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LOW-DOSE CAFFEINE DISCRIMINATION AND SELF-REPORTED MOOD EFFECTS IN NORMAL VOLUNTEERS

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A caffeine versus placebo discrimination procedure was used to determine the lowest caffeine dose that could produce discrimination and self-reported mood effects in normal volunteers. During daily sessions under double-blind conditions, caffeine-abstinent subjects orally ingested a capsule containing 178 mg caffeine or placebo. Before beginning discrimination training, the compounds were identified to subjects by letter codes. Fifteen, 30, and 45 min after capsule ingestion, subjects guessed the capsule's letter code. Correct guesses at 45 min earned money. After each session, subjects received a supplementary capsule containing caffeine or placebo to ensure that, within each phase of the study, subjects received the same daily dose of caffeine equal to the training dose. Five of the 15 subjects acquired the caffeine versus placebo discrimination within the first 20 sessions (≥75% correct); 6 other subjects acquired the discrimination with additional training. Nine subjects who acquired the discrimination were subsequently trained at progressively lower caffeine doses. In general, the lowest dose to produce discrimination (≥75% correct) was also the lowest dose to produce self-reported mood effects: 4 subjects showed discrimination and self-reported mood effects at 100 mg caffeine, 2 at 56 mg, 1 at 32 mg, and 1 at 18 mg. One of these subjects also showed self-reported mood effects at 10 mg. The present study documents discriminative stimulus and self-reported mood effects of caffeine at doses below those previously shown to affect any behavior in normal volunteers.

Key words: caffeine, behavioral pharmacology, psychophysics, mood, drug discrimination, subjective effects, humans

Although large numbers of people consume caffeine daily in coffee, tea, soft drinks, chocolate, and over-the-counter medications, the degree to which these relatively low dietary doses of caffeine affect behavior is not well understood. Caffeine's behavioral effects in studies conducted with humans have usually been subtle, variable, or absent, particularly at low doses. In fact, most investigations have failed to find behavioral effects of caffeine at doses below 200 to 300 mg (Bättig, 1985; Gilbert, 1976), amounts equal to 2.5 to 3.5 cups of average-strength coffee.

Recent investigations have begun to characterize lower caffeine doses as behaviorally active, but even these effects have been variable. Although caffeine reinforcement, for example, has been demonstrated experimentally (Griffiths, Bigelow, & Liebson, 1986, 1989; Griffiths & Woodson, 1988; Hughes et al., 1991), reinforcement by dietary doses of caffeine (e.g., 100 mg caffeine per cup of coffee or capsule) has been seen in only 30% to 60% of normal experimental subjects (Griffiths & Woodson, 1988; Hughes et al., 1991). Some investigators have failed to find any evidence of low-dose caffeine reinforcement (Stern, Chait, & Johanson, 1989).

Only rarely have doses of caffeine below 100 mg altered self-reports of mood or performance. An impressive series of studies found that caffeine enhanced auditory vigilance and reaction time at doses as low as 75 mg (Clubley, Bye, Henson, Peck, & Riddington, 1979), 64 mg (Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987), and 32 mg (Lieberman, Wurtman, Emde, & Coviella, 1987). As little as 64 mg caffeine has been shown to affect self-reports of mood (Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987). However, some of these results have eluded efforts at replication, even by the same investigators in the same laboratory (Clubley et al., 1979; Lieberman, Wurtman, Emde, & Coviella, 1987; Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987). Whether these variable and subtle effects of dietary caffeine doses reflect variation in human biological sensitivity or

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limitations of the experimental methods is unclear.

Operant stimulus discrimination techniques, developed and refined by psychophysicists (Blough & Blough, 1977), have recently been used to assess thresholds of caffeine sensitivity in humans (Griffiths et al., 1990). Historically, these discrimination procedures have been effective in determining the limits of organisms' sensitivities to various auditory and visual stimuli (Blough & Blough, 1977), and on rare occasions, to drugs (Colpaert, Niemegeers, & Janssen, 1980; Overton, 1979; Zenick & Goldsmith, 1981). In general, these procedures involve establishing discriminations between the presence and absence of a particular stimulus and then progressively decreasing the strength of that stimulus until the stimulus fails to control responding.

Using this basic methodology, Griffiths et al. (1990) taught 7 caffeine-abstinent subjects a caffeine (178 mg or 100 mg) versus placebo discrimination and then exposed them to progressively lower caffeine doses until each subject failed to discriminate. All subjects acquired the initial discrimination (100 or 178 mg vs. placebo) within 30 days. Three subjects discriminated 56 mg of caffeine, 3 discriminated 18 mg, and 1 subject maintained the discrimination at 10 mg. These doses are well within the range of caffeine doses found in individual portions of commonly consumed foods and beverages: A typical 148-mL (5-oz) cup of roasted and ground coffee, for example, contains 85 mg caffeine; the same amount of tea contains 40 mg; a 355-mL (12-oz) can of regular cola soft drink contains 36 mg; and a 30-g (1-oz) chocolate bar contains 20 mg (Barone & Roberts, 1984). This drug-discrimination procedure revealed behavioral effects of dietary doses of caffeine previously though to be behaviorally and physiologically inactive, thereby extending the known limits of human sensitivity to caffeine.

It is significant that behavioral pharmacologists served as both the investigators and the subjects in that study. Informed of the drugs under study and of their likely effects and knowledgeable of the pharmacokinetic and pharmacodynamic effects of caffeine, these subjects brought unique histories to the experiment that may have altered their ability to acquire and maintain the low-dose caffeine versus placebo discriminations. The extent to which these extraordinary low-dose caffeine effects were due to the discrimination procedure or to the nature of the subjects is unclear.

Furthermore, although Griffiths et al. (1990) demonstrated discrimination of very low caffeine doses, no other behavioral measures (e.g., performance measures or self-reports of mood) were collected at the lowest doses. Thus, it is not clear whether the discrimination measure is uniquely sensitive to low doses of caffeine or if other measures might be equally affected. Consistency of sensitivity across measures cannot be assumed, particularly given previous findings that measures can differ considerably in their caffeine sensitivity. Interestingly, a previous investigation found self-reports of mood to be particularly insensitive to low caffeine doses (Lieberman, Wurtman, Emde, & Coviella, 1987); these investigators found that 32, 64, 128, and 256 mg of caffeine improved auditory vigilance and reaction time without affecting self-reports of mood.

The primary purpose of this study was to assess thresholds of caffeine discrimination in normal, minimally instructed volunteers, uninformed of the specific drugs under study or of their likely effects. This study also sought to determine whether subjects' self-reported mood effects would also reveal thresholds of behavioral sensitivity to caffeine roughly comparable to the discrimination measure.

METHOD

Subjects

Eighteen healthy adults were recruited to participate through advertisements in newspapers and on bulletin boards. The research protocol was approved by the appropriate institutional review board for human research, and subjects gave their informed consent before beginning the study. Subjects were considered for the study if they were healthy, not pregnant, had a high school degree, held full-time employment, consumed at least 100 mg of caffeine per day, and were not currently using illicit drugs. Urine samples were taken throughout the study; samples for the women were analyzed to ensure that they did not continue in the study if pregnant.

Three subjects did not complete the study. One was discharged due to medical problems unrelated to the study, and another withdrew due to schedule conflicts. After the 3rd day of

Table 1
Subject characteristics.

