the initial day of the study, subjects were given an examination by a physician and provided initial exposure to the laboratory task (no marijuana doses were administered). The physical examination served to ensure subjects were free of any medical conditions that would preclude participation. Initial exposure to the task served to stabilize performance prior to initiating dose administration.

Each day of the study, subjects arrived at approximately 8:00 a.m. Breath and urine samples were collected at approximately 8:15 a.m. Subjects participated in four experimental sessions each lasting about 50 min. The first testing session began at 8:30 a.m., prior to administration of the dose for that day. Following dose administration at 9:45, subjects completed three more test sessions (10:00 a.m., 1:00 p.m., and 2:00 p.m.). Between sessions, subjects stayed in a waiting room with magazines, books, and a TV. Lunch was provided at 12:00 p.m. Subjects were not allowed to eat any other food or smoke cigarettes between 8:00 a.m. and 3:00 p.m. Compliance with nonsmoking instructions was verified by expired CO samples taken at 8:25 a.m. and 12:30 p.m.

Behavioral Testing Procedures

On the first day of the experiment, prior to the first testing session, subjects were read the following instructions:

> In this task, you will be required to match shades of the color gray that are presented as squares on the computer screen. To perform this task, you will use the computer mouse.
>
> First, you will see the word CLICK near the center of the computer screen. Move the cursor (or arrow) over the word CLICK and press the right button on the mouse. As soon as you press the button, the word CLICK will disappear and a gray square will appear just above it in the center of the screen.
>
> The gray square will stay on the screen for a few seconds, then it will disappear and the screen will be blank for a while. This period in which the screen is blank will vary from about a half second to more than 20 seconds. After the screen is blank, four more gray squares will appear in each of the four corners of the screen. To make a correct response you must move the cursor (arrow) over the gray square that is identical to the one that was shown in the middle of the screen, and then press the right mouse button. You have a limited amount of time to make your selection.
>
> If you move the mouse over the correct square and press the mouse button, the squares will go off the screen and a money counter will appear at the top showing that you have earned 10 cents. If you choose the wrong square or wait too

long, the squares will go off the screen and the counter will show zero.

You will be presented with many trials during this session. Please stay in the room until you see a message that reads ''Session Over.'' This message will also show how much money you earned during the session. Do you have any questions?

Memory testing employed a delayed match-to-sample (DMTS) procedure. Stimuli consisted of eight grayscale squares, approximately 3 cm by 3 cm, presented against a black background. The grayscale stimuli were created in Microsoft Paint® with the following properties: hue = 160, saturation = 0, luminosity = 220 to 115 in 15-unit increments. At the beginning of each trial, the message ''Click'' was shown slightly below the center of the screen. Placing the cursor over the message and making a mouse click removed the message and immediately presented the sample stimulus (gray square) directly in the center of the screen. This requirement was used as an orienting procedure. The sample stimulus remained on the screen for 2 s followed by one of four delays: 0.5, 4, 12, or 24 s, during which the screen was blank. After the delay (or retention interval), four comparison stimuli appeared in each of the four corners of the screen.

A correct match-to-sample response was defined as moving the mouse onto the comparison that was identical to the sample and making a mouse click within 4 s of the presentation of the comparisons. The 4-s time constraint was employed to make the task sufficiently difficult so as to produce differential performance (e.g., Baron & Menich, 1985; Critchfield & Perone, 1993), in this case as a function of retention interval length. Pilot testing confirmed that this time constraint was necessary. Once subjects became familiar with the DMTS trial requirements and performance became stable (typically within a few sessions) few too-slow errors were made across the remainder of the experiment. After either a mouse click occurred or 4 s had elapsed, the comparison stimuli were removed and a monetary counter showed the outcome of that trial: $0.10 (shown in green) for a correct response or $0.00 (shown in white) for an incorrect response. Each trial was separated by a 3-s intertrial interval.

Cumulative earnings were not displayed during the session in order to prevent subjects from discriminating duration of the session completed and to anchor each trial to a common baseline (e.g., Kahnemann & Tversky, 1979). Each session consisted of 128 trials, allowing for all variables to be counterbalanced: each sample stimulus (16 times), comparison (16 times), location (each comparison in each location four times), and retention interval (32 times) occurred an equal number of times. The same sample stimulus could not occur on more than two consecutive trials. The correct comparison location could not be the same on more than four consecutive trials. At the end of each session, all stimuli were removed from the screen and a message box appeared with the text ''Session Over. You have earned $[cumulative total] this session.''

Marijuana Cigarettes and Administration

Marijuana cigarettes supplied by NIDA were used and ranged across three doses: placebo cigarettes containing 0.0001% w/w Δ^9-THC; half of 2.20% Δ^9-THC (one half placebo and one half active cigarette, hereafter referred to as M1); and 3.89% Δ^9-THC (both halves active, hereafter referred to as M2). Cigarettes were stored at −20 °C and cut in half and humidified before smoking. The purpose of dividing the cigarettes into two halves was to achieve a low dose (M1) sufficiently effective to demonstrate an intermediate effect that was distinguishable from both the high dose and placebo. Subjects smoked the two cigarette halves immediately prior to the beginning of the second experimental session of the day (9:45 a.m.). Smoking was cued by a series of textual instructions that appeared on the monitor screen: ''get ready'' for 2 s; ''inhale'' for 3 s; ''hold your breath'' for 10 s; ''exhale'' for 1 s and then a blank screen for 29 s. The sequence repeated continuously until both halves of the cigarette were smoked. Number of inhalations per dose was recorded by observation and verified via the computer program that presented the smoking cues and that also tracked the number of 45-s cycles completed. Inhalations were compared across all conditions. This current paced, cued smoking procedure has been widely used and produces reliable physiological- and subjective-effects data indicative of acute marijuana intoxication (Chait, 1989; Cherek, Lane, & Dougherty, 2002; Haney, Comer, Ward, Foltin, & Fischman, 1997; Lane & Cherek, 2002).

