Behavioral characterization of cognitive and psychiatric deficits in the Arctic mouse model of Alzheimer's Disease

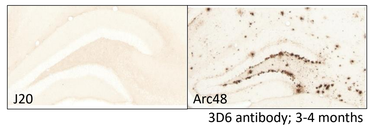
Nicole D. Schartz & Andrea J. Tenner
Department of Neurobiology and Behavior

Abstract

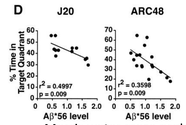
Alzheimer's Disease (AD) pathology is characterized by amyloid plaques and neurofibrillary tangles. As the disease progresses, inflammation, gliosis, and neuronal injury/loss may contribute to cognitive decline. The Arctic mouse model of AD contains the human APP transgene with three mutations (Swedish, Indiana, and Arctic) that increase the risk of AD. These mice have a higher proportion of fibrillar amyloid beta and form plaques that are detectable at 3-4 months of age (Cheng et al., 2007). Although early studies of this model reported a deficit in spatial memory and altered anxiety-like behavior at early stages in males (Cheng et al., 2007), and we recently reported a deficit in object location memory in a cohort at 10 months of age (Hernandez et al., 2017), a thorough characterization of cognitive, locomotor, and psychiatric behaviors at the advanced disease state is lacking. In the present study, we characterized the behavior of 10-month-old Arctic mice with a battery of tests to determine anxiety (EPM, OF), hippocampal-dependent memory (OLM, Contextual FC, Y-maze) and locomotion (OF) in both males and females. Our study was conducted over three cohorts to determine reproducibility and reliability of these tests. We were able to replicate previous findings that Arctic mice spend more time in open arms during EPM, indicative of reduced anxiety-like behavior, and we reliably determined that Arctic mice freeze less in a conditioned environment, suggesting a deficit in contextual memory. Interestingly, we did not reliably replicate findings that Arctic mice have a deficit in object location memory, suggesting that the deficits detected in this test may be sensitive to small changes in the kinetics of pathology including inflammation, and thus other tests may be optimal for this model. We have developed and validated a battery of behavioral tests that can now be used to determine the effects of therapeutics on cognitive and psychiatric deficits in the Arctic mouse model of AD.

Background

Arctic mice have accelerated Aβ plaque deposition in the hippocampus compared to J20 mice, and amyloid *56 levels correlate inversely with spatial memory



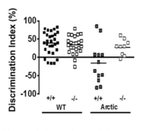
3D6 antibody; 3-4 months



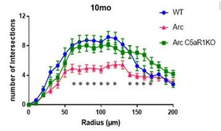
Morris water maze probe trial; 3-4 months

Cheng et al. *J. Biol. Chem 282* (2007)

We previously reported that the Arctic mice have hippocampal-dependent memory deficits, loss of hippocampal neuronal complexity, and increase in microglial inflammatory gene expression at 10 months, all of which are rescued with genetic ablation of the complement C5a receptor 1 (C5aR1 KO).



Object Location Memory



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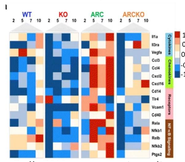


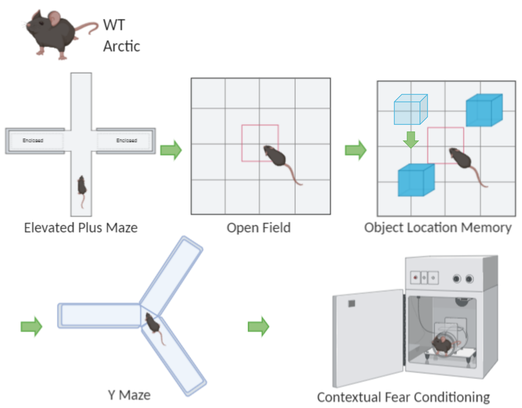
Bulk RNA-seq on microglia

Hernandez et al. *Mol Neurodegeneration 12*, 66 (2017).

