Thigmotaxis helps differentiate normal and pathological ageing processes in a mouse model of Alzheimer's Disease

Daniel Alveal-Mellado 1,2; Lydia Giménez-Llort 1,2
1. Institut de Neurociències, Universitat Autònoma de Barcelona, Spain; 2. Psychiatry and Forensic Medicine Dept., Universitat Autònoma de Barcelona, Spain

INTRODUCTION

- Differentiating impairments in spatial orientation caused by the early stage of Alzheimer's Disease (AD) from normal ageing process is a challenge, even in preclinical studies, due to both entities' similar magnitude of affectation [1].
- The Morris Water Maze (MWM) test evaluates spatial learning in mice; nonetheless, a more thorough analysis is required to understand the cognitive impairments associated with AD [2,3].
- In the original MWM protocol [4], animals learn to find a hidden platform in a pool for consecutive days (Place task or PT stage). Then, the platform is removed (RMV stage), and the distance travelled in the quadrant where the platform was previously located is considered an indicator of spatial retention.
- In the present work, we added a training CUE stage [5] and analysed the trajectories used to reach the platform.

AIMS

To determine the sensitivity of a swimming strategies approach for detecting differences in the spatial learning and reference memory of a group of experienced 3xTg-AD mice and their age-matched non-transgenic (NTg) counterpart in the MWM test.

METHODS

Here, 15 (C57BL/6J) and 22 3xTg-AD mice were evaluated at two-times points (12 and 16-months of age) in the MWM test, using a modified 5-days protocol by adding a training CUE stage (day 1) with a visible platform, followed by a PT (days 2-5) and RMV stage (2.5 hr. after PT). Animals performed 4 trials per day and a quantitative analysis of the mean distance covered until finding the platform was further followed by a manual multiple swim pattern identification within a single trial, using the video tracking software ANY-MAZE version 6.33.

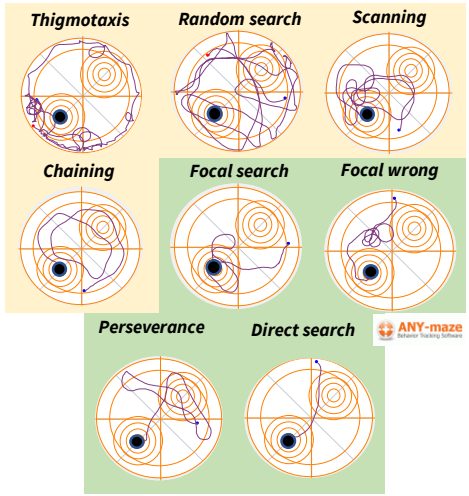

Figure 1. Sequence of swimming strategies. Patterns were classified into eight different swimming strategies [3]. Time spent on each (quantitative) and the number of episodes (qualitative) were analyzed. Furthermore, a distinction between non-hippocampus (yellow) and hippocampus-dependent search (green) was considered.