Dosing Sequence

Doses were administered in ascending order with intervening placebo doses preceding each active dose. Two determinations of each active dose were obtained, and thus the dose sequence was placebo, M1; placebo, M2; placebo, M1; placebo, M2. Placebo doses were administered until the DMTS performance data stabilized. Data were considered stable when the coefficient of variation (*SD/M*) of the percentage correct scores from all four test sessions within a day was below 0.15, with no linearly increasing or decreasing trend. Therefore, multiple placebo doses were sometimes administered between active doses. For all analyses herein, only data from the stable placebo sessions that preceded the active doses are reported.

Cardiovascular and Self-Report Measures

Immediately prior to and following marijuana smoking, the subject's breath carbon monoxide level, heart rate, and systolic and diastolic blood pressure were measured. Immediately after obtaining the postsmoking cardiovascular measures, subjects completed a rating form. They were asked to estimate the subjective effects of the marijuana cigarette on a 5-point scale (anchored by "0—not at all" and "4—extremely") by rating the following statements: "I feel an effect of the marijuana smoke," "My heart is pounding faster than normal," "I feel dizzy, lightheaded," and "I feel a typical marijuana high."

Data Analyses

The dependent measures related to cardiovascular and subjective effects were analyzed for statistical significance via analysis of variance (ANOVA). For number of inhalations, cardiovascular, breath CO, and subjective effects data, one-way repeated measures ANOVAs were conducted with repeated measures on dose (placebo, M1, M2). Cardiovascular and breath CO data were calculated as change scores from pre- to postsmoking. Tukey HSD tests of all pairwise comparisons were used for post hoc analyses.

The primary measurement goal was to determine how the acute marijuana administration affected forgetting functions with respect to initial discrimination and rate of forgetting. Previous studies that have examined forgetting functions in nonhumans have calculated log *d* based on experimental procedures with two stimuli and two comparison locations (Parkes & White, 2000; White, 1985; White & Ruske, 2002). Because the present procedure used eight stimuli and four comparison locations, discriminability was calculated as logit $p = \log[p/(1 - p)]$, where p is the proportion correct. Logit p values were calculated at each delay interval, then plotted graphically and fitted to the negative exponential function $y = a \cdot \exp(-b \cdot \sqrt{t})$ (see White, 1985; White & Ruske, 2002). Expressed in this manner, the parameters a (intercept) and b (slope, or rate of decline) provide an index of initial discriminability and rate of forgetting (delay-dependent discriminability). The parameter t corresponds to time, or the individual delay values. When performance is less than 50% accurate the calculated value of logit p is negative and cannot be fitted to a function of the form $y = a \cdot \exp(-b \cdot \sqrt{t})$. Mathematically, the equation does not conform to a function with a value below 0. To correct for this problem, all data were scored as logit $p + 1$. Adding a constant of 1 allowed the use of the equation for forgetting functions. The behavioral data also were analyzed at a molar level by calculating overall percentage correct for each dose, collapsed across retention intervals, thereby providing a global assessment of the effects of marijuana smoking on DMTS performance.

The impact of the marijuana doses on percentage correct and on the a and b parameters from the fitted functions was evaluated for statistical significance via repeated measures ANOVA, with Tukey HSD tests of all pairwise comparisons for post hoc analyses. All calculations and analyses were performed using Jandel Sigma Plot®, Jandel Sigma Stat® (SPSS, Chicago, IL) and custom software written in Microsoft Visual Basic® (Redmond, WA).

All behavioral data were taken from the second test session of the day. The onset of acute subjective, biological, and behavioral effects of smoked marijuana occurs within 5 min of smoking (Azorlosa, Greenwald, & Stitzer, 1995; Huestis, Henningfield, & Cone, 1992), and the peak behavioral effects are typically reported within the 1st hr of smoking (Chait & Pierri, 1992). Thus we limited our analyses to Session 2, which began immediately after drug administration.

Table 1

Shown are the number of inhalations, carbon monoxide (CO) boost, cardiovascular, and subjective effects following marijuana administration. Values represent mean (± *SEM*) of all 5 subjects. Values for CO, systolic and diastolic blood pressure (BP), and heart rate represent change scores (post- minus presmoking). The rightmost column shows statistical outcomes from comparisons across doses with one-way repeated measures ANOVA.

Dependent measure	Placebo	M1	M2	$F(2, 18)$, p
Inhalations	9.90 (0.27)	10.03 (0.26)	11.60 (0.45)	8.38, < .004
Δ CO	12.45 (0.66)	12.50 (1.12)	13.30 (0.86)	1.17, *ns*
Δ Systolic BP	−4.35 (2.48)	−0.60 (4.35)	0.30 (2.97)	0.22, *ns*
Δ Diastolic BP	0.70 (1.56)	3.70 (2.60)	−2.00 (2.02)	1.57, *ns*
Δ Heart Rate	2.95 (1.62)	24.90 (5.01)	33.40 (4.67)	19.91, < .001
"I feel an effect of marijuana smoke"	0.85 (0.20)	2.40 (0.43)	3.20 (0.20)	29.15, < .001
"My heart is pounding faster than normal"	0.40 (0.13)	1.50 (0.31)	1.90 (0.23)	9.64, < .002
"I feel dizzy, light-headed"	0.50 (0.17)	1.10 (0.23)	1.50 (0.31)	5.33, < .016
"I feel a typical marijuana high"	0.65 (0.18)	2.50 (0.37)	3.20 (0.13)	46.61, < .001

RESULTS

Marijuana Administration

Table 1 shows data from the marijuana administration procedure at each dose, including the number of inhalations, the cardiovascular and breath CO pre/post change scores, and the subjective effects measures. Table 1 also provides *F* values and degrees of freedom for each ANOVA. The means of the repeated administrations of each dose, as well as the details of the statistical outcomes from the one-way repeated measures ANOVAs are presented. For the number of inhalations, there was a significant main effect of dose, $p < .004$. Tukey post hoc tests ($\alpha = .05$) showed the number of inhalations at the M2 dose to be greater than both M1 and placebo. This difference implies that subjects adjusted (or decreased) their smoke intake at the high dose and required roughly one and one half extra inhalations to smoke an equivalent amount of the cigarette. Adjustment of inhalation has been observed in previous studies, and has been attributed to subjects' rapid discrimination of the psychoactive effects of the high-THC content marijuana (Heishman, Stitzer, & Yingling, 1989; Kelly, Foltin, & Fischman, 1993; Lane & Cherek, 2002). However, CO boost levels were not significantly different, suggesting that overall smoke intake was equivalent across the three doses.

