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Circadian Rhythms and Memory in Aged Humans and Animals

GORDON WINOCUR and LYNN HASHER

People have strong preferences for the times at which they engage in everyday activities, such as shopping, reading newspapers, and listening to music (Yoon, 1998). These preference patterns are quite different across the adult lifespan, with college-age young adults preferring to perform many activities in the afternoon and evening, and older adults preferring the morning (Hasher, Zacks, & May, 1999; May, Hasher, & Stoltzfus, 1993). One explanation for these patterns is that by the afternoon, older adults are tired and lack motivation, whereas young people are more likely to be alert and functioning at near-optimal levels. In fact, the scenario may be more complicated than this; it may relate to diurnal biological rhythms that are different for older and younger adults, and that in addition are disrupted in old age. The altered behavioral patterns are consistent with a substantial shift toward peak arousal and activity in the morning that has been found for both older humans and lower animals (see, e.g., Hoch et al., 1992; Ingram, London, & Reynolds, 1982; Peng & Kang, 1984). This age-related shift has been linked to changes in a wide range of circadian rhythms that affect, for example, sleep–wake cycles, eating and drinking patterns, glucose uptake, and heart rate, as well as circulating hormones (e.g., melatonin, adrenocorticotropic hormone) and neurotransmitter function (e.g., acetylcholine, norepinephrine; Brock, 1991; Burwell, Whealin, & Gallagher, 1994; Edgar, 1994; Horne & Ostberg, 1977; Hrushesky, 1994; Ingram et al., 1982; Stone, 1989).

Recent work in several laboratories suggests that variations in circadian arousal rhythms may also influence human cognitive function, with optimal performance associated with testing that occurs near peak times of arousal as opposed to off-peak times. This pattern is termed the "synchrony effect" (May & Hasher, 1998). Given considerable evidence that older and younger adults experience peak arousal times at different times of day (e.g., Adan & Almirall, 1990; May & Hasher, 1998; Mecacci & Zani, 1983; Yoon, 1998), the suggestion is that age-related patterns of performance could well differ across the day, from morning (a peak time for as many as 75% of older adults) to late afternoon (near a peak time for at least 35% of college students).

Indeed, a growing literature suggests that levels of cognitive performance for some tasks do change across the day. With respect to age comparisons, however, they change in different directions: Older adults show better performance in the morning than in the afternoon, and younger adults show the reverse pattern (see Hasher et al., 1999; Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1998; May & Hasher, 1998; Yoon, May, & Hasher, 1998). In humans, the synchrony effect has been demonstrated in a variety of paradigms, most reliably on tasks that incorporate a substantial inhibitory component—that is, tasks that require ignoring concurrent distraction, ignoring no longer relevant information, or suppressing inappropriate response tendencies.

For example, one task involved presenting a verbal puzzle (three unrelated words that could be related by a missing fourth word) in either the presence or absence of verbal distraction. All participants were instructed to ignore the distraction while solving the word problem. Although young adults were able to ignore the distraction in an afternoon testing period, they were unable to do so in a morning testing period. Older adults (consistent with views that inhibitory control declines with age) were unable to ignore the distraction at either time of testing, but distraction was far more disruptive (in terms of reductions in the numbers of problems solved) in the afternoon than in the morning (May, 1999).

Another study in this series used a version of a stop-signal paradigm, in which on most trials, people must respond as quickly as possible to make a simple category decision (e.g., is a couch an instance of the category "furniture"?). On a small proportion of trials in this study, a signal indicated that a classification response should be withheld. Although there were no differences as a function of time of testing on the standard classification trials, there were substantial differences on the stop-signal trials. In particular, both younger and older adults were more likely to fail at withholding when tested at a nonoptimal time than when tested at an optimal time (May & Hasher, 1998).

From a neuropsychological perspective, an interesting feature of the various inhibitory tasks is that they are associated with frontal lobe function. For example, the stop-signal test is reminiscent of other tasks (e.g., alternation, go/no-go) that require suppression of a prepotent response following a discrete signal, and that are sensitive to impairments in attentional processes and response control in animals and humans with frontal lobe damage (see, e.g., Freedman & Oscar-Berman, 1986; Winocur, 1991). Indeed, it has been suggested that the synchrony effect in aged humans is the direct result of circadian disruption of frontal lobe function (Intons-Peterson et al., 1999; May & Hasher, 1998).

