AGE-RELATED CHANGES AND COGNITIVE PERFORMANCE LEVELS IN WORKING MEMORY ACROSS THE LIFESPAN OF MALE FISCHER 344 RATS

By

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Abstract

Loss of cognitive function is a very common symptom of aging in humans. This decline has also been observed across several different rat models and these models can be used to gain an insight into cognitive decline. This study looked at how working memory changes in male Fischer 344 (F344) rats throughout their lifespan. Three age groups of young, (6mo), middle aged (15mo) and old (23mo) rats underwent the Morris water maze protocol for working memory using inter-trial intervals of 30 seconds, 30 minutes, and 2 hours. The old rats were significantly worse at performing the working memory tasks were than the young and middle-aged rats for the 30 minute ($p=0.0028$) delay, but none of the other inter-trial intervals revealed significant differences. These rats were initially tested on a reference memory water maze protocol and categorized into high performers, average performers, and low performers within each age group. These categorizations were then used to see if the level of cognitive functionality from the spatial reference memory task match the performance of the rats on the working memory task. Results show that the working memory categorization for performance level does not match the performance level categorization for reference memory. The spatial reference memory task relies on the hippocampus while the working memory task primarily relies on the prefrontal cortex. Although there are connections between these two structures that interact, the differences in level of cognitive performance between the two tasks suggests that the mental operations engaged by these tasks work independently such that impairment in one does not predict impairment in the other.

1. Introduction

There is a wealth of research and literature regarding the age related decline of cognitive capabilities. Specifically, studies have been done to explore spatial reference memory in rat that show a clear age-related decline in spatial memory[1,2]. These studies point out that memory impairments in rats starts at around 12-15mo of age and progressively worsens until 24mo of age, and this age-related decline in cognition is observed across different strains of rats. Based on these findings we ran spatial reference memory tests using the Morris swim task to categorize the rats as high performers, average performers, or low performers within their age group. Some studies have looked at cognition in aged rats that have been exposed to enriched environments and other studies have looked at effect of malnourishment on cognition and other factors[3–5]. However, cognitive differences under normal laboratory environments remains unknown. The study that comes closest to answering some of these issues is one by Gallagher et al. (1993), where they develop a learning index based on water maze trial performances for aged and young rats[6]. This study did not, however, explore differences within the age-groups. Thus, the current aim of the study is to determine how cognitive capabilities differ not only with increasing age but also within a given age group while keeping the environmental factors at play constant. The study also explores if cognitive performance on one memory task is a predictor of performance in another memory task.

The correlation between hippocampal formation and spatial memory is well established, and there are also studies establishing the critical nature of the prefrontal cortex in working memory, with the hippocampus[7–11] being important for the spatial component of the working memory task. This experiment seeks to compare performance in reference memory tasks with working memory tasks. In the reference memory task, the rat is dropped from a designated starting location and tries to find the platform by associating the proximal and distal cues in the room with the platform location. The working memory task works similarly except the platform location is different each day and there is a delay period between the first trial (information trial) and the second trial (retention trial) such that the rat must remember the platform location during the duration of the interval. Both reference memory and working memory have strong correlates to the hippocampus but working memory also has connections to extra-hippocampal regions such as the prefrontal cortex[12,13]. Thus, the behavior in this task targets both the hippocampus and the prefrontal cortex. This study utilizes three age groups of male Fischer 344 (F344) rats, 6 months (young), 15 months (middle-aged), and 23 months (aged), and tests working memory in each age group. First this experiment will determine whether working memory is impaired with age. The second portion of the experiment will elucidate if there are some rats that perform better or worse than the other rats within the same age group. Previous studies have shown that working memory deficits arise in middle age[14] and thus, we hypothesize to find that the middle-aged and the aged rats will do significantly worse than will the young rats. We use three delay intervals of 30 seconds, 30 minutes, and 2 hours. Since we are primarily using the 30 second delay interval to acclimate the rats to the working memory protocol, we do not expect to see age-related performance differences for that delay interval. However, we hypothesize that there will be an age related decline from the young to the old rats in the 30 minute and 2 hour delay intervals. While there is a decline in the aging rats’ performances at the water maze task, we still hypothesize to see high performing, average performing, and low performing rats in each age group and expect the stratification of performance in working memory task to match the stratification of performance in the reference memory task.

2. Materials and Methods

2.1 Subjects

A total of 120 male Fischer 344 (F344) rats were used for the reference memory task. An equal 40 rats in each age group. Not all rats were used in the subsequent working memory task. Rats that had debilitating conditions or those that were borderline between any two of the three performance categories, determined via the ShinyApp as described below, were excluded from continuing on in the study. A total of 95 male Fischer 344 rats were used for the working memory task; 32 young, 32 middle-aged, and 31 old. Rats were housed in a room with 12:12 hour light/dark cycles (lights on at 9:00) at 25^{o} C and rats had access to food and water *ad libitum*. Rats were given health checks and were weighed upon arrival. All animal procedures were conducted in accordance with approved institutional animal care procedures and NIH guidelines.

2.2 Apparatus

Both the reference memory and the working memory task were conducted in a water maze apparatus. The maze was a large circular tank (184 cm in diameter and 43 cm deep), that contains within it a removable escapable platform. The tank is filled with 26-28^{o} C water to a level that is ¾ inches above the platform surface that is made opaque by adding approximately 908g of white non-toxic powder paint, such that the submerged platform is not visible. The room (2.3m x 2.7m x 2.5m) consists of 4 different distal cues (geometric designs on white paper) on black curtains and 2 proximal cues consisting of a chair and a metal board. The platform was located in a different position each day for the working memory task. A black jacket made with duct tape was strapped around each rat with Coban wrap which enabled the rat to be tracked by an overhead video camera (VP114 tracking unit, HVS Image, England). If tracking was lost due to the rat going underwater, then the experimenter immediately rescued the rat with a net.