There was a large significant effect of marijuana dose on heart rate change from pre- to postsmoking, $p < 0.001$. Tukey tests ($\alpha = .05$) showed heart rate changes at both marijuana doses to be statistically different (greater) than placebo. Heart rate increase is among the most reliable dose-related indicators of acute marijuana administration (Huestis et al., 1992). There was not a significant effect of dose on either systolic or diastolic blood pressure. For the subjective effects data, there was a significant effect of dose on all four questions: "I feel an effect of marijuana smoke," $p < .001$; "My heart is pounding faster than normal," $p < .002$; "I feel dizzy, light-headed," $p < .016$; and "I feel a typical marijuana high," $p < .001$. Significant differences on Tukey post hoc tests ($\alpha = .05$) were observed between placebo and both the M1 and M2 doses for every question except "I feel dizzy, light-headed," in which only the higher M2 dose was different from placebo. Collectively, these data serve to document and replicate the well-known physiological and subjective effects of smoking marijuana.

Behavioral Data

All data presented in the Results section were taken from Session 2 during peak marijuana effects (see Methods section). Approximately 4% of all errors made in Session 2 were too-slow errors. These were included in the analyses but were not systematically related to delay or dose (see below). On days of active THC administration, during Sessions 3 and 4 (which occurred in the afternoon following lunch) several subjects showed signs of sedation, and per-

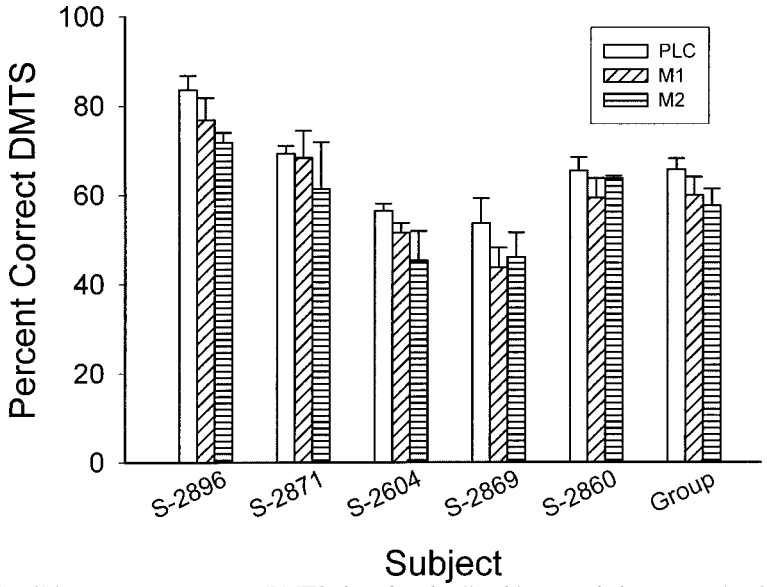

Fig. 1. Mean (+ *SD*) percentage correct DMTS data for the 5 subjects and the group (+ *SEM*) at each dose. Each bar pattern represents a different dose, with multiple determinations at each dose. PLC indicates placebo; M1 indicates half placebo and half 2.2% Δ^9-THC; M2 = 3.89% Δ^9-THC. See text for dose administration details.

formance was marked by frequent too-slow errors. These errors were not related to delay length, but accounted for highly variable performance during these sessions. The Appendix provides the number of too-slow errors and logit p values with and without too-slow errors for all subjects, sessions, and doses.

Figure 1 displays the overall percentage correct value for each subject across the three doses, expressed as the mean ($\pm$ *SD* for individuals, $\pm$ *SEM* for group) of the multiple administrations of each dose. For all 5 subjects, at least one of the marijuana doses produced a global decrement in performance compared to placebo. Four subjects showed a decrement in performance at the M2 dose; 4 showed a decrement at the M1 dose; and 3 showed a decrement at both doses. One-way ANOVA with repeated measures across dose revealed that these differences were statistically significant, $F(2, 18) = 10.73$, $p < .001$. Tukey tests ($\alpha = .05$) showed both marijuana doses to be different from placebo (lower overall percentage correct). Note that, because these data were collapsed across retention intervals, Figure 1 somewhat obscures the magnitude of the decline in performance. However, the global decrement in performance documents the known effect of marijuana on memory impairment.

Figure 2 displays the forgetting functions for each dose for each of the 5 subjects, as well as the group average. The figure reveals that, typically, the marijuana-induced disruption in DMTS performance increased as a function of retention interval. Note that irrespective of baseline (placebo) levels of performance, marijuana disrupted remembering systematically at the longer retention intervals. For example, under placebo Subject 2896 showed a nearly flat forgetting function whereas Subject 2869 had a much larger decline in logit p as a function of retention interval. Yet the forgetting functions of both subjects were altered by the same relative amount under the M2 dose. For Subjects 2869, 2871, and 2896 changes in forgetting functions were dose related. For Subjects 2860 and 2604, both the M1 (half 2.2%) and M2 (3.89%) doses produced equivalent decrements in DMTS performance. Importantly, performance was systematically impaired at the longer retention intervals, but very little decrement in DMTS performance occurred at the short (0.5 s) retention interval. Subject 2871 is the only subject with any notable decrement in logit p at the shorter interval.

