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The Effects of Caffeine and Directed Attention on Acoustic Startle Habituation

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SCHICATANO, E. H. AND T. D. BLUMENTHAL. *The effects of caffeine and directed attention on acoustic startle habituation.* PHARMACOL BIOCHEM BEHAV **59**(1) 145–150, 1998.—The present experiment tested the effects of caffeine on acoustic startle habituation during different attention tasks in which subjects either (a) attended to the acoustic startle stimulus (auditory attention; $n = 9$) (b) attended to a visual search task during presentation of acoustic startle stimuli (visual attention; $n = 10$), or (c) were given no specific instructions during acoustic startle testing (no attention; $n = 9$). Startle eyeblink responses were measured after subjects received either caffeine (1 mg/kg) or placebo. Caffeine significantly delayed response habituation in the no attention group and in the auditory attention group, but had no effect on habituation in the visual attention group. These data show that startle habituation can occur with minimal attention being directed to the acoustic startle stimulus, and that visual attention cancels the effects of caffeine on startle habituation. © 1998 Elsevier Science Inc.

Caffeine Startle Habituation Humans Attention Brainstem Reflex

THE acoustic startle reflex is a brainstem reflex characterized by contraction of the facial and skeletal muscles elicited by a sudden and intense acoustic stimulus. This simple brainstem reflex is sensitive to its stimulus parameters (3,4), modulated by pharmacological agents (6,11), and affected by task variables such as attention (14,23). With regard to the latter, a number of studies have shown that the startle eyeblink response is facilitated when attention is directed to the startle stimulus, or to the same modality as the startle stimulus, compared to when attention is not engaged (2,15). Likewise, when attention is directed away from the acoustic startle stimulus modality, the startle reflex is decreased. These findings demonstrate that the startle reflex can be modulated by cognitive (attentional) control. The nature and localization of this type of startle modulation has not been elucidated.

The startle reflex has been used to study habituation and sensitization (7,9,15). Habituation of the startle reflex has been observed across many species (7). Leaton, Cassella, and Borszcz (16) have observed acoustic startle habituation in decerebrate rats, suggesting that minimal cortical processes (if any) are needed for the development of habituation. However, the question of whether habituation is modified based on what an organism is paying attention to has not been examined. For instance, by directing a subject's attention towards a visual stimulus during acoustic startle stimulus testing, we investigated whether habituation occurred in a situation in which processing of the acoustic startle stimulus was minimized.

Caffeine has been shown to improve performance in vigilance tasks and to enhance attention (19,25–27). Smith et al. (25,26) reported that caffeine delayed habituation of the skin conductance response (SCR) to auditory stimuli. In other studies, caffeine delayed habituation of the acoustic startle reflex in a dose-dependent fashion (21). Because a 2 mg/kg dose of caffeine delayed startle habituation, the present experiment tested the effects of a 1 mg/kg dose of caffeine on startle habituation to investigate the range of caffeine's effects.

The effects of caffeine on startle show that caffeine alters the way in which startle typically changes to repeated startle stimuli (i.e., startle plasticity). Because caffeine has effects on arousal and attention, the present study was also designed to test the interaction between caffeine and different attentional tasks on the startle reflex. We assessed whether caffeine delayed habituation in three different attention task conditions in which subjects either 1) attended to the acoustic startle stimulus, 2) attended to a visual search task during acoustic startle stimulus presentation, or 3) were given no attention task to perform. In all three task conditions, the acoustic startle reflex was used as the behavioral measure. Because caf-

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feine increases arousal and attention, we predicted that the effects of caffeine on startle habituation would be weakened when subjects attended away from the startle stimulus, i.e., toward a visual search task.

