

Early spontaneous behavioural signs of Alzheimer's and Huntington's Disease in transgenic mouse models in a home cage situation

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Introduction

Behavioural studies on mouse models for human neurodegenerative diseases such as Alzheimer's disease (AD) and Huntington's disease (HD) are frequently conducted by using test batteries. The specifically evoked and separately studied responses may be confounded by stress, transportation, novelty, handling caused by human interference. Reduction of those confounding effects is very important for both the characterisation of **early behavioural signs** as well as for testing drugs aimed at slowing down or stopping the progression of neurodegeneration. This can be achieved by observing and testing animals in their home cage.

Aim

The main objective of this work is to detect early behavioural signs in R6/2 mice (HD-model), APP85SwePS1dE9 mice (AD-model) and 3xTg-AD (AD-model) by using a fully automated home cage environment.

Methods

Mice were singly housed in a home cage (PhenoTyper®, Noldus Information Technology, Wageningen, The Netherlands) for several weeks. Mice were subjected to a fully automatic operant conditioning task within the home cage. Behaviour was continuously monitored using EthoVision® XT (Noldus Information Technology, Wageningen, The Netherlands). More detailed analysis was carried out using MatLab (MathWorks, Natick, Massachusetts, USA). For a better characterisation of mouse locomotor behaviour, a velocity profile (see figure 1) was calculated (modified after Draai et al, 2001). This allowed us to make a better distinction between periods mice were moving slowly (lingering) and faster (progressing).

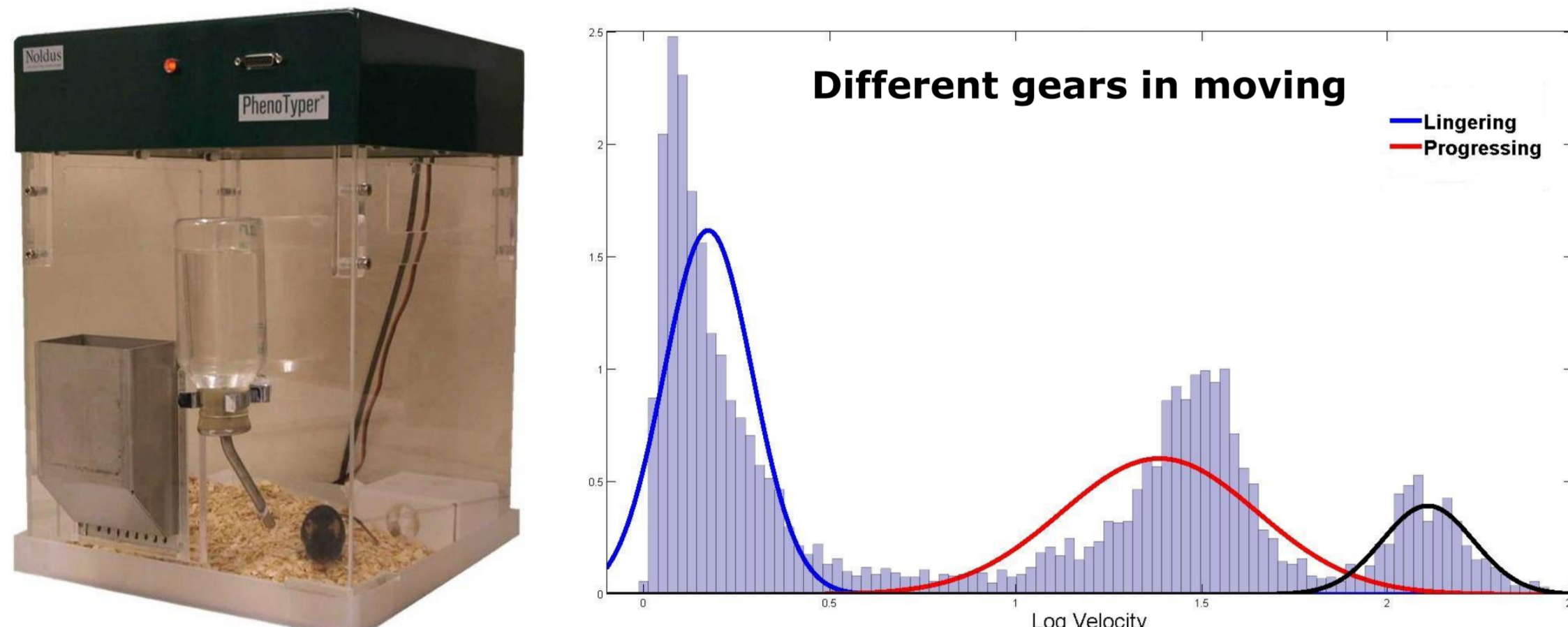


Figure 1. On the left the PhenoTyper cage, on the right an example of the velocity profile of a mouse. Lingering, Progressing and a third curve of very high velocities are clearly separated.