Table 2 shows parameter values (a = intercept, b = slope) for each subject, obtained from fitting the negative exponential equation to the data from each dose (i.e., from

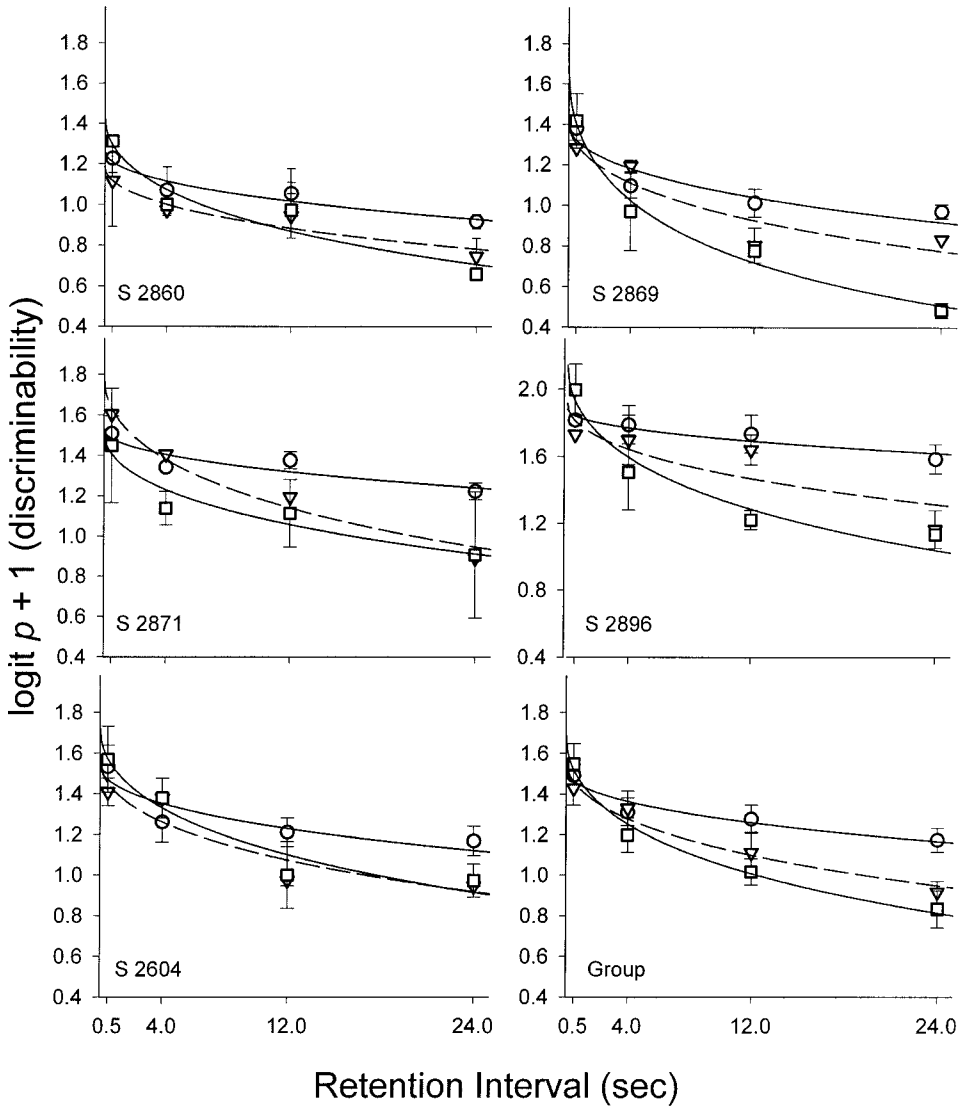

Fig. 2. Mean discriminability, calculated as logit $p + 1$, as a function of delay interval between sample and comparison stimuli. Each panel shows an individual subject, with the group mean (± *SEM*) in the bottom right panel. In each panel, each symbol represents the mean (± *SEM*) of a different dose with multiple determinations at each dose. Curves represent negative exponential forgetting functions fit to the data from each dose. ○ and solid curve indicate placebo; ▽ and dashed curve indicate half placebo and half 2.2% Δ^9-THC (M1); □ and solid curve indicate 3.89% Δ^9-THC (M2). Note different scaling on *y* axis for Subject 2896. See text for details on the calculation of logit $p + 1$ and the negative exponential function.

the data shown in Figure 2). Individual subject data from each of the four daily test sessions and of each individual dose are shown in the Appendix. The data were generally well described by the equation. R^2 values ranged from 0.70 to 0.98, and only 1 subject had an R^2 value below 0.80. An ANOVA on the parameter values statistically confirmed the patterns shown in Figure 2. For the *a* parameter, there was not a significant difference among the doses, $F(2, 8) = 1.72$, *ns*. There was a large significant difference among the doses for the *b* parameter, $F(2, 8) = 11.66$, $p < .004$. Tukey tests ($\alpha = .05$) revealed that only the M2 dose was different from placebo.

Two features of the design and analysis may have produced an unintended systematic influence on the data: the inclusion of the too-slow errors and the repeated ascending dose sequence. To evaluate the possibility that ei-

Table 2

Parameter (a = intercept, b = slope) and goodness-of-fit (R^2) values from the negative exponential forgetting functions shown in Figure 2. Values are provided for each dose, each of the 5 subjects, and the group function. See text for details on the negative exponential function.

Subject	Dose	a	b	R^2
2860	Placebo	1.26	0.06	0.92
	M1	1.18	0.09	0.92
	M2	1.43	0.14	0.91
2869	Placebo	1.40	0.08	0.86
	M1	1.42	0.12	0.86
	M2	1.66	0.24	0.98
2871	Placebo	1.53	0.04	0.80
	M1	1.79	0.13	0.97
	M2	1.51	0.10	0.91
2896	Placebo	1.88	0.03	0.88
	M1	1.91	0.08	0.70
	M2	2.14	0.15	0.94
2604	Placebo	1.54	0.06	0.82
	M1	1.57	0.11	0.84
	M2	1.72	0.13	0.94
Group	Placebo	1.52	0.05	0.92
	M1	1.57	0.10	0.97
	M2	1.68	0.15	0.98

ther of these features affected the data, independent analyses were carried out using the data from Session 2. Too-slow errors were evaluated by conducting a three-way ANOVA comparing the logit p values on error type (with vs. without too-slow errors) as a between factor and repeated measures on the factors of dose and delay interval. There was not a significant main effect of error type on logit p value, $F(1, 74) = 0.09$, *ns,* and there were no significant interactions: F values for dose by error type, delay by error type, and dose by delay by error type were 0.00, 0.08, and 0.03, respectively. Additionally, a Pearson correlation analysis on logit p values with and without too-slow errors produced a correlation coefficient of 0.99, $p < .0001$. These analyses make clear that inclusion of the two-slow errors in the data analyses did not affect the calculation of the logit p values or the forgetting functions. Further details of the too-slow errors are available in the Appendix, which provides the raw number of too-slow errors and the logit p values calculated with and without too-slow errors for all subjects, sessions, doses and delay values.

