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Strategies in transgenic research: the importance of genetic background

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Increasingly sophisticated and precise molecular genetic tools are applied to mice in order to study the cellular mechanisms underlying higher brain functions, including learning and memory. However, several studies have produced unclear or conflicting results. One reason for this is that performance in the behavioral tests used to assess learning and memory is influenced by various non-cognitive phenomena and can thus easily be affected by mutations through mechanisms unrelated to memory function. We conducted principal component analysis to demonstrate this for place navigation in the watermaze, one of the most widely used paradigms to assess memory and hippocampal function. In addition, meta-analysis reveals that genetic background and environment alone produce sufficient variation to span the range of most, if not all, behavioral variables and can thus easily mask or fake mutation effects if genetic studies are not designed properly.

We suggest that the chance of obtaining useful results is maximized if behavioral deficits are differentiated by combining complementary behavioral protocols and by analyzing multiple complementary parameters in each of them. Mutation effects must be contrasted statistically against the influences of genetic background and environment. In most situations, this is most efficiently achieved if (i) mutations are backcrossed to and maintained in one or (preferably) two well-characterized, commonly available inbred strains and (ii) if mutant and wild-type littermates are analyzed on a hybrid or mixed genetic background, that is in F1 or F2 generations derived from the inbred stocks. This does, however, not eliminate the so called “flanking allele problem”, genetic bias resulting from genetic linkage between the targeted locus and neighboring genes. If necessary, such bias can be removed using simple modifications of the standard breeding schemes.