Results

At the age of 4 months, female APP85SwePS1dE9-mice showed an increase in locomotion activity (figure 2). This was neither found in male mice of the same strain nor in the 3xTg-AD strain.

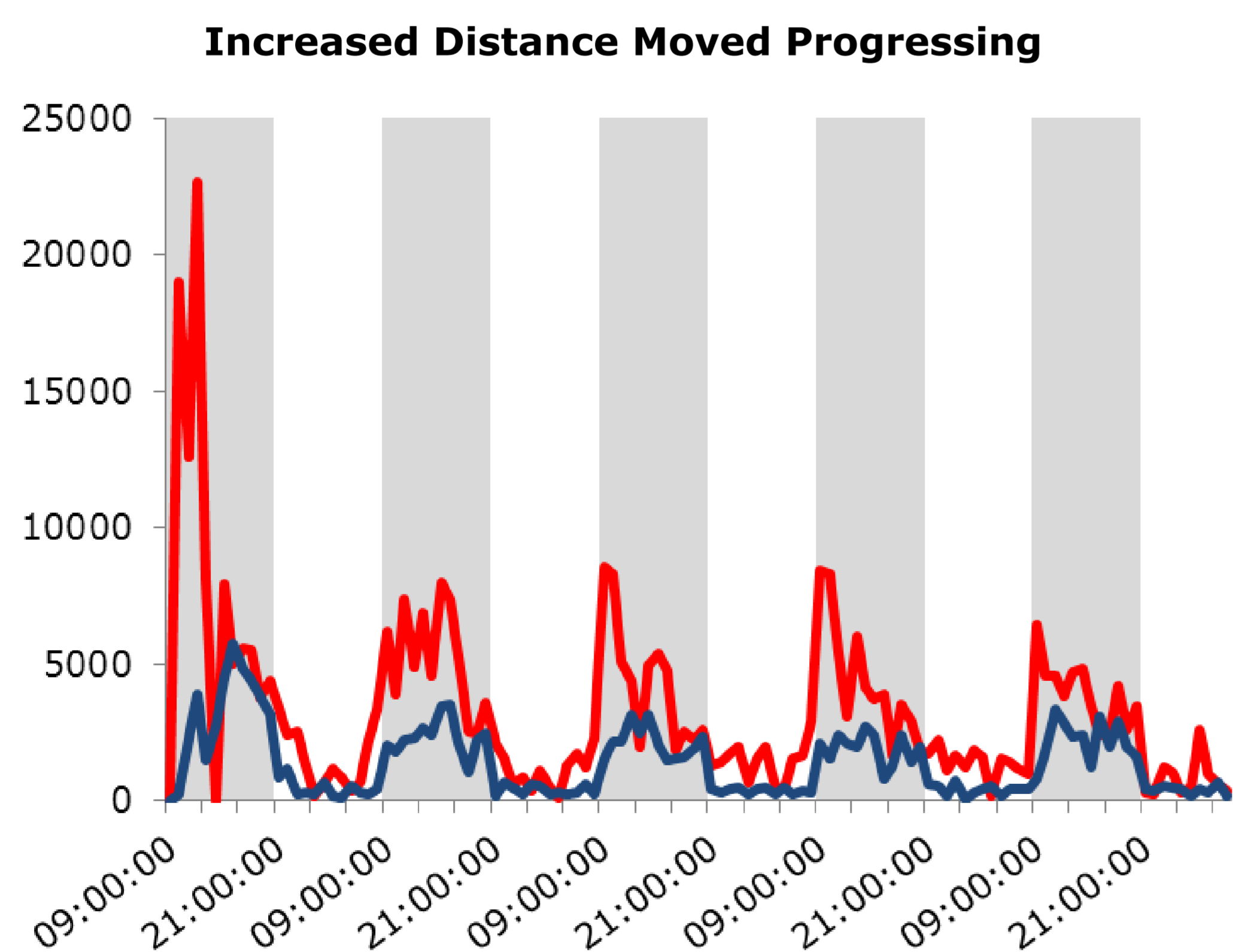


Figure 2. Locomotion activity in 4 months old female APP85SwePS1dE9-mice. Data of transgenic mice is shown in red; the blue line indicates WT littermates.