The effects of dose order were evaluated via two-way repeated measures ANOVA comparing the logit p values on active dose order (M1, M2, M1, M2) and delay value with repeated measures on both factors. There was no significant main effect of dose order, $F(3, 12) = 1.12$, *ns* and no significant dose order by delay interaction, $F(9, 36) = 0.63$, *ns*. Additionally, to assess if any systematic change in baseline performance occurred over time, the four placebo values were evaluated via two-way repeated measures ANOVA comparing the logit p values across the four placebo doses and delay values with repeated measures on both factors. There was not a significant main effect of order across the placebo doses, $F(3, 12) = 3.02$, *ns* and no significant placebo by delay interaction, $F(9, 36) = 1.13$, *ns*. These analyses indicate that the dosing design used in the study did not systematically effect stimulus discrimination, as measured by logit p.

DISCUSSION

The acute administration of smoked marijuana to adult humans produced changes in rates of forgetting but not in initial discriminability. Relative to performance after placebo administration, these impairments were a function of delay interval length. Specifically, Δ^9-THC increased the slope parameter of negative exponential forgetting functions in all 5 subjects. The use of a DMTS procedure with a range of retention intervals thus allowed for determination of the mechanism through which marijuana disrupted memory performance by delineating between delay-independent and delay-dependent effects. As noted by White (1985), ''In the absence of a delay-interval manipulation, discriminability recorded at a single delay confounds a particular level of initial discriminability with a certain rate of decrement in discriminability'' (p. 31). To our knowledge, previous studies of marijuana effects on human memory have not separated these components.

Generally, the data are consonant with many previous studies of acute marijuana effects on human memory performance (Chait & Pierri, 1992), but at least one recent study stands in contrast to the present findings. Curran et al. (2002) examined the effects of oral Δ^9-THC on human memory using an extensive battery of 12 neuropsychological tests measuring, among other things, implicit memory (selective reminding, free recall, prose recall), working memory (serial digit manipulation, rapid visual information pro-

cessing), and attention (choice reaction time, digit search and identification). The results indicated no effect on working memory tasks, significant impairment on implicit memory tasks, and selective but inconsistent impairment on attention tasks. Unfortunately, differences in (a) route of drug administration, (b) the inclusion of a continuously presented series of different tasks (e.g., sequence and fatigue factors), and (c) substantial differences in test procedures hinder direct comparisons of the present study with Curran et al.

Previous studies with nonhuman subjects have used DMTS procedures with the data expressed as forgetting functions to examine the effects of other memory-impairing drugs. Using a delayed auditory conditional discrimination procedure with a range of delay intervals, Kirk, White, and McNaughton (1988) showed that the anticholinergic drug scopolamine produced deficits in performance. Initial discriminability was decreased at all doses, but rate of forgetting was only impaired at the two highest doses. In subsequent studies, White and colleagues demonstrated that the administration of both muscarinic agonists (Ruske et al., 1997) and glucose (Parkes & White, 2000) attenuated the impairing effects of scopolamine on DMTS performance, and did so by improving performance at short delay intervals. Thus the diminution of memory impairment was related directly to improvement in the initial discriminability. Based on both pharmacological data and studies of patients with Alzheimer's disease, White and Ruske (2002) have concluded that disruption of memory related to the cholinergic (i.e., acetylcholine) system is due to impairment in initial discrimination rather than rates of forgetting. One factor that may account for the discrepancy between White et al.'s conclusions and the present data is that marijuana has a unique neurobiological mechanism of action unrelated to the cholinergic system.

In a series of studies with rodents, Hampson, Deadwyler, and colleagues (Deadwyler et al., 1996; Hampson & Deadwyler, 1999; Hampson, Simeral, Kelly, & Deadwyler, 2003; Heyser et al., 1993) demonstrated that (a) cannabinoid receptors on hippocampal neurons were highly active during delayed matching (and delayed nonmatching) performance; (b) that their activity was directly related to performance levels; and (c) that both administration of cannabinoid agonists (including Δ^9-THC) and hippocampal lesions produced significant impairment in performance. Importantly, their data also revealed that memory impairment was a systematic function of delay interval and dose. The present data are quite consistent with Hampson and Deadwyler et al.'s findings and extend support to human subjects, suggesting that marijuana impairs memory function by increasing the rate of forgetting. This impairment may be related to disruption of cannabinoid receptor (e.g., CB1) function in the hippocampus, and provides one explanation for the behavioral differences in memory performance induced by Δ^9-THC versus those observed by White and colleagues (Kirk et al., 1988; Parkes & White, 2000; Ruske et al., 1997; White and Ruske, 2002) following administration of other classes of drugs. It should be acknowledged that White et al.'s work using nonhuman subjects has been carefully designed, systematically conducted, and has achieved greater levels of control than can be attained when administering smoked substance to human subjects in an outpatient setting. This level of experimental control also may be a factor in the above-noted differential outcomes. It is possible that extraexperimental variables may have influenced our subjects' performances in an unidentified but nontrivial manner.

The action of different neurobiological systems may correspond to different aspects of behavioral performance on laboratory tests of memory. Procedures that distinguish individual memory components will help elucidate the biological and behavioral interaction involved in memory processes. The present data take a step in that direction using human subjects. Replication of this experiment with cannabinoid antagonists and drugs with different neurobiological mechanisms of action will further this agenda.

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APPENDIX

Number of too-slow errors, logit p [$\log(p/1-p)$] values with too-slow errors included, and logit p values without to slow-errors for each subject, each individual dose, and each of the four daily sessions. Too-slow errors were defined as responses made > 4 s after the presentation of the comparison stimuli, and were counted as incorrect responses.

