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Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse

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Abstract

If begun early in life, exercise effectively reduces the development of cognitive deficits in transgenic mouse models of Alzheimer's disease (AD). However, the effectiveness of exercise, once the cognitive impairments are established, is not as clear. In terms of translating research in animal models to treatments involving exercise in Alzheimer's disease patients, it is critical to evaluate exercise intervention at time points that address not only prevention, but also treatment of cognitive decline. We provided exercise wheels to Tg2576 (TG) (n=12) and C57BL6 (WT) (n=17) mice at 17-19 months of age for three weeks. At this age animals have significant cognitive impairment and neuropathology consistent with AD. Age matched sedentary TG (n=13) and WT (n=12) mice were also included, as well as groups provided access to an immobile wheel (TG n=9, WT n=12). After three weeks, animals were evaluated in a radial arm water maze. Significant impairments were observed in the sedentary TG mice compared to WT in reference/long-term and working/short-term memory, as well as in probe trials. Exercised TG mice demonstrated improvements in memory, which made them indistinguishable from WT mice on all tasks. In addition, animals provided with an immobile wheel exhibited improvement in some, but not all cognitive measures. Our findings demonstrate that exercise can improve cognitive performance in a mouse model of AD even if applied after the development of pathology.

Keywords

exercise; Alzheimer's; Tg2576; aging; RAWM; intervention

Introduction

Cognitive decline has been consistently reported in human aging. [29,33] This age-related decline of cognitive ability also occurs in mice. [32] Cognitive decline, however, can be modified by environmental factors. For example, several researchers show that changing from a sedentary lifestyle to an active lifestyle results in cognitive benefits in both humans and mice. [9,16,25] Further, exercise improves cognition in aging humans and can delay the onset of dementia. [25] Exercise is beneficial through multiple pathways such as increased growth factors, increased metabolism, improved cerebrovascular function, increased neurogenesis and

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plasticity, and increased immune system efficacy. [6,10,11,25] One important question that remains is whether exercise improves cognitive ability in advanced states of dementia. Transgenic mouse models, developed to mimic the pathological progression of Alzheimer's disease, the most common of the dementias, provide opportunities to explore the effects of exercise on AD. Recently published data by Adlard et al. using the TgCRND8 model of AD demonstrates that 5 months of voluntary wheel running begun at 1 month of age improves performance on the Morris water maze (MWM) compared to sedentary animals of the same age. [2] Adlard's findings support an exercise-induced improvement in cognition if exercise is begun at a young age, prior to the development of AD pathology.

Though previous studies demonstrate that exercise begun in youth can contribute to a healthy cognitive profile throughout old age, we do not yet know if exercise initiated late in life has cognitive benefits. Until a recent study published by van Praag et al. (2005), it was unclear whether exercise could enhance learning in aged mice, even those not engineered to develop AD pathology. [32] In 19 month C57Bl/6 males (the background strain for the Tg2576 mouse model of AD used in the current study), 6 weeks of voluntary wheel running increased the amount of time animals spent in the target quadrant of the platform in the MWM, though escape latency improved only in young (3 month) runners. [32] This evidence suggests that aged wild-type mice may benefit from exercise begun late in life. It is not known if AD models, such as the Tg2576, will respond similarly to exercise begun in old age.

A possible role of exercise in improving cognition in aging animals is suggested by experiments with environmental enrichment. Typically an enriched rodent environment includes access to a running wheel and a larger cage size. Previous studies have demonstrated a beneficial effect of such environmental enrichment on cognition in mouse AD models. [4,20] It is unclear what the mechanism is for this cognitive improvement. Lazarov et al. (2005) exposed transgenic AD mice at 1 month of age to 5 months of environmental enrichment and discovered decreases in Aβ pathology. [24] Jankowsky et al. (2005) found cognitive improvement in the same transgenic model as Lazarov, using a similar enrichment paradigm, but found increases in Aβ pathology. [19] Both studies included exercise wheels in the enriched environment, but exercise alone was not evaluated. In Arendash et al. (2004), enrichment included a large living space, with toys, tunnels, and an exercise wheel present in the environment. [4] This environmental enrichment improved cognitive performance in old (16-22 mos) Tg2576 mice, confirming enrichment can enhance cognitive ability in aged mice. [4] Kempermann et al. (2002) demonstrated that enrichment results in neurogenesis in aged C57Bl/6 if begun at middle age (10months). [20] In an important study by van Praag et al (1999), exercise alone increased neuronal proliferation as much as the enriched environment, demonstrating that running alone could be responsible for the effects of enrichment on improved cognitive performance. [31] Conversely, a recent paper by Pietropaolo et al. (2006) that compared enriched housing with a running wheel, enriched housing with a locked wheel, standard housing with a running wheel, and standard housing with a locked wheel suggests enrichment alone is most beneficial on cognitive performance. [28] Pietropaolo et al. found the combination of enrichment and running had similar effects to enrichment with a locked wheel present. Both improved the acquisition of the platform location in Morris water maze. However, the animals that ran in a standard housing environment were unique from the other groups in their lengthened time needed to extinguish a learned response.

