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The Effects of the Naltrexone Implant on Rodent Social Interactions and Cocaine-Induced Conditioned Place Preference

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MITCHEM, L. D., C. K. KRUSCHEL, E. DALLMAN, K. A. ANDERS, M. CZAPIGA, J. J. PANOS, AND R. E. STEINPREIS. *The effects of the naltrexone implant on rodent social interactions and cocaine-induced conditioned place preference.* PHARMACOL BIOCHEM BEHAV **62**(1) 97–102, 1999.—Two experiments were conducted to determine the behavioral properties of the naltrexone implant on: 1) rodent social interactions; and 2) the appetitive properties of cocaine. Rats were surgically implanted with a naltrexone implant (placebo, 10 or 30 mg) and placed into an open field for the recording of social interactions. The naltrexone implants increased latency to initiate contact and decreased pinning, bouts of grooming, and crawl unders on all 7 days. Other rats were surgically implanted with naltrexone (60, 120, or 240 mg) and habituated to a two-chambered conditioned place preference apparatus. After 6 days of conditioning, place preference was computer recorded. Cocaine produced a dose-dependent conditioned place preference in the rats implanted with placebo or 60 mg of naltrexone. The 120 and 240 mg naltrexone implants blocked the emergence of cocaine-induced place preference. The results indicate that naltrexone implants produce significant social behavioral effects within 1 day, and are effective at attenuating the conditioned place preference produced by cocaine. © 1998 Elsevier Science Inc.

Cocaine Naltrexone implants Social behavior Conditioned place preference Addiction

COCAINE abuse has become a problem of epidemic proportions in the United States. The psychological, social, financial, and physical sequelae of cocaine abuse have been well documented (14,40). Cocaine produces lethality via several mechanisms, including ventricular fibrillation, cardiac arrest, and apnea (25). The most effective treatment appears to be a combination of psychotherapy and pharmacological intervention (42,43). It has been suggested that the drugs used to treat opiate addiction may be efficacious in treating cocaine addiction (20). Naltrexone is a pure opiate antagonist that became commercially available in 1985 (17). Naltrexone has no known abuse potential of its own, because it blocks the opiate receptors rather than stimulating them, as do opiate agonists and mixed agonist/antagonist compounds used to treat opiate addiction (e.g., methadone and buprenorphine). These latter compounds bind to the opiate receptor sites and produce analgesia, euphoria, and sedation. In addition, they have been shown to have abuse potential in animal models (31,38). Therefore, the use of naltrexone may be efficacious in the treatment of opiate and cocaine addiction. However, research has shown that with standard administration regimens outpatient populations tend to discontinue the use of naltrexone after a few days or weeks (22,28,32,33).

The National Institute on Drug Abuse (NIDA) has developed a naltrexone implant, for use in animal research, which has been used to study the effects of naltrexone on the development of drug dependence, reinforcing properties, and tolerance. Hence, research has shown that the naltrexone implant has effectively blocked morphine tolerance and dependence in the rat (6). The naltrexone implant (30 mg) has been used to successfully attenuate morphine-induced conditioned place preference (2). Naltrexone implants have also been used to determine naltrexone's effect on opiate receptor binding sites. Chronic treatment with naltrexone increases the number of

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binding sites with opioid receptors (14,15). However, there is still very little known about the properties of the naltrexone implants, including the time course in which the naltrexone implants have a significant effect on the behavior of animals and the effects of the naltrexone implants on the appetitive properties of cocaine.

Based on the previous studies, which have examined the ability of naltrexone to attenuate morphine-induced conditioned place preference, we hypothesized that naltrexone should also be able to attenuate cocaine-induced conditioned place preference. Given the paucity of existing data on the time course in which naltrexone produced any behavioral effects, we first wanted to determine if naltrexone would interfere with normal social functioning in rats. By examining social interaction we could determine if the implants interfered with the rat's normal functioning through sedation, motor impairment, lack of contact, etc). Otherwise, it would be difficult to determine if naltrexone attenuated the appetitive effects of cocaine in the second study or if naltrexone was just so pervasively anhedonic that the rats did not engage in any of their normal behaviors. Furthermore, by studying naltrexone's effect on social behavior, one could also establish a time-dependent effect (e.g., naltrexone's long-term delivery system), in its ability to continue to alter behavior. By establishing this latter fact, it would provide further evidence to support the notion that naltrexones effects are working continuously throughout the entire conditioning place-preference sequence.