			0.5 s		
Subject	Dose	Session	Too slow	Logit p with	Logit p without
S-2860	Placebo 1	1	1	0.109	0.141
		2	0	0.342	0.342
		3	2	0.281	0.368
		4	1	0	0.028
	M1 − 1	1	0	0.222	0.222
		2	1	−0.109	−0.084
		3	3	0.222	0.347
		4	4	0.109	0.255
	Placebo 2	1	0	0.165	0.165
		2	0	0.165	0.165
		3	3	0.165	0.279
		4	3	0.054	0.151
	M2 − 1	1	1	0.408	0.459
		2	1	0.281	0.322
		3	1	0	0.028
		4	2	−0.109	−0.058
	Placebo 3	1	0	0.342	0.342
		2	1	0.342	0.388
		3	1	0.165	0.200
		4	2	0.109	0.176
	M1 − 2	1	2	0.109	0.176
		2	1	0.342	0.388
		3	1	0.109	0.141
		4	1	0.222	0.260
	Placebo 4	1	2	0.342	0.439
		2	1	0.054	0.084
		3	1	−0.165	−0.141
		4	1	0.222	0.260
	M2 − 2	1	0	0.342	0.342
		2	0	0.342	0.342
		3	5	0.222	0.456
		4	4	−0.054	0.062
S-2869	Placebo 1	1	0	0.732	0.732
		2	0	0.281	0.281
		3	3	0.054	0.151
		4	2	0.165	0.237
	M1 − 1	1	0	0.477	0.477
		2	0	0.281	0.281
		3	1	0.407	0.459
		4	1	0.222	0.260
	Placebo 2	1	0	0.732	0.732
		2	0	0.342	0.342
		3	1	0.165	0.200
		4	2	0.109	0.176
	M2 − 1	1	0	0.637	0.637
		2	0	0.553	0.553
		3	2	0.222	0.301
		4	1	0.407	0.459
	Placebo 3	1	0	0.637	0.637
		2	0	0.342	0.342
		3	1	0.637	0.716
		4	3	0.553	0.796
	M1 − 2	1	0	0.553	0.553
		2	0	0.281	0.281
		3	3	0.342	0.497
		4	0	0.222	0.222

APPENDIX

(*Extended*)

4 s			12 s			24 s		
Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without
1	0.109	0.141	0	−0.165	−0.165	1	0	0.028
2	−0.222	−0.176	1	−0.281	−0.260	1	−0.109	−0.084
2	−0.281	−0.237	3	−0.054	0.030	3	−0.222	−0.151
2	0.109	0.176	0	−0.342	−0.342	4	−0.553	−0.477
0	0.222	0.222	0	−0.054	−0.054	1	−0.281	−0.260
0	−0.054	−0.054	0	−0.165	−0.165	1	−0.342	−0.322
1	0.054	0.084	5	−0.165	−0.032	3	−0.281	−0.214
3	0.222	0.347	1	0	0.028	2	−0.281	−0.237
0	0.407	0.407	1	0.165	0.200	0	−0.109	−0.109
3	0.222	0.347	0	0.281	0.281	0	−0.054	−0.054
2	0	0.058	1	−0.342	−0.322	2	−0.407	−0.368
1	0	0.028	2	0	0.058	4	−0.222	−0.125
1	0.054	0.084	2	0	0.058	2	−0.222	−0.176
1	0.000	0.028	0	−0.165	−0.165	1	−0.342	−0.322
1	−0.054	−0.028	0	−0.342	−0.342	1	−0.985	−0.970
5	−0.054	0.099	4	0.054	0.189	1	−0.109	−0.084
1	0.342	0.388	2	−0.222	−0.176	1	−0.342	−0.322
1	0	0.028	0	0.054	0.054	1	−0.165	−0.141
2	−0.477	−0.439	0	−0.637	−0.637	2	−0.281	−0.237
3	−0.281	−0.214	2	−0.732	−0.699	2	−0.732	−0.699
0	0.165	0.165	2	0.222	0.301	2	−0.281	−0.237
1	0.000	0.028	0	0.054	0.054	1	−0.165	−0.141
5	−0.342	−0.230	6	−0.553	−0.437	4	−0.407	−0.325
3	0	0.090	2	−0.342	−0.301	1	−0.407	−0.388
2	0.054	0.117	0	−0.281	−0.281	2	−0.281	−0.237
2	0.281	0.368	2	0.165	0.237	1	0	0.028
5	−0.342	−0.230	0	−0.553	−0.553	2	−0.732	−0.699
1	−0.054	−0.028	2	−0.165	−0.117	2	−0.342	−0.301
3	0.281	0.419	0	0	0	0	0.054	0.054
1	0.000	0.028	0	0.109	0.109	2	−0.342	−0.301
5	−0.407	−0.301	6	−0.222	−0.067	5	−0.477	−0.376
3	−0.054	0.030	3	−0.165	−0.090	2	−0.407	−0.368
1	0.222	0.260	0	0.342	0.342	0	0.054	0.054
0	−0.054	−0.054	1	0.165	0.200	0	−0.109	−0.109
1	−0.222	−0.200	3	−0.109	−0.030	7	−0.407	−0.250
1	0.342	0.388	2	0.000	0.058	2	−0.165	−0.117
0	0.109	0.109	0	0.000	0.000	1	0.222	0.260
0	0.165	0.165	0	−0.281	−0.281	0	−0.165	−0.165
4	0.109	0.255	3	0.109	0.214	1	−0.165	−0.141
1	−0.054	−0.028	1	0.109	0.141	0	−0.222	−0.222
0	0.407	0.407	0	0.109	0.109	1	0.281	0.322
0	0.222	0.222	0	−0.165	−0.165	1	0.054	0.084
1	−0.222	−0.200	1	0.222	0.260	1	−0.165	−0.141
0	0.342	0.342	1	0.165	0.200	1	0.000	0.028
1	0.553	0.620	0	0.222	0.222	0	0.477	0.477
1	0.165	0.200	0	−0.222	−0.222	0	−0.477	−0.477
3	−0.054	0.030	1	−0.165	−0.141	2	−0.407	−0.368
3	−0.222	−0.151	0	−0.281	−0.281	4	−0.342	−0.255
2	0.281	0.368	0	0.222	0.222	0	0.165	0.165
0	0.054	0.054	0	0.054	0.054	0	0.000	0.000
0	0.000	0.000	2	0.222	0.301	2	−0.222	−0.176
5	0.109	0.301	1	0.342	0.388	1	0.054	0.084
0	0.222	0.222	0	0.342	0.342	0	0.000	0.000
0	0.222	0.222	0	−0.109	−0.109	0	−0.165	−0.165
2	0.281	0.368	2	−0.165	−0.117	1	0.000	0.028
1	−0.054	−0.028	2	0.342	0.439	1	0.109	0.141