Our primary goal was to determine the effects of three weeks of voluntary wheel running in aged Tg2576 (TG) and C57Bl/6 (WT) mice. The Tg2576 mouse strain over-expresses the 695-amino acid form of the human amyloid precursor protein containing a $Lys^{670} \rightarrow Asn$, $Met^{671} \rightarrow Leu$ mutation. [17] Tg2576 mice express 5.5 times the amount of APP endogenous to the wild type. The pathological features of this model have been well characterized, and suggest that the Tg2576 is a useful model of Alzheimer's disease. [7,17,21,30] Elevated levels

of $A\beta_{1-40}$ and $A\beta_{1-42/43}$, pathological hallmarks of AD whose causal role is still under debate, are present at 11 months as determined by ELISA, as are dense core classic senile plaques. [17]

Though the Tg2576 has been tested on several behavioral tasks, the results of tests for learning and memory impairments have been varied and difficult to interpret. (Table 1) We therefore felt it was important to employ a task that engages memory at both long-term and short-term intervals in a spatial task where the animal must remember the platform location in order to escape, as well as search through multiple arms to find locate the platform. The radial-arm water maze (RAWM) is a recent addition to the behavioral tasks available to investigators of learning and memory. [26] The RAWM combines the spatial working memory task of the radial arm maze with the spatial reference memory task of the traditional Morris water maze. [27] Though experiments have not been done to correlate performance on RAWM to Aβ levels, the RAWM has proven more sensitive than Morris water maze in detecting cognitive deficit in several transgenic AD models. [5,8,26] The present study compares TG and WT at a time-point (17-19 months) when significant AD-like pathology is established in the Tg2576. [17, 18,22,30] Three weeks of wheel running was chosen because multiple neuroprotective mechanisms are engaged at this duration of exercise, including increased neurogenesis, increased expression of brain-derived growth factor, improved cerebrovascular function, resistance to ischemic damage, and improved immune function. [1,12,13,15,22] Thus, we felt that initial improvements in cognitive function would be detectable at this same time-point.

To investigate the exercise effects versus the potentially enriching effects of simply having a wheel in the cage, we included a wheel locked control group. While the main focus was on the aged AD model, we study also examined exercise-induced improvements on performance in aged WT mice. To our knowledge, no studies have previously examined the effects of exercise in the aged Tg2576 model. We hypothesized that cognitive deficits would be present in the TG mice compared to the WT mice. We further hypothesized that three weeks of voluntary wheel running would improve the cognitive performance of the TG mice. We do not hypothesize as great an improvement in cognition in the wheel locked group.

Materials and Methods

Animals

All animal protocols were approved by the Institutional Animal Care and Use Committee at the University of California, Irvine. We used C57Bl6 (WT) and Tg2576 (TG) (Hsiao, 1997) from an established colony (ca. 2000) at University of California, Irvine. [17] We assigned WT (n=47) and TG (n=37) mice to exercise, sedentary or wheel locked groups at 16-18 months of age. Distribution of groups and genders is shown in Table 1. Running was voluntary and monitored by computer software (Vital-view©, Mini-Mitter) to record distance run by each animal over the three week period. Animals were cognitively tested at approximately 17-19 months of age.

Radial-arm water maze

The RAWM protocol used in this study was provided by Dr. David Morgan (Health Science Center, University of South Florida) (personal communication) and consisted of three days of testing. It has been previously used in studies of Tg2576 animals with success. [3,34] We performed RAWM testing in a room with visual cues posted on the four walls. The maze consisted of five-arms, placed in a water bath such that the tops of the dividers were above water. We placed the platform in one arm for each mouse (arm placement randomized between animals), kept consistent throughout the first two days for that mouse. We placed individual mice in a different arm location sequentially on all trials. We tested the animals in cohorts of

four animals, with a minimum of 30 minutes and a maximum of 60 minutes consolidation between blocks of 5 trials. Each animal received a total of 15 trials per day. At the end of each trial, the mouse was allowed to sit on the platform for 20 seconds. The experimenter guided the animal to the platform if it failed to find the platform on its own after 60 seconds. If the animal chose an incorrect arm (arm not containing platform), it was gently pulled back to the start arm. We scored animals on latency (i.e. time to find platform), errors (entries of entire body into arm not containing platform), and failures (failure to find the platform after 60 seconds) on days 1 and 2. We adapted the method for separating reference and working memory scores from Hyde et al as follows. [18] For all cognitive measurements, the experimenter scoring the animals was blind to group assignment and genotype.

Reference/ “Long-term” memory

For each block of five trials, the first trial after a 30+ minute consolidation period is considered a reference or “long-term” memory trial. Thus, on day 1, animals were scored for reference memory latency and errors on trials 6 and 11. On day 2, animals were scored on trials 1, 6, and 11. The first trial of day 2 occurs more than 12 hours after the last trial of day 1.

Working/ “Short term” memory

The remaining trials are working or “short-term” memory trials. Less than 4 minutes elapses between each working memory trial for each mouse. On day 1, we scored animals on working memory latency and errors on trials 1-5, 7-10, and 12-15. On day 2, animals were scored for latency and errors on trials 2-5, 7-10, and 12-15.

Failures

We recorded failures to locate the platform across both days 1 and 2. A failure consisted of an inability to find the platform after the maximum allowable time of 60 seconds.

Extinction

On day 3, we placed the platform in a new location for each animal. On the first five trials, we analyzed the number of times the animals returned to the old platform location as memory for the original platform location.

Control measures

We performed a final test for swim speed and a test with a visible platform one day after completion of testing. The swim speed task involved timing the animal over a fixed distance. For the visual task, we drained roughly 1 inch of water from the tank so that the platform surface was visible above the water line. We recorded latency to find and crawl onto the visible platform. If the animal failed climb onto the platform after 120 seconds in the visual task, it was given the maximum latency score of 120 seconds.

Statistics

A 2×3 repeated measures ANOVA was performed for reference memory latency and working memory errors. Posthoc analysis was by Fisher's LSD. Due to unequal variance, non-parametric tests (Friedman's rank test) were performed for the reference memory errors and working memory latency, and results analyzed posthoc using Dunnett's T3 post hoc comparison for groups of unequal variance. One-way ANOVAs were performed for genotype effects and gender effects on swim speed, visual task latency, and for failures. One way ANOVAs were also performed for genotype effects and gender effects on swim speed and visual task latency. Gender was run as a covariate in all other tests. It was found not to contribute significantly to

measures other than swim speed and was therefore removed as a predictor. For all tests, $p \leq 0.05$ was considered significant.

