# Faster Responding of Tg2576 Mice in the Touch Screen Version of the Progressive Ratio Task

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## 1 BACKGROUND

Due to the limited effectiveness of approved drugs such as the cholinesterase inhibitor donepezil or NMDA receptor inhibitor memantine, which are essentially symptomatic, new therapeutic treatments to cure Alzheimer's disease (AD) or at least hamper its progression are urgently required. Performance of mouse models of AD in locomotor and learning tests is important for evaluation of the translational validity of the model and subsequent screening of potential anti-AD therapeutics. Various genetic mouse models of AD are known to exhibit alterations of open field behaviour as well as altered (usually deficient) memory in Morris water maze, Barnes maze, contextual fear conditioning, novel object recognition or other similar tests. However, in most such studies, behavioural outputs markedly differ from those usually assessed in AD patients, whereas it would be desirable that preclinical investigations rely on the approaches that ensure maximal translation in the clinic. Furthermore, despite avolition/apathy is a frequent neuropsychiatric symptom in AD patients, altered motivation and/or goal-directed learning have been relatively less studied in mouse models of Alzheimer's disease.

Touchscreen tasks have been lately employed to assess various cognitive domains in murine transgenic models of AD, such as TgCRND8, 3Tg×AD, CVN and TgTau-P301L mice (Romberg *et al*., 2011; Romberg *et al*., 2013; Bharmal *et al*., 2015; Piiponniemi *et al*., 2017). Tg2575 mice are one of the most well characterized, and widely used model of AD. Here, we explored if 10-month-old Tg2576 mice, which overexpress a mutant form of amyloid precursor protein with the Swedish mutation (KM670/671NL), had altered motivational behaviour in the touch screen version of progressive ratio (PR) reinforcement task.

## 2 METHODS

Tg2576 mice were procured from Taconic Biosciences A/S (Lille Skensved, Denmark). The initial cohort comprised 26 Tg2575 and 22 WT female mice that were 10 months old at the start of the experiment and were not homozygous for *rd1* mutation. However, as five mutant and seven WT mice failed to pass fixed ratio 5 (FR5) stage criterion (described below), data from only 21 Tg2575 and 15 age-matched WT female mice were used for the final analysis. Mice were housed in groups of 2–5 in a temperature- and humidity-controlled environment under a 13:11 h light/dark cycle (lights on at 07:00 am and off at 8:00 pm). Cages (IVC type II, Allentown, Inc., Allentown, NJ, USA) were kept at negative pressure and furnished with corn cob-derived bedding (Scanbur, Karlslunde, Denmark), nesting material (aspen wool, Tapvei Oy, Kortteinen, Finland), and a tinted polycarbonate tunnel (Datesand, Manchester, UK). Mice were fed Teklad Global 16%-protein rodent diet (Envigo, Huntington, UK). During experiments, were kept on a restricted food regimen, at 85–90% of their free-feeding weight in order to maintain motivation for the task, with water *ad libitum*.

**Figure 1.** Schematic illustration of the setting for the Fixed/Progressive Ratio task in a Bussey-Saksida touch screen operant chamber.

Animals were tested in Bussey-Saksida mouse touchscreen chambers operant chambers (Loughborough, Campden Instruments, UK) housed within sound attenuating boxes. Masks with 5 square windows were used for the fixed ratio (FR) and progressive ratio (PR) schedules (Figure 1). Mice received one training session per day, 5–7 days per week. During each of the 30 trials per daily session, solid white stimulus was displayed on the touchscreen always in the central window. IR light beams allowed photodetection of animal actions, enabling the quantification of horizontal locomotor activity and nose pokes oriented towards the touchscreen and food tray. Operant chamber outputs were controlled by a graphical task design software (ABET II Touch software; Campden Instruments). During operant pretraining in fixed ratio (FR) task, Tg2576 and WT mice were trained to make a fixed number (1, 2, 3 and 5) of touches to the illuminated window on a touch-sensitive screen in exchange for small nutritional reward (Heath et al., 2015). The criteria for FR1, FR2 and FR3 stages were the completion of 30 trials in less than 60 min and the consumption of all earned rewards. We adopted the following criteria for the next FR5 stage: a) all animals received at least seven FR5 daily sessions; b) further FR5 sessions were given after seven days if the mice failed to complete 30 trials on three last consecutive days; c) the maximum number of FR5 sessions was capped at 15. Immediately after attaining FR5 criterion, the animals were tested for PR responding for 3 consecutive days, during which in order to get the reward, they had to emit an increasing number of touches according to escalating PR4 schedule (1, 5, 9, …n + 4). Following PR4 stage completion, the animals had a 3-day break from PR testing whereupon they were moved to PR8 schedule (1, 9, 17 …n + 8).

## 3 RESULTS

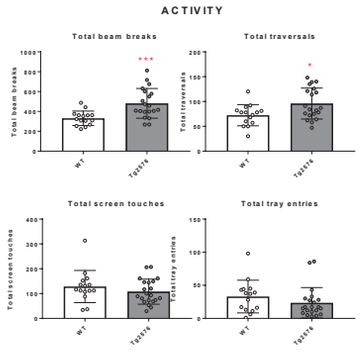


**Figure 2.** Locomotor activity of Tg2576 and WT mice on the first 30-min exposure to the touch screen chamber.

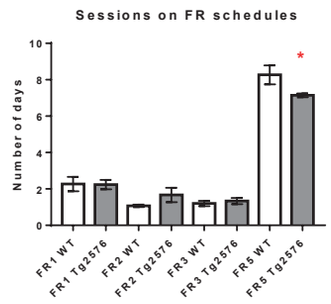


**Figure 3.** Duration of pretraining of Tg2576 and WT mice at increasingly strenuous FR1, FR2, FR3 and FR5 stages until achievement of corresponding criteria.