APPENDIX

(*Continued*)

			0.5 s		
Subject	Dose	Session	Too slow	Logit p with	Logit p without
	Placebo 4	1	0	0.985	0.985
		2	0	0.553	0.553
		3	1	0.637	0.716
		4	0	0.281	0.281
	M2 − 2	1	0	0.342	0.342
		2	0	0.281	0.281
		3	2	0.000	0.058
		4	—	—	—
S-2871	Placebo 1	1	1	−0.054	−0.028
		2	0	0.342	0.342
		3	1	0.637	0.716
		4	0	0.165	0.165
	M1 − 1	1	0	0.109	0.109
		2	1	0.732	0.829
		3	0	0.732	0.732
		4	1	0.407	0.459
	Placebo 2	1	0	0.637	0.637
		2	0	0.732	0.732
		3	0	0.553	0.553
		4	1	0.553	0.620
	M2 − 1	1	0	0.407	0.407
		2	1	0.732	0.829
		3	0	0.222	0.222
		4	1	0.477	0.535
	Placebo 3	1	1	0.553	0.620
		2	0	0.407	0.407
		3	1	0.553	0.620
		4	1	0.477	0.535
	M1 − 2	1	0	0.477	0.477
		2	1	0.477	0.535
		3	0	0.637	0.637
		4	0	0.109	0.109
	Placebo 4	1	1	0.407	0.459
		2	1	0.553	0.620
		3	0	0.553	0.553
		4	0	0.477	0.477
	M2 − 2	1	1	0.165	0.200
		2	1	0.165	0.200
		3	0	0.222	0.222
		4	1	0.109	0.141
S-2896	Placebo 1	1	0	0.845	0.845
		2	0	0.845	0.845
		3	1	0.732	0.829
		4	0	0.845	0.845
	M1 − 1	1	0	0.637	0.637
		2	1	0.732	0.829
		3	0	0.477	0.477
		4	1	0.407	0.459
	Placebo 2	1	0	0.985	0.985
		2	0	0.732	0.732
		3	0	0.845	0.845
		4	1	0.342	0.388
	M2 − 1	1	0	0.637	0.637
		2	0	0.845	0.845
		3	0	0.281	0.281
		4	2	0.553	0.699
	Placebo 3	1	0	0.845	0.845
		2	1	0.845	0.970
		3	0	1.491	1.491
		4	0	1.491	1.491

APPENDIX

(*Extended*)

4 s			12 s			24 s		
Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without
0	0.477	0.477	0	0.281	0.281	0	0.407	0.407
0	0.165	0.165	0	0.000	0.000	0	−0.054	−0.054
1	0.407	0.459	2	0.000	0.058	4	−0.477	−0.398
2	0.342	0.439	0	0.109	0.109	4	0.054	0.189
0	0.222	0.222	0	−0.109	−0.109	1	0.000	0.028
0	−0.222	−0.222	0	−0.222	−0.222	0	−0.553	−0.553
1	0.054	0.084	1	−0.109	−0.084	5	−0.407	−0.301
—	—	—	—	—	—	—	—	—[a]
0	−0.054	−0.054	2	0.000	0.058	0	0.222	0.222
1	0.342	0.388	0	0.477	0.477	0	0.222	0.222
1	0.342	0.388	2	0.342	0.439	0	0.222	0.222
1	0.477	0.535	1	0.407	0.459	0	0.222	0.222
0	0.845	0.845	1	0.281	0.322	1	0.165	0.200
1	0.407	0.459	1	0.109	0.141	2	−0.109	−0.058
0	0.281	0.281	1	0.637	0.716	1	0.165	0.200
0	0.477	0.477	0	0.222	0.222	1	−0.054	−0.028
0	0.109	0.109	0	0.109	0.109	0	0.054	0.054
0	0.342	0.342	1	0.407	0.459	0	0.165	0.165
1	0.407	0.459	2	0.054	0.117	1	0.553	0.620
1	0.109	0.141	2	0.477	0.602	0	0.407	0.407
0	0.553	0.553	1	0.477	0.535	0	0.222	0.222
1	0.222	0.260	0	0.281	0.281	0	0.222	0.222
4	0.342	0.564	1	0.165	0.200	0	0.342	0.342
0	0.342	0.342	1	0.165	0.200	1	0.165	0.200
0	0.109	0.109	2	0.109	0.176	0	−0.109	−0.109
1	0.342	0.388	1	0.342	0.388	0	0.165	0.165
1	0.222	0.260	1	0.109	0.141	1	0.165	0.200
0	0.222	0.222	1	0.222	0.260	2	0.109	0.176
0	0.054	0.054	0	0.281	0.281	1	0.109	0.141
0	0.407	0.407	0	0.281	0.281	1	−0.109	−0.084
0	0.342	0.342	0	0.553	0.553	0	0.165	0.165
2	0.109	0.176	0	0.054	0.054	0	0.109	0.109
0	0.281	0.281	0	−0.054	−0.054	1	−0.165	−0.141
1	0.342	0.388	0	0.281	0.281	0	0.342	0.342
1	0.281	0.322	1	0.342	0.388	0	0.054	0.054
1	0.054	0.084	1	0.165	0.200	1	−0.109	−0.084
3	0.000	0.090	0	−0.054	−0.054	0	−0.165	−0.165
2	0.054	0.117	1	−0.054	−0.028	0	−0.407	−0.407
1	0.222	0.260	0	−0.281	−0.281	0	0.109	0.109
0	0.342	0.342	1	−0.054	−0.028	1	0.000	0.028
0	0.845	0.845	1	0.477	0.535	1	0.477	0.535
0	0.985	0.985	0	0.477	0.477	0	0.553	0.553
0	1.176	1.176	0	0.407	0.407	1	0.637	0.716
1	0.553	0.620	0	0.342	0.342	0	0.477	0.477
0	0.553	0.553	0	1.176	1.176	0	0.477	0.477
0	0.845	0.845	0	0.732	0.732	0	0.281	0.281
1	0.281	0.322	0	0.477	0.477	1	0.845	0.970
1	0.477	0.535	1	0.477	0.535	0	0.342	0.342
0	0.845	0.845	0	0.407	0.407	0	0.109	0.109
0	0.985	0.985	0	0.985	0.985	0	0.845	0.845
0	0.637	0.637	1	0.342	0.388	4	0.342	0.564
0	0.477	0.477	2	0.222	0.301	1	0.165	0.200
0	0.985	0.985	0	0.477	0.477	1	0.985	1.161
0	0.732	0.732	0	0.281	0.281	0	0.109	0.109
2	0.553	0.699	1	0.000	0.028	1	0.165	0.200
1	−0.054	−0.028	3	−0.222	−0.151	2	−0.407	−0.368
0	0.477	0.477	0	0.637	0.637	0	0.732	0.732
0	0.637	0.637	0	0.637	0.637	0	0.477	0.477
0	0.637	0.637	0	0.553	0.553	0	0.553	0.553
0	0.637	0.637	2	0.553	0.699	2	0.222	0.301

