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Aging and Time-of-Day Effects on Cognition in Rats

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This study used an animal model to investigate the importance of the time at which testing occurs for age differences in learning and memory. Groups of old and young rats were entrained to a 12-hr light–dark schedule and administered tests of delayed alternation and inhibitory avoidance conditioning at the beginning or end of their high-activity cycle. Apart from normal age differences in test performance, the behavioral results demonstrated that old but not young rats were affected by the time of testing. In both tasks, old rats tested late in the activity cycle performed significantly worse than did old rats tested early in the cycle, under conditions that challenged memory processes that are known to involve the hippocampus. The results indicate that circadian disruption in old age can adversely affect memory and related cognitive function, with important implications for inhibitory control.

Age-related changes in circadian rhythms are well documented and affect a wide range of functions that include the sleep–wake cycle, eating and drinking patterns, glucose uptake, heart rate, as well as the availability of various hormones (e.g., melatonin, ACTH) and neurotransmitters (e.g., acetylcholine, norepinephrine; Brock, 1991; Burwell, Whealin, & Gallagher, 1992; Edgar, 1994; Horne & Ostberg, 1977; Hrushesky, 1994; Ingram, London, & Reynolds, 1982; Stone, 1989). There has been little study of the impact of circadian disorganization on cognitive function, but available evidence suggests that such a relationship exists. For example, several reports have linked changes in sleep–wake patterns in old age to age-related memory loss (Bliwise, 1989; Nesca & Koulack, 1994; Stone & Gold, 1988).

Older animals and humans exhibit a substantial shift toward peak arousal and activity in the morning (Hoch, et al, 1992; Ingram et al, 1982; Peng & Kang, 1984), and recent evidence suggests that their cognitive abilities may follow a similar pattern. For example, the acquisition and retention of new information has been found to vary with the time of day that the task is performed, with older adults performing better in the morning than in the late afternoon and younger adults generally showing the reverse pattern (Anderson, Petros, Beckwith, Mitchell, & Fritz, 1991; May, Hasher, & Stoltzfus, 1993). Older people's ability to suppress irrelevant information and perform neuropsychological tests also varies across the day, with optimal performance typically occurring in the morning when they are most active (Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1998; May & Hasher, 1998; May, in press). The observation that optimal cognitive performance corresponds to peak arousal periods has been characterized as the *synchrony effect* (May & Hasher, 1998).

There are numerous reports that aged rats perform worse than young adult rats on a wide range of learning and memory tests (see Barnes, 1990; Kubanis & Zornetzer, 1981; Moscovitch & Winocur, 1992), but a possible link between such differences and age-related changes in circadian rhythms has not been investigated in an animal model. In addition, there appear to be no documented reports in which time of testing was taken into account in comparisons of cognitive function in young and old animals. The latter is important because light–dark periods and testing schedules vary considerably between laboratories. It is possible that uncontrolled times of testing coupled with age-related circadian differences contribute to observed age differences in performance. These issues are addressed in the present study.

Groups of old and young rats were administered two behavioral tests that are sensitive to effects of normal aging. The first was a delayed alternation task (VIDA) in which rats must alternate lever-press responses on trials that are separated by a variable interval (Winocur, 1986; 1988a). The second was a test of inhibitory avoidance in which rats must recall an aversive experience to suppress a learned (but no longer appropriate) approach response (Winocur, 1985; 1988b). Apart from their sensitivity to age effects, these tasks were selected because they assess dissociable aspects of learning and memory that have been related to different

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brain regions (Winocur, 1985, 1991) and because they incorporate a substantial inhibitory component. In humans, time-of-day, or synchrony, effects have been reported most frequently on tasks that require a measure of inhibitory control (Hasher, Zacks, & May, in press). To test for such effects, approximately half the rats were tested at the beginning of their high-activity cycle, and the other half were tested at the end of this period.

