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Age-Related Changes in the Spontaneous Motor Rhythms of the Senescence-Accelerated Mouse (SAMP8)

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The present study examined the effect of age on the spontaneous motor rhythms of mice during wheel running. The spontaneous motor tempo (SMT) of wheel running was measured for the P8 strain of the senescence-accelerated mouse (SAMP8) by recording the sequence of time intervals (measured in milliseconds) for successive revolutions of a run-wheel over the course of 16 days. Analyses of the distribution of interrevolution intervals of 2-, 7-, and 12-month-old SAMP8 revealed an age-related slowing of wheel running and a corresponding increase in variability consistent with Weber's law. All three age groups also demonstrated a practice effect over the course of testing best described by a power law. These findings provide evidence of age-related changes in the spontaneous motor rhythms of the SAMP8 that occur as early as 7 months of age. The results are consistent with age-related changes in human subjects and suggest that spontaneous wheel-running behavior in rodents may be a good model for studying SMT.

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A common complaint of older adults is a decline in motor function, which can potentially lead to falls and injuries (Hausdorff et al., 1997). Ostensibly, one aspect of motor function is the fluency of movements as revealed by motor rhythm. Motor rhythm can be externally driven (paced by a rhythmic stimulus) or self-determined (unpaced). Unpaced motor rhythms have been given various names, including personal tempo (Temperley, 1963), mental tempo (Mishima, 1968), internal tempo (Boltz, 1994), and spontaneous motor tempo (Fraisse, 1963, 1982). In this article, we will use the term spontaneous motor tempo (SMT) to refer to the rate of unpaced movements.

Previous research suggests that SMT in humans measures important characteristics of the internal clock involved in the perception and production of short temporal intervals, namely that it measures the optimal time interval for rhythmic performance (Boltz, 1994; Collyer, Broadbent, & Church, 1994; Drake, Jones, & Baruch, 2000). Developmental studies of motor rhythms reveal a range of rhythmic movements, such as bouncing and hand clapping, which appear at a young age (Fitzpatrick, Schmidt, & Lockman, 1996; Goldfield, Kay, & Warren, 1993; Thelen, 1994). For young adults, mean interresponse intervals (IRIs) in SMT tasks are typically between 500 and 600 ms, although there are substantial individual differences (Collyer et al., 1994; Fraisse, 1982).

With regard to aging, studies that have examined SMT in conjunction with other aspects of rhythmic motor performance suggest a general slowing of SMT with a corresponding increase in variability (Drake et al., 2000; Vanneste, Pouthas, & Wearden, 2001). The increase in variability of SMT tends to be proportional to the slowing of SMT, such that the relationship follows Weber's law. Weber's law predicts that variability of the perception of a stimulus is proportional to the perceived magnitude of that stimulus (Geischeider, 1976). This law generally holds for the perception and production of short temporal intervals, as well as other psychological processes (Allan, 1979; Engen, 1972; Geischeider, 1976; Getty, 1975).

Overall, age-related changes in the characteristics of SMT may impact an individual's capacity to effectively coordinate movement sequences with events in the environment (Drake et al., 2000). Consistent with this view, studies on the timing of human gait have shown a general slowing and increased variability of walking with age (Hausdorff, Edelberg, Mitchell, Goldberger, & Wei, 1997; Hausdorff et al., 2001). These changes appear to be associated with increased gait instability and increased risk of falls.

The use of animal models has the potential to greatly enhance our understanding of the age-related changes of SMT. Spontaneous wheel running of rodents may provide an excellent way to study SMT in animals because it is a voluntary rhythmic behavior that is generally performed with a high degree of consistency and coordination (see

Sherwin, 1998, for an excellent review). Activity rhythms in rodents exhibit a daily (circadian) rhythm that is entrained to the naturally occurring light-dark cycle, with nocturnal rodents conducting most of their wheel running at night (Pittendrigh & Daan, 1976). They can be phase-shifted with a change in the light-dark cycle, and show a near 24-h periodicity in constant conditions (Pittendrigh & Daan, 1976). Rodents demonstrate clear age-related changes in daily activity rhythms that are characteristic of those frequently considered part of the normal aging process in humans, including a decrease in the amplitude of wheel-running rhythms and greater fragmentation across the light-dark cycle (Davis & Menaker, 1980; Possidente, McEldowney, & Pabon, 1995; Wax, 1975; Witting et al., 1994).

