Psychopharmacology (1994) 115:383–388

Psychopharmacology

The expected drug and its expected effect interact to determine placebo responses to alcohol and caffeine

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Received: 8 September 1993 / Final version: 17 November 1993

Abstract. This study tested placebo responses in psychomotor performance when caffeine or alcohol was expected. Fifty male university students were assigned to one of four placebo groups or to a no-treatment control group. Two groups received placebo caffeine and two received placebo alcohol. Subjects performed 12 trials on a pursuit rotor task and performance was measured by the percent time on target. Then they received information about the expected drug effect on the task. One caffeine placebo group (C+) and one alcohol placebo group (A+) were led to expect enhanced performance on the task. The other caffeine placebo group (C–) and alcohol placebo group (A-) were led to expect impaired performance. Subjects subsequently performed 12 trials on the task. An interaction was obtained between the expected type of effect and the expected type of drug. The C+ group displayed superior performance compared to the C- group, and the reverse relationship was observed between the A+ and A– group. In addition, subjects led to expect alcohol-induced impairment (A–) performed better than subjects led to expect caffeine-induced impairment (C–). Subjects also reported greater motivation to resist impairment when they expected alcohol rather than caffeine. The research indicates that understanding and predicting placebo responses may require consideration of the drug that is expected as well as its expected effect.

Key words: Expectancy – Placebo – Alcohol – Caffeine – Psychomotor performance – Humans

Research on placebo responses to alcohol using a two-factor balanced placebo design has examined a range of social and psychomotor behaviors, including aggression (Lang et al. 1975), sexual arousal (Wilson and Lawson 1976), mirth (Vuchinich et al. 1979), social anxiety (Wilson and Abrams 1977), simulated driving performance (Rimm et al. 1982), pursuit rotor tracking (Connors and Maisto 1980), finger tapping, stylus monitoring, standing and walking steadiness (Williams et al. 1981) and complex perceptual motor performance (Vuchinich and Sobell 1978). Reviews of this research have concluded that the expectation of receiving alcohol evokes strong, reliable placebo responses in social and affective behavior but this expectancy has little effect on psychomotor performance (Marlatt and Rohsenow 1980; Hull and Bond 1986).

Marlatt and Rohsenow (1980) suggested that reliable placebo responses in social and affective behaviors occur because individuals share common cultural expectations about how alcohol affects these activities. Likewise, others have argued that experiments fail to observe placebo responses in motor performance because individuals may differ in the type and degree of effect that a moderate dose of alcohol is expected to have on these activities (Maisto et al. 1981). This seems plausible because experiments that have tested placebo responses to alcohol in motor behavior have used laboratory tasks that were unfamiliar to subjects (e.g., Williams et al. 1981; Rimm et al. 1982). As a result, subjects may have uncertain, or inconsistent expectancies about the type of effect that alcohol may exert on their task performance. This perspective implies that subjects must expect a common particular effect from a drug before a robust placebo response could be observed.

If subjects all expect the same specific effect from a drug, they should also display the same type of placebo response. No research has yet tested this hypothesis with respect to placebo responses to alcohol. However, some research using a psychomotor task to examine placebo responses to caffeine has obtained evidence consistent with this hypothesis (Fillmore and Vogel-Sprott 1992). These investigators manipulated the type of effect (impairment or enhancement) that caffeine was expected to have on subjects' performance of a psychomotor task. A

This work was supported in part by a Natural Sciences and Engineering Research Council of Canada Grant A8321 to the third author and by a grant from the Alcoholic Beverage Medical Research Foundation.

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group led to expect enhancement displayed significantly better performance than a group led to expect impairment, and the performance of a no-treatment group was intermediate. Thus it appeared that a placebo response was obtained in motor performance when caffeine was expected, and the type of placebo response was congruent with the expected type of effect on performance.

