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A study of remote spatial memory in aged rats

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Abstract

The effect of aging on remote spatial memory was tested in a group of 2-year-old rats (VR-O) that, as young adults, were reared for 3 months in a complex 'village' environment. The VR-O rats exhibited significant savings in finding the locations of specific reward compartments within the village, relative to a group of old rats (VNR-O) experiencing the village for the first time. The VNR-O rats were also impaired, relative to naive young rats, in learning the reward locations. Probe tests indicated that the VR-O rats retained allocentric spatial memory for the environment and were not using sensory or other non-spatial cues to guide behaviour. Overall, the results indicate that the aged rats experienced a decline in the ability to learn and remember detailed spatial relationships and that the VR-O group's successful performance on the remote spatial memory test was guided by a form of schematic memory that captured the essential features of the village environment. The potential contribution of the hippocampus to the pattern of lost and spared learning and memory observed in the aged rats was discussed.

Keywords: Aging; Remote spatial memory; Hippocampus; Animal model

1. Experiment 1

Spatial memory, based on the ability to form and remember allocentric spatial relationships in a complex environment, is known to be particularly vulnerable to the effects of normal aging in animals and humans (Barnes, 1979; Light, 1983; Park et al., 1983; Gallagher and Pelleymounter, 1988; Moffat et al., 2006). The loss of spatial memory in old age is related to failures in recalling contextually bound episodic events and has been attributed to changes in the hippocampus, a brain region that is functionally linked to spatial information processing (O'Keefe and Nadel, 1978; Maguire et al., 1996, Rosenbaum et al., 2001) and one of the first structures to show significant deterioration as part of the aging process (Gallagher et al., 1995; Geinisman et al., 1995; Winocur and Gagnon, 1998).

Although there has been considerable research into age differences in spatial memory, the focus has been mainly on recently experienced events, with scant attention paid to effects of age on recalling very old or remote spatial memories. To our knowledge, this issue has not been investigated systematically in humans, and there appears to be only one relevant report in the animal literature (Beatty et al., 1985). These investigators tested spatial learning and memory in a radial arm maze, a task that is known to be sensitive to the effects of aging, as well as hippocampal lesions. The results showed that 26-month-old rats, trained on the radial arm maze 2 years earlier, performed significantly better than old rats administered the task for the first time. It should be noted that

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this study did not test remote memory for spatial locations and what appeared to be preserved was a working memory strategy in a spatial context.

There are numerous challenges to assessing remote spatial memory in old age. For example, it is necessary to exert strict control over the subjects' experience with the environment, while ensuring that the experience was adequate to allow the formation of memory representations that can support accurate recall after very long intervals. As well, it is important that subjects have no contact with the environment between the original experience and remote memory testing. These factors are taken into account in a recently developed test, used initially to assess spatial memory in rats with hippocampal lesions (Winocur et al., 2005). In that test, young adult rats are reared socially in a complex environment ('village') that contains desirable reward objects (e.g., food, water) in different locations. Following an interval, the animal's ability to find specific rewards is assessed as a test of spatial memory.

In Experiment 1, the village paradigm was used to investigate remote spatial memory in aged rats under conditions that model those in effect when elderly humans attempt to remember specific locations learned a long time ago but were not experienced subsequently. Two groups of old rats – one reared for 3 months as young adults in the village and the other experiencing the village for the first time – were tested on their ability to find specific reward locations in the village. At test, rats reared in the village performed significantly better than naive old rats that were also impaired relative to a group of young rats exposed to the village for the first time. Additional testing in Experiment 2 showed that the reared rats were not guided by internal or external sensory cues but, rather, by a map-like allocentric spatial representation of the environment that they had acquired through their early experience in the village.

1.1. Method

1.1.1. Subjects

Sixteeen, male Long-Evans rats, approximately 23 months of age at the beginning of the experiment, participated in the research. The rats were acquired as young adults from Charles River laboratories in St. Constant, Quebec, and reared in the Trent University animal facility. Throughout the present study, the rats were maintained on 12:light/12:dark cycle, with all testing conducted during the dark phase of the cycle. Throughout testing, rats were placed on a 23 h food- or water-deprivation schedule, depending on the incentive condition to which they were assigned.

The study was approved by the Trent University Animal Care Committee and the rats were regularly examined by a veterinarian.

