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Short communication

Age-related changes in detection of spatial novelty

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ABSTRACT

Age-related changes in novelty detection for object–place associations was assessed in 6-mo and 25-mo-old Fisher 344/Brown Norway (F344/BN) rats. Old rats showed significant deficits compared to young rats in detecting spatial displacement of objects. The data suggest that object–place novelty detection is impaired in aged F344/BN rats using a rapidly acquired, exploratory-based task. The results may have important implications for the selection of efficient memory paradigms for future aging studies.

The detection of changes in a previously explored environment may require a comparison between sensory information from the current environment and an internal representation of the environment stored in memory. The hippocampus has been suggested to be an important substrate to support a match–mismatch process to compare current environmental sensory information with an internal memory representation [1–5]. Recent studies have shown that tasks measuring natural exploratory behavior may be useful and time efficient paradigms for studying memory, and particularly this match–mismatch process [3,6]. As discussed by Lee et al. [3], normal animals tend to recognize changes in a familiar environment by increasing exploration of stimuli moved to a novel location, relative to unchanged stimuli. However, animals with damage to the hippocampus [6] or its subregions [3] do not demonstrate increased exploration of spatial changes in the environment, indicating that the hippocampus may play a critical role in processing novel spatial information.

There is an extensive literature from human and animal research implicating the medial temporal lobes, and particularly the hippocampus, in age-related deficits in learning and memory [7]. Some studies have reported preserved numbers of neurons in the hippocampus of aged rats [8–10] and nonhuman primates [11]; however, others have reported decreased neuronal density in rats [12]. In addition, some studies have reported a lack of a relationship between hippocampal cell numbers and spatial learning deficits [8,12]; however, hippocampal volume (measure by MRI) has been reported to correlate with water maze performance in aged rats [12]. Since neuronal loss in the hippocampus is unlikely to fully account for the memory deficits in aged animals and humans, it has been postulated that age-related memory decline may stem from functional changes in the hippocampus [12–14], localized synaptic loss [15], and subregion-specific epigenetic and transcriptional changes in the hippocampus [16]. For example, neurogenesis is reduced in aged animals [17] and is related to performance on hippocampal dependent tasks and hippocampal volume [12]. Recent evidence has suggested that these newborn neurons may be involved in mnemonic processes particularly dependent on the dentate gyrus subregion of the hippocampus [18].

Since subtle but significant age-related changes occur in various regions of the hippocampal formation, normal aging often is associated with impairments on tasks that rely on intact functioning of the hippocampus and surrounding regions. For example, aged nonhuman primates and rodents demonstrate parallel impairments to animals with hippocampal damage on a variety of memory tasks, including tasks measuring spatial memory [19–24], temporal order memory [25], contextual memory [26], delayed recognition memory [27–29], odor memory [30], and transitive inference [31].

The present study was designed to assess age-related changes in novelty detection for object–place associations in Fischer 344/Brown Norway (F344/BN) rats using a rapidly acquired, exploratory-based task utilized in previous studies [3,6]. Thirty-six F344/BN male rats (Harlan Laboratories) approximately 6-mo ($n = 18$) and 25-mo ($n = 18$) of age were used as subjects. The F344BN is a hybrid between female Fisher 344 rats and male Brown Norway

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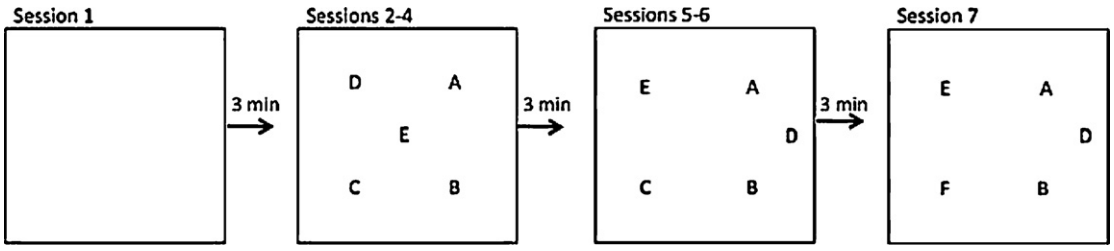

Fig. 1. A schematic representation of the task paradigm showing the locations of the various objects (A–F) used during the seven 6-min exploratory sessions. Each session was followed by a 3-min intersession interval.

rats. Subjects were housed in pairs in standard plastic containers located in a colony room and supplied continuous access to food and water. To maximize exploratory behavior, rats were handled 5–10 min everyday for 14 days prior to testing to minimize neophobia. The colony room was kept on a 12 h:12 h light:dark cycle and all testing was conducted during the light phase. All experimental procedures were reviewed and approved by the Institutional Animal Use and Care Committee at San Diego State University.

The testing apparatus consisted of a 90 cm square platform that was 1.5 cm in thickness and elevated 65 cm above the floor. The apparatus was constructed of wood, painted white, and was located in a small, well-lit room with a video camera mounted to the ceiling to record exploration. Various visually dissimilar objects 10–15 cm in height were used for the task, for example a toy truck, rubber duck, water bottle, and dog toy. The objects were similar to those used in previously published experiments [3,25]. Objects were mounted on metal washers and held in place on the apparatus using magnets to prevent a rat from displacing the objects. Multiple copies of each object were used during testing to minimize specific olfactory cues associated with a particular object.

