Glucose Treatment Attenuates Spatial Learning and Memory Deficits of Aged Rats on Tests of Hippocampal Function

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WINOCUR, G., AND S. GAGNON. Glucose treatment attenuates spatial learning and memory deficits in aged rats on tests of hippocampal function. NEUROBIOLOG AGING 19(3) 233–241, 1998.—Groups of old and young rats were administered three tests of spatial learning and memory that are known to be sensitive to hippocampal dysfunction: the radial arm maze (RAM), spatial non-matching-to-sample (SNMTS), and a spatial vs. local cue-preference task. Old rats performed worse than young rats on the RAM and SNMTS tasks; on the cue-preference task, young rats were biased to use spatial cues, whereas old rats exhibited strong preferences for distinct, local cues. Peripheral injections of glucose (100 mg/kg) improved performance by old rats on the RAM and SNMTS, which correlated with measures of glucose metabolism. Glucose treatment did not affect old rats performance on the cue-preference task. There was evidence that glucose-treatment improved performance of young rats in the RAM test, but not the other tests. The results extend the range of tasks on which glucose-induced cognitive enhancement has been demonstrated in aged rats, and provides further evidence that memory loss resulting from hippocampal dysfunction is especially amenable to glucose treatment. © 1998 Elsevier Science Inc.

IT is now well established that age related deficits in cognitive function can be reduced temporarily by glucose treatment. In rodents, this effect has been observed reliably on tests of inhibitory avoidance conditioning (14,16) and spontaneous alternation (29) and, in humans, on tests of logical memory (6,20) and delayed recall (20). Despite obvious differences, these tasks are all sensitive to dysfunction of the hippocampus, a feature that is in line with the proposal that glucose enhances memory performance through its facilitation of cholinergic activity within the hippocampal system (13,15).

In a recent study, Winocur (36) demonstrated the selective action of glucose on hippocampal function in a test of conditional associative learning (CAL). In that test, rats were rewarded for selecting one lever in response to a particular pattern of visual stimuli and a second lever in response to another pattern. By varying the interval between the presentation of the stimuli and the opportunity to respond, it was possible to alter the memory requirements of the task. Previous work showed that young adult rats with lesions to the prefrontal cortex (PFC) were impaired in learning the CAL rule and in performing the task at short intervals (34). Increasing the length of the interval did not affect PFC rats, relative to controls. By comparison, rats with lesions to the hippocampus performed the CAL task normally at short intervals but were severely impaired at long intervals. Normal old rats show signs of both types of impairment (33,36), but when treated with glucose, improvement was observed only at long intervals, that is, the hippocampal measure.

The present study extends our investigation of glucose attenuation of age-related cognitive decline on tests of hippocampal function. The effects of glucose were assessed on three tests of learning and memory that require the animal to utilize spatial information in different ways. The tests are: 1) Olton’s radial arm maze (RAM), which assesses memory for an updated list of spatial stimuli; 2) spatial non-matching to sample (SNMTS), in which trial-specific information must be remembered in choosing correct locations; and 3) a cue-preference test that compares associative strength between different cues (local or spatial) and food reward.

It is well known that rats with hippocampal dysfunction are

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233
reliably impaired on the RAM (25, 37) and on tests of SNMTS (10, 29). The cue-preference task, recently developed in our lab, is conducted in a cross-maze in which rats initially learn to obtain food in a black arm that is always in the same spatial location. At test, food can be obtained by returning to the arm at the same location, which is now painted gray, by selecting the black arm, which is now in a different location, or a third, neutral arm. Recently, Conley (4) showed that, whereas normal rats preferred the arm in the familiar spatial location, hippocampus-lesioned rats consistently chose the black arm. Normal old rats also have been tested on the RAM (12), SNMTS (1, 9), and cue-preference (5) task, with the consistent finding that their patterns of performance were very similar to those of rats with hippocampal lesions.

