A Comparison of Discrimination and Reversal Learning for Olfactory and Visual Stimuli in Aged Rats

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Abstract

The present study investigated age-related differences in discrimination and reversal learning for olfactory and visual stimuli in 6 mo and 24 mo old rats. Rats were trained to discriminate between two pseudo-randomly selected odors or objects. Once each animal reached a criterion on discrimination trials, the reward contingencies were reversed. Young and aged rats acquired the olfactory and visual discrimination tasks at similar rates. However, on reversal trials, aged rats required significantly more trials to reach the learning criterion on both the olfactory and visual reversal tasks than young rats. The deficit in reversal learning was comparable for odors and objects. Furthermore, the results showed that rats acquired the olfactory task more readily than the visual task. The present study represents the first examination of age-related differences in reversal learning using the same paradigm for odors and objects to facilitate cross-modal comparisons. The results may have important implications for the selection of memory paradigms for future research studies on aging.

Keywords

Aging; Discrimination; Reversal Learning; Olfactory; Visual Object

Introduction

A number of research studies have suggested that problems with remembering and detecting odors may be an early indication of cognitive impairment and dementing diseases in non-demented older adults (Devanand et al., 2002; Djordjevic, Jones-Gotman, De Sousa, & Chertkow, in press; Gilbert & Murphy, 2004b; Graves et al., 1999; Wang et al., 2002; Wilson, Arnold, Schneider, Tang, & Bennett, 2007). Studies have shown older adults to be impaired relative to young adults on a variety olfactory tasks (Doty, Shaman, Kimmelman, & Dann, 1984; Gilbert, Pirogovsky, Ferdon, Brushfield, & Murphy, in press; Gilbert, Pirogovsky, Ferdon, & Murphy, 2006; Larsson & Backman, 1998; Murphy, Bacon, Bondi, & Salmon, 1998; Murphy, Cain, Gilmore, & Skinner, 1991; Murphy et al., 2002; Nordin & Murphy, 1998; Wysocki & Gilbert, 1989). Deficits in odor memory have been reported in healthy older adults at risk for AD based on family history (Schiffman, Graham, Sattely-Miller, Zervakis, & Welsh-Bohmer, 2002) or genetic risk factors (Gilbert & Murphy, 2004a, 2004b; Graves et al., 1999; Murphy et al., 1998). A longitudinal study demonstrated that healthy older anosmics genetically at risk for AD showed a five times greater risk of cognitive decline compared to

that of healthy older normosmics without genetic risk factors for AD (Graves et al., 1999). Other studies have reported that that patients with low odor identification scores who were unaware of their olfactory loss were more likely to develop AD by a two year follow up than other patients (Devanand et al., 2002). A number of researchers have emphasized the importance of the use of animal models to examine age-related changes in cognition and behavior (Gallagher & Rapp, 1997; Schoenbaum, Nugent, Saddoris, & Gallagher, 2002a; Solomon, Beal, & Pendlebury, 1988; Woodruff-Pak & Thompson, 1985). However, few studies have examined age-related odor memory impairments in rodents.

As discussed by Kraemer & Apfelbach (2004) the modality of a stimulus to be remembered is critical when determining efficient learning. Studies have shown that rats can readily learn and maintain a high level of performance on odor memory tasks (Alvarez, Wendelken, & Eichenbaum, 2002; Bunsey & Eichenbaum, 1996; Darling & Slotnick, 1994; Fortin, Agster, & Eichenbaum, 2002; Fortin, Wright, & Eichenbaum, 2004; Gilbert & Kesner, 2002, 2003; Kesner, Hunsaker, & Gilbert, 2005; Kesner, Gilbert, & Barua, 2002; Lu, Slotnick, & Silberberg, 1993; Slotnick, Hanford, & Hodos, 2000; Slotnick, Kufera, & Silberberg, 1991; Van Elzakker, O'Reilly, & Rudy, 2003; Wood, Agster, & Eichenbaum, 2004). In addition, it has been shown that acquisition rates and retention of memory for olfactory stimuli may be greater than for visual stimuli in young adult rats (Broadbent, Squire, & Clark, 2007; Rozin & Kalat, 1972). However, it is not clear whether the memory superiority for olfactory stimuli is preserved later in the life of a rat, since selective pressure for olfactory function may not exist following the reproductive lifespan of the animal.