Results

Prior to statistical analyses, we normalized animals by their total running distances over the three week intervention. To normalize running behavior, we excluded animals with running distances greater than or less than two standard deviations from the mean from all cognitive tests (total excluded animals: WT n=6, TG n=4). A separate analysis of the excluded animals showed effects on reference and working memory in the same direction as those discussed below. The average distance run per day of the included animals did not differ significantly between WT and TG (mean rotations per day were 4794 ± 996 and 4390 ± 820, respectively). Gender had no effect on distance run in either genotype.

We did not observe any significant differences in working or reference memory in WT mice with exercise or locked wheels compared to sedentary. Because only TG groups showed an effect of exercise and/or wheel presence, we will focus on their results in further analysis.

Failures

We analyzed the number of times animals achieved the maximum time allotted (60 seconds) without locating the platform as "failures." We found significant effects of treatment condition (WHEEL, SED, RUN) and genotype (TG, WT) on number of failures across both days of testing using a one-way ANOVA for group assignment ($F_{5, 69} = 4.218$, p=0.002). In post-hoc analysis, TG_{SED} failed to find the platform significantly more often than WT_{SED} (p=0.002) and TG_{RUN} (p=0.02). Conversely, TG_{RUN} did not statistically differ from WT_{SED}. (Figure 1)

Reference/ "Long term" memory

We found a significant effect of genotype (TG, WT) ($F_{1, 69} = 6.57$, p=0.01) and also condition (RUN, WHEEL, SED) ($F_{2, 69} = 2.98$, p=0.05) on reference memory latency during day 2 of testing. Posthoc analysis of individual trials by Fisher's LSD revealed that on the first day of testing, no significant differences existed for escape latency on trials 6 and 11. However, on the first trial of the second day, when more than 12h had passed since the previous trial, TG_{SED} took significantly longer to find the platform than the WT_{SED} (p=0.05) (Figure 2, top). Interestingly, at this timepoint the TG_{RUN} does not differ from WT_{SED}. The TG_{SED} was the only group that did not improve (evaluated as percent savings) between day 1, trial 1, and day 2, trial 1. (Figure 2, bottom) We found no significant differences in reference memory errors (data not shown). However, it is of note than in reference memory errors, TG_{SED} again failed to improve (% savings) from day 1, trial 1 to day 2, trial 1. (Figure 3).

Working/ "Short term" Memory

Group × Condition significantly affected working memory latency across trials ($\chi^2 = 21.04$, p=0.001). TG_{SED} took significantly longer to find the platform on than WT_{SED} across all working memory trials ($p \leq 0.05$). (Figure 4, top) TG_{RUN} did not significantly differ from the WT_{SED} on any trial. On the final group of trials (trials 11-15) on both days, TG_{RUN} time to find the platform was significantly less than that of TG_{SED} (day 1 p=0.005, day 2, p=0.02). (Figure 4, bottom) No differences were observed in number of errors during working memory trials.

Extinction

On the third day of testing, we moved the platform to a new location. Animals who learn the task on days 1 and 2 return more frequently to the old arm during this testing. As expected, the

TG_{RUN} animals returned to their old platform location significantly more often than the TG_{SED} animals on the first two trials of day 3 (p=0.02). (Figure 5, top) WT_{RUN} also exhibited a similar trend to return to the old arm more than WT_{SED} over the first five trials, though it did not achieve statistical significance (p=0.1). (Figure 5, bottom)

Wheel locked animals

In the post-hoc analysis of failures, TG_{WHEEL} showed fewer failures to find the platform than TG_{SED} (p=0.04) and like TG_{RUN}, no longer differed from WT_{SED}. (Figure 1) On the long-term memory trial, comparing trial 1 of day 2 to trial 1 of day 1, TG_{WHEEL} showed a decrease in escape latency such that it no longer differed from WT_{SED}. (Figure 2, top) Interestingly, when we look at percent savings from day 1 to day 2, TG_{WHEEL} improved similar to TG_{RUN}. (Figure 2, bottom) Like TG_{RUN}, TG_{WHEEL} did not significantly differ from the WT_{SED} on any working memory/short-term memory trial. However, on the final group of working memory trials (trials 11-15) on both days, TG_{WHEEL} improved to point midway between the TG_{SED} and TG_{RUN}. (Figure 4, bottom) Unlike TG_{RUN}, the TG_{WHEEL} group did not differ from TG_{SED} group on day 3 of testing. TG_{WHEEL} did not show an increased tendency to return to the old platform location. (Figure 5, top)

Control measures

Mean swim speeds and latencies to find the visible platform are shown in Table 2. We did not observe any differences in swim speed between TG and WT groups. Regardless of genotype, males showed significantly slower swim speeds than females (p=0.03). It is important to note that we did not observe any significant differences in swim speed between treatments in either genotype (RUN, WHEEL, SED). In testing for latency to find the visible platform, we found no differences in visual task times due to gender. The mean time to find and mount the platform was lower in pooled WT animals (i.e. all 3 conditions) than the mean of all TG animals (p<0.01). This was not perceived as a vision failure, as TG mice approached the platform and then swam away from it (instead of crawling onto it), but rather a failure in ability to shift strategy to locate the platform with dividers absent (see discussion). Further, we observed no significant differences between conditions in either genotype in finding the visible platform.

Discussion

Using the RAWM, our study reveals clear reference/long-term memory deficits in TG at 17-19 months of age, compared to their WT counterparts, as well as impaired working or short-term memory. Both impairments are reduced in the Tg2576 mouse exposed to three weeks of exercise. In addition, three weeks exposure to a locked wheel also reduces the TG impairment on long term memory, as revealed on trial 1 of day 2. The TG_{RUN} mice were indistinguishable from the WT_{SED} on all memory measures. The TG_{RUN} animals showed significant improvement on working memory measures compared to the TG_{SED}. This is not true of the TG_{WHEEL} animals, which showed moderate, but not significant, improvement compared to TG_{SED}. TG_{RUN} returned to the original platform location significantly more often than TG_{SED} during the extinction trials on day 3 (when the platform was moved), confirming improved long term memory, but perhaps also suggesting a decreased extinction of previously learned platform location. These data are the first to indicate that voluntary exercise improves memory impairment in aged animals transgenic for Alzheimer's pathology.