A primary objective of the present study was to determine if glucose contributes to a normalization of performance in aged rats on all three tests of hippocampal function. Such an outcome would provide compelling evidence for the effectiveness of glucose on overcoming hippocampal-based impairments. If, on the other hand, glucose is selective in its effect, the pattern of selectivity becomes important because the tests differ considerably in terms of their cognitive requirements.

**METHOD**

*Subjects*

All rats used in this experiment were Long-Evans males obtained from the Trent University Breeding Center. The old rats were approximately 22 months old and weighed between 480 and 550 g when tested, and the young adult rats were approximately 7 months old and weighed between 375 and 440 g. Old and young rats spent most of their lives in group cages, housing 4 to 6 rats. About a month before behavioral testing, rats were transferred to individual wire-mesh cages. Water was available at all times, but food was provided in accordance with experimental conditions. Rats were examined regularly by a veterinarian to ensure that they were healthy and able to participate in the study.

As young adults, the old rats had participated in operant conditioning experiments involving delayed alternation and conditional associative learning. To ensure that the young rats had similar experience, at about 5 months of age they were administered the delayed alternation task. During these times, the rats were transferred to individual cages and then returned to their group cages.

*Behavioral Testing*

Three weeks before behavioral testing, the designated rats were handled regularly and gradually reduced to about 80% of normal body weight. Throughout testing, rats were maintained at constant weight by being fed 20 to 25 grams of lab chow each day.

**RAM.** Fifteen old rats and 10 young rats were tested on the RAM. The maze consisted of eight arms (85 × 7 cm) radiating horizontally from a central cylindrical platform (34 cm in diameter). A recessed food-cup was located in the floor at the end of each arm.

Testing procedures for the RAM were based on those developed by Olton and Samuelson (26) and modified by Winocur (37). The rats, which were on a 23½-h food-deprived schedule, received 4 days of preliminary training in which broken pieces of Froot Loop cereal were scattered throughout the entire apparatus. For the first 3 days, rats were placed in pairs and were allowed to explore the apparatus for about 15 min.; this procedure was repeated on the fourth day, except that rats were placed individually in the apparatus. After preliminary training, the rats received one test trial per day for 10 consecutive days. A trial consisted of baiting each cup with a single piece of Froot Loop cereal and individually placing the rat on the center platform. The rat was removed after all eight arms had been entered, or after 10 min. had elapsed. An arm was scored as having been entered if all four feet were in the arm. Records were kept of the arms entered and the order in which they were entered. Errors were indicated as reentered arms.

On the eleventh day of testing, rats were injected peripherally with saline 30 min. prior to testing in order to familiarize them with the injection procedure. Testing was then conducted in the usual way. On the following 4 days, rats were injected, on alternate days, with 100 mg/kg of glucose or an equal volume of saline about 30 min. before the beginning of testing. The first day in the series was always a saline treatment session.

**SNMTS.** Thirteen old rats and six young rats were administered the SNMTS task. The apparatus, which was made of wood and painted flat gray, consisted of an elevated three-arm starburst maze with a stem that included a start box. Each arm was 64 cm long × 17 cm wide; the start box was 20.5 × 17 cm; and the stem was 46 × 17 cm. The start box and the three goal arms were separated from the stem by guillotine doors (17 cm high × 16 cm wide). A recessed food-cup, 3.5 cm in diameter, was located at the end of each goal arm. The start box was covered by a Plexiglas top in which several holes (5 mm in diameter) were drilled. The apparatus was placed on a table in a quiet room with overhead ceiling illumination.

