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Enhancing caffeine reinforcement by behavioral requirements following drug ingestion

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Abstract. Each morning eight adults with caffeine versus placebo discrimination histories ingested letter-coded capsules containing 100 mg caffeine or placebo and then engaged in a relaxation or vigilance activity. Subjects were first exposed to caffeine and placebo once each with each activity. Then each day for 10 days subjects made two choices; they chose which compound they would prefer if vigilance were scheduled and which they would prefer if relaxation were scheduled, with the restriction that they could not choose the same compound with both activities; only one choice (randomly selected) was reinforced. Eight of eight subjects always chose caffeine with vigilance. The next choice condition was identical, except that subjects were free to take either compound with both activities. Six of six subjects reliably chose caffeine with vigilance. Four reliably chose placebo with relaxation. In the final condition, each day for 10 days subjects chose between each drug and each of 52 monetary values; those choices were made separately for vigilance and relaxation; only one choice (randomly selected) was reinforced. For six of seven subjects, the maximum dollar value at which subjects chose drug over money was higher for caffeine in vigilance than for placebo in either activity. For five subjects, the maximum value at which subjects chose caffeine over money was higher in vigilance than in relaxation. Overall, this study demonstrates enhanced caffeine reinforcement when a vigilance activity followed drug ingestion.

Key words: Caffeine – Drug reinforcement – Drug self-administration – Drug choice – Reinforcement – Choice – Humans

Although caffeine has been shown to function as a reinforcer in humans (Griffiths and Woodson 1988; Griffiths et al. 1989; Hughes et al. 1991), caffeine reinforcement in normal volunteers has been difficult to demonstrate, even among regular caffeine consumers. In five studies of caffeine versus placebo choice in normal volunteers that used within-subject designs (Griffiths and Woodson 1988; Hughes et al. 1991,1992; Oliveto et al. 1992a,b) only between 10% and 50% of subjects reliably chose caffeine over placebo. In two studies which assessed caffeine versus placebo choice using group designs, fewer than 45% of subjects chose caffeine over placebo in choice tests (Stern et al. 1989; Evans and Griffiths 1992). Because most subjects in these studies were regular caffeine consumers for whom caffeine may have served as a reinforcer under normal dietary conditions, the failure to demonstrate caffeine reinforcement reliably is intriguing and underscores the fact that the conditions under which caffeine functions as a reinforcer are not well understood.

This study was conducted to attempt to identify conditions under which caffeine would serve reliably as a reinforcer. Towards this end, two conditions were controlled that have not been controlled in previous studies. First, subjects were taught a caffeine versus placebo discrimination prior to assessing caffeine reinforcement. Second, when assessing caffeine reinforcement, the behavioral requirements following drug ingestion were controlled and experimentally manipulated.

Subjects were taught a caffeine versus placebo discrimination prior to assessing caffeine reinforcement to ensure that subjects could reliably differentiate and label caffeine and placebo. In previous studies, in place of caffeine versus placebo discrimination training, subjects have been provided only one or two forced-exposure sessions to each of the drug conditions (i.e., caffeine and placebo) prior to assessing caffeine versus placebo choice. One function of these forced exposure sessions is to establish letter- or color-coded labels by which subjects can subsequently choose between the drug conditions. However, studies of caffeine versus placebo discrimination suggest that this minimal forced exposure history may not be sufficient to establish the letter- or color-coded labels reliably. Caffeine versus placebo discriminations are often acquired slowly, requiring extended and explicit training involving repeated exposure to both caffeine and placebo (cf Silverman and Griffiths 1992).

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The behavioral requirements following drug ingestion were controlled in this study because the results of a previous study (Silverman et al. 1994a) suggest that the behavioral requirements following drug ingestion can alter a drug's reinforcing effects. In that study, *d*-amphetamine (15 mg) served as a positive reinforcer when subjects were required to engage in a computer vigilance activity following drug ingestion, but not when a relaxation activity followed ingestion; triazolam (0.25 mg) served as a positive reinforcer only when the relaxation activity followed ingestion. In previous studies on caffeine reinforcement, the behavioral requirements following drug ingestion have not been explicitly controlled. In those studies, after drug ingestion, subjects have been free to engage in any activities of their choosing. In the present study, a series of choice conditions were conducted to determine if the reinforcing effects of a dietary dose of caffeine (100 mg) could be increased by manipulating the behavioral requirements following drug ingestion; the behavioral requirements were manipulated by having subjects engage in a relaxation or a computer vigilance activity.

Materials and methods

Subjects

Eleven healthy adults were recruited to participate in the study through advertisements in newspapers and on bulletin boards. The research protocol was approved by the 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, had no previous diagnoses of any serious psychiatric condition including drug or alcohol abuse or dependence, were not pregnant, had a high school degree, were employed or in school, consumed at least 50 mg caffeine per day, and were not currently using illicit drugs. Monthly urine samples were collected and analyzed for illicit drug use and, in women, for pregnancy; no instance of either was detected.