The foregoing research with caffeine placebos may imply that the expected effect of alcohol may also govern the response to an alcohol placebo. However, there are some reasons for suspecting that the placebo responses may not be congruent with the expected effect of alcohol. Unlike caffeine-induced impairment, society has many sanctions against alcohol-induced impairment. Punishments for impaired driving and information on accidents and hazardous consequences of behavior under alcohol are frequently reported in the media. If subjects entering an experiment have learned that alcohol impairment of motor behavior is usually associated with undesirable consequences, they may attempt to compensate for this impairment. Thus when alcohol is expected and a placebo is received, such compensation should result in improved performance. Furthermore, this compensation may result in performance that exceeds that displayed by subjects expecting alcohol to enhance performance. Therefore, the expected type of drug (caffeine or alcohol) and the expected effect (enhancement or impairment) may interact to determine the placebo response.

The present research was designed to test the interaction by administering caffeine placebos and alcohol placebos to different groups of subjects. The expectation of enhancement or impairment should yield a placebo response consistent with the expected effect of caffeine. However, when subjects expect alcohol, those expecting impairment should display greater improvement than those who expect enhancement. Also when impairment is expected, placebo responses to alcohol should reveal improved performance as compared to placebo responses to caffeine.

Materials and methods

Subjects

Ethical approval for the project was obtained from the University Office of Human Research. Male volunteers were asked to participate in a study of the effect of alcohol or caffeine on a motor skill. Subjects were recruited using posted advertisements on campus and through a "subject pool" of student volunteers. All students were of legal drinking age in the province of Ontario and their ages ranged between 19 and 34 years. Fifty subjects were randomly assigned to one of five groups (group $n = 10$) and were paid 6 dollars for their participation.

All subjects were asked to report any medication taken 24 h before the experiment, and to eat no food for 2 h prior to the experiment. In addition, the caffeine placebo groups were asked to abstain from caffeine for 2 h before the experiment and the alcohol groups were asked to abstain from alcohol for 24 h before the experiment. These restrictions aimed to enhance the belief that a drug would be received during the experiment.

Apparatus and materials

A computerized pursuit rotor (PR) tracking task requiring psychomotor coordination was used to measure subjects' performance. The task consisted of a computer and monitor on a table top, 75 cm above the floor. The subjects sat in a chair directly in front of a computer screen that displayed the task. Subjects were required to track an on-screen target (diameter = 1.3 cm) that moved at 23 rev/min clockwise around a rectangular track (14 cm X 11.5 cm) with inclined angles (length = 2.75 cm). To track the target, the subject controlled an on-screen circular sight (diameter = 1.3 cm) with cross-hairs by moving a computer mouse on the table top. The subject was required to keep the sight over the rotating target as long as possible during a trial. The computer measured the performance as the percentage of time on target (%TOT) during each trial and stored the trial scores on a computer disk.

To better ensure that subjects' expectancies solely influenced behavior, no feedback and no consequences were associated with performance. This was achieved by the computerized PR task. It controlled the entire testing of performance, provided no feedback, and allowed each subject to perform alone in the room thereby eliminating the influence of the presence of the experimenter. Therefore the experimenter was only in the test room with the subject to introduce the task. Previous research has shown that expectancy effects were reliably obtained whether or not the experimenter who explained the task was blind to the subjects' expectancy treatments (Fillmore and Vogel-Sprott 1992).

Coffee consumption history. Subjects in the caffeine placebo groups completed a questionnaire that provided a measure of their daily consumption of coffee (Kirsch and Weixel 1988). Subjects reported the number of cups drank in one typical day.

Alcohol consumption history. Subjects in the alcohol placebo groups completed a questionnaire concerning their drinking habits (Vogel-Sprott 1992). Subjects reported information that yielded four measures concerning their drinking behavior: frequency, dose, duration, and rate. Frequency referred to the number of drinking occasions per week. Dose referred to the amount of alcohol (ml absolute alcohol/kg) typically consumed during a single drinking occasion. Duration referred to the time span (hours) of a typical drinking occasion. Rate referred to the dose of alcohol typically consumed per hour during a drinking occasion, and was calculated by dividing the dose by the duration.

Pre-treatment expectancies. Subjects' a priori expectancies about the effect of caffeine or alcohol on their performance were also measured. After subjects were familiar with the task, but before any treatment was administered, caffeine placebo subjects were asked to predict how coffee would affect their performance on the PR task, using a 9-point scale ranging from 1 "largely impair", to 9 "largely enhance", and 5 indicating "no effect". Subjects were also asked to indicate how certain they were of their expectancy using a scale with 5-point increments ranging from 0 "no certainty whatsoever" to 100 "complete certainty". The placebo alcohol subjects completed identical scales with respect to alcohol effects.