Method

Subjects

Twenty-nine old and 18 young, male, Long–Evans rats, born in the Trent University Breeding Centre, completed all aspects of the study. At the time of behavioral testing, old rats were approximately 22 months old (range: 21– 23 months) and young rats were 6 months old.

All of the rats were naive to the tasks administered but had some experience with unrelated behavioral testing. Rats were regularly examined by a veterinarian. Two old rats and 1 young rat died during the experiment. In addition, 2 old rats developed severe respiratory infection and, at the advice of the veterinarian, were removed from the experiment to protect the health of the other rats. Data from rats that did not complete the study were not included in the analyses.

Tests and Materials

VIDA. Five identical Skinner boxes were used for this test, allowing 5 rats to be tested simultaneously. Each box was equipped with a single retractable lever located to the right of a central feeder and was contained in a sound-proof chamber (52 × 52 × 52 cm) that was illuminated by a 3-W light mounted in the ceiling.

During training and the reinforced trials of testing, each lever-press produced a single, 45-mg Noyes food pellet in the central feeder. A 486 personal computer controlled all operations, recording the latency to make the first response in each trial and the number of responses per trial.

Initially, food-deprived rats were trained to press the lever for food according to a continuous reinforcement (CRF) schedule. Training consisted of one, 20-min session per day and continued until a response rate of 75 responses per session was achieved over 2 consecutive days. During CRF training, each lever-press was rewarded by a food pellet. After each session, rats were returned to their home cages and given approximately 20 g of standard Lab Chow (Ralston-Purina, St. Louis, MO).

VIDA testing was initiated the day after criterion was reached on CRF training. Each test session consisted of 12 reinforced (go) trials alternating with 12 nonreinforced (no-go) trials. The single lever was always present during the go and no-go trials, each of which was 20 s long. Each lever-press during the go trials produced a food pellet, whereas lever-presses during the no-go trials were not rewarded. The go and no-go trials were separated by a variable intertrial interval (ITI), during which the lever was retracted. The ITIs were 0, 5, 10, 20, 40, or 80 s long, with each interval occurring twice after go trials and twice after no-go trials, so that each ITI occurred four times per session. The sequence for ITIs was varied for each session, which always began with a go trial. All rats received one session per day for 15 days.

Inhibitory avoidance. This test was conducted in a chamber (60 × 40 × 30 cm) divided into start boxes and goal boxes, each of which was separated from the central runway by manually controlled sliding doors. The apparatus, which was located in a dimly illuminated room, was constructed of wood and painted flat gray except for the floor, which consisted of a series of metal rods. A metal spout attached to a water bottle protruded through the back wall of the goal box, 8 cm above the floor. Both the sliding door in the start box and the water spout were connected to timers that measured latency to drink after the door was removed. The water spout and metal rods in the goal box were attached to a shock generator that, on shock trials, delivered a 1.5-mA current through the rat's mouth.

The experiment began with a habituation period that consisted of two daily sessions in which each rat was placed in the apparatus for 30 min, with unlimited access to the entire apparatus. During the habituation sessions, the rat could drink freely, but no other water was provided on these days. Approach training began the day after the second habituation session. An approach training trial consisted of placing the rat in the start box, removing the sliding door, and allowing the rat to approach the water spout and drink for 10 s. Five such trials were administered on each day of approach training. On the third trial of the following day, rats received a 1.5-mA shock when contact was made with the water spout.

Shock-avoidance testing took place 24 hr after approach training and again 6 weeks later. Each test session involved a single trial in which the rats were placed individually in the start box and allowed up to 5 min to contact the water spout in the goal box. Water was available in the test trials and, upon reaching the spout, the rat was allowed to drink for 10 s. The latency to contact the water spout after the sliding door was removed was recorded for all training and test trials.

Procedure

Six weeks before the beginning of behavioral testing, the rats were transferred from group cages to individual cages with food and water always available. They were maintained on a 12-hr light–dark schedule with lights on between 8:00 p.m. and 8:00 a.m. Entrainment to this circadian rhythm was confirmed by measuring drinking patterns twice a day, at the end of the light and dark cycles.

