LOCATION, BUT NOT CUE, CHANGES HELP TO REDUCE INTERFERENCE BETWEEN COMPETING RESPONSES

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Location, But Not Cue, Changes Help to Reduce Interference Between Competing Responses

by

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Abstract

Although response reversal learning is subject to interference, providing contextual changes between reversals can reduce this interference and facilitate response reversal learning. The contextual changes that facilitate response reversal learning (i.e., room and direction changes) also cause global remapping in hippocampal place cells. This hippocampal remapping may allow rats to differentially encode memories thus enabling them to learn a response reversal task since the learning in one context will not interfere with the learning that took place in another context. In the present experiment rats were presented with contextual changes including changing rooms, maze orientation, and the color and shape of the room. The only rats that showed improved performance across reversals were rats that received changes in maze orientation or rooms between reversals. Changes in color and shape of the experimental enclosure did not facilitate response reversal learning. Since changes to color and shape have been linked to hippocampal rate remapping we speculate that global remapping, but not rate remapping, allows rats to differentially encode memories.

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Location, But Not Cue, Changes Help to Reduce Interference Between Competing Responses

Associations between neutral and unconditional stimuli are both formed and extinguished in environments that are not predictive of the onset of the unconditional stimulus. The environment in which learning and extinction take place is referred to as the context for learning. Any particular context consists of a combination of multiple stable features that serve as a background to conditional and unconditional stimuli. Individual stable features within a context may be changed without changing the context (Rudy, 2009).

Changes in context are important to the retrieval of learned associations even though the amount of feature variation needed for a change in context to occur is not well defined (Rudy, 2009). The importance of context change has been demonstrated when renewal (Frohardt, Guarraci & Bouton, 2000), spontaneous recovery (Bouton & Moody, 2004), response reversal learning (Chiszar & Spear, 1969; Cheng, 2005; Wright, Williams, Evans, Skinner, & Martin, 2009), and stimulus reversal learning (McDonald, King & Hong, 2001; Thomas, Mckelvie & Mah, 1985; Walsh, Skinner & Martin, 2007) have been studied. The results from these studies could be attributed to a reduction of interference caused by a change in context. Proactive interference occurs when a previously learned association interferes with the acquisition of new learning. Retroactive interference occurs when new learning interferes with the recall of a previously learned association (Bouton & Moody, 2004).

Recent findings suggest that changes in context that reduce both proactive and retroactive interference can be connected with changes that occur in the hippocampus. The following review will summarize the behavioral data on the role of context to acquisition and recall of learned associations. It will also summarize the data that suggest a role for the hippocampus in utilizing contextual changes for the reduction of interference.

Behavioral Data

If a subject is presented with multiple exposures to a CS alone any associative strength between the CS and US will return to zero. This is what's known as extinction. Extinction has been described as a learned association that interferes with the recall of previously learned associations as opposed to the destruction of the previously learned association (Bouton, 2004; Pavlov, 1927). Since contextual changes reduce interference a change in context should mitigate the effect of extinction. The importance of context to extinction was demonstrated by Frohardt et al. (2000) who studied the renewal effect. Rats, that had previous exposure to box A and box B, had a "lights off" cue paired with a mild electric shock in box A. Once the association was formed the rats underwent extinction, where the "lights off" stimulus was presented without shock. The rats received the extinction trials in either box A, where they received the original pairing between the stimulus and the shock, or box B, where they had never received shocks. Both boxes were located in different experimental rooms. The change in boxes and rooms provided the rats with different contexts. When placed back into box A and exposed to the "lights off" stimulus the rats that received their extinction trials in box B displayed more fear behavior than rats that were extinguished in box A.

The findings from Frohardt et al.'s (2000) study indicated that changing the context between acquisition, extinction, and test trials successfully reduced the interference experienced by the rats. Learning from the extinction trials interfered with learning from the acquisition trials if the rat had not received a change in context, this resulted in reduced fear on test. Learning from the acquisition trials was protected from interference from the extinction trials when a change in context occurred, resulting in a renewal of the fear response. Subsequent experiments have replicated this finding (Bouton & Ricker, 1994) and revealed that the renewal effect also occurs in appetitive situations (Bouton & Ricker, 1994; Rhodes & Killcross, 2007).

Context has also been shown to facilitate the retrieval of learned associations even when the context is a single background cue. Spear (1971) exposed rats to a conditioning box that had two different colored ends, white and black, where shocks could be delivered. Half the rats were exposed to a tone when they had to avoid the black end of the apparatus while the other half were not exposed to a tone. Once the behavior of avoiding the black end was acquired the rats were trained to avoid the white end in the absence of the tone. Sixty minutes after acquisition the rats were placed back into the apparatus and presented with the tone. Rats that had previous exposure to the tone avoided the black end more than the rats that did not have previous exposure to the tone. In this experiment the tone, since it was a stable feature of the environment, was a contextual cue. Rats showed renewed fear responding after extinction if they were exposed to a context that was similar to the context in which they were previously shocked.

The passage of time has been considered a type of contextual change, which can be used to explain the phenomenon of spontaneous recovery (Bouton & Moody, 2004). Pavlov (1927) observed that previously extinguished associations would spontaneously return with the passage of time. This observation indicated that the learned association had not been lost during extinction but had been actively inhibited during non-reinforcement and that a change in context brought about by the passage of time resulted in the re-emergence of the extinguished association (Bouton & Moody, 2004; Pavlov, 1927).