2.3 Experimental Design

First, the rats were trained on the reference memory task on the Morris water maze. The first six days involved six trials of reference memory task where the platform was submerged under water followed by a probe trial where the platform was removed and the rats swam for 60s. The next two days were the visual trials where the platform was above the water such that it was visible to them. Six trials were carried out on each day of the visual trials. The rats were then trained on a delayed-match-to-place version of the water maze (working memory task)[10,11]. Rats received 2 trials a day, an information and a retention trial, for nine consecutive days with varying inter-trial delay intervals. Three delay intervals were used: 30 seconds, 30 minutes and 2 hours. During the interval, the rats were either held in the experimenter's hands away from the water maze (30 second trial) or placed in a heat-controlled incubator away in a room separate from the water maze room. The rats were dropped off in one of seven different drop locations and they swam to one of 6 different platform locations (4 quadrants; inner and outer platform location per quadrant minus the quadrant where the rat is dropped off).The first trial of each day was the information trial where the submerged platform was placed in a novel location, different in quadrant and distance from the edge of the maze from the previous placement. After performing the information trial, the rats rested for the designated inter-trial delay interval. The submerged platform was located in the same position for the second trial (retention trial) as the information trial but the start position was different. The 30 second inter-trial interval was used for the first three days in order to acclimate the rats to the working memory procedure. On the following 6 days the inter-trial interval alternated between 30 minutes and 2 hours and each delay interval was used three times. The rats had 60 seconds to locate the platform and if they failed to do so in the allotted time, then the rats were placed on the platform for 30 seconds.

2.4 Behavioral analysis

The rat's swim path was reconstructed as a series of x-y coordinates and analyzed using ANY-maze (Wood Dale, IL). The Corrected Integrated Path Length (CIPL) was derived for each trial. Performance was calculated by subtracting the CIPL of each rat on the retention trail from the CIPL of the information trial. The path length difference was averaged across the 3 trials for each delay period, with a larger path length difference indicating better performance. This path length difference was then analyzed with one factor ANOVA to obtain variance for each data set. Rats were first categorized into cognitive performance categories of high performers, average performers, and low performers. In order to do so, the categories previously obtained from reference memory was used. These data were obtained using *ShinyApp* which compares historical performance of F344 rats in the Morris Water Maze that were run through this lab and compares those rats to the present batches of rats that were run for this study. Based on the historical database a threshold is created for high performing, average performing, and low performing (**Figure 1**). The CIPL data was used to create a residual score which was used in conjunction with the 25% and 75% cutoffs to generate the high and low performance criteria. Thus, the working memory data was sorted based on the rats' previous reference memory behavioral classification. Then the performance for each age group was analyzed with two variable T-test assuming equal variances. The ANOVA test and the T-test were also run to compare the behavioral categorization of the rats in the reference memory against the working memory. Statistical significance was calculated using the Turkey Correction with α set at 0.05.

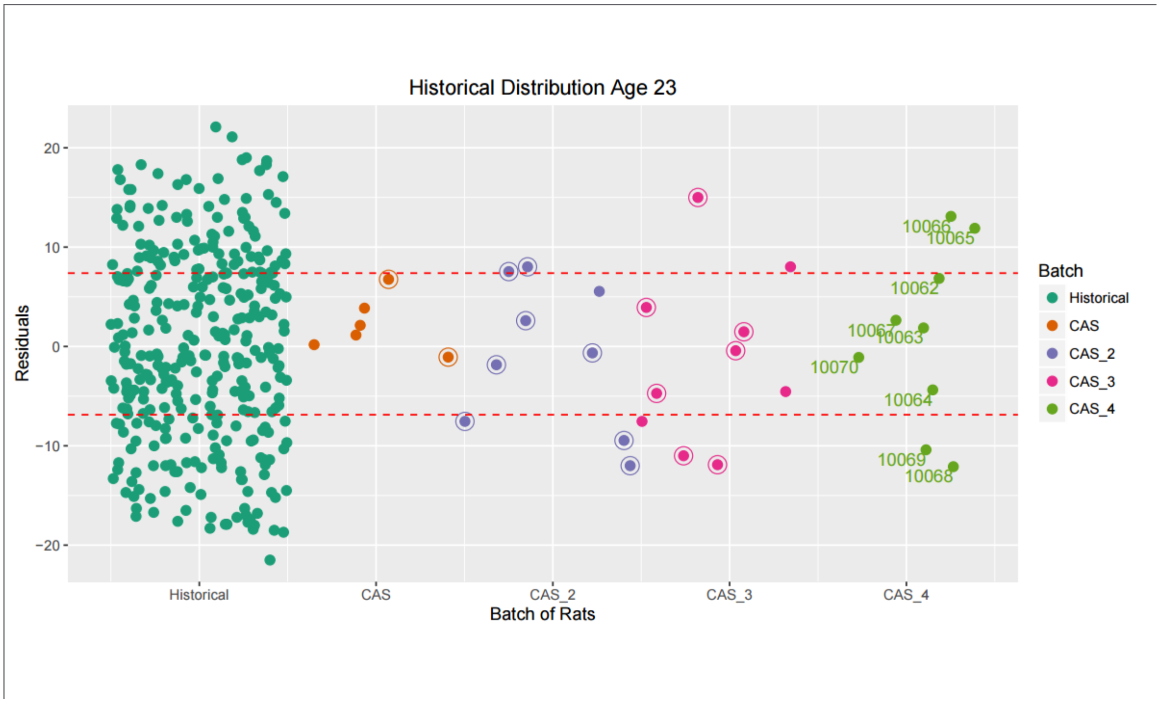


Figure 1: Results from the *ShinyApp* demonstrating the distribution of high, average, and low performing old aged F344 rats. The dark green dots (far left) represent the historical data of 23 month old rats run in the lab and all the other dots represent the different batches of rats run for this experiment. All the dots that lie above the threshold of the ~8 residuals represent poor performers and everything below the threshold of ~-6 residuals represent high performers.