The question arises as to whether a synchrony-like effect can be demonstrated in an animal model. Although research in this area is in its infancy, this effect does appear to occur. Work in our laboratory and others (e.g., Gallagher & Burwell, 1989; Stone, 1989; Winocur & Hasher, 1999) has shown that age differences on tests of learning and memory in rats are greater late in the animals' activity cycle, when arousal levels are lowest, than at the beginning of the cycle. Of particular interest, this pattern of performance coincides with significant alterations in measures of circadian rhythmicity in the older rats.

In this chapter, we review recent and current work that demonstrates a link between altered circadian patterns in old age and cognitive performance, with a particular emphasis on memory function. Two research programs, involving aged humans and animals, are described; although the respective paradigms and strategies necessarily differ, there is a remarkable convergence in the findings. The results of this research highlight the potential importance of disrupted circadian rhythms for cognitive aging, as well as providing some insights into their neuropsychological correlates.

HUMAN STUDIES

In a study highlighting the impact of the synchrony effect on even very simple memory performance in aged humans, a simple word span task was administered to groups of young and old adults. Participants were asked to recall an increasingly long series of words (from two to six items) immediately after each list was presented, with span measured as the longest series correct (Yoon et al., 1998). Testing took place in the morning (at 8:00 or 9:00 A.M.) or in the afternoon (at 4:00 or 5:00 P.M.). Performance on the immediate memory test revealed a synchrony effect (see Figure 22.1): Older and younger adults were virtually equivalent in the morning. However, they differed substantially in the afternoon, with the pattern for older adults showing a decline in performance from morning to afternoon testing, whereas performance for young adults showed an improvement. Thus the performance on a simple span task measure of immediate memory changes across the day, and does so differently for younger and older adults. And it does so in a manner consistent with each group's general circadian arousal pattern, since the older adults were strong "morning-type" individuals and the younger adults were strong "evening-type" people (see Yoon et al., 1998, for norms).[1]

A similar synchrony pattern was observed in a series of studies on recognition of prose information (Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1999; May et al., 1993; Yoon, 1998). In the May and colleagues (1993) and Yoon (1998) studies, participants read a prose passage and were tested after a brief delay with an "old–new" decision procedure. This procedure included, as foils (or never-presented items), statements that were either related or unrelated to information in the original passage. The Yoon study varied the similarity of foils to target items as well. Both studies showed a substantial increase in false

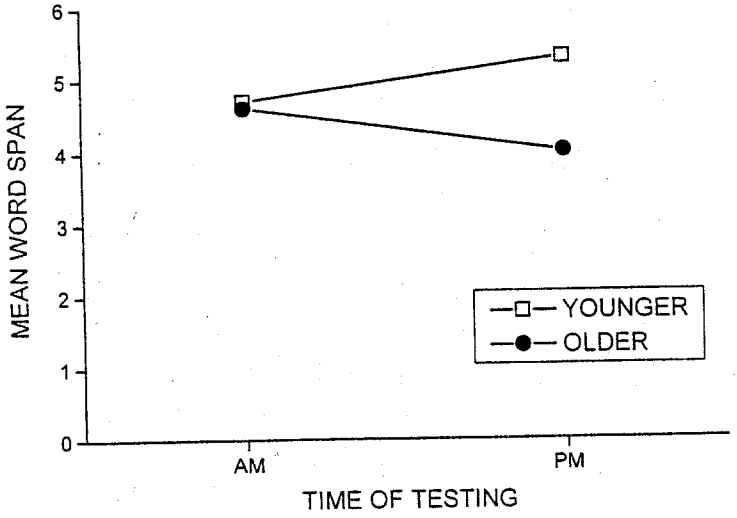

FIGURE 22.1. Mean word span for older and younger adults tested in the morning or the afternoon. Data from May and Hasher (2001).

