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REINFORCING EFFECTS OF CAFFEINE IN COFFEE AND CAPSULES

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In a residential research ward the reinforcing and subjective effects of caffeine were studied under double-blind conditions in volunteer subjects with histories of heavy coffee drinking. In Experiment 1, 6 subjects had 13 opportunities each day to self-administer either a caffeine (100 mg) or a placebo capsule for periods of 14 to 61 days. All subjects developed a clear preference for caffeine, with intake of caffeine becoming relatively stable after preference had been attained. Preference for caffeine was demonstrated whether or not preference testing was preceded by a period of 10 to 37 days of caffeine abstinence, suggesting that a recent history of heavy caffeine intake (tolerance/dependence) was not a necessary condition for caffeine to function as a reinforcer. In Experiment 2, 6 subjects had 10 opportunities each day to self-administer a cup of coffee or (on different days) a capsule, dependent upon completing a work requirement that progressively increased and then decreased over days. Each day, one of four conditions was studied: caffeinated coffee (100 mg/cup), decaffeinated coffee, caffeine capsules (100 mg/capsule), or placebo capsules. Caffeinated coffee maintained the most self-administration, significantly higher than decaffeinated coffee and placebo capsules but not different from caffeine capsules. Both decaffeinated coffee and caffeine capsules were significantly higher than placebo capsules but not different from each other. In both experiments, subject ratings of "liking" of coffee or capsules covaried with the self-administration measures. These experiments provide the clearest demonstrations to date of the reinforcing effects of caffeine in capsules and in coffee.

Key words: caffeine, coffee drinking, choice, progressive work requirement, subjective effects, behavioral pharmacology, drug abuse, drug self-administration, humans

As the most widely consumed psychoactive drug in the world (Gilbert, 1984), it is surprising that the reinforcing effects of caffeine in humans have been neither widely studied nor well documented (Griffiths & Woodson, 1988c). The first unequivocal demonstration of the reinforcing effects of caffeine in humans was provided in a discrete-trial choice study that was done as part of a series of experiments to investigate the self-administration and reinforcing effects of caffeine in residential volunteers with histories of heavy caffeine use as well as histories of drug and/or alcohol abuse (Griffiths, Bigelow, & Liebson, 1986; Griffiths, Bigelow, Liebson, O'Keeffe, et al. 1986). Across different days, subjects received experimenter-scheduled exposures to color-coded caffeinated or decaffeinated beverage coffee under double-blind conditions; subsequently, subjects were given a choice between the two coffees. When subjects had recent histories of caffeine exposure and were presumably caffeine tolerant and/or dependent, caffeinated coffee was rated as better liked than decaffeinated coffee and was preferred to decaffeinated coffee in choice tests. However, when subjects were not caffeine tolerant or dependent, caffeinated coffee was not reliably preferred to decaffeinated coffee, nor were there pronounced differences in ratings of liking. Under these conditions some subjects preferred decaffeinated to caffeinated coffee, citing adverse subjective effects (suggesting caffeine toxicity) as reasons for avoiding caffeinated coffee.

Two subsequent studies extended these findings by using discrete-trial choice procedures to examine preferences between caffeine and placebo capsules in normal subjects with "usual" histories of caffeine use (Griffiths & Woodson, 1988b; Stern, Chait, & Johanson, 1989). In the first of these (Griffiths & Woodson, 1988b), forced exposure and choice opportunities occurred when subjects were abstinent overnight from their normal dietary

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caffeine intake. After two forced-exposure days on which subjects received color-coded capsules containing either caffeine (100, 200, 400, or 600 mg) or placebo, subjects had a choice day on which they chose which one of the two types of color-coded capsules would be ingested. Subjects were exposed to 10 experimentally independent choices at each of several dose levels. Although there were substantial differences across the subjects, group data showed significant caffeine positive reinforcement at 100 and 200 mg, and individual subject data showed significant caffeine positive reinforcement in 5 of 12 subjects at one or more doses. Percentage selection of caffeine was inversely related to dose, with 4 subjects showing significant caffeine avoidance at 400 and/or 600 mg.

The second study in normal subjects used a similar choice procedure in which subjects received four forced-exposure days (two each with caffeine and placebo) followed by three choice days (Stern et al., 1989). Unlike the previous study, forced exposure and choice opportunities were not scheduled to occur in a caffeine-abstinent state. Two doses of caffeine (100 and 300 mg were examined in each subject using a crossover design. Choice of the low caffeine dose was not different than chance, whereas choice of the high caffeine dose was significantly lower than chance (38.9%). The design of this study did not permit a rigorous analysis of the choice behavior of individual subjects. However, when subjects were divided into groups of caffeine-sensitive choosers and nonchoosers, a consistent relationship emerged between caffeine choice and subjective effects; nonchoosers reported primarily aversive subjective effects after caffeine (increased anxiety and dysphoria), whereas choosers reported stimulant and "positive" mood effects.

All three of the above-described studies used discrete-trial choice procedures as the strategy for examining the reinforcing effects of caffeine. In addition to discrete-trial choice procedures, concurrent-schedule choice procedures and progressive-ratio schedules have been used for differentiating the relative reinforcing effects of drugs (Griffiths, Brady, & Bradford, 1979; McLeod & Griffiths, 1983; Pickens, Cunningham, Heston, Eckhert, & Gustafson, 1977). The present studies used variations on these procedures to extend systematically the series of residential ward studies investigating the self-administration of caffeine in subjects with histories of heavy caffeine use (Griffiths, Bigelow, & Liebson, 1986; Griffiths, Bigelow, Liebson, O'Keeffe, et al., 1986). More specifically, Experiment 1 used a variation on a concurrent-schedule choice procedure to elaborate knowledge about the reinforcing effects of caffeine by examining preference between capsules containing either caffeine or placebo. Unlike previous choice studies with caffeine in which a single choice opportunity occurred on each choice day (Griffiths, Bigelow, & Liebson, 1986; Griffiths & Woodson, 1988b; Stern et al., 1989), the present experiment allowed multiple choice opportunities each day. Because previous research suggested that recent history of caffeine intake may be an important determinant of the reinforcing effects of caffeine (Griffiths & Woodson, 1988c), Experiment 1 examined preference for caffeine under conditions in which subjects had a recent history of heavy caffeine intake and in which subjects had been caffeine abstinent.