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) on various dimensions of personality (NEO Personality Inventory, Costa and McCrae 1985) and anxiety (State-Trait Anxiety Inventory, Spielberger et al. 1970). Medical histories and brief physical examinations indicated that all subjects were in good health, with no medical contraindications to normal caffeine consumption. All 11 subjects were trained in a caffeine versus placebo discrimination; however, 3 of the 11 subjects did not enter the main portion (the choice phases) of the study for reasons described under "Caffeine versus placebo discrimination training phase" below.

Table 1 displays characteristics for the eight subjects who participated in the choice phases of the study. Caffeine intake was calculated as described previously (Silverman and Griffiths 1992). The mean self-reported caffeine consumption estimated from a questionnaire given before beginning the study was 214 mg/day and ranged between 54 and 355 mg/day. These caffeine intakes are consistent with amounts consumed by adults in the United States who consume caffeine regularly (Graham 1978).

Setting

Subjects reported to a room with experimental stations which were separated by room partitions. Each station was equipped with a large cushioned chair (appropriate for the relaxation activity) and a microcomputer keyboard and monitor.

General Procedures

Overview of experimental phases and conditions. Subjects participated sequentially in three phases (described in detail below): a caffeine versus placebo discrimination training phase, a caffeine versus placebo choice phase (including both paired and unpaired choice conditions), and a drug (caffeine or placebo) versus money choice phase.

Daily procedures. Experimental sessions lasting 75 min were conducted daily Monday through Friday. First, subjects completed self-report questionnaires (see below) and provided a saliva sample. If drug administration was scheduled for that session, the subject then ingested a capsule. For the 60-min period that followed, the subject engaged in one of three activities: a drug discrimination activity (during the caffeine versus placebo discrimination training phase), or a vigilance or relaxation activity (during the choice phases). Before leaving the laboratory, the subject again completed the self-report questionnaires. Other session procedures specific to each phase are described below.

Instructions to subjects. Subjects were told that the purpose of the study was to examine the behavioral and mood effects of compounds normally found in foods and beverages which they ingest as a part of their daily diet (including chlorogenic acids, aspartame (Nutrasweet), diterpenes, caffeine, tannin, sugar, theobromine, and

Table 1. Characteristics of the 8 subejcts who participated in the choice phases of the study

Subject	Age (years)	Gender	Weight (kg)	Years of education	Pre-study self-reported caffeine intake (mg/day)	Self-reported cigarettes (number/day)	Use of oral contraceptive (Yes/No)	Sessions to acquire 100 mg caffeine versus placebo discrimination*
S1	39	F	75	16	143	0	N	26
S2	31	M	86	20	259	0	N	58
S3	26	F	64	19	186	10	Y	34
S4	23	M	84	16	269	0	N	22
S5	25	F	59	13	355	0	N	24
S6	27	M	64	18	116	0	N	15
S7	37	F	66	17	330	0	N	17
S8	24	F	60	18	54	0	N	71

* This number includes the number of sessions required to train the 320 mg caffeine versus placebo discrimination, the 178 mg caffeine versus placebo discrimination, and the 100 mg caffeine versus placebo discrimination.

theophylline). They were told that throughout the study they would receive only two of the compounds listed above or one of the compounds 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., A and B) that were unique for each subject.

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 to the exact drugs under study, subjects were not told directly to eliminate caffeine from their diets. Instead, the following dietary restrictions were imposed which, if followed, would eliminate all dietary and medicinal sources of caffeine. The only beverages allowed were milk, fruit juices, water, and a specified list of caffeine-free sodas and drinks (e.g., lemonade); chocolate products were prohibited. To divert attention from caffeine, food items without caffeine were also restricted, including all foods containing saccharin or aspartame (Nutrasweet). Finally, the subjects were asked not to take any medications, except for oral contraceptives, acetaminophen, or ibuprofen. Subjects were also asked to inform the investigators if they took any medications.

Cigarette smoking was allowed except during experimental sessions. Moderate alcohol use was allowed up to 10 h 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 monitor compliance with the dietary restrictions, saliva samples (5 ml each) were collected before capsule administration every weekday and on a random basis on weekends. At least one sample per phase (see below for description of phases) per subject was analyzed for caffeine using gas chromatography methods (similar to Jacob et al. 1981, but using 5-methylcotinine as the internal standard). Additional samples were analyzed if the analyses of a subject's initial samples suggested non-compliance with the dietary restrictions.

In an effort to ensure that subjects did not begin the study physically dependent on caffeine, subjects were instructed to begin dietary restrictions 7 days before beginning the caffeine versus placebo discrimination training described below. Subjects received capsules containing placebo on each of those 7 days.

Capsule preparation and administration procedures. Identically-appearing caffeine and placebo capsules (size 0, opaque hard gelatin capsules) were prepared from combinations of caffeine anhydrous (USP) and powdered lactose. At approximately the same time each weekday morning and before 11:00 a.m., subjects ingested one capsule (with 150 ml water) under close staff supervision and double-blind conditions. To minimize possible development of caffeine physical dependence, caffeine was never administered on more than 3 consecutive days.

