Abstract

There is limited evidence for the conditioning of stimulant-like drug effects to previously-neutral stimuli in humans. Two studies tested whether the facilitatory effects of caffeine on cognitive performance can be conditioned to the context of drug administration. In Experiment 1, sixteen participants were divided equally into two groups: one group (the “paired” group) received 250 mg caffeine in a novel beverage prior to completing two computerized performance tests; the other group (the “unpaired” group) received the same beverage without caffeine (i.e., placebo) before testing. After the performance tests, the unpaired group received the caffeinated drink, and the paired group received placebo in a different context from that in which testing had taken place. The performance tests comprised a test of simple reaction time to a visual stimulus and a test of logical reasoning (the semantic verification task). The procedure was repeated over four separate conditioning trials. On a subsequent fifth session, the test for a conditioned response, all participants received placebo before test. Simple reaction time was significantly reduced by caffeine over the four conditioning trials, and on the test for conditioned responding the paired group performed significantly faster than the unpaired group, indicating the development of a conditioned response. In Experiment 2, twelve participants attended four conditioning trials in which either 250 mg of caffeine (two sessions) or placebo (two sessions) were paired with two visually distinct environments. After completing the conditioning sessions, tests for conditional responding were conducted by administering placebo in both contexts. During the conditioning phase, caffeine significantly improved reaction time performance relative to placebo, and this advantage was maintained at test in the CS+ context when placebo was administered in both contexts. Therefore the facilitatory effects of caffeine on performance can be elicited, in the absence of drug, by previously-neutral contextual stimuli that have been paired with drug administration.

Keywords: Caffeine

1. Introduction

The behavioural effects of drugs can sometimes be elicited, in the absence of drug, by environmental stimuli that were present at the time of drug administration. It is commonly assumed that the context of drug administration acquires influence over a drug's effects by means of Pavlovian conditioning. The development of conditioned drug effects in non-human animals is supported by an extensive literature (e.g., [3,27,31,37,38]), but in humans there have been few demonstrations of drug effects being conditioned to previously-neutral stimuli. Conditioning studies with human participants have often focused on the role of conditioned responses in the development of context-dependent tolerance, after the work of Siegel [32]. For example, studies of conditioned tolerance to the effects of alcohol have demonstrated the apparent emergence of a conditioned compensatory response following repeated pairings of alcohol with a particular test environment, such that drug-opposite responding can be measured in the test context when alcohol is absent (e.g., [21,24]). Similarly, conditioned compensatory responses have been identified in humans following repeated, environment-specific administrations of opiate drugs (e.g., [7,25,35]) or the muscle relaxant, carisoprodol [11]. There have been fewer studies testing whether psychostimulant drug effects in humans can be conditioned to neutral stimuli. Evidence for cocaine-conditioned increases in heart rate and diastolic blood pressure was provided by Muntaner et al. [23], and Foltin and Haney [12] also demonstrated conditioned increases in heart rate and systolic blood pressure, as well as conditioned changes in skin temperature and subjective reports, following pairings of smoked cocaine with a specific test environment. Hence the cocaine studies have tended to demonstrate conditioned responses in a similar direction to those produced by the drug itself, rather than drug-opposite, conditioned compensatory responses.

Such studies have typically measured simple physiological responses, such as heart rate, blood pressure, blink reflex and skin temperature, but compensatory improvements in aspects of cognitive performance have also been reported following alcohol-environment
conditioning [30]. Neither of the two studies using cocaine included performance measures, and to date there is a paucity of research testing whether changes in performance measures induced by some stimulant drugs can be conditioned to previously-neutral stimuli. In this context, caffeine constitutes a useful test compound, since there are several reports that it can improve performance on a range of psychomotor and cognitive measures (e.g. [1,6,9,20,33,39]). The only suggestion that certain such effects may be conditioned to the context of drug administration is from a study of caffeine’s effects on sleep latency by Zwyghuizen-Doorenbos et al. [42]. Although not the main focus of their study, they reported that caffeine-induced decreases in latency by Zwyghuizen-Doorenbos et al. [42]. Although not the main focus of their study, they reported that caffeine-induced decreases in reaction times and error rates on a 40 min auditory vigilance task are several reports that it can improve performance on a range of psychomotor and cognitive measures (e.g. [1,6,9,20,33,39]). The only suggestion that certain such effects may be conditioned to the context of drug administration is from a study of caffeine’s effects on sleep latency by Zwyghuizen-Doorenbos et al. [42]. Although not the main focus of their study, they reported that caffeine-induced decreases in reaction times and error rates on a 40 min auditory vigilance task are several reports that it can improve performance on a range of psychomotor and cognitive measures (e.g. [1,6,9,20,33,39]). The only suggestion that certain such effects may be conditioned to the context of drug administration is from a study of caffeine’s effects on sleep latency by Zwyghuizen-Doorenbos et al. [42]. Although not the main focus of their study, they reported that caffeine-induced decreases in reaction times and error rates on a 40 min auditory vigilance task were tested between 10:00 am and 4:00 pm. Each participant in the paired group was yoked with a participant from the unpaired group and these yoked pairs were tested at the same time of day.

