THE ROLE OF CAFFEINE IN MEMORY EXTINCTION

BY

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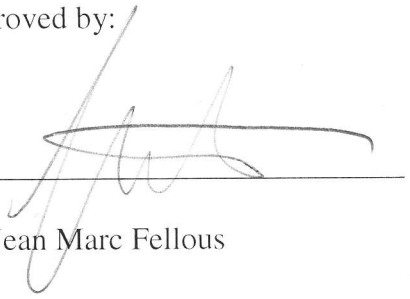

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The Role of Caffeine in Memory Extinction

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Honors Thesis Psychology

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Abstract

Worldwide caffeine consumption is rising exponentially. It has been found that caffeine is a non-selective adenosine receptor antagonist. It affects the A_{2A} receptors of the ventral tegmental area (VTA). The VTA is responsible for assessing rewards and determining motivation to seek rewards. Therefore, it is interesting and important to understand what it could do to probability extinction. Rats received caffeine or saline intraperitoneal injections (randomized per day). The rat was presented pellets a certain percentage of the time through a tube accompanied by a sound, which was referred to as acquisition. For extinction, pellets were no longer presented, but the sound continued and how many attempts the rat made to find a pellet was recorded. Extinction continued till the rat did not try to find a pellet for five trials in a row. We found that only high probability acquisition were significantly different between saline and caffeine. The results indicated that increased locomotor activity, repetition, and anxiety could not be the sole reason caffeine caused delayed extinction. We proposed that an increase of caffeine may have lead to compulsive behavior and a longer extinction for high probability.

Introduction

Worldwide caffeine consumption is rising exponentially. The consumption of caffeine has been found to affect cognition by increasing focus and attention (Nehlig et al. 2010). However, caffeine affects many other cognitive functions through its interaction with dopamine. It has been found that caffeine is a non-selective adenosine receptor antagonist (Maia et al. 2011). It affects the ventral tegmental area (VTA). The VTA is responsible for assessing rewards and determining motivation to seek rewards (Song et al. 2010). In addition, caffeine effects the striatum through blocking the A_{2A} receptors. The striatum is the main projection target of dopamine neurons (Song et al. 2010). In blocking the A_{2A} receptors, it could eventually lead to behavioral changes, such as increase in repetitive behavior and increase in anxiety (Tanimura et al. 2010) (Braunn et al. 2011). These receptors are co-localized with D_2 receptors and affecting the A_{2A} receptors indirectly affects the D_2 pathway, in the striatum (Maia et al. 2011). In the striatum, the D_2 pathway has been labeled the "No Go" pathway meaning that blocking the D_2 receptors leads to activation of the "No Go" pathway and suppression/inhibition of behavior (Salamone et al. 2009). Therefore, caffeine affects cognitive functions through its indirect interaction with dopamine receptors associated with reward recognition.

Since caffeine has been found the affect the VTA it may affect extinction of rewarding events as well (Fiorillo 2003). Extinction is a form of learning that decreases the frequency of a conditioned response when the condition stimulus which signals it is repeatedly unreinforced (Myers et al. 2002). A conditioned stimulus is typically a light or tone that becomes associated with an event through repeated pairing. This event causes a conditioned response in the individual as a result.

It is important to understand the affects of caffeine on probabilistic extinction because life situations are usually uncertain. When making a decision, the amount of effort one is willing to make depends on the amount and probability of obtaining a reward (Song et al. 2010). In addition, conditions of a situation are continually changing. Therefore, it is important for an individual to be able to notice changes in probability or extinction of the previous situation. However, extinction does not occur in a similar way for all probabilities. It has been found that probabilistic extinction follows an inverted-u shape in rats (Song et al. 2010) and humans (Lewis et al. 1957) with 50% probability taking the longest amount of time to extinguish and 100% and 25% probability taking the shortest amount of time (Song et al. 2010). This could be that it is more difficult to identify a 50% probability stopped during extinction as compared to 100% or 75%. Also, 25% probability may not be enough of a motivational factor to continue long after extinction (Song et al. 2010).

Dopamine has a role in extinction (Maia et al. 2011). It has been found that dopaminergic firing at the presentation of a conditional stimulus (light or tone) is proportional to the probability of reward (Fiorillo 2003). It has been found that the basal ganglia is the potential neural substrate where probability learning happens. It has been suggested that higher probability rewards are associated with an increased activation of the “Go” pathway leading to an increase in synaptic connection in the form of learning and a decrease in activation of the “No Go” pathway leading to a decrease in synaptic connection and less learning. On the other hand, lower probability rewards are associated with an increased activation of the “No Go” pathway leading to an increase in synaptic connection in the form of learning and a decrease in activation of the “Go” pathway leading to a decrease in synaptic connection and less learning (Maia et al. 2011).

Since caffeine indirectly interacts with dopamine to affect cognition and dopamine plays a role in extinction, it has been hypothesized that caffeine will affect extinction of probability events. We predicted that caffeine will impair extinction of probabilistic rewards because blocking the A_{2A} receptors will indirectly lead to a decrease in the "No Go" pathway. The conditioned stimulus was a sound (beep, bark, cashtill, or drum) and the conditioned response was looking for a pellet that was presented a certain percentage of the time. Extinction was measured by the number of attempts to locate a pellet once pellets are no longer being presented with the conditioned stimulus. Rats were injected with either saline or caffeine before conditioning and extinction occur.