A few studies have reported deficits in olfactory memory in aged rats. Studies have found that olfactory sensitivity was decreased in aged rats relative to young rats (Apfelbach, Russ, & Slotnick, 1991; Kraemer & Apfelbach, 2004). However, differences in olfactory discrimination have not been detected between young and aged animals (Kraemer & Apfelbach, 2004; Luu, Pirogovsky, & Gilbert, in press; Roman, Alescio-Lautier, & Soumireu-Mourat, 1996; Schoenbaum et al., 2002a). On reversal trials when the reward contingencies were reversed, aged rats showed significant impairments compared to young rats (Roman et al., 1996; Schoenbaum et al., 2002a). Therefore, reversal tasks involving olfactory stimuli may be very sensitive to age-related changes in rodents. However, existing studies investigating age-related changes in reversal learning for olfactory stimuli have not made direct comparisons with reversal learning for stimuli from a different sensory modality. As a result, it is not clear whether olfactory reversal learning is any more or less affected by aging than reversal learning for stimuli encoded via other sensory modalities. Thus, it is unclear whether aged rats are a good model for understanding how age-related brain changes might result in impairments in odor memory in older humans.

Studies have reported deficits in reversal learning in aged humans, nonhuman primates, and rodents (Mell et al., 2005; Schoenbaum, Setlow, Saddoris, & Gallagher, 2006; Schoenbaum et al., 2002a; Tsuchida, Kubo, & Kojima, 2002; Voytko, 1999). However, not all studies involving aged primates have reported age-related changes in reversal learning for all types of stimuli (Lai, Moss, Killiany, Rosene, & Herndon, 1995; Rapp, 1990; Tsuchida et al., 2002; Voytko, 1999). Although some studies have demonstrated that rats show age-related impairments on reversal learning tasks involving olfactory stimuli, it has not been clearly demonstrated whether the learning impairment is comparable to stimuli presented in other modalities. Therefore, the present study investigated age-related differences in discrimination and reversal learning for olfactory and visual stimuli in young and aged rats in order to determine whether odor learning is as affected by aging as visual object learning in rats. The same paradigm was used for olfactory stimuli and visual stimuli in order to facilitate cross-modal comparisons. The results of the present experiments offer valuable insight into whether aging has a similar deleterious effect on odor memory in rats and whether aged rats are a suitable

animal model for studying the effect of aging on odor memory in older humans. In addition, olfactory based tasks may be very attractive to researchers examining age-related changes in cognition in rats because the tasks are rapidly acquired. Therefore, the results may have important implications for the selection of memory paradigms for future research studies on aging.

Methods

Subjects

Forty Fischer 344/Brown Norway (Harlan Laboratories) male rats approximately 6 months ($n = 20$) and 24 months ($n = 20$) of age were used as subjects. The strain is an inbred hybrid offspring of a male Brown Norway rat and a female Fischer 344. Each age group was evenly divided and pseudo-randomly assigned to an olfactory or visual object condition in order to provide cross modal comparisons. Each rat was individually housed in standard plastic tubs located in a colony room. The colony room was maintained on a 12h: 12h light/dark cycle and all testing were conducted during the light phase. All rats had unlimited access to water but were food deprived to 80–90% of their free-feeding weight.

Apparatus

The testing apparatus consisted of a box with a 30 cm × 12 cm floor and four 12 cm high walls. The apparatus was constructed out of wood and all surfaces of the apparatus were painted gray. One removable guillotine door was placed in the center of the box to divide the box into two separate compartments, a start chamber and a choice chamber. The door could be manually opened and closed by the experimenter. One row of three evenly spaced 2 cm diameter and 1.5 cm deep food-wells were drilled into the floor in each chamber. The row of food-wells was positioned 5 cm from the guillotine door and each food-well was separated by 1.5 cm.

Stimuli

Odors—Olfactory stimuli consisted of powdered odorants (cinnamon, cumin, baby powder, or ginger) mixed in sand and presented in clear plastic cups (3 cm diameter and 3 cm high) as described in previous studies (Agster, Fortin, & Eichenbaum, 2002; Bunsey & Eichenbaum, 1996; Dudchenko, Wood, & Eichenbaum, 2000; Dusek & Eichenbaum, 1997; Fortin et al., 2002; Gilbert & Kesner, 2002, 2003; Kesner et al., 2002; Rondi-Reig, Libbey, Eichenbaum, & Tonegawa, 2001; Van Elzakker et al., 2003). Approximately 4–8 g (depending on the particular odor) of the powdered odorant was mixed in 160 g of sand. A food reward, a half piece of Froot Loop cereal, was buried beneath the surface of the sand in order to eliminate any potential visual cues.

Visual Objects—Visual stimuli consisted of small, visually dissimilar objects such as a toy die-cast metal car or a plastic film canister (approximately 4 cm – 6 cm high). The objects were mounted on small flat metal washers (5 cm diameter and 2 mm thick) to stabilize the objects and to completely cover the opening of the food-wells. Selected visual and olfactory stimuli used in the experiment were chosen based on data obtained from prior experiments (Gilbert & Kesner, 2002, 2003). Multiple copies of each object were randomly used during testing to minimize specific olfactory cues associated with a particular object.