1.1.2. Apparatus

The village (1.2 m × 1.2 m × 1.2 m), shown in Fig. 1, was located in the centre of a room with standard laboratory furniture (e.g., desks, book shelves) and pictures on the walls. The room was dimly and uniformly illuminated by overhead lightings. The village contained two levels, with interconnected walkways within and between the levels. Two walkways leading to the lower levels were situated across from the entrance to the reward compartments in the north-east and south-west corners. The walls and ceiling were made of wire mesh, and the walkways of aluminum sheet metal. The upper level, also constructed of sheet metal, consisted of a gathering area in the middle of the upper level with four walls each containing a central opening. This area served as a start box for training and test trials. A compartment containing food (south-east corner), water (north-west corner), an assortment of toys (north-east corner), or a female rat (south-west corner), was attached to each of four corners on the lower level. The compartment containing the female rat was separated from the village by a wire mesh screen, whereas the other compartments could be entered freely.

Fig. 1. The complex 'village' environment.

1.1.3. Procedure

Old rats were assigned to the Village-Reared (VR-O, $N = 4$) or the Village-Non-reared (VNR-O, $N = 12$) condition.

1.1.3.1. VR condition. Rats in the VR-O condition originally participated as part of a control group in our investigation of the effects of hippocampal lesions on spatial memory conducted almost 2 years earlier (Winocur et al., 2005). The VR-O rats were 3 months old at the beginning of that study and about 8 months old upon completion. For the first 3 months of that study, the VR-O rats spent 8 h/day in the village during the high-activity part of their diurnal cycle. During these sessions, the rats were allowed to explore the entire village, with access to all the reward sites, which were always in the same locations. After each session, the rats were returned to individual cages, where they were deprived of food and water.

At the end of the 3-month village exposure period, the VR-O rats (as young adults) were maintained on food or water

restriction and tested, over a 10-day period, on their ability to find the location of the appropriate reward in the original village environment.

Following testing, the village-reared rats were placed in individual cages where they lived with food and water available on an *ad lib* basis. From time-to-time, they participated in other studies in which they were administered various tests in a circular pool that included spatial and non-spatial memory, non-matching-to-sample rule learning, and delayed non-matching-to-sample testing.

At approximately 23 months of age, about 15 months after their last exposure to the village, the VR-O rats were again placed on food or water restriction in preparation for re-testing in the village.

1.1.3.2. VNR condition. The rats in this condition (VNR-O) came to the lab at the age of 3 months. Between 3 and 12 months of age, they participated in several experiments, including some of the same tasks as the VR-O rats. While the VNR-O rats received comparable amounts of behavioural testing as the VR-O rats, the VNR-O rats had no prior experience with the village. At the age of approximately 23 months, the VNR-O rats were placed on food or water restriction in preparation for testing in the village.

1.1.4. Testing

The village was located in the same position in the room where the VR-O rats had been tested as young adults. The room contained all the original furniture, pictures, etc., and the reward compartments were in the same locations in the village relative to the original configuration of distal cues.

After a week of food or water restriction, the VR-O and VNR-O groups were given a daily exposure to the village over 3 consecutive days. VR-O rats that had previously been tested with food as reward were food-deprived, while the VR-O rats that were tested originally with water as reward, were water-deprived. For each of these sessions, the 4 VR-O rats and groups of 4 VNR-O rats were placed in the village and allowed 1 h to freely explore the environment, with access to all the reward sites. After each session, the rats were returned to their home cages and maintained on food or water restriction.

Twenty-four hours after the last exposure session, formal testing was initiated.

The VR-O and VNR-O rats were tested in groups of 4 with a 7–8 min interval separating the trials for each rat. A trial began with the rat placed individually in the start area. On each trial, the rat was directed to enter the village through a different doorway to ensure the use of different routes to the reward compartment. When the rat found the appropriate reward compartment, it was allowed to eat or drink for 10 s and was then placed in a holding cage where it awaited the next trial. If the rat failed to find the reward compartment within 300 s, it was removed from the village, placed in the holding cage to await the next trial, and assigned an error score of 10 for that trial.

For purposes of scoring errors, the floors and walkways of the village were divided into zones demarcated by intersections which served as choice points from which the rat could move in the direction of the reward compartment or in a direction away from it. A rat was considered to have made an error whenever it arrived at a choice point and turned in a direction away from the reward compartment. For example, if the rat entered the village facing due south with the reward compartment in the south-east corner (see Fig. 1) and turned due west (the rat's right), an error would be counted. Every turn at subsequent choice points that took the animal in a direction away from the reward compartment counted as an additional error.