Self-report questionnaires. Immediately before and 60 min after ingesting the capsule at the beginning of each session, subjects completed a 49-item version of the Addiction Research Center Inventory (ARCI), a true-false questionnaire with empirically derived scales that are sensitive to various classes of abused drugs (Haertzen 1974), and a caffeine questionnaire (Silverman and Griffiths 1992). In addition, they completed a drug liking and drug strength questionnaire.

On the drug liking and drug strength questionnaire, subjects answered the question "Do you like the way the drug makes you feel right now?" using a 9-point scale from "dislike very much" to "like very much," with a center point of "feel neutral." Subjects answered the question "Strength of drug effect?" using a 5-point scale from "no drug effect" to "very strong drug effect." For ratings made prior to drug ingestion each day, subjects were instructed to rate "feel neutral" for drug liking and "no drug effect" for drug strength.

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. Each weekend or holiday capsule contained placebo (unknown to the subject). Other details of weekend and holiday procedures, including collection of saliva samples, were the same as previously reported (Silverman and Griffiths 1992).

Subject payments. Subjects were paid $4 per session for completing each session and a bonus of $4 per session for completing the experiment and complying with all the requirements of the study.

Caffeine versus placebo discrimination training phase

To ensure that subjects could differentiate caffeine and placebo prior to entering the choice phases, subjects were first taught a caffeine versus placebo discrimination. During each session, each subject ingested one capsule containing either caffeine or placebo. The sequence of caffeine and placebo was randomized across days. At 30-s intervals beginning immediately after drug ingestion and continuing for 60 min, subjects could guess which of their two letter-coded drugs they had received. At the end of each session, the subject was told which letter-coded drug they had received. Correct guesses earned money and incorrect guesses lost money. Other details of the discrimination training procedures were the same as those employed by Silverman et al. (1994b).

Initially the caffeine dose was 320 mg. The caffeine dose was decreased to 178 mg and then to 100 mg when the subject responded correctly on five consecutive sessions (based on the final guess of each session) at each caffeine dose. (S1 reported adverse effects at 320 mg caffeine and requested a dose decrease after four sessions at 320 mg; her dose was decreased to 178 mg caffeine and no other problems were reported.) If the subject was correct (final guess of each session) on the first five sessions of the 100 mg caffeine condition or when the subject was correct on nine out of ten consecutive sessions in that dose condition, discrimination training was stopped and the caffeine versus placebo choice phase was begun. Training in each of the dose conditions (320 mg, 178 mg, and 100 mg caffeine) continued until the subject met the discrimination criterion for that condition.

Of the 11 subjects who participated in the discrimination training, all subjects acquired the 320 mg caffeine versus placebo discrimination in 5–48 sessions and the 178 mg caffeine versus placebo discrimination in 5–51 sessions. Three subjects did not complete the discrimination training phase and therefore did not participate in the choice phases. After acquiring the 178 mg caffeine versus placebo discrimination, one subject withdrew from the protocol for reasons unrelated to the research. The two subjects who were slowest to acquire the 320 mg and 178 mg caffeine versus placebo discrimination, requiring 74 and 79 sessions in total, were discontinued from the experiment without training on the 100 mg caffeine versus placebo discrimination.

Due to the large number of sessions required to teach S2 and S8 the discrimination (see Table 1), those subjects did not participate in all of the choice conditions or phases. S2 only participated in the paired-choice condition and drug versus money choice phase; S8 only participated in the paired-choice condition.

Caffeine versus placebo choice phase

Two choice conditions were conducted to determine if caffeine versus placebo choice would be affected by the behavioral requirements following drug ingestion. The behavioral requirements were varied by requiring subjects to engage in one of two activities for 60 min following drug ingestion, a relaxation activity or a vigilance activity.

All sessions followed the daily schedule described above. On each session of this phase, subjects engaged in the relaxation or

Multiple-Choice Form

For each number, indicate (check) whether you prefer the drug or the money today

If Vigilance is Scheduled

#	Drug	Money
1	A	$0.25
2	A	$0.28
3	A	$0.30
4	A	$0.33
5	A	$0.37
6	A	$0.40
7	A	$0.44
8	A	$0.49
9	A	$0.54
10	A	$0.59
11	A	$0.65
12	A	$0.71
13	A	$0.78
14	A	$0.86
15	A	$0.95
16	A	$1.04
...	...	...
47	A	$20.04
48	A	$22.05
49	A	$24.25
50	A	$26.68
51	A	$29.35
52	A	$32.28

#	Drug	Money
1	B	$0.25
2	B	$0.28
3	B	$0.30
4	B	$0.33
5	B	$0.37
6	B	$0.40
7	B	$0.44
8	B	$0.49
9	B	$0.54
10	B	$0.59
11	B	$0.65
12	B	$0.71
13	B	$0.78
14	B	$0.86
15	B	$0.95
16	B	$1.04
...	...	$1.15
47	B	$20.04
48	B	$22.05
49	B	$24.25
50	B	$26.68
51	B	$29.35
52	B	$32.28