METHOD

Subjects

Subjects were 30 low caffeine users (average age = 19 years, 3 months; range = 18.1–21.4 yrs; SD = 1.1 years) chosen from an undergraduate Introductory Psychology class. Subjects were chosen based on their responses to a 34-item questionnaire indicating low or no caffeine intake. Subjects indicated the number of times that they consumed items such as brewed coffee, instant coffee, instant tea, noncaffeine free sodas, etc. When considering the wide range of caffeine-containing substances, these subjects reported consuming the equivalent of one or two caffeinated sodas per week at most. No subject reported ingesting on average more than two sodas per week. Likewise, each subject consumed on average at least one soda during the week. Subjects who drank coffee were excluded from the study. Subjects who smoked, had any hearing loss, or were unable to consume caffeine for health reasons were also excluded from the study. Subjects were randomly assigned to one of three attention task groups (see below). Subjects received either caffeine (1 mg/kg) or placebo solutions on separate days, with at least one week separating testing sessions.

Stimuli

Startle stimuli were 95 dB (re: 20 μPa; A scale) broadband noise (20 Hz to 20 kHz), with a duration of 50 ms and a rise time of 0.1 ms (4). The interstimulus interval (ISI) randomly varied from 15–25 s (average ISI = 20 s). In both the caffeine and placebo conditions, subjects were presented with 30 trials of startle stimuli, similar to past caffeine–startle experiments (20,21).

Materials

The caffeine solutions consisted of pure anhydrous caffeine (Carolina Biological Supply) dissolved in flat tonic water and mixed with Tang orange drink. The caffeine dose was 1 mg/kg for each subject, approximately 60–80 mg per subject. The placebo solution consisted of flat tonic water mixed with Tang orange drink. Because flat tonic water has a bitter taste, the placebo and caffeine drinks tasted similar. Fluid volume per body weight was identical for both placebo and drug solutions. Each subject drank approximately 60 ml of fluid (solution plus orange drink) containing either caffeine or placebo.

Apparatus

Acoustic stimuli were produced by a Coulbourn S81-02 noise generator and a Coulbourn S81-06 signal generator, gated through a Coulbourn S84-04 electronic switch, a Coulbourn S82-24 audio-mixer amplifier, and presented to the subjects through Telephonics TDH-49P stereo headphones. Stimulus intensity was calibrated by presenting a continuous stimulus from the headphones to a Quest Electronics 215 sound level meter (A scale) fitted with a headphone coupler.

Reflex eyeblink responses were assessed from periorbital EMG activity collected using miniature Sensormedics biopotential electrodes (Ag/AgCl) filled with conducting paste. The EMG signal was amplified by a Coulbourn S75-01 high-gain bioamplifier/coupler with filters passing 90–250 Hz. The amplifier output was sent to a Coulbourn S76-01 contour-following-integrator with a 10-ms time constant. The output of the integrator was digitally sampled by a MacPacq MP10 interface every ms for 1000 ms after startle stimulus onset. Responses were viewed and stored on a Macintosh SE microcomputer.

Procedure

The use of students from an Introductory Psychology class was approved by the Wake Forest University Institutional Review Board. Subjects were contacted by the experimenter and asked to refrain from consuming caffeine in any form for 12 h prior to each experimental session. Subjects were told that they would be presented with "startle noises" during the session, and that they might receive caffeine at least once during the experiment. Subjects were allowed to consume their normal amount of caffeine during the week between sessions. When the subject arrived, he/she was first weighed, then asked to read and sign an informed consent form and to fill out a background questionnaire that reestablished whether the subject had any health reasons for not taking caffeine. On this questionnaire, subjects also reported not taking any caffeine within the last 24 h. Subjects were also told that the purpose of the study was to test the effects of caffeine on the startle blink reflex.

The subject received an oral dose of either the caffeine or placebo solution, which was given in a double-blind fashion. Caffeine is rapidly absorbed, reaching maximal plasma levels within about 30 min following oral administration in humans (12). Twenty minutes after ingestion of the solution, the experimenter began the electrode preparation procedure. The experimenter cleaned the area just below the subject's left eye with a cotton swab dipped in rubbing alcohol, and attached two electrodes, one below the center of the eye, and the other immediately lateral to the first, as close to the orbital ridge as possible. A ground electrode was placed on the medial surface of the left forearm. Subjects were seated in a chair, were given the appropriate attention task instructions, and were presented with the first acoustic stimulus via headphones 30 min after ingesting the mixed solution. Each subject was exposed to 30 broad-band noise trials. The entire testing session lasted approximately 15 min.

