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The Effects of Different Doses of Caffeine on Habituation of the Human Acoustic Startle Reflex

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SCHICATANO, E. J. AND T. D. BLUMENTHAL. *The effects of different doses of caffeine on habituation of the human acoustic startle reflex.* PHARMACOL BIOCHEM BEHAV 52(1) 231-236, 1995.—Research in this laboratory showed that caffeine (4 mg/kg) delays habituation of the acoustic startle reflex in humans. The present study examined the effects of 2- and 6-mg/kg doses of caffeine on acoustic startle habituation in moderate-high and low caffeine users. Eyeblink responses to 30 trials of 85-dB noise stimuli were measured beginning 30 min after oral ingestion of either placebo or 2 or 6 mg/kg of caffeine. The 2-mg/kg dose of caffeine delayed startle habituation in both moderate-high and low caffeine users. The 6-mg/kg dose produced no differential effects on startle responding from placebo. In moderate-high users, following habituation, startle responding was smaller in the placebo condition compared to both caffeine conditions. In low users there were no differences in posthabituation responding between doses, suggesting that this dose effect is dependent on a history of chronic caffeine usage.

Caffeine Startle Habituation Humans Arousal Brainstem Reflex

CAFFEINE is a widely used psychoactive substance (21) and has been studied using a variety of cognitive/behavioral tasks (12,14,15). In humans, caffeine has been shown to improve vigilance and performance on cognitive tasks (12,14), enhance sustained visual attention (23), and reverse the negative effects of sleep deprivation on mood and alertness (16). It has been hypothesized that caffeine interacts with a multitude of variables, such as user level, type of environment (novel vs. boring), and dose, in producing some of these cognitive/behavioral effects (19).

Using psychophysiologic measures in humans, several researchers have reported that caffeine increases skin conductance in a dose-related manner (5,6,19). Davidson et al. (6) and Smith et al. (19) reported that caffeine enhances physiologic responses to redundant external stimuli (i.e., caffeine reduces habituation of the skin conductance response). Specifically, in both moderate-high and low caffeine users, caffeine slowed habituation of skin conductance to auditory stimuli (19). These results are similar to those of Wolpaw and Penry (24), who found that caffeine prevented a decrease in N1P2 amplitudes to auditory-evoked responses caused by habituation. Using the acoustic startle paradigm in humans, Schicatano and Blumenthal (17) showed that caffeine delays habituation of the acoustic startle reflex without affecting the size of the initial response. Together, these findings indicate that caffeine produces persistent responding to redundant stimulation (i.e., caffeine delays habituation).

The reported effects of caffeine on psychophysiologic measures such as the skin conductance response and evoked potentials suggest that caffeine may increase arousal (6,19,24). It is therefore possible that the effects of a 4-mg/kg dose of caffeine on startle habituation may be due to increases in arousal (17). If caffeine modulates startle habituation by increasing arousal, then varying the caffeine dose should produce differential effects on startle. Specifically, caffeine dose effects should resemble an inverted U-shaped relationship that is commonly reported in the arousal literature. To test this theory, the present experiment assessed the effects of placebo and 2- and 6-mg/kg doses of caffeine on startle. In the case of startle habituation, a high dose of caffeine would produce

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effects similar to that of placebo. These doses were used as linearly related low and high end points to the 4-mg/kg caffeine dose that was previously shown to modulate startle habituation (17). Because the present experiment used human subjects, an 8-mg/kg dose was not employed, because of the increased possibility of an aversive reaction in subjects not accustomed to ingesting caffeine.

Several studies have examined the psychophysiologic effects of caffeine given to persons with a history of moderate-high caffeine intake. For instance, Smith and co-workers (18,19) showed that the slowing of habituation of the skin conductance response produced by caffeine was more pronounced in moderate-high users of caffeine than in low users. Schicatano and Blumenthal (17) demonstrated that the delay of habituation to acoustic startle stimuli when given a 4-mg/kg dose of caffeine was similar in both moderate-high and low users. It is plausible that lowering the dose of caffeine (<4 mg/kg) may weaken the habituation effect in moderate-high users, as moderate-high users may possess some degree of tolerance to caffeine's effects (9). Moderate-high users may be less sensitive to the effects of a 2-mg/kg dose of caffeine compared to low users. Evidence showing little or no tolerance development following chronic caffeine exposure has also been reported (13). Thus, the question of whether drug history reduces caffeine's effects on startle habituation was assessed in the present study by comparing moderate-high and low caffeine users given a 2-mg/kg caffeine dose. Also, the present experiment compared physiologic differences between moderate-high and low caffeine users without any drug in their system, following the administration of a placebo.