Support for the idea that a context will be treated as different when time intervenes between two exposures was provided by Spear (1971). Rats were placed in an apparatus with two differently colored ends, white and black, and they were shocked whenever they entered the black end. The rats learned to avoid the black end. After the association between the black end and shock was formed, the conditions were reversed and the rat received shocks whenever they stayed in the white end. The rats were removed from the apparatus for a period of time once they had learned to avoid the white end. If the rat was placed back into the apparatus when only three minutes had passed the rat continued to avoid the white end of the apparatus. If the rat was placed back into the apparatus when 60 minutes had passed the rat avoided the black end (Spear, 1971). This indicated that the passage of time had affected the rats' treatment of the context in which the black and white discriminations had taken place. It appears that a contextual change in time helps reduce retroactive interference and thus facilitates the response of the first learned association in both Spear's (1971) experiment and spontaneous recovery.

Context changes also affect the retrieval of learned associations between responses and reinforcers. Response reversal learning requires a subject to learn to make a particular response (e.g., turn right or left) in order to obtain a reinforcer. Once the subject learns to make the correct response, the response requirement is reversed. Subjects often show proactive interference, taking more time to learn the new response reinforcer relationship because the first learned response must be extinguished before the appropriate response can be acquired. After the animal has acquired the second association the original reward contingency is reinstated. Re-acquisition of the first learned association may be slower than when it was learned initially since the second learned response must first be extinguished, demonstrating retroactive interference.

Chiszar and Spear (1969) demonstrated that a change in context between reversals reduced both proactive and retroactive interference. Two different, but comparable, mazes were set up in two different rooms. Rats were trained to turn left to receive a food reward. When a rat reached criterion on the first problem the reward contingency between the response and the food reward was reversed. Half the rats in the experiment received no additional changes between reversals (No Change) while the other half experienced a change in rooms between reversals. The rats that received the change in room between reversals made fewer errors to reach criterion than rats that received no contextual changes. When the rats reached the criterion for the reversal trials, the reward contingency was reversed again, such that it was identical to the first problem. The rats that received a change in context between reversals were protected from interference. When no contextual change occurred, the most recently learned association interfered with the current task.

Changing locations between trials appears to facilitate the recall of the events from previous trials by reducing interference. When placed on a radial arm maze rats have a strong tendency to forage for food on arms not yet visited. A revisit to an arm previously entered can be interpreted as an error in recalling a visit to that arm. Roberts (1981) showed that rats could recall the arms visited on up to three different mazes simultaneously if they were positioned in different locations. Retroactive interference was observed when the location of the maze did not change. Rats were forced to enter four randomly chosen arms on an eight arm radial maze and received a food reward at the end of each arm. Once the four forced choices were made the rats were forced to enter four randomly chosen arms on a second maze. The location of the second maze was either next to (second maze had the same z-y coordinates but shifted along the x-axis) or above the original maze (second maze had the same z-x coordinates but shifted along the y-axis). The original maze never changed location. The rats were then allowed to freely explore the original maze. The rats avoided arms that were previously visited on the original maze. In the next experiment rats were forced to enter four arms on the original radial arm maze. Once the four forced choices were made the rats were exposed to randomly chosen arms on the maze when it was in the same location. Exposure was achieved by the experimenter placing the rat at the end of the arm and gently holding them until the food reward was consumed. Once rats received exposure to the four random arms they were allowed to freely explore the maze. Rats that were exposed to four random arms after the forced choices on the original maze did not avoid arms they were forced to enter on the first trial as frequently as rats that were exposed to a change in maze location. Not changing location between trials appeared to cause interference that could otherwise be prevented by a change in location.

The reduction of interference caused by a change in context is not just limited to response reversal learning. McDonald et al. (2001) trained rats to search lit arms in an eight arm radial maze for food. On each trial, four arms were lit randomly and the rat was left on the maze until all the food had been recovered or 10 minutes had elapsed. When the rat received the food reward on a lit arm, the lights for that arm were turned off. Once rats reached criterion of 85% choice accuracy over the course of two days of training, they were subjected to a reversal. In the reversal the rats had to forage for food in the non-lit arms. Half the rats received room change after the reversal, while the other half did not. Once criterion was reached the rats were given a renewal trial that took place in the original context. In the renewal trial none of the arms were baited and only the first eight arm entries were recorded. Rats that had received a change in room took fewer trials to reach criterion than rats that received no change, indicating that the contextual change in room helped reduce proactive interference.

Evidence of changes in context reducing interference between reversals in stimulus reversal learning has also been shown in vertebrate species other than rodents. In a stimulus reversal learning experiment conducted by Walsh et al. (2007), seals were trained to choose between two items in order to receive a food reward. Once the seals chose the correct item to a criterion of 18 correct choices out of 20, the conditions of reward were reversed. If the seals experienced a change in tank between reversals they took fewer trials to reach criterion than seals that experienced no contextual change between reversals. Here again we can see that a contextual change in location helped reduce the proactive interference experienced by the seals when they were required to make a response that was opposite to a response they had already acquired.

Context changes also protect invertebrates from proactive and retroactive interference. Cheng (2005) trained bees to search for a bottle cap full of sugar water to one side of a green landmark on table one. Each bee was given 10 training trials to locate the sugar water. After ‘task 1’ the bees were given a test phase, where the green landmark was placed on table one and four empty bottle caps surrounded it. The amount of time spent searching each quadrant around the landmark was recorded. After the first test the bees were given ‘task 2’, where they were exposed to a blue landmark with the sugar water located on the opposite side from where it was in ‘task 1’. Half the bees were trained on ‘task 2’ on the same table as ‘task 1’ while the other half were trained on a new table, which was located a few meters from table one. The change in tables served as a change in context. Once the bees received 10 trials on ‘task 2’ they were tested in the same conditions as ‘task 1’. Bees that received training in ‘task 2’ with a change in location searched the correct bottle cap more often than bees that did not receive a contextual change. These findings, combined with the findings discussed above, indicated that contextual cues can reduce interference between learned responses in both invertebrate and vertebrate species.