The behavioral procedure was adapted from a paradigm used in previously published studies [3,6]. Testing on each task involved seven 6-min exploratory sessions, each with a 3-min inter-session interval where the rat was removed from the testing room and placed in plastic housing containers. During Session 1, each rat was introduced to the testing environment with no stimuli present to allow for habituation to the environment. During Sessions 2–4, four objects (A–D) were arranged in a rectangular configuration (45 cm × 40 cm), with the fifth object (E) located at the approximate center of the configuration (see Fig. 1). For Sessions 5–6, the rectangular configuration was changed to a polygon configuration where object D was moved to a novel peripheral location and object E, which had previously been located in the center position, was moved to the location previously occupied by object D. For Session 7, the polygon configuration was maintained; however, object C was replaced with a novel object (F). The assignment of objects to specific locations varied randomly for each rat.

A camera mounted on the ceiling above the apparatus recorded exploratory behavior during all test sessions. The software program WINTV2000 was used to store all video files electronically for later analysis. Object exploration was defined as the animal's nose entering a 1 cm halo around the perimeter of the stimulus as measured by the Object Scan software package (Clever Sys. Inc.). The Object Scan software enables the researcher to specifically track the nose of the animal to accurately measure object exploration.

Index scores were calculated as described by Lee et al. [3]. An object habituation index was calculated by subtracting the total interaction time of all five objects from Session 4 from the total interaction time of all five objects from Session 2 (a positive score indicating that there was more interaction during Session 2 than Session 4). A spatial mismatch index (SMI) was used to examine the exploration of the displaced objects during Sessions 5–6. The SMI was calculated by taking the sum of the exploration time for the displaced objects for Sessions 5–6 (i.e. object D and object E) and subtracting the sum of the exploration time for these displaced objects for Sessions 3–4 (a positive score indicating that there was more interaction with the displaced objects than the same objects in the familiar locations). Additionally, a within session SMI was calculated to examine exploration of displaced versus non-displaced objects by taking the exploration time of displaced objects and subtracting the exploration time of non-displaced objects within Session 5. Session 7 was used to create an object mismatch index. This index was calculated to quantify the identification of object change by subtracting the total interactions of the unchanged objects during Session 7 (objects A–E) from the sum of the interactions with the novel object (object F).

Fig. 2A shows the habituation index scores for 6-mo and 25-mo-old rats. A one-way analysis of variance (ANOVA) showed that the habituation index scores of 6-mo-old rats were not significantly different from those of 25-mo-old rats $F(1, 34) = .53$, $p = .47$. An analysis also was conducted to examine age-related differences in total object exploration and habituation across Sessions 2, 3, and 4. A 2 × 3 ANOVA with group (6-mo, 25-mo) as a between group variable and session (2, 3, 4) as within group variable revealed a significant main effect of session $F(2, 68) = 30.58$, $p < .001$. However, the analysis did not detect a significant main effect of group $F(1, 34) = .20$, $p = .66$, or a group × session interaction $F(2, 68) = .24$, $p = .79$. As shown in Fig. 3, both groups showed habituation to the objects across Sessions 2–4. However, there were no significant age-related differences in total object exploration or habituation.

Fig. 2B shows the spatial mismatch index scores for 6-mo and 25-mo-old rats. A one-way ANOVA showed that the SMI scores of 6-mo-old rats were significantly higher than those of 25-mo-old rats, $F(1, 34) = 4.23$, $p < .05$. To examine exploration differences between object E (in location previously occupied by object D) and object D (moved to novel location), a 2 × 2 × 2 ANOVA was conducted to examine with group (6-mo, 25-mo) as a between group variable, and session (5 and 6) and object (D and E) as within group variables. The analysis revealed that overall exploration of object E [6-mo = 11.53 (SE 3.45), 25-mo = 5.68 (SE 3.55)] was significantly greater than exploration of object D [6-mo = 1.29 (SE .34), 25-mo = .65 (SE .34)] across both group and session $F(1, 35) = 9.23$, $p < .01$. However, the analysis did not reveal significant main effects of session $F(1, 35) = .11$, $p = .75$ or group $F(1, 35) = 1.73$, $p = .20$.

Since differences between 6-mo and 25-mo-old rats on SMI scores could be due to age-related differences in total object exploration or motivation, an analysis was conducted to examine total object exploration time during Sessions 5 and 6. A 2 × 2 ANOVA with group (6-mo, 25-mo) as a between group variable and session (5 and 6) as within group variable did not reveal significant main effects for group $F(1, 34) = 1.31$, $p = .26$ or session $F(1, 34) = .70$, $p = .80$. In addition, the analysis did not reveal a significant group × session interaction $F(1, 34) = .06$, $p = .79$. As shown in Fig. 3, there were no significant age-related differences in total