Finally, the effects of 2 and 6 mg/kg of caffeine on dishabituation of startle were investigated. Dishabituation is a measure of the recovery from habituation. In a previous experiment we have shown that 4 mg/kg caffeine produced dishabituation in low users, an effect not observed in moderate-high users, or when moderate-high and low users were given placebo (17).

METHOD

Subjects

The low users group consisted of 10 subjects, two men and eight women (average age = 18 years, 8 mo), from an undergraduate Introductory Psychology class. Subjects were chosen based on their responses to a 34-item questionnaire indicating low or no caffeine intake (i.e., <100 mg caffeine/week). For example, when considering the wide range of caffeine-containing substances, these subjects reported consuming only one or two caffeinated sodas per week at most.

The moderate-high users group consisted of 11 subjects, three men and eight women (average age = 19 years, 7 mo), from an undergraduate Introductory Psychology class. Subjects were chosen based on their responses to a questionnaire indicating moderate-high caffeine intake (i.e., average = 300 mg/day, range = 220–500 mg/day). Because we estimated caffeine intake based on self-reported consumption, only the average and range of caffeine consumption are reported here, because these values provide a more realistic approximation of actual caffeine intake than would a single number.

The average caffeine intake for each subject was derived from self-reported consumption of various foods and beverages based on a five-point scale (A–E). This scale represents the reported range of consumption of a specific item to be at least three to four times per month, one to four times per week, once per day, two to five times per day, and more than five times per day. Examples of the 16 items that subjects responded to in the written caffeine questionnaire are caffeinated instant coffee, brewed coffee, cocoa, soda (not caffeine free), and chocolate. A caffeine conversion table described in (2) was used to translate the subject's reported daily caffeine intake into milligram values. Subjects filled out the caffeine questionnaire before they were chosen for this study. Because only subjects who met the appropriate caffeine intake criterion were allowed to participate in this study (e.g., for moderate-high users, persons who consumed >220 mg/day), no subjects were dropped from the experiment.

Stimuli

Startle stimuli were 85 dB (20 μPA; A scale) broadband noise (20–20 kHz) with a duration of 50 ms and a rise time of 0.1 ms. A 75-dB, 1000-Hz tone with a rise time of 10 ms and a duration of 50 ms was used to elicit dishabituation. The interstimulus interval (ISI) randomly varied from 20–30 s (average ISI = 25 s).

Materials

The caffeine solutions consisted of 100% pure anhydrous caffeine (Carolina Biological Supply) dissolved in flat tonic water and mixed with Tang orange drink. The caffeine doses used were 2 and 6 mg/kg for each 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 containing either caffeine or placebo.

Apparatus

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 amplifier, a Yamaha M-35 stereo amplifier, and presented to the subjects through an Onkyo S-30 loudspeaker. Stimulus intensity was calibrated by presenting a continuous stimulus from the loudspeaker to a Quest Electronics 215 sound level meter (A scale) held at the location of the subject's head.

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 millisecond 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 before each experimental session. Subjects were allowed to consume their normal amount of caffeine during the weeks between sessions. When the subjects arrived, they were first

weighed, then asked to read and sign an informed consent form and fill out a background questionnaire.

The subject received an oral dose of either one of the caffeine solutions or the placebo solution, which were given in a double-blind fashion. Caffeine is rapidly absorbed, reaching maximal plasma levels within about 30 min following oral administration in humans (11). Twenty minutes following 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 alcohol, and attached two electrodes, one below the center of the eye and the other immediately temporal 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 located approximately 1.5 m in front of a loudspeaker, and were presented with the first acoustic stimulus 30 min after ingesting the mixed solution. Each subject was exposed to 42 trials: 30 broadband noise trials, followed by six tone trials, then six trials of the original broadband noise stimulus. The entire testing session lasted approximately 20 min.

