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Effects of Aging on Food-Entrained Circadian Rhythms in the Rat

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MISTLBERGER, R. E., T. A. HOUPT AND M. C. MOORE-EDE. *Effects of aging on food-entrained circadian rhythms in the rat.* NEUROBIOL AGING **11**(6) 619–624, 1990.—Twenty-four hour schedules of restricted food availability entrain a component of the circadian activity rhythm in rats via a food-entrainable pacemaker separate from the light-entrainable pacemaker. The effect of aging on food-entrained circadian rhythms was examined in 6 rats maintained on a restricted diurnal feeding schedule from age 3–21 months and again from 24–25 months. Food-entrainment, measured as behavioral anticipation of a 1-hr daily mealtime during the middle of the light period and persistence of this anticipation rhythm during food deprivation, was apparent in the aged rats when recorded in wheel-running cages from 20–21 months of age. Despite the long duration of restricted diurnal food access, the aged rats, like young rats, rapidly reverted to nocturnal activity when transferred to ad lib feeding. When restricted diurnal feeding was reinstated at 24 months age, these rats, now recorded in food-bin monitoring cages, required more time for a food anticipation pattern to emerge and showed a lower amplitude food anticipation rhythm compared to a group of young adult rats. These age-related changes are similar to those that characterize photically entrained circadian rhythms and suggest that both components of the rat's multioscillatory circadian timekeeping system deteriorate in parallel over the life span.

Entrainment Food deprivation Circadian rhythms Aging Food anticipation

AGING is associated with changes in several basic parameters of circadian rhythms in mammals [for reviews, see (10,14)]. These include 1) increases (36,39) or decreases (20, 24, 34) in the period of circadian activity rhythms "free-running" in environments free of time cues (zeitgebers), 2) a reduced amplitude of circadian rhythms of activity, sleep and wake, temperature and other physiological variables in aged animals, including humans, under free-running or photically entrained conditions (11, 18, 19, 25, 29, 36), 3) a more positive phase angle of entrainment to daily light-dark (LD) cycles (8), and 4) a retarded rate of reentrainment to an inverted LD cycle (21,26). These observations suggest that the biological systems mediating the generation and entrainment of circadian rhythms in mammals may deteriorate with aging. This deterioration is likely responsible for a number of "circadian" disorders characteristic of elderly humans, including sleep-wake disturbances and reduced tolerance to shift-work [reviewed in (14)]. More fundamentally, loss of temporal order within biological systems may be primary to the aging process itself.

Studies of aging and biological timekeeping have focused primarily on the characteristics of free-running and photically entrained circadian rhythms. However, circadian rhythms can also be entrained by a number of periodic nonphotic stimuli, including daily cycles of temperature (33), physical activity (17), maternal interactions (22) and food availability [reviewed in (2,15)]. Perhaps the best studied of these is periodic food access. Rats restricted to a single meal at a fixed time each day show a prominent daily rhythm of food anticipatory activity. This rhythm of food anticipation exhibits many characteristics indicating that it is generated by a food-entrainable circadian pacemaker (1, 3, 5, 27, 30, 31). This pacemaker appears to be separate from the pacemaker that generates light-entrainable circadian rhythms, since a single variable, such as wheel-running activity, can exhibit two rhythmic components with different periodicities, one entrained to mealtime and a second free-running or entrained to a LD cycle (1, 3, 27). Ablation of the hypothalamic suprachiasmatic nuclei eliminates the light-entrainable, free-running rhythmic component (3, 30, 31). Some physiological variables, such as those related to gastroenteric processes and metabolism, may be regulated exclusively by the food-entrainable pacemaker, whereas a few others, such as the rhythm of pineal melatonin synthesis, appear to be regulated only by a light-entrainable pacemaker (2).

Despite the prominent role of food availability as a circadian zeitgeber in a number of species, the published literature on food-entrainment in aged animals is quite limited (23,32). In the present study we sought to characterize the generation and peristence of food-entrained circadian rhythms of behavior in male rats up to 24 months age.