Methods

Animals

Six, brown Norway, male rats (8-10 months) weighing 325-350 g were used. The animals were housed individually. The humidity and temperature controlled colony at University of Arizona was kept in a reverse 12 hr light/ 12hr dark cycle room. Water was freely available. However, food was rationed so that the rat would become 85% of its total weight.

Stimuli and Apparatus

For both extinction and acquisition, a chamber with three holes was used (see figure 1). It had been decided to eliminate the center hole. This decision resulted from functional mechanics and the idea that only two holes were needed to produce the necessary probability. For each of the holes, a tube extended into the chamber ending in a scoop. These two tubes were used for acquisition and pellet (4 mg) presentation. When presented, the pellet traveled down the tube stopping in the scooped tip. The scooped tip prevented the rat from seeing if a pellet had been presented until approaching the tip. Each of the two functioning hole of the chamber contained another tube. These tubes were used for extinction. The ends of the tubes did not extend into the chamber and were blocked at the end. When a pellet was inserted into the tubes, it still produced the sound of a pellet moving down the tube, but without actually presenting a pellet to the rat. This would prevent the rat from knowing whether or not a pellet was presented based on sound.

Each insertion of a pellet in either the acquisition or extinction tubes was accompanied by a sound. The sounds were bark, beep, cashtill, or drum. The sounds were formatted using audio computer programs to insure that they all had the same loudness, length (0.5 sec), and format (.wav). The loudness was selected through observation for a level that was loud enough that the rat appeared to notice the sound, but not so loud that the rat showed signs for fear or

nervousness. Once this sound level was determined, it was maintained through the entire experiment for all rats. Great length was taken to insure the sounds were the same in loudness, length, and format to insure that there was no bias for one over another. In addition, to assure that no bias occurred the sounds were paired to a different acquisition probability for each rat. That was if for some reason the rats liked or noticed on sound over another, it would be balanced out in the results. There were two speakers. Both speakers were placed directly next to the chamber and pointed towards the chamber to make the sound hit the chamber from one unified location.

Drugs and Selection of Doses

It was determined that 10 mg/kg caffeine injected (intraperitoneal) into a rat was about equivalent to 2-3 cups of coffee ingested for humans (Fredholm 1999). It has, also, been previously determined that the LD_{50} for caffeine for rats is around 200 mg/kg (Eichler 1976). In order to insure an effect of caffeine was seen without approaching dangerously or stressfully high concentration levels of caffeine, a dose of 25 mg/kg mixed in 0.9% saline solution was determined.

Caffeine was administered in an intraperitoneal injection 30 minutes before the start of the experiment because this seemed to be the time length allotted for previous studies to ensure caffeine had time to enter the bloodstream and affect the body (Benowitz 1990). The rats received pure 0.9% saline injections as well during control trials. This was to prevent the stress of injections affecting the results. One full day was allowed between injection to make sure that caffeine did not affect the sleep cycle and had time to exit the body. All rats received both saline and caffeine injections. The injections were randomized per experimental day.

Pre-training Procedure

All rats were pre-trained for 2-4 days (for about 30 min to 1 hr each day) before beginning experiments. Pre-training consisted of a different sound that was not used in the experiment to prevent becoming familiar or favoring that sounds over time. Pre-training consisted of 100% probability acquisition were a 4 mg pellet was presented through one of the acquisition tubes after the sound was played. Another pellet was not presented until the rat successfully discovered the first pellet. Pre-training continued until the rat could successfully respond to the sound being presented for 30 trials in a row twenty seconds apart. Once this was achieved the rat began experimental sessions the following day.

Locomotion Data

Before starting the extinction experimental procedure, the locomotion of the rat was measured after both saline and caffeine injections through the use of a motion device. This device measured a variety of items including movement time, total distance, stereotypy count, stereotypy time, and location of rat in cage. Measurement began 30 minutes after injection and lasted for one hour.

Experimental Procedure

Thirty minutes after injection, the rat was placed in the chamber and probability acquisition began (see figure 2). During this phase, a sound cue would signal either the presentation or not of a 4 mg pellet through one of the tubes. It consisted of twenty trials that were twenty seconds apart. Out of the twenty trials, the number of times a pellet was actually presented was based of which probability session was being tested (25%, 50%, 75%, or 100%). The order of probability was counterbalanced. The first and last trial of every acquisition consisted of a pellet being presented and there was no more than four no presentation trials in a

row. This was to prevent the start of extinction before the extinction session began. Each rat completed two probability acquisitions each day lasting approximately 30 minutes.

Immediately following each acquisition session, extinction occurred. There was no time gap between acquisition and extinction. For the extinction session, a pellet was placed in one of the extinction tubes following the same sound used in acquisition until the rat did not approach the appropriate hole for five consecutive trials in a row. Approaching the appropriate hole was measured by whether or not the rat went to the corresponding tip of the acquisition tube to see whether or not a pellet was produced. The rat had to actually approach the end of the acquisition tube in order for it to be considered an attempt. The number of attempts was recorded as an estimation of how long it took for extinction to occur.