APPENDIX

(*Continued*)

			0.5 s		
Subject	Dose	Session	Too slow	Logit *p* with	Logit *p* without
	M1 − 2	1	0	1.491	1.491
		2	0	0.732	0.732
		3	0	0.477	0.477
		4	1	0.732	0.829
	Placebo 4	1	1	0.637	0.716
		2	0	0.845	0.845
		3	1	0.637	0.716
		4	0	0.985	0.985
	M2 − 2	1	0	1.176	1.176
		2	0	1.149	1.149
		3	2	0.165	0.237
		4	0	0.845	0.845
S-2604	Placebo 1	1	1	0.407	0.459
		2	0	0.845	0.845
		3	1	0.732	0.829
		4	1	0.407	0.459
	M1 − 1	1	0	0.477	0.477
		2	0	0.477	0.477
		3	0	0.222	0.222
		4	0	0.477	0.477
	Placebo 2	1	0	0.342	0.342
		2	1	0.407	0.459
		3	1	0.553	0.620
		4	1	0.342	0.388
	M2 − 1	1	1	0.281	0.322
		2	1	0.732	0.829
		3	0	0.407	0.407
		4	0	0.732	0.732
	Placebo 3	1	0	0.222	0.222
		2	0	0.477	0.477
		3	0	0.109	0.109
		4	0	0.477	0.477
	M1 − 2	1	0	0.477	0.477
		2	0	0.342	0.342
		3	0	0.342	0.342
		4	0	0.553	0.553
	Placebo 4	1	0	0.553	0.553
		2	0	0.407	0.407
		3	0	0.637	0.637
		4	1	0.477	0.535
	M2 − 2	1	0	0.637	0.637
		2	0	0.407	0.407
		3	1	0.637	0.716
		4	5	0.342	0.643

[a] Data for S-2869, M2-2, Session 4 were lost due to computer failure.

APPENDIX

(*Extended*)

4 s			12 s			24 s		
Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without	Too slow	Logit *p* with	Logit *p* without
1	0.637	0.716	0	0.407	0.407	0	0.477	0.477
0	0.553	0.553	0	0.553	0.553	0	0.054	0.054
2	0.222	0.301	1	0.000	0.028	1	0.222	0.260
2	0.281	0.368	0	0.222	0.222	0	0.281	0.281
2	0.477	0.602	0	0.553	0.553	0	0.222	0.222
0	0.553	0.553	0	0.845	0.845	0	0.477	0.477
0	0.637	0.637	1	0.407	0.459	0	0.342	0.342
2	0.985	1.462	0	0.732	0.732	0	0.732	0.732
1	0.637	0.716	0	0.477	0.477	0	0.281	0.281
0	0.281	0.281	0	0.165	0.165	0	0.165	0.165
2	0.165	0.237	1	−0.637	−0.620	1	−0.407	−0.388
0	0.553	0.553	2	0.054	0.117	2	0.054	0.117
0	0.165	0.165	2	0.342	0.439	0	−0.109	−0.109
0	0.109	0.109	0	0.109	0.109	1	0	0.028
1	0.342	0.388	1	0	0.028	1	0.109	0.141
0	0	0	1	0.222	0.260	2	0.109	0.176
1	0.109	0.141	2	0.165	0.237	2	0.281	0.368
0	0.477	0.477	0	0	0	1	0	0.028
0	0.109	0.109	0	0.342	0.342	0	0.222	0.222
1	0.407	0.459	0	0.407	0.407	1	0.281	0.322
0	0.342	0.342	1	0.222	0.260	0	0.165	0.165
0	0.553	0.553	0	0.109	0.109	0	0.222	0.222
0	0.281	0.281	0	0.165	0.165	1	0.281	0.322
0	0.109	0.109	0	0.165	0.165	1	0	0.028
0	0.109	0.109	1	0	0.028	2	0.281	0.368
1	0.477	0.535	1	−0.165	−0.141	0	−0.109	−0.109
4	0.165	0.325	5	0.222	0.456	1	−0.165	−0.141
3	0.477	0.681	2	0.054	0.117	0	0.477	0.477
0	0.407	0.407	0	0.109	0.109	0	0.222	0.222
0	0.165	0.165	0	0.222	0.222	0	0.109	0.109
2	0.222	0.301	0	0.281	0.281	0	−0.054	−0.054
1	0.054	0.084	0	0.407	0.407	2	0.109	0.176
1	0.637	0.716	1	0.109	0.141	0	0.109	0.109
1	0.281	0.322	0	−0.054	−0.054	0	−0.109	−0.109
1	0.222	0.260	2	0.222	0.301	2	0.109	0.176
0	0.407	0.407	2	0.222	0.301	2	0.054	0.117
1	0.407	0.459	1	0.222	0.260	0	0.342	0.342
0	0.222	0.222	0	0.407	0.407	1	0.342	0.388
1	0.109	0.141	0	0.054	0.054	2	0	0.058
1	0.109	0.141	0	0.109	0.109	4	−0.280	−0.189
1	0.407	0.459	0	0.407	0.407	0	0.109	0.109
0	0.281	0.281	0	0.165	0.165	0	0.054	0.054
2	0.165	0.237	0	0.342	0.342	2	0.281	0.368
2	0.552	0.699	0	0.342	0.342	2	0.281	0.368