

Mice with Alzheimer's disease (APP.V717I) learn in social context

A. Kiryk¹, R. Filipkowski¹, M. Wawrzyniak¹, V. Liudyno¹, E. Knapska¹, T. Gorkiewicz¹, M. Balcerzyk¹, F. Van Leuven², L. Kaczmarek¹

¹Nencki Institute, Warsaw, Poland, ²Department of Human Genetics, KULeuven, Leuven, Belgium



Abstract

Social learning is an adaptive behavior allowing animals to acquire information from others. We report a novel experimental model of social transmission, using the IntelliCage to house a group of mice and execute place learning. Transgenic mice, carrying the mutant human V717I of the amyloid precursor protein were impaired in this test, only when deprived possibility to learn from wild-type littermates. Surprisingly, we observed an advantageous effect of housing the demented mice with wild-type ones on learning the spatial location of reward. In control experiments, in order to confirm the AD-related pathology, we tested the APP.V717I mice in the Morris water maze and found them impaired in spatial learning. Furthermore, in the brains of old transgenic mice we found diffuse and neuritic plaques. We conclude that learning in social context alleviates deficits in mouse model of Alzheimer's disease.

- **APP.V717I mice** harbor a mutated form of APP695[V717I] under control of mouse *thy1*-gene promoter.
- Transgene expression is limited to the central nervous system after birth, mainly in the second and third week of life.
- Transgenic mice are well characterized behaviorally and histologically:
 - ✓ Early clinical impairments (3-9 months):
 - increased aggression (Moechars *et al.*, Neuroreport 1998)
 - neophobia, decreased LTP, excitotoxicity (Dewachter *et al.*, Exp Geront 2000)
 - disturbances in learning and memory (Moechars *et al.*, Neuroscience 1999; Moechars *et al.*, J Biol Chem 1999)
 - ✓ Late (12-15 months) amyloidopathy:
 - diffuse and neuritic plaques and the vascular amyloid deposits comparable to the diagnostic post-mortem pathology in the brain of Alzheimer's patients (Van Dorpe *et al.*, Am J Path 2000).

Behavioral testing

Three groups of APP.V717I mice and their non-transgenic siblings at different ages were used:

Young

5-month old (WT = 12, APP.V717I = 11)

Middle-aged

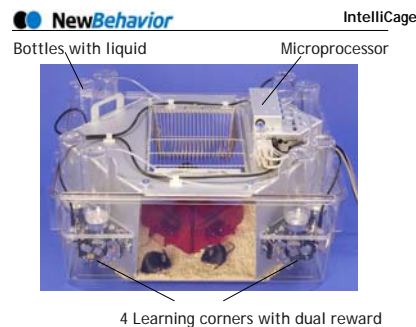
12-month old (WT = 12, APP.V717I = 12)

Old

18-month old (WT = 10, APP.V717I = 10)

Conclusions

1. The results obtained in the Morris Water Maze and IntelliCage tests demonstrated cognition impairment already early in life of APP.V717I mice compared to their wild-type littermates.
2. Surprisingly, when mixed with their wild-type siblings, APP.V717I mice were able to fulfill the same tasks in the IntelliCage. Transgenic mice effectively observe and acquire needed information about the availability and location of the appetitive stimulus from their WT cage-mates.
3. IntelliCage can be used as a novel experimental model of social transmission of information in mice.