Shaping Procedure

During the first week of training, each animal was handled for ~ 0.25 hr daily and allowed to individually explore the test apparatus for 0.25 hr. During the exploration period, the guillotine door was removed from the apparatus and ~ 6 pieces of Froot Loop cereal were distributed across the surface of the apparatus (not in the food-wells). Once the animal was exploring the

apparatus consistently, the guillotine door was subsequently raised and lowered to allow the rat to shuttle back and forth between chambers to retrieve a food reward. Each rat assigned to the olfactory task was shaped in the home cage to dig in a clear plastic cup filled with unscented sand to retrieve a food reward. Shaping began by placing a half piece of Froot Loop cereal on the surface of the sand allowing the animal to retrieve the reward. Across subsequent shaping trial presentations, the food reward was buried, partially at first and then deeper in the sand, until the rat was digging in the sand even when the reward was not visible. Once the animal was consistently retrieving the food reward in the home cage, the rat was placed in the apparatus and allowed to shuttle back and forth to retrieve the food reward from the digging cup containing the unscented sand. Digging cups were stabilized so that the rat could not displace the cups or spill the contents. This procedure was followed 12 times each day. Once an animal was digging consistently, the animal was assigned to the olfactory discrimination task.

Rats assigned to the visual object task followed similar shaping procedures; however, each rat was shaped to displace a neutral object rather than to dig in a sand-filled cup in order to receive a food reward. The neutral visual stimulus consisted of a wooden object 2 cm wide and 5 cm tall that was painted white. The object was placed to cover the center-most food-well in the choice chamber of the apparatus. Shaping began by placing a piece of cereal in front of the object on the maze surface. The animal was placed in the start chamber of the apparatus with the guillotine door between the start and choice chambers in the closed position. The animal was allowed to exit the start chamber, retrieve the reward from the choice chamber, and consume the reward with the door in the closed position. Once an animal retrieved the food reward consistently, the food reward was placed in the food well previously covered by the object and the object was positioned on the side of the food well opposite the animal. On each ensuing trial, the object was positioned to cover a larger portion of the food well until the base of the object completely covered the baited food well. This procedure was followed 12 times each day. Once an animal consistently displaced the object when the food well was completely covered, the animal was assigned to the visual object discrimination task.

Olfactory Discrimination Task

Olfactory discrimination was assessed using a two-choice discrimination task described by Kesner et al. (2002). A total of four odors were used in the experiment including cinnamon, ginger, baby powder, and cumin; however, each rat discriminated between only two odors. Odor pairings were determined so that each odor was used equally and all odor pairings were balanced (e.g., cinnamon was used in the same number of pairings as baby powder). For each rat, one odor was randomly assigned as the rewarded odor and the other odor was assigned as the non-rewarded odor. The rat began each trial in the start chamber of the apparatus with the door to the choice chamber closed. The door was opened and the rat was allowed to choose between the two odor cups presented side-by-side in the choice chamber of the apparatus 6.5 cm apart. If the rat dug in the odor cup containing the rewarded odor, the rat received a food reward. However, if the rat dug in the odor cup containing the non-rewarded odor, the rat did not receive a reward and was not allowed to dig in the odor cup containing the rewarded odor. On the next trial, the odor cups containing the two odors were presented in the other side of the apparatus (the start chamber from the previous trial) and the door was opened to allow the animal to choose between the odor cups. Thus on each trial the rat shuttled back and forth between the two chambers so that the experimenter did not need to handle the rat between trials. The position of each odor varied pseudo-randomly on each trial with respect to the left and right position in the choice chamber to eliminate position bias. Each rat received 12 trials per day and was tested until the animal reached a criterion of 9 correct choices out of a sliding block of 10 consecutive trials within the 12 trials. The experimenter recorded the digging response of each rat and the number of trials required to reach the criterion was used as the dependent measure. A 30 s interval was implemented between each trial.

Olfactory Reversal Task

Once each animal reached the learning criterion of 9 correct choices out of a sliding block of 10 consecutive trials, the reward contingencies were reversed on the following day of testing. The previously rewarded odor became the non-rewarded odor and the previously non-rewarded odor became the rewarded odor. Thus, a Froot Loop was buried in the cup containing the rewarded odor and no Froot Loop was buried in the cup containing the non-rewarded odor. Olfactory reversal learning was assessed using the same procedure and criterion as described for the olfactory discrimination task.

Visual Object Discrimination

Visual object discrimination was assessed using the same procedure and criterion as described for the olfactory task; however, two objects were used rather than two odors. A total of four dissimilar objects were used in the experiment. On each trial, the rewarded object was positioned to cover a baited food well containing a food reward, whereas the non-rewarded object covered an adjacent un-baited food well. If the rat displaced the rewarded object, the rat received a food reward. However, if the rat displaced the non-rewarded object, the rat did not receive a reward and was not allowed to displace the rewarded object.