2.1.3. Test drinks

The drink was a blend of grapefruit juice (60 ml), orange juice (30 ml), and pineapple juice (10 ml; all drinks from Tesco, UK). The caffeine drink contained 250 mg of arrowroot and 250 mg of caffeine (Tocris, UK). The non-caffeinated drink contained 250 mg of arrowroot only. Arrowroot is a white powder (similar in appearance to anhydrous caffeine) with no psychoactive properties. It was added to the placebo beverage to match for any perceptual changes that may have occurred as a result of adding white powder to the solution. The caffeine dose was based on previous studies that showed enhanced psychomotor performance following caffeine [20,42]. The juice blend was rated as novel, and pilot tests confirmed that its flavour successfully masked the taste of the caffeine.

2.1.4. Cognitive measures

2.1.4.1. Simple reaction time (SRT) task. For 100 consecutive trials, a stimulus (an asterisk) was presented in the middle of the computer screen. Participants pressed the space bar on the computer keyboard as quickly as possible after the asterisk appeared. The stimulus was presented for up to 1 s and the interstimulus interval (ISI) varied randomly between 1 and 2.5 s to avoid anticipatory responding. Ten practice trials preceded testing.

2.1.4.2. Semantic verification test. This task was based on Baddeley [2] and Warburton [39]. A sentence describing the on-screen arrangement of two letters (e.g. A is above B) was presented on the screen along with the letters A and B, presented one above the other. The participants pressed a key to indicate whether the sentence was true or false in relation to the actual arrangement of the letters (m for true, v for false). There were 160 sentences involving four different grammatical constructions (“above”, “not above”, “below” and “not below”). The arrangement of letters, number of true and false statements, and number of positive and negative statements were counterbalanced to give equal numbers of each stimulus arrangement. Each stimulus arrangement was randomly presented for up to 10 s and the ISI was 1000 ms. Ten practice trials preceded testing.

2.1.5. Procedure

Participants were tested over five sessions. For sessions 1–4 (the conditioning phase), they were taken to a cubicle (comprising table, chair, and computer) and given either the caffeinated juice drink (paired) or non-caffeinated juice drink (unpaired). Yoked pairs were tested in adjacent cubicles. After 30 min, the participants completed the SRT and semantic verification tasks (order counterbalanced across sessions and participants). Then, both participants were taken to a different environment and given the reverse drink (i.e. non-caffeinated for the paired group and caffeinated for the unpaired group) so that by the test day (session five) both groups had received equal amounts of drug in the overall context of the study. The procedure for session five (test) was the same as for sessions 1–4, except that all participants received the non-caffeinated juice drink in the test cubicle. Finally, a questionnaire asked participants to indicate what substance (if any) they thought they had received, whether they noticed any differences in the procedure or drinks on the final day, and what they thought the experiment was attempting to test.

2. Experiment 1

2.1. Method

2.1.1. Participants

Eighteen undergraduate students from the University of Birmingham were recruited (10 female, mean age 19.3 years, range 18–26 years). One participant did not complete the test sessions. By self-report, they were regular consumers of caffeine (at least three cups of tea or coffee per day; no upper limit), non-smokers, and not taking any prescribed medication (excluding oral contraceptives) or recreational drugs. Participants were recruited via posters, and to reduce expectancy effects they were informed at the first session that they might receive a drink containing a small amount of aspirin, caffeine, paracetamol or antihistamine. The study was approved by the intramural Ethics Committee. Participants received course credits for taking part.
2.1.6. Analyses

Mean reaction times (SRT and semantic verification) and numbers of errors (semantic verification) for the conditioning phase (days 1–4) were contrasted between groups using a two-way ANOVA with day (within subject) and group (between subjects) as factors. The data from one session for a participant in the paired group was discarded due to incorrect use of the response keys. Where a main effect of group was revealed during the conditioning phase, comparison of the performance of the paired versus unpaired group at test (day 5) was made using an independent t-test.

2.2. Experiment 1: results

2.2.1. Cognitive measures

2.2.1.1. Simple reaction time. Mean reaction times for the paired and unpaired groups over the four conditioning trials are shown in Fig. 1. There was a main effect of group \( F(1,15)=9.93; P<0.01 \), but no significant effect of day \( F(3,45)=1.82; P=0.16 \), and no significant interaction \( F(3,45)=0.70; P=0.55 \). The paired group was consistently faster than the unpaired group across all four sessions. As shown in Fig. 1, the enhanced performance of the paired group was maintained at test \( t=2.8, df=15, P=0.05 \), even though caffeine was no longer present.