METHOD

Subjects and Procedures

Six male Long-Evans rats were housed at 60 days age in

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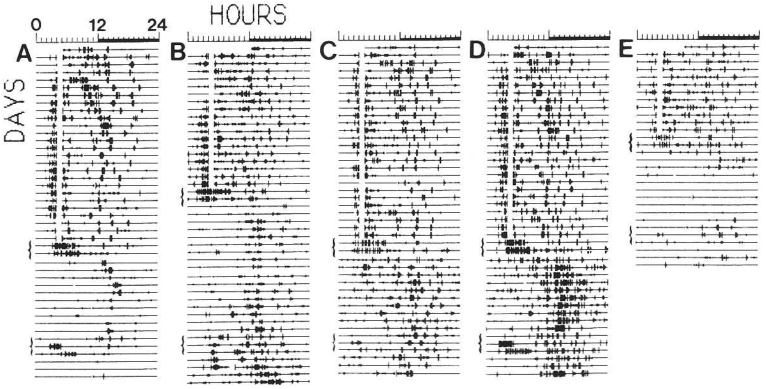

FIG. 1. Actograms of wheel-running activity in 5 old rats. Each line represents one day, with consecutive days aligned vertically and time within a day (10-min intervals) plotted left to right. Vertical deflections from the zero-activity line of each day are proportional to the amount of activity within that 10-min interval. Daily mealtime during restricted feeding is indicated by a blank. Food deprivation days are indicated by brackets on the left margin of each chart. Food was freely available during all other days. Lights-off period is indicated by the heavy bar on the hours time line.

individual plastic cages in a colony room with controlled light (LD 12:12) and temperature (21°C). At 90 days age the rats were placed on a restricted feeding schedule that provided 10–15 g of standard rat chow at noon each day, 4 hr after lights-on. This chow was usually completely consumed before lights-off. After 17 months on this feeding schedule the rats were transferred to Wahmann running-wheel cages housed in individual isolation chambers equipped with incandescent lighting (LD 12:12; 10 lux) and fans. Rat chow was provided at noon each day as before but removed 1 hr later. After one month the rats were food deprived for 48 hr, provided with rat chow ad lib for 10 or 17 days and then food deprived again for 72 hr. Food was provided ad lib for the last week of recording after which the rats were returned to a colony room. The 48-hr and 72-hr periods of food deprivation served to determine whether any daily rhythm associated with feeding time was a true, self-sustaining rhythm, i.e., one that persists for several cycles in the absence of daily feeding cues.

After 3 months of ad lib food access the aged rats (now 24 months) and 4 young rats (3 months) were placed in individual opaque plastic cages equipped with food-bins accessible through a 2-in. square opening on one wall of each cage. A fifth young rat was placed in a similar plastic cage with a tilt-floor. Food (powdered rat chow with corn oil) was freely available in the food-bin for 14 days. The rats were food deprived for 42 hr beginning at dark onset and then fed for 1 hr each day (6 hr after lights-on; LD 12:12) for 24 days. The rats were then food deprived for 48 hr, fed for 6 hr and again deprived for 48 hr. Ad lib food access then resumed for a final 4 days of recording.

Data Collection and Analysis

Activity counts of rats in Wahmann wheels and the tilt-floor cage were detected by microswitch closures monitored continually by an Apple computer. Food-bin directed activity of rats in plastic cages was detected by interruption of an infrared light source focused over the food-bin. Activity counts from each source were summed and stored at 10-min intervals. Data were periodically transferred to an Atari 1040st computer for graphical and numerical analyses.

RESULTS

Wheel-Running Activity: Aged Rats

Actograms of wheel-running activity are presented for 5 of the 6 aged rats in Fig. 1. One aged rat did not produce sufficient daily wheel counts to permit meaningful analysis. Despite individual differences in the amount of daily wheel running in these 5 rats, the temporal distributions of activity were quite uniform across animals. Each rat showed a concentration of activity preceding the daily mealtime by 1–2 hr. Nocturnal activity was relatively low and largely confined to the first 6 hr of darkness. When the rats were food deprived and left undisturbed for 48 hr the daily rhythms of mealtime-associated activity persisted. Wheel running began 1–2 hr before the usual mealtime and continued for 1–3 hr thereafter. Upon resumption of ad lib feeding, after nearly 18 months of restricted diurnal feeding, the rats reverted to a nocturnal activity pattern. This transition was abrupt in two rats (Fig. 1A, B), both of which showed low levels of wheel running confined to the first 4 hr of dark. Two other rats (Fig. 1C, D) showed more overall activity in the light and dark, but also rapidly lost the distinct meal-associated activity component. The fifth rat showed very little running during ad lib feeding.