The inhibitory avoidance task was administered first. For this task, rats were placed on a 23.5 water-deprivation schedule and, after the habituation sessions, were subjected to the 6-day training period and the 24-hr test. After the 24-hr shock avoidance test, rats were placed on an ad-lib food and water diet and maintained on the same light–dark cycle. Two weeks later, a 23.5-hr food-deprivation schedule was instituted, and, 1 week after that, training and testing on the VIDA task were initiated.

After VIDA testing, the water deprivation, ad-lib food schedule was reinstated for 1 week. At that time, 6 weeks had elapsed since the 24-hr shock avoidance test, and rats were retested on this task, according to the same procedures.

Before the beginning of behavioral testing, approximately equal numbers of old and young rats were arbitrarily assigned to early or late testing conditions. Thus, four subgroups were created: Subgroup OE (old rats tested early in the dark cycle; $n = 15$), Subgroup OL (old rats tested late in the dark cycle; $n = 14$), Subgroup YE (young rats tested early in the dark cycle; $n = 9$), and Subgroup YL (young rats tested late in the dark cycle, $n = 9$). For rats in the early condition, testing commenced within 1 hr of the beginning of the dark cycle, and, for those in the in the late condition, approximately 1 hr before the end of the dark cycle. Rats in each condition were always tested at the same time of day.

Table 1
Amount of Water (in Milliliters) Consumed By Old and Young Groups at the End of Their Dark and Light Cycles

	Dark cycle		Light cycle	
	M	*SD*	*M*	*SD*
Old	44.29	9.39	23.69	3.82
Young	51.06	5.91	20.82	3.15

Note. Scores are averaged over the last 3 days of the entrainment period.

Results

Light-Dark Entrainment

There were no age differences in terms of daily water intake ($F < 1$), but old rats drank less water than young rats during the dark cycle, and more during the light cycle (see Table 1). This observation was confirmed by a significant Group × Cycle interaction, $F(1, 43) = 13.55$, $p = .001$. Overall, the old rats drank, on average, 64.9% of their daily water intake during the dark cycle compared with 71.2% by the young rats, a difference that was highly significant, $F(1, 45) = 29.92, p < .0001$. This result is consistent with reports of reduced diurnal differences in water intake (Burwell et al., 1992; Gallagher & Burwell, 1989).

Inhibitory Avoidance

All rats achieved asymptotic performance during approach training, and although the latency to reach and drink from the water spout was slightly greater for old rats than for young rats, group differences were not statistically significant. In comparison, at the 24-hr test, old rats exhibited shorter response latencies than young rats, (Mann–Whitney test, $U = 149.0, p < .01$), indicating a general effect of age on withholding the approach response (see Figure 1). There was no effect of the time of testing in either the young ($U = 35.0$, $p < .50$) or the old ($U = 91.0$, $p < .52$) groups.

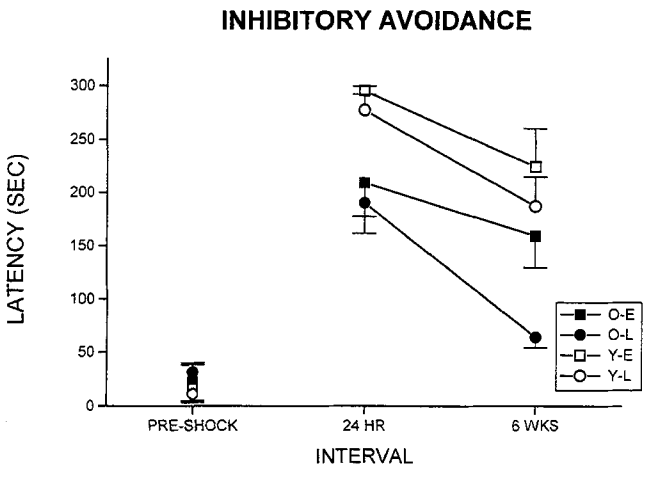

Figure 1. Response latencies for old (O) and young (Y) groups at short and long delays in the inhibitory avoidance test. Error bars represent *SEM*. E = early testing; L = late testing.