To measure the SMT of wheel running, the sequence of time intervals between successive wheel revolutions can be recorded during sustained bouts of running, rather than simply counting the number of wheel revolutions that occur per unit time (Eikelboom & Mills, 1988; Eikelboom, 2001; Mondon, Dolkas, Sims, & Reaven, 1985). When the sequence of time intervals is measured, the mean inter-revolution interval (IRI) during consistent bouts of running can be used to provide a measure of average SMT, with the standard deviation of the IRIs providing a measure of timing variability (i.e., the consistency of these rhythms). This type of analysis of wheel-running behavior has not been previously reported.

The aims of the present study were twofold. First, we were interested in exploring age-related changes in SMT using a rodent model, in order to assess the generality of the previous SMT studies involving humans. Second, we were interested in providing a novel assessment of age-related changes in the sensorimotor behavior of a particular mouse strain, the SAMP8. The SAM (senescence-accelerated mouse) model, in general, has been previously used to explore various age-related changes in behavior with distinct lines developed to study different age-related pathologies (Takeda, Hosokawa, & Higuchi, 1994; Takeda et al., 1981). The P8 line of the SAM model (SAMP8) has a median life span between 10 and 17 months (Flood & Morley, 1998; Takeda, 1999) and is primarily used to study age-related changes in learning, memory and circadian rhythms (Asai, Ikeda, Akiyama, Oshima, & Shibata, 2000; Flood & Morley, 1998; McAuley, Miller, Beck, Nagy, & Pang, 2002; Miyamoto et al., 1986; Miyamoto et al., 1997, Sanchez-Barcelo et al., 1997).

Several previous studies have reported age-related changes in the sensorimotor function of the SAMP8, but none have examined SMT. Tasks involving agility and swimming speed show a decline in performance between 2 and 12 months of age (Flood & Morley, 1998; Markowska, Spangler, & Ingram, 1998). However, spontaneous motor exploration as measured in an open field and in foot-shock sensitivity was not altered (Flood & Morley, 1992, 1998; Ikegami, Shumiya, & Kawamura, 1992; Miyamoto et al., 1986; Yagi, Katoh, Akiguchi, & Takeda, 1988). The decreased swimming speed in an aversive task would suggest that SMT might also exhibit slowing with age.

The present study examined SMT in the SAMP8 by performing an analysis of successive IRIs of a running wheel for 2-, 7-, and 12-month-old SAMP8 over the course of 16 days. Results consistent with the human data would predict longer and more variable IRIs in older SAMP8 than in younger SAMP8. Moreover, if the timing of wheel running is consistent with the human timing literature, then IRI variability should conform to Weber's law. One way to assess Weber's law is to calculate a coefficient of variability (CV), obtained by dividing the IRI standard deviation by the mean IRI. Age-related changes in variability consistent with Weber's law would predict a constant CV across age.

METHOD

Animals

Twenty-nine virgin, male SAMP8, ages 2 months ($n = 10$), 7 months ($n = 9$), and 12 months ($n = 10$), were subjects for the study. Mice were bred and raised in the animal research facility at Bowling Green State University. Two to four same-sex littermates were housed together, with food (Harlan Teklad Rat Diet 8664) and water available ad libitum. Lights in the animal rooms were on a 12 h light/12 h dark cycle (lights on at 7:30 AM). All procedures followed the National Institute of Health (NIH) guidelines for handling and caring for animals and were approved by the Bowling Green State University Animal Care and Use Committee. At the start of testing, all mice were naïve and in good health without noticeable motor impairments or cataracts. The average weights (pretest) of the three age groups of SAMP8 were 28.1±1.79 g, 36.8±1.89 g, and 38.9±1.79 g, respectively (mean±SEM).