[1]All participants in the Hasher, May, and Yoon studies were administered the Horne and Ostberg (1977) Morningness–Eveningness Questionnaire, a paper-and-pencil inventory that has been shown to correlate highly with physiological markers of circadian arousal (see, e.g., May et al., 1993).

alarms to related items (i.e., calling a new, related item "old") at nonoptimal as compared to optimal times. When the corrected recognition data (hits – false alarms) were arrayed as a function of time of day (see Figure 22.2), the pattern of recognition performance mirrored that of the span task: Younger and older adults looked quite similar in the morning and quite different in the afternoon, with accuracy declining for older adults in the afternoon and increasing for younger adults. Again, this pattern is consistent with what is known about each group's general circadian arousal pattern.

In a recently completed study (May & Hasher, 2001), recall of two short passages was tested both immediately after reading each passage and following a 20-minute filled interval. Figure 22.3 shows a forgetting score, indicating the difference between the number of ideas recalled on the immediate test and the number recalled on the delayed test. Once again, there were small differences between older and younger adults when they were tested in the morning, and substantial differences when tested in the afternoon. Here, the young adults showed a small decline in the rate of forgetting (actually, an improvement in retention) in the afternoon compared with the morning. Older adults, however, showed a dramatic increase in forgetting from the morning to the afternoon. The data from the span and the prose recognition studies show once again that performance changes across the day in a manner consistent with each group's circadian arousal patterns.

It is important to note that the memory findings for both younger and older adults cannot simply be attributed to tiredness. In the case of each of the studies mentioned, there was additional evidence that time of testing did not influence performance on other measures. For example, in the stop-signal study, the speed of responding on unsignaled or go trials did not change across the day for either younger or older adults (May & Hasher, 1998). In the memory studies, verbal ability was tested using a difficult vocabulary test. Once again, verbal ability, which was not at ceiling level for any group tested at any time, did not show changes across the day. Thus neither tiredness nor lack of motivation is a

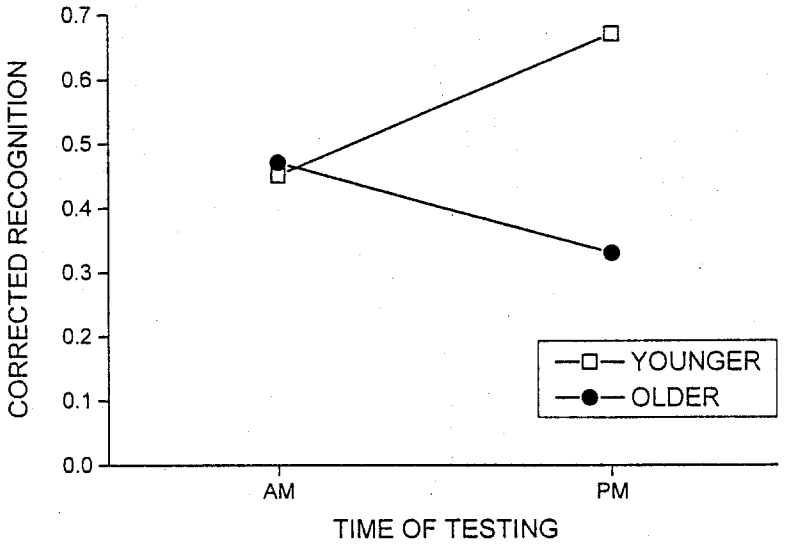

FIGURE 22.2. Corrected recognition (hits – false alarms) for older and younger adults tested in the morning or the afternoon. From May, C. P., Hasher, L., & Stoltzfus, E. R. (1993). Optimal time of day and the magnitude of age differences in memory. *Psychological Science*, 4, 326–330. Copyright 1993 by Blackwell Publishers. Reprinted by permission.

