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Music-induced Context Preference Following Cocaine Conditioning in Rats

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Abstract

Traditional models of drug-seeking behavior have shown that exposure to associated environmental cues can trigger relapse. These learned associations take place during repeated drug administration, resulting in conditioned reinforcement. Although considerable investigation has occurred regarding simple conditioned stimuli, less is known about complex environmental cues, particularly those that may be salient in human addiction. Recent studies indicate that music can serve as a contextual conditioned stimulus in rats and influence drug-seeking behavior during abstinence. The purpose of the present study was to further assess the effectiveness of music as a conditioned stimulus in rats, to determine rats' preferences for two contrasting pieces of music, and to determine rats' preferences for music versus silence. To this end, we created an apparatus that gave instrumental control of musical choice (Miles Davis vs. Beethoven) to the rats themselves. After determining baseline musical preference, animals were conditioned with cocaine (10 mg/kg) to the music they initially preferred least, with alternating conditioning sessions pairing saline with the music preferred most. The animals were subsequently tested in a drug-free state to determine what effect this conditioning had on musical preference. The results indicate that music serves as an effective contextual conditioned stimulus, significantly increasing both musical preference and locomotor activity after repeated cocaine conditioning. Furthermore, we found that rats initially favor silence over music, but that this preference can be altered as a result of cocaine-paired conditioning. These findings demonstrate that, after repeated association with reward (cocaine), music can engender a conditioned context preference in rats; these findings are consistent with other evidence showing that musical contextual cues can reinstate drug-seeking behavior in rats.

Keywords

Conditioning; Music; Cues; Cocaine; Reward; CPP

A distinctive characteristic of drug seeking is that it can be induced and maintained by conditioned stimuli (CS), even after extended periods of abstinence. Both human and animal models of relapse demonstrate that exposure to cues previously paired with drug reward elicit craving and induce drug-seeking behavior (Childress et al., 1999; Di Ciano & Everitt, 2003; Fuchs, Ramirez, & Bell, 2008; O'Brien, Childress, Ehrman, & Robbins, 1998). Drug-associated stimuli evoke memories of reward, allowing maladaptive addictive behaviors to

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acquire increased salience. Through repeated association with the rewarding effects of a drug, these CS acquire powerful conditioned reinforcing properties that are not easily diminished (Lee, Milton, & Everitt, 2006). Therefore, it is of great importance to elucidate the behavioral mechanisms through which drug-associated stimuli exert their effects.

Numerous studies examining the role of drug-paired CS have relied almost exclusively on simple discrete or discriminative CS (e.g., a tone or light). While meeting the standard of neutrality prior to conditioning, these CS fail to replicate the complexity of contextual cues present in human drug experiences. The conditioned place preference (CPP) paradigm has been used extensively to examine more complex contextual cues (Bardo, Rowlett, & Harris, 1995; Tzschentke, 2007). Indeed, the CPP assay has proven to be an extremely valuable tool to measure reward. However, the effect observed with CPP is dependent upon CS-reward interactions that are acquired and maintained within the same apparatus. While there is nothing inherently wrong with this measure of reward, one could potentially make a stronger case for the influence of a reward-paired contextual CS if the conditioning and test environments were not comparable. For example, one could measure baseline preferences of two different CS in a CPP apparatus, pair drug with one of these two distinct CS in an entirely different apparatus, and then return animals to the CPP apparatus to determine what effect this conditioning had on CS preferences. In an A-B-A paradigm of this kind, if a contextual CS was able to influence drug seeking behavior in a setting different from where the rewarding associations were made, there would be more certainty that the CS was the decisive factor, rather than “place” serving as a possible confound. Furthermore, one could state that the subjects experienced a conditioned context preference (CCP) rather than a place preference, because they were never conditioned to a specific place that contained contextual cues; instead they were only conditioned to the specific contextual CS itself.