One form of social interaction in rats is called rough-and-tumble play. This form of mock fighting is rewarding to both of the participants, even though the animals demonstrate dominant and submissive posture. There are many types of behaviors that occur (3); however, pinning is one of the most informative examples of social behavior. There is evidence to suggest that the opiod system plays a modulatory role in the control of social behavior (27,30). For example, systemic injection of opiate antagonists reduces pinning among rats, while the opiate agonist morphine can increase pinning (4,27,29). The purpose of the first experiment in this study was to determine the effects and time course of the naltrexone implants on social interactions between unfamiliar male conspecifics.

Once we verified that the naltrexone implants would indeed have an effect on behavior throughout the 7-day period, we examined their effects on the appetitive properties of cocaine. The conditioned place preference paradigm has been used to study the appetitive properties of a wide variety of drugs (1,39), including cocaine (7,8,10,16). In this study, the conditioned place-preference paradigm is particularly relevant because of the implant's long-term delivery of naltrexone. Thus, it could prevent the emergence of cocaine-induced conditioned place preference without the need for additional injections. Therefore, in the second experiment we employed the conditioned place-preference paradigm to explore this issue.

METHOD

Subjects

A total of 120 male Sprague–Dawley rats that were approximately 60 days old served as subjects in these experiments (Harlan–Sprague–Dawley, Indianapolis, IN). These rats weighted about 250 g at the start of the experiment. All rats were housed individually from the time of weaning through the duration of the experiment, except during the observation times. Rats were maintained on a 12 L:12 D cycle (lights on at 0700 h), and at 20° in a home colony room. Standard rat chow and water were available ad lib.

Apparatus

To avoid novelty effects from the use of a center chamber, a two-chambered conditioned place-preference apparatus was used. The apparatus consisted of a square Plexiglas box divided into two visually and tactually distinct chambers. A removable guillotine door separated the chambers. Each chamber was 28 × 31 × 55 cm. One chamber had a wire mesh floor with cedar bedding and walls with 1″ black and white horizontal stripes. The other chamber had a wire mesh floor with bed-o-cob and walls with 1″-thick black and white vertical stripes. Each chamber was equipped with eight infrared sensors that were used to detect activity counts. The sensors were evenly spaced 6.5 cm apart and 4.5 cm from the bottom of the chamber. The sensors were interfaced to an IBM compatible computer for data collection.

Drugs

Naltrexone implants and cocaine HCl were donated by the National Institute On Drug Abuse (Rockville, MD). The doses of the naltrexone implants that were used in both experiments included the placebo, 10, 30, 60, 120, and 240 mg. The doses of cocaine that were used in this study were, 5.0, 10.0, and 20.0 mg/kg, and these doses were selected from the literature on cocaine-induced conditioned place preference (10,12, 16,18,34,41). The cocaine was dissolved in a 0.9% saline vehicle. The sodium pentobarbital (18 mg/kg) used for anesthesia was obtained from Sigma Chemical Co. (St. Louis, MO).

Procedure

The rats were anesthetized using sodium pentobarbital (18 mg/kg) and a 2 × 2 cm patch of the rat's outside hind quarter was shaved. A small incision made approximately 1 cm in length over the shaved area. The rats were then surgically implanted subdermally with either a placebo, 10-, 30-, 60-, 120-, or 240-mg implant. The incisions were closed using surgical wound clips and treated with Clotisol (Petcare Industries, Inc., Cherry Hill, NY) and antibacterial ointment to prevent infection. The rats were monitored throughout the experiment for signs of infection or excessive weight loss (more than 15% of their body weight). None of the rats exhibited these signs, and all remained in the study.