Subject	Age (years)	Gender	Weight (kg)	Years of education	Occupation	Self-reported caffeine intake (mg/day)	Self-reported cigarettes (number/day)	Oral contraceptive (Yes/No)
S1	50	F	77	12	Data entry operator	526	20	No
S2	21	F	50	16	Research assistant/student	213	0	No
S4	22	F	70	12	Secretary	340	0	Yes
S5	20	M	61	13	College student	161	0	No
S6	24	F	59	17	Research assistant/student	311	0	Yes
S7	33	F	66	14	Medical technician/student	186	0	No
S8	42	F	57	14	Psychotherapist	273	0	No
S9	29	M	95	16	Secretary	645	20	No
S15	31	F	59	13	Adolescent house manager	441	40	No
S16	25	F	63	16	Video producer	198	0	Yes
S17	39	M	77	14	Pulmonary technician	933	20–40	No
S18	37	F	73	14	House cleaner	351	20	No
S19	29	F	54	13	Accounting supervisor	346	0	Yes
S24	40	F	63	12	House cleaner	1,228	20–40	No
S27	29	F	56	15	Research assistant/student	341	0–20	No

caffeine exposure, 1 subject withdrew due to adverse drug-related effects including upset stomach and increased anxiety; these effects were consistent with hypersensitivity to caffeine.

Subjects participated in an initial interview and physical examination before beginning the study. Standardized self-rated psychometric inventories indicated that all subjects were within the normal limits (±2 *SD*) of various dimensions of personality (NEO Personality Inventory; Costa & McCrae, 1985) and anxiety (State-Trait Anxiety Inventory; Spielberger, Gorsuch, & Lushene, 1970). Medical histories and brief physical examinations indicated that all subjects were in good health, with no medical contraindications to normal caffeine consumption.

Table 1 displays characteristics of the 15 subjects. Caffeine intake was calculated using estimates by Barone and Roberts (1984) for coffee (60 mg/150 mL of instant and 85 mg/150 mL of ground roasted), tea (30 mg/150 mL of instant and 40 mg/150 mL of leaf or bagged), caffeinated soft drinks (18 mg/180 mL), chocolate candy (20 mg/30 g bar), and cocoa/hot chocolate beverage (4 mg/150 mL). The mean self-reported caffeine consumption was 433 mg per day and ranged between 161 and 1,228 mg per day.

In an effort to have subjects begin the study with comparable recent histories of caffeine consumption, the first 8 subjects (S1, S2, S4, S5, S6, S7, S8, and S9) received 178 mg caffeine per day for 9 consecutive days immediately before beginning discrimination training. In spite of this history, discrimination performance varied considerably across subjects. Therefore, this procedure was not used with subsequent subjects.

Setting

Subjects reported to a room with six subject stations that were separated by room partitions. Each station was equipped with a chair and table for completing questionnaires, a Commodore® computer keyboard and monitor, and an additional comfortable chair for reading or relaxing when experimental tasks were not scheduled.

Procedure

Instructions to subjects. Subjects were told that the purpose of the study was to examine the effects of moderate doses of various chemical compounds and psychoactive agents (i.e., chlorogenic acids, diterpenes, caffeine, tannin, sugar, theophylline, and theobromine) found in coffee, tea, chocolate, and soft drinks. They were told that throughout the course of the study they would receive only two of the drugs listed above or one of the drugs and an inactive placebo. They were not told specifically which two drugs they would receive. Instead, the two

drugs were identified by letter codes (e.g., O and G) that were unique for each subject. Subjects were told that every day they would receive both of their drugs in random order, one at the beginning of the session and the other just before leaving the research unit, and that they would be paid for correctly guessing the letter code of the first drug administered each day. To discourage communication between subjects about their drugs and drug effects, they were told that different subjects might receive different drugs in different colored capsules. (In fact, each subject was assigned unique capsule colors.)

Dietary restrictions. Except for caffeine received as part of the daily protocol, all outside sources of caffeine intake were restricted, including coffee, tea, soda, chocolate, and caffeine-containing over-the-counter and prescription medications. To keep subjects blind as to the exact drugs under study, subjects were not told directly to eliminate caffeine from their diets. Instead, subjects were provided with an extensive list of allowed and restricted foods, drinks, and medications that, if followed, would eliminate all outside sources of caffeine. In addition, to avoid drug interactions, use of over-the-counter and prescription medications (except oral contraceptives) was discouraged.

Cigarette smoking was allowed except during experimental sessions. Moderate alcohol use was allowed 10 hr before experimental sessions, but use of illicit drugs was prohibited. Finally, subjects were instructed to eat either no breakfast at all or a light and consistent (i.e., the same content every morning) breakfast on mornings before sessions.

To facilitate compliance with the dietary restrictions, subjects were told that saliva and urine samples would be collected on a random basis to determine whether the dietary restrictions were being followed. In fact, random saliva samples (5 mL each) were taken before capsule administration on approximately 40% of the days, including weekends. At least one sample per dose condition (see below for description of dose conditions) per subject was analyzed using gas chromatography methods (similar to those of Jacob, Wilson, & Benowitz, 1981, but using 5-methylcotinine as the internal standard). Additional samples were analyzed if the analyses of a subject's initial samples suggested noncompliance with the dietary restrictions. Monthly urine samples were collected and analyzed for illicit drug use; these revealed no instances of illicit drug use.

Subjects were asked to report use of any over-the-counter or prescription medications throughout the study. S1 reported using ibuprophen on half of the study days. Four subjects (S6, S7, S9, and S27) reported use of over-the-counter analgesics (none of which contained caffeine) on 10 or fewer occasions during the study. S27 reported use of Fiorinal® (aspirin, butalbital, and caffeine) once.

Drug-discrimination procedures. Experimental sessions were conducted Monday through Friday. During each session, each subject orally ingested two capsules under double-blind conditions approximately 60 min apart; one contained caffeine and the other placebo. The order of the capsules was randomized each day with the restriction (unknown to the subject) that neither drug be administered first on four or more consecutive sessions. Inspection of the data showed that caffeine was administered first approximately as often as placebo: No subject received caffeine first on fewer than 35% or more than 60% of the sessions for which discrimination accuracies were calculated and presented below.

Fifteen, 30, and 45 min after ingesting the first capsule, the subjects guessed which of their two letter-coded drugs they had received. After each drug guess, subjects also rated their degree of confidence in the accuracy of their guess and the magnitude of the drug effect on a 4-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = very much). Next, under staff supervision, the subject opened a sealed envelope and read the enclosed letter code for the first drug administered on that day. If the 45-min guess was correct, the subject immediately received a voucher exchangeable for $10.00. If the guess was incorrect, the subject did not receive a voucher. Before leaving the research room, the subject received the second capsule scheduled for that day. The second capsule was administered so that, within each phase of the study, subjects received the same daily dose of caffeine.

Self-report questionnaire. Immediately before and 15, 30, and 45 min after ingesting the first capsule, subjects completed a 17-item self-report questionnaire. Subjects rated each

item on a 4-point scale (described above). Previous research showed that a variation of this questionnaire was sensitive to caffeine (Griffiths et al., 1990). The questionnaire items included (1) alert, (2) well-being, (3) desire to talk to people, (4) motivation to work, (5) concentration, (6) energy/active, (7) self-confidence, (8) affection for loved ones, (9) foggy/hazy/not clear-headed, (10) headache, (11) sleepy, (12) irritable, (13) depressed, (14) anxious/nervous, (15) upset stomach, (16) trembling/shaky/jittery, (17) heart pounding.

Addiction Research Center Inventory. Immediately before and 45 min after ingesting the first capsule, subjects also completed a 49-item version of the Addiction Research Center Inventory (ARCI). The ARCI is a true-false questionnaire with empirically derived scales that are sensitive to various classes of abused drugs (Haertzen, 1974). Each scale is named after the drug(s) previously shown to affect that scale. Five scales were scored: the Morphine/Benzedrine Group (MBG) scale (ARCI 464), a putative measure of drug-induced euphoria; the Pentobarbital/Chlorpromazine/Alcohol Group (PCAG) scale (ARCI 452), a scale assumed to measure sedation: the Lysergic Acid Dithylamide (LSD) scale (ARCI 454), a putative measure of dysphoria and somatic symptoms; the Benzedrine Group (BG) scale (ARCI 465), an amphetamine scale consisting mainly of items commonly assumed to relate to intellectual efficiency and energy; and the A scale (ARCI 466), a measure specific for dose-related effects of *d*-amphetamine.