2.2.1.2. Semantic verification task. There was no significant main effect of group on mean reaction times \( F(1,15)=0.001; P=0.98 \), and no significant group × day interaction \( F(3,44)=1.5; P=0.23 \). However, there was a significant main effect of day \( F(3,44)=37.47; P<0.001 \). As shown in Table 1, reaction times became faster over the four conditioning trials. Analysis of errors revealed no significant main effects either of group \( F(1,15)=0.67; P=0.43 \) or day \( F(3,44)=1.56; P=0.22 \), and no significant interactions between these factors \( F(3,44)=0.33; P=0.8; \) Table 1.

2.2.2. Post test questionnaire

In the paired group, only one of the nine participants thought they had received caffeine. Five participants said they thought they had received a drug but were unable to identify the substance, and three participants did not know if they had been given a drug. Two of the eight participants in the unpaired group indicated that they thought they had been given caffeine, and two said they had received a drug other than caffeine (antihistamine and paracetamol). Three participants thought they had received no drug, and one did not know if they had been given drug. None of the participants reported noticing a change in the procedure or drinks on the final test day, and none identified that the experiment was examining conditioning or learning, although four of the paired group and six of the unpaired group thought the study was investigating the effects of drugs on cognitive performance.

2.2.3. Summary

The results of Experiment 1 indicate that environmental stimuli paired with the consumption of caffeine can evoke drug-like responding in the absence of caffeine: response speed in a simple reaction time task was enhanced in those participants who had experienced the effects of caffeine in the test environment (paired group), but not in those who had received caffeine outside the test environment (unpaired group). To test the generalizability of the results, a second experiment was conducted using a different experimental design and addressing a possible shortcoming of Experiment 1, namely that drug administration was not double-blind.

3. Experiment 2

A within-subjects differential conditioning paradigm was adopted. For half of the conditioning trials, one context (CS+) was paired with caffeine, and for the other half of the trials placebo was administered in a different context (CS−). These sessions were followed by two tests of conditioning, in which responses to placebo were assessed in the CS+ and the CS− contexts. Foltin and Haney [12] used a similar procedure to examine the effects of pairing two sets of neutral cues with either placebo- or cocaine-smoking, and reported cocaine-like physiological responding and craving to the cocaine-paired cues only. Differential procedures have also been effective in conditioning the effects of alcohol [14], nicotine [8,19], and the rated pleasantness of caffeine [41].

To maximise the likelihood of obtaining unconditioned caffeine effects on performance (a prerequisite for conditioning), participants were screened before the main experiment to identify caffeine consumers who display caffeine-induced performance enhancements. Similar procedures have been used in caffeine discrimination studies to identify participants who are able to discriminate drug from placebo (e.g. [26]).

No significant effects of caffeine on the semantic verification task were observed in Experiment 1, so this task was replaced by tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB): rapid visual information processing (RVIP); match-to-sample visual search (MTS); simple reaction time (SRT); choice reaction time (CRT) and spatial recognition (SR). Hence we tested multiple processes which have been widely reported to be sensitive to caffeine [6,13,39,40].

<table>
<thead>
<tr>
<th>Conditioning day</th>
<th>1</th>
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<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td><strong>Unpaired</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Mean reaction time (ms)</td>
<td>2967.8</td>
<td>2373.9</td>
<td>2037.0</td>
<td>1962.5</td>
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<tr>
<td>(290.9)</td>
<td>(204.5)</td>
<td>(151.2)</td>
<td>(185.0)</td>
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<tr>
<td>Errors</td>
<td>7.9</td>
<td>6.8</td>
<td>4.7</td>
<td>6.3</td>
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<tr>
<td>(1.7)</td>
<td>(1.9)</td>
<td>(1.4)</td>
<td>(1.4)</td>
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<tr>
<td><strong>Paired</strong></td>
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<tr>
<td>Mean reaction time (ms)</td>
<td>2774.7</td>
<td>2345.0</td>
<td>2198.9</td>
<td>2064.6</td>
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<tr>
<td>(137.4)</td>
<td>(98.0)</td>
<td>(110.8)</td>
<td>(152.0)</td>
<td></td>
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<tr>
<td>Errors</td>
<td>11.1</td>
<td>6.9</td>
<td>7.4</td>
<td>7.5</td>
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<tr>
<td>(4.0)</td>
<td>(2.0)</td>
<td>(2.5)</td>
<td>(1.8)</td>
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Table 1 Reaction times (ms) and numbers of errors on the semantic verification task over the 4 conditioning trials for both the caffeine-paired and caffeine-unpaired groups in Experiment 1. Standard deviations in parentheses.