Directly after extinction, there was a ten minute break to allow for set up for the next percentage acquisition. During this break, the rat was placed back into its normal cage. The sound cue was switched to the new corresponding sound. The rat was placed back into the chamber and the next percentage acquisition session began. After two acquisition and extinction sessions were completed, the rat was placed back into its cage until the following day. It should be noted that the order of probability acquisition varied between rats.

Data Acquisition

The number of attempts to approach the appropriate acquisition tube during extinction was recorded. In addition, the tone presented, whether a pellet was presented or not, and the response of the rat was, also, recorded. Pellet presentation, rat response, drug administration, and tone presentation were measured in real time.

Data Analysis

For both the caffeine and saline sessions, the average number of attempts made during extinction was found for each percentage for each rat. From those numbers, the average number of attempts for each percentage for each rat was found. In order to normalize the average values for each rat, it was divided by the saline average for all probability acquisitions for the given rat. Using these normalized numbers, an overall average for each percentage for saline versus caffeine was found. A t-test for saline versus caffeine was performed in order to determine the significance of any effect of caffeine. A t-test was, also, performed to indicate any differences between acquisition probabilities for the saline and caffeine conditions.

As for reaction time, the time the rat made a response to the sound cue was subtracted from the pellet presentation time. For each rat, an average reaction time was found for each percentage acquisition for both acquisition and extinction. Reaction times were normalized using based off the saline data for each rat similar to how the number of attempts were normalized. T-test and standard deviation was used to determine significance between saline and caffeine and significance between the different probability sessions themselves.

Results

Caffeine Delays Extinction

The normalized number of attempts after extinction for saline and caffeine was plotted against each probability acquisition session (figure 3). This was done in order to determine if caffeine or saline effects extinction of probability acquisition sessions. From previous work, it had been determined that saline trend followed an inverted-u shape (Song et al. 2010). The graph did not quite produce an inverted-u shape for saline. The normalized number of attempts for 100% acquisition was higher than expected. As for caffeine, it produced an upward trend from 25% to 100% with a significant difference between saline and caffeine for 75% and 100% acquisition. This indicated that caffeine delays extinction of associations that occurred with high probability during extinction.

Caffeine's Effect on Locomotion Does Not Explain Its Effect on Extinction

Out of the motion data collected, two graphs were produced of movement time and total distance plotted against time in minutes (figure 4 and 5). Both of these are an indication of locomotion activity. They were measured in order to determine if caffeine's effect on locomotion could explain any effect on extinction. It has been found that caffeine seems to increase activity, overall. The amount of both movement time and total distance decreased with time for both the saline and caffeine conditions. There was a slight trend that caffeine increased activity, but that was not significant. The effect of caffeine on extinction of probabilistic rewards was not due to a change in locomotion activity.

In looking at reaction time, a graph was produced for both the acquisition and extinction reaction times (figure 6 and 7). This data was analyzed as another way to determine if caffeine's effect on locomotion was responsible for its effect on extinction. A significant difference

between saline and caffeine reaction times, overall, would indicate a difference in locomotion activity between the saline and caffeine sessions. For the acquisition reaction time graph, only one significant difference between saline and caffeine was determined at 25% probability, but not for any other probability. As for the extinction reaction time graph, there was a significant difference between saline and caffeine for 25% and 75% probability, but not for the other two probabilities. We found some significant differences at 25% and 75% probability, but there was no consistency in the data when compared to caffeine's effect on extinction. Instead of producing a difference for higher probabilities, the significant differences appear to be more random. This indicated that caffeine's effect on extinction was not due to a change in reaction time.

As a final indicator of whether or not caffeine's effect on locomotion causes its effect on extinction, the influence of probability order on extinction for caffeine was determined (figure 8). Since the level of caffeine in a rat decreased over time, caffeine's effect on locomotion was decrease with time as well. No significant difference was found between if the probability was presented first or second during acquisition for saline. Although the caffeine level in the body was decreasing with time, this change has no effect on extinction.

The stereotypy count and time for saline and caffeine sessions was plotted versus time (figure 9 and 10). It has been found that stereotypy measurement can be a measure of repetitive behavior level. It has, also, been determined that adenosine agonists decrease stereotypy behavior frequency or repetitive behavior (Tanimura et al. 2010). The stereotypy count and time decreased with time for both the saline and caffeine sessions with caffeine slightly increased with caffeine, but not significant. This would indicate that the effect of caffeine on extinction of probabilistic rewards is not due to an increase in stereotypy.

For the motion data, the location of the rat over the course of the hour was tracked. It has been found that being in the center of an open area is associated with lower levels of anxiety. In addition, previous research has found that caffeine has been correlated to an increase in anxiety (Braun et al. 2011). The percentage of time in the center was plotted for both the saline and caffeine conditions indicating level of anxiety (figure 11). Although not significant the caffeine percentage of time in the center was slightly higher than the saline percentage of time in the center. Our dose of caffeine did not induce anxiety. The effect of caffeine on probabilistic extinction is not due to caffeine induced anxiety in our experiment.