During the 72 hr food deprivation after 10 or 17 days of ad lib feeding, 3 of the rats showed a clear reappearance of diurnal activity at a circadian phase formerly associated with mealtime during restricted feeding. In 2 rats (Fig. 1A, D), this bout of activity was evident during the second and third days of food deprivation. In a third rat (Fig. 1B) it appeared on all three days and persisted during 2 following days of ad lib feeding. A fourth rat (Fig. 1C) showed wheel running at a similar phase but this was much less distinct. The remaining rat (Fig. 1E) showed only sporadic bouts of running during food deprivation, with no substantial concentration of activity occurring at the prior mealtime.

Food-Bin and Tilt-Cage Activity: Young and Old Rats

Actograms of food-bin activity for 5 old rats and 4 young rats and of tilt-floor activity for one young rat are presented in Fig. 2. One aged rat (Fig. 1E) died after 13 days of restricted feeding; its data are omitted from these analyses. During ad lib food access all rats showed a predominantly nocturnal activity pattern. Average histograms of 7 ad lib feeding days for each rat suggest that the amplitude of this daily rhythm is lower in the aged rats (Fig. 3). To evaluate this apparent difference statistically, LD ratios were calculated for the 7 days prior to food restriction (Table 1). The aged rats showed a mean ratio of activity in the light to activity in

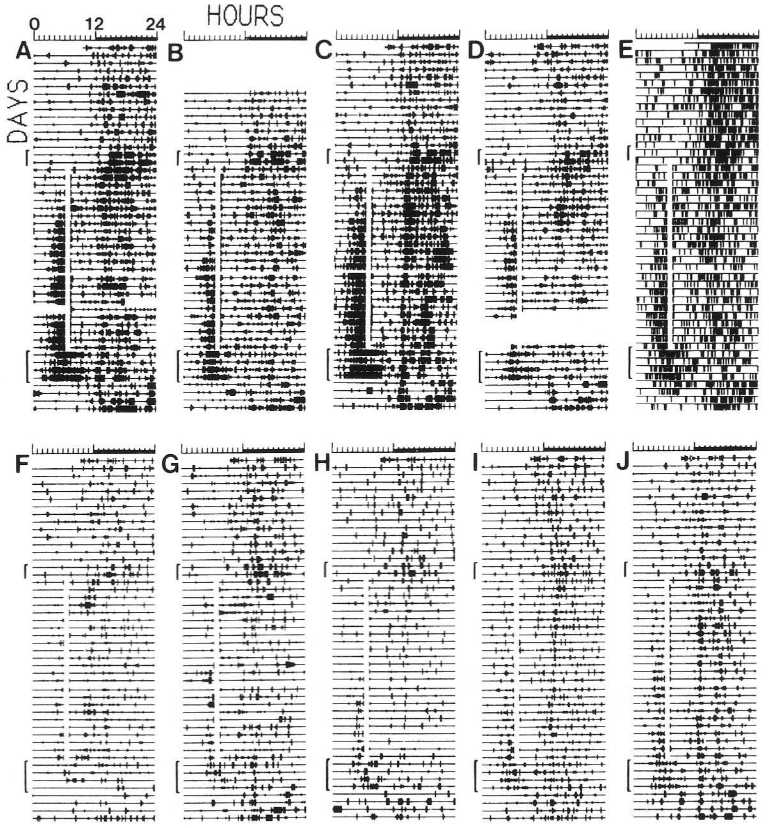

FIG. 2. Actograms of food-bin activity in 4 young rats (A–D) and 5 old rats (F–K) and of tilt-cage activity in one young rat (E). Conventions as in Fig. 1, except for chart E, in which vertical deflections represent 10-min intervals when activity was above the mean for that day. Missing data is represented by blank days.

the dark (0.21) that was significantly higher than the mean ratio of the young rats (0.10) (Mann-Whitney U-test, $p<0.02$).

