The Barnes Maze Test - a Dry Land Behavioral Test to Analyze Alzheimer's Disease Mouse Models for Spatial Learning Deficits

Roland Rabl*, Iera Hernandez-Unzueta*, Stephan Kurat, Estibaliz Santiago, Stefanie Flunkert, Birgit Hutter-Paier

QPS Neuropharmacology, Parkring 12, 8074 Grambach, Austria - *contributed equally

QPS helps you navigate

BACKGROUND

Alzheimer's disease is a progressive neurodegenerative disease that manifests as memory loss, cognitive dysfunction and dementia. Due to it's high prevalence several rodent models and behavioral tests are being studied. Spatial learning and memory of AD rodent models is often assessed via navigational cues in mazes such as the Barnes Maze and the Morris Water Maze. In this context, the Barnes maze is considered less stressful compared to water mazes and also useful for rodent models with minor motor deficits.

Therefore, in this study we established the Barnes Maze test to study spatial learning deficits in two different symptomatic Alzheimer's disease transgenic mouse models in order to diminish stress levels.

MATERIALS AND METHODS

Transgenic and non-transgenic mice of two different Alzheimer's disease mouse models were tested in the Barnes Maze:

- 5xFAD (male and female): 8 months old
- APP_{SL} (male) : 10 months old

Transgenic 5xFAD mice bear 3 mutations in the APP695 gene [APP K670N/M671L (Swedish), I716V (Florida), V717I (London)] as well as 2 mutations in the presenilin 1 gene [PS1 M146L, L286V] which induce amyloid β overexpression and cause a β-sheet plaque formation accompanied by strong neuroinflammation in the cortex and hippocampus resulting in spatial and long-term memory deficits. On the other hand, APP_{SL} mice overexpress the human $APP751_{SL}$ gene with Swedish and London mutations leading to an accumulation of amyloid β peptide in the frontal cortex causing cognitive deficits.

The Barnes Maze consists of an elevated circular platform with 18 holes located around the edge by which mice try to escape due to the bright lightning and the open space. One of the holes contains an escape box underneath that animals have to find and remember by prominent 3D-landmarks surrounding the maze.

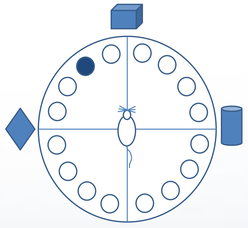
One hour prior to testing, animals are brought to the Barnes Maze testing room for acclimatization. Then, the animals are placed on the center of the maze and are free to move for 120 seconds or until they reach the escape box. A computerized video tracking system (Noldus Ethovision XT) is used for recording.

Animals were trained for four days, performing the test four times each day with an interval of 10 minutes between each trial.

A probe trial was carried out on the fifth day. Mice were placed on the maze for 120 seconds but without the escape box.

The following parameters were evaluated:

- Latency to the first contact with the target hole
- Duration on the maze
- Velocity
- Distance (data not shown)
- Number of target visits (Probe trial)



RESULTS

Transgenic 5xFAD mice showed a significantly higher latency to find the escape box on the first two days of training (Fig. 1A) and higher duration on days 1, 2 and 4 (Fig. 1B), whereas the velocity was not affected by the genotype (Fig. 1C). On day 1, latency (Fig. 1D) and duration (Fig. 1E) decrease between trials was greater in the non transgenic animals than in the transgenic mice. A significant increase of the latency (Fig. 1F) and decrease of the percentage of target entries (Fig. 1G) was also observed in transgenic 5xFAD mice during the probe trial compared to non-transgenic mice.