All subjects were given caffeine, 2 or 6 mg/kg, and placebo solutions on separate days, with at least 1 week separating the testing sessions to prevent long-term habituation from occurring. Subjects participated in three sessions, with one-third of the subjects receiving the 2-mg/kg dose of caffeine first, one-third of the subjects receiving the 6-mg/kg dose of caffeine first, and one third of the subjects receiving the placebo solution first. The alternate drug conditions were given in the remaining two sessions. The sequence of drug administration was completely counterbalanced.

Data Analysis

The dependent variables consisted of 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 elicited, 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 dose (placebo and 2 or 6 mg/kg) were within-subject variables, and drug history (moderate-high vs. low users) was a between-subject variable. Habituation was assessed by an orthogonal trend analysis of the first 10 trial blocks (BMDP2V). Posthoc tests comparing individual trial blocks were analyzed in a one-way analysis of variance (ANOVA) (BMDP4V). A one-way ANOVA was also used to test where habituation reached asymptote in the different conditions. Peak habituation 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. Finally, response amplitude in the first trial block was compared between drug and user level conditions to determine differences in initial startle reactivity.

The tone trials in this experiment were designed to produce dishabituation, which would be evident by a larger response on trial block 13 compared to trial block 10. These data were analyzed in separate one-way ANOVAs for drug and for user level conditions, with user level representing the between-subject variable, and trial block and dose being within-subject variables. This specific trial block comparison involved comparing the average response to the last three noise presentations in the first 30 trials and the average response to the first three noise presentations following the tone stimuli.

Response amplitude in the first trial block for the placebo condition was compared between moderate-high and low users using a one-way ANOVA. In addition, overall startle response amplitude for the placebo condition over the first five trial blocks, and over the last five trial blocks, were compared between moderate-high and low users.

RESULTS

No significant main effect of dose condition or history was found for response amplitude, latency, or probability. No significant interactions between dose, history, and trial block were observed over 10 trial blocks for response amplitude. No significant differences were observed on the first trial block between dose conditions or history with regard to response amplitude, latency, or probability, indicating that neither dose nor history affected initial startle reactivity. Figure 1 shows that low users did exhibit larger startle responses than moderate-high users but, possibly because of intragroup variability, this effect was not significant.

An orthogonal trend analysis revealed a significant quadratic trial block effect over 10 trial blocks for response amplitude [$F(1, 19) = 25.86, p < 0.0001$]. Posthoc ANOVAs indicated no significant decreases in response amplitude following trial block 4 for low users and trial block 5 for moderate-high users, demonstrating that habituation reached asymptote on these trial blocks. Therefore, specific trend analyses were conducted for the first five trial blocks to provide a more sensitive test of the habituation effects. For response amplitude, no significant main effects of dose condition or history were observed in the first five trial blocks. A significant quadratic trial block effect was revealed in the first five trial blocks [$F(1, 19) = 7.14, p < 0.01$] and a significant dose × quadratic trial block interaction on the first five trial blocks was found [$F(1, 19) = 10.68, p < 0.01$] (see Fig. 1). No other significant interactions were found in the first five trial blocks.

Differences in the habituation of response amplitude were assessed for each caffeine dose condition. When given either placebo or a 6-mg/kg dose of caffeine, response amplitude was significantly different between trial blocks 1 and 2 for low users [$F(1, 9) = 5.41, p < 0.05$, and $F(1, 9) = 11.22, p < 0.01$, respectively] and moderate-high users [$F(1, 10) = 7.21, p < 0.05$, and $F(1, 10) = 9.10, p < 0.01$, respectively]. In both the placebo and 6-mg/kg conditions, all subsequent trial blocks were significantly different from trial block 1 (Fig. 1). In the 2-mg/kg condition, no significant differences in response amplitude between trial block 1 and trial blocks 2 or 3 were observed in low or moderate-high users, but a significant difference between trial blocks 1 and 4 was found in both low users [$F(1, 9) = 10.12, p < 0.01$] and moderate-high users [$F(1, 10) = 5.59, p < 0.05$] (see Fig. 1). Taken together, these findings show that habituation of response amplitude occurred by trial block 2 (trials 4–6) in the placebo and 6-mg/kg conditions, but not until trial block 4 (trials 10–12) in the 2-mg/kg condition.