Apparatus

Wheel-running activity was monitored using four Wahmann running wheels (110 cm circumference, 7.5 cm width) located in a room separated from the animal colony room. The room was illuminated at 165 lux during the light phase. A cage (22.5 × 12.5 × 12.5 cm) was attached to each wheel, containing food and water, and the mice were able to freely move between the cage and the wheel. A magnet attached to the wheel's axis of rotation detected a wheel revolution. An electronic switch sent a signal to an IBM-compatible computer and custom software recorded the time of each wheel revolution to the nearest millisecond. The series of IRIs was calculated from the resulting sequence of time stamps.

Procedure

Mice were individually monitored in the run-wheel apparatus for 16 days as part of a concurrent study of circadian rhythms. To assess circadian rhythms, the mice were maintained on a 12:12 h light/dark cycle for the first 6 days and then were maintained in constant darkness.

Data Analysis

Spontaneous motor rhythms were assessed over the 16 days by analyzing the distribution of IRIs for each 24-h period. IRIs were filtered according to the following criteria prior to any analyses. First, IRIs longer than 20 s were removed from the analysis because these were assumed to be due to the mouse leaving the wheel for an extended period of time rather than being part of a consistent bout of running. Second, we removed any IRI less than 1 s, as these were likely attributable to a reversal in the direction of the wheel (e.g., rocking back and forth), rather than a complete revolution. The 1-s and 20-s criteria were based on observations of the mice in the wheels. For the filtered IRI data, estimates of central tendency using the median did not typically differ from the mean. Consequently, the mean was used in all subsequent analyses and is reported below. To assess variability of IRIs, we calculated the CV by dividing the standard deviation by the mean for each day of testing.

Statistical analyses were performed using SPSS for Windows (Version 10.1, SPSS, Chicago, IL). Analysis of variance (ANOVA) was used to assess differences in mean IRI and CV as a function of age and day. For both ANOVAs, the Geisser-Greenhouse procedure (Geisser & Greenhouse, 1958) was used to correct for violations in the assumption of sphericity. An arc sine transformation was applied to the CV data prior to the ANOVA in order to correct for possible violations in the assumption of normality. Neither correction altered any of the statistical results. All post hoc comparisons between the three age groups were performed using Tukey's honestly significant difference (HSD) with an alpha level of 0.01.

RESULTS

Figure 1 shows the mean IRI for each of the 16 days of testing for the three age groups. A two-way mixed-measure ANOVA on mean IRI demonstrated main effects of age ($F(2, 26) = 26.19$, $p < .001$) and day ($F(15, 390) = 33.74$, $p < .001$), but not a significant interaction between the two ($F(30, 390) = 1.3$, $p > .2$). As shown in Figure 1, all age groups gradually increased their average running rate (i.e., decreased the mean