Recent research indicates that music can serve as an effective contextual conditioned stimulus in rats. For example, music has been shown to enhance MDMA-conditioned reward in rats (Feduccia & Duvauchelle, 2008). This study showed increases in both locomotor behavior and extracellular dopamine in the nucleus accumbens after music was paired with MDMA during operant self-administration. Another recent investigation established that rats have the ability to differentiate music composed by Bach versus Stravinsky, and even transfer this ability to novel musical selections by the same composers (Otsuka, Yanagi, & Watanabe, 2009). Both of these studies concluded that music evoked no primary reinforcing property by itself. Our laboratory has also recently shown that after repeated pairing between music and methamphetamine, the music alone is able to produce significant increases in locomotor activity and significant increases in extracellular dopamine in the basolateral amygdala and nucleus accumbens (Polston, Rubbinaccio, Morra, Sell, & Glick, 2011). Taken together, these reports indicate that music can serve as an effective contextual CS in rats.

Recent clinical studies also reveal that music can be used as an effective treatment for a multitude of disorders. Music therapy has shown promise as an efficacious treatment for sleep disorders, anxiety, chronic stress, pain, psychosis, autism, depression, post-traumatic stress disorder, respiratory disease, and as an adjunct therapy for addiction (Bauldoff, 2009; Bradt & Dileo, 2009; de Niet, Tiemens, Lendemeijer, & Hutschemaekers, 2009; Gold, Solli, Kruger, & Lie, 2009; Jung & Newton, 2009; Mays, Clark, & Gordon, 2008; Nilsson, 2008; Rossignol, 2009). Considering the enormous potential that music therapy offers, there is a growing need to develop preclinical models that incorporate music as an important variable.

Accordingly, we developed an apparatus that gave instrumental control of musical choice to the rats themselves. While allowing subjects to manipulate their own environment can be problematic in experimental paradigms, in this instance it permitted examination of complex

contextual cues that would otherwise be difficult to investigate. Giving rats control of their auditory surroundings allowed for examination of baseline preference between two contrasting pieces of music (Miles Davis vs. Beethoven), and assessment of preference between music and silence. More importantly, it allowed us to determine if drug-paired conditioning with these musical selections would increase an animal's preference for that music. Post-conditioning changes in musical preference would indicate that rats have the ability to process this complex auditory contextual stimulus and show that music can be an effective contextual CS in rats-- which was the primary goal of this investigation. We postulated that after repeated cocaine-paired conditioning sessions, significant increases in musical preference would be observed for the music that had been paired with cocaine.

Method

Subjects

Naïve male Sprague-Dawley rats (Taconic Germantown, NY), weighing between 225 and 275g at the start of the experiment, were group housed in a temperature and humidity controlled colony room under a standard 12:12 light/dark cycle. Food and water were provided ad libitum for the 36 subjects used in these experiments. Protocols were designed and implemented in accordance with the "Guide for the Care and Use of Laboratory Animals" (1996) and were approved by the Institutional Animal Care and Use Committee of Albany Medical College. Rats were given at least one week of acclimation time prior to experimental procedures.

Drugs

Cocaine hydrochloride (Sigma-Aldrich Company, St. Louis, MO) was dissolved in 0.9% sodium chloride (saline) at a concentration of 10 mg/ml. Cocaine (10 mg/kg) and vehicle (saline) were both administered by the intraperitoneal route.

Apparatus

Baseline and test sessions, the former entailing assessment of baseline musical preferences, were conducted in Plexiglas® preference chambers (71cm×25cm×46 cm), consisting of two identical compartments separated by a guillotine door. Each compartment (35cm×25cm×46 cm) was painted matte black, and had a stainless steel bar floor. Motion detectors (IR-TEC) were mounted at each end of the apparatus, such that one motion detector covered compartment one and the other detector covered compartment two. These motion detectors were interfaced with a custom built electronic circuit that was connected to two (Panasonic) stereo systems. When motion was detected within a compartment, the relay circuit would provide power to the stereo speakers that corresponded with that side of the apparatus. Thus, this system allowed the rats to control the music they were hearing by moving between compartments. Upon entering either side of the musical preference apparatus, the music associated with that side would begin at a random point within the musical composition. The music would then continue as long as the rat remained on that side, and would loop back to the beginning of the track if the end of the song was reached. A ceiling mounted digital video camera (Panasonic) along with Any-Maze™ video tracking software (Stoelting Inc., Wood Dale, IL) was used to analyze activity in the apparatus. Anymaze™ is a versatile animal tracking system, that when interfaced with a video camera and computer, is capable of simultaneously monitoring several metrics necessary for these experiments. Through operationally defining the two music compartments, the program automatically generated detailed readings of time spent in each compartment in seconds and the distance that the animal traveled in meters. Since time spent in each compartment translated to the time spent hearing each musical selection, this system provided an automated way to determine musical

preference. Videos were periodically recorded during sessions, and later analyzed to ensure that Anymaze was functioning correctly.