3. Results

3.1 Data Points for all rats

There were several data points collected for each trial a rat went through, including the duration to find the platform, total path distance measured, as well as the mean speed of the rat. The data point of interest is the Corrected Integrated Path Length (CIPL) which measures the sum of the distances from the target at each acquired point during the trial with a correction factor to compensate for the initial distance from the goal for each starting location[15]. This value is measured for both the information trial and the retention trial. The CIPL of the retention trial was subtracted from the information trial to give the CIPL difference and then this difference was averaged for each inter-trial interval (30 seconds, 30 minutes, and 2 hours). A higher CIPL difference indicates that the rat took a long time to swim the information trial but found the platform much quicker during the retention trial. Thus, a higher CIPL difference indicates the theoretical ability of the rat to remember the platform location in between trials.

3.2 Spatial Working Memory Performance Results

After finding the average CIPL difference for each delay interval, the path length difference averages were compiled for rats in each age group. These results were then averaged to give an overall record of how each age group of rat performed at each delay interval (**Figure 1**). A single-factor ANOVA was performed for the data set with the mean CIPL differences which revealed approximately equal variances within each delay interval. Subsequently, a 2 way ANOVA test with Turkey's multiple comparisons test was run between young vs. old, young vs. middle-aged, and middle-aged vs. old, to determine which of these values were statistically significant (Table 1). Of all the T-tests done old rats performed significantly worse than did the young or the middle-aged rats at the 30 min interval (**Figure 2**). Results from the 30 second, and the 2 hour delay interval were not statistically significant and the data reflects large error bars which shows a greater variability in the data set.

Turkey's multiple comparisons test	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
30 Seconds					
Young vs. Middle-aged	1.638	-4.708 to 7.984	No	ns	> 0.9999
Young vs. Aged	4.148	-2.198 to 10.49	No	ns	0.305
Middle-aged vs. Aged	2.51	-3.837 to 8.856	No	ns	0.9314
30 Minutes					
Young vs. Middle-aged	0.1915	-6.155 to 6.538	No	ns	> 0.9999
Young vs. Aged	5.247	-1.099 to 11.59	Yes	*	0.0034
Middle-aged vs. Aged	5.789	-1.291 to 11.40	Yes	*	0.0023
2 Hours					
Young vs. Middle-aged	-3.54	-9.886 to 2.806	No	ns	0.4747
Young vs. Aged	-0.6191	-6.965 to 5.727	No	ns	> 0.9999
Middle-aged vs. Aged	2.921	-3.425 to 9.267	No	ns	0.7204

Table 1: Turkey's multiple comparisons test showing statistical significance of performance amongst different age groups of rats across the three delay intervals (30s, 30m, and 2hrs). Mean CIPL difference was used for each batch of rats and a 2 way ANOVA test was used to produce these results. None of the comparisons were significant except for the difference between aged rats and the young and middle-aged rats in the 30 minute delay interval.

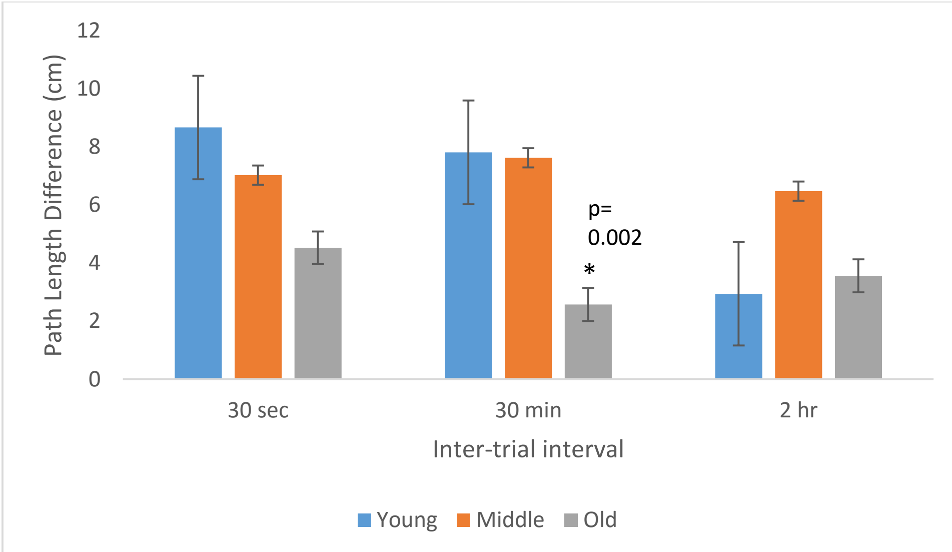


Figure 2: Working memory performances of young, middle aged, and aged male F344 rats. The colored bars show the mean path length difference (CIPL difference) calculated by subtracting the path length of the retention trial from the path length of the information trial, by age. Paired T-Test (with equal variance) showed no significant difference between groups at each delay interval. Turkey Correction of the paired T-test values indicate that the only significant result is present in the 30 min delay interval where the old rats perform much worse than the young or the old rats. There is also a slight decrease in the path length difference as the delay interval increases showing that performance decreases with increasing inter-trial interval.