Fig. 1. Mean simple reaction times (ms) are faster in the paired (caffeine in the test context) than unpaired (placebo in the test context) groups over the four conditioning trials and at test (all participants given placebo) in Experiment 1. Bars represent SEM.
3.1. Method

3.1.1. Screening

21 participants (15 female; mean age 21.3 years, range 18–29 years) with an average daily caffeine intake of 262.3 mg (range 175–625 mg) took part in return for cash (£10) or course credits. Caffeine administration, the battery of tests and the experimental procedure were the same as in the main study except that (a) the sessions took place in a different environment so that there was no pre-exposure to the conditioned stimuli prior to the conditioning trials; and (b) practice versions of the SRT and CRT tasks (two blocks of 15 trials) were included. Each participant attended two sessions (caffeine and placebo), drug order was counterbalanced across participants and administration was double-blind. Inter-session intervals were between 24 h and 14 days. Participants were informed that they should not consume any psychoactive substances from 23:00 h on the night before testing, and that compliance would be verified by a saliva sample. Testing was between 12:00 and 18:00 h, at approximately the same time of day for a given participant. On arrival, participants confirmed abstinence from psychoactive substances and provided a saliva sample (to encourage compliance—not analysed). Practice on the SRT and CRT tasks (two blocks each) was completed before drug capsule ingestion. A 30 min interval allowed for drug absorption, during which the participants sat quietly (reading material was provided). The experimenter then administered the performance tests. Participants were included in the main study if their reaction times after caffeine were consistently faster than their reaction times after placebo. To maintain the double-blind, two additional experimenters examined the data and selected the participants. Twelve participants were accepted (8 female; mean age 22 years, range 18–29 years) with an average daily caffeine intake of 256.8 mg (range 175–625 mg) in return for cash (£30) or course credits.

3.1.2. Experimental design

This within-subject design required participants to attend two trials in which caffeine was paired with one context (CS+) and two trials in which placebo was paired with a different context (CS−). The number of conditioning sessions was based on the results of a pilot study showing that caffeine speeded reaction times relative to placebo on early conditioning trials, but this effect was lost over subsequent trials due to systematic performance gains in the placebo condition (possibly early conditioning trials, but this effect was lost over subsequent trials showing that caffeine speeded reaction times relative to placebo on early conditioning trials, but this effect was lost over subsequent trials due to systematic performance gains in the placebo condition (possibly reflecting the early development of conditioned responses in the caffeine-associated context, which then generalized to the broader context of the experimental setting). Conditioning trials were followed by two tests of conditioning, in which placebo was administered in both contexts: CS− and CS+ sessions were alternated and capsule order (placebo/caffeine vs. caffeine/placebo) and the context which served as the CS+ were counterbalanced across participants. Both alternating (i.e. a CS+ always followed by a CS− trial) and randomised procedures have been used previously [8,14,41]. Capsule order, room order and the room in which caffeine was received were fully counterbalanced.

3.1.3. Conditioned stimuli

The CS+ and CS− test rooms were matched in size, and both contained a table, chair and computer. They were differentiated by colour (black versus white-painted walls and ceiling), olfactory cues, and by pictures on the walls. Distinct odours were produced using Glade plug-in diffusers [SC Johnson, Surrey]: fragrances were based on a pilot study (N = 20 participants). Ratings were made using 100 mm visual analogue scales with the anchors “not at all” (0) and “extremely” (100). The two fragrances chosen were “Bamboo and White Fresia” (added to the white cube) and “Smells of the Orient” (added to the black cube), since they were well matched for pleasantness [t = 0.22, df = 19, P > 0.05], pungency [t = 0.36, df = 19, P > 0.05] and novelty [t = 0.85, df = 19, P > 0.05], yet were also considered distinct (similarity score of 30 mm on a 100 mm VAS).

The same participants also completed a VAS (100 mm) to rate eight A6-size picture prints (from GB poster.com) for “liking”, “familiarity” and “interest” (“not at all” to “extremely”). The two best matched were pictures of Neuschwanstein Castle, Germany, and Bora Bora Island, which did not significantly differ on any of the ratings (liking [t = −0.34, df = 21, P > 0.05]; familiarity [t = 0.39, df = 21, P > 0.05]; interest [t = 0.87, df = 21, P > 0.05]). Full-size (91 × 61 cm) versions of these prints were subsequently placed in the white and black cubicles respectively.

3.1.4. Performance measures

All tasks were from the CANTABellipse battery (Cambridge Cognition, Cambridge, UK). Participants responded using a specialised press pad placed 15 cm in front of a touch-sensitive computer screen. The tasks are described below in the order in which they were completed.

3.1.4.1. Simple reaction time (SRT). There were 2 blocks of 15 trials. The stimulus was a small yellow spot presented for 250 ms inside a white circle that remained centrally on screen throughout the test. Each trial began with the participants depressuring a key until the spot appeared, at which point they touched the screen (inside the white circle) as quickly as possible. The next trial did not begin until the participants had once again depressed the press pad key. ITI varied randomly between 750 and 2250 ms to reduce anticipatory responding and the task was preceded by a practice block of ten trials.

3.1.4.2. Choice reaction time (CRT). There were 4 experimental blocks of 15 trials each in which 5 white circles were arranged around a central point on the screen; these remained on screen throughout. On each trial, a yellow spot appeared in one of the circles, and participants had to touch this circle as quickly as possible. ITIs and practice trials were as for SRT.