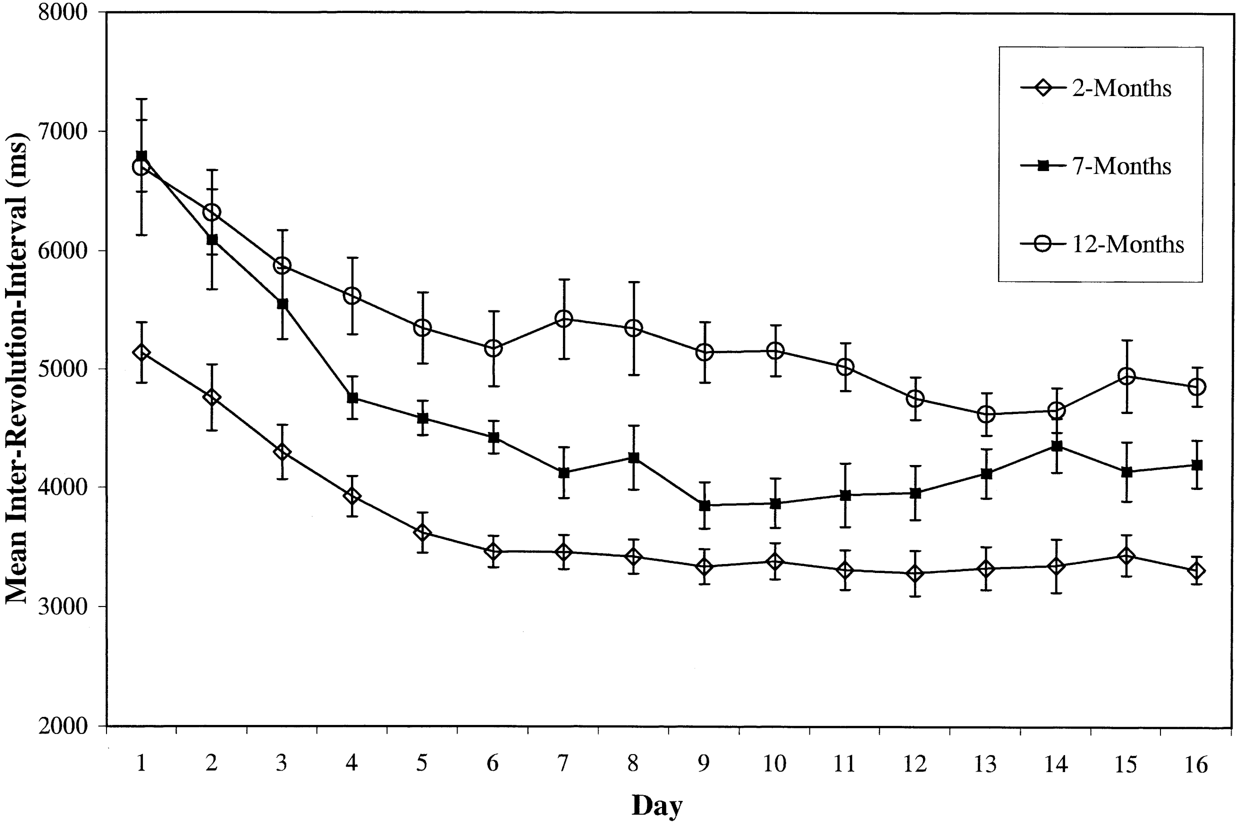

FIGURE 1 Mean interrevolution intervals (IRIs) for each of the 16 days of the experiment for the 2-, 7-, and 12-month-old SAMP8.

IRI) over the course of testing. Collapsed over age, the mean IRI on Day 1 was 6074 ms, but was reduced by almost 2 s to 4120 ms by Day 16. Clear age differences were also evident on each day of testing. Overall, the spontaneous wheel running of the aged SAMP8 was slower than the young SAMP8, with the age-related differences in mean IRI fairly constant across days. On the final day, mean IRIs for the 2-, 7-, and 12-month-old SAMP8 were 3315 ms, 4204 ms, and 4929 ms, respectively. Post hoc comparisons between the three age groups revealed significant differences in mean IRIs for all pair-wise tests ($p < .01$).

One possible explanation for the slower wheel-running rhythms of the older SAMP8 is simply that the older SAMP8 are heavier than the younger SAMP8, and so are unable to run as fast due to their weight. Indeed, both pre- and post-test weights were significantly correlated with age ($r = .578$, $p < .01$ and $r = .716$, $p < .01$, respectively). However, evidence against this explanation comes from a comparison of 7- and 12-month-old SAMP8. No significant difference in the weights was observed for 7- and 12-month-old SAMP8 (both pre- and post-test), but there was still a large significant difference in the average IRI duration between the two age groups ($p < .01$; Figure 1). To further address this issue, we constructed samples of weight-matched mice in the three age groups and reran the ANOVA. Results for the analysis of the weight-matched groups ($n = 4$ in each age group) were similar to the overall analysis; a significant main effect of age ($F(2, 9) = 7$, $p < .05$) and a significant main effect of day ($F(15, 135) = 16.48$, $p < .001$) were observed without an interaction between these two factors.