If Relaxation is Scheduled

#	Drug	Money
1	A	$0.25
2	A	$0.28
3	A	$0.30
4	A	$0.33
5	A	$0.37
6	A	$0.40
7	A	$0.44
8	A	$0.49
9	A	$0.54
10	A	$0.59
11	A	$0.65
12	A	$0.71
13	A	$0.78
14	A	$0.86
15	A	$0.95
16	A	$1.04
...	...	...
47	A	$20.04
48	A	$22.05
49	A	$24.25
50	A	$26.68
51	A	$29.35
52	A	$32.28

#	Drug	Money
1	B	$0.25
2	B	$0.28
3	B	$0.30
4	B	$0.33
5	B	$0.37
6	B	$0.40
7	B	$0.44
8	B	$0.49
9	B	$0.54
10	B	$0.59
11	B	$0.65
12	B	$0.71
13	B	$0.78
14	B	$0.86
15	B	$0.95
16	B	$1.04
...	...	$1.15
47	B	$20.04
48	B	$22.05
49	B	$24.25
50	B	$26.68
51	B	$29.35
52	B	$32.28

Fig. 1. An example of the drug versus money choice form. A portion of the form has been deleted to conserve space. Each of the four columns involve drug versus money choices between a letter-coded drug and an increasing range of monetary values. The two left-most columns and the two right-most columns represent drug versus money choices for the vigilance context and relaxation context, respectively. The monetary values are arranged on an incrementing scale such that each value is 1.1 times the monetary value of the preceding choice number

vigilance activity for 60 min following capsule administration. During the relaxation activity (the relaxation context), the subject was required to sit in the large cushioned chair in their station. Subjects were allowed to sit quietly or sleep. No other activities were allowed. During the vigilance activity (the vigilance context), the subject sat facing a microcomputer. A star (approximately 0.5×0.5 cm) appeared intermittently in the middle of the computer screen for 1 s. The time between star presentations was randomly selected from nine durations averaging 30 s and ranging from 10 to 50 s in 5-s increments. Subjects were told that occasionally a star would flash on the screen. They were instructed to press a key when a star appeared, but to refrain from pressing when the screen was blank. Finally, subjects were told that the computer would record the number of times that they pressed the key after a star was flashed on the screen, the number of times that they pressed the key when no star was flashed on the screen, and the number of times that they failed to press the key when a star was flashed on screen. Subjects earned $1.00 for each vigilance or relaxation session completed. No explicit contingencies were arranged for key pressing during the vigilance activity.

Forced exposure condition. Subjects participated in a 4-day forced exposure condition in which they were exposed to each of their two letter-coded compounds (100 mg caffeine and placebo) once in each of the two contexts (relaxation and vigilance). For each subject, the letter codes established during discrimination training were used. Prior to ingesting the capsule on each forced exposure session, the subject was told which letter-coded compound they were about to ingest. The order of the four types of forced exposure sessions was randomized for each subject.

Paired-choice condition. After the 4-day forced exposure condition, subjects participated in a 10-day paired-choice condition to determine the extent to which the scheduled context (relaxation or vigilance) would influence caffeine versus placebo choice. Each session, after completing the predrug self-report questionnaires, the subjects completed a paper-and-pencil drug choice form. The form indicated that on that session either the relaxation context or the vigilance context would be scheduled. The form required subjects to choose which letter-coded compound they would ingest if the relaxation context were scheduled and which compound they would ingest if the vigilance context were scheduled, with the restriction that they could not take the same letter-coded compound with both contexts. Subjects were not allowed a "No Capsule" option. After the subject indicated which letter-coded compound they would take with each context, they opened an envelope that indicated which context was scheduled for that session. The subject received the letter-coded compound requested on the drug choice form appropriate to the scheduled context and then performed the scheduled context for 60 min. The relaxation and vigilance contexts were scheduled in random order across days, with the restriction (unknown to the subject) that neither context occur on more than three consecutive sessions. Given that subjects reliably chose caffeine with the vigilance context and placebo with the relaxation context, this restriction avoided administering caffeine on more than three consecutive days (which might have increased the chance of subjects developing caffeine physical dependence). Each subject participated in ten of these paired-choice sessions.

Unpaired-choice condition. The paired-choice condition showed that the vigilance and relaxation contexts controlled caffeine versus placebo choice (see Results). However, the paired-choice condition could not determine whether caffeine functioned as a positive reinforcer maintaining choice under the vigilance context, and/or whether caffeine functioned as a negative reinforcer which was avoided under the relaxation context. The unpaired-choice condition was conducted to provide additional information about the nature of the reinforcement effects produced by caffeine in the two contexts. The unpaired-choice condition independently assessed the effects of each of the two contexts (vigilance and relaxation) on subjects' caffeine versus placebo choice.

Immediately following the paired-choice condition, subjects participated in the 10-day unpaired-choice condition. The unpaired-choice condition was identical to the paired-choice condi-

tion with the exception that when completing the drug choice form subjects were free to choose the same compound with both contexts. In addition, because subjects could select caffeine with both contexts and therefore potentially ingest caffeine every day, choice sessions were not conducted on Wednesdays to avoid giving subjects caffeine on more than 2 consecutive days. This restriction was imposed to minimize the chance of developing caffeine physical dependence. In this unpaired-choice condition in which subjects were always free to choose placebo, consistent choice of caffeine over placebo would indicate that caffeine was a positive reinforcer in that context.