TG animals exposed to an immobile running wheel (TG_{WHEEL}) were also indistinguishable from WT_{SED} animals in most working and reference memory measures and in number of failures. However, the TG_{WHEEL} group did not improve as much as TG_{RUN} on the final block of working memory trials, nor did the TG_{WHEEL} show the preference for the old platform location on day 3 extinction trials as TG_{RUN}. The TG_{WHEEL} group showed performance at

levels intermediate to the TG_{SED} and TG_{RUN} groups on the final block of working or short term memory trials. These data indicate that the presence of a locked wheel in an animal's home cage partially improves performance on the RAWM, but not as extensively as exercising on the wheel. The locked wheel itself may have served as a mild form of enrichment, consistent with a report by Arendash et al. (2004) in which similar decreases in escape latency in the RAWM following environmental enrichment were observed. [4] Our data are also interesting in light of the recent Pietropaolo study in which enrichment effects were studied with and without exercise by having either free or immobile wheels in the enriched environment. [28] In this enriched environment, there was equivalent improvement of the immobile wheel and free wheel groups. It is possible the larger housing of the enriched environment itself provided greater physical activity. In the standard (non-enriched) environment, differences in extinction tasks were obvious between mice with an immobile wheel and mice with a free wheel. Similar to our day 3 extinction trials the standard housed animals with a free wheel showed difficulty extinguishing prior learning compared to the standard cages with immobile wheels. It is unfortunate that the study did not further assess comparisons between the standard housed free wheel and immobile wheel groups. Our data suggest that both groups show improvement, but that the effect of the free wheel is greater than that of the immobile wheel's presence alone. It is impossible to say with any certainty if this was due to enrichment or exercise on the immobile wheel, though Koteja et al. (1999) have shown wheel climbing activity in mice provided a locked wheel nearly equal to running in mice with a free wheel. [23] It is possible that the mice in our locked wheel group climbed on the immobile wheel resulting in an unanticipated exercise effect.

The TG_{SED} mice showed a greater number of failures than WT_{SED} animals. It is not possible from our data to discern if these failures represent a failure to learn or simply reflect a lack of motivation in the TG_{SED} animals. Importantly, the TG_{WHEEL} and the TG_{RUN} groups did not differ from WT_{SED} group on number of failures, indicating that both conditions improve performance either by improving learning or increasing motivation.

Voluntary exercise did not alter reference or working memory performance in the WT animals. This conflicts with the recent findings of van Praag et al., who showed 45 days of running improved MWM performance in 19 month old C57Bl6 (WT) mice. [32] It is possible that the extra 24 days of running employed by van Praag (2005) represented the threshold for improvement in the WT mouse. Differences in protocol for the two tests may also contribute, as van Praag et al. did not see improvements in escape latency in their WT_{RUN} mice, but rather increased amount of time in the target quadrant. Our protocol did not include any quadrant time analysis, only latency and error. Finally, MWM involves repeated testing over a longer period of time (5 days) compared to the 3 day testing protocol used in the RAWM procedure. It is possible that the extended testing period allowed for greater memory consolidation and thus allowed for greater differences to be observed in the WT mice. In support of this idea, WT_{RUN} mice do show a trend to return to the original platform more often than WT_{SED} on the extinction trials of day 3.

For the TG animals, latency to find the visual platform was significantly higher than that of the WT animals. We do not believe this is due to any visual dysfunction, as we observed animals swimming up to and around the visual platform, rather than approaching it and climbing onto it like WT animals. TG_{RUN} animals showed improvement in finding the platform across the testing days, which relies on the ability to use the visual cues in the room. It has been suggested by King & Arendash (2002) that the Tg2576 mouse displays fear of the platform, but as the animals in our study do approach the platform, it is hard to interpret the behavior. [21] We suggest that future studies measure time to locate the platform and make contact, rather than climbing onto the platform. The visual task requires a partial strategy shift in that the arms of the maze are no longer present (though spatial cues are still present). It is possible aged Tg2576

mice are impaired in making this shift in strategies. Previous studies have observed deficiencies in strategy/task shifting in the Tg2576 mouse. [2,19] This inability to shift strategies may be analogous to executive functions of planning and problem solving in the human. [33] Our extinction data could also be interpreted as further demonstrating this impairment. While the return to the old platform location represents a better memory for the previous location, it also represents a failure to shift strategies and begin searching for a new location.

Conclusion

While three weeks of exercise or immobile wheel exposure did not eliminate spatial learning and memory deficits in TG mice, both interventions did improve RAWM performance and decrease failure rates to those observed in WT mice. The effects were greatest in the TG_{RUN} animals. The lack of extensive improvement in the WT_{RUN} and WT_{WHEEL}, coupled with previous studies showing longer exercise exposures do result in improvements in WT mice, suggests that the threshold for exercise-induced learning improvement may be lower in the TG animals. [32] Perhaps because of their greater impairment, aged TG mice exhibit the positive cognitive effects of an exercise regime sooner than WT mice. This is consistent with the concept of cognitive reserve translated to human study. The cognitive reserve hypothesis states that the more cognitive reserve (education, intellect, social interaction, etc.) an individual has, the longer a cognitive deficit will take to appear. It follows then that perhaps the more cognitively impaired or at risk an individual is, the easier it may be to effect a noticeable improvement. Recent findings by Etnier et al. (2007) indicate a greater cognitive effect of exercise in women who carry a genetic risk factor for AD, while little effect is observed in non-carriers. [14]

Perhaps more exciting is that our data supports the meta-analysis of exercise studies in the elderly cognitively impaired by Heyn et al. (2004), indicating that those in late stages of Alzheimer's pathology could show cognitive improvement with exercise even if that exercise is not begun until after the pathology is present. [16] While a total reversal of cognitive deficits was not observed, our findings lend hope to those patients looking to improve their cognitive function who have not exercised in life prior to diagnosis with Alzheimer's. Our data also suggest that the threshold for exercise induced improvement may be lower in cases of Alzheimer pathology than in normal age related decline.