Experiment 2 was also undertaken to extend knowledge of the reinforcing effects of caffeine, in this case in both capsules and in coffee within the same study. A previous study had shown that under ad-libitum conditions of availability, similar numbers of cups of caffeinated and decaffeinated coffee were self-administered when decaffeinated coffee was substituted for caffeinated coffee for 10 or more days (Griffiths, Bigelow & Liebson, 1986). Experiment 2 used a variation on a progressive-ratio schedule as a strategy to attempt to better differentiate between the self-administration of caffeinated versus decaffeinated coffee. More specifically, Experiment 2 involved making coffee or capsules available for self-administration under conditions in which the amount of work required for coffee or capsules was progressively increased over experimental days.

GENERAL METHOD

Subjects

Ten healthy male volunteers with histories of heavy coffee drinking participated. Table 1 shows individual subject characteristics. All but one of the volunteers (S-RO) were cigarette smokers and all but one (S-SI) had histories of problem alcohol drinking and/or drug abuse. Subjects reported consuming an average of 7

Table 1

Subject characteristics and sequence of experiments.

Subject	Age (years)	Weight (kg)	Education: grade level completed	History of drug abuse	History of alcohol abuse	Years of coffee drinking	Prestudy self-reported coffee consumption (cups/day)	Estimated prestudy caffeine consumption (mg/day)	Mean baseline coffee consumption (cups/day)	Experiment
S-BR	20	83	11	No	Yes	15	17	1,488	19.5	2
S-DA	27	66	12	No	Yes	11	7	1,060	9.6	2
S-HA	40	80	9	No	Yes	26	12	1,100	12.0	1 & 2
S-KA	46	57	7	No	Yes	34	7	612	10.2	2
S-KU	43	73	12+	Yes	Yes	29	20	1,270	11.1	2
S-LA	43	78	12	Yes	Yes	30	10	1,180	15.4	1 & 2
S-LO	47	69	12+	No	Yes	35	10	680	11.1	1
S-RO	31	73	12	Yes	No	15	12	1,020	12.8	1
S-SE	39	74	10	Yes	Yes	27	16	1,390	—	1
S-SI	27	64	11	No	No	7	10	1,010	10.1	1

to 20 cups of coffee per day. Prestudy caffeine consumption was estimated from dietary questionnaires to range between 612 and 1,488 mg/day, based on estimates of Barone and Roberts (1984) for coffee (60 mg/5-oz cup of instant and 85 mg/5-oz cup of ground roasted), tea (30 mg/5-oz cup of instant and 40 mg/5-oz cup of leaf or bagged), and caffeinated soft drinks (36 mg/12-oz can). This level of caffeine consumption is in the 99th percentile of adults in the United States (Graham, 1978). Details of subject screening, financial compensation, and informed consent were similar to those described previously (Griffiths, Henningfield, & Bigelow, 1982). Briefly, on the basis of physical examination, history, and routine laboratory chemistries, participants were found to be without significant medical or psychiatric disturbance other than their drug/alcohol abuse. Volunteers were recruited from the local community and paid for their participation at the rate of approximately $100 per week; none was institutionalized or under legal pressure to enroll. Subjects gave their sober informed written consent before beginning the study in accordance with the Department of Health and Human Services guidelines for protection of human subjects.

Setting

Subjects participated while residing in an eight-bed behavioral pharmacology research ward. Various recreational, reading, and craft activities were continuously available to the subjects. Cooperation with research procedures and ward routines was maintained via an earnings system in which points, which were convertible to money, were earned for various personal and ward maintenance activities, spent for minor ward privileges, and sacrificed for rule violations.

General Procedures

The subjects participated in this research singly rather than in groups, a procedure that increases the independence of each subject's data. The number of other residents on the research ward varied between 1 and 7. These other residents participated in different behavioral pharmacology experiments that sometimes involved the administration of opioids, ethanol, barbiturates, or benzodiazepines.

Other than a general explanation of experimental purpose (described below), subjects were given no instruction as to what they were "supposed" to do or of what outcomes might be expected. To reduce the possibility that subjects would receive instructions or explanations that might confound the results, ward staff were explicitly instructed to refrain from discussing experiments with subjects, except to provide an objective description of the routines and procedures that subjects must follow. Subjects received explicit instructions about details of the daily research procedures and the residential ward rules, including the fact that they should remain in the ward dayroom area from

7:15 a.m. to 5:30 p.m. daily except for necessary brief trips to the bathroom.

Subjects were told that the general purpose of the research was to investigate the subjective and behavioral effects of a variety of chemical compounds contained in coffee (Experiments 1 and 2) and of different kinds or strengths of coffee (Experiment 2). They were told that, in addition to caffeine and other methylxanthines, other less familiar but potentially just as powerful compounds that might be administered included chlorogenic acid, kahlweol, cafestol, tannin, and sugar.

During the experiments caffeine was experimentally administered in coffee or capsules as described below; other sources of caffeine (e.g., caffeinated soft drinks, coffee, tea, chocolate, etc.) were monitored and forbidden.

Initial Baseline Period of Coffee Drinking

Before initiating Experiment 1 or 2, all subjects except S-SE participated in a baseline period of coffee drinking to verify that subjects were heavy consumers of caffeine. During this period, which ranged from 6 to 9 days across subjects, caffeinated coffee (100 mg/cup) was available ad libitum between 7:30 a.m. and midnight; subjects were instructed to consume as much or as little coffee as they desired.

EXPERIMENT 1: CHOICE BETWEEN CAFFEINE AND PLACEBO CAPSULES

The objective of Experiment 1 was to extend information about the reinforcing effects of caffeine by examining preference between capsules containing either caffeine or placebo under conditions in which subjects had 13 choice opportunities each day. In order to examine whether a history of recent exposure to caffeine would be a determinant of the reinforcing effects of caffeine, we examined preference for caffeine both when subjects had a recent history of heavy caffeine intake and when subjects had been caffeine abstinent.

METHOD

Six subjects with histories of heavy coffee drinking participated in Experiment 1 (Table 1). After the coffee drinking baseline period described above, subjects participated in a choice protocol in which they had an opportunity to choose repeatedly between ingesting one of two color-coded capsules 13 times each day. Every hour on the hour between 8:00 a.m. and 8:00 p.m., staff members asked the subject whether he wanted to take a capsule. Subjects could decline to take a capsule or could choose to take one of the two color-coded capsules available. Capsules were ingested orally immediately after each choice.