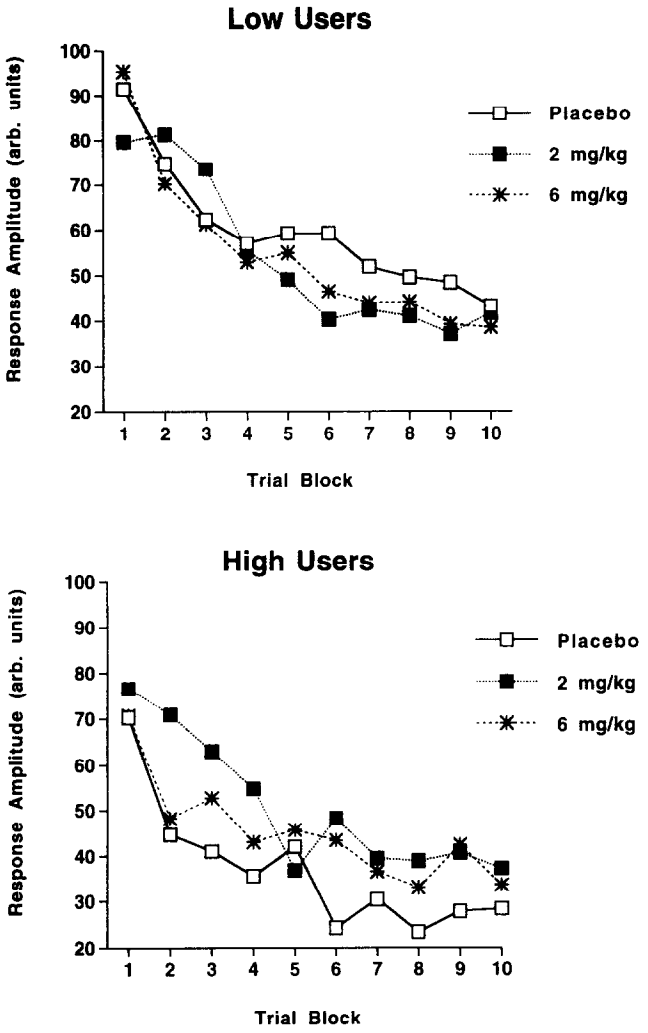

FIG. 1. Startle response amplitude as a function of trial blocks in low and moderate-high caffeine users receiving either placebo or 2 or 6 mg/kg of an oral dose of caffeine. (No differences between low and moderate-high users were found in the present study. However, separate figures are presented to provide a clearer illustration of the data.)

A marginally significant interaction between dose and history conditions was observed over 10 trial blocks [$F(2, 38) = 2.99$, $p < 0.06$]. Because this interaction was no longer significant when tested in the first five trial blocks, this effect was expected to be more pronounced in an analysis of the last five trial blocks (trial blocks 6–10). Another reason for analyzing the last five trial blocks is based on the finding that habituation reached asymptote on or before trial block 5. Thus, an additional analysis of the last five trial blocks would assess posthabituation reactivity. An orthogonal trend analysis of the last five trial blocks yielded a drug × history interaction [$F(2, 38) = 3.41$, $p < 0.05$]. Subsequent comparisons (ANOVAs) demonstrated that in moderate-high users, both 2 and 6 mg/kg caffeine produced higher response amplitude than placebo on the last five trial blocks [$F(1, 10) = 4.60$, $p < 0.05$ (Fig. 2). No significant dose effects were revealed in the last five trial blocks for low users.

A significant linear trial block effect was demonstrated over 10 trial blocks for response latency [$F(1, 19) = 13.54$, $p < 0.001$] and for response probability [$F(1, 19) = 5.83$, $p < 0.05$]. These significant trial block effects showed that both response latency and probability habituated. No other significant main effects or interactions were observed for response latency or probability in either five- or 10-trial block analyses.

Planned comparisons between moderate-high and low users when receiving placebo were performed to assess differences between moderate-high and low caffeine users with no caffeine in their system. No differences between moderate-high and low users when given placebo were observed for response amplitude, latency, or probability.

In the present experiment no significant dishabituation was found for response amplitude, latency, or probability. Likewise, neither the dose nor the history condition produced any significant effects during the dishabituation phase of the experiment.