Drug versus money choice phase

To further explore the control of caffeine reinforcement by the contexts, a drug versus money choice phase was conducted using a multiple-choice procedure (Griffiths et al. 1993). Sessions in this condition followed the same basic schedule as sessions in the caffeine versus placebo choice phase. This phase involved two conditions, a 6-day forced exposure condition followed by a 10-day drug versus money choice condition. Letter codes were the same as in previous phases.

Forced exposure condition. The 6-day forced exposure condition was similar to the forced exposure condition described above in that on four of the days subjects were exposed to each of their two letter-coded compounds (100 mg caffeine and placebo) once in each of the two contexts (relaxation and vigilance); in addition, subjects had two other sessions in which they were exposed to the relaxation and vigilance contexts (one per session), but received no drug administration. These no-drug sessions were added because in the subsequent choice condition subjects could choose money over drug and as a result receive no drug on some sessions.

Drug versus money choice condition. On each day of this condition, the subject completed a drug versus money choice form illustrated in Fig. 1. The drug versus money choice form consisted of 208 choices; for each choice the subject was required to choose between a letter-coded drug condition (caffeine or placebo) and a monetary value. Subjects made both caffeine versus money and placebo versus money choices assuming that the vigilance context was scheduled for the session (two left columns), and then again, assuming that the relaxation context was scheduled (two right columns). Only 1 of the 208 choices was reinforced each day. A random selection procedure was conducted to determine which 1 of the 208 choices would be reinforced. The random selection procedure comprised the following three operations:

1) Immediately after completing the form, the subject opened an envelope that indicated which context (vigilance or relaxation) was scheduled for that session and therefore indicated which two columns on the drug versus money choice form would remain active (i.e., continued to be included in the random selection procedure) for that session (e.g., the left two columns would remain active if the vigilance context was scheduled).
2) Then the subject drew one letter at random from a container holding that subject's two drug letter codes. The result of that draw indicated which drug would be available on that session and therefore indicated which column on the drug versus money choice form would remain active.
3) Then the subject drew one number at random from a container holding the numbers from 1 to 52. The chosen item corresponding to the randomly selected number was then delivered. If a monetary value had been chosen, the amount of money corresponding to the randomly selected number was added to the subject's earnings, but the subject did not receive any drug that day; any money earned was paid to the subject upon completion of the study. If a letter-coded capsule had been chosen, the subject received the capsule, but no money was added to the subject's earnings. Regardless of whether the subject received money or drug, the subject then completed the session, which included performing the scheduled activity for 60 min. The subject participated in ten of these drug versus money choice sessions.

Data analysis

Caffeine versus placebo choices. Choice in both the paired-choice and unpaired-choice conditions were analyzed for each subject using the binomial probability distribution. Significant choice in both paired-choice and unpaired-choice conditions was defined as selecting the same letter-coded compound in a particular context on eight of the ten choice opportunities ($\geq 80\%$; $P < 0.05$). Because in the paired choice condition, subjects made only one caffeine versus placebo choice for both the vigilance and relaxation contexts (i.e., they chose to take caffeine with vigilance and placebo with relaxation or the reverse), choice in the vigilance and relaxation contexts was not analyzed separately. In contrast, because in the unpaired choice condition, subjects made caffeine versus placebo choices separately for the vigilance and relaxation contexts, choice was analyzed separately for each context.

Drug versus money choice. For each individual, drug versus money choices on the drug versus money choice form were analyzed as the maximum dollar value at which subjects chose drug over money. That dollar value was defined as the "cross-over point". For analysis of data across sessions for each subject, a repeated measures ANOVA was used with Drug Condition (placebo and caffeine) and Context (relaxation and vigilance) as between-session factors; Tukey's HSD tests were used to compare the cross-over points for the four drug-context conditions (i.e., caffeine-vigilance; caffeine-relaxation; placebo-vigilance; placebo-relaxation).

Self-reports. Data for the self-report questionnaires administered during the caffeine versus placebo forced exposure condition were analyzed for the group of subjects by repeated measures ANOVAs with Drug Condition (placebo and caffeine) and Context (relaxation and vigilance) as between-session factors, and Time (pre- and post-drug) as the within-session factor. Data for the self-report questionnaires administered during the drug versus money forced exposure condition were analyzed for the group of subjects by repeated measures ANOVAs with Drug Condition (placebo, caffeine, and no drug) and Context (relaxation and vigilance) as between-session factors, and Time (pre- and post-drug) as the within-session factor. For both forced exposure conditions, Tukey's HSD tests were used to compare the drug conditions (caffeine and placebo) at each time point collapsed across vigilance and relaxation sessions. Tukey's HSD tests also were conducted to compare the effects of the two contexts (relaxation and vigilance) within each drug condition.