3.3 Working Memory: Cognitive Categorization

Another element of this study was categorizing the F344 rats as either high performing, average performing, or low performing and determining if their behavioral performance in the reference memory task predicts their performance in the working memory task. First the data from the *ShinyApp* was used to categorize the rats based on their spatial reference memory performance. This was done using the residual scores calculated by *ShinyApp* which are based off of the CIPL on the reference memory tasks. Then the data from the working memory tasks was sorted based on their reference memory performances. The average CIPL difference was calculated within the high performers, average performers, and low performers for each age group (young, middle, and old aged) at each inter-trial interval (30 seconds, 30 minutes, 2 hours). The results from these calculations are highly variable and not significant (**Figures 3, 4**). The only result that is consistent is the average performers for each age group consistently have the worst performance with the 2 hour delay interval, but this is not statistically significant. All these rats were categorized based on the reference memory results and the data from working memory suggests that the categories of cognitive performance in reference memory task cannot be applied to predict performance on the working memory task.

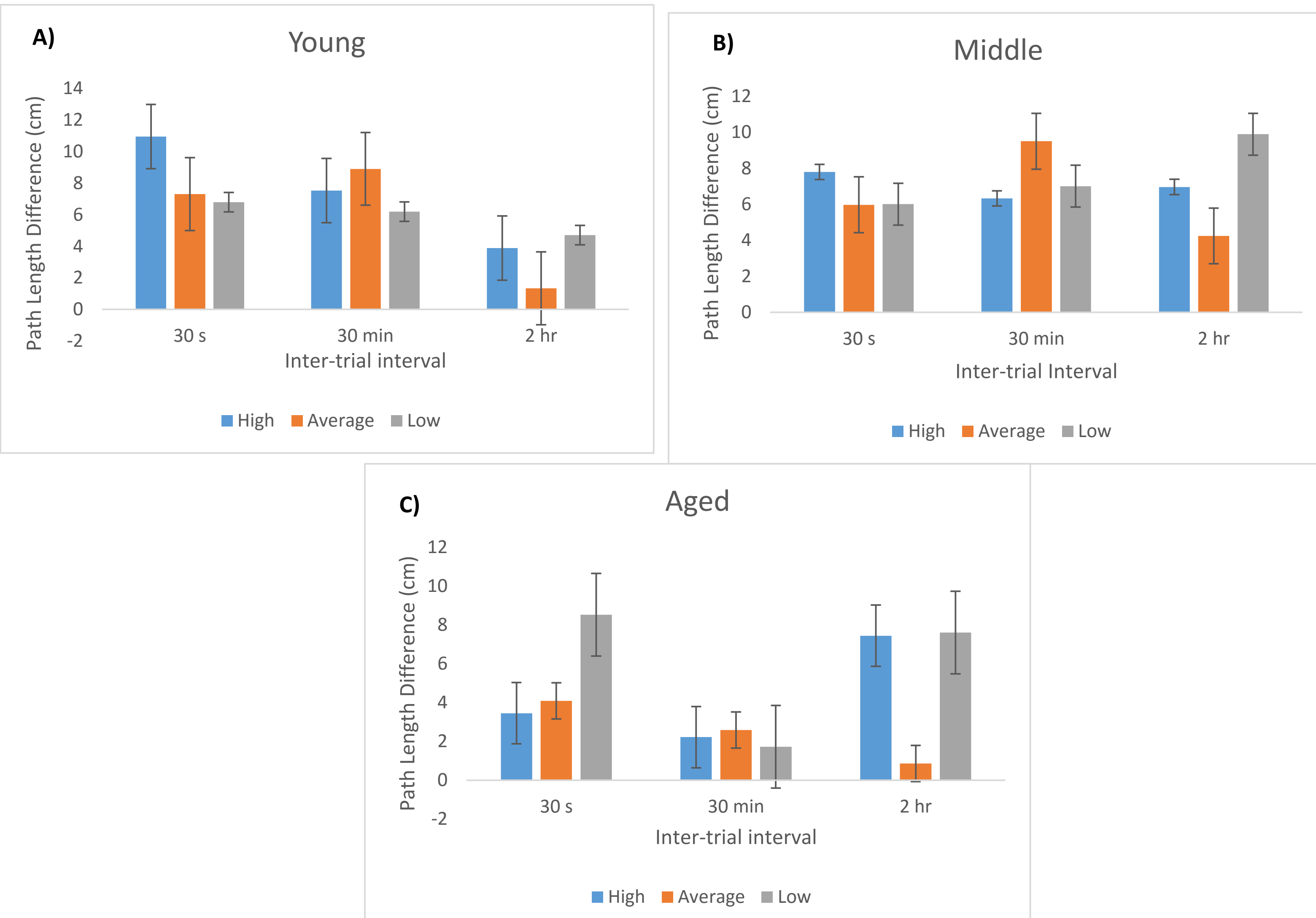
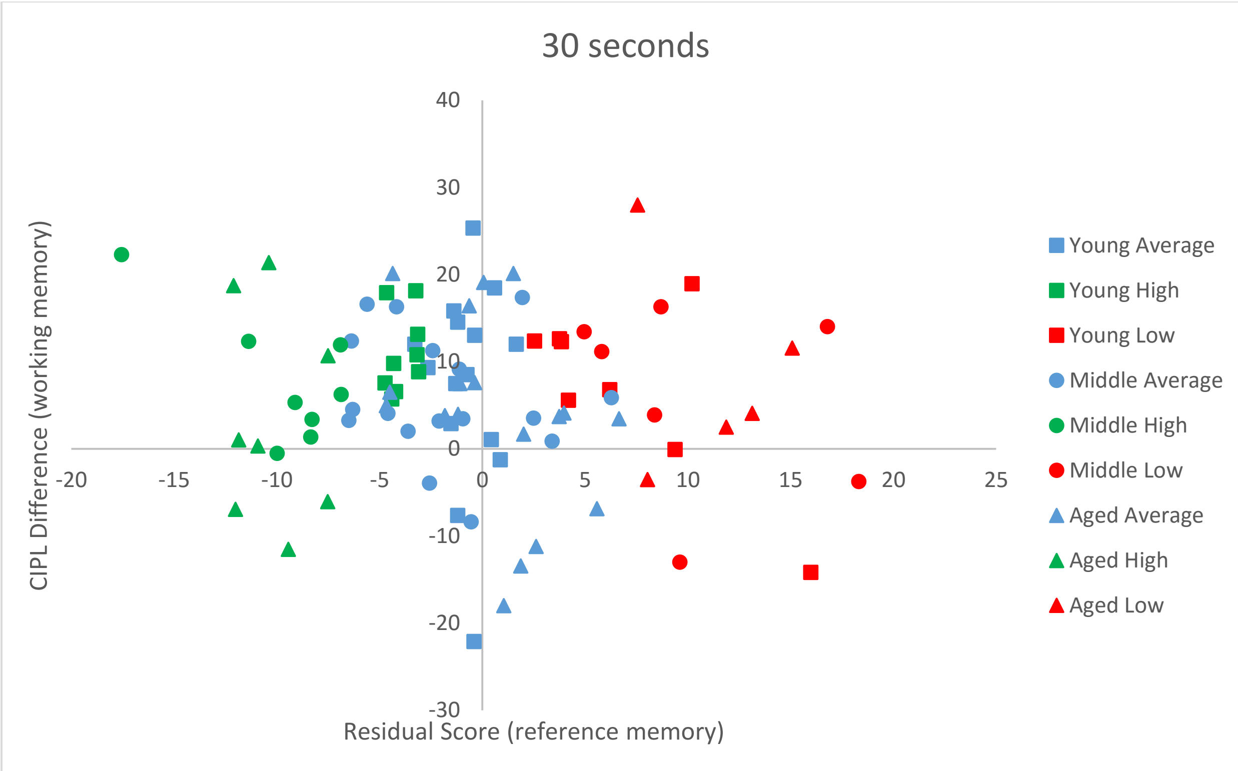
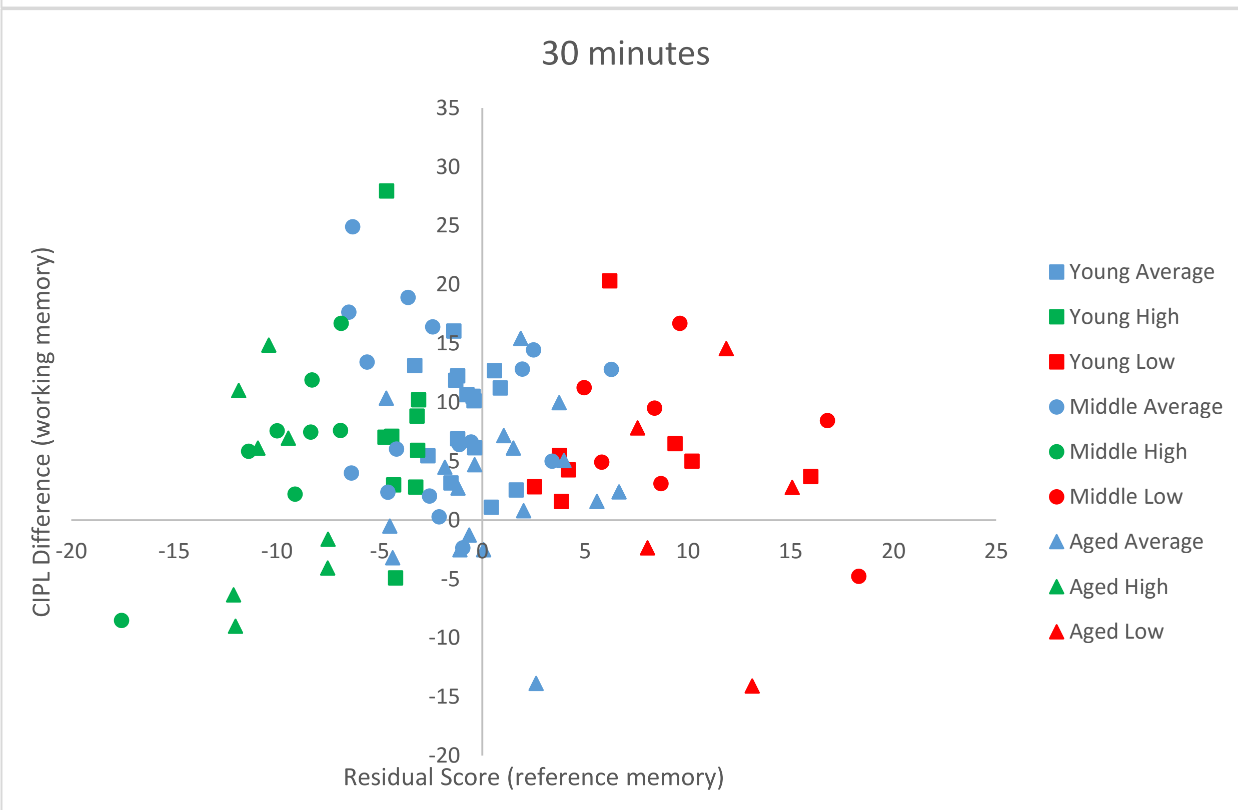


Figure 3: A) Comparison of high, average, and low performance of young rats over inter-trial interval lengths B) Comparison of high, average, and low performance middle-aged rats over various inter-trial interval lengths C) Comparison of high, average, and low performance old rats over various inter-trial interval lengths. There is large variability within each data set for each group and there are no clear trends. Two variable T-test with a Turkey Correction reveals no statistical significance between any of the data points.