Subjects were told that they were free to take as many or as few of the available capsules as they wished. They were told that the contents of the two available capsules might or might not be different but the contents of capsules having a given color code would not vary within or across days (e.g., a red capsule would always contain the same dose of compound). In order to examine the within-subject replicability of preference results, the capsule color codes were changed (i.e., novel color codes were introduced) once or twice during the study with 4 of the 6 subjects. On these occasions, subjects were told on the day of the change that the color codes and possibly the contents of the capsule had been changed. Four of the 6 subjects were exposed to a number of consecutive days of caffeine withdrawal (i.e., days involving no caffeine ingestion), either immediately before the availability of the first set of capsules or between the availability of two different sets of color-coded capsules. The number of days and sequence of the experimental conditions for each subject appear in Figure 1. Termination of the final experimental condition was determined by the duration that the subject agreed to participate in research.

At 8:15 p.m. each day, subjects completed a rating scale for capsule preference in which they indicated whether or not they preferred one type of color-coded capsule over the other. If they had a preference, they rated the degree to which they "liked the subjective effects" of both types of color-coded capsules (4-point scale from 0 = not at all to 3 = very much). Finally, subjects were requested to write general descriptive comments about what they liked and/or disliked about the different capsules.

Capsule Preparation and Dispensing

Caffeine and placebo capsules were prepared from combinations of caffeine anhydrous (USP) and powdered lactose. Each caffeine capsule contained 100 mg caffeine. Seven different colors of size 0 hard gelatin capsules were used to prepare distinctive one- or two-

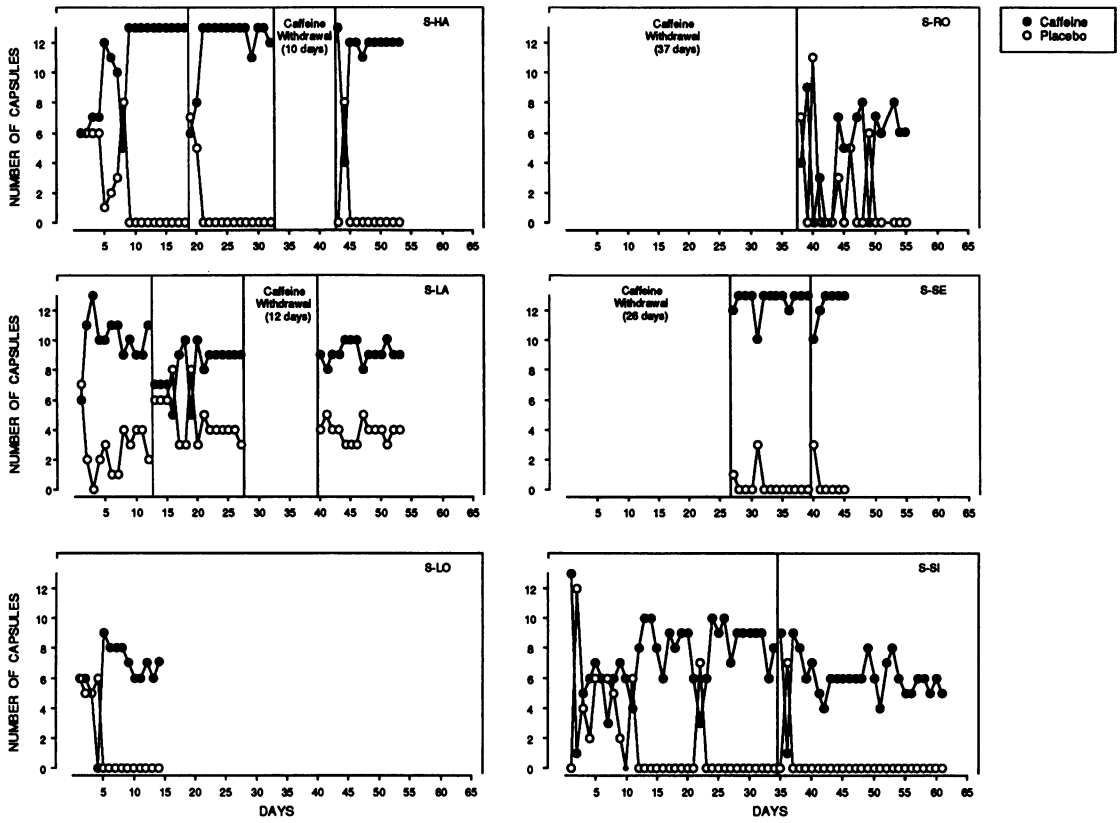

Fig. 1. Number of 100-mg caffeine (filled points) and placebo (open points) capsules self-administered over consecutive days by each of the 6 subjects in Experiment 1. Vertical lines indicate a change in condition: Either novel color codes associated with caffeine and placebo capsules were introduced or a change was made between capsule availability and caffeine withdrawal. Phases labeled "caffeine withdrawal" indicate days on which no caffeine was ingested.

color capsules. When a subject choose to self-administer a capsule, capsule ingestion took place under staff supervision: The subject sat behind the nurse's station, a staff member placed the capsule in the subject's mouth, and the subject consumed approximately 120 cc water. The availability and dispensing of capsules were under double-blind conditions: Neither the subject nor any of the ward staff were informed of the contents of the capsule.

Results

As shown in Table 1, the baseline period of ad-libitum coffee drinking, to which 5 of the 6 subjects were exposed, verified that subjects were heavy consumers of caffeine. Grand mean and range of the number of cups per day were 12.4 (9.6 to 19.5). Across subjects, mean baseline coffee consumption was significantly correlated with estimated prestudy caffeine consumption (Pearson $r = 0.68$, $p < .05$).

Figure 1 shows the patterns of capsule self-administration over consecutive days. When given the opportunity to choose between caffeine and placebo capsules, all 6 subjects developed a clear preference for caffeine. Although there were within- and between-subject differences, when subjects were exposed to new color codes they typically sampled both types of color-coded capsules on the initial few days of availability and on subsequent days consistently self-administered more caffeine capsules than placebo capsules. The figure also shows that Subjects S-HA, S-LA, S-SE tended to self-administer the maximum number of capsules per day available (12 or 13 caffeine plus placebo capsules per day), and the other 3 subjects usually self-administered five to nine