Discussion

By injecting caffeine we explored the effect on extinction of probability reward. Acquisition consisted of 20 trials. The number of pellets presented depended on the probability of the acquisition session. Extinction immediately followed acquisition and lasted until the rat did not approach the appropriate end of the acquisition tube. There was a ten minute break between the two probability sessions completed each day. It was found that caffeine delays extinction of associations that occurred with high probability during acquisition.

Caffeine's effect on extinction is not due to its effect on locomotion activity because although there seems to be an increase in locomotion activity for caffeine (figure 4 and 5), this would suggest that caffeine would affect extinction of all four probabilities because activity level was increased for all. However, only 75% and 100% probability acquisition was delayed with caffeine. This indicates that caffeine's effect on extinction is not due to a change in locomotion because the overall trend of caffeine on locomotion is increased as compared to saline (figures 6 and 7). This would suggest that caffeine would affect all probability extinctions equally because it would increase locomotion activity equally for all probabilities. It delays reaction time because the rats become more distracted and tend to explore more. Finally, a change in locomotion activity does not explain caffeine's effect on extinction because there was no difference in the order in which probability was presented for caffeine (figure 8). Although the caffeine concentration in the body decreased with time, and, therefore, locomotion effect of caffeine decreased with time, this did not affect extinction. Therefore, the effect of caffeine on extinction of probabilistic rewards was not due to a change in locomotion activity.

An Increase in Stereotypy Behavior Does Not Explain Caffeine's Effect on Extinction

Tanimura et al. 2010 found that stereotypy behavior was related to repetitive behavior in rats and that adenosine agonists decreased stereotypy frequency. There was a general increase in our experiment of stereotypy, but not significant. Therefore, this does not explain caffeine's effect on extinction (figure 9 and 10). This would suggest that caffeine would affect all probabilities the same by delaying extinction because of an increase the repetitive behavior of seeking the reward.

Increase in Anxiety Does not Explain Caffeine's Effect on Extinction

It was found that high doses of caffeine, 100 mg/kg, were related to anxiety (Braun et al. 2011). However, anxiety did not play a factor in this study because percentage of time in the center was higher for caffeine, overall (figure 11). This would indicate a slightly lower level of anxiety for rats that have had a caffeine injection. The lack of anxiety detection for caffeine could be explained by the difference between 25 mg/kg caffeine injection given for this experiment and the 100 mg/kg injection given for the Braun et al. 2011 experiment. Anxiety did not seem to play a role in extinction in our experiment because, although a change was noted, it was not significant. Even when it did produce anxiety at high doses, it could not explain caffeine's role on memory extinction for 75% and 100% probability alone because it would affect all probabilities the same.

Possible Explanation: Caffeine May Delay Extinction Due to Increase in Compulsive Behavior

A possible explanation for caffeine delaying extinction of associations that occurred with high probability during acquisition is the co-localization of adenosine and dopamine receptors that may lead to compulsive behavior and a longer extinction (figure 12). It has been determined that caffeine in a nonselective adenosine receptor antagonist, which suggests that it effects A_{2A} receptors by blocking their activity. In addition, it has been found that D_2 receptors and A_{2A}

receptors are co-localized in the striatum (Salamone et al. 2009) (Svenningsson et al. 1999). Therefore, if caffeine blocks the A_{2A} receptor activity, it would affect the D_2 "No Go" pathway (Maia 2011). By blocking the A_{2A} receptors, they inhibit extinction by blocking the "No Go" pathway which would prevent the suppression of behavior.

Dagher et al. 2009 found that compulsive tendencies increased significantly in patients after starting the treatment of L-Dopa for Parkinson's disease. L-Dopa is an increase in dopamine activity in the brain. This would mean that D_2 receptor activity would increase which in turn would inhibit the "No Go" pathway which would inhibit suppressive behavior, similar to what caffeine may be doing. This increase in L-Dopa and decrease in D_2 "No Go" pathway led to compulsive behavior. Before taking L-Dopa, there was no or little compulsive tendencies seen in the Parkinson's disease patients. After taking L-Dopa, the patients illustrated a significant increase in compulsive tendencies, including gambling and addiction. Therefore, it's reasonable to predict that caffeine's effect on 75% and 100% probability may be due to an increase in compulsive behavior. This would, also, explain why it only effect more certain probabilities because the compulsive behavior needed a more certain reinforcement during acquisition to initiate.

Overall, the result in a delay in extinction for 75% and 100% probability could indicate an increase of compulsive behavior due to caffeine. Although it is difficult to directly indicate how this finding may affect humans, it is now know that caffeine could cause compulsion for more certain events. In the future, it would be interesting to look into whether a similar experiment comparing L-Dopa and saline would produce the same results. If so, this would support the conclusion that the delay in extinction for caffeine was due to an increase in

compulsive behavior. Also, it would be interesting to look at electrophysiology and the activity of the cells in the VTA and striatum to see how both areas are affected.