During the 42 hr of food deprivation preceding food restriction, both groups of rats showed increased nocturnal activity, with little change in the amount of diurnal activity. When food was restricted to a single daily meal, the young rats rapidly developed a pattern of intense anticipatory food-bin or tilt-floor activity. This is dramatically evident in histograms averaging the last 12 days of restricted feeding in each rat (Fig. 4A–E). The aged rats, with the exception of the one that died on day 13, also displayed premeal activity during food restriction (Fig. 4F–J). However, the average histograms reveal that, compared to young rats, premeal activity of aged rats was shorter in duration and had a lower peak relative to their own nocturnal activity peak. In addition, inspection of the actograms indicated that little premeal activity was evident before the third week of restricted feeding. To statistically evaluate these results, food anticipation was quantified as the ratio of activity during the 2 hr preceding mealtime (hours 4–6 of lights-on) to activity occurring during the rest of the day (excluding mealtime). This ratio was calculated for a set of 7 ad lib feeding days (using hours 4–6 of lights-on) and for the first and second 12-day blocks of food restriction. In the young rats, this ratio was significantly increased during both the first ($p<0.03$) and second ($p<0.01$) blocks of restricted feeding days (Wilcoxon matched-pairs signed-ranks test; Table 1). In the old rats, this ratio was significantly different from ad lib feeding days only during the second block of restricted feeding days ($p<0.01$). In addition, the old rats showed a significantly lower anticipation ratio compared to the young rats during both the first ($p<0.01$) and the second ($p<0.01$) blocks of restricted feeding days (Mann-Whitney U-test). Thus, the old rats took longer to exhibit food anticipation and showed weaker food anticipation than did the young rats.

When the young and old rats were food deprived for 4 days following restricted feeding, the activity bout formerly associated with mealtime persisted and was in most cases intensified. When ad lib feeding resumed for a final 4 days the activity rhythms reverted to a predominantly nocturnal pattern. Light-dark ratios (Table 1) were higher for ad lib feeding days prior to food restriction, i.e., the amplitude of the daily rhythm was decreased, but this trend did not reach statistical significance in either group ($p<0.07$).

DISCUSSION

This study demonstrates that aged rats, at least up to 24 months of age, can anticipate a daily scheduled meal and that this rhythm of food anticipatory behavior persists during food deprivation but not during ad lib feeding. These basic characteristics of food entrainment are consistent with those observed in young adult rats in this and previous studies (3, 5, 27). However, comparisons of young and old rats in the present study reveal alterations of both LD and food entrainment with age. Old rats showed both a delayed appearance and a reduced amplitude of food anticipatory rhythms during the second food restriction test. These changes are similar

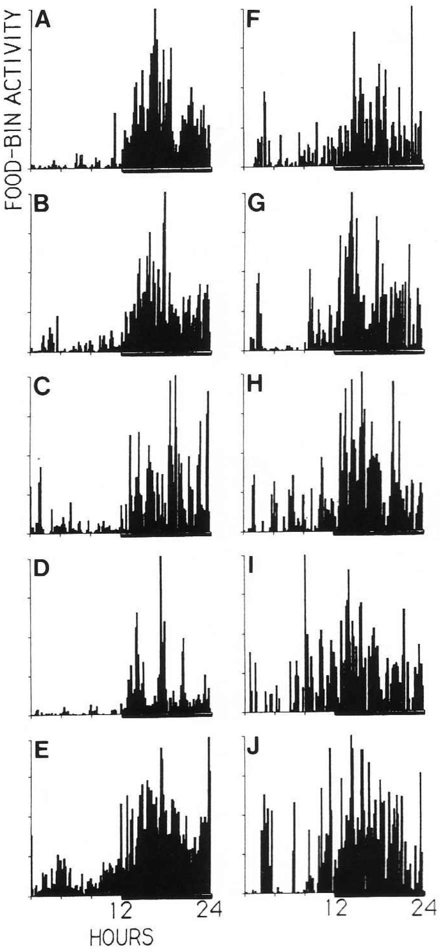

FIG. 3. Histograms of activity in each 10-min interval of the day averaged over 7 days of ad lib feeding prior to food restriction for young (A–E) and old rats (F–K). Lights-off is indicated by the heavy bar along the abscissa.