3.1.4.3. Rapid visual information processing (RVIP). A series of single digits appeared sequentially on the screen, each for 600 ms, before being replaced by the next. Participants responded via the press pad when they identified one of three 3-digit number strings (3-5-7; 2-4-6; 4-6-8). The task ran for 6 consecutive blocks (total task time: 6 min), each containing 9 target strings, although data from the first block were not analysed. A 2 min practice trial preceded the test.

3.1.4.4. Match to sample visual search (MTS). An abstract pattern (target) appeared centrally on the screen, and 1.5 s later distracter patterns appeared in boxes surrounding this central pattern; one of the distracters was identical to the target. To initiate each trial, a press pad key was depressed until the identical pattern was identified, then the participant touched the matching pattern on screen. If the response was incorrect (indicated by a red cross on the screen), participants continued choosing until correct. There were 3 levels of difficulty according to the number of distracters: 2 (level 1), 4 (level 2) or 8 (level 3). Reaction duration, movement duration and errors were recorded. The task was preceded by a practice block of 3 trials (one per level; data not analysed).

3.1.5. Mood measures

Mood was assessed using a questionnaire adapted from Rogers et al. [43]. Seventeen adjectives (“Friendly”, “Alert”, “Cheerful”, “Drowsy”, “Anxious”, “Energetic”, “Angry”, “Muddled”, “Calm”, “Tired”, “Depressed”, “Tense”, “Clear-headed”, “Relaxed”, “Thirsty”, “Jittery” and “Headache”) were rated on a 100-mm visual analogue scale from 0 mm (not at all) to 100 mm (extremely). Participants were told to consider each line as the extreme spectrum of each emotion/sensation and to bisect the line appropriately to show how they were feeling at that specific moment. After the final session, participants were asked if they were aware of ever experiencing caffeine
withdrawal effects upon abstinence, and if so, if they felt that they had experienced caffeine withdrawal effects during any of the experimental sessions.

3.1.6. Procedure

Testing took place between 12:00 and 18:00 h, and participants attended each session at approximately the same time of day. The interval between any two sessions did not fall below 24 h or exceed 7 days. First, mood measures were taken and participants gave a saliva sample and signed a form confirming overnight abstinence. A capsule was then administered containing caffeine (250 mg; Sigma-Aldrich Co, Poole, UK) or placebo (arrowroot matched for the weight of caffeine; Supercooky, Leeds, UK) with water (100 ml). The gelatine capsules were Shionogi Qualicaps, size-00, Madrid, Spain. Participants were left alone for 30 min, then the experimenter returned to administer the tests. The tests for conditioned responses followed the same procedure, except that participants received placebo in each test environment. At the end of the sixth session, participants completed the post-experiment questionnaire and were debriefed and paid or awarded course credits for their time. This study was approved by the intramural Ethics Committee.

3.1.7. Analysis

Reaction times for SRT, CRT and MTS were split into reaction (RD) and movement (MD) durations: RD was the time taken to release the press pad following target presentation, and MD was the time taken to move the hand from the press pad to the screen. Scores below 100 ms were considered anticipatory and removed, and durations more than 3 standard deviations above an individual’s mean score were deemed outliers and removed (SRT: 1.6% and 1.4%; CRT: 1.5% and 1.2%; MTS 0% and 0.1% removed from RD and MD data respectively). No upper limit was applied to the MTS RD data. However, the MD response simply requires participants to move their hand from press pad to screen (15 cm), therefore an upper limit was included for MTS MD. When a MD score was removed for MTS, the corresponding RD score was also removed (total removed <0.01%). Outliers were not considered for RVIP as participants had a limited time to respond, after which the responses were deemed errors and removed by the software. Three types of errors were possible: missing a target (commission error); a correct response to a non-target (i.e. false alarm); or responding to a target too soon (i.e. an anticipatory response before all three targets were presented). The error types were analysed separately, but there were no differential effects, so the data for total errors are reported. Due to a technical problem, the task data for one experimental session for one participant was lost. Linear regression was used to estimate the missing data points [34]: each complete data set was used as the predictor in turn, and the regression equation yielding the best significant fit was used to estimate the missing data point.

Data for the conditioning trials were analysed by 2 × 2 repeated measures ANOVA with drug (caffeine, placebo) and trial (first or second within drug) as within-subjects factors. For MTS data an additional within-subjects factor of level (one, two, and three) was included. Mood measures were taken at three timepoints during the sessions and therefore an additional within-subjects factor of time (baseline, pre-task, post-task) was included for the mood data. Paired t-tests (CS+ compared with CS−) or 2-way ANOVA with conditioned stimulus type and block as factors were used to determine whether the responses to placebo in the CS+ context differed from responses to placebo in the CS− context.