Conditioning sessions were conducted in a distinctly different apparatus. In contrast to the black, segmented, rectangular boxes used for musical preference testing, conditioning sessions were carried out in clear cylindrical Plexiglas® chambers, 36 cm in diameter, with stainless steel bar floors. The distinct differences in color, shape, and size made these chambers an ideal conditioning environment, consistent with our intent to provide as much contrast as possible between the test and conditioning environments.

Music

Miles Davis' "Four" (Prestige *Blue Haze*, 1954) and Beethoven's "Für Elise" (piano) were the two musical tracks used in these experiments. The Miles Davis selection was chosen because it had been used successfully in past conditioned learning paradigms in our laboratory (Polston et al., 2011). The Beethoven selection was used because it was distinctly different from the Miles Davis selection. These musical selections were also chosen because they both have repetitive melodies, helping to make them easily recognizable and identifiable. During baseline, conditioning, and test sessions, these compositions were played on a continuous loop, at a volume that allowed the auditory range to remain between 65 and 75 decibels. This decibel range was chosen because it had been used successfully in past investigations involving rats and music (Feduccia & Duvauchelle, 2008; Otsuka et al., 2009; Polston et al., 2011).

Procedure

Experiment 1: On day one, rats were transported to the sound attenuated room that housed our musical preference apparatus. Rats were randomly placed on one side of the apparatus and allowed to roam freely for 60 min, in order to determine baseline musical preference between Miles Davis and Beethoven. These musical selections were novel at the time of baseline testing. On days 2–5, rats were subjected to two 60 min conditioning sessions per day. Similar to a biased CPP design, test subjects (n=12) received one daily conditioning session that paired cocaine (10 mg/kg) and the music they initially preferred least, and one daily conditioning session that paired the preferred music with saline. Control subjects (n=8) received saline during both conditioning sessions. Therefore, animals in the test group received four cocaine-music pairings with their least preferred music and four saline-music pairings with their preferred music. Animals in the control group received a total of eight saline-music conditioning sessions, four with the preferred music and four with the least preferred music. Animals were injected i.p. just prior to being placed in the conditioning chamber, and the music was started immediately. These two daily conditioning sessions occurred in the morning and afternoon, with four to six hours elapsing between sessions. These morning and afternoon sessions were counterbalanced, such that, if an animal received cocaine treatment in the morning on day one, they would receive saline treatment in the morning on day two. These eight total conditioning sessions took place on four consecutive days. On day six, rats were placed back in the musical preference chambers to determine what effect the conditioning sessions had on musical preference.

Experiment 2: On day one, rats were transported to the sound attenuated room containing the musical preference chambers and placed in the apparatus for 60 min to determine baseline preference between Beethoven and silence (no music). The Beethoven musical selection was chosen because it was the previously preferred musical choice from Experiment 1. Silence was produced by simply turning off the stereo system that interfaced with that particular side of the apparatus. Sixty min conditioning sessions took place on days 2–5, with test subjects (n=8) receiving one daily conditioning session pairing cocaine (10

mg/kg) and Beethoven, and one daily conditioning session pairing saline with silence. Control subjects ($n=8$) received saline during both daily conditioning sessions. Therefore, animals in the test group received four cocaine-music pairings with Beethoven, and four pairings of saline with silence. Animals in the control group received a total of eight saline conditioning sessions, four with Beethoven and four with silence. Although subjects exhibited a significant group preference for silence over Beethoven, the biased design employed in this experiment was slightly different than in Experiment 1. In Experiment 1, we conditioned each animal to its least preferred musical selection, while in this experiment we conditioned all subjects to Beethoven, which statistically was the least preferred choice of the entire group. Animals were injected i.p. just prior to being placed in the conditioning chamber, and the music or silence condition was started immediately. These two daily conditioning sessions occurred in the morning and afternoon, with four to six hours elapsing between sessions. These morning and afternoon sessions were counterbalanced, such that, if an animal received cocaine treatment in the morning on day one, they would receive saline treatment in the morning on day two. After the four consecutive conditioning days, animals were returned to the musical preference apparatus and tested on day 6 to determine what effect this conditioning had on Beethoven vs. silence preference.

