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Behavioral correlates of hippocampal dysfunction in mice

D.P. Wolfer

Neuroanatomy and Behavior, Institute of Anatomy, University of Zurich

When tested in procedures that were originally developed and validated for rats, mice may use different problem solving strategies and may be affected by experimental manipulations in different ways than rats. Based on pioneering studies in rats, place navigation in the watermaze has become a very popular paradigm to test spatial memory also in mice. We have conducted a meta-analysis comprising various mouse strains as well as 86 different genetically engineered lines and find that performance of mice in this task is limited by behavioral flexibility rather than by spatial memory.

Normal mice explore a variety of strategies while gradually improving their efficiency to find the hidden platform. First orienting toward the sidewalls, they soon scan the pool in an increasingly systematic manner until navigation becomes more and more precisely directed toward the goal. While early learning stages depend on behavioral flexibility, processing and remembering spatial information becomes only important at later learning stages. Using a software algorithm, we categorized training trials into six exclusive strategies according to the predominant swimming strategy: circling, floating, wall hugging, random swimming, scanning, chaining, focal searching, direct swims. Analysis of relative frequencies and strategy transitions between trials revealed that mice tend to perseverate on non-spatial strategies at early learning stages. This tendency is given up more or less rapidly, leading to a relatively unstable use of spatially focused strategies.

Hippocampal lesions disrupt the flexibility of mice to explore different swimming strategies during early learning, essentially limiting their choice to wall hugging or floating and preventing progression to stages where processing of spatial information becomes relevant. Most mutations, including those that disrupt signaling pathways involved in synaptic plasticity or model human cognitive deficits, produce either the same syndrome or a milder form in which progression to spatially directed strategies is only delayed. Strikingly, a selective spatial impairment in absence of inflexibility during early learning was observed only in two models, in Arg3.1/Arc null-mutants and in mice lacking glucocorticoid receptors in the brain.