Training and testing procedures were similar to those described in detail by Gagnon and Winocur (9). Rats were familiarized with the task over an 8-day period. In the first 3 days, bits of Froot Loop cereal were scattered throughout the apparatus. Rats were placed individually in the start box, the Plexiglas cover was placed over the start box, and the guillotine door was raised. Rats were allowed to walk freely in the stem and the three arms, and eat the Froot Loops. The session ended when all the cereal was eaten or after 15 min. elapsed. On Days 4 and 5, Froot Loops were placed only in the three food-cups and rats had 15 min. to find and eat them. On Day 6 to 8, one Froot Loop was placed in each food-cup, the guillotine door of the start box was raised, and the rat was allowed to visit the three goal arms and eat the food. After consumption of the Froot Loops, the rat was returned to the start box, and the procedure was repeated for a total of five trials each day.

SNMTS training was initiated on Day 9. A complete trial consisted of two forced-choice study runs followed by a single test run. On the first study run, the rat was placed in the start box, the cover was flipped down, and the guillotine door was raised. Only one arm was open and baited with a single Froot Loop (the guillotine doors of the other two arms were lowered). As soon as the rat entered the open arm (i.e., four paws were in the arm), the guillotine door was lowered and the rat was allowed to eat the food. The rat was then returned to the start box for the second study run. The procedure for the second run was identical to that of the first except that a different goal arm was baited and open.

After eating the food in the second forced-choice study run, the rat was returned to the start box for the test run. About 5 s elapsed between the rat’s removal from the goal area following the second study run and the beginning of the test run. On the test run, the rat was placed in the start box and, after a few seconds, the guillotine door was raised. All three goal arms were open but only the arm that it had not visited on the two study runs was baited. As soon as the rat entered an arm (all four paws in the arm), the guillotine door was lowered. If the selection was correct, the rat was allowed to eat the Froot Loop and was returned to a holding cage for a 30-s intertrial interval. If the rat selected an unbaired arm, it was immediately placed in the holding cage to await the next trial which began 30 s later. Rats were administered 12 such trials over 15 consecutive days.
The day after the last training session, the rats were injected with saline and, 30 min. later, received 15 trials on the SNMTS task. Over the next 4 days, the rats were injected, on alternate days, with 100 mg/kg of glucose or a comparable volume of saline, 30 min. before NMTS testing. The first day of the sequence was always a saline-treatment day.

Cue-Preference Test. A total of 23 old rats and 21 young rats were administered the cue-preference test. The apparatus for this task was a 4-arm, cross-maze constructed of wood and painted flat gray. The arms were of equal size (56 cm long × 15 cm wide with 2.5 cm sides) and radiated horizontally from a central area (15 × 15 cm). A recessed food-cup was placed 2.5 cm from the end of each arm. The arms were designed so that the gray floor could be easily replaced by a black floor that was also constructed of wood. The maze, which rested on a table, was positioned so that each arm faced due North, South, East, or West. A guillotine door separated the central area from each of the arms.

Rats received three daily familiarization sessions in which they were allowed to explore and eat pieces of Froot Loop cereal that were scattered throughout the maze. Each session ended when all the food was eaten or when 15 min. had elapsed.

The procedure for Days 4 and 5 was similar except that Froot Loops were available only in the food-cups. On Days 6 to 8, the food-cups were again baited and the animals received a number of simulated trials. On these trials, each rat was placed in one of these arms and allowed to eat from any one of the food-cups. When the food was eaten, the rat was removed and placed in a holding cage for a 60-s inter-trial interval. Five such trials, each beginning with the rat placed in a different arm, constituted a daily session.

For forced-choice training, which began on Day 9, the East arm was fitted with a black floor panel. For each trial, the black-East arm was open, as was another randomly selected arm which served as the starting arm. The other two arms were blocked by their guillotine doors. Only the black-East arm was baited. The rat was placed in the starting arm and allowed to enter and eat the Froot Loop in the black-East arm. The rat was then transferred to a holding cage for 60 s to await the next trial. The rats received 10 such daily trials for three consecutive days. For the forced-choice training sessions, rats were assigned, in approximately equal numbers, to a saline condition or a glucose condition. About 30 min before each day’s session, each rat was injected with either 100 mg/kg of glucose or an equal volume of saline depending on the condition to which they had been assigned.