30 seconds
CIPL Difference (working memory)
Residual Score (reference memory)
40
30
20
10
0
-10
-20
-30
-20
-15
-10
-5
0
5
10
15
20
25
Young Average
Young High
Young Low
Middle Average
Middle High
Middle Low
Aged Average
Aged High
Aged Low


30 minutes
CIPL Difference (working memory)
Residual Score (reference memory)
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-20
-15
-10
-5
0
5
10
15
20
25
Young Average
Young High
Young Low
Middle Average
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Middle Low
Aged Average
Aged High
Aged Low

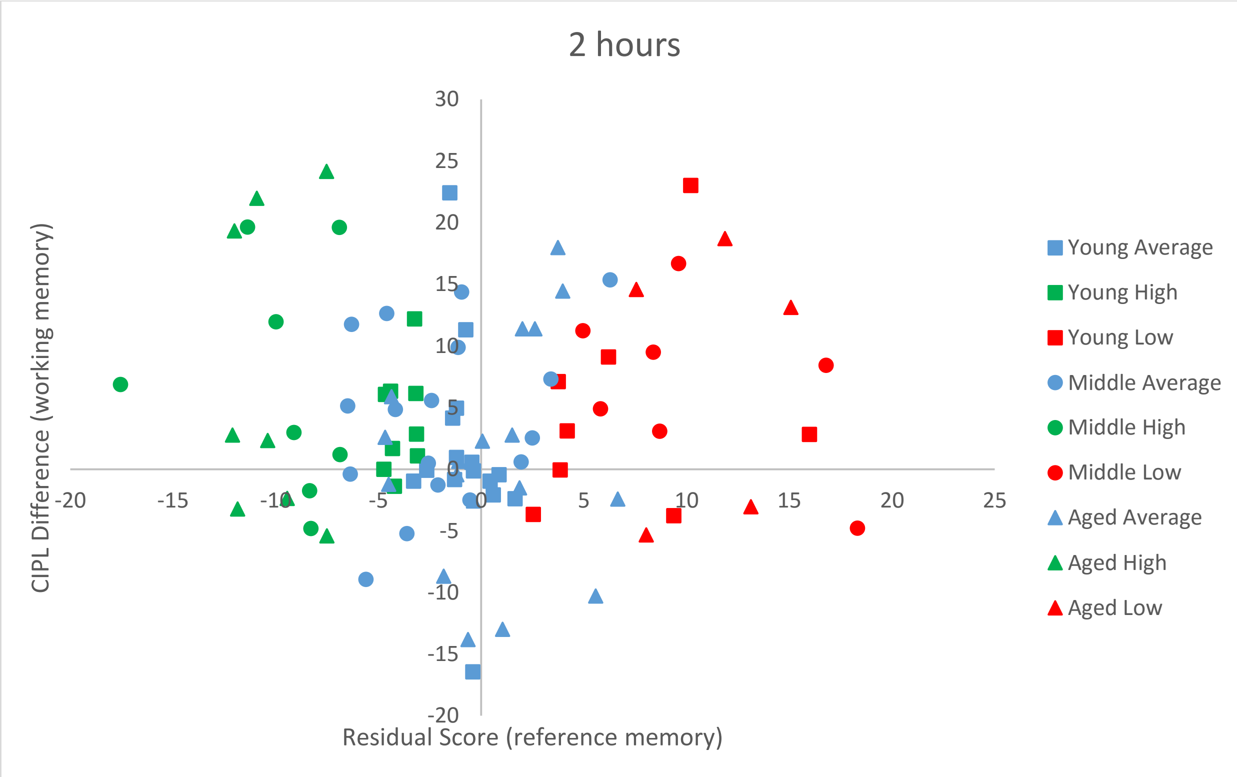

Figure 4: Relationship between cognitive performance on reference memory (residual score) and working memory (CIPL difference) tasks. A) Comparison of young, middle-aged, and aged rats based on their performance levels on the reference memory task against the CIPL difference on the 30 second delay interval for the working memory task. B) Comparison of young, middle-aged, and aged rats based on their performance levels on reference memory task against the CIPL difference on the 30 minute delay interval for the working memory task. C) Comparison of young, middle-aged, and aged rats based on their performance levels on reference memory task against the CIPL difference on the 2 hour delay interval for the working memory task. Data suggests that there is no correlation between working memory performance and reference memory performance.