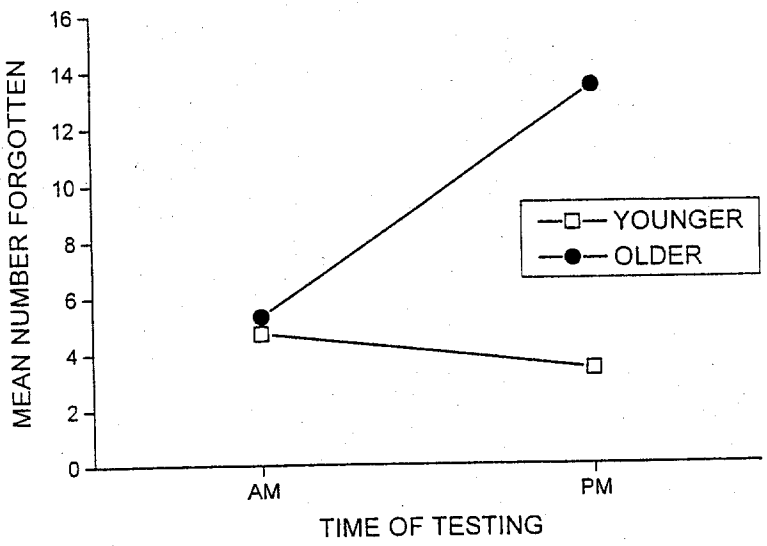

FIGURE 22.3. Mean number of words forgotten (test 1 – test 2) for older and younger adults tested in the morning or the afternoon. Data from May and Hasher (2001).

likely explanation for these findings. Instead, these data are all consistent in showing reduced memory performance at nonoptimal times of day.

The studies with human subjects were not designed specifically to assess underlying brain mechanisms, but there is evidence that frontal functions are implicated in the synchrony effect, at least in some tasks (e.g., the span effect; false recognition with related foils). At the same time, medial temporal lobe impairment may have contributed to the false recognition (Melo, Winocur, & Moscovitch, 1999; Schacter, Verfaellie, & Pradere, 1996), as well as to poor recall in the delayed test. The issue of neural correlates of the synchrony effect is taken up again in the next section.

It has also been suggested that memory failures associated with the synchrony effect are related to a basic disruption in inhibitory control over working memory functioning. Such control allows irrelevant information from various sources (perceptual and conceptual; the immediate present and the recent past) to disrupt the acquisition and retrieval of information (Hasher et al., 1999). Other work in this series suggests that (in adult humans at least) working memory functions, which of course are linked to frontal lobe function, also vary in efficiency across the day (see Hasher et al., 1999; Yoon et al., 1998).

ANIMAL STUDIES

In its initial stages, our animal research had several objectives. The first was to determine whether the synchrony effect (or some approximation of it) could be demonstrated in a rat model, and whether the effect could be related to independent measures of circadian rhythmicity. Second, tasks with neuropsychological validity were selected in an attempt to relate any such effects to dysfunction in specific brain regions. Third, employing multidimensional tests that measure different aspects of learning and memory made it possible to determine whether time-of-testing effects are general, or whether they act selectively on

specific processes. An important implication of this research is that although aged rats reliably perform worse than young rats on various behavioral tests, time of testing is rarely taken into account. Because light–dark periods and testing schedules vary considerably between labs, uncontrolled time of testing, combined with age-related circadian disruption, may have contributed to some of the observed differences in performance.

In the first study (see Winocur & Hasher, 1999), old and young rats were administered a variable-interval, delayed-alternation (VIDA) test and a runway test of inhibitory avoidance conditioning (IAC). These tests were selected because they (1) measure a variety of learning and memory processes; (2) are sensitive to dysfunction in specific brain regions (e.g., frontal lobes, hippocampus; see Winocur, 1985, 1991); and (3) require a rat to inhibit competing responses to obtain reward—an important component that emerged from Hasher and colleagues' work with humans.

Before behavioral training, rats were housed in individual cages and maintained on a 12-hour light–dark schedule with lights on between 8:00 P.M. and 8:00 A.M. Rhythmic entrainment to this schedule was confirmed by measuring water intake patterns at the end of the light and dark periods. After about 3 weeks, when the rats had adjusted to the schedule, there were no age differences in daily water intake. There was, however, an important difference in the groups' drinking patterns: Old rats drank significantly less water than young rats during the dark periods, and more during the light periods.

For the IAC task, rats were water-deprived and trained to run down an alley and drink from a water spout. When this response had stabilized, shock was administered on one of the training trials, followed by shock avoidance testing 24 hours and 6 weeks later. Each test session consisted of a single trial in which rats were allowed up to 5 minutes to contact the spout and drink for 10 seconds (sec). No shock was administered on these trials.