RESULTS

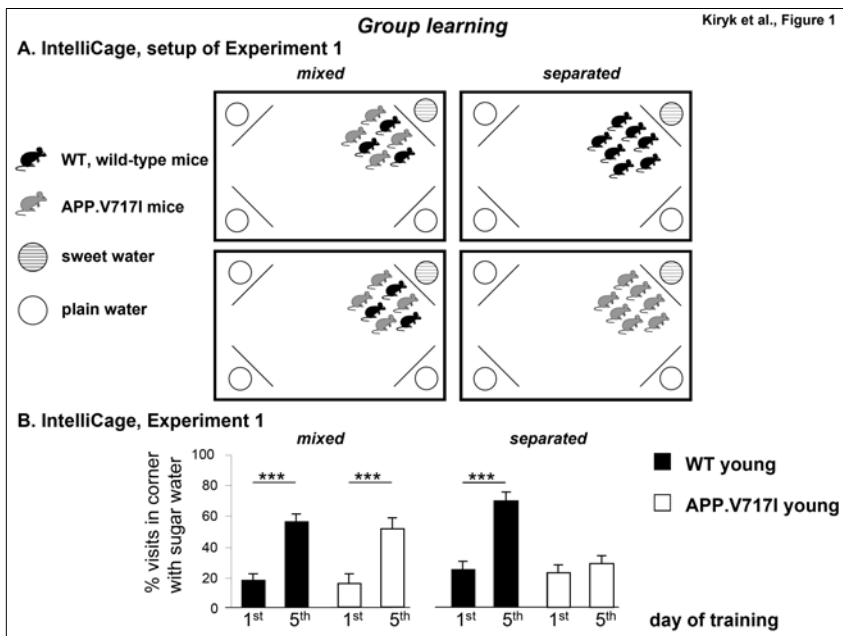


Figure 1. Group learning. **A.** Place learning experiments in the IntelliCage. At first mice were housed in mixed groups according to their genotype (WT – black; APP.V717I – grey) and coped with the same task (*mixed*). Groups of mice had access to sugar water (hatched circles) in 1 corner and to plain water (open circles) in 3 corners of each cage. Then, the mice were separated in new cages and tested in the same task as before (*separated*). **B.** The example of results of young mice: WT group developed a strong preference for the corner with sugar water during the 5th day of training both when they were mixed and separated (black bars). Transgenic mice (empty bars) were able to acquire the information about the sugar water location when housed with WT mice (*mixed*) but not when housed by themselves (*separated*). Results are presented as a ratio of visit in the rewarded corner to visits to all corners.

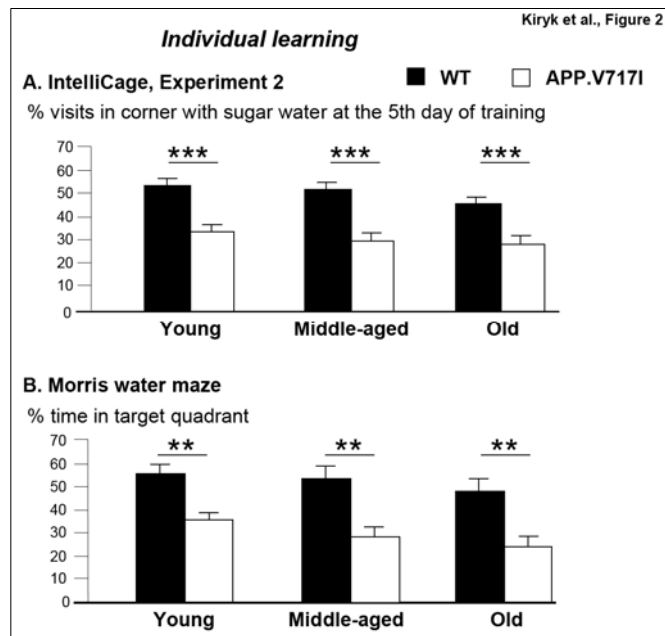


Figure 2. Individual learning in the IntelliCage system and the Morris water maze. **A.** In IntelliCage system, mice were assigned to corners individually and each mouse had an access to one corner with sugar water with no access to other corners with plain water available from the top of the cage. Place learning was evaluated as a preference for visiting the rewarded corner on the 1st and the 5th day of learning. Compared with WT mice (black bars), APP.V717I mice (empty bars) achieved a lower number of correct responses. The graph shows the percentage of visits to the rewarded corner. **B.** In the Morris water maze, the time spent searching for the platform in the target quadrant during the probe trial was analyzed. Mice from WT groups, displayed much more selective memory when probed 24 hours after training.