Attention Tasks

Subjects were placed in one of three attention task groups; auditory attention, visual attention, or no attention (control). All subjects were presented with 30 identical startle noise stimuli. In the auditory attention group, subjects kept a running count of acoustic startle stimuli that were presented. After every 9th stimulus, they verbally reported "the number of noises that were not as loud as the first noise." The main point of the auditory attention task was to insure that subjects were attending to the acoustic startle stimulus. In the visual attention group, subjects sat in a chair with a tray table placed directly in front of them. On this table was a sheet of paper containing the word search task. Subjects searched for four-letter strings of nonwords (e.g., OBEX, MPTP) in a letter matrix (12 rows of 75 letters), kept a running count of each word that they found, and verbally reported this number following the search for each individual word. During this search, subjects were presented with startle stimuli. The main point of the visual attention task was to focus attention on a visual search task, completely removed from the acoustic startle stimulus.

In the no attention (control) group, subjects were given no specific instructions except to sit quietly during stimulus presentation. The room was soundproofed and the background noise level was <30 dB.

Two subjects were deleted from the experiment, one from the auditory attention group, and one from the no attention group. One subject reported taking an antihistamine prior to the second testing session, and was unable to participate in another session. An equipment malfunction during the data acquisition procedure prevented the use of the second subject. A final total of nine subjects were in the auditory attention group (four females, five males), 10 subjects were in the visual attention group (five females, five males), and nine subjects were in the no attention group (three females, six males). Subjects participated in two sessions, with one-half of the subjects receiving the 1 mg/kg dose of caffeine first, and one-half of the subjects receiving the placebo first in the visual attention group, five subjects received caffeine first in the auditory attention group, and five subjects received placebo first in the no attention group. The alternate drug condition was given in the second session.

Data Analysis

The dependent variables included response amplitude, latency, and probability, measured by EMG recordings from the orbicularis oculi muscle below the left eye. Response amplitude was measured as the difference between response onset and peak in arbitrary units, response latency was measured as the time from stimulus onset to response onset, and response probability was measured as the percentage of trials on which a response was recorded, given that a response could have been recorded. When scoring data, only responses beginning within 20–100 ms after startle stimulus onset were included, to eliminate nonreflexive responses from the data.

The startle response amplitudes, latencies, and probabilities for each subject were first condensed into 10 blocks of three consecutive trials each. Trial block and drug condition (placebo or caffeine) were within-subject variables, and attention task was a between-subjects variable. Response amplitudes in the first trial block were compared in the drug conditions and the attention task groups (using a three-way ANOVA; $3 \times 2 \times 2$) to determine differences in initial startle reactivity. Habituation was assessed by an orthogonal trend analysis across trial blocks (BMDP2V). Habituation was defined as the first trial block where response amplitude was significantly different from trial block 1. A one-way ANOVA assessed differences between responding on trial block 1 and subsequent trial blocks. A one-way ANOVA was also used to test when habituation reached asymptote in the different conditions. Peak response decrement was considered to occur on the last trial block after which no later trial blocks were significantly different. A subsequent orthogonal trend analysis included only trial blocks up to the point at which habituation reached asymptote. This subsequent analysis provided a more sensitive comparison of the habituation curves by excluding later trials where the curves were asymptotic. Post hoc tests comparing individual trial blocks were analyzed in a one-way ANOVA (BMDP4V).