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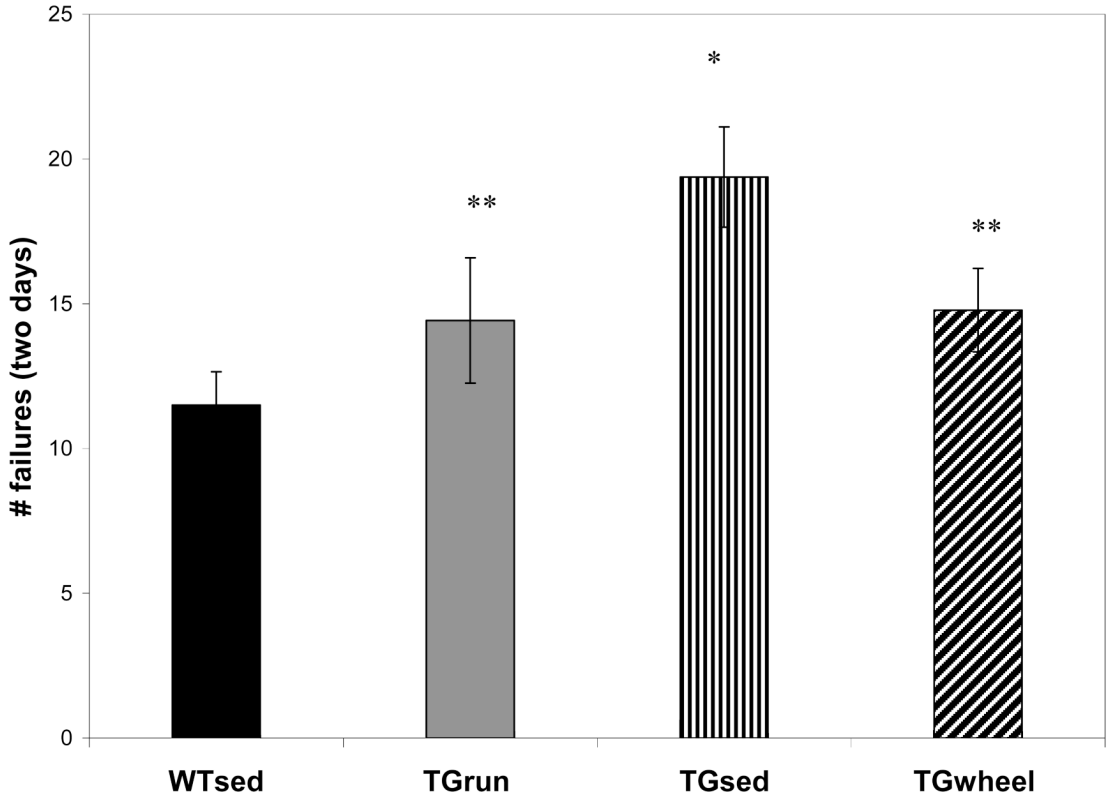
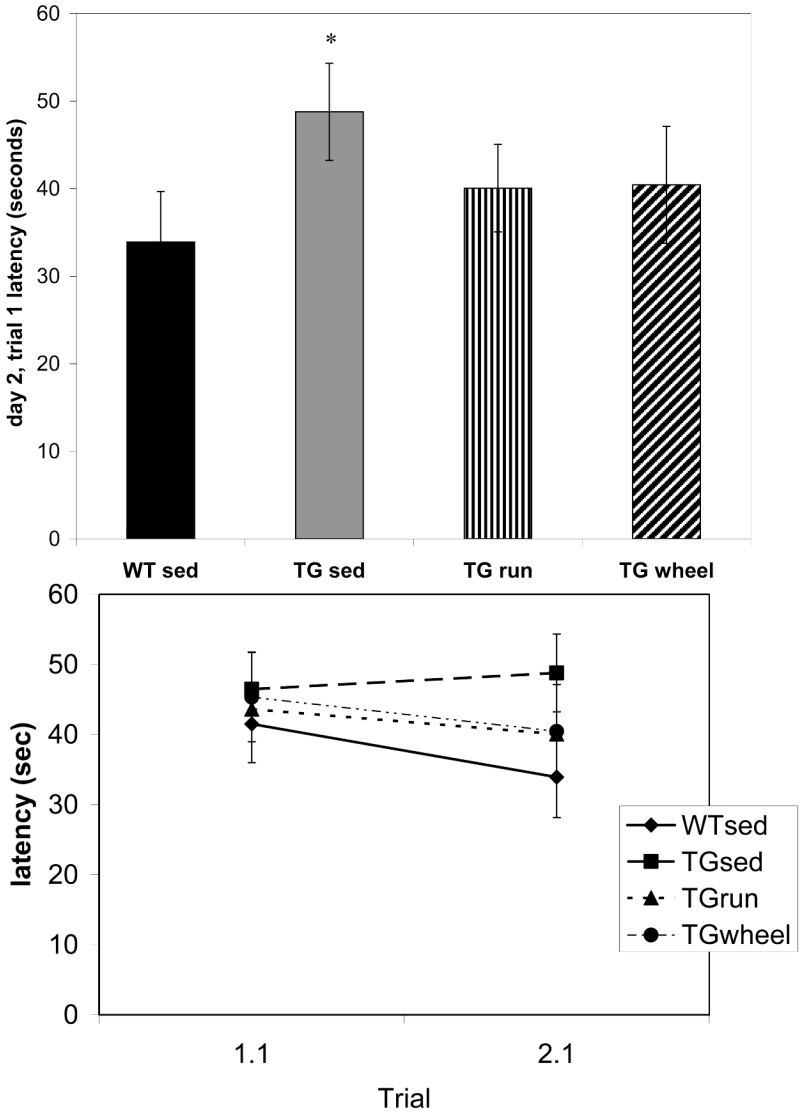


FIGURE 1.