After the 24-hour IAC test, water was made available on an *ad libitum* basis, but food was restricted in anticipation of VIDA testing. This test, conducted in a Skinner box with a single retractable lever, is a go/no-go alternation task with a variable interval (0–80 sec) between the go and no-go trials. The lever was present during the trials, but retracted during the intertrial intervals (ITIs). During go trials, each lever press produced a food pellet, whereas lever presses during no-go trials were not reinforced. Each ITI occurred twice after go trials and twice after no-go trials, with the ITI sequence varied in each test session. Rats received 15 daily sessions on the VIDA task, before being placed on *ad lib.* food and water. A few weeks later, the water deprivation schedule was reinstated prior to the 6-week IAC test. (See Winocur, 1991, for a detailed description of the procedure.)

All rats received the same behavioral testing, except that approximately half the subjects in each age group were tested within 1 hour of the beginning of the dark cycle (AM), and the other half were tested within 1 hour of the end of the dark cycle (PM).

VIDA test results, averaged over the final block of three sessions, are presented in Figure 22.4 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 a low ratio signifies good performance.

The block 5 data confirm a significant effect of age on performance at all ITIs, including ITI-0, where there was virtually no delay between trials. Of particular interest is the clear evidence of a time-of-day (TOD) effect in old rats. Old rats tested early in the dark cycle (group O-AM) performed significantly better than the old rats tested late in the dark cycle (group O-PM), but only at ITIs 40 and 80. Notably, at the longer ITIs, the performance of the O-AM group approached (but did not equal) that of the younger groups. Importantly, time of testing did not affect performance in the younger rats, indicating a

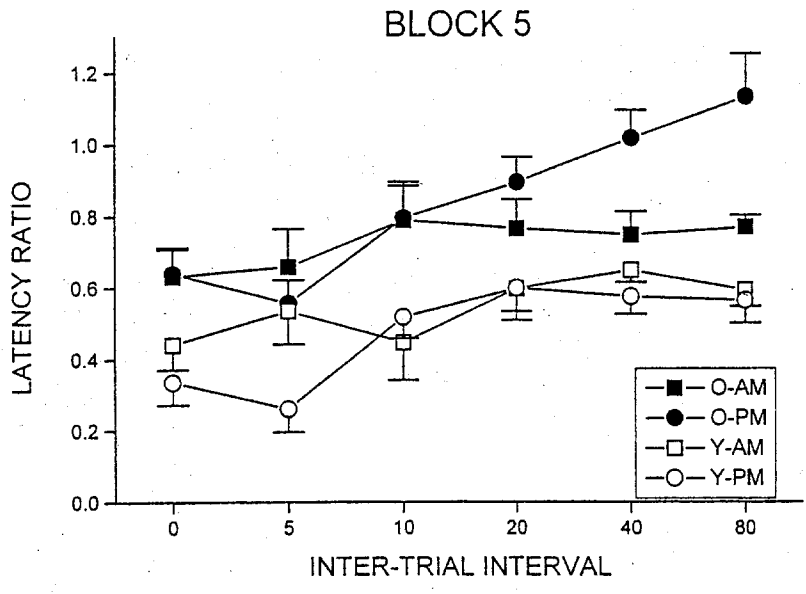

FIGURE 22.4. Latency ratios for old (O) and young (Y) rats on block 5 of the VIDA test. AM, testing in the morning (early in the dark cycle); PM, testing in the afternoon (late in the dark cycle). From Winocur and Hasher (1999). Copyright 1999 by American Psychological Association. Reprinted by permission.

failure to demonstrate the full synchrony effect that has been reported in young and old human adults.

It is also important that the TOD effect was selective for longer ITIs, in that previous research has shown that successful VIDA performance at these delays is controlled by hippocampal function (Winocur, 1985). By comparison, acquisition of the VIDA rule, as reflected in ITI-0 performance and where no TOD effect was observed, has been linked to frontal cortex and thalamic function (Winocur, 1991).

With respect to performance on the IAC task, there were no age differences in acquiring the approach response, but there was a clear age effect on postshock avoidance behavior at both test sessions (see Figure 22.5). There was a significant TOD effect as well, in that the O-AM group performed better than the O-PM group at the 6-week test. Once gain, this effect was not seen in the younger rats.