Vigilance performance. For the vigilance task administered during the drug versus money forced exposure condition, three measures were analyzed: "misses" (the number of times the subject did not press the key within 5 s after the appearance of a star on screen), latency of key presses (the average latency of key presses occurring within 5 s after a star appeared on the screen), and "false alarms" (the number of times that the subject pressed a key more than 5 s after a star appeared on screen). Repeated measures ANOVAs were used for the analysis with Drug Condition (caffeine, placebo, and no drug) as a within-subject factor. Post hoc comparisons between caffeine, placebo, and no drug were examined using Tukey's HSD Test.

For all statistical tests, effects were considered to be significant for $P \leq 0.05$. For repeated measures ANOVAs, Huynh-Feldt (Huynh and Feldt 1976) corrected P values are reported.

Results

Discrimination training

The last column in Table 1 shows the number of discrimination training sessions required for each subject to reach the discrimination criterion at 100 mg caffeine.

Self-reported mood effects and vigilance performance

In both the caffeine versus placebo forced exposure condition and the drug versus money forced exposure condition, caffeine produced a typical profile of self-reported mood effects. In both force-exposure conditions, relative to placebo, caffeine significantly (i.e., significant Drug × Time interaction and significant post hoc caffeine versus placebo difference at the 60-min time point without significant caffeine versus placebo difference at the predrug time point) increased ratings of "alert," "motivation to work," "energy/active," and "trembling/shaky/jittery," and scores on the BG scale of the ARCI; caffeine signficantly decreased ratings of "sleepy" and scores on the PCAG scale of the ARCI. The contexts did not differentially alter subjects' ratings within the caffeine or placebo conditions (i.e., there were no significant Drug × Context × Time interactions in either forced exposure condition).

Tukey's post hoc comparisons of the vigilance data indicated that caffeine significantly ($P \leq 0.05$) decreased the total number of misses relative to both the placebo and no drug conditions. Neither latency nor false alarms was affected by the drug conditions.

Caffeine versus placebo choices

The top panel of Fig. 2 shows the caffeine versus placebo choice results for the paired-choice condition. Each of the eight subjects showed statistically significant contextual control of caffeine choice by always choosing to take caffeine when the vigilance context was scheduled (on ten of the ten choice opportunities; binomial probability distribution, $P < 0.001$).

The bottom panel of Fig. 2 shows the choice results for the unpaired-choice condition. All six subjects showed significant caffeine choice by reliably choosing (on nine or more of the ten choice opportunities; binomial probability distribution, $P \leq 0.01$) caffeine over placebo in one or both of the two contexts. Furthermore, four of the six subjects showed statistically significant contextual control of caffeine choice by reliably choosing to take caffeine when the vigilance context was scheduled (on nine or more of the ten choice opportunities; binomial probability distribution, $P \leq 0.01$), and placebo when the relaxation context was scheduled (on ten of the ten choice opportunities; binomial probability distribution, $P < 0.001$).

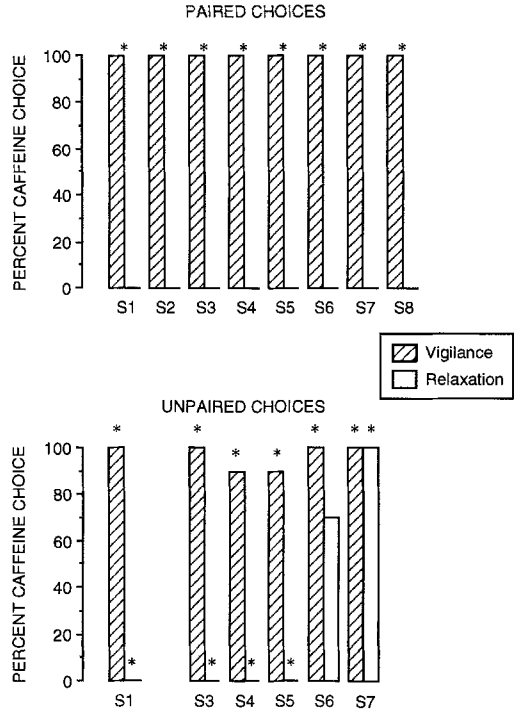

Fig. 2. The *top panel* shows data for the paired-choice condition for the ten choice opportunities of that condition (eight subjects). Data for vigilance and relaxation contexts are represented by *striped* and *open bars*, respectively. The *asterisks* above the bars indicate which subjects showed statistically significant contextual control of drug choice according to the binomial probability distribution ($\leq 80\%$; $P \leq 0.05$). Subject codes are shown below each pair of bars. The *bottom panel* shows data for the unpaired-choice condition consisting of 20 choice opportunities (10 for the vigilance context and 10 for the relaxation context) for each subject (six subjects). *Asterisks* above the bars indicate significant caffeine choice ($\leq 80\%$; $P \leq 0.05$) or significant caffeine avoidance ($\leq 20\%$; $P \leq 0.05$). Other details are the same as upper panel