Figure 2 reports mean CV for the 16 days of the experiment for the three age groups. A two-way mixed-measure ANOVA on CV revealed a main effect of day ($F(15, 390) = 21.70$, $p < .001$), but no main effect of age ($F(2, 26) = .66$, $p > .5$) or significant interaction ($F(30, 390) = 1.5$, $p > .1$). Mean CVs, collapsed across all 16 days, for the 2-, 7-, and 12-month-old SAMP8 were .16, .17, and .16, respectively. The lack of an effect of age on CV indicates that although spontaneous wheel running of the young SAMP8 was faster than the aged SAMP8, the age-related increase in variability was not more than predicted by Weber's law. All of the mice showed decreases in CV across days. Collapsed over age, mean CV decreased from .22 on Day 1 to 0.13 on Day 16. Overall changes in CV were best explained by a power law of practice with $R^2 = .94$.

Given that both SMT and circadian rhythms appear to be altered by age, an interesting issue is whether the two are correlated. In order to address this question, we compared our SMT measures with three circadian rhythm measures obtained from the wheel-running bin counts: τ (a measure of circadian period during constant conditions), circadian rhythm amplitude, and the proportion of run-wheel activity that occurred during the normally inactive light phase (a measure of circadian

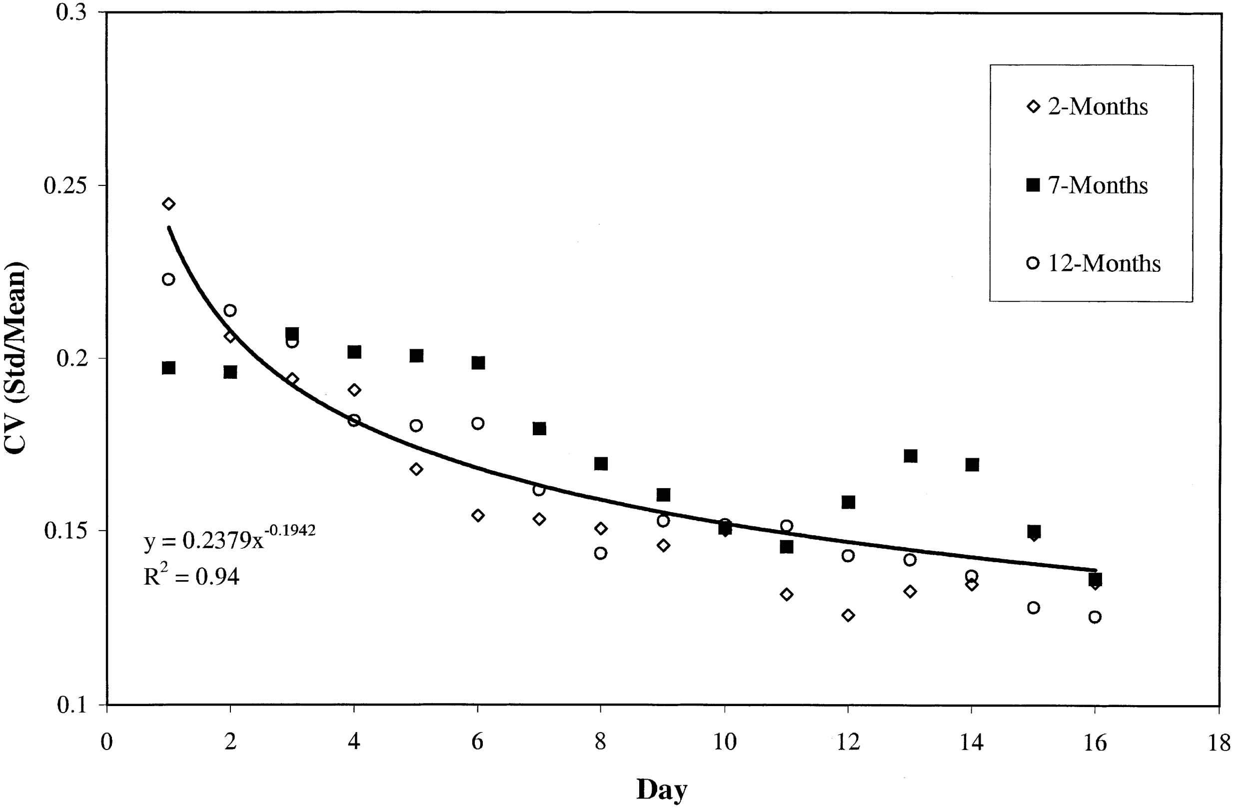

FIGURE 2 Mean coefficient of variability (CV) for each of the 16 days of the experiment, for the 2-, 7-, and 12-month-old SAMP8. The solid black line shows the best fitting power function collapsed across age.

TABLE 1 Relationship Between SMT and Circadian Rhythm Measures

	Circadian rhythm measures		
Predictors	τ	Rhythm amplitude	Rhythm disruption
Age	.316	$-.815^{**}$	$.650^{**}$
Mean IRI	$.448^{*}$	$-.697^{**}$	$.498^{**}$
IRI standard deviation	$.586^{**}$	$-.495^{**}$	$-.490^{**}$

**Correlation is significant at the .01 level (two-tailed).

*Correlation is significant at the .05 level (two-tailed).