However, as can be seen in Figure 1, a different pattern emerged when rats were tested 6 weeks later. Once again, there was a significant age difference in the latency-to-drink measure that favored the young group ($U = 125.0, p < .004$) but, in the second test, the time of testing was important for the old rats. Rats in Subgroup OE performed much better than did their counterparts in Subgroup OL ($U = 60.0, p < .05$). In comparison, Subgroups YE and YL did not differ ($U = 27.5, p < .25$).

Because of the design of the experiment, some rats drank water in the 24-hr test, whereas others failed to make contact with the water spout within 300 s. Conceivably, this differential experience affected performance on the second test in ways that could affect interpretation of the results. That is, rats that obtained water in the first test may have been more motivated to approach the water spout in later testing than did rats that failed to obtain water. In that case, shorter latencies by the former group would not necessarily reflect memory loss for the shock experience. This was especially important for Subgroup OL, in which only 6 of the 10 rats drank from the water spout during the first test. Overall, Subgroup OL showed shorter latencies at the 6-week test, but approach latencies of the 6 drinkers ($M = 58.3$ s) were slightly (and nonsignificantly), slower than those of the 4 nondrinkers ($M = 47.7$ s). Similar analysis of the other groups' response times provided no evidence that obtaining the water reward on the initial test influenced performance on the second test.

VIDA

All rats acquired the lever-pressing response during CRF training in 5–9 sessions, and there was no difference between old and young groups on this measure, $t(46) = 0.51, p > .10$. Similarly, there was no effect of time-of-day in either the young ($t < 1$) or old ($t < 1$) group on CRF acquisition. Similar comparisons were made on the number of responses made by each rat in the last CRF session and, again, there were no significant group differences ($ps > .05$).

For VIDA testing, only the data based on latency measures are presented. As in previous studies that used this task (Winocur, 1986, 1991), the response output data yielded essentially the same information and were considered redundant.

VIDA test results, averaged over the final block of three sessions (Days 12–15), are presented in Figure 2 in the form of go/no-go latency ratios. At each ITI, ratios were calculated by dividing the mean latency to the first response in the go trials by the mean latency to the first response in the no-go trials. A low ratio would result from shorter latencies in the go trials than in the no-go trials. Thus, the lower the latency ratio, the better the rat's performance.

Consistent with previous results (Winocur, 1986, 1988a), Block 5 data revealed a significant age effect on the VIDA task, $F(1, 43) = 37.46$, $p < .001$. Subsequent analyses revealed that young rats performed better than did old rats at each ITI ($ps < .03$), including ITI-0, $F(1, 43) = 10.18, p < .003$. The latter result is noteworthy in that, at ITI-0 (where the lever retracted and returned to the apparatus instantaneously) specific memory function was minimally chal-

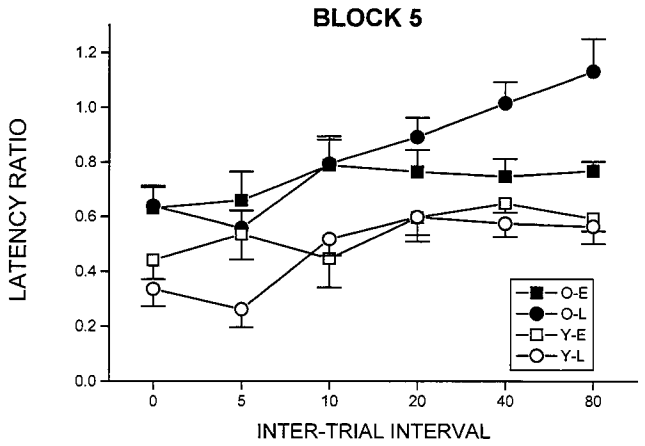

Figure 2. Latency ratios for old (O) and young (Y) groups on Block 5 of the VIDA test. Error bars represent *SEM*. E = early testing during dark cycle; L = late testing during dark cycle.

lenged, and performance on these trials reflected the rats' acquisition of the response alternation rule. The Group × ITI interaction was not statistically significant ($F < 1$).