Motivation to resist the drug effect. At the conclusion of the experiment but before debriefing, subjects rated the degree to which they felt that it was desirable to resist the effect of the drug. The desirability was rated on a scale ranging from 0 "not at all desirable" to 10 "extremely desirable". Caffeine placebo subjects provided ratings with respect to caffeine effects and alcohol placebo subjects provided ratings with respect to alcohol effects. It was predicted that subjects led to expect alcohol-induced impairment would report more desire to resist the drug effect than subjects led to expect caffeine-induced impairment.

Procedure

Consent forms were signed after explaining the general procedure of the experiment and answering any of the subjects' questions. Caffeine placebo groups completed the coffee consumption questionnaire. They were then weighed and told that they would receive a dose of caffeine based on their body weight in the form of coffee. Alcohol placebo groups completed the alcohol consumption questionnaire. They were then weighed and informed that they would receive a mixed drink containing a moderate dose of alcohol based on their body weight.

Baseline training. Baseline training on the PR consisted of twelve 50-s trials separated by 30-s rests. Trials were performed in three blocks of four trials each, with 2-min rests between blocks. Each subject was taken to a testing room that contained the PR task. After the task was explained to the subject, he performed a 50-s familiarization trial and the experimenter answered any questions that the subject had regarding task requirements. During the first block of trials the experimenter remained in the room to ensure that the task instructions had been understood and then left the subject alone to complete the baseline training. When baseline training was completed subjects returned to the waiting room.

Treatment

Caffeine placebo groups (C+ and C–). In the subject's presence, the experimenter boiled a kettle and added five heaping tablespoons of decaffeinated coffee into a plastic funnel with a paper coffee filter that drained into a coffee mug. Previous research indicated that subjects were most likely to believe that an apparent dose of this size actually contained caffeine (Kirsch and Weixel 1988). The decaffeinated coffee came from a coffee container placed in the subject's view bearing a label of a well-known brand of caffeinated coffee. The subject was told that a strong dose was being used in order to see the effects fairly quickly. Once the water boiled, the experimenter poured 150 ml water into the funnel containing the ground coffee. While the coffee was brewing the subject reported his pre-treatment expectancy concerning how the dose of coffee would affect his performance on the PR task. The beverage was served to the subject and he was allowed 5 min to drink the coffee.

After the beverage had been consumed, subjects received information from the experimenter that was designed to manipulate the expected effect of caffeine. Subjects in the C+ group were told, "Research has found that caffeine improves fine motor coordination. The drug improves fine motor coordination on tasks that involve the manipulation of small objects, like bead stringing. Our task measures this same skill, and the purpose of the study is to determine how caffeine produces this improvement." The experimenter provided the same information to subjects in the C- group, except they were told that caffeine impairs performance. Subjects then rested for 10 min during which they read magazines.

Alcohol placebo groups (A+ and A–). Before these subjects returned to the waiting room the experimenter lightly sprayed the room with an alcohol mist to produce a slight alcohol scent and add credibility to the placebo. In addition, flat tonic water representing alcohol was in a bottle of a well-known brand of vodka in clear view of the subject. In the presence of the subject, the experimenter mixed 100 ml flat tonic from the vodka bottle with 200 ml carbonated tonic mix in a clear measuring cup. Subjects were told that the drink contained a moderate amount of alcohol because alcohol placebos may be more credible when the dose expected is moderate rather than high (Knight et al. 1986; Martin et al. 1990).

After pouring the placebo mixture into two glasses, the experimenter used a lemon juice container to place a few drops of alcohol on each drink so that subjects would smell alcohol. Subjects were told that the experimenter added lemon juice to flavor the drink. The amount of alcohol was negligible (e.g. 2–3 ml) and produced no detectable blood alcohol level. After the beverage was prepared, the subject reported his pre-treatment expectancy concerning how the dose of alcohol would affect his PR performance. The beverage was then served, and the subject drank the contents of both glasses in 2 min. The alcohol placebo groups then received an expectancy treatment that was identical to that given to the caffeine placebo groups. Thus one group was led to expect that alcohol would improve their PR performance (A+) and the other group was led to expect impaired PR performance (A–). The subjects then rested for 10 min. Just prior to post-treatment testing on the PR task, the subject provided a breath sample for analysis by a breathalyser test. Although no blood alcohol level could be registered, the subject was told that his blood alcohol content was approximately 50 mg/100 ml and testing would commence. This was done to further confirm the belief that alcohol had been consumed.