The types of contextual changes that enable a subject to differentially encode memories have not been properly identified. Additionally, the types of contextual changes that provide a subject with protection from interference can vary between species. This was highlighted by behavioral studies with pigeons (Thomas et al., 1985) and rats (Wright et al., 2009). Thomas et al. (1985) showed that changes in lighting provided protection from interference in pigeons, while similar changes were not sufficient to provide protection from interference in rats (Wright et al., 2009).

Thomas et al. (1985) trained pigeons to peck a particular color key light when a house light was turned on and a tone was sounded. The pigeons were then trained to peck a different color key light when the contextual cues of light and noise were reversed. If the pigeons were exposed to a contextual change in light they learned the reversal just as well as pigeons that received a contextual change in both light and noise. Pigeons that received a contextual change in noise alone, however, did not perform as well as the other two groups.

Changes in light and noise appear to be ineffective in reducing interference between learned associations in rats. Wright et al. (2009) trained rats in a response reversal task that was similar to the experiment by Chiszar and Spear (1969) discussed above. In Wright et al.'s study the rats were divided into three groups: cue, room, and cue+room. Cue rats received changes in light and noise between reversals while room rats received a change in room between reversals. cue+room rats received changes both in the room and in light and noise between reversals. Rats that received a change in room quickly acquired the response reversal while rats that were only exposed to a contextual change in light and noise took more trials to reach criterion on the reversal.

Hippocampal Data

Findings from lesion studies suggest that the contribution of contextual cues to discrimination learning is mediated by the hippocampus (Rudy, 2009). It appears that the hippocampal system does not represent all types of contextual changes in the same way. Electrophysiological findings reveal that the hippocampus represents changes in environments, such as wall color, differently from changes in location (Leutgeb et al., 2005). Additionally, it appears that there are types of contextual changes that enable rats to form rapid conditional discriminations, and types of contextual changes that do not (Wright et al., 2009). It is possible that the effectiveness of a contextual cue change at facilitating response reversal learning could be dependent on how that cue change is represented in the hippocampus.

Electrophysiological data indicates that the hippocampus can represent contextual changes in two ways (Leutgeb et al, 2005). These two kinds of representations have expanded our understanding of how hippocampal place cells represent cues. When a change in context occurs the firing patterns of hippocampal place cells may change. Changes in hippocampal firing patterns have been referred to as remapping events. Remapping of place cells has been produced when changes in distal cues (Leutgeb et al., 2005; Lever, Wills, Cacucci, Burgess, O'Keefe, 2002; O'Keefe & Speakman, 1987), changes in proximal cues (Jeffery & Anderson, 2003; Leutgeb et al., 2005; Lever et al., 2002; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005), and self-motion cues (Colgin et al., 2010) occur. The remapping changes that have been observed fall into two classes: rate remapping occurs when the position of the place fields remain constant in relation to one another but the activity level of the place cells either increases or decreases; global remapping occurs when the position of the place fields change in relation to one another or they appear or disappear completely.

Rate remapping can be caused by a change in the environment, such as the color of the walls or shape of an enclosure. Leutgeb et al. (2005) exposed rats to a change in the experimental enclosure while keeping the location of the enclosure constant. Single cell recordings of hippocampal place cells revealed a change in the activity levels of the place cells when the enclosure was switched from a box with white walls to a box with black walls, or vice versa. Since the firing locations of the place fields remained constant to one another, the type of remapping was categorized as rate remapping. The same was true when the shape of the enclosure was changed from a square to a circle, or vice versa. Rate remapping has also been observed when there was an inconsistency between distal and proximal cues between trials. O'Keefe and Speakman (1987) had rats explore a cross maze for a food reward while single cell recordings of hippocampal place cells were taken. The cross maze was located within a controlled cue environment with several distal cues located around the maze. When the distal cues were rotated a majority of the rats' place fields appeared to track the distal cues as well as change their rate of firing. It appears that the observed rate remapping indicates that the rats noticed changes within one particular environment and that rate remapping not only reflects changes in cues but also the relationship of on set of stable cues (the cues manipulated by O'Keefe) to another set of stable cues (background cues that were not manipulated by O'Keefe) .

Global remapping occurs when an enclosure is moved to a new location between trials (Leutgeb et al., 2005). In this instance the firing pattern of place cells in the new location differs completely from the pattern observed in the original location. Disruptions in the rats' path-integration system, which allows the rat to navigate using self-motion cues, can also cause global remapping to occur even while remaining in the same location. Disruptions to the path integration system can be caused by abruptly turning the rat around 180-degrees before placing them in the apparatus (Knierim, Kudrimoti, & McNaughton, 1998). Additionally, the types of environmental changes that would normally cause rate remapping can cause global remapping if the rat is given the opportunity to recognize the two types of environmental changes as distinct places. Colgin et al. (2010) had rats wander freely between two geometrically distinct enclosures (circle and square shaped) via a short corridor. The rats were tested later in a box whose shape could gradually be changed from one shape to another between trials. The hippocampal place cells showed global remapping when the enclosure was changed between a circle and a square. The ability to actively move between the two environments enabled the rats to form two unique representations of the two environments. It appears that the global remapping that was observed indicates that the rats perceive a change in location.