To assess differences in habituation (post hoc) between the attention task groups as a function of drug condition, proportional response amplitudes were analyzed in an orthogonal trend analysis. In this analysis, response amplitudes on trial block 1 for each of the three attention task groups were assigned a value of 100. Proportional values on subsequent trial blocks were determined by dividing response amplitude on later trial blocks by response amplitude on trial block 1 within subjects. Using percent response amplitudes instead of absolute amplitudes ensured that differences in the magnitude of response decrement between the attention task groups was not due to the observed differences in initial values between these groups, nor to intersubject differences that might be due to factors not related to the independent variables of the present study.

RESULTS

All subjects correctly identified the number of noises presented during the auditory attention task.

Response Amplitude

A significant main effect of attention task was found when analyzing response amplitude on the first trial block, $F(2, 25) = 5.77$, $p < 0.01$. Response amplitude on the first trial block did not differ between the auditory attention group and the no attention group, but significantly smaller responses were observed in the visual attention group compared to both the no attention group, $F(1, 17) = 11.42$, $p < 0.005$, and the auditory attention group, $F(1, 17) = 7.89$, $p < 0.01$. No differences between caffeine and placebo were found on the first trial block, showing that caffeine did not affect initial startle reactivity. A significant main effect of attention task was found for the entire session, $F(2, 25) = 4.80$, $p < 0.01$ (Table 1). Subsequent pairwise comparisons between each of the three tasks indicated that response amplitude did not differ between the auditory attention group and the no attention group. However, significantly smaller responses were observed in the visual attention group compared to both the no attention group, $F(1, 17) = 9{,}11$, $p < 0.005$, and the auditory attention group, $F(1, 17) = 7.22$, $p < 0.01$ (Table 1).

For response amplitude, significant linear, $F(2, 25) = 232.27$, $p < 0.0001$, and quadratic, $F(2, 25) = 79.78$, $p < 0.0001$, trial block effects were observed over 10 trial blocks. These trial block effects did not interact with attention task or drug conditions over 10 trial blocks. Attention task and drug condition also did not interact.

TABLE 1

AVERAGE STARTLE RESPONSE AMPLITUDE, LATENCY, AND PROBABILITY AS A FUNCTION OF THREE ATTENTION TASKS

Attention Task		Amplitude (arb. units) Mean ± SD	Latency (ms)	Prob. (%)
No Attention	Mean ± SD	49 ± 13.8	44 ± 1.4	97 ± 2
	F-Value	9.1	6.0, 8.1	6.2
	Diff. From	V	V, A*	V
Auditory Attention	Mean ± SD	64 ± 10.8	41 ± 1.3	96 ± 2
	F-Value	7.2	8.1, 22.0	4.4
	Diff. From	V	N, V	V
Visual Attention	Mean ± SD	17 ± 6.4	52 ± 1.8	73 ± 7
	F-Value	9.1, 7.2	6.0, 22.0	6.2, 4.4
	Diff. From	N, A	N, A	N, A

Averages are from the entire session and during the placebo condition only.

N = Significantly different than "no attention" group.

A = Significantly different than "auditory attention" group.

V = Significantly different than "visual attention" group.

All *F*-values are $F(1, 17)$, $p < 0.05$, except where noted. *$F(1, 16)$.

Post hoc ANOVAs indicated no significant decreases in response amplitude following trial block 5 in the no attention group, following trial block 5 in the auditory attention group, and following trial block 3 in the visual attention group. Because habituation reached asymptote on or before trial block 5 in all attention task groups, a more sensitive trend analysis was conducted to include only the first 5 trial blocks.