Control group. A fifth group of subjects served as no-treatment controls. The only purpose of this group was to provide a measure of any change in performance owing to practice effects. Following baseline training, these subjects returned to the waiting room and were told that they had been assigned to a no-treatment condition and would receive no drug (caffeine or alcohol) during the experiment. These subjects remained in the waiting room for the equivalent amount of time as the treatment groups.

Post-treatment performance. All subjects subsequently entered the test room alone and performed 12 trials on the PR, comparable to those administered during baseline training (i.e., three blocks of four trials). Twelve trials were given in order to compare the results to those of Fillmore and Vogel-Sprott (1992), who found a robust expectancy effect on the initial three trials that weakened with time as practice trials continued. After the 12 trials, all subjects except the controls completed a scale (motivation to resist drug effect), and were then debriefed.

Manipulation checks. To ensure that subjects were completely free to report on the credibility of their beverage and the expectancy manipulation, a post-experimental inquiry was conducted after subjects were fully debriefed and paid.

Criterion measures and data analyses. During baseline training, performance on the PR task improved gradually over trials. Thus the mean of the three highest trials scores on the last block of baseline training trials was used to measure subjects' pre-treatment performance (i.e., mean%TOT). Because the effect of the expectancy manipulation should be most evident immediately upon performing the task (Fillmore and Vogel-Sprott 1992), the mean of the first three post-treatment trials was used to provide a measure of post-treatment performance (i.e., mean%TOT).

Treatment effects could be tested by analyzing post-treatment scores using the pre-treatment score as a covariate, or by analyzing the pre- post-treatment change in scores. Both analyses were performed and produced identical conclusions. Because the covariance analysis yields adjusted group means and the change score provides a direct, untransformed measure of the response to treatment, analyses based on change scores are reported.

Results

Manipulation checks

When asked to comment on the credibility of the placebo, all A group subjects reported they believed they had alcohol and all C group subjects reported they believed they had caffeine. In addition, all subjects reported that they believed the expectancy-related information provided by the experimenter, and were unaware that it was an experimental treatment.

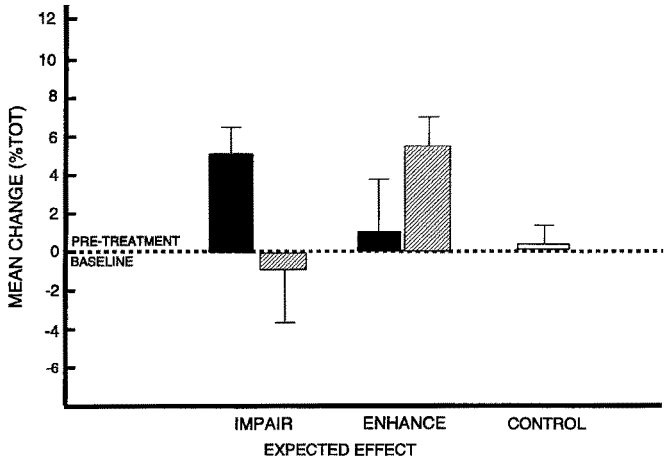

Fig. 1. Mean change in performance (%TOT) of five groups (group $n = 10$). *Vertical bars* indicate standard error of the mean. ■, alcohol; ▨, caffeine

Pre-treatment performance

A one-way analysis of variance of the pre-treatment performance scores revealed no significant main effect of group [$F(4, 45) = 1.655$, $P = 0.177$]. Thus the performance of the groups did not differ prior to any treatment. The mean (SD) score of all 50 subjects was 54.153%TOT (SD = 12.162).