rhythm disruption). Details of the methods used to obtain these measures are described in a previous report (McAuley et al., 2002). Correlations with circadian rhythm measures were examined for three predictor variables: mean IRI, IRI standard deviation, and age (Table 1). IRI standard deviation was used for these correlational analyses rather than CV because the formula for CV includes mean IRI, thus not permitting an independent assessment of the relationship between variability and circadian rhythm measures.

As reported previously, age was negatively correlated with rhythm amplitude ($r = -.82$, $p < .01$), positively correlated with rhythm disruption ($r = .65$, $p < .01$), but not correlated with τ ($r = .32$, $p > .05$). The present study shows that SMT measures were also significantly correlated with circadian rhythm measures. In particular, mean IRI was negatively correlated with rhythm amplitude ($r = -.70$, $p < .01$) and rhythm disruption ($r = -.50$, $p < .01$), and positively correlated with τ ($r = .45$, $p < .05$). This last finding is particularly interesting because age was not significantly correlated with τ, suggesting that spontaneous wheel-running speed explains a portion of the variability in τ that is not explained by age. IRI standard deviation (a measure of motor variability) was also found to predict circadian rhythm measures. IRI standard deviation was negatively correlated with rhythm amplitude ($r = -.50$, $p < .01$), and positively correlated with rhythm disruption ($r = .49$, $p < .01$) and τ ($r = .59$, $p < .01$).

DISCUSSION

The present study investigated whether spontaneous wheel running in mice could be used as a measure of SMT. To this end, the results of the present study assessing spontaneous wheel-running behavior is compared to studies with humans involving finger tapping and walking, two common ways to assess SMT. A second aim was to examine the age-related changes in SMT using a mouse model of aging, the SAMP8. Our results demonstrate that older SAMP8 had slower and more variable SMTs than did younger SAMP8, with differences appearing as early as 7 months of age. The general slowing of SMT with age is consistent with other studies reporting age differences in running speed (Mondon et al., 1985; Sherwin, 1998; Skalicky et al., 1996). The increased variability of SMT, however, is a novel finding, and permits comparisons to analogous timing measures in young and aged humans.