A significant quadratic trial block × drug × attention task effect was found over the first five trial blocks, $F(2, 25) = 3.32$, $p < 0.05$ (Fig. 1). No significant differences in habituation between the attention task groups were seen following placebo administration. Following caffeine administration, a significant quadratic trial block × attention task effect was revealed over the first five trial blocks, $F(2, 25) = 3.99$, $p < 0.05$. Post hoc ANOVAs compared percent response amplitude on trial block 1 to subsequent trial blocks to determine onset of habituation. To examine the effects of caffeine vs. the effects of placebo within each attention task group, differences in onset of habituation between the caffeine and placebo conditions were compared. In the no attention group, when given placebo, significant habituation was observed on trial block 2, $F(1, 8) = 5.17$, $p < 0.05$, whereas, when given caffeine, significant habituation was not observed until trial block 4, $F(1, 8) = 9.47$, $p < 0.01$ (Figs. 1 and 2). In the auditory attention group, when given placebo, significant habituation was found on trial block 2, $F(1, 8) = 5.17$, $p < 0.05$, whereas, when given caffeine, significant habituation was not observed until trial block 5, $F(1, 8) = 18.37$, $p < 0.01$. In the visual attention group, significant habituation was found on trial block 2 for both the placebo, $F(1, 9) = 4.71$, $p < 0.05$, and caffeine conditions, $F(1, 9) = 5.79$, $p < 0.05$, illustrating no difference in habituation onset as a function of drug in the visual attention group. Taken together, these data demonstrate that habituation onset occurred later in the caffeine condition compared to the placebo condition, but only in the no attention and auditory attention groups.

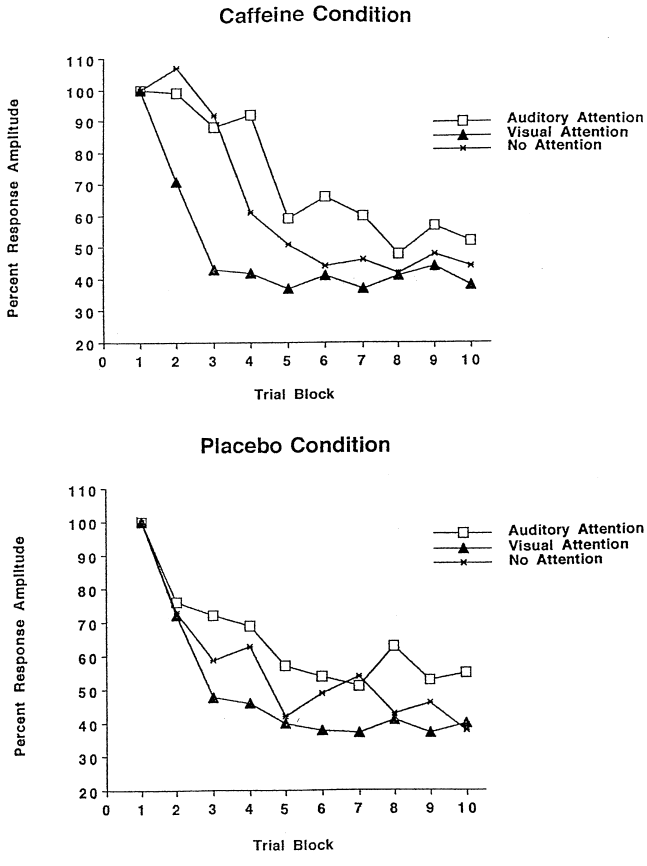

FIG. 1. The effects of directed attention in the caffeine and placebo conditions as a function of trial blocks. Percent startle response amplitude over 10 trial blocks was illustrated, with each trial block consisting of three trials.