The amount of time required to reach the compartment on each trial was also recorded. Because the latency measures paralleled the error scores, they are not reported here but are available on request.

Rats received 5 daily trials over 10 consecutive days. At the end of each daily test session, the rats were returned to their home cages, where they received food and water for 1 h.

1.2. Results

Half of the rats in the VR-O and VNR-O groups were motivated to find the food location and the other half were motivated to find water. As there were no differences in performance between food- and water-deprived sub-groups, their scores were combined to form single VR-O and VNR-O groups.

The performance of the VR-O and VNR-O groups, in terms of the average number of errors/test session, is presented in Fig. 2. For purposes of comparison, the cor-

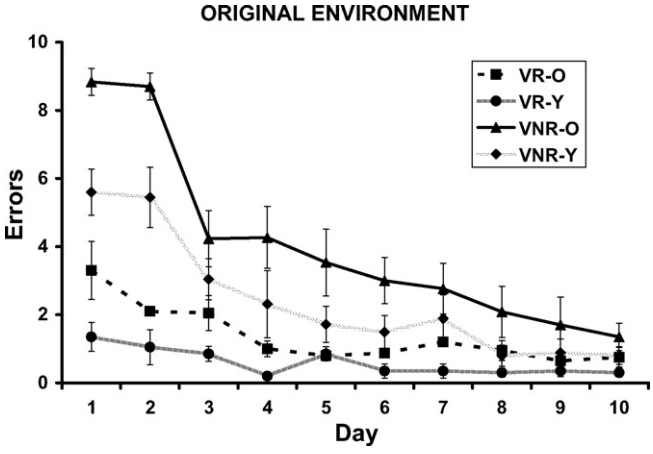

Fig. 2. Mean numbers of errors made in finding reward locations in the village in Experiment 1, by old rats that had been reared in the village (VR-O), the VR-O rats tested as young adults following rearing in the village (VR-Y), old rats that had no prior experience in the village (VNR-O), and young rats that had no prior experience in the village (VNR-Y). The same rats comprised the VR-O and VR-Y groups. Data for the VR-Y and VNR-Y groups were reported in an earlier study (Winocur et al., 2005). The publisher has confirmed that no permission is required to reproduce these data. Error bars refer to SEM.

responding scores of the VR-O rats, when they were tested on this task as young adults, are also presented (Group VR-Y). In addition, Fig. 2 provides the error scores for a group of young adult rats tested on this task as non-reared controls in the brain-damage study (Group VNR-Y) and originally reported in the Winocur et al. (2005) paper. The outcome of comparisons involving the VNR-Y group is qualified by the fact that this group was not tested contemporaneously with the old groups.

Since two groups – VR-O and VR-Y – are comprised of the same rats, it would be inappropriate to perform an overall analysis of variance (ANOVA) on the data presented in Fig. 2. Therefore, ANOVA was performed on the scores of the VR-O, VNR-O, and the VNR-Y groups, with group as the 'between' factor and days as the 'within' factor. This analysis yielded a significant group × days interaction, $F(18, 198) = 2.79$, $p < .0005$ as well as a main effect of group, $F(2, 22) = 5.74$, $p = .01$, and a main effect of days, $F(9, 198) = 26.56$, $p < .0005$. Simple contrasts on the group variable were performed with reference to the VNR-O group. As expected, there was a significant difference between the VNR-O and the VNR-Y groups, $t(22) = 2.42$, $p = .02$, indicating that old rats, with no prior experience in the village, took longer than similarly naïve young rats to learn the locations of specific rewards. The VNR-O group also performed significantly worse than the VR-O group, $t(22) = 4.57$, $p = .006$. The latter finding indicates preserved spatial memory in the VR-O rats, resulting from their experience in the village 15 months earlier.

A comparison of the VR-O rats' performance with their performance on the task when they were young (VR-Y) provides a description of changes in spatial memory over the rats' life span. As can be seen in Fig. 2, overall, the VR rats made more errors in old age than they did as young adults $t(3) = 3.56$, $p = .038$, indicating that there was some age-related loss of spatial memory. However, the memory loss over time was relatively small, especially when the performance of the VR-O group is compared with that of the VNR-O group.

2. Experiment 2

In Experiment 1, old rats, reared in a complex environment as young rats, exhibited preserved remote memory for learned spatial locations in that environment. Their performance declined only slightly from their performance when they were initially tested 15 months earlier, and was substantially better than that of old rats tested for the first time.