There is clear evidence in the Block 5 data of the VIDA task that age differences in performance were modulated by differences in circadian rhythms (see Figure 2). The time of day at which testing occurred did not exert a main effect on overall performance, but this variable interacted significantly with the effect of age, $F(1, 43) = 4.07$, $p < .05$. This interaction was due entirely to the differential effect of time-of-day on the performance of the old rats. An ANOVA conducted on the latency ratios of Subgroups OL and OE revealed a significant Time-of-Day × ITI interaction, $F(5, 135) = 2.58$, $p < .03$, that, according to a Tukey's test, was due to the poorer performance of Subgroup OL at ITIs 40 ($p < .02$) and 80 ($p < .01$). Similar analyses performed on the young subgroups, yielded no significant differences.

An additional analysis was performed on the Block 5 data to determine whether age differences on the VIDA task and time-of-day effects were related to an impairment in response inhibition. This type of deficit can be expected to result in a loss of inhibitory control that would be reflected in an exaggerated tendency to press the lever during no-go trials. In fact, this pattern was exhibited by Subgroup OL at long ITIs, where the time-of-day effect was observed. Table 2 provides absolute latencies for all groups on the go and no-go trials averaged over short (ITIs 0, 5, and 10 s) and long (ITIs 20, 40, and 80 s) ITIs in Block 5. There were no differences between Subgroups OL and OE at short ITIs, but at long ITIs, a highly significant Subgroup × Type-of-Response interaction, $F(1, 27) = 27.94$, $p < .0001$, confirmed that differences between the aged subgroups were significantly greater on the no-go trials than on the go trials.

On the other hand, there was no evidence that an inhibitory control deficit contributed to the differences between young and old groups on this task. Although the Age × Type-of-Response interaction was significant at short ITIs, $F(1, 45) = 9.48$, $p < .005$, and long ITIs, $F(1, 45) = 17.43$, $p < .0001$, these effects were due to the old rats exhibiting longer response latencies on the go-trials than did young rats (see Table 2). This outcome, along with the absence of group differences on the no-go trials in the short and long ITI conditions, is incompatible with an inhibitory control deficit hypothesis.

Drinking Pattern–Behavior Relationships

As indicated above, there was a significant difference between old and young rats in the distribution of water intake over the light–dark cycle. To determine whether this effect, which resulted from a reduction in diurnal differences in water intake in the old rats, was directly related to behavioral performance, the ratio of each rat's water intake during the dark cycle to that during the light cycle was correlated with corresponding response latencies on both tests of the inhibitory avoidance task and with latency ratios at all ITIs of the VIDA task. Of particular interest was a possible relationship between the measures of water intake and the performance of Subgroup OL on the 6-week avoidance test and at long ITIs of the VIDA task, where significant time-of-day effects were observed. In fact, there were no significant correlations between the distribution of water intake and performance on any of the behavioral measures (Pearson product–moment correlation test; $ps > .05$).

Discussion

The results confirm the existence of age differences in learning and memory, as measured by the VIDA and inhibitory avoidance tasks (Winocur, 1986, 1988a, 1988b). The important new finding is that, on both tasks, performance by the old but not the young rats was affected by the time of day that testing was administered, at least at long delays which challenged memory for specific events.