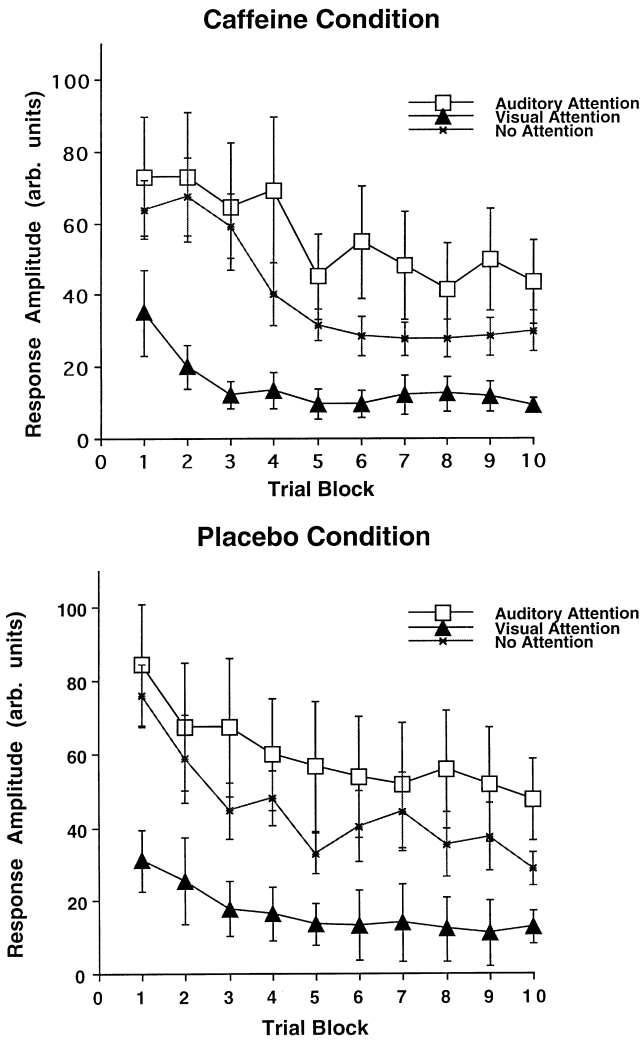

FIG. 2. The effects of directed attention in the caffeine and placebo conditions as a function of trial blocks. Startle response amplitude in arbitrary units over 10 trial blocks was illustrated, with each block consisting of three trials.

Response Latency

No difference between attention tasks or between drug conditions were found on the first trial block for response latency. A significant main effect of attention task was observed for response latency over 10 trial blocks $F(2, 25) = 12.90$, $p < 0.001$. Response latency was significantly faster in the auditory attention group compared to the visual attention $F(1, 17) = 21.97$, $p < 0.005$, and no attention $F(1, 16) = 8.13$, $p < 0.01$, groups (Table 1). Response latency was also significantly

faster in the no attention group compared to the visual attention group, $F(1, 17) = 6.00$, $p < 0.05$. No significant trial block effects or interactions between trial block, drug, or task were found for response latency over 10 or 5 trial blocks.

Response Probability

No difference between attention tasks or between drug conditions were found on the first trial block for response probability. A significant main effect of attention task was observed for response probability over 10 trial blocks $F(2, 25) = 4.69$, $p < 0.01$. Response probability was greater in both the auditory attention group, $F(1, 17) = 4.40$, $p < 0.05$, and the no attention group, $F(1, 17) = 6.24$, $p < 0.05$, than in the visual attention group (Table 1). The auditory attention and no attention groups did not differ with regard to response probability.

A significant linear trial block effect was found for response probability over 10 trial blocks $F(2, 25) = 8.41$, $p < 0.01$, demonstrating that response probability habituated. No interactions between trial block, drug, or task were found for response probability over 10 or 5 trial blocks.

DISCUSSION

In the present experiment, directing attention to a visual search task during presentation of an acoustic startle stimulus resulted in a decrease in startle amplitude and probability and an increase in startle latency. These findings support previous research by showing that the attentional modulation of startle is sensitive to the attended modality, such that the startle reflex is larger when the modality of the startle stimulus and attended stimulus match compared to when they do not match (2,15). Because the startle reflex does not require attention or controlled processing for its elicitation (1,18), these effects of attention on startle suggest the existence of a top-down mechanism of early information processing (28). It has been reported that state variables such as fear and anxiety modulate startle via structures extrinsic to the startle brainstem circuit (e.g., the amygdala) (8). The neural systems underlying the effects of attention on startle have not been identified.

The question might be raised as to whether or not subjects actually attended to the appropriate stimulus in the designated task conditions. Following the auditory attention task, all subjects correctly identified (verbally) the number of stimuli presented. Furthermore, the decrease in response amplitude and probability and the increase in response latency seen during the visual attention task indicated that subjects were attending to the visual search task, i.e., away from the startle stimulus (Table 1).