Treatment effects

The change in%TOT from pre- to post-treatment was calculated by subtracting the pre-treatment performance score from the post-treatment performance score for each subject. Thus, a positive change indicated an improvement in performance and a negative change represented a deterioration in performance. A 2 (expected drug) X 2 (expected effect) variance analysis of the change scores revealed the predicted interaction between expected drug and expected effect [$F(1, 36) = 5.133$, $P = 0.030$]. No main effects of expected drug [$F(1, 36 = 0.103$, $P = 0.750$] or expected effect [$F(1, 36) = 0.465$, $P = 0.500$] were obtained. The mean change scores for the groups are illustrated in Fig. 1. Zero on the vertical axis represents subjects' pre-treatment performance level. A positive change indicates post-treatment improvement (i.e., an increase in%TOT), and a negative change indicates impaired post-treatment performance (i.e., a decrease in%TOT). Simple effect analyses using the mean square error of the interaction term tested the predicted differences between groups with one-tailed t tests. Consistent with the hypothesis, the results showed that the C+ subjects displayed improved performance (mean change = +5.47%TOT) compared to the mean change of −0.80%TOT, displayed by group C- [$t(36) = 2.08$, $P = 0.022$]. Also in accord with the hypothesis, the A- group, led to expect impairment, displayed greater improvement (mean change = +4.70%TOT) than A+ subjects who were led to expect enhancement (mean change = +1.33%TOT). Although the mean difference between groups A+ and A– did not attain significance [$t(36) = 1.12$, $P = 0.135$], the A- subjects displayed significantly more improvement than C- subjects, as predicted [$t(36) = 1.83$, $P = 0.038$]. Figure 1 also shows that in the absence of any treatment, the control group displayed essentially no change in performance.

In order to test the robustness of the placebo responses over the entire set of 12 post-treatment trials, each subject's pre-treatment performance score was subtracted from the mean of his 12 post-treatment scores. The predicted order of group means based on this measure of change was still evident (A– = 3.88; A+ = 2.76; C– = 1.92; C+ = 5.92). However, a 2 (expected effect) X 2 (expected drug) variance analysis revealed that the expected drug X expected effect interaction no longer attained significance [$F(1, 36) = 1.844$, $P = 0.183$]. Thus the effect appeared to weaken over time with successive trials. This trend was also observed under caffeine placebo treatments in the study by Fillmore and Vogel-Sprott (1992).

Motivation to resist the drug effect

The predicted interaction between the expected drug and the expected effect implied that subjects should find it more desirable to resist alcohol-induced impairment than caffeine-induced impairment. This was confirmed by a one-tailed t test of the desirability ratings of the A– and C– groups. The A– group reported more desirability to resist impairment than did the C– group [$t(18) = 2.123$, $P = 0.024$]. The mean (SD) ratings for groups A– and C– were 7.3 (2.9) and 4.5 (3.0), respectively.

The subjects expecting enhancement (i.e., groups A+ and C+) rated a very low desirability to resist this effect, with 12 of the 20 subjects (60%) reporting 0 (no desire to resist the drug effect). The overwhelming endorsement of this rating and the resulting lack of variability precluded a t test to compare the groups. The low mean ratings of both groups were similar (A+ = 1.8; C+ = 0.3), and the overall mean rating was 1.05. Thus there appeared to be little or no desire to resist enhanced performance induced by either alcohol or caffeine.

Pre-treatment expectancies

All subjects predicted how the drug that they were to receive would affect their task performance. The overall range of pre-treatment expectancies was very narrow. The modal response was 3 (moderately impair), and was chosen by 18 of the 40 subjects. The subjects' ratings were used to classify individuals into one of three categories in terms of their pre-treatment expectations of impairment (score < 5), or enhancement (score > 5), or of no effect (score = 5). Subjects' pre-treatment expectancies were independent of the type of drug expected ($\chi^2 = 4.433$, $df = 2$, $P = 0.109$). They were also independent of the expectancy treatment received by caffeine placebo sub-

jects ($\chi^2 = 4.000$, $df = 2$, $P = 0.135$), and by alcohol placebo subjects ($\chi^2 = 1.059$, $df = 2$, $P = 0.589$). Because all groups apparently held similar expectations concerning drug effects prior to treatment, these expectancies cannot account for the differences in post-treatment performance. The rating of pre-treatment expectancies showed greater certainty about the effects of alcohol (mean = 67.25, SD = 21.0) than caffeine (mean = 49.75, SD = 29.3).