3.2. Experiment 2: results

3.2.1. Simple reaction time (SRT)

3.2.1.1. Conditioning trials. There was a significant effect of drug for reaction duration \(F(1,11) = 5.00; P < 0.05\), with faster responding after caffeine than placebo. There was no main effect of trial \(F(1,11) = 0.56; P > 0.05\) nor a drug-by-time interaction \(F(1,11) = 0.92; P > 0.05\). There were no main effects of drug or trial and no significant interaction \(F(1,11) < 0.32; P > 0.05\) for movement duration (Table 2).

3.2.1.2. Conditioning tests. Participants were faster in the CS+ context than the CS− context for both reaction and movement durations. This effect was significant for movement duration \(t = −3.31, df = 11, P = 0.01\), but not for reaction duration \(t = −1.47, df = 11, P > 0.05\) (Table 2).

3.2.2. Choice reaction time (CRT)

3.2.2.1. Conditioning trials. There was a significant effect of drug for reaction duration \(F(1,11) = 5.32; P < 0.05\), and a borderline-significant effect for movement duration \(F(1,11) = 4.67; P = 0.05\), with faster responding after caffeine relative to placebo. There were no main effects of trial or significant interactions between trial and drug for either measure \(F(1,11) < 3.15; P > 0.05\) (Table 2).

3.2.2.2. Conditioning tests. Participants responded faster in the caffeine-paired context compared to the placebo-paired context. This difference was significant for movement duration \(t = −3.03, df = 11, P < 0.05\), but not for reaction duration \(t = −1.21, df = 11, P > 0.05\) (Table 2).

3.2.3. Rapid visual information processing (RVIP)

3.2.3.1. Conditioning tests. For reaction time, there were no main effects of drug \(F(1,11) = 0.30; P > 0.05\) or trial \(F(1,11) = 0.79; P > 0.05\) but there was a significant drug-by-trial interaction \(F(1,11) = 6.45; P < 0.05\). Responding was faster after caffeine relative to placebo on trial one only \(t = −2.30, df = 11, P < 0.05\). There were no main effects of drug \(F(1,11) = 0.11; P > 0.05\) or trial \(F(1,11) = 0.44; P > 0.05\) on errors but there was a significant drug-by-trial interaction \(F(1,11) = 8.16; P < 0.02\). There were significantly fewer errors after caffeine relative to placebo on trial one \(t = −3.29, df = 11, P < 0.001\).

3.2.3.2. Conditioning tests. There was no significant difference between the two contexts for reaction time \(t = 0.83, df = 11, P > 0.05\) or errors \(t = 0.54, df = 11, P > 0.05\).

3.2.4. Match-to-sample visual search (MTS)

3.2.4.1. Conditioning trials. There were no main effects of drug \(F(1,11) < 1.12; P > 0.05\) for any level of MTS reaction duration. For all levels, there was a reaction time decrease across trials which approached significance for level one \(F(1,11) = 4.34; P = 0.061\), and reached significance for levels two \(F(1,11) = 12.09; P < 0.01\) and three \(F(1,11) = 5.93; P < 0.037\). There were no significant drug-by-trial interactions

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Reaction times (ms) for the simple reaction time (SRT) and choice reaction time (CRT) tasks taken over the 2 conditioning trials and test session for both the CS+ and CS− contexts in Experiment 2. Reaction duration (RD) and movement duration (MD) are shown. Standard deviations in parentheses.</td>
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<tr>
<td>Conditioning (Training) Trial 1</td>
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<tr>
<td>SRT RD</td>
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<td>MD RD</td>
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<td>CRT RD</td>
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were no other significant effects for reaction durations, movement durations or errors \( [t < 1.81; df = 11, P > 0.05] \).

3.2.4.2. Conditioning test. There were no significant effects for reaction durations, movement durations or errors \( [t < 1.81; df = 11, P > 0.05] \).

3.2.5. Mood

3.2.5.1. Conditioning trials. There were significant increases in ratings of "headache" (0–30 min) after caffeine relative to decreases after placebo \( [F(1,11) = 13.07; P < 0.005] \). There were no other significant effects of drug or trial \( [F(1,11)< 3.16; P > 0.05] \). There was a near significant drug-by-trial interaction for "mental clarity" \( [F(1,11) = 3.60; P = 0.08] \), with increases after caffeine on trial one \( (M = 6.0, SD = 38.9) \) compared to a decrease after placebo \( (M = 41.5, SD = 22.9) \) \( [t = 1.39, df = 11, P > 0.05] \). In contrast, there was a decrease after caffeine \( (M = 6.5, SD = 26.0) \) and no change after placebo \( (M = 0.5, SD = 24.0) \) on trial two \( [t = -0.78, df = 11, P > 0.05] \). There were no other significant interactions \( [F(1,11)<2.40; P > 0.05] \).