Startle habituation has been observed in decerebrate animals (16), suggesting that habituation is a process, probably occurring in the brainstem, that requires little or no higher cortical processing. In the present study, habituation was defined as the point at which the startle reflex significantly decreased in size compared to an initial level of responding. In the present experiment, acoustic startle habituation was evident in the visual attention group, i.e., when subjects were attending away from the startle stimulus (Figs. 1 and 2). Therefore, it can be concluded that minimal processing of the habituating stimulus is necessary for acoustic startle habituation to occur.

These findings do not delineate between the two distinct forms of behavioral plasticity, habituation and sensitization (17,22). That is, the change in reactivity to repetitive stimulation observed here may have been the product of either of these two opposing neural processes (13). While both processes may have been affected by the experimental procedures, an investigation of the functional balance between them is beyond the scope of this article.

The present data replicate and extend previous findings from our laboratory, by showing that a 1 mg/kg dose of caffeine (approximately 80–100 mg) delayed acoustic startle habituation. Previous studies demonstrated that caffeine at 2 and 4 mg/kg doses delays startle habituation, whereas a 6 mg/kg dose has no effect (20,21). Those previous experiments used a startle testing procedure that was similar to the one used in the no attention task in the present experiment. The delay of habituation produced by a low dose of caffeine (1 mg/kg) in the present study illustrates the sensitivity of startle habituation to the effects of caffeine. Also, this dose of caffeine is closer to that which is typically consumed in a single cup of coffee (12). The lower dose limit of caffeine's effects on startle has not been determined. Further studies might use even smaller caffeine doses than presently employed. Although a 1 mg/kg dose of caffeine did not affect habituation during the visual search task, testing of a higher dose of caffeine in a visual attention condition would help to determine whether this lack of effect was partially due to a weak caffeine dose used in the present study.

Also, in the visual search task, response amplitudes started at a significantly lower initial level compared to the other tasks. Thus, it is possible that a low initial response amplitude value precluded caffeine from having any effect on habituation. However, the fact that habituation in the visual attention group reached 40% of the initial response amplitude (this decrease was in the range found in the other two groups) demonstrates that the extent of habituation in itself was not altered because of an initial low response amplitude.

The present findings also show that caffeine delayed startle habituation when subjects attended to the startle stimulus, but not when attention was directed away from the startle stimulus. The fact that caffeine no longer delayed habituation when subjects were attending away from the acoustic startle stimulus suggests that some degree of attention to the startle stimulus is necessary for caffeine to produce its effects. However, because no differences in habituation were observed between the auditory attention and no attention groups during placebo sessions, the mere presentation of startle stimuli may cause attention to be directed to that modality. In this case, disrupting attention via a visual task removes the attention paid to the startle stimulus, and removes the delay of habituation caused by caffeine.

In the present study, caffeine did not affect initial startle reflex amplitude, latency, or probability in any of the three attention task groups, showing that the effects of caffeine were specific to changes in the characteristics of the response that occurs over trials. It seems unlikely that these effects of caffeine were due solely to an attentional mechanism. Caffeine is known to produce an elevation in arousal (19). Smith and colleagues (24,25) have reported that a caffeine-induced increase in SCR was due to arousal. Similarly, Bruce, Scott, Lader, and Marks (5) and Dimpfel, Schober, and Spuler (10) showed that caffeine's effects on EEG could be attributed to arousal. Thus, one cannot rule out the contribution of arousal to caffeine's effects on startle habituation. Tharion et al. (27) showed that, when attending to a visual task, auditory evoked potentials were decreased more when subjects were given caffeine compared to when given placebo. Visual vigilance performance was enhanced by caffeine, suggesting that caffeine increased attention to the visual task. The present experiment demonstrated an interaction between caffeine and attention in the habituation of the startle eyeblink reflex.

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