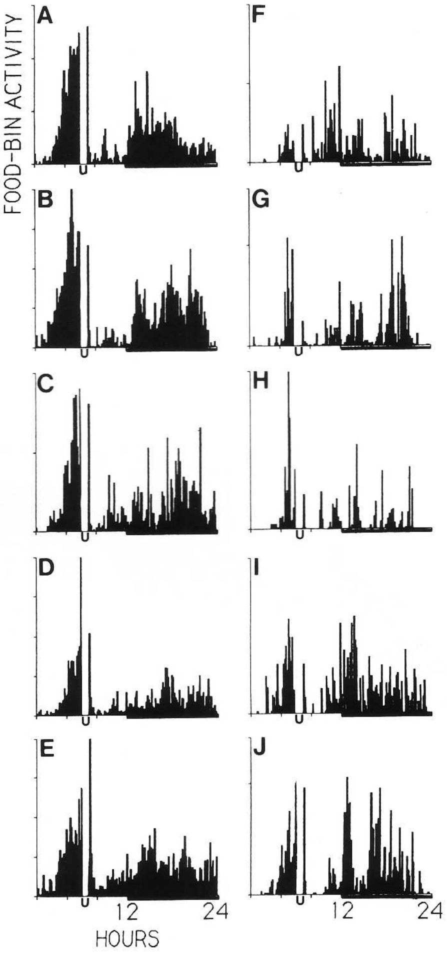

FIG. 4. Histograms of activity in each 10-min interval of the day averaged over the last 12 days of food restriction in young (A–E) and old (F–J) rats. Lights-out is indicated by the heavy bar along the abscissa and daily mealtime by the u below the abscissa. Activity during the 1-hr daily meal is omitted to emphasis meal anticipatory activity.

to those that characterize photically entrained rhythms in aged rats, which include a reduced amplitude of LD-entrained rhythms and a slower rate of reentrainment to inverted LD cycles (10, 21, 26). Thus, the age-related changes that affect the neural mechanisms mediating photic entrainment of circadian rhythms also apparently afflict the circadian timekeeping mechanism regulating nonphotic entrainment.

There are several reasons to suspect that age-related changes of food entrainment are underestimated in this study. First, we followed our animals only until the 25th month of life and, with the exception of one rat, not until death, which may have been several months away. Second, our aged rats were maintained on a chronic food restriction schedule for most of their adult life. Long-term caloric restriction is known to extend life span (12) and

TABLE 1

LIGHT-DARK AND FOOD ANTICIPATION RATIOS FOR CIRCADIAN RHYTHMS OF YOUNG AND OLD RATS

	Light-Dark Ratio		Anticipation Ratio		
Group	Pre-RF	Post-RF	Pre-RF	RF1	RF2
Young	0.10 (0.07)	0.19 (0.11)	0.03 (0.02)	0.20 (0.14)‡	0.50 (0.09)§
Old	0.20 (0.10)*	0.36 (0.18)	0.05 (0.04)†	0.05 (0.03)	0.29 (0.1)*¶

Values represent mean ± standard error of 5 animals in each group. Significantly different from young rats: *$p<0.02$; †$p<0.05$; ¶$p<0.01$. Significantly different from pre-food restriction ad lib fed days: ‡$p<0.03$; §$p<0.01$. RF, restricted feeding; RF1, restricted feeding days 1–12; RF2, restricted feeding days 13–24.

may actually retard the rate of aging within some, although apparently not all, physiological systems in mammals (4,13). It is not known whether caloric restriction delays the appearance of age-related changes that are normally manifest within the circadian timekeeping system by 24 months age. However, it is conceivable that our aged rats were younger physiologically than they were chronologically. Twenty-four-month-old rats that have never been exposed to caloric restriction may show more dramatic changes in both photic and nonphotic entrainment.

A third factor bearing on the magnitude of age-related changes observed in our rats is that food anticipatory rhythms may be generated more rapidly in rats that have previously been exposed to a feeding schedule (5,31). This may be because the food-entrainable oscillators are self-sustaining, even when they are not expressed in behavior as when food is freely available (5,27). When a new restriction schedule is initiated the food-entrainable oscillators may already be operating covertly with an appropriate circadian phase, thus reducing the number of feeding cycles required before anticipatory rhythms emerge. It is therefore possible that the delayed appearance of food anticipatory rhythms measured in the second stage of this study might have been accentuated if the aged rats had not previously been entrained to a feeding schedule at about the same diurnal phase. However, this argument is somewhat weakened by the fact that our rats were fed ad lib for 3 months prior to the second food restriction schedule. Food-entrainable circadian rhythms in young rats usually become strongly dampened over this duration of ad lib feeding (27), and there is no reason to suspect that this is not equally if not more characteristic of old rats.