DISCUSSION

In previous studies, caffeine (4 mg/kg) delayed habituation of the acoustic startle reflex in both moderate-high and low caffeine users (17). The present study showed that 2 mg/kg caffeine significantly delayed habituation of the acoustic startle reflex in both moderate-high and low users. There was no difference between the effects of a 6-mg/kg dose of caffeine and placebo on startle responding. Table 1 combines our previous findings with the results of the present experiment, indicating the effects of a range of caffeine doses and user levels on startle habituation. When considering the range of dose effects in Table 1, it becomes evident that caffeine's effects on startle habituation have an inverted U-shaped relationship. That is, caffeine's effects on startle were present at a low and intermediate dose, but not at the highest dose tested.

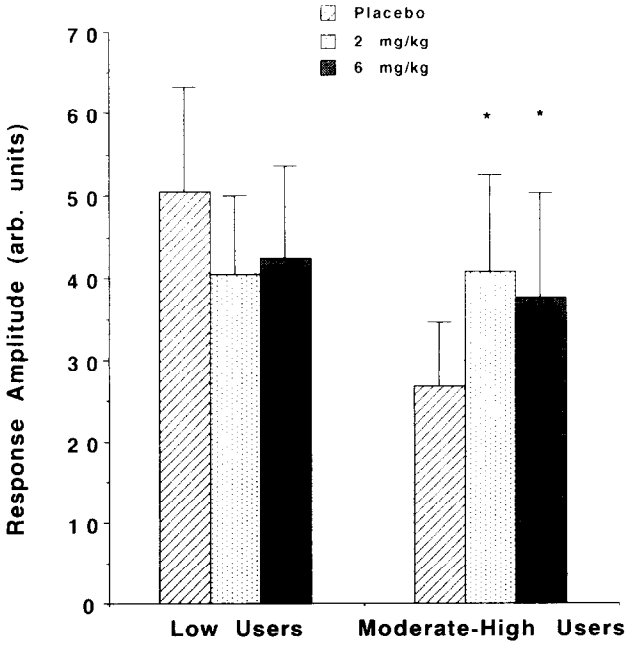

FIG. 2. Average startle response amplitude for trial blocks 6–10 in low and moderate-high caffeine users receiving either placebo or 2 or 6 mg/kg of an oral dose of caffeine. (Bars represent 1 SEM). *Significantly different from the placebo condition.

TABLE 1

EFFECTS OF A RANGE OF CAFFEINE DOSES ON STARTLE AMPLITUDE HABITUATION AS A FUNCTION OF USER LEVEL

	Trial Block 2 (Trials 4–6)	Trial Block 3 (Trials 7–9)	Trial Block 4 (Trials 10–12)	Trial Block 5 (Trials 13–15)
Placebo				
High users	*			
Low users	*			
2 mg/kg				
High users			*	
Low users			*	
4 mg/kg				
High users				*
Low users			*	
6 mg/kg				
High users	*			
Low users				

*Trial block at which habituation of startle amplitude begins. The 4/mg/kg data points were taken from Schicatano and Blumenthal (17).

In the present study, both response latency and probability habituated, but the caffeine dose did not affect habituation of these response measures. These data are consistent with previous findings showing that response latency and probability were not affected by caffeine (17). It has been proposed that distinct neural mechanisms underlie response amplitude, latency, and probability (4). The present findings support this hypothesis by illustrating that the pharmacologic modulation of startle habituation by caffeine is evident only for response amplitude and not for response latency or probability.

Past psychophysiologic studies of caffeine have suggested that the effects of caffeine on other psychophysiologic measures were primarily due to an increase in generalized arousal. For instance, using quantitative EEG techniques in humans, Dimpfel et al. (8) and Bruce et al. (5) showed decreases in α and θ power following acute caffeine administration. In EEG experiments, decreases in α and θ power are typically associated with increases in neural excitability (22). Caffeine produced an increase in the CNV (contingent negative variation), a negative EEG potential that increases proportionally with cortical excitability and generalized alertness (20). These EEG findings, combined with the fact that caffeine increases skin conductance (18,19), suggest that the effects of caffeine on startle may be attributed to an increase in arousal.