Alzheimer's disease

Alzheimer's: diminished cognitive performance

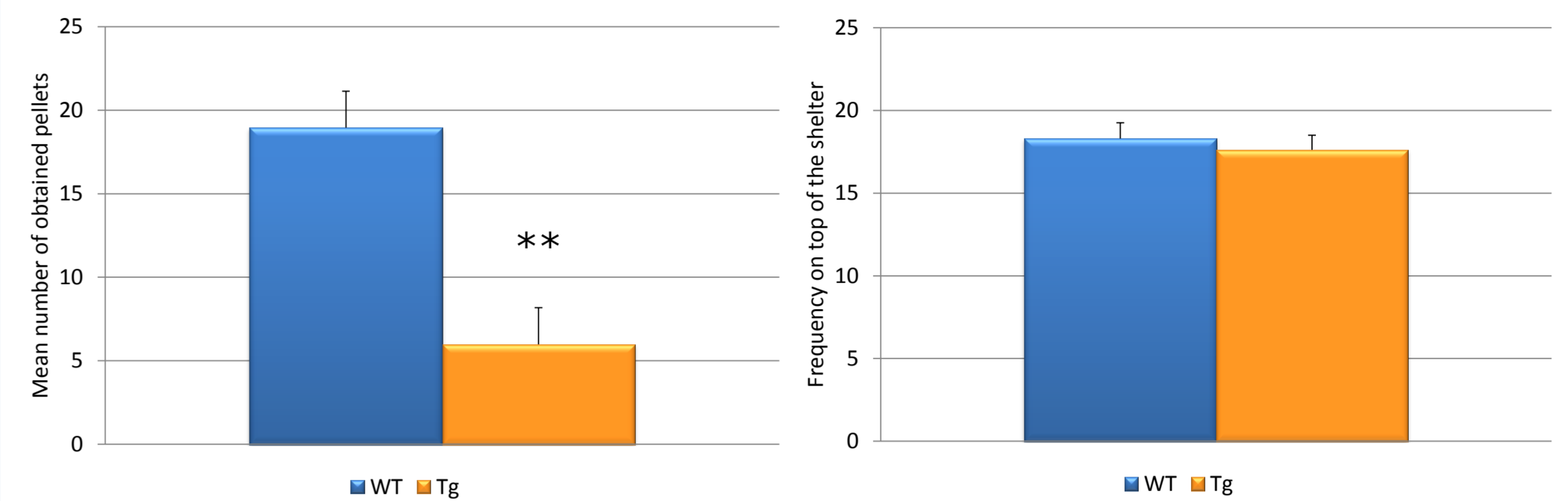


Figure 3. Mice could obtain sucrose pellets by going on top of the shelter after collecting the previously dropped pellet. On the right the number of obtained pellets per session is shown (** $p < 0.001$); on the right the frequency mice went on top of the shelter. Data is represented as mean \pm SEM.

Female transgenic APP85SwePS1dE9-mice showed a significant decrease in the performance on the operant conditioning task, but the frequency on top of the shelter did not differ compared to WT littermates (figure 3).

R6/2-mice did not show indications of cognitive deficits, but a reduced level of activity was already seen at the age of 4 weeks. This is seen both in the time they spent inside the shelter (figure 4, left) and on top of the shelter (figure 4, right).