Twenty-four male rats were used in the social behavior observation study. Eight of these rats had been implanted with the placebo implants, eight with the 10-mg naltrexone implants and eight with the 30-mg naltrexone implants. Thus, there were four pairs of rats in each group, and rats were always exposed to the same partner each time they were observed. The observation chamber was a simple open field with Plexiglas walls and wire mesh floors over bed-o-cob (56 × 56 × 36 cm). The day after implantation, observations began and continued for 7 consecutive days. These were conducted in 10-min blocks by two trained observers who were blind to the implant dose of each rat. The observers recorded the same four behaviors, including latency to establish contact, frequency of pins, frequency of allogrooming, and crawl unders. The observers also qualitatively assessed the locomotor activity of the animals to ensure that their movement was normal and there was no sedation. Immediately following the observation period, both rats were returned to their respective

home cages until the next day. Ninety-six rats were used in the conditioned place-preference experiment and were implanted with either placebo, 60-, 120-, or 240-mg implant doses (n = 24 in each implant group). These implant doses were based on extensive pilot data. We had originally attempted to attenuate the emergence of cocaine-induced conditioned place preference using the 10- and 30-mg implant doses because these were the doses that had successfully attenuated social interactions. However, the 10- and 30-mg implant doses did not produce appreciable effects in the conditioned place-preference paradigm. Rats were assigned to a side paired with cocaine in random fashion, such that half of the rats in each drug condition received drug (cocaine) in the horizontally striped chamber and half received drug in the vertically striped chamber. Twenty-four hours prior to conditioning, each rat was habituated to the entire apparatus with the guillotine door removed for 15 min. Conditioning and testing were also conducted in 15-min blocks. On the day after habituation, conditioning began and lasted for 4 days. On days 2 and 4, rats were injected with an intraperitoneal dose of cocaine or saline vehicle and placed immediately in the chamber that they had been randomly assigned to for drug pairings. On days 3 and 5, all rats received saline and were placed in the chamber opposite to the one they had received drug in the day before. During conditioning, the guillotine doors were closed so that the rats only had access to one side of the apparatus. On the sixth day, rats were tested, in the absence of drug. During testing, rats were allowed free run of the entire apparatus. The amount of time spent in each side and locomotor activity were computer recorded, as indexed by sensor breaks.

RESULTS

In the social behavior experiment, interrater reliabilities were calculated using the Pearson r. Interrater reliabilities for all behaviors were greater than 0.85, with the majority falling above 0.95. Therefore, all statistics were performed on the arithmetic mean of the observers' scores. Each behavior was analyzed separately using analysis of variance (ANOVA), with repeated measures across days. The results of the social behavior experiment are presented in Figs. 1 through 4. With respect to latency to establish contact (Fig. 1), there were significant main effects for drug treatment, $F(2, 21) = 36.47$, $p < 0.001$, days, $F(6, 126) = 33.19$, $p < 0.01$, and the interaction between these two factors, $F(12, 126) = 6.99$, $p < 0.001$. There were no significant differences on day 2. On days 1, 4, and 7, there was a significantly shorter latency to establish contact in the placebo group compared to both the 10.0-mg group and the 30.0-mg group. On days 3, 5, and 6, there were significantly shorter latencies for both the placebo group and the 10.0-mg, compared to the 30.0-mg group.

With respect to pins (Fig. 2), there were significant main effects for drug treatment, $F(2, 21) = 10.21$, $p < 0.001$, days, $F(6, 126) = 4.09$, $p < 0.001$, and the interaction between these two factors, $F(12, 126) = 2.77$, $p < 0.005$. On days 1, 3, and 4, there were no significant differences between implant treatments. On day 5, there were significantly more pins in the placebo group compared to the 30.0-mg group. On days 2, 6, and 7, there were significantly more pins for both the placebo group and the 10.0-mg group, compared to the 30.0-mg group.

The results for instances of grooming are presented in Fig. 3. There were significant main effects for drug treatment, $F(2, 21) = 60.95$, $p < 0.001$, days, $F(6, 126) = 8.83$, $p < 0.001$, and the interaction between these two factors, $F(12, 126) = 3.92$, $p < 0.001$. On day 2, there was significantly more grooming in the placebo group compared to the 30.0-mg group. On day 3, there was significantly more grooming in both the placebo group and the 10.0-mg group, compared to the 30.0-mg group. On days 1, 4, 5, 6, and 7, there were significantly more instances of grooming in the placebo group compared to both the 10.0-mg group and the 30.0-mg group.