Experimental Hypothesis

It has been shown that changes in context protect animals from proactive and retroactive interference. This protection appears to be based on changes in location (Chiszar & Spear, 1969; Frohardt et al., 2000; McDonald et al., 2001; Walsh et al., 2007; Wright et al., 2009) since changes in cues alone do not produce the same level of protection (Wright et al., 2009). In particular, changes in location produce protection while changes in lighting and noise do not. This protection from interference may be dependent on a functioning hippocampus since hippocampal lesions produce defects in contextual conditioning under certain conditions (Ji and Maren, 2007; Biedenkapp and Rudy, 2009). It is still unclear whether it is only contextual changes that are of the type that would produce global changes in the hippocampus that will protect rats' learned associations from proactive and retroactive interference. The types of cue changes manipulated by Wright et al. (i.e., changes in light and noise) may have produced neither rate nor global remapping in the hippocampus. Investigators have reported that place cells remain unchanged when lights are turned off (Quirk, Muller, & Kubie, 1990). In the current study we investigated if contextual cue changes that are of the type that might produce hippocampal rate remapping are sufficient to reduce interference in a response reversal task.

Experiment 1

There is evidence that changes in the color and shape of an enclosure are represented in the hippocampus (Leutgeb et al., 2005). To test if the types of cue changes that would produce rate remapping are sufficient to reduce interference, rats were exposed to changes in the color and the shape of an enclosure between reversals. These cue changes have been shown to produce rate remapping but not global remapping (Leutgeb et al., 2005). Rats were placed on a T-maze within a curtained enclosure that was arranged in one of four combinations of colors and shapes (black circle, white circle, black square, white square) and were rewarded for making a correct response at the choice point (turn left or turn right). Once the rat had reached a criterion of nine out of 10 trials correct, both the color and shape of the curtain arrangement were changed (i.e., black to white, circle to square) and the required response was reversed (left to right). This continued until the rats completed four reversals. These rats were compared to control rats that received no contextual changes between reversals as well as to rats that received a change in maze orientation (90-degree rotations) between reversals. We used a maze rotation in this experiment because previous work (Wright et al., 2009) revealed that maze rotations supported response reversal learning.

Methods

Subjects

Twenty-four juvenile male naive Long Evans rats, that weighed 100g to 150g at the beginning of the experiment, were used. The rats were kept on a 12 hour light, 12 hour dark cycle with lights on at 0800. After a week of acclimatization the rats were put on food deprivation such that they would gain approximately 5% of their body weight per week. The rats were housed individually in clear plastic cages (45 x 25 x 21 cm) with secure metal lids and bedding covering the bottom. All procedures used in Experiment 1 and 2 were approved by Memorial University's Institutional Committee on Animal Care and follow the Canadian Counsel on Animal Care guidelines.

Apparatus

The experimental room (455cm x 330cm x 260cm) had a door on the south wall that was closed during trials and open between trials. Panels of curtains (60cm x 144cm) were hung from hooks in the ceiling to create a square (244cm x 244cm) or a circle (244cm diameter) in the center of the room. The experimenter could easily carry rats through the curtained enclosure.

A T-maze was placed in the center of the curtained enclosure. The three arms (56cm x 25cm) were painted white and connected to a center platform (25cm x 25cm). The maze was elevated 68 cm from the floor. At the end of each arm was a food cup well. Half a Froot Loop™ could be placed inside and not be visible from the surface of the maze.

At the start of each day the rats were transferred from their home cages to a metal rack with metal holding cages measuring (25cm x 20.5cm x 18cm). The rack of cages was wheeled from the housing room down a hallway to the experimental room and held just outside the experimental room.

Procedure

Pre-training occurred in the housing room. The rats were placed on a table scattered with numerous Froot Loops™. Rats were kept on the table for one to five minutes or until they ate a Froot Loop™. Rats were given one to two trials each day. Pre-training ended when each rat was eating Froot Loops™ within one minute of being placed on the table.

Rats were matched based on the speed that they found and ate the Froot Loop™ on the last pre-training trial and placed into one of three groups [No Change (n=8), Direction Change (n=7), Cue Change (n=9)]. All groups were trained on a response task where they had to turn right or left to locate food on the T-maze. For rats in the No Change condition the arm containing the Froot Loop™ was changed to the opposite arm between reversals but nothing else changed. For rats in the Direction Change condition the baited arm was changed to the opposite arm and the T-maze was rotated 90 degrees clockwise if the start arm was facing the north wall and counter-clockwise if the start arm was facing the east wall. For rats in the Cue Change condition the baited arm was changed to the opposite arm between reversals and the curtained enclosure was changed to the opposite arrangement (Squares changed to circles, Black changed to white, and vice versa). The four possible curtain arrangements [Black Circle, White Circle, Black Square, White Square] were evenly distributed among the three groups.

During training the rats were placed outside the room with the curtained enclosure. There were five training trials on each day. During a training trial a rat was brought into the curtained enclosure and placed on the start arm of the maze where it was given one minute to make a choice before being removed. Half a Froot Loop™ was placed in the food well of either the left or right arm. A correct trial occurred when the rat found the Froot Loop™ and ate it. The rat was then removed from the maze. An incorrect trial occurred when the rat put all four paws on the arm that was opposite the correct arm.

The rat was removed from the maze once it reached the empty food cup or when it tried to leave the incorrect arm. During the first 10 trials rats were allowed to visit both arms before being removed from the maze. After trial 10 the rats were removed after making the first choice. When a rat reached a criterion of nine correct trials out of 10, training ended. On the next day (the first reversal) the location of the reward was reversed to the opposite arm and training continued. The same procedure was followed for the second, third, and fourth reversals.