At the end of each dose condition (see below for description of dose conditions), each subject completed an end-of-condition questionnaire indicating whether each of their two letter-coded drugs increased, decreased, or had no effect on each of the 17 items listed above. In addition, subjects rated on a 4-point scale (described above) each of the 17 items on the basis of its relative importance for making the discrimination.

Performance tasks. Immediately before and 45 min after ingesting the first capsule, 8 subjects (S1, S2, S4, S5, S6, S7, S8, and S9) performed two performance tasks that have been described previously—circular lights (Griffiths, Bigelow, & Liebson, 1983) and the digit symbol substitution task (McLeod, Griffiths, Bigelow, & Yingling, 1982). During the 1-min circular lights task, the subject was required to press as rapidly as possible a series of 16 buttons (circularly arranged around a 54-cm diameter) in response to the randomly sequenced illumination of their associated lights. During the 90-s digit symbol substitution task, the subject was required to key in geometric patterns associated with one of nine digits displayed on a video screen.

Order of discrimination-session activities. At times during a session in which more than one activity was scheduled, activities were completed in the following order: the circular lights task, the digit symbol substitution task, the 49-item version of the Addiction Research Center Inventory, the 17-item self-report questionnaire, and the drug identification.

Free-time activities. When not completing questionnaires or performing performance tasks, subjects sat in comfortable chairs and were free to engage in sedentary activities that would not disturb other subjects in the room. Subjects read books and newspapers, knitted, did paperwork, rested, or sometimes slept. No eating or drinking was allowed during the session.

Subject payments. Subjects were paid for their participation. Each subject earned a base pay of $6.00 per session for completing each session and a bonus of $2.50 per session for completing the experiment and complying with all the requirements of the study. Subjects also earned $10.00 for each correct 45-min drug identification, which was paid immediately after each daily session. The base pay was paid weekly, and the bonus was paid after each subject completed participation in the experiment.

Weekend and holiday procedures. Before each weekend or holiday, subjects were given one capsule to take at home for each day that they would not report to the research unit. Subjects were instructed to take the capsule before 12 noon on the appropriate day. Each weekend or holiday capsule contained the amount of caffeine administered during a discrimination-training session, unless otherwise specified. In addition, for each of these nonexperimental days, subjects were given a test tube for a saliva sample and a sealed envelope to be opened before ingesting the take-home capsule. The envelope contained an instruction to provide or not to provide a saliva sample on that day. If the instruction directed the subject to provide

a sample, the subject provided the sample, placed the sample in the refrigerator, and brought the sample to the laboratory at the time of the next session.

Capsule preparation. Caffeine and placebo capsules (size 0, opaque hard gelatin capsules) that looked identical were prepared from combinations of anhydrous caffeine (USP) and powdered lactose.

Capsule administration procedures. During discrimination-training sessions, subjects orally ingested capsules under staff supervision. Each capsule was taken with 150 mL of water. Drug administration procedures were designed to ensure that subjects swallowed the capsules without opening them and tasting the contents. To accomplish this, three precautions were taken: (a) The research assistant poured the capsule into the subject's mouth from a clear plastic cup; (b) immediately after the capsule and water were ingested, the research assistant inspected the subject's mouth with a tongue depressor to ensure that the capsule was swallowed; and (c) throughout the procedure, the research assistant watched the subject to ensure that the capsule was not removed from the mouth.

Initial caffeine versus placebo discrimination training. All subjects initially participated in a condition in which the caffeine dose was 178 mg. After 20 sessions in this condition, the caffeine dose was changed to 320 mg for S1, S2, S4, S5, S6, and S7 in an effort to enhance the discriminative-stimulus effects of caffeine. The percentage of correct drug identifications did not improve significantly in any subject and deteriorated slightly in 4 of the 6 subjects. As a result, the caffeine dose was not increased for any of the remaining subjects. S1 and S6 were returned to 178 mg caffeine for 20 sessions, and both acquired the discrimination. S1 continued in the decreasing-dose phase of study (see below). S4, S5, S6, and S7 were discharged after completion of the 320-mg condition.

For the remaining subjects, the 178 mg caffeine versus placebo discrimination training was terminated when the accuracy for the final guess (the 45-min guess) was at or above 75% correct for 20 consecutive sessions. If the discrimination accuracy was below 75% at the end of the first 20 sessions, the condition was extended (a) in blocks of 10 sessions until the accuracy for the last 20 sessions was at or above 75% or (b) for a maximum of 40 sessions in total, whichever came first.

Subjects S16 and S19, who did not acquire the discrimination within 40 sessions at 178 mg caffeine, subsequently acquired the discrimination when postsession capsule (i.e., the capsule administered at the end of each discrimination session) administration was discontinued and placebo capsules instead of caffeine were administered on weekends. Subsequently, their discriminations were maintained when the postsession capsules were reinstated.

Decreasing-dose phase. Nine of the 11 subjects (S1, S8, S9, S15, S16, S18, S19, S24, and S27) who acquired the 178 mg caffeine versus placebo discrimination participated in the next phase, in which the caffeine dose was progressively decreased until discrimination accuracy fell below 75% correct in 20 sessions. Each subject was exposed to each dose for 20 sessions. If the discrimination accuracy for the final guess (the 45-min guess) was at or above 75% correct for the 20 sessions, the caffeine dose was decreased to the next lower dose. If the discrimination accuracy for a dose condition was below 75% correct, the caffeine dose was increased to 178 mg for the subsequent 20 sessions. This final 178-mg condition was extended in blocks of 10 sessions until discrimination accuracy reached 75% or greater for 20 consecutive sessions. The sequence of dose conditions was 178, 100, 56, 32, 18, and 10 mg. The criterion of 75% or greater accuracy was chosen because it represents the threshold for statistical significance ($p < .05$, binomial probability distribution).

Data analysis. For each subject, discrimination accuracy at each dose was analyzed using the binomial probability distribution. Significant discrimination performance was defined as correctly identifying the capsule contents on 15 or more of the last 20 sessions ($\geq$75%; $p < .05$).

Self-reported mood (17-item questionnaire and ARCI) and performance measures (digit symbol substitution task and circular lights for S1, S8, and S9) were analyzed for each individual who participated in the decreasing-dose phase of the study. Analyses used the last 20 sessions of the initial and final 178-mg conditions and the 20 sessions for each of the other dose conditions to which each subject was exposed. For each subject's data, repeated mea-

sures ANOVAs were calculated with three factors: dose (all doses to which the subject was exposed), drug (caffeine vs. placebo), and time (precapsule and 15, 30, and 45 min after capsule for the 17-item self-report questionnaire; precapsule and 45 min for ARCI, digit symbol substitution task, and circular lights). Post hoc comparisons were made between caffeine and placebo at the four time points for each dose condition using Tukey's HSD test. Subject ratings on the 17-item self-report questionnaire or ARCI scales for an individual were considered significantly affected by caffeine if post hoc comparisons indicated a significant caffeine versus placebo difference at the 45-min time point but not at the precapsule time point.