Huntington's disease

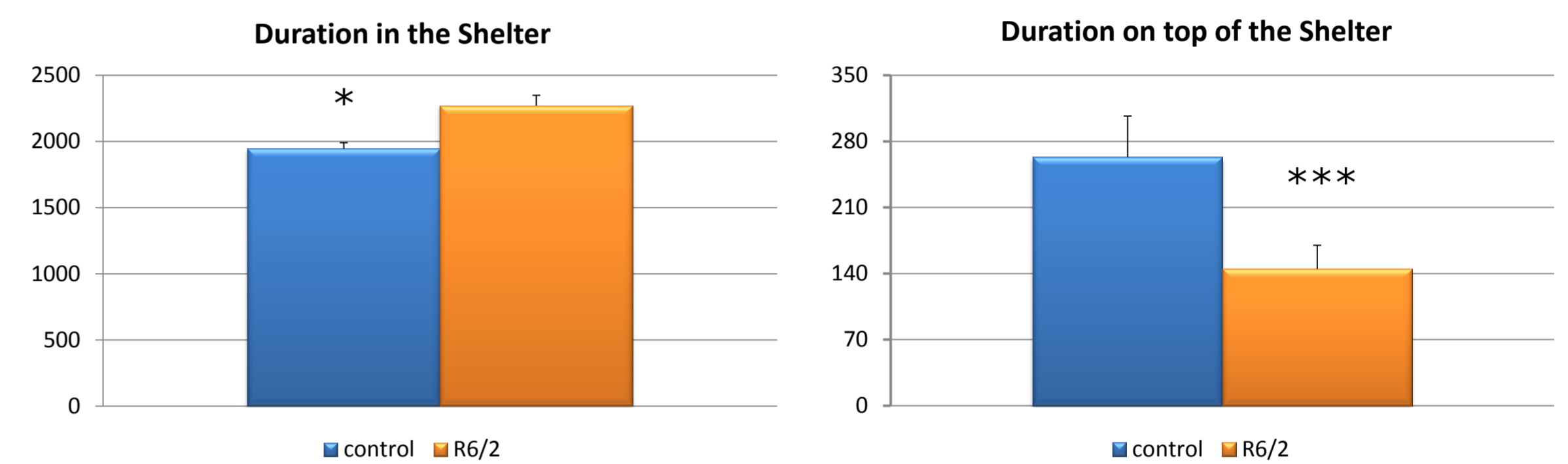


Figure 4. Both the duration in the shelter and on top of the shelter show a early clear difference in the behaviour of the R6/2 when compared to their wild type littermates. Asterisks indicate significant differences between wild-type control R6/2 transgenic mice (* $p < 0.05$, *** $p < 0.0001$). Data are represented as mean \pm SEM

Analysis of the activity level by looking at the distance moved confirmed the found indications of hypoactivity. However, as shown in figure 5, only by differentiating between lingering and progressing it is possible to see a significant difference in the spontaneous locomotor behaviour of R6/2.