Data Analysis

Difference scores were tabulated by subtracting the time spent in the chamber during baseline sessions from the time spent in the chamber during test sessions. These difference scores were then analyzed by comparing test and control groups via independent samples t -tests. Locomotor activity and baseline musical preference were also compared using t -tests.

Results

Experiment 1: Baseline assessment of musical preference indicated that rats preferred Beethoven to Miles Davis. Of the 20 rats examined, eighteen of them showed a preference for Beethoven, and only two showed a preference for Miles Davis. Rats spent significantly more time on the Beethoven ($M=2478.7$, $SD=357.1$) side of the apparatus during baseline preference testing than on the Miles Davis ($M=1121.3$, $SD=357.1$) side of the apparatus ($t_{(38)} = 12.02$, $p < .0001$). The animals in our test group, receiving cocaine in association with their least preferred music, showed an increased preference for that music when compared to control animals. Difference scores show that animals conditioned with cocaine ($M=387.2$, $SD=419.3$) spent significantly more time in the presence of the cocaine-paired music than control ($M=-115.0$, $SD=564.1$) animals during the final preference test ($t_{(18)} = 2.29$, $p < 0.05$) (Figure 1a); additionally, these test animals exhibited significantly greater ($M=3.80$, $SD=1.31$) locomotor activity than control animals ($M=2.36$, $SD=0.80$) during the final test session ($t_{(18)} = 2.76$, $p < 0.05$) (Figure 1b). These same groups showed no significant locomotor differences during baseline testing. There were also significant locomotor differences between baseline (day 1) and final testing (day 6) within the saline/music group ($t_{(14)} = 4.10$, $p < 0.01$) as well as between baseline of the cocaine/music group and final testing of the saline/music group ($t_{(18)} = 3.51$, $p < 0.01$) (Figure 1b).

Experiment 2: Baseline preference between Beethoven and silence revealed that rats preferred silence to Beethoven. Of the 16 rats examined, twelve of them showed a strong preference for silence, and 4 displayed a slight preference for Beethoven. Rats spent significantly more time on the silent side ($M=2197.0$, $SD=456.7$) of the apparatus during baseline preference testing than on the Beethoven ($M=1403.0$, $SD=456.7$) side of the apparatus ($t_{(30)} = 4.92$, $p < 0.0001$). The animals in the test group that received cocaine conditioning with Beethoven showed an increased preference for the music when compared to control animals. Difference scores illustrate that animals conditioned with cocaine spent significantly more time ($M=452.6$, $SD=527.2$) in the presence of the cocaine-paired music

than control animals ($M=-207.9$, $SD=616.7$) during the final preference test ($t_{(14)} = 2.30$, $p < 0.05$) (Figure 2a); furthermore, these test animals exhibited significantly greater locomotor activity ($M=4.22$, $SD=1.77$) than control animals ($M=2.76$, $SD=0.65$) during the final test session ($t_{(14)} = 2.19$, $p < 0.05$) (Figure 2b). There were no significant locomotor differences between groups during baseline testing. When comparing locomotor activity between baseline (day 1) and test (day 6) sessions, there were also significant differences for the saline/music group ($t_{(14)} = 2.63$, $p < 0.05$) and between the baseline cocaine/music and test day saline/music groups ($t_{(14)} = 2.41$, $p < 0.05$) (Figure 2b).