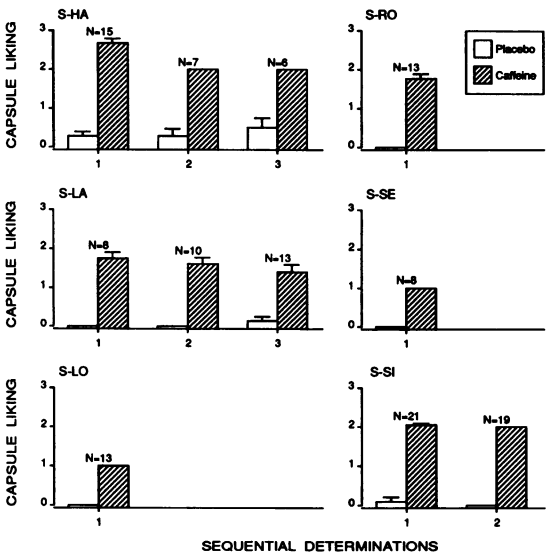

Fig. 2. Mean ratings of liking of subjective effects produced by caffeine (striped bars) and placebo (open bars) capsules self-administered by each of 6 subjects in Experiment 1. Bars show means; brackets show +1 *SEM*. Data are from days on which subjects indicated on the rating scale that they preferred one type of capsule over the other; the number of days appears over each pair of bars. The sequential determinations correspond to the sequential changes in color codes shown in Figure 1. No liking ratings were obtained (or are shown) for the second set of color codes to which S-SE was exposed because on each day of this condition this subject indicated on the daily rating scale that he did not prefer one type of capsule over the other.

capsules per day. Caffeine intake tended to be relatively stable within subjects, with little evidence for increasing or decreasing trends occurring after stable preference had been attained. Finally, the figure shows that caffeine withdrawal did not affect patterns of capsule ingestion or caffeine preference: The results for the four occasions on which new capsule colors were immediately preceded by a period of caffeine withdrawal were generally similar to the results for the eight occasions on which new capsule colors were preceded by a period of substantial daily caffeine intake.

Data from the daily rating scale for caffeine preference were usually consistent with the behavioral preference results shown in Figure 1. When exposed to new capsule color codes, subjects typically rated that they did not prefer one type of color-coded capsule over the other on initial days of availability and on subsequent days rated that they preferred the caffeine capsule color over the placebo capsule color. Subjects rarely rated that they preferred the placebo capsule over the caffeine capsule color. Consistent with these preference ratings, Figure 2 shows that subjects rated caffeine capsules as being better liked than placebo capsules.

Descriptive written comments on this same rating form also differentiated between the caffeine and placebo capsules. Caffeine capsules were described as having stimulant effects by all 6 subjects (e.g., "energy," "zip," "stimulation," "pep," "wake-me-up"); 2 subjects also described the caffeine capsules as producing increased well-being ("good mood," "natural high"); Subject S-HA, who described the caffeine capsules as increasing "energetic" and "zip" feelings, also described these capsules as increasing feelings of being "calm" and "relaxed." Placebo capsules, in contrast, were described as having no effect (4 subjects) and/or described as producing headache (3 subjects) and sleepiness (2 subjects).

EXPERIMENT 2: SELF-ADMINISTRATION OF COFFEE AND CAPSULES UNDER CONDITIONS OF PROGRESSIVELY INCREASING WORK REQUIREMENTS

Experiment 1 showed that caffeine capsules were preferred to placebo capsules under conditions of concurrent availability. Experiment 2 was undertaken to extend systematically this research on the reinforcing effects of caffeine by examining the self-administration of coffee and capsules under conditions in which the amount of work required for coffee or capsules was progressively increased over experimental days to suppress self-administration. Subsequently, the work requirement was decreased to determine whether higher levels of self-administration would be recovered.

METHOD

Six subjects with histories of heavy coffee drinking participated in Experiment 2 (Table 1). Subjects were told that the general purpose of the research was to investigate the subjective and behavioral effects of administering specially prepared experimental coffee or capsules

containing a variety of chemical compounds contained in regular coffee (see General Method).

After the coffee drinking baseline period described previously, subjects participated in a protocol that provided 10 opportunities each day to either drink a cup of coffee or, on different days, to take a capsule. Each day, one of four conditions was studied: (a) caffeinated coffee, (b) decaffeinated coffee, (c) caffeine capsules, and (d) placebo capsules. The two coffee conditions were differentiated on the basis of color-coded containers in which the freeze-dried coffee was available. The two capsule conditions were differentiated by the capsule colors. Subjects were told that the color codes for the coffee and capsules would remain the same throughout the study. Every hour on the hour between 8:00 a.m. and 5:00 p.m., each subject had the opportunity to self-administer the available substance (on different days either a color-coded coffee or a color-coded capsule), provided that he had completed a specified riding requirement on a stationary exercise bicycle sometime during the previous hour. On the first 4 days subjects were exposed to the four conditions in mixed order, and there was no riding requirement. Subjects were told to take as much or as little of the available substance as they wanted, and that they should try to associate the color codes with the effects of coffee or capsules because on later days they would have the opportunity to ride the exercise bicycle to receive the color-coded substance. For the remainder of the study, subjects were exposed to the four conditions according to a block-random sequence across days. Upon coming to the ward dayroom each morning, subjects were told the color-coded coffee or capsule condition available for self-administration that day and the exercise bicycle riding time required for self-administration of each cup of coffee or capsule. The purpose of the next phase was to determine whether differential self-administration would occur with the different conditions in the face of increasing work requirements that suppressed self-administration. Initially, the exercise bicycle riding requirement was progressively increased over successive 4-day blocks of conditions (0.5, 1, 2, 4, 8, 16, and 32 min riding per cup of coffee or capsule self-administered; for S-HA and S-KU the riding requirement was subsequently increased to 50 min because substantial self-administration continued to occur at the 32-min requirement). After the 32- or 50-min riding requirement, which was associated with low levels of self-administration, subjects were exposed to a low or intermediate riding requirement for four to six blocks of conditions to determine whether higher levels of self-administration would be recovered. The riding requirement for this final phase was selected individually for each subject as being one that had been associated with intermediate levels of self-administration during the increasing work requirement phase.

Subject and Staff Rating Scales and Questionnaires

Subjects and staff completed various rating questionnaires several times daily. At 5:15 p.m. subjects completed the Coffee/Capsule Rating Form, which consisted of six questions. On four questions subjects rated the "overall intensity," "stimulant effect," "liking," and "disliking," of the subjective effects from the coffee or capsules available that day on a 4-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = very much). On one question subjects rated their overall liking for the coffee or capsule "compared to drinking standard or 'usual' coffee" on a 9-point scale (1 = much lower, 5 = like standard coffee, 9 = much higher). On another question, which was completed only on days in which one of the color-coded coffees was available, subjects rated coffee "bitterness" on a 7-point scale (1 = not at all bitter, 4 = average, 7 = very bitter). Finally, subjects were requested to write general descriptive comments about what they liked and/or disliked about the color-coded coffee or capsule condition that was available that day.