In addition to the analyses of individual-subject data described above, analyses of group data were conducted to characterize further the self-reported effects (i.e., subject ratings on the 17-item self-report questionnaire and ARCI scores) produced by the lowest caffeine dose that each subject could discriminate. Data for these analyses were from subjects who participated in the decreasing-dose phase of the study. Data from all 20 sessions of each subject's lowest discriminated dose condition were used (i.e., data from the 178-mg condition for S15, the 100-mg condition for S9, S16, S18, and S24, the 56-mg condition for S1 and S8, and the 32- and 18-mg conditions for S19 and S27, respectively; see Figure 5). Because subjects received different numbers of caffeine and placebo sessions, repeated measures ANOVAs were conducted using caffeine (i.e., all sessions in which caffeine was administered) and placebo (i.e., all sessions in which placebo was administered) means for each subject at the different time points (i.e., precapsule and 45 min for each ARCI scale, and precapsule, 15, 30, and 45 min for each item on the 17-item self-report questionnaire). The ratings on the 17-item self-report questionnaire and ARCI scores were analyzed with repeated measures ANOVAs with two factors: drug (caffeine vs. placebo) and time (precapsule and 15, 30, and 45 min after capsule for the ratings on the 17-item self-report questionnaire, and precapsule and 45 min after capsule for the ARCI scales).

For purposes of data analysis, data from S1's 178-mg condition immediately following her 320-mg condition were used in figures describing the decreasing-dose phase of the study (i.e., Figures 3, 4, and 5).

For all statistical tests, effects were considered to be significant for $p \leq .05$. For repeated measures ANOVAs, Huynh-Feldt (Huynh & Feldt, 1976) corrected p values are reported.

RESULTS

Acquisition Phase

Figure 1 presents the discrimination accuracy at 45 min for each of the 15 subjects for the first 20 sessions of 178 mg caffeine versus placebo discrimination training. This figure shows that only 5 subjects acquired the discrimination (≥75% correct) during the first 20 sessions. S15, S16, S17, S18, S19, and S27 were given up to 20 additional training sessions in this condition. S15, S18, and S27 acquired the discrimination when given the additional training sessions.

Figure 2 shows the cumulative correct drug identifications at 45 min during the first 178 mg caffeine versus placebo condition for each of the 15 subjects. Asterisks indicate which subjects acquired the discrimination in this condition. All subjects who acquired the discrimination in this condition except S4 (S1, S8, S9, S15, S18, S24, and S27) showed a similar pattern of acquisition of the discrimination, with accuracy remaining close to chance for the initial sessions followed by a period of near-perfect responding for seven or more sessions. Subjects S16 and S19, who failed to acquire the discrimination in 40 sessions (Figure 2), acquired the discrimination in a subsequent 20-session condition in which the postsession capsule was discontinued and placebo capsules instead of caffeine were administered on weekends (data not shown). Both of these subjects maintained the discrimination when the postsession capsules and weekend caffeine capsules were reinstated.

Decreasing-Dose Phase

Discrimination accuracy. Figure 3 shows the discrimination accuracy during the last 20 sessions for each of the dose conditions studied in each subject. Subjects differed considerably in the lowest dose at which a significant discrimination was maintained: S27 discriminated 18 mg caffeine; S19 discriminated as low as 32 mg (this subject was terminated prematurely due to medical problems unrelated to the study);

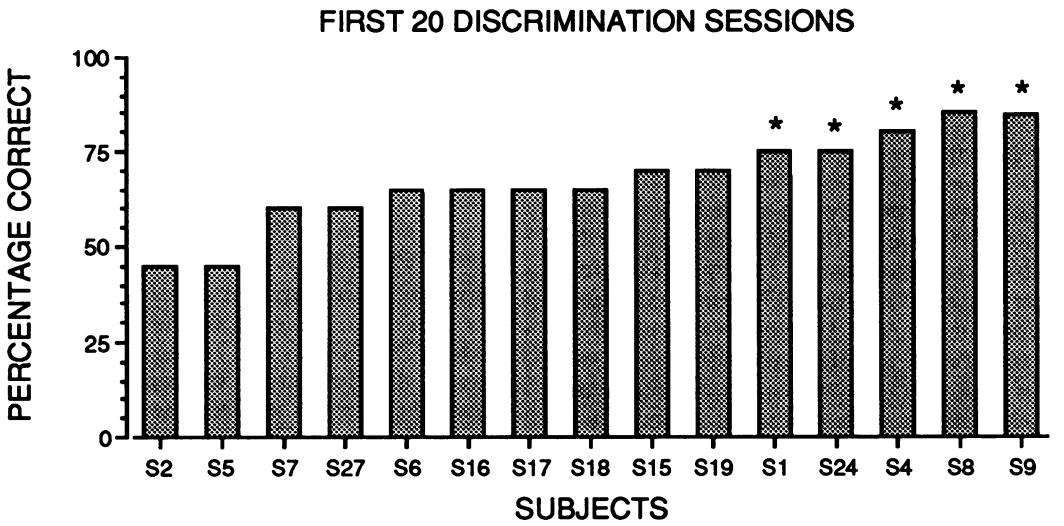

Fig. 1. Caffeine (178 mg) versus placebo discrimination accuracy over the first 20 sessions for each of 15 subjects. Data are based on the final guess (i.e., at 45 min) of each session. Each bar shows accuracy for an individual subject; numerals below bars indicate subject codes. The bars are arranged from lowest to highest accuracy. Asterisks indicate which subjects demonstrated a statistically significant discrimination ($p < .05$).

S1 and S8 discriminated 56 mg; S9, S16, S18, and S24 discriminated 100 mg; and S15 discriminated only 178 mg caffeine from placebo. Three subjects did not complete this phase of the study due to medical problems unrelated to the study: S19 was discontinued during her 18-mg condition and S1 and S16 did not complete their final 178-mg condition.

Time course of the discrimination. Figure 4 shows the time course of the caffeine versus placebo discriminations across the range of doses studied for each subject who participated in the decreasing-dose phase. Subjects differed considerably in the earliest time at which they demonstrated significant discriminations. S8, S9, S19, and S24 showed significant discrimination performance as early as 15 min after capsule ingestion. S16, S18, and S27 demonstrated onset of the discrimination as early as 30 min. S1 and S15 showed little evidence of discrimination until 45 min after capsule ingestion. In general, discrimination accuracy was an increasing function of time from capsule ingestion. Onset of the discrimination was not consistently related to dose.

Self-reported mood effects and performance effects. Figure 5 summarizes subjects' ratings of 17 items on the self-report questionnaire during the lowest caffeine dose condition at which each subject significantly discriminated caffeine versus placebo. The lowest discriminable dose of caffeine significantly affected ratings on at least one item for each of the 9 subjects who participated in the decreasing-dose phase. Doses as low as 18 and 32 mg of caffeine (S27 and S19, respectively) significantly affected ratings on that questionnaire. Analyses of group data revealed statistically significant group effects of the lowest discriminable doses of caffeine on ratings of 10 of the 17 items on the self-report questionnaire.

To display visually some of the individual-session ratings summarized in Figure 5, Figure 6 shows all of the ratings at 45 min of one item for each subject. The item with the largest q value on the Tukey's HSD test (i.e., the item with the highest level of statistical significance) was selected for each subject. Visual inspection of the data shows that all 9 subjects demonstrated a clear difference, at 45 min, in ratings between caffeine and placebo sessions.