Figures

Figure 1:

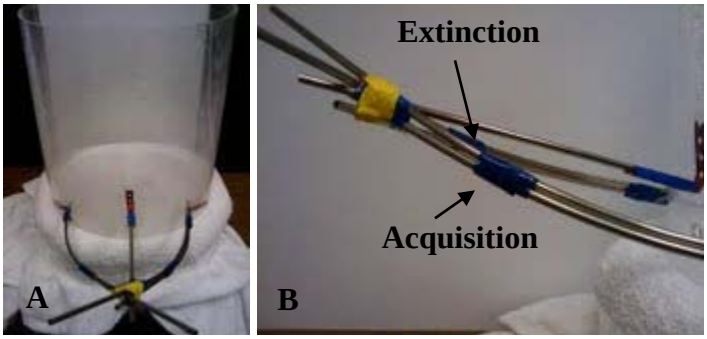

Figure 1: (A) Shows the entire chamber where the rat was placed with both the Acquisition and Extinction tubes. (B) Of the tubes: Extinction tubes on top (do not extend into chamber) and Acquisition tubes are below (extend into chamber).

Figure 2:

Day	Session probability	Acquisition phase		Extinction phase
1	25%	20 trials; 5 rewards	No temporal gap	Sound without pellet until the rat does not make attempt for 5 consecutive trials
	50%	20 trials; 10 rewards		
Day Break				
2	75%	20 trials; 15 rewards		
	100%	20 trials; 20 rewards		

Figure 2: Illustrates a possible experimental session. Probability, sound, and order were randomized.

Figure 3:

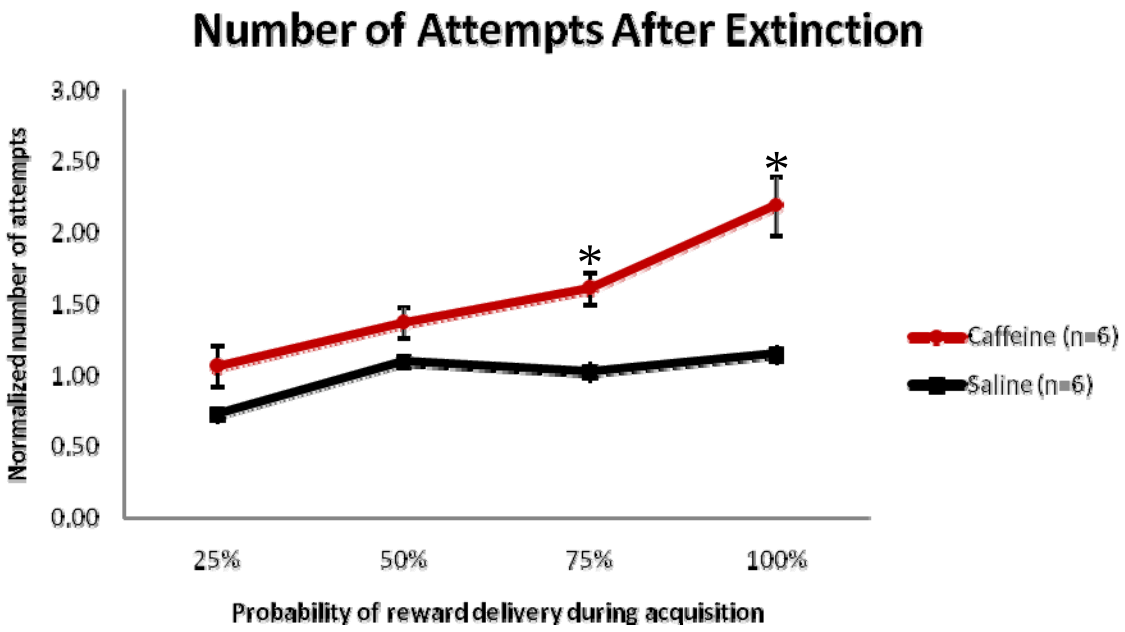

Figure 3: Shows the number of attempts after extinction for both saline and caffeine. 75% and 100% probabilities are significantly different (t-test; $p < 0.05$; N=6).

Figure 4:

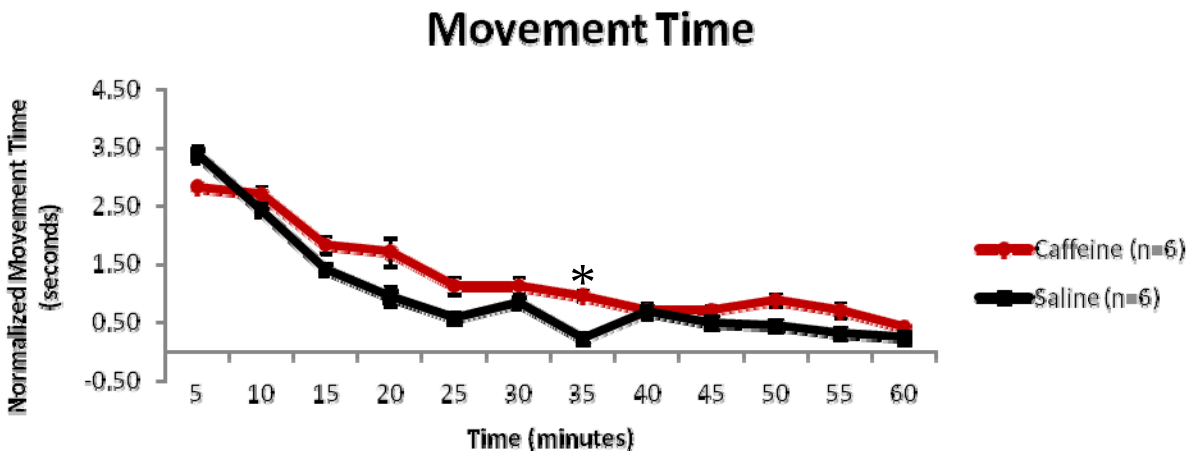

Figure 4: The normalized movement time for both saline and caffeine, which both decrease with time. Although not significant, caffeine is slightly higher than saline for most of the graph (t-test; $p < 0.05$; N=6).

Figure 5:

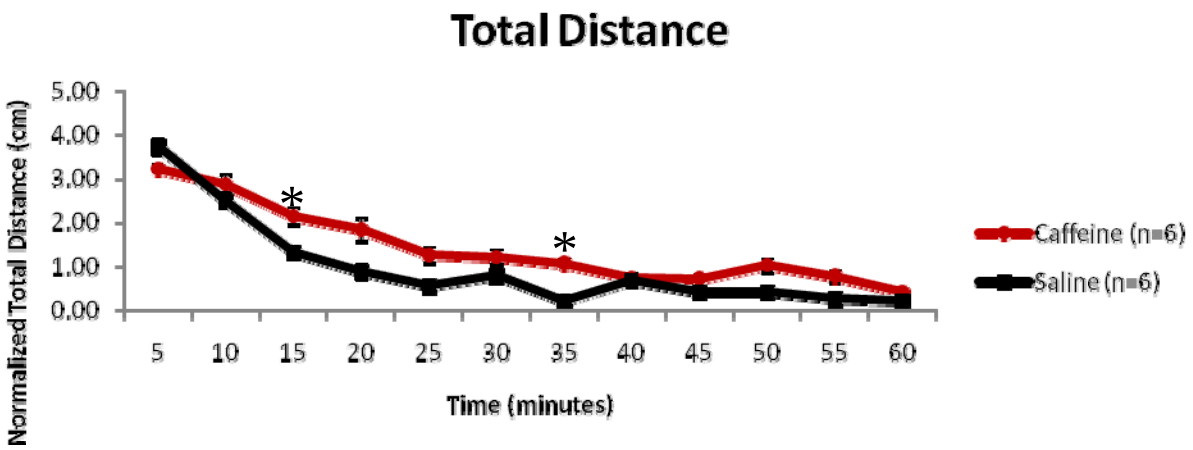

Figure 5: The normalized total distance for both saline and caffeine, which both decrease with time. Although not significant, caffeine is slightly higher than saline for most of the graph (t-test; $p < 0.05$; N=6).

Figure 6:

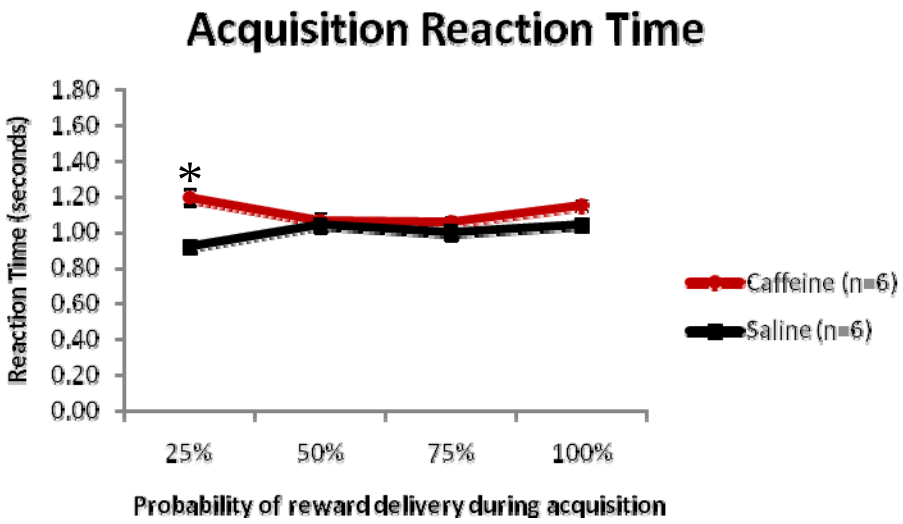

Figure 6: The reaction time for saline and caffeine during acquisition. Overall, there is not significant difference between the two. Caffeine is slightly higher, overall (t-test; $p < 0.05$; N=6).