Results

Rats that were exposed to a change in direction between reversals required fewer trials to reach criterion across reversals. Rats in the No Change and Cue Change groups showed no improvement across reversals (see Figure 1). One subject from the Direction Change group was dropped from the experiment as it refused to leave the start arm after it completed the first reversal. A 3 X 5 (Groups X Reversals) repeated measures ANOVA revealed a significant change in the number of trials to criterion across reversals [F(4, 84)=3.474, p=0.011]. There was neither a significant effect of group [F(2, 21)=1.96, p=0.166] nor a significant group X reversal interaction [F(8, 84)=1.602 p=0.137]. Similar studies have shown a significant group x reversal interaction (Wright et al., 2009) so a difference between the No Change group and the Direction Change group was expected. Analysis of the reversal X group linear interaction revealed a weak effect in the predicted direction (F(2, 21) = 2.89, p = 0.078). The Direction Change group improved across reversals [F(1, 6)=8.602, p=0.026]. The Cue Change [F(1, 8)=2.637, p=0.143] and No Change [F(1, 7)=0.395, p=0.550] groups did not improve across reversals.

Experiment 2

The results of Experiment 1 suggest that changes in the color and shape of the curtained enclosure between reversals were not sufficient to reduce proactive and retroactive interference. The next experiment was conducted in an attempt to replicate the findings from the first experiment that changes in cues fail to facilitate response reversal learning, as well as previous findings that changes in room do facilitate response reversal learning (Wright et al., 2009). Rats that are exposed to a change in room between reversals are also exposed to a change in path between reversals. Previous studies have shown that self-motion cues can cause hippocampal global remapping (Colgin et al., 2010). It is possible that the global remapping associated with a change in location could be due, in part, to a change in path taken to reach the new location. We changed paths to reach the experimental room between reversals in the hope that we would improve our chances of seeing a facilitation of response reversal learning. Changes in path was combined with changes in cues If hippocampal global remapping is important for reducing interference and changes in path can contribute to global remapping then it could be predicted that changing the path taken to reach the experimental enclosure might cause a reduction of interference and a consequent facilitation of response reversal learning.

Methods

Subjects

Twenty-four juvenile male naive Long Evans rats that weighed 100g to 150g at the beginning of the experiment were used. The rats were kept on a 12 hour light, 12 hour dark cycle with lights on at 0800. After a week of acclimatization the rats were put on food deprivation such that they would gain approximately 5% of their body weight per week. The rats were housed individually in clear plastic cages (45cm x 25cm x 21cm) with secure metal lids and bedding covering the bottom.

Apparatus

The T-maze was the same as the one used in Experiment 1. In addition to the experimental room used in Experiment 1 (Room A), a separate experimental room was used that was located on the ground level of the building (Room B). Room B (528cm x 464cm x 267cm) had no curtains in it, had windows on the south wall, a door on the north wall that led to a hallway, a door and shelves on the east wall and shelves on the west wall.

The rats were carried from the housing room to the experimental room in their home cages on a small trolley. During transit the rats were covered by a bed sheet that obscured their view of the path. This was done because visual cues along the paths could not be controlled for. The rats were taken to the experimental room either by a long path or a short path if they were taken to Room A. For the long path the rats were taken down a long hallway, up and down an elevator and were held outside the experimental room. For the short path the rats were taken down a short hallway and were held inside the experimental room but outside the curtain enclosure. If the rats were taken to Room B they were taken halfway down the long hallway, up the elevator, and down a very short hallway to the experimental room.

Procedure

Pretraining was identical to Experiment 1. Rats were matched based on their performance in pre-training and placed into one of four groups [No Change (n=11), Cue Change (n=10), Path+Cue Change (n=12), Room Change (n=11)]. All rats were trained on a response reversal task where they had to turn left or right to locate food on the T-maze. For rats in the No Change condition the arm containing the Froot Loop™ was changed to the opposite arm between reversals but nothing else changed. For rats in the Cue Change condition the baited arm was changed to the opposite arm between reversals and the curtained enclosure was changed to the opposite arrangement (Squares changed to circles, Black changed to white, and vice versa). The four possible curtain arrangements [Black Circle, White Circle, Black Square, White Square] were evenly distributed among the four groups. Rats in the Path+Cue Change condition were the same as the rats in the Cue Change condition except in addition to a changes in the goal arm and the curtain arrangement they also received a change in the path taken from the housing room to reach the start arm of the maze (if they were given a short path during acquisition then they were given a longer path during the first reversal, and vice versa). For rats in the Room Change condition the baited arm was changed to the opposite arm between reversals and the room the maze was located in changed (If acquisition occurred in room A then the reversal occurred in room B and vice versa).

During training the rats were placed outside the room with the curtained enclosure if they took the long path or inside the room with the curtained enclosure if they took the short path. There were four training trials on each day. During a training trial a rat was brought into the curtained enclosure and placed on the start arm of the maze where it was given one minute to make a choice before being removed. Half a Froot Loop™ was placed in the food well of either the left or right arm. A correct trial occurred when the rat found the Froot Loop™ and ate it. The rat was then removed from the maze. An incorrect trial occurred when the rat put all four paws on the arm that was opposite the correct arm. The rat was removed from the maze once it reached the empty food cup or when it tried to leave the incorrect arm. During the first 10 trials rats were allowed to visit both arms before being removed from the maze. After trial 10 the rats were removed after making the first choice. When a rat reached a criterion of nine correct trials out of 10, training ended. On the next day (the first reversal) the location of the reward was reversed to the opposite arm and training continued. The same procedure was followed for the second, third, and fourth reversals.