Two other studies of food-entrainment in aged rats have been reported. Richter, in 1922 (23), published the first observations of circadian rhythms in food-restricted rats and noted that food anticipation was attenuated and possibly absent in rats aged up to 24 months. The attenuation of food anticipatory rhythms observed in his rats was similar in magnitude to that found in our rats, despite differences in the anticipation metric used. However, this attenuation and the possible loss of anticipation suggested in one of his published figures of data from two-year-old rats may reflect the use of constant light during the recordings and group data for the analysis. In fact, we have observed that the appearance of food anticipation rhythms can be significantly delayed in rats maintained in constant light (Mistlberger, Houpt and Moore-Ede, unpublished observations).

In the only other study of food-entrainment and aging (29), 10-month-old retired, anestrous breeders were found to exhibit very low amplitude circadian rhythms under LD 12:12 with ad lib access to food, but apparently normal rhythms of food anticipation under a 24-hr food restriction schedule (no quantification reported). In some of these middle-aged animals, the amplitude of LD-entrained rhythms was greater during the ad lib feeding days that followed the food restriction schedule. A similar improvement of LD-entrained rhythms after food restriction was not observed in the present study; if anything, our rats showed lower amplitude LD-entrained rhythms after food restriction. However, the two studies differ along several important procedural dimensions, including the age, sex and strain of the rats used as well as the rhythms monitored, so the different results should not be construed as conflicting.

Noncircadian explanations for the age-related changes in food-entrainment should be considered. One possibility is that aged rats eat less than do young rats during a 1-hr daily food access time, either because they are less motivated to eat or physically unable to eat as fast. A smaller daily meal can perhaps be conceived as a weaker nonphotic zeitgeber, analogous to a dimmer or shorter light pulse representing a weaker photic zeitgeber. However, measurements of food intake in our study do not support this argument; the aged rats averaged 15.3 ± 1.4 g of food intake during the last week of ad lib feeding, compared to 12.9 ± 0.6 g for the young group. During the last 12 days of restricted feeding the aged rats consumed 10.0 ± 1.9 g daily, compared to 8.3 ± 1.7 g for the young rats. The percent difference between young and old rats is virtually identical for these two periods, suggesting that the two groups did not differ in their ability or motivation to feed.

The aged rats did show a paucity of total daily locomotor activity relative to young rats. This may be associated with a lower metabolic rate as a consequence of advanced age and/or long-term food restriction regimen. Chronic food restriction does result in a significant reduction in basal metabolic rate in young rats (7,9), but whether this effect is altered with aging is unknown. It is, in any case, unclear whether overall reductions in metabolism or activity should have any selective effect on the induction and amplitude of food anticipatory rhythms. The issue could perhaps be clarified by examining parameters of food anticipatory rhythms in young rats with experimentally altered metabolism (e.g., by manipulation of thyroid function).

One final aspect of the data deserves comment. The aged rats, despite a virtual lifetime of restricted diurnal food intake, reverted to a nocturnal activity pattern almost immediately or within days of being returned to ad lib food access. A similar reversion to nocturnal activity has been well documented in young rats (5,27). Clearly, a major component of the rat's circadian system remains entrained to the light schedule during restricted daily feeding schedules. This seems obviously adaptive, since it ensures that the rat will rapidly abandon daytime foraging for the relative safety of darkness when food is once again available at night. It would appear that this adaptive feature of the rat's multioscillatory system does not change substantially with age, at least not within the age range that we examined.

Age-related changes of nonphotic entrainment have implications more generally for the study of aging (15). Many psychological and physiological processes display circadian rhythms [for reviews see (6, 16, 28)] which may be influenced by schedules of restricted food availability. Food restriction schedules are in fact routinely used in animal studies of learning, memory, ingestive behavior, etc. These schedules presumably entrain food anticipation rhythms. An animal's performance on a specific cognitive task or its response to food or drugs may thus depend in part on how long the restriction schedule has been implemented (i.e., on whether entrainment has stabilized) and on precisely when training and testing sessions occur with respect to the usual feeding time (i.e., with respect to the phase of the animal's food anticipation rhythms). Aged rats take longer to exhibit food anticipation and show a reduced amplitude and duration of food anticipatory activity. It is thus conceivable that apparent changes in cognitive or regulatory processes measured in aged animals could be secondary to age-related changes of entrainment to the food restriction schedules employed in those studies. The present study suggests that the response of the circadian timekeeping system to feeding zeitgebers is in some respects attenuated with age, but further studies are necessary to determine the extent to which this may color results obtained within experimental paradigms that ultilize food restriction.

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