Drug versus money choices

The mean maximum dollar value at which each of the seven subjects chose drug over money in the vigilance and relaxation contexts is shown in Fig. 3. The maximum dollar value at which a subject chose drug over money will be referred to as the cross-over point because it is the point on the drug versus money choice form at which the subject stopped choosing drug and crossed over to choosing money. First, for all subjects except S4, the mean cross-over point for caffeine in the vigilance context was significantly ($P \leq 0.05$) higher than the mean cross-over point for placebo in both the relaxation and vigilance contexts, indicating that caffeine functioned as a reinforcer in the vigilance context. Five of those subjects (S1, S2, S3, S5, and S6) showed contextual control of caffeine choice in that the mean cross-over point for caffeine in the vigilance context was significantly ($P \leq 0.05$) higher than the mean cross-over point for caffeine in the relaxation context for each subject. Three subjects (S1, S4, and S5) showed contextual control of placebo choice in that the mean cross-over point for placebo in the relaxation context was significantly ($P \leq 0.05$) higher than the

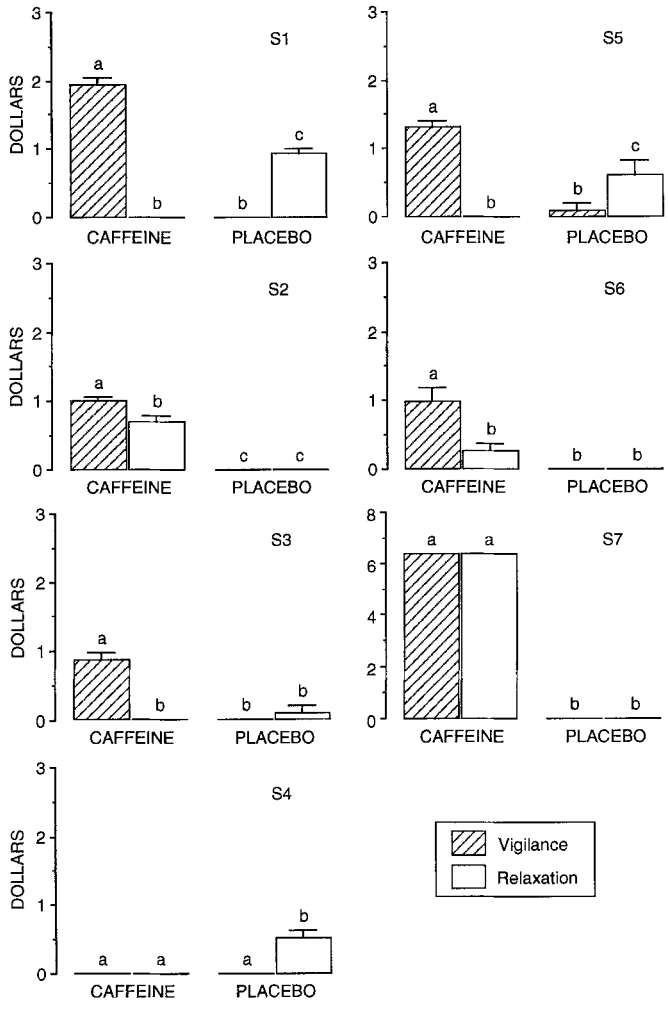

Fig. 3. The mean maximum dollar value at which each of the seven subjects chose drug over money (i.e. cross-over point) for caffeine (two *left bars*) and placebo (two *right bars*) in the vigilance (*striped bars*) and relaxation (*open bars*) contexts averaged over the ten drug versus money choice sessions; brackets show ± 1 SEM. The seven panels are labeled with subject numbers (S1–S7). Letters *a*, *b*, and *c* indicate comparisons among the drug-context conditions; within the same panel any two means designated with the same letter are not significantly different from each other at $P \leq 0.05$ (Tukey's post hoc tests)

mean cross-over point for placebo in the vigilance context for each subject.

Salivary caffeine concentrations

Analyses of the saliva samples collected during the choice phases in the mornings before capsule administration indicated that subjects did not consume substantial amounts of caffeine (e.g., amounts contained in individual servings of coffee, tea, or cola) immediately before experimental sessions. The mean salivary caffeine concentration for all of the samples analyzed was 0.06 μg/ml (median was 0.00 μg/ml and range of individual subject means was 0.00–0.56 μg/ml). However, the analyses indicated that two of the eight subjects (S4 and S8) did consume caffeine from non-experimental sources in one or more of the phases (e.g., for S4 and S8, levels of 0.56 μg/ml and 0.47 μg/ml occurred in samples collected 16 and 3 days after the last experimental administration of caffeine, respectively).

Discussion

The results of the choice conditions taken together show that caffeine reinforcement can be modulated by the behavioral requirements following drug ingestion. In the paired-choice condition, the behavioral requirements following drug ingestion modulated caffeine reinforcement in all eight subjects; however, the choice procedure employed in that condition did not determine whether caffeine was functioning as a positive or negative reinforcer. In the unpaired-choice condition and the drug versus money choice condition, caffeine generally served as a positive reinforcer when subjects were required to engage in the computer vigilance activity following drug ingestion; but, for most subjects, when required to engage in the relaxation activity following ingestion, the positive reinforcing effects of caffeine were absent (S1, S3, S4, and S5 in the unpaired choice condition; S1, S3, S4, S5, and S6 in the drug versus money choice condition) or significantly diminished (S2 in the drug versus money choice condition). The extent to which the histories provided in the paired-choice condition influenced the results of the unpaired-choice condition or the drug versus money choice phase cannot be determined from this experiment.