Drug use

A two-tailed t test compared the reported number of cups of coffee typically consumed per day by C+ and C- groups. No significant difference was obtained [$t(18) = 0.600$, $P = 0.556$]. The mean number of cups of coffee reported by the two groups overall was 2.1 (SD = 2.6). Thus differences between the C groups in post-treatment performance cannot be attributed to differences in coffee consumption.

The drinking habits reported by the alcohol placebo groups provided measures of frequency, dose, duration and rate. Two subjects failed to provide complete information and this resulted in the loss of two subjects' data on measures of duration and rate as well as the loss of one subject's data on the frequency measure. Two-tailed t tests of these data revealed no significant differences between the A groups in drinking frequency [$t(17) = 1.381$, $P = 0.185$], dose [$t(18) = -0.617$, $P = 0.545$], duration [$t(16) = -0.250$, $P = 0.806$], or rate [$t(16) = -1.241$, $P = 0.232$]. Their mean frequency of drinking was 1.3 times per week (SD = 0.9), with an average dose per occasion of 1.0 ml/kg (SD = 0.8). Drinking occasions had a mean duration of 3.9 h (SD = 2.1), and the rate of drinking averaged 0.3 ml/kg per hour (SD = 0.1).

Discussion

This research investigated placebo responses to caffeine and to alcohol. An interaction between the expected drug and its expected effect on psychomotor performance was predicted and demonstrated. In accord with other research (Fillmore and Vogel-Sprott 1992), this study demonstrated that subjects who received a caffeine placebo and expected enhancement (C+) displayed improved performance compared to C– subjects who expected impairment from caffeine. In addition, the present study showed that a reverse relationship was displayed by the two alcohol placebo groups. The A– group was led to expect impairment and displayed a greater improvement in performance as compared to A+ subjects who expected enhancement. In accord with the hypothesis, A– subjects displayed better performance than the C– subjects, and also reported more desire to counteract alcohol-induced impairment than caffeine-induced impairment.

The research included an examination of pre-treatment performance, pre-treatment expectancies, and history of drug use, to determine if these characteristics could account for the group differences. None of these factors accounted for the findings. Even though the groups did not differ in prior drug use, it is possible that individual differences in drug use *within* a group may influence the efficacy of the expectancy manipulation. Similarly, within-group variance in the strength or certainty of pre-treatment expectancies may affect the degree to which expectancies may be altered. Further research involving larger samples would be required to test these hypotheses.

Subjects' expectancies were manipulated by information provided by an experimenter. Thus it might be thought that experimenter demand influenced the results. However, demand characteristics are not a viable explanation because the responses of subjects expecting alcohol to impair performance were opposite to this expectancy, and showed improvement. In addition, subjects performed the task alone in a room with no environmental or social consequences for displaying either impaired or improved performance. Yet, despite the absence of any consequence for behavior, subjects reported greater motivation to resist alcohol-induced impairment than caffeine-induced impairment. These observations are new, and suggest that the desirability of resisting drug-induced impairment depends upon the drug under consideration. Further research is required to assess the influence of the desire to compensate for drug effects.

This research did not investigate the origins of judgements about favorable or unfavorable consequences of impairment by caffeine or alcohol. However, it seems possible that they were acquired from society, where information about the adverse consequences of alcohol-induced psychomotor impairment is prevalent, and the consequence of caffeine-induced impairment is virtually ignored. Differences in the outcomes associated with impairment from alcohol and from caffeine may account for the differences in placebo responses shown in the present research. Such an interpretation would be consistent with the findings of other studies that have manipulated rewards for performance under alcohol (Vogel-Sprott and Sdao-Jarvie 1989; Vogel-Sprott 1992). That research has shown that the response to alcohol depends upon the desirability of its outcome: when impairment is undesirable because compensating yields a reward, compensatory performance is displayed.

The results of the present research have important implications for understanding factors that affect responses to placebo and possibly to drugs themselves. Studies designed to evaluate the joint and separate influence of expecting a drug and its pharmacological effect have seldom considered subjects' beliefs regarding the expected effect of the drug, or the desirability of displaying the effect. This research demonstrates that these factors are important determinants of a placebo response. Consideration of these factors may contribute to understanding the mechanisms that underlie a placebo response and to predicting its occurrence.

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