The results for instances of crawl unders are presented in Fig. 4. There were significant main effects for drug treatment, $F(2, 21) = 38.73$, $p < 0.001$, days, $F(6, 126) = 11.61$, $p < 0.001$, and the interaction between these two factors, $F(12, 126) = 5.39$, $p < 0.001$. On days 2, 3, and 4, there were no significant differences in crawl unders. On days 1, 6, and 7, there were significantly more crawl unders in the placebo group compared to both the 10.0-mg group and the 30.0-mg group. On day 5, there were significantly more crawl unders in the placebo group compared to the 30.0-mg group.

In the conditioned place preference experiment (Fig. 5), a t-test was used to determine if the subjects exhibited a natural preference for either chamber during habituation (i.e., prior to receiving any cocaine). To determine if there was a significant overall treatment effect, a 4 × 4 analysis of variance (ANOVA) was performed. Post hoc Tukey tests were used to determine differences between treatments at each dose of co-

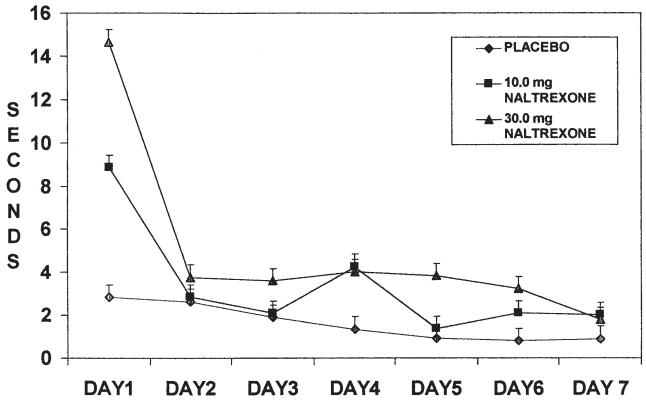

FIG. 1. The effects of the naltrexone implants on latency to establish contact. The data show significantly longer latencies to establish contact for the higher naltrexone implant doses compared to the placebo.

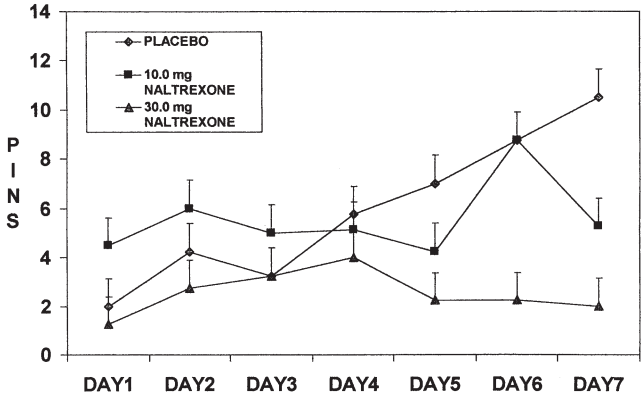

FIG. 2. The effects of the naltrexone implants on pinning. The data show significantly fewer pins for the higher naltrexone implant doses compared to the placebo.

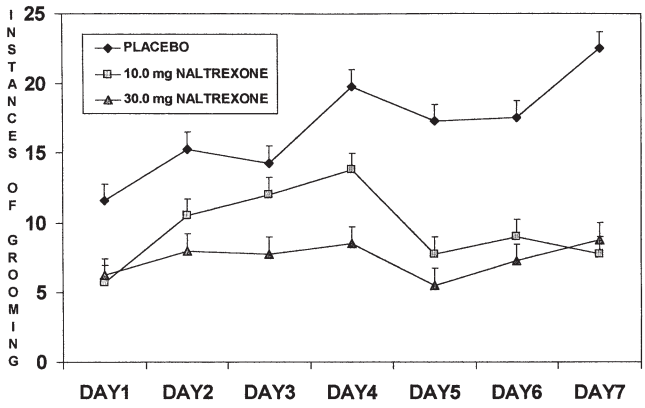

FIG. 3. The effects of the naltrexone implants on grooming. The data show significantly fewer instances of grooming in the higher naltrexone implant doses compared to the placebo.

