Natural learning in mouse populations: mice lacking the neurotrophin receptor TrkB in the forebrain show intact spatial memory but impaired behavioral flexibility

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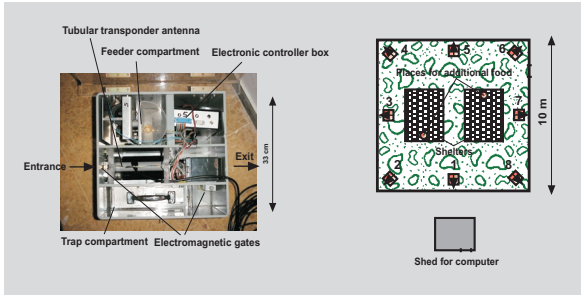
? Do mice lacking the the TrkB receptor have impaired spacial learning or reduced flexibility?

Mice lacking the neurotrophin receptor TrkB in the forebrain have been found to be unable to learn the Morris water maze task, to be impaired in radial maze learning, while they appeared less or not affected in more simple learning tasks such contextual fear conditioning (Neuron 24, 401-414, 1999). The aim of the present study was to study spatial learning of mutant mice under naturalistic conditions.

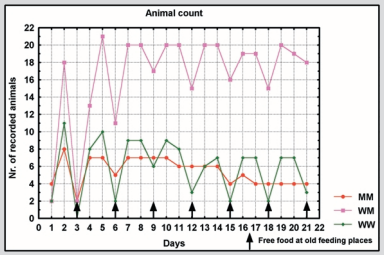
1 How to test mouse spatial learning in natural environment

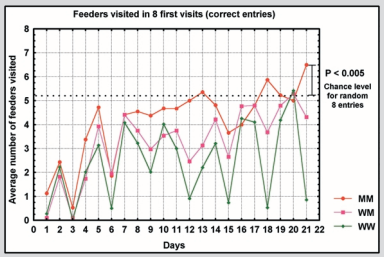
In order to clarify how such an impairment would affect the learning ability in a natural environment, we have developed a system consisting of eight computer-controlled feeder/trap units. This set-up permits to deliver (or withhold) food reward to individual transponder tagged mice visiting the traps for obtaining their daily food. The system operates inside a mouse colony kept permanently outdoors (or indoors), and records continuously visits of every mouse. After an individual mouse has entered a feeder box, other mice are barred from entering until the occupant has left. Thus, the following variables are recorded for each individual: i) time of visit; ii) place of visit; iii) food reward or not (correct choice and later re-entries). The task resembles a radial maze test but is more complicated because of protracted food delivery schedules and the necessity of adjusting behavior when faced with a box occupied by another mouse feeding inside. On the other hand, it emulates the everyday learning requirements of mice quite nicely.

Forty mice (11 wildtypes, WW; 21 heterozygous, WM; and 8 mutants, MM) were released into an oudoor pen of 10x10 m. Four feeder boxes were placed in distant corners, four boxes in proximity to two central shelters offering protection against wind and rain. Predators were barred from the pen by nets and electrical fences. A daily feeding cycle started at 8 p.m. and lasted overnight till 8 a.m. During this time, a mouse would receive a food reward of about 0.5 g at every box but only during the first visit. As it was not certain whether poorly learning mice would receive enough food, additional free food was placed inside the shelters every third day.



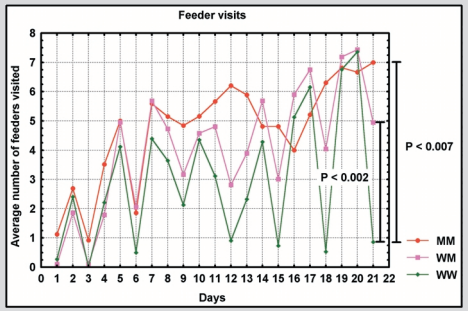
2 TrkB mutants in a natural environment are able to learn a task analogous to the eight arm radial maze





It was found that all 3 groups (WW, WM and MM) gradually learned to visit all eight feeders during a night, without significant differences between the groups. At the last trial the mutants visited on average 6.5 places with food in the first 8 visits, that is significantly more than chance level (approx. 5.25), P < 0.005. This indicates that TrkB mutants did not suffer from spatial memory deficits nor from basic learning inabilities.

3 TrkB mutants are unable to switch their search strategy



However, differences between mutants and wildtypes emerged gradually at those days with free food inside the shelters. While the wildtypes soon abandoned to visit the outside feeders during such nights, the TrkB mutants continued to patrol the boxes in their habitual way. For example, on day 21, the average number of boxes visited by the mutants was 7.0, while the average visits to those boxes dropped to 0.86 in the wildtypes (Mann-Whitney, p<0.007). The heterozygous animals performed in-between (average visits 5.0, different from wildtypes, Mann-Whitney, p< 0.002).

! Conclusio

Our data show rather convincingly that TrkB deficient mice were able to learn but, once having learned a task, were almost unable to switch quickly to another behavioral strategy.

This implies that the TrkB neurotrophin receptor must play a fundamental role in behavioral flexibility.

In addition, natural learning set-ups monitoring a collective of mice permit to recognize such slowly emerging behavioral changes (or lack thereof) much better than single test episodes of individual mice.

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