The concordance between the patterns of boxes and the arrows for the individual analyses (Figure 5) indicates that subjects were more likely to rate one of the 17 items as important (i.e., a little, moderately, or very much) in the end-of-condition questionnaire if ratings of that item had been significantly affected by caffeine during the discrimination sessions than if it had not been significantly affected. Of the items that were significantly (statistically) af-

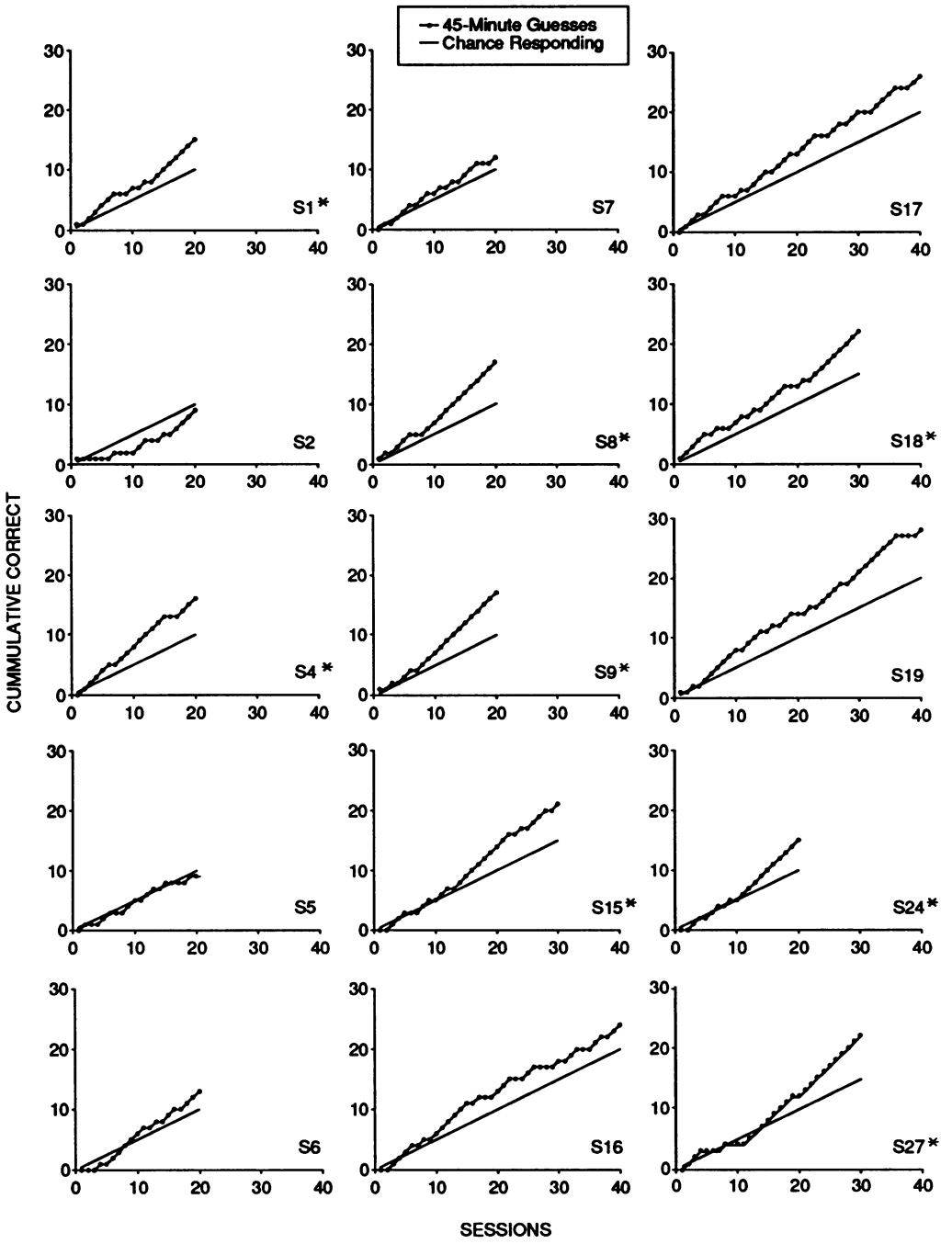

Fig. 2. Cumulative correct drug identifications during the first 178 mg caffeine versus placebo discrimination condition for each of 15 subjects. Cumulative correct drug identifications are based on the final guess of each session. Each panel presents data from an individual subject; numerals indicate the subject codes; data points present the actual data; straight diagonal lines represent the slopes predicted based on chance responding; and asterisks indicate which subjects demonstrated a statistically significant discrimination ($p < .05$).

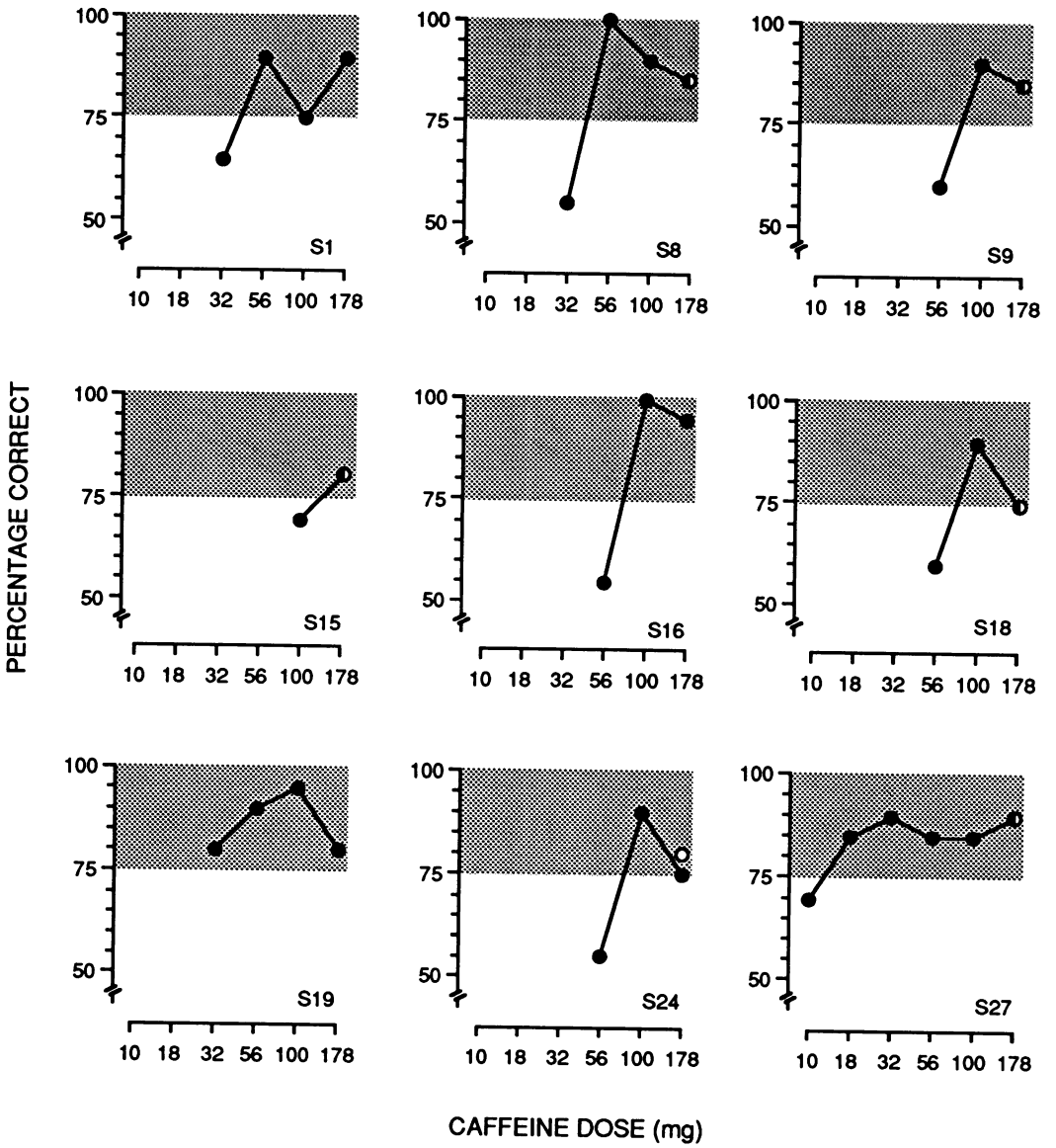

Fig. 3. Caffeine versus placebo discrimination accuracy as a function of dose in each of the 9 subjects who participated in the decreasing-dose phase. Data are based on the final guesses of the last 20 sessions of each condition. Points overlapping the shaded areas indicate statistically significant discrimination performance ($p < .05$). Doses were studied in decreasing order with 178 mg as the first (filled point) and last (open point) dose condition; overlapping data points in the 178-mg dose condition are half-filled points. Three subjects were discharged prematurely (see text): S19 in the 18-mg condition and S1 and S16 in the final 178-mg condition.

fected by caffeine during the discrimination sessions (indicated by arrows in Figure 5), 92% were rated as important on the end-of-condition questionnaire (indicated by boxes in Figure 5). Alternatively, only 25% of the items that were not significantly affected by caffeine during the discrimination sessions (indicated by absence of arrows in Figure 5) were rated as important on the end-of-condition questionnaire.