In our previous study (Winocur et al., 2005) in which rats with hippocampal lesions also showed preserved spatial memory, probe tests were devised to ensure that, when brought back to the familiar environment, they were still using allocentric spatial cues, and not non-spatial cues, to find the reward compartments. The tests also provided insight into factors contributing to the nature of the savings exhibited by the hippocampal rats. Accordingly, in Experiment 2 the VR-O and VNR-O groups were administered the same series of tests. It should be noted that the VR-O rats did not receive these tests when they participated in the original study as young controls, so that both groups experienced these tests for the first time in the present study.

2.1. Method

2.1.1. Subjects and apparatus

The subjects and apparatus of Experiment 1 were used in the present experiment.

2.1.2. Procedure

The VR-O and VNR-O rats were tested in the following conditions and in the same order. Test procedures were identical to those followed in the Winocur et al. (2005) study including administering, between each of the tests, a few trials in the Original-Environment condition to ensure that rats were still performing at baseline levels on the original task. Approximately 2–4 days separated each testing condition.

2.1.2.1. Room change. A few days after completion of Experiment 1, the village was relocated to a different room. The new room had an entirely different array of cues but the reward compartments were located in the same relationship to the village and to each other. The rats continued to be food or water restricted and were tested according to the procedures followed in Experiment 1. For the Room-Change condition, the rats received 5 trials/day for 5 consecutive days following the procedures of Experiment 1.

2.1.2.2. Floor rotation. For the Floor-Rotation condition, the village was returned to the same place in the original room. The inner floors and walkways within the village were rotated 180° but the reward compartments remained in their original locations. The rats continued to be food or water restricted. Because of a technical problem in the lab, in the Floor-Rotation condition, the rats received 3 days of testing instead of the usual 5 days.

2.1.2.3. Village rotation. Following Floor-Rotation testing, the floors and walkways were returned to their original positions. For the Village-Rotation condition, the entire village was rotated 180°. In this configuration, all the reward compartments were in a different location relative to distal cues in the room. Thus, the food compartment, which had always been in the south-east corner was now located in the north-west corner, and the water compartment, which had been in the north-west corner was now in the south-east corner, and so on. The rats were tested for 5 days according to the standard procedures.

2.1.2.4. Cue distortion. For the Cue-Distortion condition, the room was reconfigured. Some equipment and a desk that were part of the original environment were removed from

the test room. In addition, several pieces of furniture (e.g., chair, table) were relocated in the room. Other pieces (e.g., stool) and wall fixtures (e.g., light switch) remained in their original places. New furniture (e.g., bookcase) was brought in and replaced previous objects or occupied new places. There was a general reorganization of the original wall posters, with some retained in their original places, others relocated, others removed, and a few new pictures added. The village remained in its original location and orientation. The rats received 5 days of testing in the usual way.

2.2. Results

2.2.1. Room change

Fig. 3a shows that both groups made more errors/day over the 5 days of testing in the Room-Change condition than they did at the completion of testing in the Original-Environment condition (see Fig. 2). Interestingly, in this condition, the VR-O group made more errors than the VNR-O group, $F(1, 14) = 6.00$, $p = .028$, indicating that the reared rats were more affected by the room change.

2.2.2. Floor rotation

In the Floor-Rotation condition, the village was returned to the original room and the floor was rotated with the reward compartments retaining their original locations. As can be seen in Fig. 3b, the VR-O and VNR-O groups performed the task as well as they had in the Original-Environment condition and there was no significant difference between the groups, $F(1, 14) = 1.19$, $p = .294$.

2.2.3. Village rotation

In the Village-Rotation condition, the entire village was rotated 180° so that all the reward compartments were in different locations, relative to distal cues in the room. This had the effect of equally disrupting the VR-O and the VNR-O groups, $F < 1$. Both groups made significantly more errors on Day 1 of the Village-Rotation condition than they did on the last day of testing in the Original-Environment condition (VR-O: $t(3) = 64.08$, $p < .0005$; VNR-O: $t(11) = 6.98$, $p < .0005$). As can be seen in Fig. 3c, both groups recovered their optimal level of performance by Day 3.

2.2.4. Cue distortion

In the Cue-Distortion condition, there was a major rearrangement of distal cues in the original test room. As can be seen in Fig. 3d, this manipulation did not affect the performance of the VR-O and VNR-O groups, and both groups performed equally well, $F < 1$.