In contrast to previous studies which have shown caffeine reinforcement in no more than 50% of normal subjects (Griffiths and Woodson 1988; Hughes et al. 1991, 1992; Oliveto et al. 1992a,b), in the vigilance context caffeine was shown to function as a reinforcer in all subjects in this study. There was only one choice condition for one subject in which caffeine did not function as a reinforcer in the vigilance context (S4 in the drug versus money choice condition; Fig. 3). It may be important to note that analyses of saliva samples after the study was completed indicated that this subject was consuming caffeine on a regular basis throughout much of the experiment, including during the drug versus money phase.

The difference in the proportion of subjects showing caffeine reinforcement between this study and previous studies may be accounted for, in part, by two factors. First, previous studies have not provided explicit discrimination training before assessing caffeine versus placebo choice. Instead, in previous studies subjects have been provided only one or two forced exposure sessions to each of the drug conditions (i.e., caffeine and placebo) prior to assessing caffeine versus placebo choice. However, as discussed above (see Introduction), those forced exposures may not be sufficient to establish the letter-coded labels by which subjects are expected to choose between the drug conditions. In contrast, in this study subjects were taught a caffeine versus placebo discrimination prior to assessing caffeine reinforcement. Second, previous studies have not controlled the behavioral requirements following drug ingestion. In those studies, af-

ter drug ingestion, subjects were free to engage in their typical daily activities. In contrast, in this study subjects were required to engage in the computer vigilance activity on some sessions following drug administration.

It should be noted that the discrimination training phase may have functioned to select only caffeine-sensitive subjects, thereby increasing the proportion of subjects participating in the choice phase who would demonstrate caffeine reinforcement. Two subjects failed to acquire the 100 mg caffeine versus placebo discrimination in the allotted time and therefore did not participate in the choice phases. However, showing caffeine reinforcement in eight out of ten subjects (excluding the subject who withdrew from the study for reasons unrelated to the research) is still substantially higher than the percentage of subjects who have shown caffeine reinforcement in all of the previous studies. Furthermore, in the vigilance context, the reliability with which each subject chose caffeine over placebo (i.e., between 90% and 100% of the choice opportunities for each subject in the paired-choice and unpaired-choice conditions) is higher than has typically been reported in previous research.

Special efforts were made in this study to obscure the fact that the two compounds under study were caffeine and placebo (see "Instructions to subjects" and "Dietary restrictions" described above). Some results observed during the drug versus money choice phase suggest that the blinding instructions were effective. Four of the seven subjects who participated in that phase (S1, S3, S4, and S5) chose placebo over at least some monetary values in the relaxation context, suggesting that subjects were treating placebo as an active compound. Interestingly, three of those four subjects showed contextual control over placebo choice in that the cross-over point for placebo was significantly higher in the relaxation context than in the vigilance context.

Although some studies have shown that caffeine physical dependence can potentiate caffeine reinforcement, other studies have shown that caffeine can serve as a reinforcer in subjects who are not physically dependent on caffeine (Griffiths and Mumford 1994). The current study provides additional evidence that caffeine physical dependence is not a necessary condition for caffeine reinforcement. In the current study, efforts were made to minimize the development of caffeine physical dependence by never administering caffeine on more than 3 consecutive days. Self-report data collected during the two forced exposure conditions of the experiment suggest that subjects did not show a clear caffeine withdrawal syndrome under the placebo condition. Specifically, ratings of headache, the classic symptom of caffeine withdrawal, were not significantly affected by the caffeine and placebo drug conditions. Nevertheless, caffeine reinforcement was demonstrated in this study, apparently in the absence of caffeine physical dependence.

This research extends the range of findings that have shown that the potential of drugs to maintain drug self-administration is not solely dependent on their pharmacology; drug reinforcement, like reinforcement by non-drug consequences, depends on historical and current environmental circumstances (Pickens et al. 1978; Griffiths et al. 1980; Johanson and Schuster 1981; Young and Herling 1986). The current study along with the study by Silverman et al. (1994a) extends this body of research by demonstrating a new class of environmental variable (i.e., the behavioral requirements following drug administration) that can alter drug reinforcement.

The experimental demonstration of caffeine reinforcement in normal subjects has been elusive, even among regular caffeine consumers. This study further clarifies the conditions under which caffeine functions as a reinforcer by demonstrating that the behavioral requirements following caffeine ingestion can affect caffeine reinforcement. In contrast to previous methods, the methods employed in this study (i.e., providing a discrimination history and controlling the behavioral requirements following drug ingestion) appear unusually effective in demonstrating caffeine reinforcement. These methods may be useful, not only for future investigations into the reinforcing effects of caffeine, but also for studying the reinforcing effects of other behaviorally active drugs, particularly drugs or doses which appear to have subtle or variable effects.

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