Visual Object Reversal Task

Visual object reversal learning was assessed using the same procedure and criterion as described for the olfactory task.

Results

Figure 1 shows the mean (+ standard error) number of trials required by 6 mo and 24 mo old rats to reach the learning criterion on the visual object discrimination and reversal tasks. The mean (+ SE) number of trials required by 6 mo and 24 mo old rats to reach the learning criterion on the olfactory discrimination and reversal tasks are shown in Figure 2.

A $2 \times 2 \times 2$ analysis of variance (ANOVA) with age group (6 mo, 24 mo) and stimulus (odors, visual objects) as between-group factors and task (discrimination, reversal) as a within-group factor was used to analyze the data. The dependent variable was the mean number of trials required to reach the learning criterion of 9 correct choices out of a sliding block of 10 consecutive trials. The results revealed a significant main effect of group, $F(1, 36) = 5.87$, $p < .05$, indicating that 6 mo old rats outperformed 24 mo old rats. There also was a significant main effect of stimulus, $F(1,36) = 15.92$, $p < .001$, suggesting that rats were acquiring the olfactory task more readily than the visual object task. Additionally, there was a significant main effect of task, $F(1, 36) = 39.01$, $p < .001$, indicating that rats were acquiring the discrimination task at a faster rate than the reversal task regardless of stimulus modality. Furthermore, the analysis revealed a significant group $\times$ task interaction, $F(1, 36) = 8.16$, $p < .01$. A Newman-Keuls post hoc comparison test of the group $\times$ task interaction revealed that there were no significant differences in the number of trials required by 6 mo and 24 mo old rats to reach the learning criterion on the olfactory or visual object discrimination task. However, on the olfactory reversal task and the visual object reversal task, 24 mo old rats required significantly more trials to reach the learning criterion relative to 6 mo old rats ($p < .05$). In addition, 24 mo old rats required significantly more trials to reach the learning criterion on the reversal task than the discrimination task ($p < .05$). However, there were no significant differences in the number of trials required by 6 mo old rats to reach learning criterion on the discrimination and reversal tasks. The analysis did not reveal a significant group $\times$ stimulus interaction, $F(1, 36) = .11$, $p = .74$, a significant task $\times$ stimulus interaction, $F(1,36) = .26$, $p = .61$, or a significant task $\times$ group $\times$ stimulus interaction, $F(1, 36) = .06$, $p = .81$.

To examine performance differences between the olfactory and visual object conditions, the data were transformed into difference scores for each rat. Difference scores were calculated by subtracting the number of trials to reach the criterion on the discrimination task from the number of trials to reach the criterion on the reversal task. Mean (+ SE) difference scores for 6 mo and 24 mo old rats are shown in Figure 3. A 2×2 ANOVA with age group (6 mo, 24 mo) and stimulus (odors, objects) as between-group factors was used to analyze the data. The results revealed a significant main effect of group, $F(1, 36) = 8.16$, $p < .01$, indicating that 6 mo old rats showed lower difference scores than 24 mo old rats. However, the results did not reveal a significant main effect of stimulus, $F(1, 36) = .26$, $p = .61$, or a significant group $\times$ stimulus interaction, $F(1,36) = .06$, $p = .81$.

Perseverative and regressive error patterns on the reversal task were analyzed using a criterion described in previous studies (Dias & Aggleton, 2000; Hunt & Aggleton, 1998; Kim & Ragozzino, 2005; Palencia & Ragozzino, 2004; Ragozzino et al., 1999; Ragozzino, Jih, & Tzavos, 2002a; Ragozzino, Ragozzino, Mizumori, & Kesner, 2002b; Ragozzino et al., 2003). These analyses were conducted in order to provide a more fine-grained analysis of error patterns in aged rats. In this task, perseveration occurred during the reversal task when a rat continued to dig in the cup containing the odor previously rewarded on discrimination task trials. Perseveration was operationalized as digging in the incorrect cup on reversal trials for three or more trials in consecutive blocks of 4 trials. Once a rat made less than three errors in a block of four trials the first time, all subsequent errors were counted as regressive errors. As described by Kim and Ragozzino (2005), this provided a measure of the ability to maintain a new choice after initially shifting away from the previously correct choice.

A multivariate analysis of variance (MANOVA) with age group (6 mo, 24 mo) and stimulus (odors, visual objects) as between-group factors and perseverative and regressive errors as dependent measures was used to analyze the data. The results revealed a significant main effect of group for regressive errors, $F(1, 36) = 8.03$, $p < .01$, indicating that 24 mo old rats were committing more regressive errors than 6 mo old rats. However, the results did not reveal a significant main effect of group for perseverative errors $F(1, 36) = 1.83$, $p = .18$, or a significant group $\times$ stimulus interaction for either perseverative, $F(1,36) = .21$, $p = .65$, or regressive errors, $F(1,36) = .59$, $p = .45$.