Testing began on Day 12. For each test trial, all arms were open and the rat could select the East arm which now contained a gray floor panel, another arm that also contained a gray panel, or a black arm that contained the black floor panel. All choice-arms were baited with a Froot Loop. The starting arm, which was not baited, was selected on a random basis with the qualifier that it could not be the East arm or the black arm. For the test trials, the black floor panel was never placed in the East arm. For each test trial, once the starting arm was determined, the black panel was placed randomly in one of the two remaining arms. Thus, on any test trial, the rat was placed in one of the arms and confronted with a choice of going to the place that was always associated with food, the cue that was always associated with food, or a third arm that, during training, had never been associated with food. The rat was removed from the maze when it ate the Froot Loop in one of the baited arms and then placed in the holding cage for 60 s to await the next trial. The arm selected on each trial was recorded. Twelve such trials were administered on two consecutive days.

On both test days, half the animals were tested 30 min. after having been injected with either 100 mg/kg of glucose or an equal volume of saline. Thus, four sub-groups of old and young rats were created. Two were trained following saline injection and tested following saline (S/S) or glucose (S/G) injection, and two were trained following glucose injection and tested following glucose (G/G) or saline (G/S) injections. Table 1 summarizes the various treatment sub-groups and provides the number of subjects in each subgroup.

Blood-Glucose Measurement

The day after completion of behavioral testing, blood samples were taken from each rat on two separate occasions, separated by 24 h. Blood-glucose levels were measured with a glucometer (Glucometer 3; Ames Canada). Baseline glucose levels were established on each day by pricking the tail with a scalpel, drawing a drop of blood, and applying the blood to a strip of Glucofil. Thirty minutes later, the rat was injected with saline or glucose (100 mg/kg), in counterbalanced order. Blood samples were taken again at 10-, 30-, and 60-min. intervals, and glucose levels measured in the same way.

To assess the relationship between glucose regulation and performance on the various tasks, a glucose utilization index was obtained for each rat (7). The index was constructed by calculating the difference between the mean of the three glucose measurements following saline injection and the mean of the three glucose measurements following glucose injection. The glucose utilization index for each rat was then compared against its average performance scores on glucose treatment days. By this measure, the lower the index the better the animal’s ability to metabolize glucose from blood.

RESULTS AND DISCUSSION

Radial Arm Maze

Behavioral. The performance of the old and young groups is presented in Figure 1 in terms of the mean number of errors/trial averaged over blocks of two trials. As can be seen in Figure 1, throughout training, the old group consistently made more errors than the young group. Over the last 2 days of training, by which time performance in both groups had stabilized, the old rats made an average of 6.67 errors, whereas the young rats averaged only 2.00 errors. Analysis of variance (ANOVA), performed on these data, confirmed that the age difference was statistically significant, $F(1,23) = 4.70, p < 0.05$, $\omega^2 = 0.21$.

The poor performance of old rats, relative to young rats, on the RAM confirms reports of similar findings with this task (12). Examination of the scores showed that old rats tended to make most of their errors in later stages of the trials, suggesting that their performance was adversely affected by the build-up of interference from previous responses. A similar pattern has been observed in young adult rats with hippocampal lesions (37).

Figure 2 provides the average number of errors made by the old and young groups following saline or glucose injection, averaged over the two days of testing with each treatment. Figure 2 shows that the superiority of the young group carried over into the treatment condition where, once again, a significant group effect
was observed, $F(1,23) = 6.89, p < 0.02, \omega^2 = 0.19$. ANOVA also revealed a significant effect of treatment, $F(1,23) = 8.80, p < 0.01, \omega^2 = 0.21$, but a non-significant group \times treatment interaction, $F(1,23) = 2.22, p < 0.15$. These results indicate that glucose administration generally improved performance on the RAM but that the test of interaction did not provide strong evidence for a differential benefit to either group.