The age-related slowing of SMT observed in the SAMP8 is consistent with previous human studies showing an age-related slowing of SMT, as measured by preferred tapping rate (Drake et al., 2000; Vanneste et al., 2001) and walking rate (Gabell & Nayak, 1984; Hausdorff et al., 1997; Stolze, Freiderich, Steinauer, & Vieregge, 2000). In addition, the age-related increase in IRI variability we observed was proportional to mean IRI, as would be predicted by Weber's law and is consistent with studies of both human and animal timing (Allan, 1979; Getty, 1975; Gibbon, 1977; Hinton & Meck, 1997). That is, although we observed increased variability in SMT with age, we did not observe age differences in CV, indicating that relative variability remained constant across the life span of the SAMP8 (consistent with a Weber's law model). Average CV was approximately 16%, which is consistent with that reported in studies measuring gait topography in rodent locomotion (Parker & Clarke, 1990) and is consistent with human studies of SMT that show that slowing of SMT is accompanied by a proportional increase in variability (Vanneste et al., 2001)

One question that arises is whether the observed slowing of SMT with age is due to an increase in the weight of the animals over time. A similar question can be asked about studies that have reported an age-related slowing of running speed with age (Mondon et al., 1985; Skalicky et al., 1996). However, at least for the present study, this explanation seems unlikely because (1) there were no significant differences in the weights of the 7- and 12-month-old SAMP8, yet the average SMT of the 12-month-old SAMP8 was much slower than that of the 7-month-old SAMP8; and (2) there was a significant age effect on SMT across all three groups for a sample of weight-matched subjects ($n = 4$). It is also unlikely that the observed slowing is due to the older SAMP8 pausing more often between wheel revolutions because there were no appreciable differences in the shapes of the IRI distributions (i.e., the distributions for the older SAMP8 were not more positively skewed than the younger SAMP8).

One factor that affected the mean SMT and variability was experience in the run wheels. All of the subjects in this study had not previously encountered run wheels. As such, the first several days of the experiment tended to produce a general increase in wheel-running speed and a reduction in variability. Interestingly, reductions in variability due to experience did not obey Weber's law; there were changes in CV across days. Because run-wheel experience (practice) decreased CV, the general reduction in variability is not explained by the SAMP8 gradually running faster (according to a Weber's law model). Rather, it suggests that with practice the mice settled into a more consistent and coordinated running rhythm. Similar improvements in timing control with practice have been reported in human studies of gait dynamics (Hausdorff et al., 2001). It is worth noting here that in spite of the observed improvements with practice (both in terms of rate and variability), consistent age differences in the SMT of the SAMP8 remained. Overall, the SMTs of the older SAMP8 were slower than the SMTs of the younger SAMP8 each day of the study, with the reduction in variability across days appearing to follow a power law of practice.

Overall, the present study contributes to a body of research showing appreciable age-related changes in the sensorimotor function of the SAMP8 (Flood & Morley, 1998; Markowska et al., 1998). These results further highlight the need for caution in interpreting learning and memory deficits in the SAMP8 when escape latency is used as the primary dependent measure (e.g., performance on the Morris water maze task; see Miyamoto et al., 1986). Interestingly, motor learning as measured by a decrease in IRI and CV across days did not differ between ages. The lack of age-related differences in motor learning stands in contrast to previous findings of a motor-learning impairment in aged rats (Bickford, 1993; Bickford, Shukitt-Hale, & Joseph, 1999). The lack of a motor-learning impairment in the present study may be due to the relatively simple task of wheel running, which may not tax the motor-learning system sufficiently. Alternatively, SAMP8 may not show age-related deficits in motor learning even though other motor measures appear to be compromised.