At 12:30 p.m. and 8:30 p.m. subjects completed two mood questionnaires that were only identified as mood self-rating scales (Patient Self-Rating Form and the Profile of Mood States, POMS). Subjects were instructed to complete both questionnaires on the basis of how they felt at the present time. Items on the Patient Self-Rating Form have previously been shown to be sensitive to the effects of caffeine and caffeine withdrawal (Goldstein, Kaiser & Whitby, 1969; Griffiths, Bigelow, & Liebson, 1986). Subjects rated 11 mood items on a 4-point scale (0 = definitely does not apply, 1

= may apply but uncertain, 2 = definitely applies, 3 = very strongly applies): (1) alert, attentive, observant, able to concentrate; (2) content, at ease, relaxed, satisfied; (3) jittery, nervous, shaky; (4) active, stimulated, energetic; (5) sleepy, tired, drowsy, half-awake; (6) depressed, despondent; (7) talkative; (8) headache; (9) upset stomach; (10) lazy, sluggish; and (11) irritable, cross, grumpy. The second mood questionnaire was the POMS, which is an adjective rating questionnaire generally considered to be a standardized subjective mood state inventory (McNair, Lorr, & Droppleman, 1971) and which has been shown previously to be sensitive to the effects of caffeine and caffeine withdrawal (Chait & Griffiths, 1983; Griffiths, Bigelow, & Liebson, 1986). Eight empirically derived scores were obtained from the 65-item version of the POMS used: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, confusion-bewilderment, friendly, and total mood disturbance.

At 12:30 p.m. and 8:30 p.m. staff completed a questionnaire that was identified as a mood rating scale. Staff rated nine adjective clusters on the basis of observation of the subject over the previous 2 hours. The adjective clusters and 4-point scale were identical to those on the 11-item subject mood rating questionnaire except that Items 8 (headache) and 9 (upset stomach) were deleted.

The Bicycle-Riding Task

A stationary exercise bicycle was located in the dayroom area of the ward. When a subject told a staff member that he wanted to ride for the scheduled substance, the staff member started a timer located at the nursing station. Under constant staff observation, the subject was required to sit on the stationary bicycle and pedal continuously for the specified number of minutes required by the protocol. There was no pedaling speed requirement and the pedaling force adjustment on the bicycle was set at the minimum level; thus, the task required a trivial expenditure of energy. When on the bicycle, the subject could see a wall clock and was free to smoke, watch television, and talk with staff and other residents.

Coffee and Capsule Preparation and Dispensing

Individual freeze-dried coffee doses were pre-prepared by adding either 100 mg caffeine anhydrous (USP) (caffeinated condition) or a similar amount of powdered lactose (decaffeinated condition) to 2 g of Taster's Choice® freeze-dried decaffeinated coffee. Two grams of freeze-dried decaffeinated coffee contains approximately 2 mg of caffeine ("Instant Coffees," 1979). The caffeine dose in the caffeinated condition was in the mid-range of caffeine doses that normally occur in cups of brewed coffee (Bunker & McWilliams, 1979; Gilbert, Marshman, Schwieder, & Berg, 1976). Previous research showed that, in general, subjects could not differentiate reliably, on the basis of taste or appearance, between decaffeinated coffee plus lactose and decaffeinated coffee plus caffeine (100 or 150 mg/cup) (Goldstein, 1964; Griffiths, Bigelow, Liebson, O'Keeffe, et al., 1986).

When a subject chose to self-administer coffee he informed the staff. A staff member poured the dried coffee in a cup and added preheated water (approximately 70 °C) to a volume of 180 mL. Subjects were allowed to add premeasured portions of cream and/or sweetener if they desired; however, they were not allowed to change these amounts during the course of their experimental participation. To facilitate staff monitoring of coffee drinking, subjects were required to drink their coffee while sitting in a designated chair near the nurses' station.

The two different coffee conditions were differentiated to subjects and staff on the basis of color-coded containers in which each dose of freeze-dried coffee was available. Color-coded caffeine (100 mg) and placebo capsules were prepared and dispensed as described in Experiment 1. Although the different coffee and capsule conditions were differentiated on the basis of color codes, the availability was under double-blind conditions: Neither the subject nor any of the ward staff were informed of the coffee brand, amount of coffee, the substances added to the premeasured coffee packets, or the substances in the capsules.

Analysis of Group Data

To examine statistically the group results over the course of the experiment, a repeated measures ANOVA was used with data on the number of administrations and data from the Coffee/Capsule Rating Form. Factors in the analyses were Caffeine (caffeinated coffee/caffeine capsules vs. decaffeinated coffee/placebo capsules), Mode of Administration (coffee vs.

capsules), and Riding Requirement. The Riding Requirement factor consisted of the first 12 sequential riding requirements excluding the 50-min requirement in S-HA and S-KU (0, 0.5, 1, 2, 4, 8, 16, 32, R1, R2, R3, and R4, with R1–R4 designating the first four "recovery" riding requirements immediately after the 32- or 50-min riding requirement). Post hoc comparisons were made between the four experimental conditions using Tukey's HSD test.

Subject ratings of coffee "bitterness" on the Coffee/Capsule Rating Form were analyzed with ANOVA as described above but without the Mode of Administration factor. Subject and staff ratings of mood on the Patient Self-Rating Form, the POMS, and the Staff Mood Rating Form were analyzed with ANOVA as described above but with the addition of a time factor (12:30 p.m. vs. 8:30 p.m.).

For all statistical tests, effects were considered to be significant for $p \leq .05$.

Results

Figure 3 shows the number of cups of coffee and capsules self-administered over the sequential blocks of conditions by each of the 6 subjects in Experiment 2. Progressively increasing the work required for each cup or capsule from 0 to 32 or 50 min was associated with an orderly decrease in the number of cups or capsules self-administered. When the work requirement was subsequently reduced to a low or intermediate value, self-administration of three of the four conditions (caffeinated coffee, decaffeinated coffee, and caffeine capsules) increased somewhat in all 6 subjects.

The placebo capsule condition showed the most uniform and best differentiated effect. For all 6 subjects, self-administration of placebo capsules decreased more rapidly than any of the other three conditions, and in no instance were placebo capsules self-administered after the work requirement was lowered. The next best differentiated condition was caffeinated coffee. Although there was variability within and across subjects, caffeinated coffee tended to maintain higher levels of self-administration than both decaffeinated coffee and caffeine capsules.

The differences in self-administration among conditions can be seen more clearly in Figure 4 and the upper left panel of Figure 5, which show mean number of cups of coffee and capsules taken. The caffeinated coffee condition maintained the most self-administration, significantly higher than the decaffeinated coffee and placebo capsule conditions but not significantly different from the caffeine capsule condition. Both the decaffeinated coffee and the caffeine capsule conditions were significantly higher than the placebo capsule condition but not different from each other.