3.2.5.2. Conditioning test. Despite no significant differences between conditions at the conditioning test \( [t < 1.80; df = 11; P > 0.05] \), there were trends that approached significance. There were substantial increases in "sleepiness" in the CS− context relative to decreases in the CS+ context \( [t = -1.98, df = 11, P = 0.07] \). Participants demonstrated greater increases in reported "mental clarity" in the context previously paired with caffeine \( (M = 28.0, SD = 29.1) \) compared to the context previously paired with placebo \( (M = 11.9, SD = 13.5) \) \( [t = 2.10, df = 11; P = 0.06] \).

3.2.6. Post-session questionnaires

At the end of each session, participants were asked to indicate what substance they believed they had received that day. Caffeine was identified as the substance administered on 58% of CS+ trials (i.e. when caffeine was administered) and on 42% of CS− trials (i.e. when placebo was administered). Pearson's chi-square analysis did not show a significant association between condition (i.e. whether or not caffeine was administered) and reported identification of caffeine (during conditioning trials) \( [\chi^2 = 0.44, df = 1; P > 0.05] \). Half of the participants (6 out of 12) reported ever experiencing caffeine withdrawal and/or craving upon abstinence. Of these, 3 reported experiencing craving at some point during the procedure.

3.2.7. Summary

Across the conditioning trials participants were faster after caffeine compared to placebo on all aspects of SRT and CRT reaction duration. Furthermore, there was evidence of caffeine-like facilitation in the CS+ context during the conditioning tests when placebo was administered in both contexts. In addition, "mental clarity" was increased and "sleepiness" was reduced in the CS+ context at test compared with the CS− context. Taken together, these results are consistent with caffeine's performance effects being conditioned to stimuli previously paired with caffeine administration, and they and are consistent with the outcome of Experiment 1.

4. Discussion

We present the first studies to examine explicitly whether drug-like facilitation of performance can be conditioned to previously-neutral stimuli. Zwyghuizen-Doorenbos et al. [42] reported the incidental appearance of a conditioned response to caffeine on a lengthy auditory vigilance task, but coffee was used as the vehicle for caffeine, so their results may have been influenced by the interactive effects of caffeine and expectancy. Expectancy effects based on knowledge of the effects of the drug being administered, or surprise effects resulting from detection of the absence of the US at test, cannot account for the results in Experiment 1 because very few of our participants thought that they had received caffeine, and none (in either experiment) detected a difference in the drinks, capsules or test procedure on the final day. Expectancy of caffeine should have induced caffeine-like effects during the conditioning tests in Experiment 2 if participants had learned to expect caffeine in a particular context. However, identification of caffeine in the CS+ and CS− contexts did not differ significantly, suggesting little basis for a learned expectancy effect. Furthermore, very few participants could identify the room in which they had received caffeine. Hence it appears that conditioned effects were obtained despite a lack of contingency awareness, in contrast to evidence that explicit knowledge of the CS-US contingency is necessary for the acquisition of a CR (e.g. [16,17]). It is plausible that participants may have acquired implicit knowledge of the CS-US contingency, which they were unable to report explicitly, however this could not be confirmed from the information available here, but may be a potential avenue for future research.

The conditioned effects were stronger in Experiment 1 than in Experiment 2, perhaps reflecting the fewer caffeine-paired trials experienced by participants in Experiment 2 and their additional exposure to placebo in a context that had some features in common with the caffeine-paired context. However, before a Pavlovian account can be accepted as the most likely interpretation of the results from the two experiments, it is necessary to exclude other, non-associative explanations. One possibility is that mere exposure to caffeine affected responding to the contextual cues such that participants in the paired group in Experiment 1 exhibited greater arousal. However, since caffeine was also administered to the placebo-paired participants after testing, an interpretation of the effect in terms of generalized sensitization is unlikely to account for the results. A second possibility is that both the US (caffeine) and CS (test context) elicited unconditioned arousing effects, and this commonality between CS and US predisposed a generalized arousal response to the test context when the participants came to be tested in the absence of caffeine (i.e. the effect was due to "pseudoconditioning"). Similarly though, by ensuring equal exposure of participants to the US as well as the CS, our designs minimized the likelihood of pseudoconditioning. Another non-conditioning explanation of the findings might be that differential habituation to the test environment was responsible (e.g. [4,5,15]). This suggests that a caffeine-induced failure to habituate to the arousing properties of the test environment may lead to faster response times on the conditioning tests. Importantly though, there was no significant change in reaction times over trials for the placebo groups. A decrease in arousal due to habituation would be expected to slow reaction time performance over sessions.