caine and naltrexone implant. We initially had to determine whether we had constructed an unbiased chamber. A *t*-test was performed on the habituation data, for all implant doses, to rule out the possibility that the rats might have a preexisting preference for one chamber in the apparatus over the other. The *t*-test indicated that there was no significant difference in time spent in either chamber ($t = 0.479, p > 0.05$). The mean number of seconds spent on the vertically striped side during habituation was 411.2 (SEM = 26.6), and the mean number of seconds spent on the horizontally striped side was 405.82 (SEM = 31.4). Analysis of variance revealed a significant main effect for cocaine dose, $F(3, 80) = 5.51$, $p < 0.002$, and a significant main effect for implant dose, $F(3, 80) = 5.58$, $p < 0.002$. However, the interaction was not significant, $F(9, 80) = 1.14$, $p > 0.05$. The results of the saline group were not significant, indicating that the different naltrexone doses did not produce any effects on the conditioned place-preference paradigm. The cocaine post hoc comparisons indicated that rats who had previously received 5.0 mg/kg of cocaine during conditioning spent significantly more time on the side previously paired with drug for the 60-mg naltrexone group compared to the 240-mg naltrexone group ($p < 0.037$). Rats who had previously received 10.0 mg/kg of cocaine during conditioning spent significantly more time on the side previously paired with drug in the placebo implant group compared to the 240 mg naltrexone group ($p < 0.027$). For rats who had previously received 20.0 mg/kg of cocaine during conditioning, there was a trend toward significantly more time spent on the side previously paired with drug for the placebo-implant group compared to the 240-mg naltrexone group ($p < 0.058$). The implant post hoc Tukey tests indicated that within the placebo-implant group there was significantly more time spent on the side previously paired with drug for the rats who had previously received 10.0 mg/kg cocaine ($p < 0.001$) or 20.0 mg/kg cocaine ($p < 0.000$), compared to the saline control group. This finding indicates that cocaine did, indeed, produce a conditioned place preference. There was also a significant increase in time spent on the side previously paired with drug for the rats who had received 10.0 mg/kg cocaine ($p < 0.009$) and 20.0 mg/kg cocaine ($p < 0.001$), compared to the 5.0-mg/kg cocaine group. Within the 60-mg naltrexone implant group there was significantly less time spent on the side previously paired with drug for the saline group compared to the 20.0-mg/kg cocaine group ($p < 0.019$). The results of the 120-mg naltrexone group and for the 240-mg naltrexone group were not significant, indicating a successful attenuation of the emergence of the cocaine-induced conditioned place preference. Note that in this case, a significant result would be indicative of a failure of the implants to prevent the emergence of the preference.

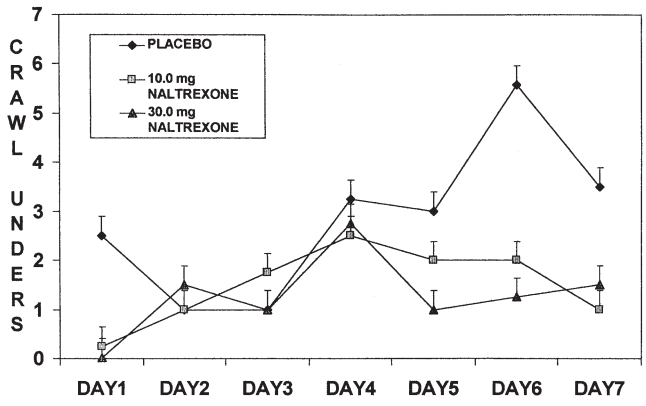

FIG. 4. The effects of the naltrexone implants on crawl unders. The data show significantly fewer instances of crawl unders for the higher naltrexone implant doses compared to the placebo.

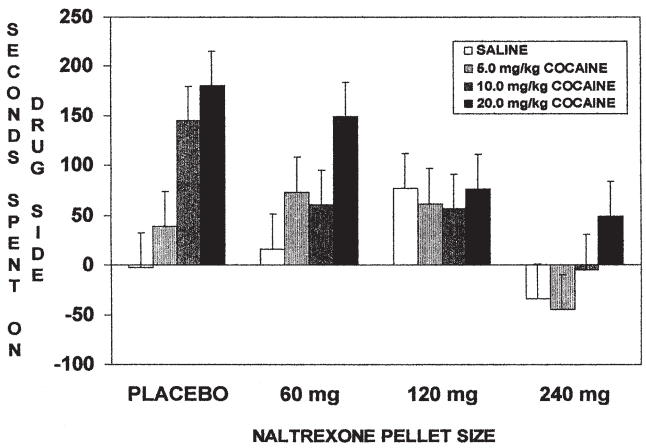

FIG. 5. The effects of the naltrexone implants on cocaine's ability to establish conditioned place preference. The data show that cocaine does produce conditioned place preference, and that the naltrexone implants can attenuate the conditioned place preference in a dose-dependent manner.