Our goal is to determine the efficacy of different modes of complement inhibition or ablation in Arctic mice, but first, we thoroughly characterized the behavioral phenotype of these mice compared to WT

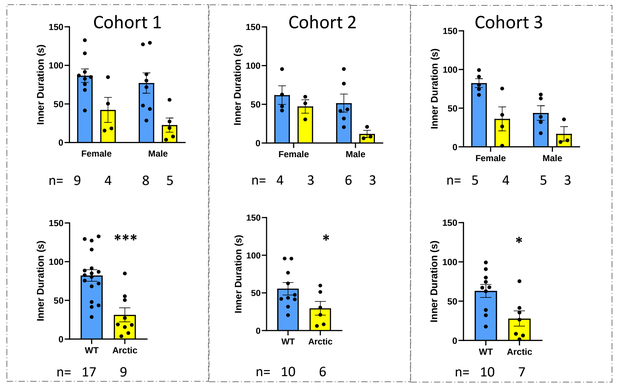
Methods

- Mice were subjected to a battery of behavioral tests over a 2-week period
- Experimenter was blinded to the genotypes during testing and scoring
- Females and males were tested concurrently at 10 months of age



- Mice were acclimated to their housing suite for at least 1 week prior to testing, and to the testing suite for 1 hour for each day of testing

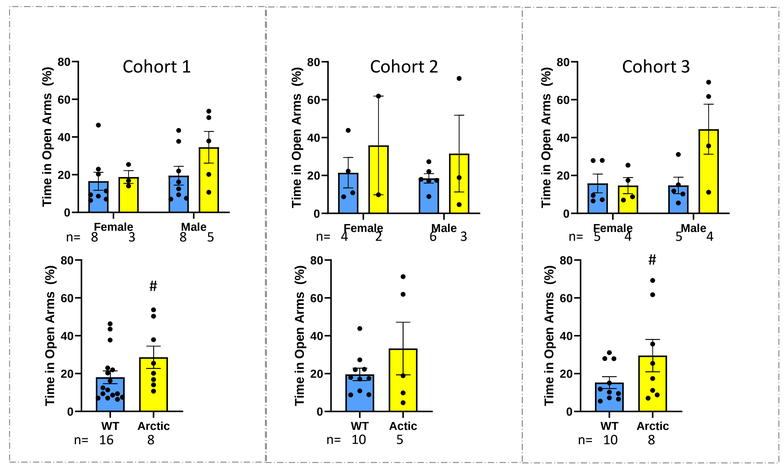
Arctic mice spend less time in the center of the open field arena compared to WT controls



Mice were recorded in the empty object location memory arena for 5 minutes
Distance travelled, velocity, and time spent in the center of the arena were measured.
Arctic mice covered less distance (cm) than WT in cohorts 1 and 3 (data not shown).
Arctic mice spent less time in the center of the arena than WT in all three testing cohorts.

Independent t-test
*, $p < 0.05$; ***, $p < 0.001$

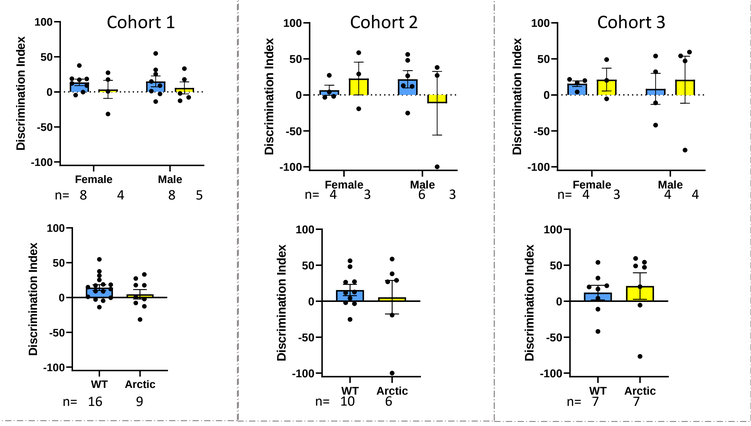
Arctic mice show a trend to spend more time in the open arms of the elevated plus maze compared to WT controls



Mice were placed in the center of the elevated plus maze and allowed to explore freely for 5 minutes.
Time spent in the open arms and time spent in the enclosed arms was calculated.
Arctic mice trended to spend more time in the open arms than WT mice.
When normalized to WT and merged, Arctic mice spent significantly more time in the open arms ($p = 0.005$)