Th IAC results are also important from a neuropsychological perspective, in that previous work has shown that performance at long delays (beyond 2 weeks), but not short delays (24 hours), is selectively affected by damage to the hippocampus (Winocur, 1985). Thus, although there are numerous differences between the VIDA and IAC tasks, it is noteworthy that in both cases the TOD effect was limited to measures that appear to be under hippocampal control.

In a recently completed study (reported here for the first time), the generality of the TOD effect in rats was further assessed. As before, old and young rats were entrained to a 12-hour light–dark schedule and tested early or late in the dark cycle, but this time in a nonspatial nonmatching-to-sample (NMS) test, conducted in a Morris water maze. This test involved a series of paired study and test trials. In each study trial, the location of a hidden platform was cued by a conspicuous black or white dowel that was suspended directly above the platform. On the subsequent test trial, both dowels were present, but the

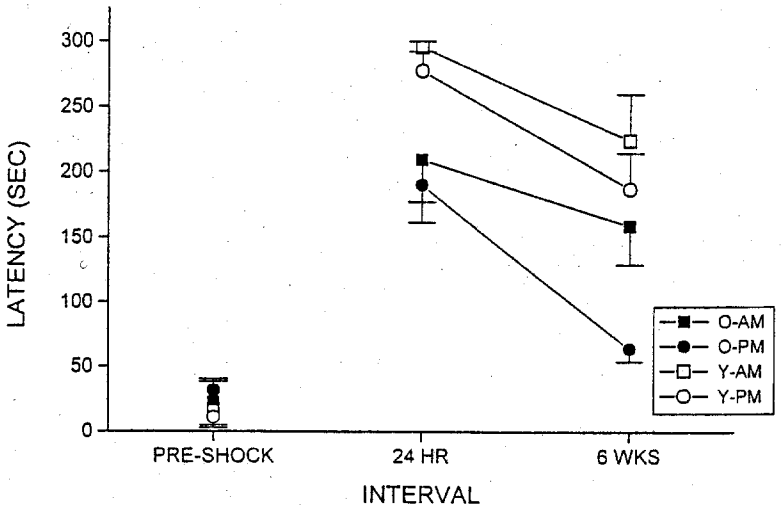

FIGURE 22.5. Response latencies for old (O) and young (Y) rats at short and long delays in the IAC task. AM, testing in the morning (early in the dark cycle); PM, testing in the afternoon (late in the dark cycle). From Winocur and Hasher (1999). Copyright 1999 by American Psychological Association. Reprinted by permission.

platform was in a different location (beneath the dowel that was not present in the preceding study trial). Initially, rats were trained with minimal delay (approximately 5 sec) between study and test trials. After 10 daily sessions of training (four trials/session), rats were administered 5 additional four–trial test sessions, with ITIs of 0, 20, 40, or 80 sec. Finally, after the completion of delayed testing, rats received an additional five sessions of delayed testing, but this time with test times reversed. That is, those rats that were previously tested early in the dark cycle were now tested at the end of the cycle, and vice versa. This reversal was conducted in an attempt to provide a powerful within-subjects demonstration of the TOD effect.

The most reliable measure of performance on the NMS task was the animal's latency to find the hidden platform on the test trials. On this measure, there was no main effect of age on NMS rule acquisition (see Figure 22.6). As well, there was no TOD effect in the old rats, but, interestingly, the data indicate that the Y-PM subgroup learned the rule at a faster rate than the Y-AM subgroup. This outcome is the opposite of that typically observed in old rats, but is reminiscent of reports that young human adults sometimes show a similar pattern (e.g., May & Hasher, 1998; Yoon et al., 1998).

Age differences in performance persisted into the acquisition–delay condition (see Figure 22.7, left), but here the main result was the disproportionately poor performance of the O-PM group at ITIs 40 and 80. At this ITI, the O-PM group performed worse than the other three groups, which, interestingly, did not differ from each other. It is also noteworthy that indications of a possible TOD effect in young rats in the acquisition condition did not extend to the acquisition–delay condition.