One particularly intriguing finding was the strong relationship observed between SMT measures and characteristics of an animal's circadian rhythm. Significant correlations were observed between mean SMT and free-running period, rhythm amplitude, and degree of rhythm fragmentation. The positive correlation found between mean SMT and free-running period (τ) is consistent with a number of previous studies indicating that increased amount of run-wheel activity in some rodent species is associated with shorter free-running periods (Mrosovsky, 1999; Shioiri, Takahashi, Yamada & Takahashi, 1991; Yamada, Shimoda, Tahakashi, & Takahashi, 1990). The present findings extend these previous results in two ways. First, the present results generalize this result to the SAMP8. Second, our results suggest that the relationship between activity and τ concerns more than the amount of activity per se, but rather the rate (tempo) that the SAMP8 turn the wheels during consistent bouts of running; faster motor rhythms are associated with faster circadian rhythms. In a follow-up analysis, where we controlled for the amount of activity, a significant, although weaker relationship, was still found between mean SMT and τ ($r = .33$, $p < .05$; one-tailed). This conclusion is further strengthened by the significant positive relationship we observed between SMT variability and τ; less variability in the timing of successive wheel revolutions was associated with shorter τ. This latter finding was also present when we controlled for the overall amount of activity ($r = .51$, $p < .01$; one-tailed). To summarize both findings, faster and more consistent motor rhythms are associated with faster circadian rhythms.

One possible explanation of the correlations observed between SMT and circadian rhythm measures is that they are simple due to these measures being correlated with changes in age. However, the finding that age was not correlated with τ does not support this explanation. Thus, one implication of these two findings is that mean SMT explains variability in τ that is not explained by age. An additional implication is that some of the conflicting studies on effects of age on τ may be confounded by differences in mean SMT, variability in SMT, as well as overall activity levels across age groups. Additional research is necessary to understand the importance of these relationships between SMT and circadian rhythm measures.

Two issues that are not addressed by this study are (1) where the changes responsible for the age-related slowing of SMT are taking place and (2) whether these changes are accelerated in the SAMP8. With regard to the first issue, the slowing of SMT may be due to changes in peripheral processes (i.e., muscle physiology, fatigue, etc.) or central processes (i.e., brain areas involved in timing or integrating motor action). Evidence against a simple fatigue explanation come from studies that show no age-related decrease in spontaneous exploration in an open field (Ikegami et al., 1992; Yagi et al., 1988). In addition, several human studies suggests that SMT supports the later of these two explanations (Boltz, 1994; Collyer et al., 1994; Drake et al., 2000). Perhaps the most convincing of these studies is Boltz (1994), who demonstrated that manipulations of SMT systematically affect peoples' ability to learn and remember the duration of events in the environment. Whether SMT in rodents captures similar properties of a central timekeeper is an open question.

With regards to the second issue, the major aim of the present study was to determine whether spontaneous wheel-running behavior in rodents could be used as an animal model of SMT in humans, and to assess whether age-related changes in wheel-running behavior followed the same pattern as age-related changes in human SMT. To this end, we used the SAMP8, a mouse model that has been used previously for its rapid aging. Our results suggest that spontaneous wheel-running behavior and the effects of age on this behavior do have similarities to human SMT. The question of whether the changes observed in SAMP8 represents a normal aging process or an accelerated one will be the focus of future studies comparing the SAMP8 with SAMR1, a subline selected for resistance to aging, and AKR/J, the background strain from which SAM sublines were selected.

In summary, the present study provides evidence that the preferred running rate of mice slows with increasing age. As such, the reported findings are consistent with previous human studies showing an age-related slowing of SMT, as measured by preferred tapping rate (Drake et al., 2000; Vanneste et al., 2001) and walking rate (Gabell & Nayak, 1984; Hausdorff et al., 1997; Stolze et al., 2000). Furthermore, the consistency of running rate decreases with age, but can be accounted for by Weber's law. That is, variability of running rate increases proportionally to the slowing of running rate. Finally, age-related changes in SMT correlated with disruptions in circadian rhythm measures. These results suggest that analysis of spontaneous wheel-running behavior may be an excellent way to study SMT in animals, allowing for more invasive examination of the neurobiological changes responsible for the age-related alterations of SMT.

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