Results

Rats that were exposed to a change in room between reversals required fewer trials to reach criterion across reversals. Rats in the No Change, Cue Change and Path+Cue Change groups showed no improvement across reversals (see Figure 2). One rat was dropped from both the Path+Cue Change and the Cue Change groups because they were unable to perform the task as they displayed persistent fear and refused to leave the start arm. A 4 X 5 (Groups X Reversals) repeated measures ANOVA revealed a significant change in the number of trials to criterion across reversals [F(4, 164)=2.620 p=0.037] and a significant effect of group [F(3, 41)=6.057, p=0.002) and a significant group X reversal interaction [F(12, 164)=2.208 p=0.013]. Further analysis of the group X reversal interaction revealed differences between the groups' improvement over reversals [F(3, 41)=5.230, p=0.004]. The Room Change group showed an improvement across reversals [F(1, 10)=17.554, p=0.002]. The Cue Change group [F(1, 10)=0.225, p=0.646], Path+Cue Change group [F(1, 11)=1.664, p=0.224], and the No Change group [F(1, 10)=3.398, p=0.095] did not improve across reversals.

Discussion

The findings from Experiment 2 replicated the observation in Experiment 1 that changes in cues did not protect rats from interference. Room changes did protect rats from interference and is consistent with previous findings (Chiszar & Spear, 1969) and with the improvement in performance seen by the Direction group across reversals in the first experiment. The addition of a path change did not improve the capacity of cue changes to protect rats from interference and will be discussed further in the General Discussion.

General Discussion

When presented with a response reversal task, rats that did not receive a change in contextual cues between reversals did not show improvement in the number of trials taken to reach criterion across reversals. Additionally, rats' performance on response reversal learning did not appear to benefit from changes in the color and shape of the experimental enclosure even when the path taken to the enclosure was different. The only rats that showed a decrease in the number of trials to reach criterion across reversals were the rats in the Direction Change and Room Change groups.

The current study replicated findings from previous studies that showed that rats can use a change in location to choose an appropriate response between two or more competing responses (Chiszar & Spear, 1969; McDonald et al., 2001, Wright et al., 2009). The results from the current study also agree with previous studies that showed that a change in context that would not produce hippocampal global remapping is not sufficient to facilitate response reversal learning (Wright et al., 2009). Facilitation of response reversal learning in rats that received changes in starting orientation between reversals is not surprising since the ability of rats to use starting orientation as a conditional cue has been previously observed (Skinner et al., 2003; Wright et al., 2009).

The failure of rats in the No Change group to improve across reversals can be attributed to proactive and retroactive interference. Competition between two competing responses can retard recall and acquisition if cues that would indicate which response is appropriate are not given to the subject (Cheng & Wignall, 2006). In order to successfully complete a reversal, rats must first stop the previously learned response and acquire the new response. This task can be difficult due to proactive interference causing the previously learned response to persist in the rats' memory. Reversals subsequent to the first may also be impeded by retroactive interference, where the most recently learned association must be stopped and a previously learned association must be recalled. Control rats, that generally receive no contextual changes between reversals, are particularly prone to errors caused by interference since they receive no external cue as to when they are required to switch their responses (Chiszar & Spear, 1969; McDonald et al., 2001; Wright et al., 2009).

The results from the current study, as well as previous studies (Chiszar & Spear, 1960; McDonald et al., 2001; Wright et al., 2009), indicate that a change in location between reversals will protect rats from interference. Rats in the Chiszar and Spear (1969) experiment that received a change in rooms between reversals made fewer errors to criterion than rats that received no change between reversals. The rats in Chiszar and Spear's experiment that received a change in room between reversals also received a change in maze. Other experiments that reported a reduction of interference attributed to a change in location also exposed the subjects to a change in maze (McDonald et al., 2001). In these experiments it is impossible to determine if the success of the rats was facilitated by the change in location, maze, or a combination of the two even though the data from McDonald et al. (2001) indicate that a change in maze alone does not produce an effect. Since the maze in the current experiment was not changed between reversals, the Room Change group rats' performance on the response reversal task can be attributed to a change in location alone. Electrophysiological data indicate that a change in maze location will cause hippocampal global remapping, even when the same maze is used. In contrast, changing the maze without changing the location may result in rate remapping (Lever et al., 2002). The performance of the Room Change group suggests that a contextual change that is of the type that would produce global remapping in the hippocampus is sufficient for reducing proactive and retroactive interference.

It was speculated that a contextual change would need to be represented in the hippocampus if it were to reduce interference. If this speculation is accurate, then changes in the color and shape of an experimental enclosure should be as effective as a change in room at reducing interference since both changes are represented in the hippocampus (Lever et al., 2002). However, this is not the case. Rats in the Cue Change and Path+Cue Change groups in the current study, as well as rats exposed to changes in light and noise in previous studies (Wright et al., 2009), appear to experience the same difficulties in response reversal learning as control rats. This suggests that the interference experienced by the Cue Change and Path+Cue Change groups and the control group is comparable. The discrepancy between the performance of the Cue Change and the Room Change groups could be accounted for by the type of hippocampal remapping that may have occurred. Changes in the color and the shape of an experimental enclosure have been shown to be associated with rate remapping while changes in room have been shown to be associated with global remapping (Leutgeb et al., 2005). The results from the current study suggest that the types of contextual changes that would produce rate remapping are not sufficient for reducing interference between two learned associations. This implies that any hippocampal representation of a contextual change is not sufficient to reduce proactive and retroactive interference, but that global remapping is necessary to reduce interference.