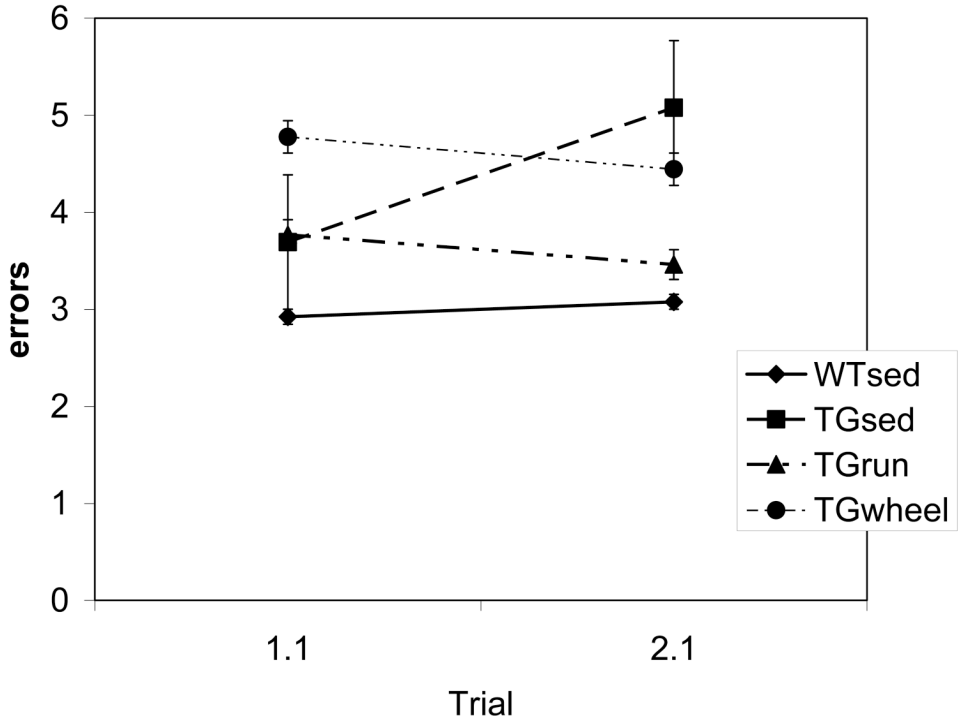
Number of failures is defined as the number of trials in which animals reached the maximum allowable time (60 seconds) without locating the platform. TG_{SED} had significantly more failures than WT_{SED}, though TG_{RUN} and TG_{WHEEL} were not significantly different from WT_{SED}. TG_{RUN} and TG_{WHEEL} had significantly fewer failures than TG_{SED}. Error bars represent ± standard error. *sig. different from WT_{SED} **sig. different from TG_{SED}



	Trial 1.1, Mean Latency	Trial 2.1, Mean Latency	% savings latency
WT_{TC}	41.5	33.9	18.3 %
TG_{TC}	46.5	48.8	- 5 %
TG_{RUN}	43.6	40.1	8%
TG_{WHEEL}	45.3	40.4	10.8%

FIGURE 2.

Reference memory latencies from day 2. On the first trial of day 2 of testing (2.1), TG_{SED} mice took significantly longer to escape the RAWM. This trial occurs more than 12 hours after the previous day of testing. The increased latency indicates an impairment in reference memory for the platform location. TG_{RUN} and TG_{WHEEL} did not differ from the WT_{SED}. The overall difference in latency between the first trial of day 1(1.1) and the first trial of day 2 (2.1) is shown in the lower panel as % savings: (mean trial 1.1 -mean trial 2.1) / mean trial 1.1. A positive value represents improvement and a negative value represents a decrement in performance between days. Error bars represent ± standard error. *sig. different from WT_{SED} **sig. different from TG_{SED}



	Trial 1.1, Mean errors	Trial 2.1, Mean errors	% savings on errors
WT_{TC}	2.9	3.1	-5.5%
TG_{TC}	3.7	5.1	-37%
TG_{RUN}	3.8	3.5	8.2%
TG_{WHEEL}	4.8	4.4	8.3%

FIGURE 3.

Reference memory errors from days 1 and 2. Errors did not differ significantly between groups. Overall differences from the first trial of day 1 (1.1) and the first trial of day 2 (2.1) are shown as % savings: (mean trial 1.1 - mean trial 2.1) / mean trial 1.1. A positive value represents improvement and a negative value represents a decrement in performance between days. TG_{SED} demonstrated an increase in number of errors between day 1 and day 2. Error bars represent ± standard error.