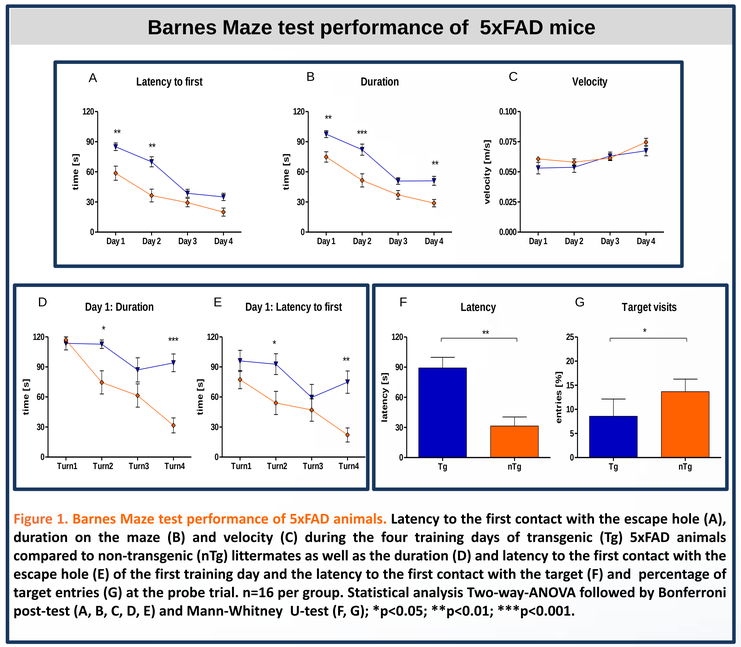


Figure 1. Barnes Maze test performance of 5xFAD animals. **Latency to the first contact with the escape hole (A), duration on the maze (B) and velocity (C) during the four training days of transgenic (Tg) 5xFAD animals compared to non-transgenic (nTg) littermates as well as the duration (D) and latency to the first contact with the escape hole (E) of the first training day and the latency to the first contact with the target (F) and percentage of target entries (G) at the probe trial. n=16 per group. Statistical analysis Two-way-ANOVA followed by Bonferroni post-test (A, B, C, D, E) and Mann-Whitney U-test (F, G); *p<0.05; **p<0.01; ***p<0.001.**

Transgenic APP_{SL} mice did not show any significant differences during the 4-day-trial performance in the latency to find the escape hole (Fig. 2A), duration on the maze (Fig. 2B) and velocity (Fig. 2C) compared to non-transgenic animals. However, on the first training day, significantly higher latency values were observed in transgenic mice (Fig. 2D) and the duration on the maze decreased much more in non transgenic animals than in the transgenic (Fig. 2E). During the probe trial, latency and the percentage of target entries was also not significant but a slight increase in the latency of transgenic mice (Fig. 2F) could be observed as well as a decrease of the target entries (Fig. 2G).

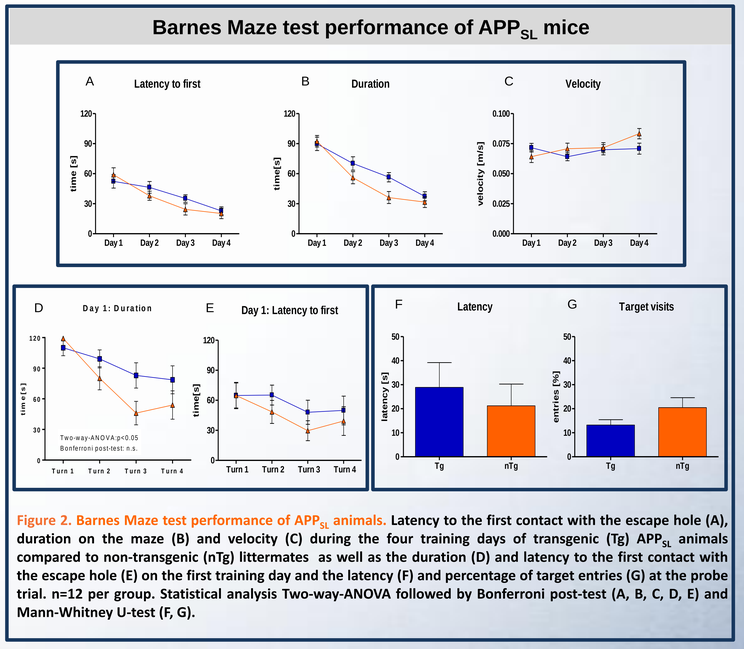


Figure 2. Barnes Maze test performance of APP_{SL} animals. **Latency to the first contact with the escape hole (A), duration on the maze (B) and velocity (C) during the four training days of transgenic (Tg) APP_{SL} animals compared to non-transgenic (nTg) littermates as well as the duration (D) and latency to the first contact with the escape hole (E) on the first training day and the latency (F) and percentage of target entries (G) at the probe trial. n=12 per group. Statistical analysis Two-way-ANOVA followed by Bonferroni post-test (A, B, C, D, E) and Mann-Whitney U-test (F, G).**

SUMMARY

Transgenic 5xFAD mice show spatial learning deficits but no differences in motor performance during the Barnes Maze test. The transgenic APP_{SL} mice also show a trend towards spatial memory impairment reaching significance on day one reflected by a steeper learning curve and increased latency during the probe trial. Since APP_{SL} do show strong learning deficits in the Morris water maze at the analyzed age (Loeffler et al., 2013) it is likely, that the stress levels caused by the two mazes affects the learning performance of the mice.

As a conclusion, the Barnes Maze test is a suitable tool to characterize the 5xFAD and to a lesser extend APP_{SL} mice of Alzheimer's disease without having the animals exposed to a further stressful environment.

Meet QPS at AAIC 2018 Booth #717

Contact: Roland Rabl | Preclinical Research Associate | QPS Austria GmbH | Parkring 12 | 8074 Grambach | Austria | roland.rabl@qps.com | www.qpsneuro.com