When rats' forage for food in a natural setting it might be adaptive to change foraging strategies according to the rats' location. The location of food in one area would not indicate where food could be located in another area. Rat's that received a change in room would have an evolutionary predisposition to dismiss previously learned responses and acquire new responses, which would facilitate response reversal learning. Additionally, it might also be adaptive for rats to maintain there foraging strategies if they remain in the same location. If the rats' did not attribute a change in color and shape of the experimental enclosure as a change in location then they would have an evolutionary predisposition to forage in the same location. The type of hippocampus remapping that occurs may be predictive to how rats represent changes in there environment, rate remapping may represent changes in stable features but no change in location while global remapping may represent changes in location.

In Experiment 2, rats that received a change in path and cues between reversals performed no better than rats that received changes in cues alone. This suggests that taking different paths to an enclosure that differed in color and shape did not protect the rats from interference. Previous studies have shown that when rats are allowed to actively move from one environment to another they will create a unique representation of each environment. If the rats were then moved from one enclosure to another the place cells in the hippocampus would show global remapping. The place cells show only rate remapping if the rats were not given the opportunity to actively move between the two environments (Colgin et al., 2010). Rats in the current study, however, were passively moved between the two environments and were never given an opportunity to actively move between the two environments. It is unclear what type of remapping passive movement might have caused, if any. It could be speculated that changes in path and cues only produced rate remapping since the performance of rats in the Path+Cue Change group was comparable to the rats in the Cue Change group and worse than the rats in the Room Change group. Cue Change changes of the type used here have been shown to produce rate remapping while room changes have been known to produce global remapping (Leutgeb et al., 2005).

It is also possible that despite being covered while moving to the experimental room, the rats in the Path+Cue Change group could have known that they were being tested in the same location between reversals. There is evidence that rats are exceptionally proficient at retaining their orientation even in the absence of visual cues (Margules & Gallistel, 1988). While being carried from the housing room to the experimental room the rats may have been able to determine that they were arriving at the same location. Covering the cages with a curtain during transport was intended to disorient the rat but may have been inadequate in doing so.

It is possible that contextual changes of the type that produce hippocampal global remapping are only necessary for reduction of interference in a small number of trials. If the rats in the Cue Change group were given additional trials it is possible that they may have eventually reached the same performance level as rats in the Room Change group. Lever et al. (2002) described an experiment where recordings of hippocampal place cells were taken when the shape of an enclosure changed from a circle to a square. At first the only differences were rate differences. As the rat received more exposure to the two environments the location of the place fields began to diverge until the place field location was different for the two enclosures. Since global remapping has been associated with the reduction of interference we could speculate that a reduction of interference could occur after many exposures to a change in context that would otherwise be expected to produce only rate remapping. Rats in the Cue Change group of the current experiment appeared to suffer from interference despite receiving multiple exposures to the two curtain arrangements. This could be because the rats in the Cue Change group did not experience enough switches between the two enclosures to cause global remapping. Rats in the Lever et al. (2002) study were switched between the circle and square environments each day while rats in the current study only received a switch in color and shape every couple of days or weeks. In five days, rats in Lever et al.'s (2002) study had received more switches between the two shapes than rats in the current experiment received in total. If the rats in the Cue Change group had received multiple exposures to the two contexts each day prior to the experiment, then the change in context may have produced global remapping. The rats in the Cue Change group might then have performed as well as the rats in the Room Change group on the response reversal task due to a reduction of interference caused by global remapping.

Rats in the Direction Change group in the first experiment showed a decrease in the number of trials to reach criterion across reversals. This indicates that changing the orientation of the rat between reversals may reduce interference. The performance of the rats in the Direction Change group replicated the findings of place learning experiments (Skinner et al., 2003) as well as experiments that manipulated start arm and goal arm orientation (Wright et al., 2009). In both studies, rats in translation conditions were trained to search an arm of a plus maze in order to receive a food reward. Whenever the maze was then translated (shifted to the left or right), such that the orientation of the start arm was not changed, the reward contingency was reversed (if the rat was initially rewarded for entering the left arm it was rewarded for entering the right arm instead). The location of the food reward relative to the room, however, did not change. When the maze was rotated 90 degrees between trials rats reached criterion in fewer trials than translation rats regardless of the start or goal locations (Skinner et al., 2003; Wright et al., 2009). The results from both studies demonstrated that rats did not learn to switch their responses at two maze positions if the starting orientation was not changed.

Rats may be able to use different start locations as a conditional cue to predict the reward contingency. Horne, Martin, Harley and Skinner (2007) trained rats on a translation task where two mazes were placed side by side. The start and goal locations were the same as in the classic translation problem, where one maze was translated between two locations. The number of trials rats took to reach criterion was fewer when two mazes were used compared to one maze moved between two locations. Horne et al. (2007) argued that since the rat can see that they are in a new start location they might use that information as a conditional cue. Rotating the maze may cause the rat to think it is starting in a new location since the rat's place cells tend to track extramaze cues (Knierim, Kudrimoti, McNaughton, 1995; O'Keefe & Speakman, 1987).

Hippocampal global remapping may not be necessary for the eventual reduction of interference at all since conditional discriminations (where a subject learns and if-then response) can be acquired when the hippocampus is lesioned (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Wiltgen, Sanders, Anagnostaras, Sage & Fanselow, 2006). Wiltgen et al. (2006) proposed the presence of two learning systems, one that involves the hippocampus and one that does not. Wiltgen et al. (2006) showed that rats with hippocampal lesions could become conditioned to a context, albeit more slowly than rats with an intact hippocampus. Wiltgen et al. (2006) also showed that if the rat received lesions directly after contextual conditioning the rats experienced retrograde amnesia. These results suggest that there is a non-hippocampal system that is able to acquire memories of a context, that this non-hippocampal system acquires memories more slowly than the hippocampal system, and that the presence of the hippocampus inhibits the non-hippocampal system from encoding memories.