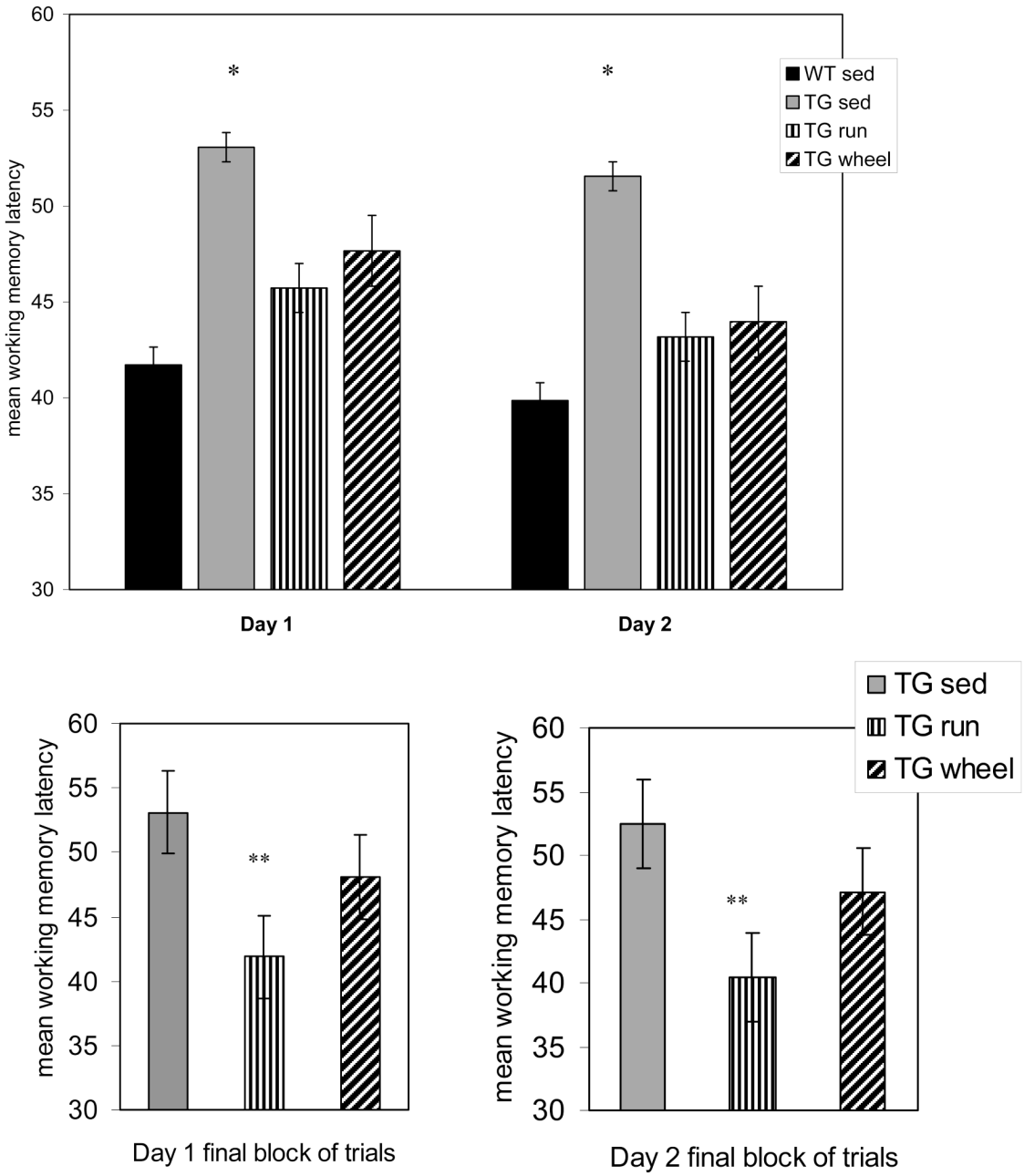


FIGURE 4.

Average working memory latencies from days 1 and 2. TG_{SED} demonstrated longer average escape latencies than WT_{SED} on working memory trials across both days of testing. TG_{RUN} and TG_{WHEEL} did not differ from the WT_{SED}. (top) TG_{RUN} performed significantly better than TG_{SED} on the third block of working memory trials on both days. (bottom) Error bars represent ± standard error. *sig. different from WT_{SED} **sig. different from TG_{SED}