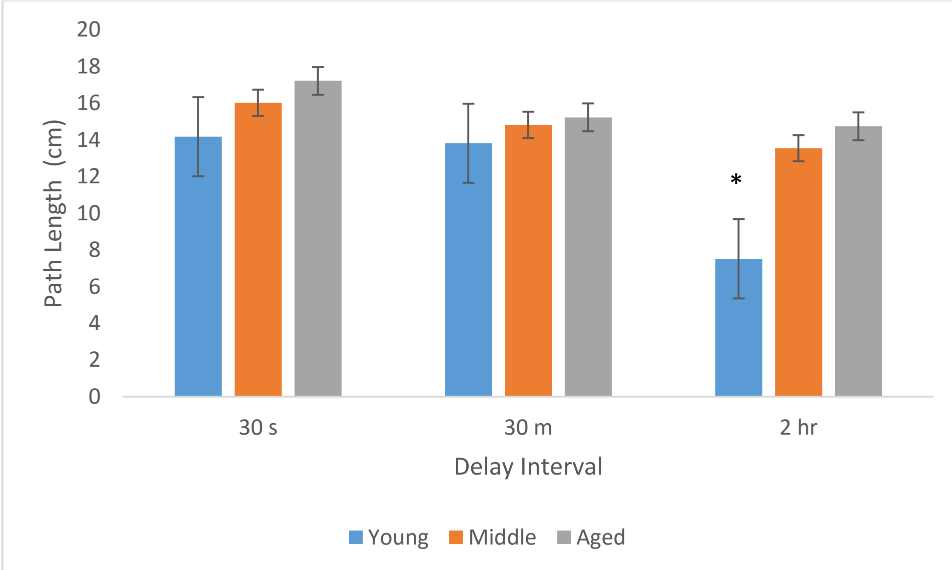

Figure 5: Information trial CIPL of young, middle-aged, and aged rats at the delay intervals of 30 seconds, 30 minutes, and 2 hours. Turkey's multiple comparisons test was used to determine statistical significance of the data which shows that the young rats are significantly better than the aged rats on the 2 hour delay interval (p=0.0278). There are no other significant differences between the age groups at the 30 second and 30 minute delay interval.

Tukey's multiple comparisons test	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
30 seconds					
Young vs. Middle-aged	-1.845	-8.368 to 4.677	No	ns	0.7647
Young vs. Aged	-3.051	-9.573 to 3.472	No	ns	0.4869
Middle-aged vs. Aged	-1.205	-7.728 to 5.317	No	ns	0.8912
30 minutes					
Young vs. Middle-aged	-0.9943	-7.517 to 5.528	No	ns	0.9245
Young vs. Aged	-1.405	-7.927 to 5.118	No	ns	0.8554
Middle-aged vs. Aged	-0.4103	-6.933 to 6.112	No	ns	0.9867
2 hours					
Young vs. Middle-aged	-6.024	-12.55 to 0.4989	No	ns	0.0745
Young vs. Aged	-7.222	-13.74 to -0.6996	Yes	*	0.0278
Middle-aged vs. Aged	-1.199	-7.721 to 5.324	No	ns	0.8923

Table 2: Turkey's multiple comparisons test showing statistical significance of performance in the information trial amongst different age groups of rats across the three delay intervals (30s, 30m, and 2hrs). Mean CIPL was used for each batch of rats and a 2 way ANOVA test was used to produce these results. None of the comparisons were significant except for the difference between aged rats and the young in the 2 hour delay interval.

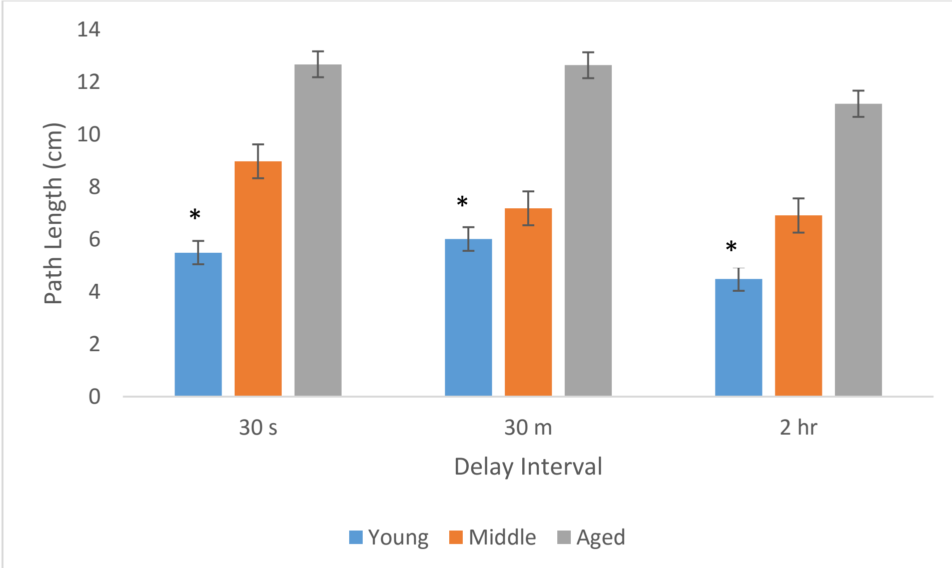

Figure 6: Retention trial CIPL of young, middle-aged, and aged rats at the delay intervals of 30 seconds, 30 minutes, and 2 hours. Turkey's multiple comparisons test was used to determine statistical significance of the data which shows that the young rats are significantly better than the aged rats on the 30 second (p=0.0245), 30 minute (p=0.0397), and 2 hour delay interval (p=0.0380).

