Behaviour and Biomarker Changes in ARTE10 mice reveal Translational Potential for Alzheimer's Disease and Mood-Related Comorbidities

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INTRODUCTION

Alzheimer's disease (AD) is characterized by progressive cognitive decline and hallmark neuropathological changes including amyloid β (Aβ) plaque deposition. Patients often suffer from prodromal and co-morbid mood symptoms including anxiety and agitation which evade current therapies. The ARTE10 transgenic mouse model, which co-expresses human APP and PS1 mutations linked to familial AD, develops early and robust Aβ pathology. Previous studies have focused on cognitive changes and pathology in advanced stages of AD. Here we aimed to comprehensively characterize the ARTE10 model for prodromal and disease state behavioural phenotypes and biomarkers.

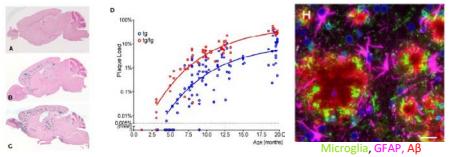


Figure 1. Amyloid load increases with age in the ARTE10 model. Homozygous mice consistently show more Aβ compared to heterozygous animals. Plaques are co-localized with GFAP and microglia. Willuweit et al. 2009.

METHODS

5-month (n=16 WT, n=13 Homozygous (HM) ARTE10) and 10-month (n=16 WT, n=16 HM ARTE10) male mice were tested. Many behavioural domains were assessed with specific assays: mood: nest building; anxiety: canopy test; hyperactivity/agitation: running wheel; sensory-motor gating: pre-pulse inhibition; cognition: Y maze and Morris Water maze (MWM). Plasma, CSF and brain samples were collected to evaluate the levels of NfL and amyloid using the MesoScale Discovery platform and then correlated to behavioural results.

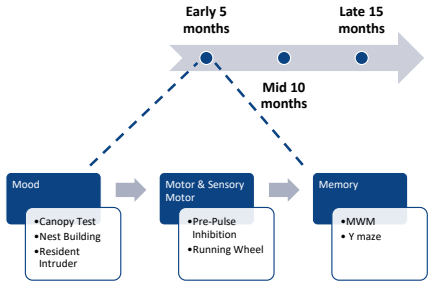
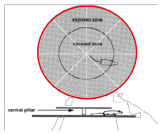


Figure 2. Experimental timeline. The full study uses a cross-sectional design.
Data presented here are only for the first 5 month and 10 months timepoints. A variety of assays were used to assess co-morbid and classical behaviours of AD.

RESULTS

IN-LIFE

ANXIETY/MOOD/AGGRESSION



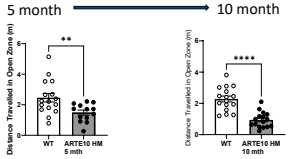


Figure 3. Canopy Test. Canopy test is used to assess anxiety-like behaviours. ARTE10s travel less in the open zone and indicates increased anxiety-like behaviours in ARTE10s. This anxiety-like behaviour becomes more pronounced with age.

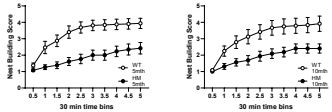


Figure 4. Nest Building (NB). NB is used to assess mood and well-being. Higher nest building scores indicate more complex nest building. ARTE10 animals take longer to reach a score of 2.5 and build less intricate nests compared to WTs at both ages.

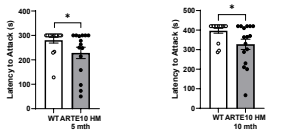


Figure 5. Resident Intruder (RI). RI is used to investigate aggression. The resident ARTE10 animals initiated attacks on the intruder mouse earlier and more often than WT controls at both ages.

SENSORY MOTOR GATING

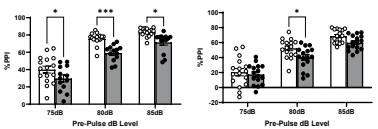


Figure 6. Pre-Pulse Inhibition (PPI). PPI is a translational test used to investigate sensory-motor gating. ARTE10 mice show PPI deficits compared to WT controls.

MOTOR Activity

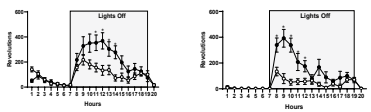
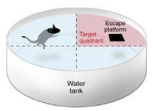


Figure 7. Running Wheel (RW). ARTE10s are naturally hyperactive during their wake period. They travel more than WTs in the running wheel at both 5 and 10 months of age.

COGNITION



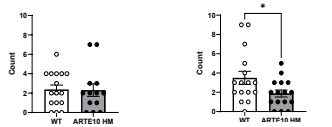
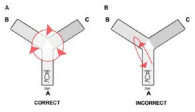


Figure 8. Morris Water Maze (MWM). Learning and spatial working memory were assessed using the MWM. Spatial working memory deficits became significant at 10 months of age.



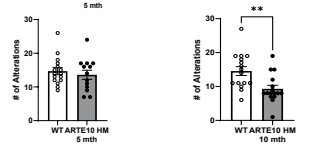


Figure 9. Y-Maze. Spatial working memory were assessed using the Y maze. Spatial working memory deficits in ARTE10 animals were only identified at 10 months of age.

BIOMARKERS

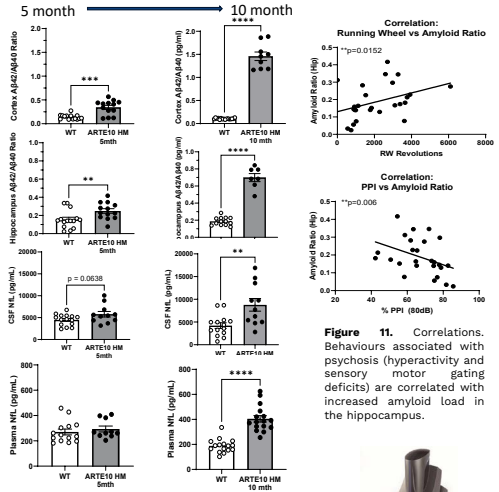


Figure 10. Aβ, NfL Levels. Aβ load was age dependently increased in the hippocampus and cortex of ARTE10s. NfL levels in CSF and Plasma also follow an age dependent increase in ARTE10's.

Figure 11. Correlations. Behaviours associated with psychosis (hyperactivity and sensory motor gating deficits) are correlated with increased amyloid load in the hippocampus.

CONCLUSIONS

- At 5 and 10 months of age, ARTE10 HM animals show signs of:
  - Increased Anxiety
  - Reduced Mood
  - Increased Aggression
  - Sensory Motor Gating Deficits
  - Hyperactivity
  - Spatial Working Memory Deficits (10m only)
- Aβ levels increase with age in ARTE10 HM mice compared to WT in the brain.
- NfL levels increase with age in both CSF and plasma in ARTE10 animals, which is a sign of neuronal damage.
- Amyloid load is correlated with hyperactivity and sensory motor deficits.
- This model is ideal for studying prodromal states, co-morbidities and age-related progressive biomarkers of AD and has significant potential for investigating efficacious therapies.

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