Discussion

The results of this study demonstrate that, after repeated cocaine exposure in the presence of music, rats developed a conditioned context preference (CCP) for the music. This was illustrated by animals spending significantly more time in the presence of the music associated with cocaine than their respective controls. These results are consistent with other recent studies showing that music can be used effectively as a contextual CS in rats (Feduccia & Duvauchelle, 2008; Otsuka et al., 2009; Polston et al., 2011). Furthermore, our findings are consistent with other CPP experiments showing that repeated administration of a drug in a particular environment causes animals to subsequently develop a preference for that environment (Bardo et al., 1995; McCallum & Glick, 2009; Tzschentke, 2007). Although our results are comparable to the results usually achieved with CPP, one major difference in our approach was that we used a different apparatus and setting for conditioning sessions than we used for test sessions. Therefore, our animals were not conditioned to environmental cues within a particular place. Instead, they were conditioned to a contextual cue in a different environment, which in this case happened to be music. Conditioning and testing in different environments provided more certainty that music was the determining factor accounting for the CCP effect.

Another interesting finding was that our animals who received cocaine conditioning with music showed significantly higher locomotor activity during final testing than controls. Previous studies pairing rewarding drugs with simple CS have shown similar locomotor effects (Bevins, Besheer, & Pickett, 2001; Rodríguez-Borrero et al., 2006). Our findings are also corroborated by recent studies showing the impact of a musical CS on locomotor activity (Feduccia & Duvauchelle, 2008; Polston et al., 2011). One potential confound in our study might be that we did not adequately control for the residual effects of cocaine itself. While it is possible that four consecutive days of cocaine administration could account for our observed CCP and locomotor effects, it is highly unlikely. In previous experiments, using a similar classical conditioning procedure, we included explicitly non-paired and no-music controls and did not see a significant locomotor effect (Polston et al., 2011).

Another factor to be considered is the possibility that habituation may play a role in the locomotor effect during final testing. It is evident from Figures 1b and 2b that, in both experiments, the animals that were not conditioned with cocaine showed significantly decreased locomotor activity when compared to either group during baseline testing. However, the apparatus was novel during baseline testing, and one would expect to see more exploratory behavior during this session as compared to the final testing session, when all animals would have had experience with the apparatus. Therefore, the data of the test and control animals during final testing are the most important data to compare; and this analysis clearly shows that the cocaine/music animals exhibited greater locomotion when compared to that of their respective controls. The most parsimonious explanation for this effect would appear to be that, after pairing the music with cocaine, the music itself evoked memories of cocaine reward, resulting in psychomotor activation.

It could also be argued that the CCP effect we found should be described as “decreased avoidance” or “decreased aversion” rather than as increased preference. That is, in Experiment 1 our animals did not shift to spending greater than half the test session in the compartment featuring drug-paired music, and thus did not exhibit what is termed as “absolute preference” (Tzschentke, 1998). However, decreased avoidance or aversion does not accurately reflect the operational definition of what constitutes a CPP effect, and therefore should not reflect what we term a CCP effect. The criterion for establishing a CPP effect is not that animals spend greater than half of the test session in one compartment, it is that they show significantly increased preference when compared to their respective controls during final testing. Indeed, in an *unbiased* CPP design, where the animals spend roughly equal amounts of time on both sides of the apparatus during baseline testing, it is quite common for animals to have spent greater than half the session on the drug-paired side during final testing. However, when using a *biased* CPP apparatus, particularly one that produces *significant bias* during baseline testing, one can show a CPP effect without the animals spending greater than half the session on the drug-paired side during final testing. Therefore, especially in Experiment 1, where animals showed a significant bias for one condition over the other, it is unnecessary for subjects to have spent more than half the test session in the presence of the drug-paired music to be able to refer to the effect as increased preference or CCP; it is only necessary for subjects to have spent significantly more time in the presence of the drug-paired music than their respective controls.

While the main purpose of this study was to determine whether music was an effective contextual CS, we were also interested in determining what an animal’s preference might be for particular kinds of music, and whether rats would prefer music or silence. The results clearly indicate that rats prefer Beethoven’s “Fur Elise” over Miles Davis’ “Four”, and that they prefer silence to Beethoven. We used the music that they had most preferred when we tested music vs. silence, and they still significantly preferred silence during baseline testing. However, in both conditions (music vs. music, music vs. silence), we were able to induce a CCP by pairing the music with cocaine. Our results suggest that rats do not find music rewarding, consistent with previous investigations (Feduccia & Duvauchelle, 2008; Otsuka et al., 2009). The fact that music is not apparently rewarding to rats may potentially make it more attractive as a contextual CS in animal models; that is, if rats experienced pleasure from the music alone, this would further complicate analysis and interpretation.