Discussion

As mentioned previously, research has shown that the normal aging process in humans may result in significant impairments in odor memory (Gilbert & Murphy, 2004a, 2004b; Gilbert et al., 2006; Murphy et al., 1991; Nordin & Murphy, 1998). Furthermore, research studies have suggested that problems with remembering and detecting odors may be an early indication of cognitive impairment and dementing diseases in non-demented older adults (Devanand et al., 2002; Djordjevic et al., in press; Gilbert & Murphy, 2004b; Graves et al., 1999; Wang et al., 2002; Wilson et al., 2007). Although studies have examined odor learning in rats, it has not been clearly demonstrated whether odor learning is as affected by aging as visual learning in rats. Prior research has shown that rats may possess superior olfactory processing capabilities (Slotnick, 2001); however, it is unclear whether this superiority is preserved across the normal aging process. Therefore, the present study represents the first direct examination of age-related differences in discrimination and reversal learning using the same paradigm for olfactory and visual stimuli to facilitate cross-modal comparisons.

Consistent with past research (Luu et al., in press; Schoenbaum et al., 2002a, 2006), the results of the present study show no significant differences between 6 mo and 24 mo old rats in acquisition of an olfactory or visual discrimination task. This finding suggests that any deficits observed on the present olfactory or visual object reversal tasks are not simply due to an

impaired ability to perceive the odors or the visual objects. However, when the reward contingencies were reversed, 24 mo old rats required significantly more trials than 6 mo old rats to reach the learning criterion on both the olfactory and visual object reversal task. In order to examine differences in performance between the odor and visual object conditions, difference scores were computed. The results show that differences scores for 6 mo old rats did not differ significantly on the olfactory or visual object tasks. Similarly, the results show that the differences scores for 24 mo old rats also did not significantly for the olfactory and visual reversal tasks. These findings suggest that 24 mo old rats show comparable impairments in reversal learning for olfactory and visual stimuli. Implications of the results will be discussed in subsequent paragraphs.

Using a criterion described in previous studies (Dias & Aggleton, 2000; Hunt & Aggleton, 1998; Kim & Ragozzino, 2005; Palencia & Ragozzino, 2004; Ragozzino et al., 1999, 2002a, 2002b, 2003) perseverative and regressive errors committed on the olfactory and visual object reversal tasks were examined in order to obtain a more fine-grained analysis of error patterns. The results show that 24 mo old rats committed significantly more regressive errors on both the olfactory and visual object reversal tasks than did 6 mo old rats. However, 6 mo and 24 mo old rats did not significantly differ in the number of perseverative errors committed on the reversal tasks. To date, conflicting reports exist regarding error response patterns observed in aged animals. For example, several studies have reported a tendency for aged animals to perseverate, or continue responding to a previously learned choice pattern, after reward contingencies have been reversed (Bartus, Dean, & Fleming, 1979; Tapp et al., 2003). However, it also has been suggested that response errors committed by aged animals may represent an impaired ability to learn new stimulus-reward associations (Jones & Mishkin, 1972; Lai et al., 1995; Mell et al., 2005), rather than a difficulty inhibiting a previously learned rule or association. Data from the current study supports the latter view, suggesting that 24 mo old rats have a difficult time maintaining a new rule after initially shifting away from previously learned association. Similar findings also have been observed in healthy older adults (Mell et al., 2005). Mell and colleagues (2005), found that aged adults required more trials than young adults to reach criterion on a reversal-learning task. However, there were no significant differences in the number of perseverative errors committed by either group (Mell et al., 2005). It should be noted that task demands and task difficulty vary substantially across the aforementioned studies examining age-related perseverations on reversal tasks. Therefore, perseverations may be minimized on tasks where reversals are more rapidly acquired, such is the case in the present task.

Prior research has shown that young rats tend to show greater acquisition for stimuli presented in the olfactory modality than for stimuli presented in the visual modality (Rozin & Kalat, 1972). Consistent with previous studies (Broadbent et al., 2007; Darling & Slotnick, 1994; Slotnick, 2001; Slotnick et al., 1991), the analyses of the present data show a main effect of stimulus, suggesting that the rats tended to acquire the olfactory task at a faster rate than the visual task. Thus, olfactory-based tasks used to study learning and memory processes in aged rats may be beneficial for behavioral research given that rats may acquire tasks involving olfactory stimuli more readily than visual stimuli. The results may have important implications for the selection of memory paradigms for future research studies on aging.