An alternative explanation for the results (albeit still based on conditioning) is that participants may have associated the negative effects of caffeine withdrawal with the unpaired context. Thus, the conditioned effects may have reflected conditioned withdrawal in the caffeine-unpaired context rather than conditioned "stimulant-like" effects in the caffeine-paired context. However, several observations make this interpretation unlikely. First, reaction time performance in the CS+ context did not deteriorate from the final conditioning trial to the conditioning test when caffeine was replaced with placebo. Thus, on the test of conditioning participants were demonstrating a caffeine-like level of performance in the CS+ context, supporting an interpretation of conditioned stimulant effects. Secondly, participants tended to show an improvement in reaction time performance in the CS− context from session one to two. Conditioning theory would predict that a CR would strengthen with additional CS-US pairings and therefore a conditioned withdrawal response would produce
weaker conditioning on session two compared to session one. Thirdly, the mood data did not show any evidence of caffeine withdrawal and the self-reported level of withdrawal during the experimental sessions was low (3 out of 12 participants), implying that withdrawal effects may have been absent in most participants, or at least too small to be explicitly identified. Surprisingly, there was a self-reported increase in headache after caffeine rather than after placebo, given that caffeine withdrawal is often associated with headache. However, as noted, the sample did not report suffering from marked caffeine withdrawal, which may have contributed to the lack of headache reduction after caffeine; the reason for caffeine-associated headache is unclear.

Finally, the nature of the study was such that only caffeine administration was explicitly paired with a test context. The withdrawal effects of caffeine have a slow onset and are persistent, suggesting that they would have been present outside of the experimental sessions. Thus, withdrawal effects would not have been discretely paired with a particular experimental cue, so conditioning theory would not predict strong conditioning in these circumstances.

Why contextual stimuli paired with caffeine should result in a drug-like response rather than a drug-opposite conditioned compensatory response is unclear, although the emergence of a compensatory response may be favoured in situations where the US results in a disruption of normal physiological functioning [28]. If the effects of caffeine in the present study are due to withdrawal-reversal in the drug-paired environment, then a drug-like CR may be predicted, since the US would be acting to restore normal physiological function rather than to disturb it. However, as noted above, participants tended not to report withdrawal, hence such withdrawal-reversal would have to apply selectively to psychological processes that are outside of conscious awareness.

The CS in the present study comprised several neutral cues that had not previously been paired with caffeine. In Experiment 1, these included the testing environment, the experimenter, the drink, and the drug administration procedure; in Experiment 2, the caffeine-associated cues were more specific to the test room, but still included several discrete visual and olfactory components. It would therefore be of interest to determine the relative salience of these various components of the CS in the generation of the CR, for example by changing the drink flavour or the experimenter on the final session, and/or the stimuli present in the test room.

The dose of caffeine used in the present studies is similar to that used in previous studies that have demonstrated improvements in various aspects of performance (e.g. [20,42]). The dose is relatively high, but similar (for example) to that found in a Tall Starbucks coffee. The aim of the present studies was not to make claims regarding the dose-related effects of caffeine, but to establish reliable drug-induced performance benefits so that these effects could be conditioned to a drug-associated context. A screening procedure was used in Experiment 2 to identify caffeine responders and so maximise the likelihood of eliciting unconditioned drug effects on performance. There is no reason to believe that similar effects would not be obtained in any situation where caffeine reliably enhances performance.

Decreased SRT after caffeine is consistent with previous findings (e.g. [20,33]) and suggests that caffeine was acting as a US to increase arousal and thereby improve SRT performance. It is also noteworthy that for both SRT and CRT in Experiment 2, performance was faster in the CS+ compared to the CS− context throughout testing. Reaction durations (SRT and CRT) were significantly faster during the conditioning trials (a significant effect on movement duration was obtained for CRT only), but the effects of the CS+ (relative to CS−) context during the conditioning test were strongest for the movement duration elements of the response. As previously mentioned, few studies have separated the reaction and movement components of response times. The results imply that the two aspects of reaction time responding may exhibit considerable overlap, and the measures may reflect underlying common processes that are not detectible on all occasions in one, single component score.

It has been argued that while caffeine produces reliable effects on response speed, its effects on higher cognitive functions such as memory and reasoning are less reliably elicited, especially in young participants (e.g. [18]), which might explain why caffeine's effects here were most consistent for reaction time. Two tasks that were insensitive to caffeine here but which have shown effects in the past are the semantic verification task and the RVIP (e.g. [13,33,39,40]). However, there are reports that caffeine does not reliably improve semantic verification (e.g. [36]). The discrepancy may relate to the amount of practice that participants receive before drug testing. In the present study, although participants completed the task on five occasions, each session was separated by at least two days and was preceded by only a brief practice block (10 trials). Similarly, Terry et al. [36] provided only limited practice before the critical tests; in contrast, participants in the Warburton [39] study were thoroughly familiarized with the task before testing. As suggested by the significant main effect of day, reaction time declined over testing. Had our participants received extended practice before each test, they may have developed more automatic response strategies, thus increasing the likelihood of observing a performance-enhancing effect of caffeine. As for the RVIP task, the 6 min duration may not have been long enough to reveal a significant influence; indeed, effects of caffeine are primarily reported using longer versions of the task [13,33,40].

In conclusion, the facilitatory effects of caffeine on reaction time can be elicited, in the absence of drug, by stimuli previously associated with drug administration. The conditioned responses can be revealed by different experimental designs, and are not easily explained in terms of sensitization, pseudoconditioning, impaired habituation processes or by explicit expectancy effects.

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References