In the present study, age differences on both tasks were noted regardless of the time of testing, but the differences were substantially greater when testing was conducted late in the rats' high-activity cycle. This pattern extends similar results derived from studies with humans (Intons-Peterson et al., 1998; May et al., 1993; May & Hasher, 1998; Nesca & Koulack, 1994). There is growing evidence that age differences in cognitive performance are relatively small when tests are given at times that correspond to the respective peak

Table 2
Response Latencies For Go and No-Go Trials at Short and Long Intertrial Intervals (ITIs) on Block 5

	Short		Long	
Group	Go	No go	Go	No go
OL	5.41	8.10	6.30	6.42
OE	6.61	9.60	7.04	8.99
YL	2.45	7.03	3.47	5.87
YE	3.93	8.69	3.81	6.17

Note. Short ITI scores are averaged over ITIs of 0, 5, and 10 s; long ITI scores are averaged over ITIs of 20, 40, and 80 s. O = old rats; Y = young rats; E = testing early in the light-dark cycle; L = testing late in the light-dark cycle.

arousal periods of young and elderly people. When tests are administered at off-peak times, the performance of elderly people declines dramatically and age-related differences in performance are greatly exaggerated (May et al., 1993; May & Hasher, 1998; Petros, Beckwith, & Anderson, 1990). In these studies, peak arousal times usually were determined by questionnaires that assess sleep–wake behaviors and preferences, such as the Horne–Ostberg Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976). Scores on this questionnaire were found to correlate reliably with physiological measures of circadian activity in young and older adults (Buela-Casal, Caballo, & Cueto, 1990; Horne & Ostberg, 1976), suggesting that the synchrony effects are related to variations in circadian rhythms. Because old age is accompanied by major alterations in the patterning of circadian rhythms, many of which affect brain function, it is reasonable to expect a connection between circadian disruption and age-related cognitive decline. The negative effects of such a connection would be most apparent when aged individuals are tested when critical diurnal rhythms are at low points in their cycles.

Although time of testing clearly affected the performance of old rats, there was no comparable effect in young rats. In studies with humans, time-of-day effects have been reported in both young and elderly adults (May et al., 1993; May & Hasher, 1998). An important difference between young and aged humans is that, in young adults, the optimal performance period can occur at different times of the day, whereas in older people, the optimal performance period typically occurs in the morning. It remains to be determined whether such individual variation exists in young adult rats and, if so, whether it is accompanied by variation in cognitive performance.

The present data did not yield a direct relationship between altered diurnal drinking patterns and performance on either the VIDA or the inhibitory task. It is important to emphasize that this outcome, which is consistent with the results of an earlier study (Gallagher & Burwell, 1989), does not rule out a link between circadian rhythmicity and cognitive function. Despite significant differences between old and young rats in their patterns of water intake, there was relatively little within-group variation in the amount of water consumed. Consequently, the measures of water consumption taken at the end of the light and dark cycles may not have been sensitive enough to predict performance of Subgroups OL and OE on the behavioral tasks. In addition, age-related disruptions in drinking patterns are undoubtedly related to other circadian changes in old age (e.g., glucose metabolism, production of central neurotransmitters) that more directly affect brain function. The latter possibility is extremely likely and highlights the need for systematic investigation of specific circadian changes that influence cognitive function in old age.

It may be argued that old rats' behavior in the present study was influenced more by the effects of time of day on performance-related variables than on cognitive processes. For example, old rats tested near the end of their high-activity cycle may have suffered from fatigue or reduced motivation relative to those tested near the beginning of the cycle and, as a result, were less efficient at performing the tasks. Several lines of evidence argue against this interpretation. In both tasks, time-of-day effects were restricted to long delay conditions that specifically challenged memory function and were not widespread, as would be expected if they were the result of performance-related variables. In the VIDA task, Groups OL and OE differed only at ITIs 20 – 80; in the inhibitory avoidance task, the effect of time of testing was apparent only at the 6-week delay and not during approach training or at the 24-hr test. In addition, in the inhibitory avoidance task, the time-of-day effect was reflected in faster latencies by Group OL, a finding that is inconsistent with excessive fatigue or diminished motivation to perform. A more likely explanation is that the old rats tested late in their activity cycle exhibited cognitive impairments that were related to changes in biological rhythmicity.