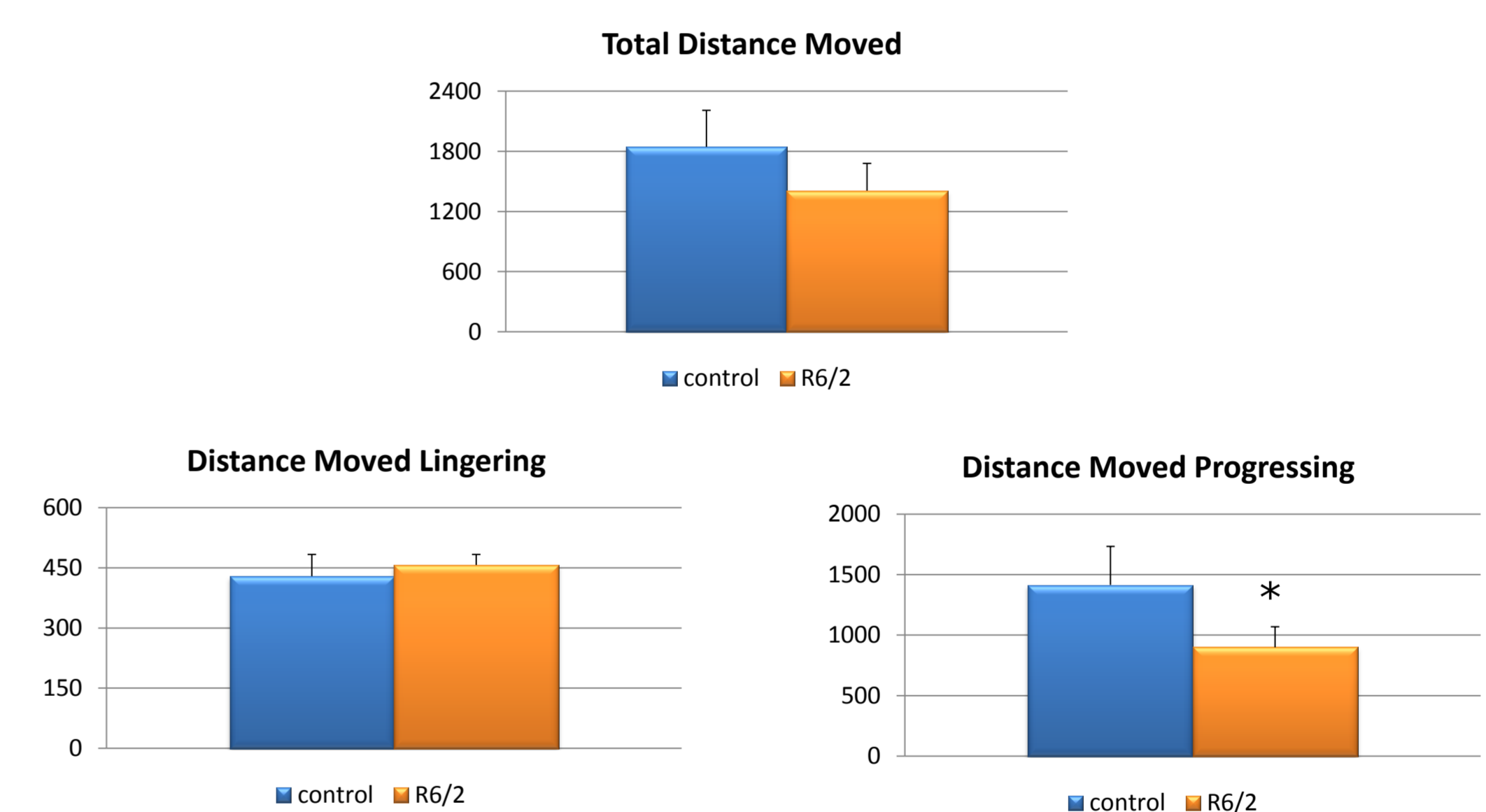


Figure 5. A significant difference in the distance moved by the mice is only visible while the mice are progressing. Asterisks indicate significant differences between wild-type control and R6/2 transgenic mice (* $p < 0.05$). Data are represented as mean \pm SEM

Conclusion

- In our approach behavioural signs of hypo-activity in the HD-model R6/2 are **already** evident at the age of **4 weeks**, whereas in **traditional test** first signs are not detected before mice are **6 weeks old**. We have not found indications of cognitive deficits in R6/2.
- In the tested mouse models for AD, transgenic females of the APP85SwePS1dE9-strain showed an **increase** in locomotion **activity** at the age of 4 months. Furthermore, a **decline** in **cognitive** performance was found when the mice were 5 months old.
- In a set-up in which activity and cognition (and more) are measured effects on cognition can be independently assessed.
- Our latest development establishing a velocity profile in order to make a distinction in lingering and progressing has resulted into a significance difference on a class of moving.
- The early characteristics found can be used for testing the efficacy of therapeutic treatments in an early phase of the disease when neuroprotective strategies may lead to slow or even stop the progression of the neurodegeneration caused by HD and/or AD.

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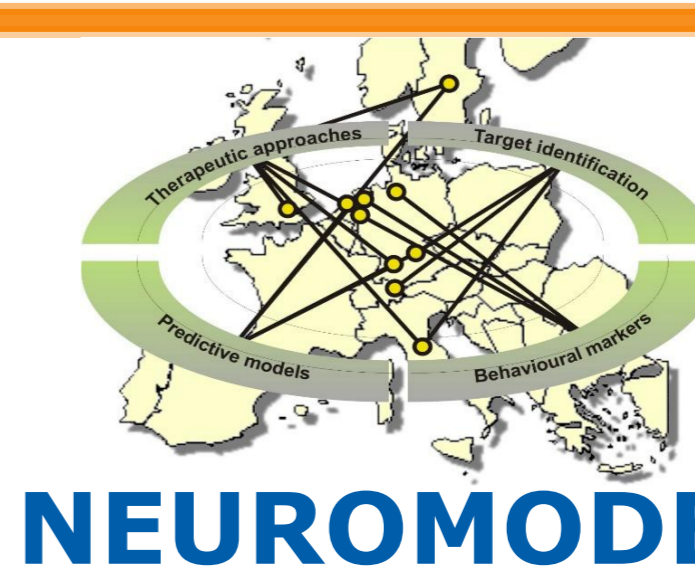
References

Mangiarini L, Santhasivam K, Seller M, Cozens B, Harper A, Hertherington C, Lawton M, Trotter Y, Lehrach H, Davies SW, Bates GP "Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice." *Cell*. 1996 Nov 1;87(3):493-506.

Dan Draai, Neri Kafkafi, Yoav Benjamini, Greg Elmer, Ilan Golani "Rats and mice share common ethologically relevant parameters of exploratory behavior" *Behavioural Brain Research* 125 (2001) 133-140



Utrecht University



Academic-industrial initial training network (ITN) on innovative treatment approaches of Huntington's and Parkinson's disease