The direction of the effects of the lowest discriminable doses of caffeine was generally consistent across the group statistical analysis, the individual statistical analyses, and the end-

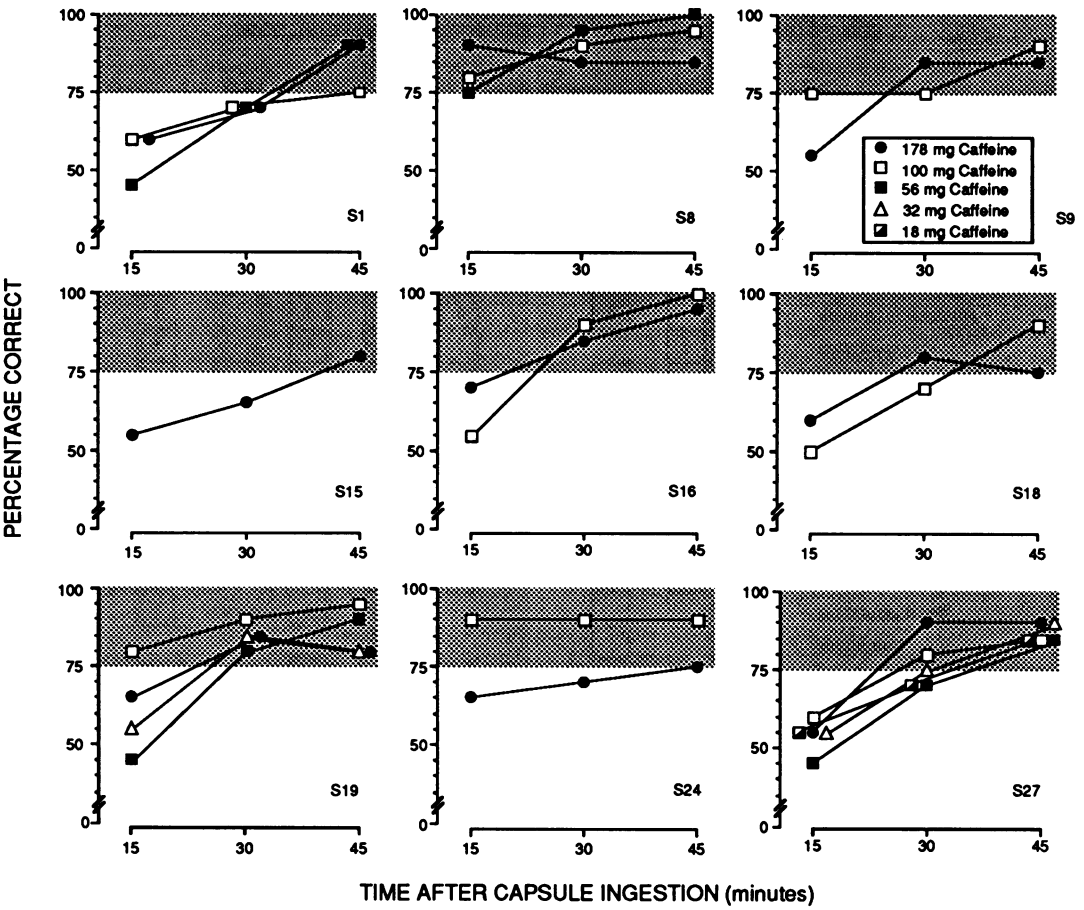

Fig. 4. Time course of the caffeine versus placebo discrimination across the range of doses studied in each of 9 subjects who participated in the decreasing-dose phase. Points overlapping the shaded areas indicate statistically significant discrimination performance ($p < .05$). Data from the final caffeine (178 mg) versus placebo condition are not presented. Different symbols represent different caffeine doses. Symbols have sometimes been displaced horizontally for clarity.

of-condition questionnaires. Relative to placebo, caffeine decreased ratings of "sleepy" and "foggy/hazy/not clear-headed" and increased ratings of "alert," "motivation to work," "energy/active," "trembling/shaky/jittery," "anxious/nervous," "desire to talk to people," "self-confidence," "well-being," "concentration," and "heart pounding." There were only three exceptions, all of which occurred in the end-of-condition questionnaires: S1 indicated that relative to placebo, caffeine decreased "trembling/shaky/jittery"; S9 indicated that caffeine decreased "motivation to work"; and S27 indicated that caffeine decreased "concentration."

In most cases, caffeine failed to affect subject ratings reliably at the same doses at which it failed to control discrimination performance reliably. Post hoc comparisons at the doses at which each subject's caffeine versus placebo discrimination accuracy fell below 75% correct showed that caffeine significantly affected ratings in only 2 subjects, S27 and S15: Relative to placebo, 10 mg of caffeine significantly increased ratings of "alert" in S27, and 100 mg of caffeine increased ratings of "alert" and "anxious/nervous" in S15. It is interesting to note that 10 mg and 100 mg of caffeine continued to exert some discriminative stimulus control in S27 and S15, although it was slightly diminished: Both subjects maintained discrimination accuracies of 70% correct in those dose conditions.