3. Discussion

In the present study, consistent with previous reports of the adverse effects of aging on spatial learning (Barnes, 1979; Gallagher and Pelleymounter, 1988; Winocur and Gagnon,

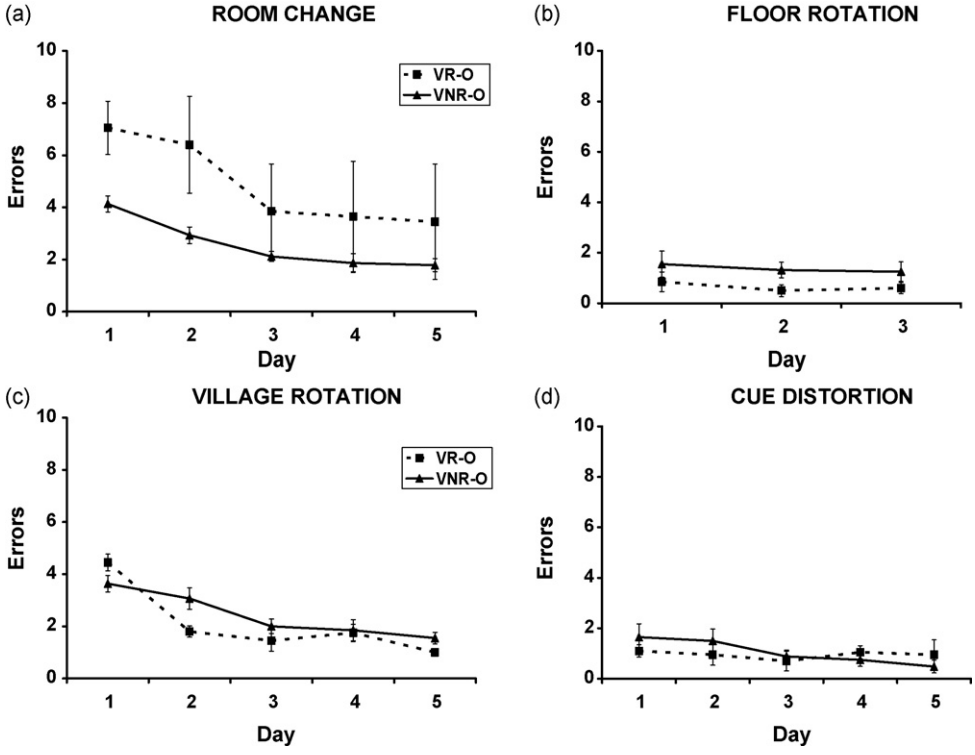

Fig. 3. Mean numbers of errors made by VR-O and VNR-O groups in the four test conditions of Experiment 2. Errors bars represent SEM.

1998), normal old rats were severely impaired, relative to young adult rats, in learning the location of specific rewards in a complex environment. In a new finding, we showed that old rats are capable of remembering spatial locations in that same environment if they had learned them well as young adults. Probe tests were conducted to ensure that the rats were relying on allocentric spatial cues, and were not using non-spatial, local or sensory cues to find the reward compartments. For example, in the Room-Change test, the village was moved to a new room with a novel set of extraneous environmental cues and the animals were tested as before. If the rats had been using non-spatial cues that were intrinsic to the village, their performance would not have been affected. In fact, both groups (and especially the VR-O group) showed a significant decline in performance over the first 3 days of testing. This finding also showed that the savings exhibited by the VR-O rats in the original environment could not be attributed to retained procedural learning. In the Floor-Rotation test, the floor of the village was rotated 180°, without affecting the locations of the reward compartments. In this case, if rats were using non-spatial cues, a drop in performance would be expected, but this did not occur in either aged group. Finally, in the Cue-Distortion test, where most of the room cues were re-arranged and in which both aged groups performed extremely well, the results clearly indicated that the rats did not use a specific set of external cues as landmarks to guide behaviour.

As can be seen in Fig. 2, when tested in the original village environment, the VR-O group was far superior to the VNR-O group. The VR-O rats exhibited some initial loss relative to their performance immediately following village rearing at the age of 3 months, but they completely recovered well before the end of testing. Given that only a few days intervened between rearing and testing when the rats were young while 15 months passed before they were retested as old rats, the important finding here is not that there was some loss in the VR-O rats, but rather that the loss was so small.