Evolutionary considerations may help explain why a particular species finds music rewarding. In the current experiments, the music was clearly composed and arranged by human beings. Therefore, it is highly likely that what the rat is hearing in our experiments is quite different from that heard and interpreted by a typical human. To address the reinforcing quality of music in other species, it may be necessary for the music to match that particular animal species’ audiogram (Otsuka et al., 2009). More advanced techniques may be necessary to adequately address whether an animal finds music rewarding. In our experiments, the rats were not able to control volume, and had little control over musical selection. However, the main purpose of this study was not to determine whether rats like music, or had an appreciation for Beethoven and Miles Davis, it was to determine whether they could differentiate between two contrasting pieces of music. In order for music to be an effective contextual CS in rats, they need to be able to recognize and distinguish between complex sound arrangements, and it certainly appears that rats have this capability.

Pleasurable music induces neurological responses in humans that are comparable to the effects induced by drugs of abuse. For instance, highly enjoyable music has been shown to activate reward-related brain regions such as the nucleus accumbens, ventral tegmental area, amygdala, and prefrontal cortex. Enhanced functional connectivity between brain regions that mediate reward may help explain why listening to music is regarded as a highly

pleasurable human experience (Blood & Zatorre, 2001; Menon & Levitin, 2005). It has also been demonstrated that music increases dopaminergic neurotransmission (Sutoo & Akiyama, 2004). The fact that human beings find music rewarding may help explain why music therapy has shown such promising results across a vast spectrum of disorders.

Although there are many conceivable and potential therapeutic uses for music, it may not be practical or possible to assess some of these directly in humans. For instance, it has been shown that contextual CS have the ability to reinstate drug seeking behavior in rats (Crombag, Bossert, Koya, & Shaham, 2008; Fuchs et al., 2008). What has not been shown is whether a contextual CS has the ability to attenuate drug seeking and relapse behaviors. If one were to pair a drug known to attenuate drug-seeking with a particular musical selection, it is possible that the musical CS alone could then attenuate drug-seeking behavior. For ethical reasons, it would likely not be feasible to propose doing this kind of study initially in human beings. Therefore, it is prudent for investigators to have preclinical animal models involving music that could be utilized in situations where testing on humans proves impractical. Studies illustrating that music can serve as an effective contextual CS in rats are an important first step in creating preclinical models that involve music.

While the influence of simple CS on goal directed behavior has been studied comprehensively, more complex contextual CS have not been adequately explored. Utilization of a complex contextual music cue allowed for examination of associative learning that may be comparable to the psychological processes that occur during subjective human drug experiences. Although there is ample literature demonstrating that cue-elicited craving is a fundamental component of addiction, there are still many factors that are not entirely understood (Volkow et al., 2006). The present study is the first to give instrumental control of musical choice to a lower order species. This was done to examine whether a rodent could differentiate between musical selections, and more importantly, to determine if music could function as an effective contextual CS in rats. Our results suggest that rats do show preferences for particular kinds of music, and that these preferences can be altered after drug-paired conditioning. Furthermore, this work demonstrates that music does serve as an effective contextual CS in rats, and that this species is a viable option for use in other preclinical models utilizing musical intervention.

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Figure 1.

Beethoven vs. Miles Davis. Music induces a conditioned context preference and increases locomotor activity in rats: (a) Difference scores between initial baseline test for music preference and test session following music conditioning with 10 mg/kg cocaine or saline; musical conditioning significantly increased the time spent listening to the music that was paired with cocaine. (b) Increased locomotor activity after musical conditioning with cocaine. Conditioning assignments are indicated in the figure. * $p < 0.05$

Figure 2.

Beethoven vs. No music. After being associated with 10 mg/kg cocaine, Beethoven produced a conditioned context preference and increases in locomotor activity in rats: (a) Difference scores between initial baseline test for music preference and test session following music conditioning with 10 mg/kg cocaine or saline; musical conditioning significantly increased the time spent listening to the music that was paired with cocaine. (b) Increased locomotor activity after musical conditioning with cocaine. Conditioning assignments are indicated in the figure. * $p < 0.05$