When asked on the end-of-condition ques-

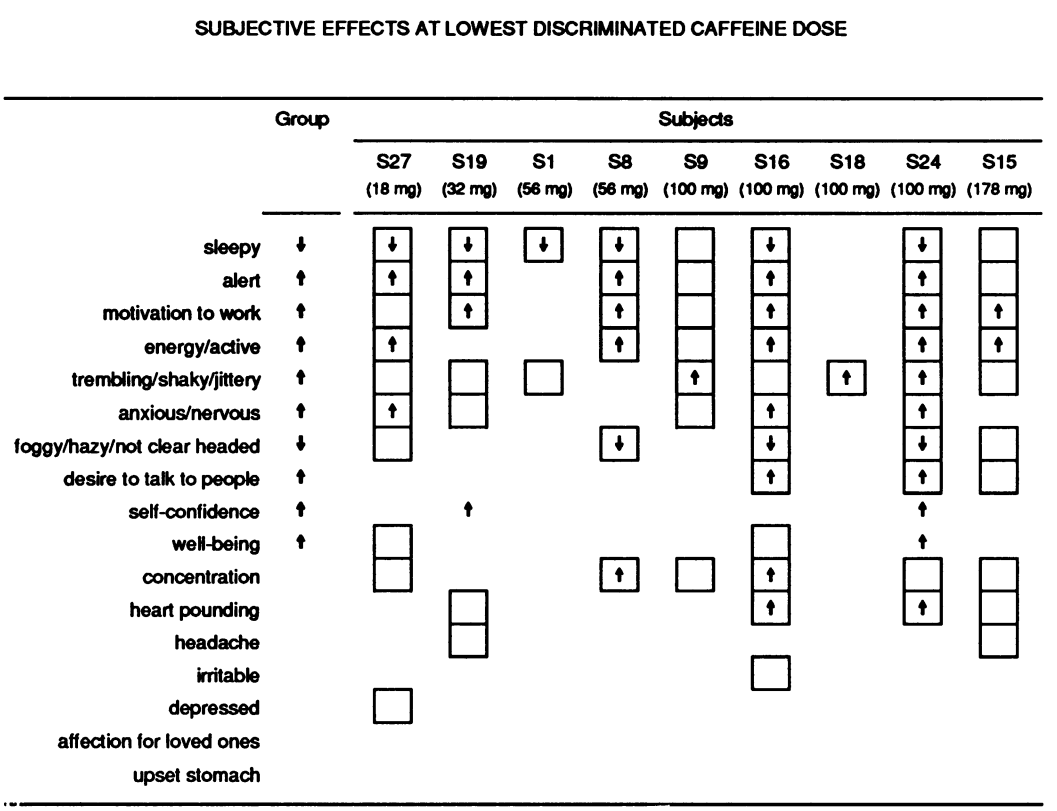

Fig. 5. Ratings of 17 items on the self-report questionnaire during the lowest caffeine dose condition at which each subject maintained the caffeine versus placebo discrimination. Column 2 presents group data. Columns 3 through 11 display individual-subject data; subject codes are indicated at top of columns; caffeine doses (mg) at which ratings were collected for each subject (for group and individual analyses) are in parentheses below subject codes. Arrows indicate statistically significant drug effect (i.e., for group analyses significant drug and/or drug × time interaction; for individual analyses significant caffeine vs. placebo difference at the 45-min time point but not at the precapsule time point). Direction of the caffeine effect relative to placebo is indicated by the direction of arrows. Boxes designate items rated by individual subjects in the end-of-condition questionnaire as important in making the discrimination (i.e., ratings of 1, 2, or 3). In all but three instances, the direction of effect for the group statistical analysis, the individual statistical analyses, and the end-of-condition questionnaire was the same (see text for exceptions).

tionnaire following each subject's lowest discriminable caffeine dose condition whether each of their two letter-coded drugs increased, decreased, or had no effect on each of the 17 items of the self-report questionnaire, S15 and S18 indicated that only caffeine altered at least one item, S1 indicated that only placebo altered at least one item, and S8, S9, S16, S24, and S27 indicated that both caffeine and placebo altered at least one item.

The lowest discriminable dose of caffeine significantly affected scores on at least one ARCI scale for all but S1 and S18. Relative to placebo, caffeine significantly decreased PCAG scores (in S27, S19, S8, S16, and S24) and significantly increased LSD scores (in S27, S19, and S9), BG scores (in S16 and S24), Amphetamine scores (in S19 and S9), and MBG scores (in S24). Group analyses showed statistically significant effects on all five scales in the same directions as the individual analyses.

No dose of caffeine significantly affected performance on the circular lights or the digit symbol substitution task.

Salivary Caffeine Concentrations

Analyses of the saliva samples provided in the mornings before capsule administration indicated that subjects generally complied with the dietary restrictions. The mean salivary caffeine concentration for all of the subjects and

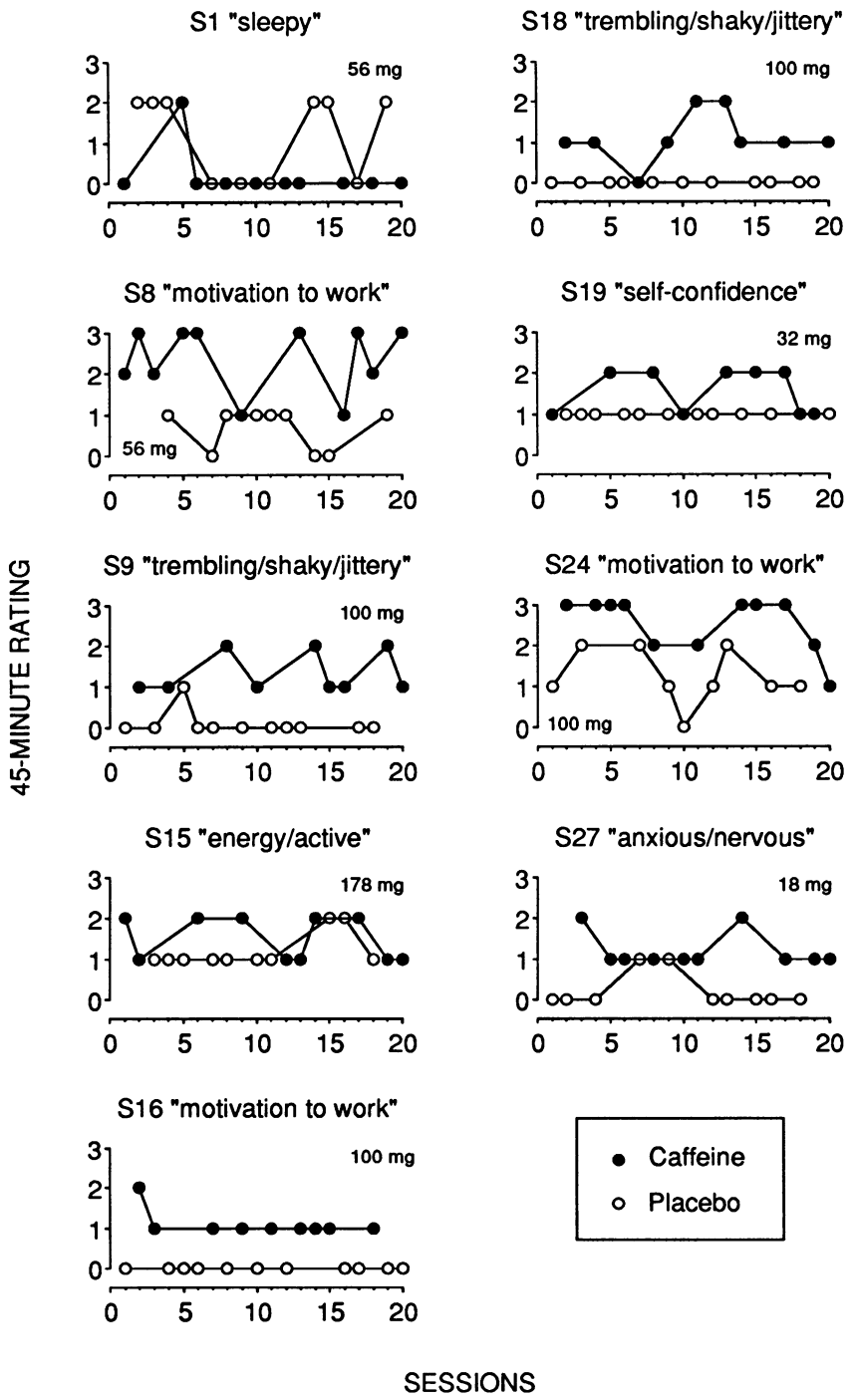

Fig. 6. Individual-session mood ratings during the lowest caffeine dose condition at which each subject maintained the caffeine versus placebo discrimination, in each of 9 subjects. Each panel presents data from an individual subject; numerals indicate the subject codes; words in quotations indicate the actual item rated; doses (mg) indicate the caffeine dose condition at which ratings were collected for each subject. The single item presented for each subject was the item with the largest q value on the Tukey's HSD test (i.e., the item with the highest level of statistical significance).

all of the samples analyzed was 0.60 μg/mL (range of individual means was 0.02 to 4.50 μg/mL). Previous research (Griffiths et al., 1990; Griffiths & Woodson, 1988) suggests that caffeine concentrations above 1.0 μg/mL are indicative of slow elimination or violation of dietary restrictions. Only S2, S4, S6, S7, and S24 provided one or more samples with caffeine concentrations of more than 1.0 μg/mL. Interestingly, 4 of these subjects (S2, S6, S7, and S24) provided samples with high caffeine concentrations in conditions in which they failed the discrimination. S2, who never acquired the discrimination, gave a saliva sample with a concentration well out of the range of any other subject (11.01 μg/mL), which suggests that S2 consumed caffeine from outside sources; three other samples provided by S2 were analyzed and had concentrations between 1.98 and 2.84 μg/mL.