Figure 7:

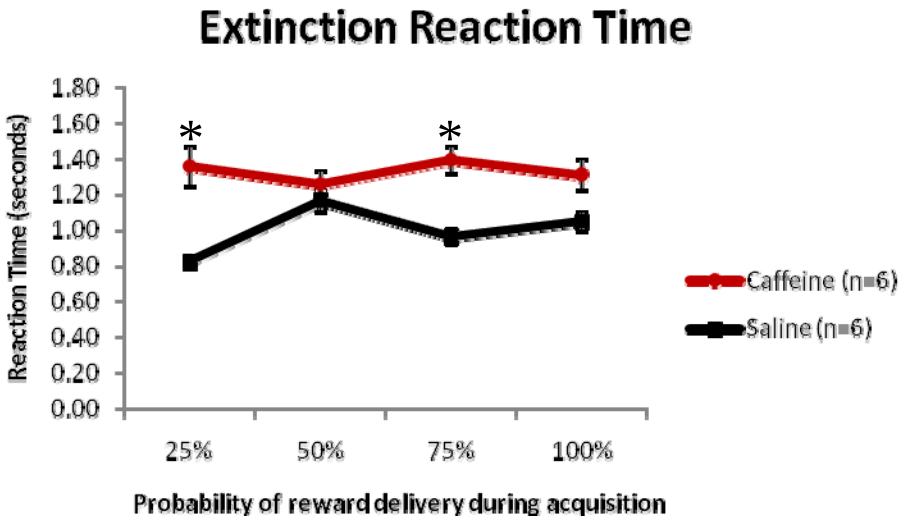

Figure 7: The reaction time for saline and caffeine during acquisition. Overall, there is not significant difference between the two. Caffeine is slightly higher, overall (t-test; $p < 0.05$; N=6).

Figure 8:

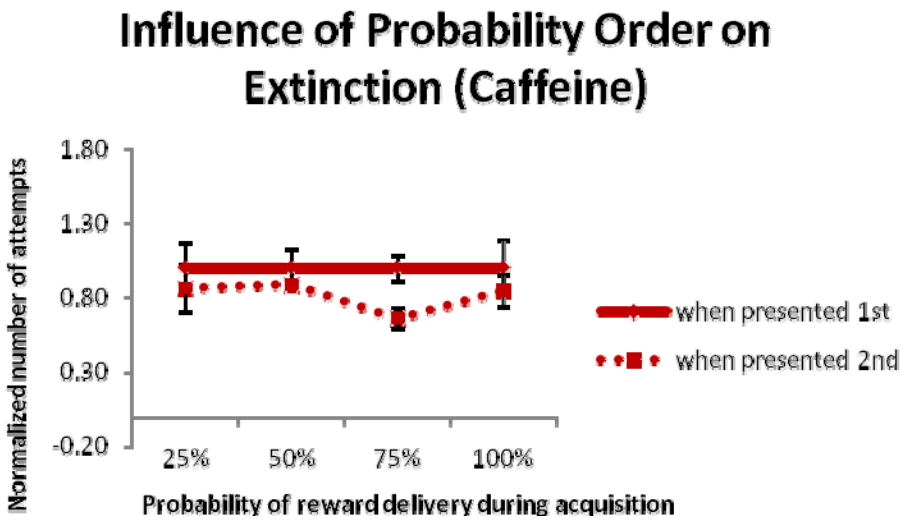

Figure 8: The influence of probability order on extinction for caffeine. No significance indicates there is not a difference between whether the probability was the first to be presented or the second.

Figure 9:

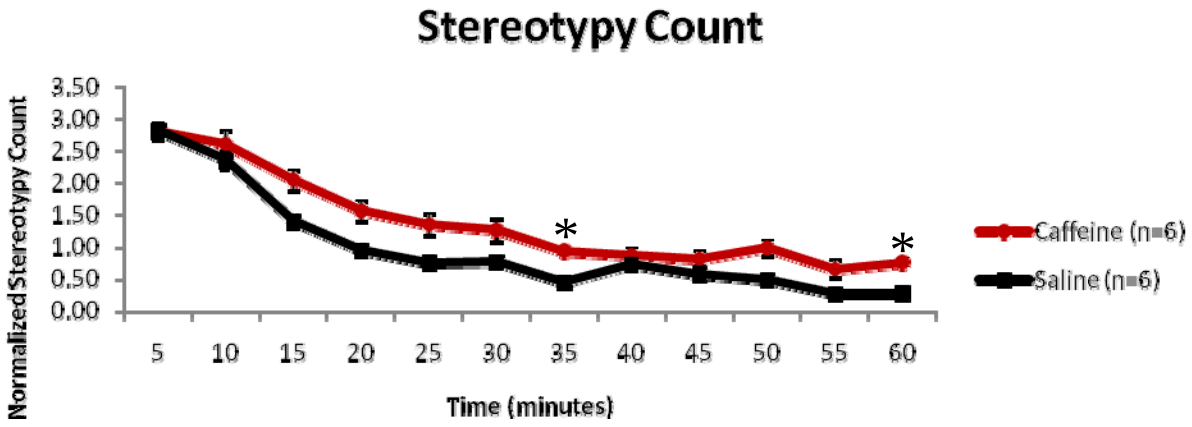

Figure 9: Shows the number of times the rat completed a stereotypy (rearing). It has been linked to repeatitive behavior. Although not significant, caffeine is slightly higher, overall (t-test; $p < 0.05$; N=6).