The normal aging process in humans is associated with a decline in cognitive functioning (Craik & Jennings, 1992). In particular, older adults show impairments on tasks that require the ability to switch cognitive sets (Albert, 1994; Grant & Berg, 1948; Mell et al., 2005; Ridderinkhof, Span, & van der Molen, 2002), such as a reversal-learning task. Impairments in reversal learning documented in old animals have been suggested to stem from age-related changes in the prefrontal cortex (Joly, Deputte, & Verdier, 2006; Mell et al., 2005; Schoenbaum, Nugent, Saddoris, & Setlow, 2002b; Tsuchida et al., 2002). The normal aging

process is shown to affect both the structure and function of the prefrontal and orbitofrontal cortices (Cerf-Ducastel & Murphy, 2001, 2003; Craik & Grady, 2002; Morgan, 1987; Murphy, Cerf-Ducastel, Calhoun-Haney, Gilbert, & Ferdon, 2005; Nielson-Bohlman & Knight, 1995; Schoenbaum et al., 2002a; Suzuki et al., 2001; Yousem et al., 1999). Prefrontal cortex dysfunction is suggested to result in a decreased ability to maintain and shift cognitive sets across humans, nonhuman primates, and rats (Anderson, Damasio, Jones, & Tranel, 1991; Bartus et al., 1979; Berg, 1948; Grant & Berg, 1948; Dias, Robbins, & Roberts, 1996, 1997; Huizinga, Dolan, &, van der Molen, 2006; Miller, 2000; Moore, Killiany, Herndon, Rosene, & Moss, 2006; Schoenbaum et al., 2002b).

As discussed by Kim and Ragozzino (2005) the subregions of the prefrontal cortex may contribute differentially to strategy switching during learning tasks. Lesions or temporary inactivations of the rodent prelimbic area do not impair reversal learning of a two-choice discrimination (Birrell & Brown, 2000; Boulougouris, Dalley, & Robbins, 2007; Ragozzino, Detrick, & Kesner, 1999; Ragozzino, Kim, Hassert, Minniti, & Kiang, 2003). However, lesions or pharmacological manipulations of the orbitofrontal region impair reversal learning for olfactory, tactile, or visual cues (Bohn, Giertler, & Hauber, 2003; Boulougouris et al., 2007; Chudasama & Robbins, 2003; Ferry, Lu, & Price, 2000; Izquierdo, Suda, & Murray, 2004; Kim & Ragozzino, 2005; McAlonan & Brown, 2003; Meunier, Bachevalier, & Mishkin, 1997; Rolls, Hornak, Wade, & McGrath, 1994; Schoenbaum et al., 2002a, 2002b). The orbitofrontal cortex may support reversal learning by governing goal-directed behavior or behavior guided by incentive values associated with a stimulus (Saddoris, Gallagher, & Schoenbaum, 2005; Schoenbaum & Roesch, 2005; Schoenbaum & Setlow, 2001; Schoenbaum, Setlow, Nugent, Saddoris, & Gallagher, 2003a; Schoenbaum, Setlow, & Ramus, 2003b; Schoenbaum, Setlow, Saddoris, & Gallagher, 2003c). This type of goal-directed behavior is thought to rely heavily on interconnections between the orbitofrontal cortex and the basolateral amygdala (Saddoris et al., 2005; Schoenbaum, Chiba, & Gallagher, 1998; Schoenbaum et al., 2003b, 2003c). Additionally, the orbitofrontal cortex has been suggested to be particularly important for odor or visual cue reversal learning (Bohn, et al., 2003; Chudasama & Robbins, 2003; Schoenbaum et al., 2002a). Cellular recordings from orbitofrontal cortex neurons in rats identified as "reversal-learning impaired" revealed reductions in neuronal firing when reward contingencies were reversed in an odor discrimination task, whereas neuronal firing patterns in normal controls and aged "reversal-learning unimpaired" rats exhibited a reverse in odor preference (Schoenbaum, et al., 2006). Taken together, the results suggest that age-related impairments in reversal learning in rats may be indicative of a functional decline in the ability to flexibly switch between intra-dimensional sets.

Many previous behavioral studies involving aged rats have used 24 mo old Fisher 344 rats (F344). The present study was conducted using a Fischer 344/Brown Norway (F344/BN) hybrid strain. The F344/BN strain has been shown to live longer than Fischer 344 rats. The 50% survival age for F344/BN male rats is 34 mo, whereas the 50% survival age for F344 male rats is 24 mo (National Institute on Aging). Therefore, the rats in the present study showed significant learning impairments at 24 months of age despite having longer average longevity than other strains of rats used in prior behavioral experiments.