Previous investigators have suggested that the delay of habituation of the skin conductance response produced by caffeine was due to arousal (18,19). The results of past experiments in this laboratory (17) as well as the present experiment demonstrate that caffeine had no effect on initial startle responding (see trial block 1 in Fig. 1). In the present experiment, our use of only 10 low users and 11 moderate-high users might not have been sufficiently powerful for examining these differences. Caffeine did, however, delay habituation of the startle reflex. Therefore, based on these findings, it can be concluded that tonic measures of startle, such as habituation, may be more related to or sensitive to arousal than is initial startle reactivity. The effects of caffeine on startle, which are present at low and intermediate doses but absent at the highest dose tested, resemble an inverted U-shaped arousal function. However, a more definitive test of this hypothesis would involve administering a wider range of caffeine doses to subjects to evaluate the presence of a quadratic dose function in a within-subject design. Also, experiments being conducted in our laboratory are currently testing stimulus intensity and attention variables on startle in subjects given caffeine. These more recent experiments will provide a better test of how different levels of arousal (due to changes in startle intensity) and attention might be affected by caffeine in the startle paradigm.

Neuropharmacologically, caffeine acts as an adenosine antagonist (20,21). Chronic caffeine administration results in tolerance to some of the drug's effects, which may result from an enhanced sensitivity of adenosine receptors (3,10). Although the present study did not directly investigate caffeine tolerance, it did examine startle in subjects with a history of caffeine usage who may differ from subjects with a history of minimal caffeine usage due to a more sensitized adenosine system. The present results show that caffeine's effects on startle habituation were not diminished in moderate-high users (i.e., there were no differences between moderate-high and low caffeine users in their sensitivity to caffeine with regard to startle habituation). These data are consistent with past experiments showing no differences in startle responding between moderate-high and low caffeine users given a 4-mg/kg dose of caffeine (17). Also, there were no differences in startle responding between moderate-high and low users when given placebo. It should be noted that even though startle amplitude was larger in low users than in moderate-high users when given placebo, this effect did not reach significance (see Fig. 1). Hence, our results indicate that habituation of the startle reflex is not changed in individuals who have experienced a history of caffeine usage.

A difference in startle responding when moderate-high caffeine users were given caffeine (either 2 or 6 mg/kg) compared to when they were given placebo was observed in the present study. Specifically, after habituation occurred, lower startle responding was observed when moderate-high users were given placebo compared to when given caffeine (Fig. 2). These dose effects were not obtained in low users, suggesting that the subject's history of caffeine use played a role in these "posthabituation" findings. Davidson and Smith (6) suggested that caffeine produces arousal and decreases the aversiveness of the habituation process (i.e., low-level arousal). Our data

demonstrated a decrease in the level of habituation following caffeine administration compared to placebo administration in moderate-high users. Perhaps one of the benefits of consuming caffeine for moderate-high users may be the effect that this drug has on maintaining a certain level of arousal, or preventing a low level of arousal from occurring. Without caffeine in their system (placebo condition), moderate-high caffeine users exhibited a significantly depressed level of responding compared to when caffeine was in their system.

In conclusion, the results of present and past experiments (17) show that caffeine delays acoustic startle habituation in a quadratic dose-related manner, indicating that these doses differentially modulate startle plasticity. Because the neuroanatomical pathway of acoustic startle is known (7), future studies with animals might consider specifically where in the brainstem caffeine is ultimately modulating startle plasticity. These studies may provide insight into the neurobiologic processes underlying caffeine's actions as a behavioral stimulant.

Finally, the role of caffeine in disrupting a neurobehavioral process such as habituation demonstrates that caffeine modulates the processing of repetitive stimuli. In a situation requiring that a person persistently respond to redundant information, caffeine may be beneficial. For instance, in a boring environment (such as driving late at night in a car) caffeine would enable a person to "not habituate" as quickly to redundant stimulation. Using the startle paradigm, we have shown that a 2- and 4-mg/kg dose of caffeine produced persistent responding to redundant acoustic stimulation, whereas a 6-mg/kg dose of caffeine had no effect. Because the startle reflex is indicative of early sensory information processing, our results suggest that 2 and 4 mg/kg of caffeine interrupt processing at a very early stage.

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