The present results show that the RAM may be added to the list

![Figure 1: Performance of young and old groups during RAM training, averaged over five blocks of two training sessions. Values shown are group means ± SEM.](image1)

![Figure 2: Performance of old and young groups on the RAM test in glucose and saline treatment conditions. Values shown are group means, averaged over two test sessions. (Error bars refer to SEM.)](image2)
of hippocampus-sensitive tasks on which normal, old rats perform better following glucose treatment. Improved performance by young rats, treated with glucose, is a more variable finding but the present results are consistent with the finding that such effects do occur on some tasks (8,19,21).

Although the group × treatment interaction did not reveal a significant differential glucose effect, a comparison of proportional improvement following glucose treatment, relative to performance in the saline condition, provided some indication that old rats benefited more than young rats from glucose. Old rats made an average of 50% fewer errors following glucose treatment, whereas glucose injection reduced the young rats’ error total by an average of 35%. This difference was in the expected direction and was on the border of statistical significance, \( t(14) = 1.72, p < 0.10 \).

**Blood-Glucose Levels and Performance.** Blood glucose measures for rats tested in the RAM are indicated in Table 2. A comparison of baseline blood-glucose, sampled at the end of RAM testing, indicated significantly higher levels in the aged rats, \( t(23) = 8.21, p < 0.0001 \). However, no relationship was found between variations in blood-glucose levels and task performance in either group. Tests of correlations between glucose levels at baseline and total numbers of errors yielded non-significant relationships in the aged, \( r = 0.41, p > 0.05 \), and young, \( r = 0.03 \), rats.

As expected, the average glucose utilization index was significantly higher in the old rats, \( t(23) = 5.26, p < 0.001 \). Moreover, rate of glucose utilization was found to be related to performance by old rats following glucose treatment. Glucose index and total errors made in the glucose condition were positively and significantly correlated in the aged, \( r = 0.62, p < 0.02 \), but not in the young, \( r = -0.08 \), group.

**Spatial Non-Matching-to-Sample**

**Behavioral.** The performance of the old and young groups over the 15 days of training on the SNMTS task are presented in Figure 3 in terms of percentage correct responses, averaged over five blocks of three training sessions. As can be seen from the figure, the old rats consistently performed worse than the young rats on this task. ANOVA, performed on scores for the last block of training trials, when performance in both groups had stabilized, revealed a highly significant group effect, \( F(1,17) = 33.37, p < 0.001 \), \( \omega^2 = 0.63 \). This finding is consistent with other reports that old rats are impaired on tests of SNMTS (1,9).

The effects of glucose and saline treatment on SNMTS performance are presented in Figure 4 in terms of mean percentage correct responses, averaged over two days of testing. As can be

![Figure 3](image)
seen, the old group performed substantially better following glucose treatment than saline treatment. By comparison, the young rats made approximately the same number of correct responses in both conditions. ANOVA, performed on these data, revealed significant group, $F(1,17) = 38.11, p < 0.001, \omega^2 = 0.66$, and treatment, $F(1,17) = 4.92, p < 0.05, \omega^2 = 0.17$, effects and a group $\times$ treatment interaction that was borderline, $F(1,17) = 3.13, p = 0.10$.

The borderline significance of the group $\times$ treatment interaction offers some evidence that the old rats may have benefitted more than the young rats from glucose treatment. A comparison of proportional change in performance showed that the old rats performed, on average, 35% better in the glucose condition than in the saline condition, whereas glucose treatment resulted in only a 3.5% improvement in performance in the young rats. This difference, which was analyzed by a $t$-test with separate variance estimates, was statistically significant, $t(16) = 2.40, p = 0.03$. In this regard, it is noteworthy that glucose treatment raised the aged group’s performance to a level approaching that of the young group in the training and treatment conditions.