In the reversal–delay condition, a highly significant age × delay interaction reflected the continued poor performance of old rats at longer ITIs (see Figure 22.7, right). This

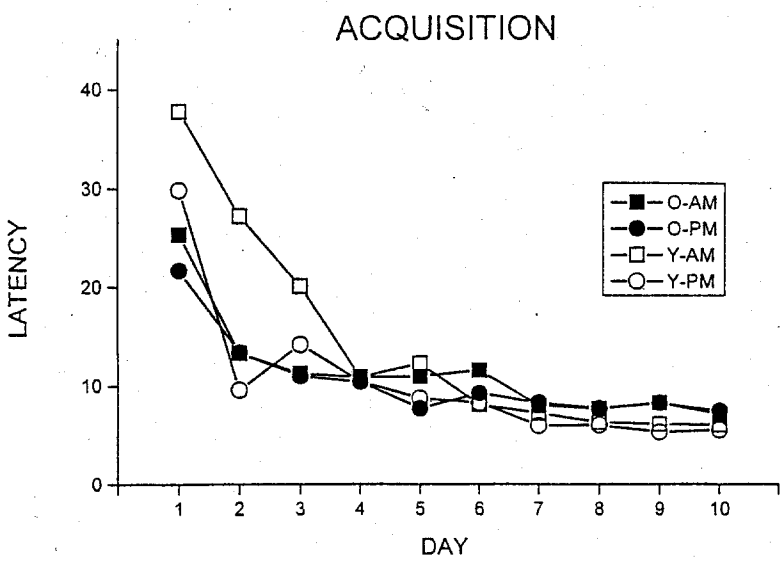

FIGURE 22.6. Response latencies of old (O) and young (Y) rats on test trials during NMS acquisition training. AM, testing in the morning (early in the dark cycle); PM, testing in the afternoon (late in the dark cycle).

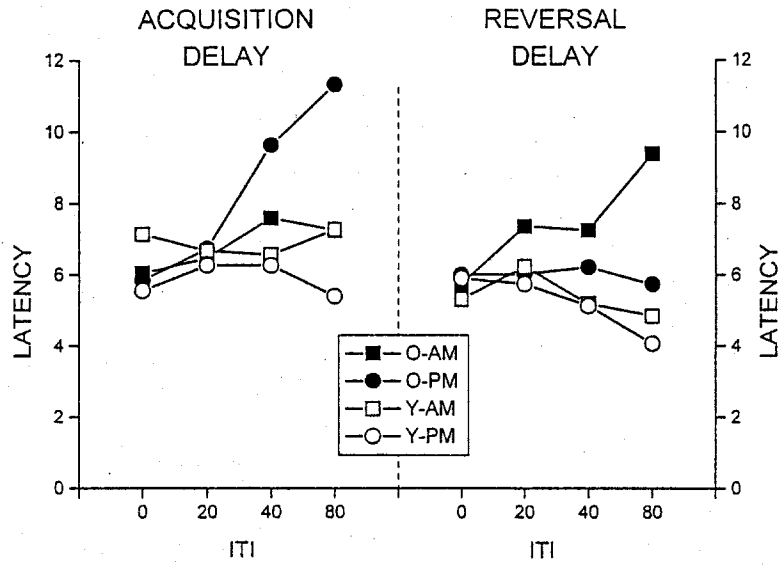

FIGURE 22.7. Response latencies of old (O) and young (Y) rats on test trials of NMS acquisition–delay and reversal–delay conditions. AM, testing in the morning (early in the dark cycle); PM, testing in the afternoon (late in the dark cycle); ITI, intertrial interval.

pattern was especially apparent in the O-PM subgroup, providing further evidence of the adverse effects of testing aged rats during suboptimal periods. In this case, the demonstration is particularly dramatic because, in the reversal–delay condition, when the same rats were tested early in the dark cycle, they performed much better than they did when tested late in the cycle. Once again, there was no evidence of a TOD effect in the young rats.

Overall, the NMS data are consistent with the results of VIDA and IAC testing. Age differences in performance were qualified by significant effects of time of testing and length of ITI in the acquisition–delay and reversal–delay conditions. These results show that cognitive performance in aged rats is strongly influenced by the stage of the activity cycle in which testing occurs, although the influence may be limited to memory processes under hippocampal control.