Tukey's multiple comparisons test	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
30 seconds					
Young vs. Middle-aged	-3.485	-9.847 to 2.878	No	ns	0.3766
Young vs. Aged	-7.184	-13.55 to -0.8223	Yes	*	0.0245
Middle-aged vs. Aged	-3.700	-10.06 to 2.662	No	ns	0.3343
30 minutes					
Young vs. Middle-aged	-1.168	-7.530 to 5.194	No	ns	0.8925
Young vs. Aged	-6.635	-13.00 to -0.2727	Yes	*	0.0397
Middle-aged vs. Aged	-5.467	-11.83 to 0.8953	No	ns	0.1024
2 hours					
Young vs. Middle-aged	-2.422	-8.784 to 3.940	No	ns	0.6178
Young vs. Aged	-6.686	-13.05 to -0.3236	Yes	*	0.0380
Middle-aged vs. Aged	-4.264	-10.63 to 2.098	No	ns	0.2381

Table 4: Turkey's multiple comparisons test showing statistical significance of performance in the retention trial amongst different age groups of rats across the three delay intervals (30s, 30m, and 2hrs). Mean CIPL was used for each batch of rats and a 2 way ANOVA test was used to produce these results. In each delay interval, the young rats were significantly better at finding the platform than the old rats.

4. Discussion

It has been established that there is a clear decline in working memory performance with respect to aging and there are a number of reasons the cognitive categorizations determined via the *ShinyApp* do not correlate to performance in the working memory version of the water maze task. A study done by Bizon et al.[11] used groups of 6 month old rats, 12 month old rats, and 22 month old rats to test for working memory using the Morris water maze apparatus. They also used path length difference as a statistical marker and found that there is an age related decline in working memory performance. One factor is the duration of the delay intervals. Previously used delay intervals of 30 minutes, 2 hours, and 6 hours have found significant results for only the 2 hour and 6 hour delay trials[10]. This could explain the difference in the discrepancies with our data. Expanding the data set to include a 6 hour delay interval could show the age-related working memory deficit that is currently not present with these data, but shown in other studies.

A confound for these data could be due to the low number of rats being tested per performance category. For the young F344 rats, there were only 9 out of 32 rats that were high performers and only 8 out of the 32 rats that were low performers. The small n could be one of the reasons why the data is not statistically significant and as further rats are added to the extreme behavioral performance categories then the data might shift accordingly. As the batches of rats are added on, the data from the *ShinyApp* keeps changing as well and the thresholds for high and low performers are slightly shifted. Since this data was used to determine categories for working memory data, these results could be skewed as well.

Another reason for the data not reflecting the actual performance for the rats is due to using path length as a statistical marker. Most young rats searched inside the circular maze and found the platform by chance during the information trial as opposed to the middle-aged and older rats which usually circled the water maze until they timed out at 60 seconds. All three age groups found the platform quicker on the retention trial but since the young rats found the platform quickly on the information trial, they had less room to improve. Thus, for the latter two age groups there was a larger difference in CIPL between the information and retention trial which was reflective of a better performance even though the young F344 rats performed the same or better than their older counterparts. For the 2 hour delay interval, the young F344 rats were able to find the platform significantly quicker than the old rats in their information trial (**Figure 5, Table 2**). Similarly, **Figure 6** and **Table 3** show that the young rats were significantly better than the old rats at finding the platform at all delay intervals for the retention trial. However, when the CIPL on the retention trial is subtracted from the information trial, the young rats' better performance is masked, especially for the 2 hour delay interval (**Figure 2**). These data are further corroborated by the fact that these rats have already been pre-exposed to the water maze trials from before when they were tested for reference memory. It can be argued that the young rats remember the water maze protocol better than the middle-aged and old rats and are thereby able to find the platform faster on the information trial.

A study done by Frick et al.[10] looked at working memory for groups of 4 month, 11 month, 17 month, and 24 month old F-344 rats but used six different Place Discrimination (PD) categories in order to quantify their data. The six PD categories used are: swim time, swim distance, head angle, quadrant time, annulus-40 time, and platform crossings. The results for reference memory task showed that 24mo rats were impaired on all six PD categories compared to 4mo old rats, 17mo rats were significantly impaired on five PD categories and 11mo rats were impaired on only one PD measure. However, only 24mo rats were impaired in one PD (swim time) category for working memory. This can be attributed to the fact that the inter-trial intervals were only 10, 20, 30, or 40 seconds long. However, all the data for the six different PD categories has been recorded in this study as well or can be extrapolated from the data taken and thus, looking at factors other than CIPL difference could lead to different results for working memory.

Overall, both the Frick et al.[10] study and the Bizon et al.[11] study found variabilities amongst different age groups of rats either at long inter-trial intervals or using different statistical markers. However, these studies show great differences between the age groups for reference memory and demonstrate an age related decline in that task. This potentially suggests that the mechanism for reference memory and working memory are independent of each other. Thus, an age-related decline in reference memory is not as noticeable in working memory. This could be the reason why using the categorization of the rats into high, average, and low performers based on reference memory does not match up to the working memory data.

Experiments in other animal models have also suggested similar results. A study done in rhesus macaques tested the monkeys on two different tasks: attentional control and set shifting. Attentional control was tested using an interference task similar to the working memory task used in our experiment. The second test was an object reversal learning task which tests set shifting. The study was performed with young and aged macaque monkeys and the results revealed that levels of performance on the interference task were not correlated with levels of performance in the object reversal task which suggest that the two mental operations work independently[16].

However, if new parameters are added to the working memory tests and then the results show an age related decline similar to that of reference memory then this would show a general cognitive decline with aging in rats across brain regions. This information can then be used to elucidate why certain rats from the same age group are high performers while others are low performers despite being present in the same environmental conditions. In addition to optimizing the current behavioral procedures, molecular analyses of the brains need to be carried out to potentially find genetic markers that could explain the discrepancies in cognitive performance within each age group for both the reference memory water maze task as well as the working memory version of the water maze task.

5. References

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