The differential benefit of glucose for aged rats was also evident when proportional changes in performance between glucose testing and baseline performance at the end of training were compared. Once again, there was virtually no difference between the young group’s scores, whereas the old group improved by almost 30%, $t(16) = 2.50, p < 0.02$.

**Blood-Glucose Levels and Performance.** As can be seen in Table 2, baseline blood-glucose levels, sampled at the end of SNMTS testing, were higher in the aged rats than in the young rats, $t(17) = 5.18, p < 0.001$. However, baseline levels did not correlate with SNMTS learning. Comparisons between percent correct responses at the end of training and blood glucose levels revealed non-significant correlations in the old, $r = -0.38, p > 0.05$, and young, $r = 0.05$, groups.

The average glucose utilization index for the old rats tested on the SNMTS was significantly higher than that of the young rats, $t(17) = 3.18, p < 0.002$. A comparison of glucose index and percent correct scores following glucose treatment revealed a significant negative correlation in the old, $r = -0.55, p < 0.05$, but not the young, $r = 0.07$, group.

### Cue-Preference Task

**Behavioral.** The data for the various conditions of the cue-preference test are presented in Table 3. The scores represent the percent responses to the spatially-cued, local-cued, and neutral arms in the 12 trial test session.

It is clear from Table 3 that the young group had a strong preference for the spatially-cued arm in all conditions. Overall, young rats learned to respond to spatial cues on approximately 60% of the test trials, which is about twice the rate that would be expected on the basis of chance. Another indication of this preference is that 19/20 young rats selected the spatially-cued arm on the first test trial in the various conditions.

To determine if the proportion of responses made by the young group was affected by treatment, ANOVAs were conducted for each type of response across all conditions. This analysis yielded non-significant differences in responses made to spatial, $F < 1$, local, $F < 1$, and neutral, $F(3,16) = 2.27, p > 0.05$, cues.

Because there was no effect of treatment, the young rats' scores were collapsed across conditions to compare the proportion of responses made to the various cues. In addition to selecting the spatially-cued arm 60% of the time, the young rats directed 25% and 15% of their responses to the black and neutral arms respectively. These comparisons showed that the young rats chose the spatially-cued arm significantly more often than the black, $t(19) = 7.99, p < 0.0001$, and neutral, $t(19) = 14.29, p < 0.0001$, arms. In addition, percentage responses to their second (black) and third (neutral) preferences also differed significantly from each other, $t(19) = 3.63, p < 0.001$. 

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![SNMTS Performance](FIG_4.png)

**FIG. 4.** Performance of old and young groups on the SNMTS task in glucose and saline treatment conditions. Values shown are group means, averaged over two test sessions. (Error bars refer to SEM).
The old group exhibited a similar pattern of behavior but its preferences were different. Old rats learned to respond most often to the black arm, and at a rate (53%) that was significantly above chance. Furthermore, on the first trial of testing, 20/23 old rats selected the black arm.

As with the young group, the old group did not differ in terms of the distribution of responses made to the different cues in the four treatment conditions. A comparison of the effects of treatment on responses across conditions, yielded non-significant differences for the old rats.

The data indicate that, while old and young groups preferred different cues at test, the relative strengths of their preferences were similar. For example, as indicated above, the young rats made 60% of their responses to the first choice, the spatial cues, while the old rats made 53% of their responses to the first choice, the black cue. The difference between groups in percentage responses made to the spatial and neutral arms were also significantly different, t(22) = 4.38, p < 0.001. However, consistent with the lack of effect of glucose treatment on this task, there were no significant correlations between the glucose index and cue preferences in either group.