In contrast to the self-administration behavior, the ratings of the Coffee/Capsule Rating Form were not significantly affected by the changes in work requirement. As presented in Figure 5, ratings of "overall intensity" and "stimulant effect" of the subjective effects from the coffee or capsules show that the two caffeine conditions were rated significantly higher than the two no-caffeine conditions. Ratings of "liking" of subjective effects and "overall liking" of capsules or coffee relative to standard coffee show the caffeine conditions were significantly higher than the no-caffeine conditions, with decaffeinated coffee being significantly better liked than placebo capsules. The magnitude of the ratings of "overall liking" shows the caffeine conditions were judged to be approximately comparable to liking of standard or usual coffee (5 = like standard coffee). Ratings of "disliking" show that the two no-caffeine conditions tended to be more disliked than the caffeine conditions, with placebo capsules being significantly different from both caffeine conditions. The caffeinated and decaffeinated coffee conditions were both rated as having approximately average "bitterness" (overall means of 3.9 and 3.6, respectively) and were not significantly different from each other (data not shown).

Descriptive written comments on the Coffee/Capsule Rating Form also differentiated among the four experimental conditions. Both the caffeinated coffee and caffeine capsule conditions were described as having positive stimulant effects (e.g., "stimulation," "alert," "energetic," "active," "awake," "concentration") by all 6 subjects; adverse stimulant effects (e.g., "jittery," "shaky") were rarely described. The primary distinction between caffeinated coffee and caffeine capsules was that the former was occasionally described as tasting good by 4 of the 6 subjects. The decaffeinated coffee condition was described as tasting good (4 subjects), and producing headache (5 subjects), sleepiness (3 subjects), and little or no effect

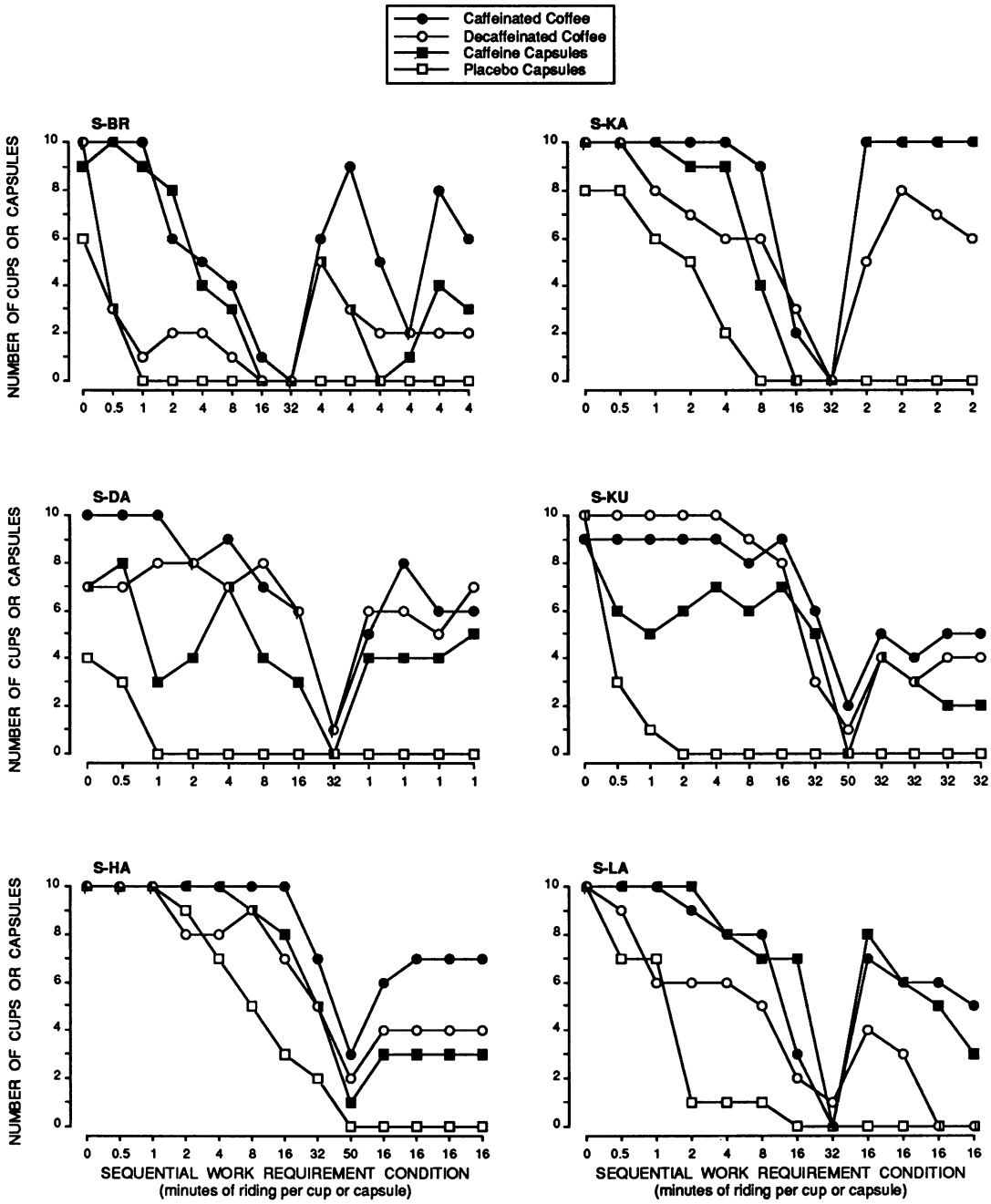

Fig. 3. Number of cups of coffee and capsules self-administered by each of 6 subjects in Experiment 2. Data are presented for each of the four conditions: caffeinated coffee (100 mg/cup)(filled circles), decaffeinated coffee (open circles), caffeine capsules (100 mg/capsule)(filled squares), and placebo capsules (open squares). Sequential blocks of conditions at the indicated work requirement (minutes of exercise bicycle riding required for each cup or capsule) are shown on the *x* axes. For Subject S-KA, the last five data points of the caffeinated coffee and caffeine capsule conditions were identical.

(4 subjects). The placebo capsule condition was described as producing headache (5 subjects), no effect (5 subjects), and sleepiness (4 subjects).