In aged humans, time-of-day effects have been observed most frequently on relatively difficult tasks that (a) direct attention away from irrelevant information or (b) require withholding a well-established response. These abilities are widely associated with frontal-lobe function and are part of the structure's role in controlling interfering influences and organizing strategic behavior (Moscovitch & Winocur, 1995; Stuss & Benson, 1986; West, 1996). In this regard, the finding that the time of testing did not influence the old rats' performance at short ITIs on the VIDA task, and ITI-0 in particular, is informative. Previous research with this task (Winocur, 1991) has shown that performance at ITI-0, a measure of alternation rule-learning, was selectively affected by frontal-lobe lesions. On the other hand, damage to the hippocampus had no effect at any of the short ITIs but severely disrupted performance at the long ITIs. Similarly, with respect to the inhibitory avoidance task, there is evidence that hippocampal lesions selectively impair memory for the shock experience at long delays. In a study that used the same avoidance task (Winocur, 1985), there was no difference between hippocampal and control groups at the 24-hr test, but there was a strong effect of the lesion at longer delays. Thus, the present results depart somewhat from findings with humans in showing that, in aging rats, long-term memory processes that are controlled by the hippocampus are especially vulnerable to time-of-day effects and related alterations in circadian rhythms.

Another aspect of the time-of-day effect that warrants further study relates to the importance of inhibitory control. In most cases, tests used in the human research incorporated substantial inhibitory components such that, to perform successfully, it was necessary to suppress inappropriate responses. On this basis, Hasher et al. (in press) concluded that a disruption in circadian rhythmicity is directly related to an exaggerated loss of inhibitory control that occurs in normal aging and contributes to impairment on many cognitive tests. The behavioral tasks in the present study also had inhibitory components, but an inhibitory-deficit hypothesis cannot, on its own, account for the results. Such a hypothesis would predict time-of-day effects at all delay intervals on both tasks, as the same degree of response suppression was required in all conditions. As indicated above, in the inhibitory avoidance task, time of testing

affected old rats' performance only at the 6-week test and, in the VIDA task, only at ITIs 40 and 80.

On the other hand, there is evidence that inhibitory requirements contributed to the time-of-day effect on the VIDA task. An exaggerated tendency to press the lever in the no-go trials of this task would reflect a failure to inhibit that response, which is appropriate for the go trials where it is reliably associated with reward. Subgroup OL exhibited this tendency at long ITIs in the no-go trials, where the time-of-day effect was observed. This result, combined with the finding that time-of-day effects were specific to long-delay conditions in both tasks, argues that, in our animal model, memory function is particularly vulnerable to effects of age-related disruption of circadian rhythms and that memory failure can result in an increased bias to perform well-learned, but inappropriate, responses (see also Winocur, Moscovitch, & Bruni, 1996).

Although the present results point to a time-of-day effect on long-term memory processes, it would be premature to conclude that such effects are limited to hippocampus-controlled functions. Other brain regions (e.g., frontal lobes) are implicated in both tasks, and it is likely that, under other conditions or in other tests, time of testing could be shown to affect other expressions of brain function in old animals. Indeed, this has been shown to be the case in aged humans (May et al., 1993; May & Hasher, 1998). There is also much work to be done in specifying the precise relationships between circadian disruption in old age and cognitive function. Future research can be usefully directed at identifying which rhythmically-controlled responses are directly related to cognitive performance and whether such relationships hold for younger as well as older individuals. In providing evidence that, in old rats with altered diurnal drinking patterns, memory function varied with the time of testing and corresponding arousal–activity levels that are governed by circadian rhythms, the present study has demonstrated that these issues can be profitably investigated in an animal model.

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