Independent t-test
#, $p = 0.1$

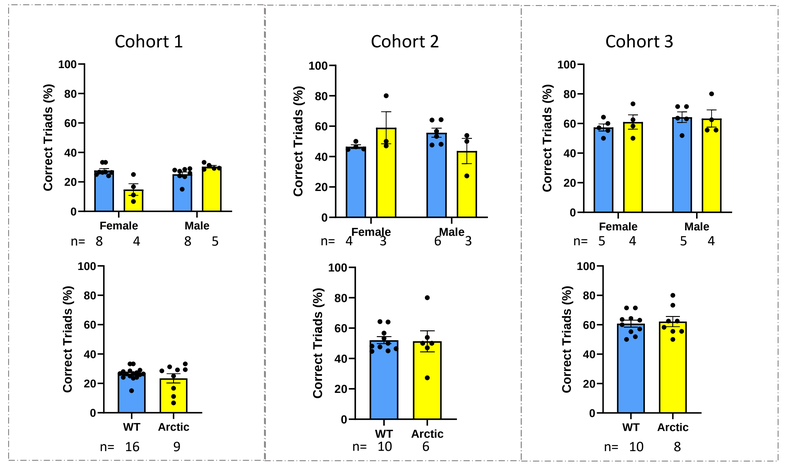
The object location memory test results in high variability in performance between cohorts



OLM training took place in 2X 10-minute sessions separated by 2 hrs wherein mice explored two objects in opposite and symmetrical locations.
24 hours after training, one of the objects was moved 90° from the original location and mice were given 5 minutes to explore
Discrimination index was calculated [(Novel-Familiar)/(Novel+Familiar)*100
Mice that explored objects for less than 2 seconds were excluded from analysis

Independent t-test

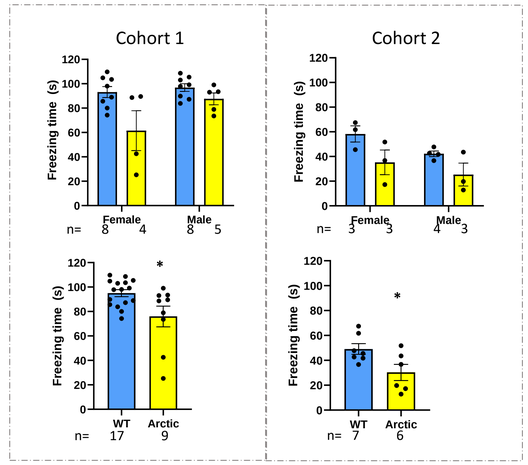
Y maze consistently revealed that Arctic mice do not have a deficit in working memory in this "spontaneous alteration" test



The Y maze is a 3-armed maze with distinct markings at the end of each arm.
Mice were given 8 minutes to freely explore each arm.
Correct triads (entering each arm consecutively) was calculated over total possible correct triads (total arm entries -2)
No differences were observed between WT and Arctic mice

Independent t-test

Arctic mice have a deficit in hippocampal-dependent contextual fear conditioning compared to WT controls



Mice were placed in a conditioning chamber for 2 minutes, then received a mild shock (0.5mA, 2 sec), and remain in the chamber for another 1.5 minutes.
After a 24-hr delay, mice are returned to the chamber for 6 minutes.
Immobility was recorded and normalized to baseline.
Data shown include freezing during first two minutes of day 2 minus first two minutes of day 1

Independent t-test
*, $p < 0.05$

Summary & Conclusions

- We observed consistent behavioral patterns between cohorts in the Elevated Plus Maze, Open Field, Y maze, and Contextual fear conditioning
- We previously reported that Arctic mice have a deficit in the OLM test (Hernandez et al. 2017). While we were able to replicate these findings in the first cohort, subsequent cohorts at the same age resulted in mixed findings
- Whereas object location memory did not produce replicable results between cohorts, contextual fear conditioning consistently revealed a hippocampal-dependent memory deficit in Arctic mice, suggesting that this test is more reliable than OLM
- With this data, we have designed a battery of behavioral tests to determine the effects of potential therapeutics on AD-associated cognitive deficits and psychiatric behaviors, including negative controls, in the Arctic mouse model of AD

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