On the first day of exposure to touchscreen chambers, Tg2576 mice exhibited higher locomotor activity than age-matched WT mice: the mutants made more infrared beam breaks and traversals of the chamber (Figure 2).

Tg2576 and WT mice required similar number of sessions to achieve criteria during FR1, FR2 and FR3 stages (Figure 3). However, Tg2576 mice achieved FR5 criterion slightly faster than did WT counterparts ($P$ = 0.0188, Mann-Whitney test).

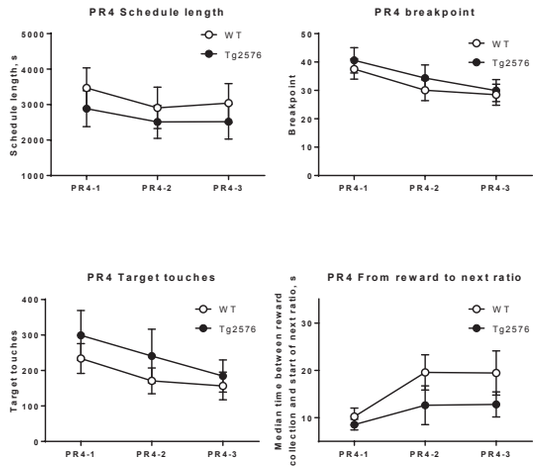


**Figure 4.** Similar motivation-related behavioural indices in Tg2576 and WT mice.

Motivation-related behaviour during PR4 schedule was similar in Tg2576 and WT mice (Figure 4), as repeated measures ANOVA failed to reveal main effect of group on the breakpoint, i.e., the number of target touches in the last trial for which a reward was earned (a classical measure of progressive ratio task performance). The lack of statistically significant differences in the schedule length, the total number of target touches and the interval from reward collection to the start of the next ratio trial (Figure 4) also supported the notion about unperturbed motivation in Tg2576 mice.

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## 3 RESULTS CONT'D

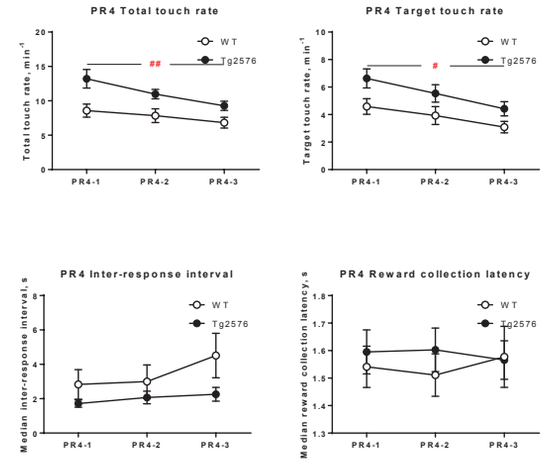


**Figure 5.** Measures of the velocities of goal-oriented reactions in Tg2576 and WT mice.

Intriguingly, Tg2576 mice demonstrated significantly faster total and target touch rates (Figure 5), whereas inter-touch interval and reward collection latency were not statistically different between the two groups. We then analysed the specificity of touches during PR4 schedule and found that the proportion of target touches was similar in mutants and WT mice (Figure 6). During the more challenging PR8 schedule, none of the PR parameters studied was different between Tg2576 and WT mice.

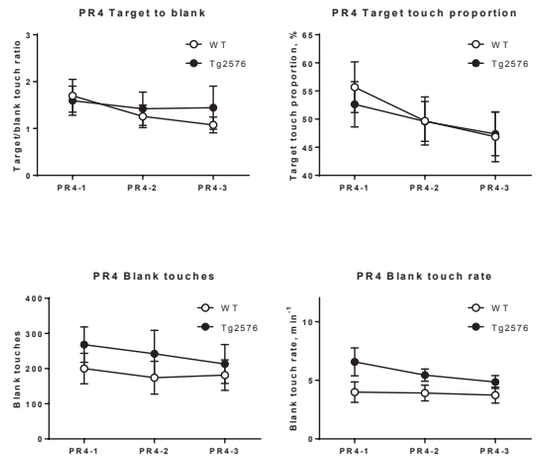


**Figure 6.** Measures of the specificity of the interaction with touch-sensitive screen in Tg2576 and WT mice.

## 4 CONCLUSIONS

- Tg2576 mice were hyperactive during their first exposure to touchscreen chambers
- Tg2576 had normal instrumental learning abilities during fixed ratio reinforcement schedule; moreover they required slightly but significantly less time to acquire FR5 criterion than WT mice.
- Tg2576 mice exhibited normal motivational behaviour in the PR4 and PR8 progressive ratio schedules, but tended to make touches to the screen at a significantly higher rate during the initial P4 test. This perseveration suggests that Tg2576 mice may be used as a model of agitated behaviour that is a frequent feature in Alzheimer's disease.