In summary, the results of the present study suggest that odor learning may be as affected by aging as visual learning in rats. As mentioned previously, the present study is the first to use the same paradigm to make direct comparisons between a visual task and an olfactory task utilizing the same paradigm. The results suggest that aged rats may be a suitable animal model for studying the effect of aging on odor memory in older humans. According to Schoenbaum and Setlow (2001), the development of a rodent model for the effects of aging on the medial temporal lobe system has provided considerable information relevant to understanding

cognitive decline in normal aging. Achieving a better understanding of the role that the PFC plays in the aging process will greatly depend on the development of an adequate animal model. The present study illustrates the robust effect of aging on reversal learning for stimuli from different sensory modalities. In addition, olfactory based tasks may be very attractive to researchers examining age-related changes in cognition in rats because the tasks are rapidly acquired. Therefore, the results may have important implications for the selection of memory paradigms for future research studies on aging.

Acknowledgements

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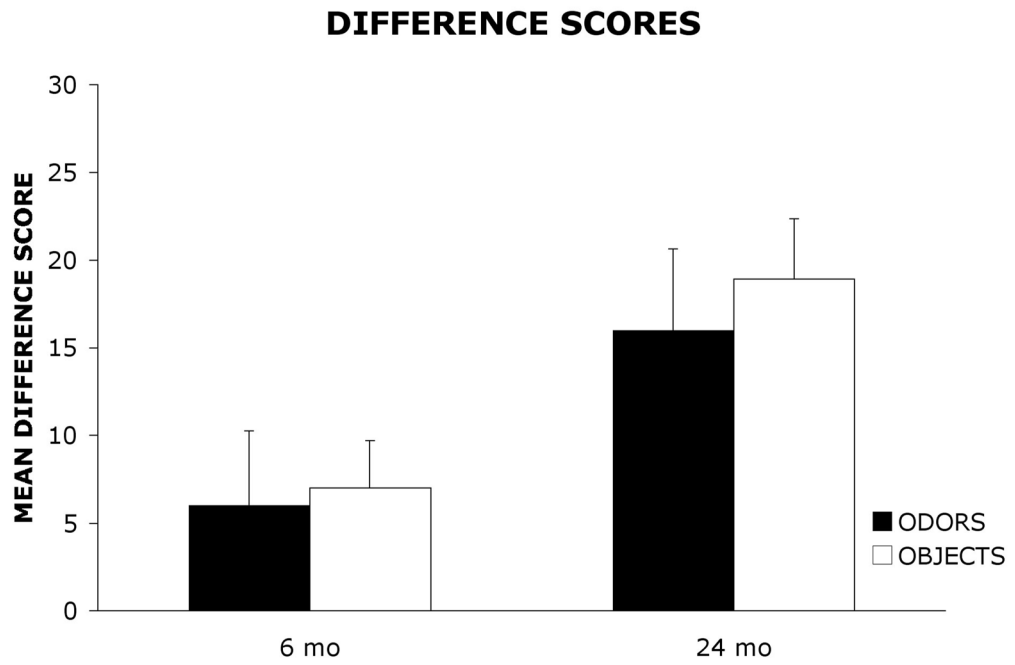
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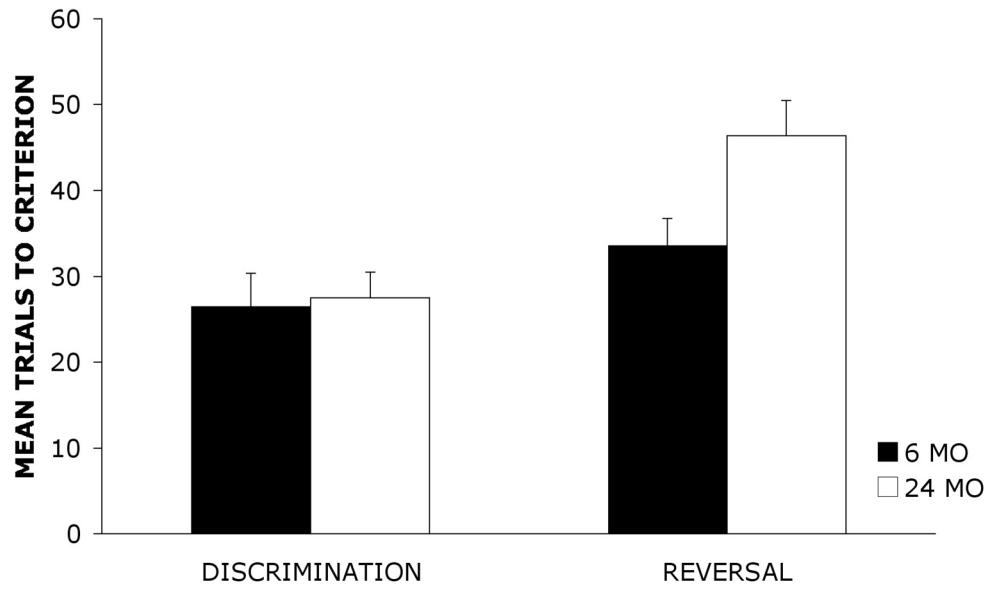
Figure 1.
Mean trials to criterion (±standard error) for 6 mo and 24 mo old rats on a visual object discrimination and reversal task.
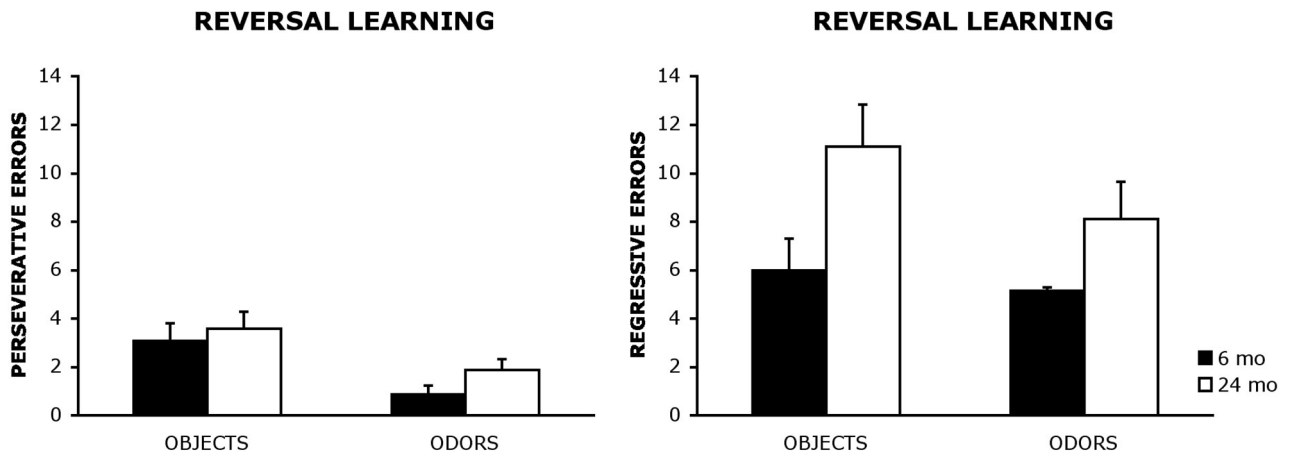
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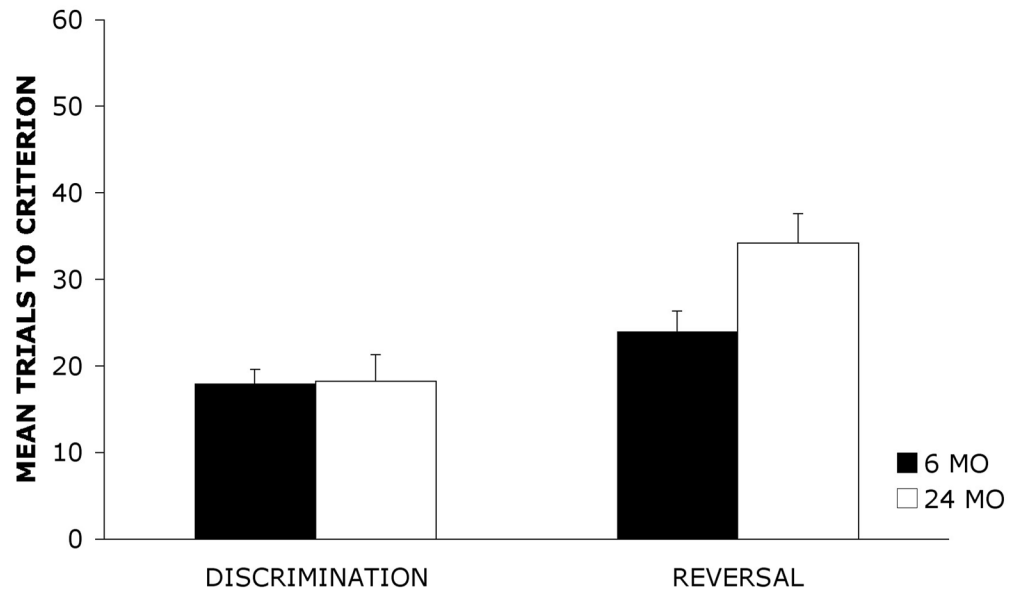
Figure 2.
Mean trials to criterion (±standard error) for 6 mo and 24 mo old rats on an olfactory discrimination and reversal task.

DIFFERENCE SCORES

Figure 3.
Mean difference scores (±standard error) for 6 mo and 24 mo old rats on the visual object and olfactory conditions.

REVERSAL LEARNING

REVERSAL LEARNING

Figure 4.
Mean perseverative and regressive errors (±standard error) committed by 6 mo and 24 mo old rats on a visual object and an olfactory reversal task.