As in the human studies (see above), a concern about data such as these is that TOD effects are related to performance factors such as general fatigue or lack of motivation. Several points argue against this interpretation. For example, in all three tasks, TOD effects were limited to long-delay conditions that challenged hippocampus-controlled memory function, and were not linked to other cognitive processes, as would be expected if they were the result of performance-related variables. Similarly, it is significant that in the VIDA and IAC tasks, old rats advanced through all stages of shaping and training as quickly as the younger rats did. Moreover, there were no age differences in learning the NMS rule. Finally, in the IAC task, the TOD effect was reflected in shorter latencies in the O-PM subgroup—a finding that is clearly inconsistent with excessive fatigue or diminished motivation. Taken together, the evidence favours the view that old rats, tested late in their activity cycle, exhibited cognitive dysfunction that was related to changes in biological rhythmicity.

The consistent finding that the TOD effect in aged rats was manifested selectively on measures of memory function under hippocampal control and not on tests of frontal lobe function is somewhat at odds with the human data, which suggest a more general effect. Because only a limited number of behavioral tests have been utilized in TOD research, it is premature to draw firm conclusions about the generality of such effects. The frontal lobe is a complex structure with numerous subregions that control a diverse range of attentional, mnemonic, and executive functions (Moscovitch & Winocur, 1995; Stuss & Benson, 1986), and it is entirely possible that future research with brain-damaged and aged animals will reveal meaningful relationships between some of these functions and circadian patterns.

One of the aims of the animal research was to assess the importance of task-related inhibitory demands on the TOD effect. As indicated above, Hasher and colleagues (1999) have suggested that disruption of circadian rhythms may be directly related to an exaggerated loss of inhibitory control that occurs in normal aging and contributes to impairment on many cognitive tasks. Our tasks all had inhibitory components to varying degrees, but in general, TOD effects were independent of any difficulties with response control. The one important exception occurred in the VIDA study, where the O-PM subgroup exhibited exaggerated lever pressing after long ITIs in the no-go trials. However, it could not be determined whether that tendency contributed to the overall deficit or was a symptom that resulted from the memory failure during the long delays. This issue may relate to the nature of the tests employed and the underlying processes that support successful performance. For example, the frontal lobe (Mishkin, 1964) and the hippocampus (Kimble, 1968) both participate in inhibitory control, but in different ways, and it may be important to consider these differences in assessing the time-of-testing impact on inhibitory mechanisms.

Finally, an important objective of this research program was to determine whether variations in cognitive performance among aged rats are related directly to changes in their rhythmically controlled drinking patterns. Despite clear evidence that water intake by aged

rats in the dark cycle was accompanied by relatively poor cognitive performance, the two measures did not correlate with each other in any of the tasks. This result does not rule out a link between circadian rhythmicity and cognitive function, but it is more likely to reflect the sensitivity of this particular measure of rhythmicity. Age-related disruptions in drinking patterns are undoubtedly related to other circadian changes in old age that more directly affect brain function. This complex issue requires systematic investigation of relationships between specific circadian changes and various aspects of cognitive function.

SUMMARY AND CONCLUSIONS

Cognitive aging in humans is influenced by a wide range of biological, environmental, and psychosocial factors (Craik & Trehub, 1982; Zacks, Hasher, & Li, 2000). Many of the same influences are known to contribute to age differences in learning and memory in lower animals (Winocur, 1988, 1998). There is now convincing evidence that time of testing must be added to the list of variables that can affect cognitive performance generally and memory in particular, in both animals and humans. Indeed, with respect to humans, it is interesting to speculate that if all cognitive studies were run early in the morning, our views of age-related changes in memory might be quite different from the view of dominant, inevitable decline that is prevalent in the cognitive gerontology literature. In fact, there is reason to believe that the majority of participants, both young and old, are actually tested in the afternoon (May et al., 1993). To that extent, it is necessary to consider the possibility that conclusions regarding human age differences in memory may be at least slightly exaggerated.

Although considerable work is needed in this area, there is promising evidence that synchrony and TOD effects on memory performance are related to a mismatch between circadian arousal levels and the time of testing. At this point, we know that memory function in aged animals and humans are closely linked to circadian rhythms that are reflected in variable patterns of wakefulness, activity, and water consumption. The challenge is to specify those circadian rhythms that have a direct impact on cognitive processes, as well as those processes and neural mechanisms that are particularly vulnerable to age-related circadian disruption.

ACKNOWLEDGMENTS

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