**GENERAL DISCUSSION**

The results confirmed that the three tasks used in this experiment are sensitive to the effects of normal aging. The observed age differences in performance on the RAM were similar to those reported in previous investigations (12). The aged rats’ relatively poor learning of the SNMTS task replicates the findings of Gagnon & Winocur (9) on the same task, and is consistent with reports of age-related impairment on other SNMTS tasks (1). The results of the cue-preference test did not reveal age-differences in performing this task. Rather, they showed that, given a choice between equally probable spatial and non-spatial local cues, old rats prefer to use local cues in forming associations between rewarding events. In contrast, young adults were clearly biased toward spatial cues.

The behavior of aged rats on the three tasks was very similar to that seen in young adult rats with bilateral lesions to the hippocampus, tested under similar or identical conditions (e.g., RAM: 25,37; SNMTS: 10,29; cue-preference: 5). These parallel results are consistent with previous observations that old rats are reliably impaired on learning and memory tests of hippocampal function, and typically show similar deficit patterns (11,17,28,32,38). While other brain regions undoubtedly are involved in performing the RAM, SNMTS, and cue-preference tasks, the hippocampus is among the first structures to decline with age (2,3), and the present results offer further evidence that old rats are vulnerable on tasks that require an intact hippocampus for normal performance.

In demonstrating glucose-enhancement on the RAM and SNMTS tasks, the present study extends the range of tests in which glucose has been shown to improve learning and memory performance in old rats. Attenuation of age-related deficits following glucose treatment has been reliably seen in tests of inhibitory avoidance (16) and spontaneous alternation (30), but to a lesser degree on food-motivated appetitive tasks (e.g., 36). The present results provide compelling evidence that glucose can improve performance of aged animals on tasks that differ considerably in terms of their cognitive demands.

Whereas glucose treatment significantly improved the perfor-
mance of old rats on the RAM and SNMTS tasks, glucose did not restore the use of spatial cues in the cue-preference task. There were many differences between the three tasks, but a common feature of the RAM and SNMTS tasks is that successful performance depended on memory for highly specific experiences. In the RAM, rats must remember the arms that were previously entered during that session and, in the SNMTS task, they must remember the two arms that were baited in the study trials. By comparison, during testing in the cue-preference task, rats would be rewarded for adopting any one of three strategies: 1) follow extra-maze, spatial cues, 2) follow intra-maze, local cues, or 3) visit any arm at random. The cues were invariant from trial-to trial and there was no requirement to remember specific experiences. In all treatment conditions, the young rats consistently learned to adopt a spatial strategy, whereas the old rats learned to follow local cues in consistently selecting the black arm.

This outcome indicates that glucose effects do not generalize to all aspects of hippocampal function that are affected in old age. The question arises as to whether the effects are specific to tests of spatial memory or extend to forms of non-spatial memory in which the hippocampus may be involved (e.g., 33,34). The glucose behavioral literature is not particularly helpful on this point. The various avoidance and alternation tasks, on which glucose-enhancement effects have been most frequently observed in aged animals, all involve spatial memory. In Winocur’s (36) conditional associative learning task, the rats had to associate different stimuli with different responses. While not strictly a spatial memory task, there was a spatial component in that the visual stimuli and the levers associated with the stimuli were always spatially aligned. On the other hand, in that study, glucose improved performance only in delay conditions, suggesting that the effect was on memory functions, and independent of the use of spatial information. Clearly, further research is needed to resolve this important issue.

There was some evidence that glucose administration improved performance of young adult rats in the RAM test where, despite a relatively low baseline error rate, the young group improved its performance by about 35% following glucose injection. This was somewhat less than the 50% improvement exhibited by the old group on this test, although the possibility of a floor effect in the young rats’ performance must be recognized. There was little evidence that glucose enhanced young rats’ performance in the SNMTS task as their performance was virtually identical in groups on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect in the group on this test, although the possibility of a floor effect.