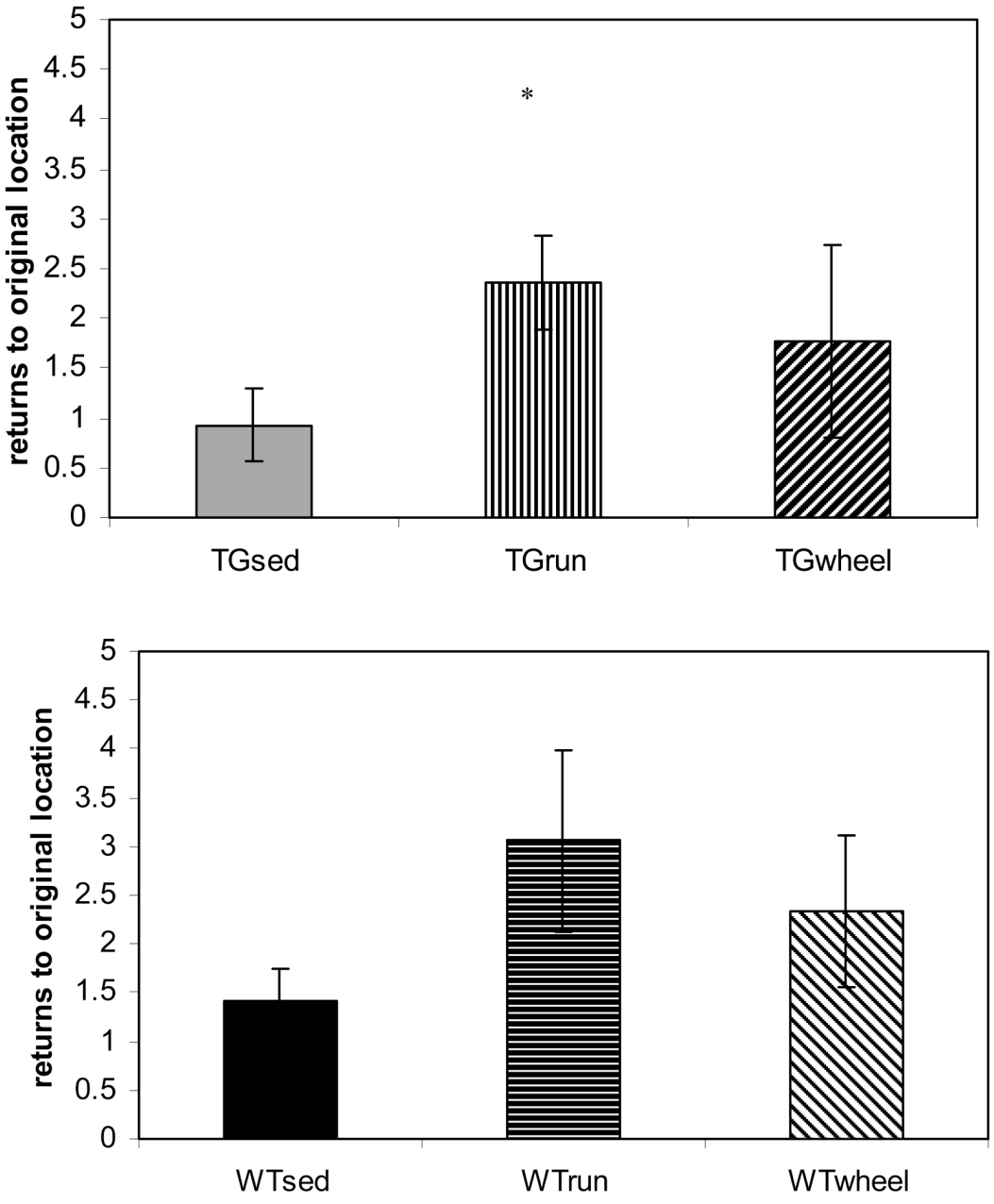


FIGURE 5.

In reversal training, returns to the original arm indicate a higher amount of retention for the platform's previous location, similar to a probe trial in standard Morris water maze. TG_{RUN} animals returned to their old arm significantly more than TG_{SED} ($p=0.02$). WT_{RUN} had a trend to return to the old arm more than WT_{SED} over the first five trials ($p=0.1$). Error bars represent ± standard error.*sig. different from WT_{SED} **sig. different from TG_{SED}

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TABLE 1

Cognitive measures observed in Tg2576 compared to the WT

	Y-maze	T-maze	MWM I	MWM II	RAM	RAWM I	RAWM II	Visual platform	Circular holeboard
Hsiao, 1996	↔3 mos ↓10 mos		↔2, 6 mos* ↓ 9-10 mos ↓ 12-15 mos	↓ 10 mos				↔ 9-10mos**	
Pompl, 1999									↔7 mos (learning), ↓ reversal learning
Chapman, 1999		↔2 mos ↓10 mos ↓16 mos							
Arendash, 2001 (Pre-vaccination)	↔5-7mos		↔5-7 mos			↓15mos (IgG vaccinated)	↔5-7mos		↔5-7 mos
King & Arendash, 2002	↓3 mos ↔9 mos ↔ 14 mos ↓19 mos		↔3 mos ↔9 mos ↔14 mos ↔19 mos	↔3 mos ↔9 mos ↔14mos ↔19 mos				↓3 mos ↓9 mos ↓14 mos ↓19 mos	↔3 mos ↔9 mos ↔14 mos ↔19 mos
Sigurdsson, 2004 (IgG vaccinated)					↓19 mos				
Ognibene, 2005	↓7-12 mos	↑7-12 mos***							

↓=performed worse than WT

↑=performed better than WT

↔=no different than WT

Y-maze: tendency to alternate arm choice, T-maze: choice of novel arm, MWM I: escape latency, MWM II: time spent in target quadrant after platform removal, RAM: errors, RAWM I: latency, RAWM II: errors

* 6month Tg animals differed from WT on last day of testing only

** 10 mos Tg animals differed from WT on days 2 and 4, but no differences were observed on day 1

*** elevated plus maze measure of exploration of arms

TABLE 2

	WT_{SED} m=3, f=8	**TG_{SED} m=6, f=5**	**WT_{RUN} m=8, f=9**	**TG_{RUN} m=8, f=4**	**WT_{WHEEL} m=3, f=7**	**TG_{WHEEL} m=4, f=3**	**ALL WT m=14, f=24**	**ALL TG m=18, f=12**
Swim speed (meters/sec)	0.15±0.02 m=0.18±0.06 f=0.14±0.02	0.11±0.03 m=0.05±0.01 f=0.23±0.02	0.16±0.03 m=0.15+0.03 f=0.17+0.04	0.18±0.03 m=0.16±0.03 f=0.23±0.04	0.23±0.02 m=0.29±0.00 f=0.22±0.02	0.19±0.03 m=0.17±0.03 f=0.11±0.00	0.15±0.01 m=0.17±0.02 f=0.17±0.02	0.17±0.01 m=0.11±0.02 f=0.22±0.02
Visual Task (sec)	25.6±5.7 m=21±6.7 f=26.7±14	54.4±15* m=59.5+20.5 f=55.2+26.5	31.8±5.7 m=18.5+3.1 f=32.9±8.9	46.6±10 m=48.6±16.5 f=25.5±11.7	30.0±11 m=18.3±2.2 f=35±15	57.4±16 m=82±21.9 f=24.7±0.88	27.0±3.9 m=18.8±2.5 f=31.45±5.7	50.9±8* m=59.7±10.9 f=37.7±11.8

WT_{SED}= sedentary wild-type, WT_{RUN}= exercised wildtype, WT_{WHEEL}=locked wheel exposed wildtype

TG_{SED}=sedentary Tg2576, TG_{RUN}= exercised Tg2576, TG_{WHEEL}=locked wheel exposed Tg2576

ALL= grouped conditions for given genotype

* significantly different from WT