DISCUSSION

The current study demonstrates behavioral activity of caffeine doses lower than those previously shown to affect the behavior of normal human volunteers. Many previous investigations into the behavioral activity of caffeine in normal volunteers have failed to find caffeine effects below 200 or 300 mg (Bättig, 1985; Gilbert, 1976), and only rarely and inconsistently have such studies shown behavioral effects of caffeine doses below 100 mg (Clubley et al., 1979; Lieberman, Wurtman, Emde, & Coviella, 1987; Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987). In contrast, of 9 subjects in this study who were taught a 178 mg caffeine versus placebo discrimination and were then exposed to progressively lower caffeine doses, the lowest doses to produce both discrimination and self-reported mood effects were well below 200 mg: 4 showed significant discrimination and self-reported mood effects at 100 mg, 2 at 56 mg, 1 at 32 mg, and 1 at 18 mg. One of these subjects also showed self-reported mood effects at 10 mg. These results extend the generality of a previous study (Griffiths et al., 1990), which found significant discriminative-stimulus effects of caffeine at comparable doses in highly instructed and atypical subjects.

This is the first study to show significant self-reported effects (e.g., ratings of mood) of caffeine at doses below 64 mg. Although Griffiths et al. (1990) demonstrated discriminative-stimulus effects at doses well below 64 mg, they did not collect self-reports at doses below 100 mg. Although previous investigations found performance effects at 32 mg (Lieberman, Wurtman, Emde, & Coviella, 1987) and 64 mg (Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987), only 64 mg altered self-reports of mood states. In contrast, this study found that in almost half of the subjects who participated in the decreasing-dose phase (4 of 9), caffeine doses between 56 and 10 mg altered ratings of numerous items on the self-report questionnaire as well as on standardized scales of the Addiction Research Center Inventory.

In general, significant self-reported mood effects and significant discrimination were observed at the same caffeine doses: In 7 of the 9 subjects, the lowest discriminated (≥75% correct) caffeine dose was also the lowest dose to produce statistically significant self-reported mood effects; no subject showed significant self-reported mood effects at doses at which their discrimination accuracy fell below 70% correct. These results show that the self-reported mood and discrimination measures were equally sensitive in revealing the behavioral activity of low caffeine doses.

The degree to which the demonstrated sensitivity of these two measures are interdependent cannot be determined from this study. The demonstration of significant self-reported mood effects at the lowest caffeine doses, for example, may have been dependent on the concurrent measurement and reinforcement of the discrimination responses. Similarly, the acquisition and maintenance of the low-dose discriminations may have been facilitated by the concurrent collection of self-reported mood data. Future research will be necessary to explore these relationships between discrimination and self-reports of mood.

This study provides novel information about acquisition of a drug discrimination in humans. Previous drug-discrimination studies (e.g., Bickel, Bigelow, Preston, & Liebson, 1989; Chait & Johanson, 1988; Chait, Uhlenhuth, & Johanson, 1984; Evans & Griffiths, in press; Preston, Bigelow, Bickel, & Liebson, 1987, 1989) have arranged, prior to discrimination-training sessions, sampling sessions in which subjects are told which drug they are about to receive. Often, subjects ac-

quire the discrimination promptly after these sampling sessions; if not, the subjects are typically discharged from the study. Apparently, in many subjects, the sampling sessions begin to establish the discrimination, even though subjects do not emit responses that allow monitoring of acquisition. In contrast, sampling sessions were not employed in the current study and all subjects were continued in training for 20 to 40 sessions, enabling monitoring of discrimination accuracy beginning with the initial exposures to 178 mg caffeine and placebo (Figure 2). Seven of the 8 subjects who acquired the discrimination in the initial condition (S1, S8, S9, S15, S18, S24, and S27) showed a similar pattern of acquisition of the discrimination, with accuracy for each subject remaining close to chance for 7 to 21 sessions of this condition followed by a period of near-perfect responding for seven or more sessions (Figure 2).

The protracted acquisition of the caffeine discrimination may provide a partial explanation for the variable reinforcing effects of caffeine observed in experimental studies with normal volunteers. Although caffeine has been shown to function as a reinforcer in humans (Griffiths et al., 1989; Griffiths & Woodson, 1988; Hughes et al., 1991), studies with normal volunteers have found that the reinforcing effects of caffeine vary considerably within and across individuals, with approximately 50% of subjects showing 100 mg caffeine to function as a reinforcer (Griffiths & Woodson, 1988; Hughes et al., 1991). These studies required subjects to choose between caffeine and placebo by letter or color codes after only one session of letter- or color-coded exposure to both caffeine and placebo. The results of the current study suggest that subjects may require many such sampling sessions before being capable of correctly identifying and choosing caffeine and placebo by the correct letter or color code. Perhaps, then, some subjects do not reliably choose caffeine over placebo in these studies because they do not accurately identify caffeine and placebo by their respective codes, given the nature and limited number of sampling sessions.

In an effort to enhance the discriminative-stimulus effects of caffeine, 6 subjects (S1, S2, S4, S5, S6, and S7) were exposed to a discrimination-training condition in which the caffeine dose was increased from 178 mg to 320 mg. Interestingly, the percentage of correct drug identifications did not improve substantially in any subject and deteriorated slightly in 4 of the 6 subjects. Although systematic research is needed, it is possible that daily dosing with caffeine in excess of 300 mg may diminish acute effects of caffeine, possibly due to tolerance. Such a mechanism may account for numerous previous observations of lack of robust effects of caffeine under conditions in which prior caffeine exposure has not been adequately reduced and controlled.

Although most of the findings of the current study are consistent with the results obtained by Griffiths et al. (1990), several important differences were observed. In contrast to the results of Griffiths et al., the lowest discriminated dose was not correlated with gender or with within-session onset of caffeine effects. The nature of the self-reported mood effects also differed across the two studies: Whereas Griffiths et al. found that 100 mg of caffeine did not produce any dysphoric self-reports, the current study showed that the lowest discriminable doses of caffeine (i.e., doses between 100 and 18 mg) produced significant increases in reports of "trembling/shaky/jittery" and "anxious/nervous" (Figure 5) as well as significant increases in scores on the LSD scale of the ARCI, a scale commonly assumed to measure drug-induced dysphoria.

This study also extends a recent study of caffeine's discriminative-stimulus effects (Evans & Griffiths, in press) that showed that subjects taught a 200 or 300 mg caffeine versus placebo discrimination and given test doses of 50 and 100 mg caffeine only infrequently identified either 50 or 100 mg as caffeine. However, when subjects in this study were explicitly taught to discriminate comparable caffeine doses, 8 of the 9 subjects reliably discriminated 100 mg caffeine and 4 of the 9 reliably discriminated 56 mg.

Using a drug-discrimination procedure, the current study demonstrated the behavioral activity of caffeine doses lower than those previously shown to affect the behavior of normal volunteers. Dietary doses of caffeine, equal to or less than the amounts found in individual portions of coffee, tea, soft drinks, and even chocolate, produced significant discrimination and self-reported mood effects in 1 or more subjects. These results further extend the range of conditions under which low dietary caffeine

doses are known to affect human behavior and suggest that more consumers of caffeinated foods and beverages than previously recognized are ingesting behaviorally active doses of caffeine daily. Future application of the discrimination methodology may be useful in further characterizing the subtle effects of the world's most widely consumed behaviorally active drug.

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