DISCUSSION

The initial experiment represents the first exploration of the effects of the naltrexone implant on rodent social behavior. Our results indicate that the naltrexone implant did not produce any sedative effects. However, social behavior in rats was decreased at both the 10.0 and 30.0 mg implant doses. The 60.0-mg implant dose was piloted, but it practically eliminated social interactions. Therefore, higher doses were not explored in this paradigm. In the placebo group, latency to establish contact decreased over the 7-day period such that the rats took more time to establish contact on day 1 than on sub-

sequent days. Furthermore, the number of pins and instances of grooming increased over days, as did the number of crawl unders. This is likely a function of the rats becoming more familiar with each other. Naltrexone attenuated the emergence of the increased number of pins over days. In general, latency to initiate contact increased, while pins, grooming, and crawl unders decreased in a dose-dependent manner.

These findings are consistent with the literature on the effects of opioids on rodent social interactions (4,27,29). To date, very little research has been done with the naltrexone implant; therefore, there is no information available on the time course in which they initiate a significant effect on behavior. The present experiment indicated that both the 10 and 30 mg implants produce a significant impact on behavior just 1 day after implantation.

In the conditioned place-preference experiment, we were able to construct an unbiased apparatus were animals did not display a preference for one chamber over the other during habituation. Cocaine produced a conditioned place preference in the animals treated with the placebo implants, and these findings are consistent with the literature (16,18,19,21, 24,34,35). The saline group's results were not significant, indicating that the different naltrexone doses did not produce any effects on the conditioned place-preference paradigm. Furthermore, the naltrexone implants attenuated the conditioned place-preference produced by cocaine in a dose-dependent manner. The rats with placebo and 60-mg naltrexone implants spent more time on the side previously paired with drug than the rats in the groups receiving the 240-mg naltrexone implants. These results are consistent with the literature on attenuation of cocaine-induced conditioned place preference with systemically administered naltrexone (7). Naltrexone is found to inhibit conditioned place preference produced by cocaine at doses that are considerably higher than those shown to inhibit social behavior in the same species. Different behavioral effects are, of course, going to require different amounts of the drug. Furthermore, the naltrexone has to attenuate the effects of the powerful reward produced by cocaine. This would ultimately require a higher dose of naltrexone.

In the present study we were unable to gather data on the dissolution rate of the naltrexone implants. NIDA has conducted some research in this area. They found that each batch of implants has a slightly different dissolution rate. According to the mean dissolution rate data, 96.5% of the naltrexone can be recovered from the implants within 3 h. This indicates that the naltrexone is already being released into the rat's system within 3 h. One day after implantation 81.5% of the naltrexone can be recovered, 74.2% 2 days after, 58.3% 4 days after, 39.5% 8 days after, and 15.1% 16 days after implantation. This data indicates that the naltrexone continues to be released for at least 20 days (26). From the first experiment we also know that the implants are producing significant behavioral effects within 24 h of implantation. Therefore, it is likely that the naltrexone implants were working throughout the 6-day course of conditioning.

The results we found in the second experiment are likely due to interactions between the opiate and dopamine system. Other researchers have suggested that the opiate and dopamine systems may be working together to mediate reward (13). The mesocorticolimbic system is widely believed to be the biological substrate for the rewarding effects of cocaine (11,23). Dopamine has been implicated as the neurotransmitter involved in cocaine abuse, and cocaine is believed to mediate this effect by blocking reuptake (9). There are opiate receptors and dopamine receptors throughout the mesocorticolimbic system and opiod-containing terminals directly synapse onto dopaminergic neurons in the ventral tegmental area (36). Given that cocaine increases dopamine and naltrexone reduces extracellular dopamine concentrations (5,37), a blockade of opiate receptors produced by naltrexone could inhibit the release of dopamine. Based on our current findings, the search for a more effective treatment for cocaine abuse could be augmented by further study on the biological mechanism responsible for the behavioral effects we saw in the second experiment.

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