The variable effect of glucose on the young rats is generally consistent with the literature on glucose effects on cognitive performance in young adults. In the majority of studies that compared old and young animal or human subjects on tests of learning and memory, the typical finding is glucose-enhanced performance in aged groups and little, if any, such effects in young adults (see 13,15,23 for reviews). On the other hand, there are contrary reports that young adults may also benefit from glucose treatment (23). The reason for this variation is not clear, particularly in the animal research, but several factors, including task and dosage, appear to be relevant. For example, there is evidence that relatively low doses may be most effective in improving normal young animals’ memory for inhibitory avoidance (19) and operant bar-pressing (22,24) responses. By comparison, higher doses appear to be more effective when baseline performance levels have been disrupted by adverse treatments, such as hypothermia (8). The present results also point to the importance of task-related factors but, clearly, more investigation of this issue is warranted.

The analysis of blood glucose showed that baseline glucose levels were significantly elevated in old rats, confirming that glucose regulation declines with age (6,14,20). Interestingly and in contrast to some reports (20), there was no evidence that age differences in baseline performance on the RAM and SNMTS tasks were related to variations in blood glucose levels in old rats. On the other hand, improved performance by old rats on the RAM and SNMTS tasks following glucose treatment correlated significantly with the glucose utilization index, which measures peak increases in blood glucose and recovery to baseline levels following glucose injection. This pattern of results, which has been observed previously in aged rats (31,36) and humans (6,7), suggests that, whereas age-related memory loss is associated generally with high blood glucose, the elderly subjects that are most likely to benefit from glucose treatment are those that have the most residual capacity to take up glucose and transport it to brain regions. On the other hand, no relationship was found between glucose utilization and performance in the young rats.

This is not surprising because glucose uptake is not a problem for these animals, but it does suggest that any beneficial effects of glucose in young rats are probably mediated by some other mechanism.

Finally, an important issue that must be addressed is the possibility that glucose-induced improvements on the RAM and SNMTS tasks in the aged rats were the result of performance, rather than cognitive, changes. For example, administering glucose to food-deprived old rats may have reduced their hunger levels and facilitated attention to spatial cues. Alternatively, glucose treatment may have made the old rats more responsive to the rewarding properties of food, thereby providing additional incentive. These interpretations could be discounted in our previous study (35), because glucose effects were selective, affecting performance on the conditional learning task only in the delay conditions. The behavioral data of the present study are not, in themselves, as informative on this issue, but other results that will be reported in detail elsewhere (18), point to a direct effect on memory processes.

A few days after completion of behavioral testing, all rats in the present study were sacrificed and their brains were examined histologically. The purpose was to investigate possible relationships between structural changes in various brain areas and age-related changes in cognitive performance. This analysis yielded several findings including, unexpectedly, significant correlations between dendritic branching in hippocampus and performance on the RAM and SNMTS tasks following glucose treatment. These relationships were not observed in other brain regions, e.g., prefrontal cortex, cingulate gyrus. The question as to whether glucose treatment directly promoted dendritic growth or interacted with branching associated with the aging process is discussed in the other paper (18). The relevant point here is that the selective interaction of glucose with hippocampal growth processes provides compelling evidence that glucose effects are directed at memory processes mediated by hippocampal function (see also 14,27). This view is further supported by evidence, from animal and human research, that glucose-enhanced cognitive performance is most reliably seen in memory tests that are sensitive to hippocampal dysfunction (6,20). It is also supported by recent physiological evidence that enhanced memory performance following glucose treatment is related directly to increased synthesis of the neurotransmitter, acetylcholine, in the hippocampal system (27).

In summary, the present results confirm that tests of spatial learning and memory that are sensitive to hippocampal impairment are also sensitive to the effects of normal aging. It was also found that glucose administration can reduce age-related deficits on such tasks when normal spatial memory is an essential requirement for successful performance. There was also evidence that, on certain tasks, young rats performance may improve following glucose
treatment. The results extend the range of tasks on which glucose-induced cognitive enhancement has been demonstrated, particularly in aged rats, and provides further evidence that memory loss resulting from hippocampal dysfunction is especially amenable to glucose treatment.

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