Figure 10:

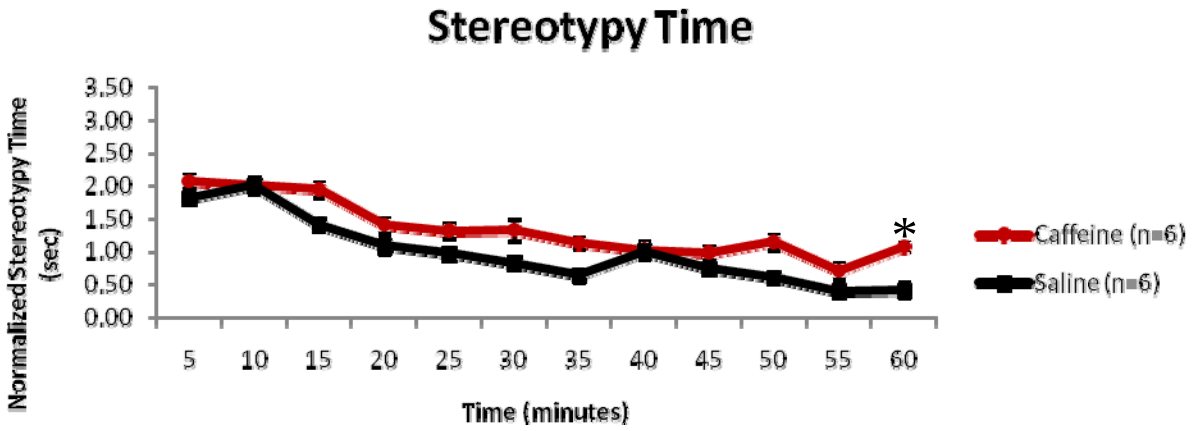

Figure 10: Shows the amount of time the rat spent completing a stereotypy (rearing). It has been linked to repeatitive behavior. Although not significant, caffeine is slightly higher, overall (t-test; $p < 0.05$; N=6).

Figure 11:

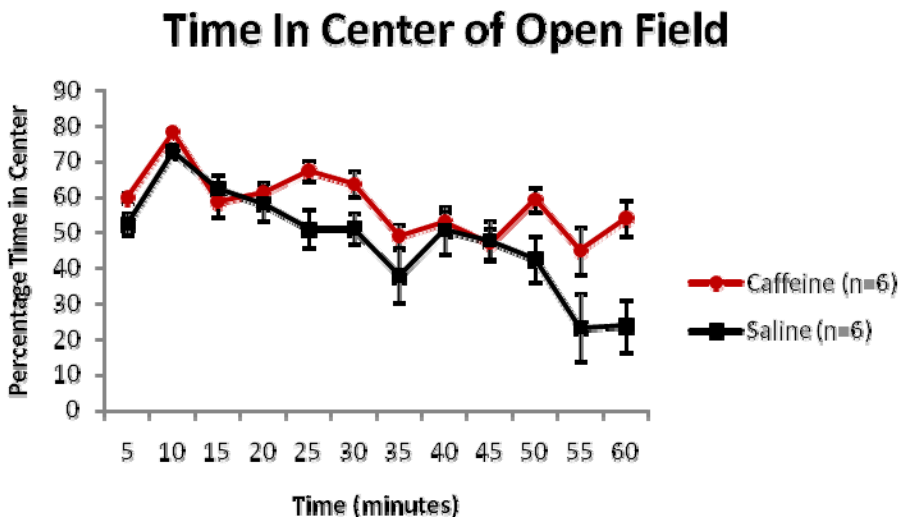

Figure 11: Shows the percentage of time in the center for both saline and caffeine. Since caffeine is slightly higher, it indicates less anxiety associated with caffeine.

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Figure 12:

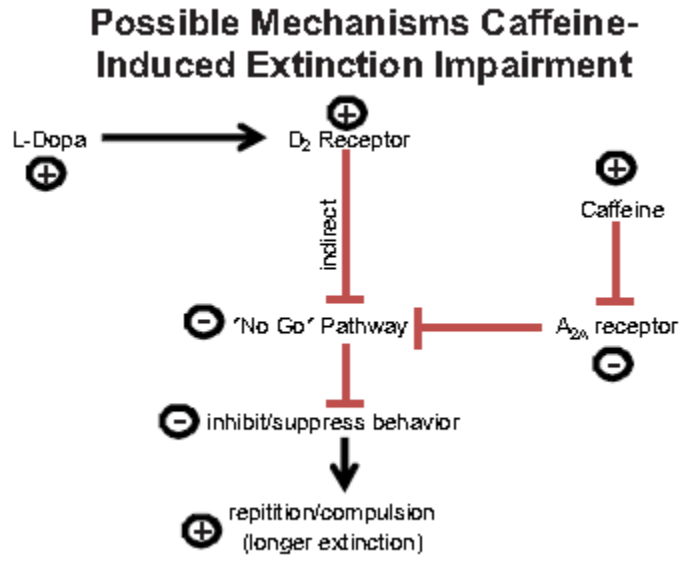

Figure 12: A possible mechanism for caffeine-induced extinction impairment. Caffeine indirectly affects D_2 pathway by blocking A_{2A} receptor activity. This leads to decreasing inhibiting/suppressing behavior and an increase in repetition/compulsive activity.

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