Support for the two systems theory comes from a study by Frankland et al. (1998) that examined contextual conditioning in mice with hippocampal lesions. Mice were exposed to two different conditioning chambers, box A and box B, located in different rooms. On the first day hippocampal lesioned and sham mice were given a 10-minute exposure to both boxes. On the second day the mice were shocked 148 seconds after being placed in box A but not shocked when they were placed in box B. The following two days were test days, which were identical to the second day except the amount of time the mice spent freezing before the delivery of the shock was recorded. Mice with hippocampal lesions showed equal fear to both box A and box B while mice with an intact hippocampus showed more fear to box A than box B. If mice with damage to their hippocampus were subjected to two additional days of testing they began to show less fear in box B compared to box A. This suggests that mice with a damaged hippocampus may be using the slower non-hippocampal system to learn the conditional discrimination. Furthermore, if the mice with hippocampal damage were exposed to a novel box, box C, in a novel room they showed little fear while maintaining fear of box A. Since exposure to box C was only given after extended exposure to box A the non-hippocampal learning system may have acquired enough information about box A to make the distinction between the two boxes.

The presence of a non-hippocampal learning system that can learn conditional discriminations in the absence of the hippocampus can also explain discrepancies between appetitive and aversive reinstatement experiments. In reinstatement CS – US pairings are presented followed by extinction trials. Both acquisition and extinction of the CS – US association occur within the same context. After extinction the subjects are then presented with the US alone in either the same context as training and extinction or in a new context, this is known as the reinstatement trial. Rats with an intact hippocampus displayed the CR to the CS when tested in the original context if they were reinstated in the same context but not if they were reinstated in a different context (Fox & Holland, 1998; Frohardt et al., 2000). Rats with hippocampal damage performed the same as normal rats if they were given multiple reinstatement trials (Fox & Holland, 1998), which are necessary for appetitive reinstatement, but not if they were given only one reinstatement trial (Frohardt et al., 2000), which is sufficient for aversive reinstatement. Similar results have been observed with the renewal effect when rats were given multiple extinction trials (Frohardt et al., 2000). This can be attributed to the necessity of the hippocampus for rapid learning and the ability of the slower non-hippocampal learning system to take over in the absence of the hippocampus.

Since repeated exposure to a change in visual cues produces a reduction of interference even in the absence of the hippocampus (Lever et al., 2002) it is reasonable to assume that there is some system upstream from the hippocampus that mediates eventual conditional discriminations as well as the eventual switch from rate to global hippocampal remapping. A potential candidate for the non-hippocampal system that is responsible for hippocampal-independent contextual learning is the neocortex (Tyler & Rudy, 2007). It is unclear how many trials is necessary for the non-hippocampal system to acquire contextual information and it is possible that the necessary exposure may vary depending on the type of contextual changes as well as the task. The non-hippocampal system may enable encoding of contextual changes that would produce hippocampal rate remapping or even no remapping at all. Some types of conditional discriminations are retarded when the hippocampus is lesioned while other types of conditional discriminations are unaffected (Rudy, 2009). A reason why conditioning of non-hippocampal-dependent cues are not as readily observed as hippocampal-dependent cues could be because the non-hippocampal system acquires associations so slowly that the effects are overshadowed by the performance of the hippocampus. Additionally it may be possible that the rat will acquire a performance strategy, such as win-stay/lose-shift, before the non-hippocampal system acquires the conditional discrimination. This would cause rats in a control group to appear similar to rats that are only exposed to non-hippocampal-dependant cue changes.

General Conclusion

It is unclear what feature variations contribute to the facilitation of response reversal learning. Previous studies have shown that changes in ambient cues, such as changes in light and noise, are insufficient for producing a facilitation of response reversal learning (Wright et al., 2009). The current study has also shown that a change in the color and shape of the experimental enclosure, as well as the path taken to reach the experimental enclosure may also be insufficient for producing a facilitation of response reversal learning. Electrophysiological data suggests that the hippocampus represents changes in the color and shape of an enclosure differently from a change in location (Leutgeb et al., 2005). It is possible that environmental changes that are represented in the hippocampus as global remapping are sufficient for facilitating response reversal learning while environmental changes that are represented in the hippocampus as rate remapping are not.

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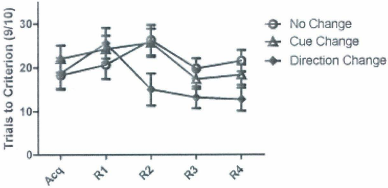

Figure 1. Mean (+SEM) trials to criterion on the acquisition task (Acq) and 4 reversals (R1, R2, R3, R4) for the Cue Change, Direction Change, and No Change groups of Experiment 1.

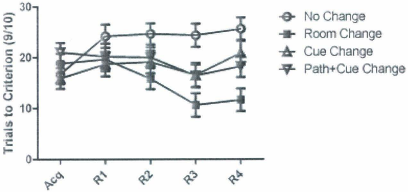

Figure 2. Mean (+SEM) trials to criterion on the acquisition task (Acq) and 4 reversals (R1, R2, R3, R4) for the Cue Change, Path+Cue Change, Room Change, and No Change groups of Experiment 2.