It is also significant that, on the probe tests in Experiment 2, the VR-O rats performed at virtually the same level as did a group of village-reared young controls tested in the same way in the Winocur et al. (2005) study. The VR-O group in the present study and the young group of the previous study (not reported here) performed extremely well and did not differ on the Cue-Distortion and Floor-Rotation tests. As well, they performed similarly in learning the reward locations in the Room-Change and Village-Rotation tests. These results suggest that once spatial memories are acquired, their representations in the aging brain can be used efficiently to adjust to changes in spatial environments.

The finding that remote spatial memories can survive into old age is consistent with the widely held view, based on longstanding evidence and anecdotal reports (Erber et al., 1980; Howes and Katz, 1988; Craik and Jennings, 1992), that older adults' remote memory is superior to their recent memory. However, in light of recent research, this notion bears closer scrutiny. For example, Levine et al. (2002) and St Jacques and Levine (2007) used the Autobiographical Interview, a sensitive test of autobiographical memory, to show that older adults retained memories for general knowledge about personal and public events (semantic memory) relatively well over the life span. However, they were poor at recalling events within their spatial-temporal context and in significant detail (episodic memory), regardless of the age of the memories (Addis et al., 2008). The same results were reported by Piolino et al. (2006), using a semi-structured autobiographical questionnaire that is sensitive to differences in episodic and semantic memory. These results suggest that when older adults exhibit preserved remote memory, they are recalling non-episodic, semantic information and that they are impaired when required to remember detailed, contextually dependent information.

The findings of preserved remote spatial memory in the VRO group in Experiment 1 can be interpreted along the same lines. Memories are initially formed episodically in relation to the context in which they were acquired. Once established, and with time and experience, the core information inherent in these representations is integrated with pre-existing knowledge to form less detailed semantic or schematic memories. The same process is thought to occur with respect to spatial memory (Rosenbaum et al., 2001; Moscovitch et al., 2005). In the present study, the young rats raised in the village had the opportunity to learn the locations of various reward objects in relation to specific contextual cues, as well as to form a more schematic representation of the entire environment that was less contextually bound. With the passage of time, spatial memories that are rich in contextual detail tend to decline but the schematic forms of those memories are more likely to survive. Thus, in a test of spatial memory after very long delays, it is the schematic version of the memory that is more likely to be available and guide navigation throughout the village.

The results of the present study parallel those of Winocur et al. (2005) who reported that young adult rats with hippocampal lesions exhibited similar savings of pre-operatively acquired spatial memories in the village environment, whereas hippocampally lesioned rats with no prior experience in the village were severely impaired in learning new spatial relationships. The latter findings are consistent with a large body of evidence that the hippocampus is crucial to the process of forming and retaining context-dependent, episodic memories without being involved in recalling semantic or schematic memories (Viskontas et al., 2000; Manns et al., 2003; Gilboa et al., 2005; Steinvorth et al., 2005; Rosenbaum et al., 2007). Given that the hippocampus is one of the first brain regions to show clear signs of structural change with age, it follows that the pattern of lost and spared remote memory seen in older adults may be related to hippocampal atrophy (Jernigan et al., 2001; Killiany et al., 2002; Raz et al., 2005). In other words, the failure of older adults to recall remote episodic memories, at least in part, is the result of hippocampal dysfunction, while their relatively preserved remote semantic memories can be attributed to the greater

integrity of extra-hippocampal structures, where such memories are represented.

While a declining hippocampus undoubtedly affects memory function in old age, other regions are also compromised in the aging brain. Notable amongst these is the prefrontal cortex, a structure known to be involved in strategic cognitive operations and, particularly, in the retrieval of remote memories (Mangels et al., 1996; Winocur and Moscovitch, 1999; Levine et al., 2002). An important question that follows from the issues raised in this paper relates to those brain regions in which spatial memories are represented once they are consolidated, or transformed into schematic memories. Investigations of long-term memory in animals and humans, using a variety of behavioural tasks in combination with functional imaging and gene-expression techniques, have identified several structures, including the parahippocampal gyrus, retrosplenial cortex, caudate nucleus, posterior and anterior cingulate cortex, and parietal lobe, as possibly being involved in this aspect of memory representation and its retrieval (Rosenbaum et al., 2004; Wiltgen et al., 2004; Frankland and Bontempi, 2005; Moscovitch et al., 2005). This work is very encouraging but it remains to be seen if the same structures are implicated in the re-organization of the aging brain that is necessary to support the retrieval of remote memories.

Disclosure statement

The authors declare that there are no actual or potential conflicts of interests involving them or the institutions with which they are affiliated.

The study was approved by the Trent University Animal Care Committee and conducted according to the guidelines of the Canadian Council on Animal Care.

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