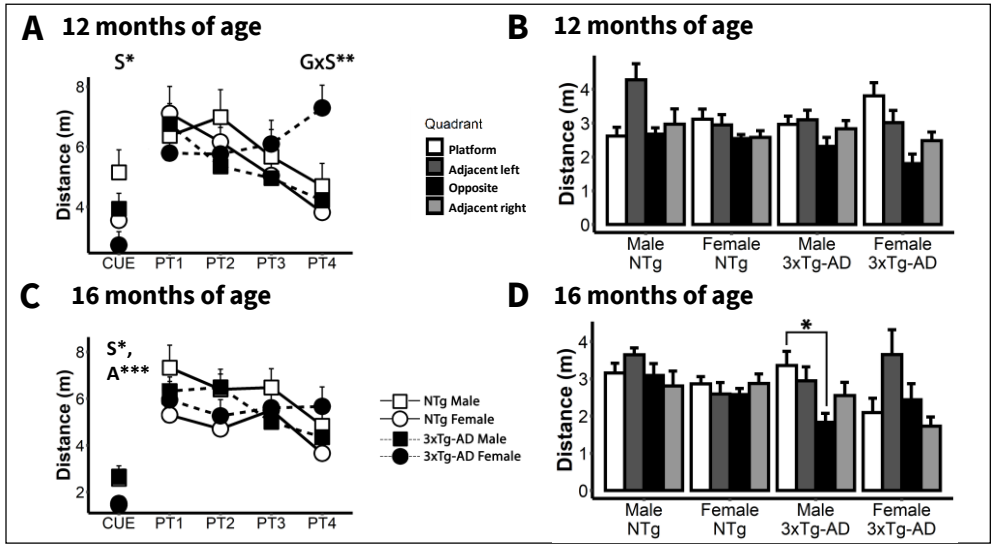

Figure 2. A and C, CUE and PT stages of the MWM test in 12-and 16-month-old mice. B and D, RMV phase of 12-and 16-months of age, respectively. Distance travelled in the quadrants respecting previous platform location was evaluated in RMV stage. Data are expressed by mean ± SEM. Mixed ANOVA 2x2x2. S, sex effect; GxS, genotype per sex interaction; A, age effect; * p<0.05; ** p< 0.01; *** p<0.001

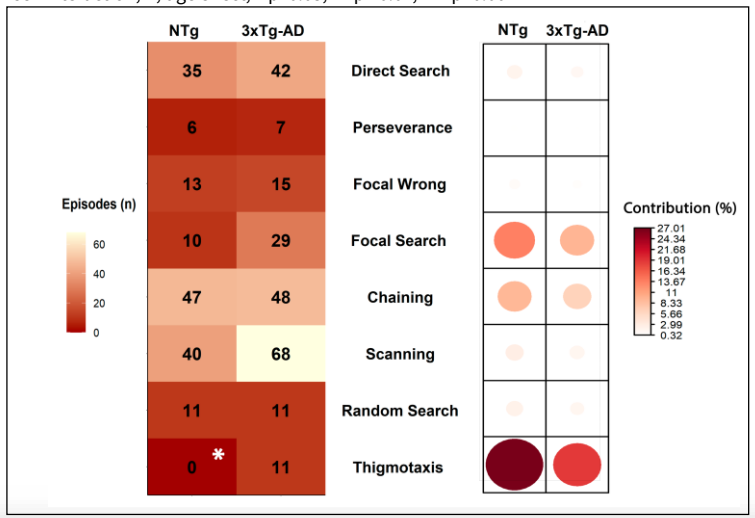

Figure 3. Frequency of episodes of each strategy at 16 months of age during the four days of PT (days 2-5) (left) and relative contribution of each strategy to the total chi-square test for independence (right). Fisher's exact test was applied as a pairwise row comparison. *p<0.05

RESULTS

In the CUE stage, when a visible flag was available, the classical parameter of distance covered until finding the platform showed that all animals learned the basic principles of the test more rapidly with a second experience (at 16 months of age) (Fig.2.A and C).

In the RMV stage, short-term memory was assessed 2.5 hr. after the last PT trial. Here, the 16-month-old 3xTg-AD male mice covered more distance in the previous platform quadrant location compared with the opposite one (Fig. 2 D). Although significance was found, a more accurate analysis is required, and preference cannot be ruled out by chance.

Persistence in thigmotaxis episodes (i.e. swimming close to walls of the pool), a non-hippocampus-associated search strategy, was found in the pathological AD-like model at 16 months of age but not in the NTg group (Fig.3).

CONCLUSIONS

Considering these preliminary results, a qualitative multiple strategies analysis within a single trial in the MWM test shows that the frequency of Thigmotaxis episodes is a valuable tool for differentiating an NTg and 3xTg-AD mouse strain despite a similar performance when quantitative parameters were analysed.

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