Mood questionnaires completed by subject and staff at 12:30 p.m. and 8:30 p.m. showed robust effects of the caffeine conditions on subject mood and behavior. Statistical analysis of group data showed that caffeine significantly increased subject ratings of content/at ease/relaxed/satisfied, jittery/nervous/shaky, active/stimulated/energetic, vigor (POMS), and friendly (POMS) and significantly decreased subject ratings of sleepy/tired/drowsy/half-awake, headache, and fatigue (POMS). Staff ratings of subject mood, based on observing the subject on the research ward, showed that caffeine significantly increased ratings of content/at ease/relaxed/satisfied, active/stimulated/energetic, and talkative and significantly decreased ratings of sleepy/tired/drowsy/half-awake and lazy/sluggish.

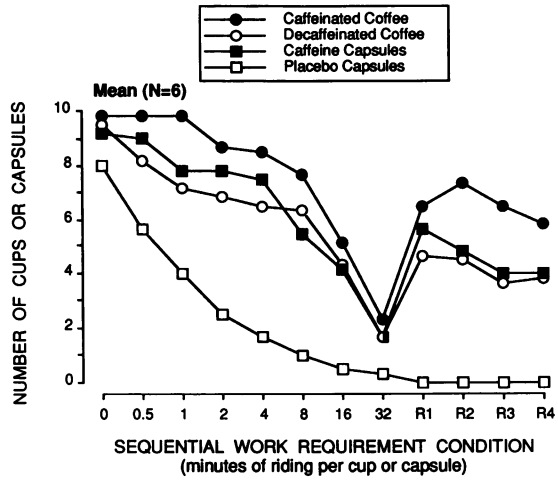

Fig. 4. Mean number of cups of coffee and capsules self-administered by the 6 subjects in Experiment 2. Mean data are derived from individual data shown in Figure 3. The first 12 sequential exercise bicycle riding requirements, excluding the 50-min requirement in S-HA and S-KU, are shown on the x axis. R1–R4 designate the first four "recovery" riding requirements immediately after the 32- or 50-min riding requirement.

GENERAL DISCUSSION

The present data provide the clearest demonstrations to date of the reinforcing effects of caffeine. Experiment 1 used a choice procedure to show that caffeine capsules were preferred to placebo capsules under conditions in which subjects had multiple choice opportunities each day. Experiment 2 systematically extended this research on the reinforcing effects of caffeine by using a variation of a progressive-ratio schedule as a strategy for differentiating the relative reinforcing effects of caffeine in coffee and in capsules. This study showed that caffeinated coffee maintained higher levels of self-administration than decaffeinated coffee and, similarly, caffeine capsules maintained higher levels of self-administration than placebo capsules.

In both experiments, ratings of "liking" generally covaried with the behavioral measures of reinforcing efficacy. Figures 1 and 2 show these data for individual subjects in Experiment 1. In Figure 5, comparison of the "self-administration" panel and the "overall liking relative to standard coffee" panel shows the covariation of average self-administration and liking data in Experiment 2. Inspection of individual subject data in Experiment 2 (not shown) also reveals the covariation between number of cups or capsules self-administered and ratings of overall liking.

The results of Experiment 2 extend the range of conditions under which caffeine has been demonstrated to function as a reinforcer in coffee (Griffiths & Woodson, 1988c). Although one previous study showed that subjects with recent histories of heavy coffee drinking reliably chose caffeinated over decaffeinated coffee in choice tests, other studies of ad-libitum coffee drinking had indicated that ad-libitum consumption of decaffeinated coffee occurred at the same rate as consumption of usual-strength caffeinated coffee (Griffiths, Bigelow, & Liebson, 1986; Griffiths, Bigelow, Liebson, O'Keeffe, et al., 1986). Experiment 2 showed that when an operant work requirement was imposed, caffeinated coffee maintained higher levels of self-administration than did decaffeinated coffee.

The results of Experiment 2 also document the reinforcing effects of decaffeinated coffee: Decaffeinated coffee was shown to maintain higher levels of self-administration than placebo capsules. This extends a previous observation suggesting the reinforcing effects of decaffeinated coffee: When decaffeinated coffee was substituted for caffeinated coffee on a double-blind basis for 10 or more days, the number of cups of decaffeinated coffee showed only a

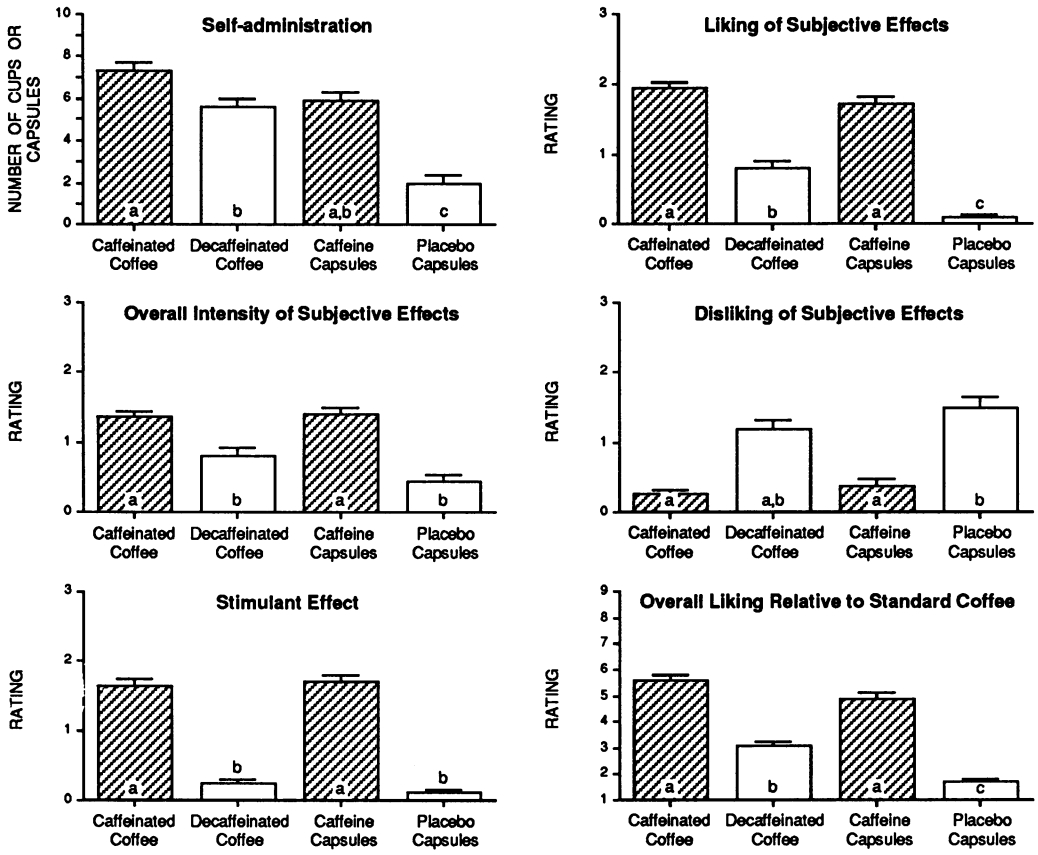

Fig. 5. Mean number of cups of coffee and capsules self-administered (upper left panel) and mean data from questions on the Coffee/Capsule Rating Form for each of the four conditions in Experiment 2. Bars show mean data derived from the 12 sequential exercise bicycle riding requirements shown in Figure 4; brackets show +1 *SEM*. Letters a, b, and c indicate the results of statistical comparisons among the four conditions; within a panel, any two bars designated with the same letter are not significantly different from each other at $p < .05$.

small, nonsignificant decrease on the first few days after substitution (Griffiths, Bigelow, & Liebson, 1986). The extent to which drinking of decaffeinated coffee is maintained by conditioned reinforcers established by past pairing with caffeine or, alternatively, by pharmacologically active substances in coffee other than caffeine (Boublik et al., 1983; Cohen & Booth, 1975; Spiller, 1984) cannot be determined.

The present study extends information about across-day patterns of caffeine self-administration. Experiment 1 permitted the examination of caffeine self-administration in capsules under relatively unconstrained conditions (up to 1.3 g caffeine/day) for periods of 14 to 61 consecutive days. As shown in Figure 1, when new capsule colors were introduced, an unstable period of capsule sampling was usually followed by relatively stable day-to-day self-administration of caffeine, typically with no periods of spontaneous abstinence. This pattern of stable daily intake of caffeine is similar to that which occurred in previous residential ward studies involving relatively unconstrained self-administration of caffeinated coffee in a subject population similar to that in the present study (Griffiths, Bigelow, & Liebson, 1986; Griffiths, Bigelow, Liebson, O'Keeffe, et al., 1986).

Although several studies suggest that a recent history of substantial caffeine intake may potentiate the reinforcing effects or subjective liking of caffeine (Goldstein & Kaizer, 1969; Goldstein et al., 1969; Griffiths, Bigelow, & Liebson, 1986), studies have also provided isolated examples demonstrating that caffeine can

function as a reinforcer in absence of such a history (Griffiths & Woodson, 1988a, 1988b). The results of Experiment 1 extend these observations by showing that a recent history of substantial caffeine intake was not a necessary condition for caffeine to function as a reinforcer: Preference for caffeine over placebo capsules occurred whether or not preference testing was preceded by a period of 10 to 37 days of caffeine abstinence.

In both experiments, the descriptive written comments by subjects regarding what they liked and disliked about the different capsule and coffee conditions are consistent with previous findings about the subjective effects of caffeine and caffeine withdrawal. As in previous studies with heavy caffeine users (Goldstein & Kaiser, 1969; Goldstein et al., 1969; Griffiths, Bigelow, & Liebson, 1986), caffeine conditions were most often described as producing stimulant effects that were liked by the subjects (e.g., increased energy, activeness, alertness, concentration, etc.). Adverse stimulant effects of caffeine (e.g., jittery, shaky) that have been reported in nontolerant subjects (Goldstein & Kaiser, 1969; Goldstein et al., 1969; Griffiths, Bigelow, & Liebson, 1986) were rarely reported by these subjects who had histories of heavy coffee use. The placebo capsule and decaffeinated coffee conditions were most often described as producing no effect or as producing symptoms typical of acute caffeine withdrawal (e.g., headache, sleepiness) (Griffiths & Woodson, 1988a).

The descriptive written comments regarding what subjects liked and disliked about the different conditions were also consistent with the profile of mood effects of the caffeine conditions versus the no-caffeine conditions in the subject-completed mood questionnaires in Experiment 2. On caffeine days, subjects rated themselves as being more content, jittery, active, vigorous, and friendly and less sleepy, fatigued, and headachy. The apparent robustness of these effects is suggested by the finding that staff ratings of subjects based on observing subjects on the research ward showed caffeine-associated increases in content, active, and talkative ratings and decreases in sleepy and lazy ratings.

The generality of the present results is limited to the extent that the subject population was atypical. Subjects were recruited specifically for the study because they had histories of consuming high levels of caffeine. Furthermore, the majority of the subjects also had histories of alcohol and/or drug abuse problems. As discussed above, recent studies in subjects with more usual histories of caffeine and other substance use suggest that there may be substantial individual differences in the normal population with respect to the reinforcing and positive subjective effects of caffeine administration (Griffiths & Woodson, 1988b; Stern et al., 1989).

There was no evidence that the taste of caffeine confounded the results between the caffeinated and decaffeinated coffee conditions in Experiment 2. The present study used a subject-rated scale of coffee bitterness that had been demonstrated previously to be sensitive to high concentrations of caffeine in coffee (Griffiths, Bigelow, Liebson, O'Keeffe et al., 1986) to determine whether subjects differentiated the caffeinated and decaffeinated coffee conditions on this basis. The failure of these ratings to differentiate between the conditions extends the results of several previous studies suggesting that despite known wide individual differences in the ability detect the taste of caffeine, decaffeinated coffee plus lactose is generally not differentiated reliably from decaffeinated coffee plus 100 mg of caffeine (Griffiths, Bigelow, & Liebson, 1986; Griffiths, Bigelow, Liebson, O'Keeffe et al., 1986).

The present studies significantly extend recent research that used discrete-trial choice procedures to provide the first unequivocal evidence that caffeine could function as a reinforcer in humans (Griffiths, Bigelow, & Liebson, 1986; Griffiths & Woodson, 1988b). Using variations on concurrent schedule and progressive-ratio schedule procedures, the present experiments provide clear demonstrations of the reinforcing effects of caffeine in both capsules and coffee, document the reinforcing effects of decaffeinated coffee, and indicate that a recent history of heavy caffeine intake (tolerance and/or dependence) is not a necessary condition for caffeine to function as a reinforcer. Future research should determine the extent to which the reinforcing effects of caffeine are responsible for maintaining socially sanctioned patterns of chronic use characteristic of 80% to 90% of the adults in North America (Gilbert, 1976; Graham, 1978). The continued investigation of the reinforcing effects of caffeine should provide a useful model for

elaborating interactions among pharmacological and behavioral variables influencing self-administered drugs and, thereby, ultimately provide understanding into the general nature of drug-dependence processes.

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