

Testing the Genetics of Behavior in Mice: Response

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Wahlsten, D., Crabbe, J., and Dudek, B. (1999) Testing the genetics of behavior in mice. *Response. Science*, 285: 2069-2070.

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Article:

Our colleagues make important points about the stability of genetic differences in mouse behavior across laboratories.

We agree completely with the points raised by Picciotto and Self. We find the stability of several effects reassuring. Also, there were virtually no effects of shipping animals, which is exceedingly good news and should facilitate validation of results, including characterizations of knockout mice, across laboratories.

Pohorecky identifies several important variables that are likely to influence rodent behavior under test conditions like those we used. Social dominance is clearly an important variable, unmeasured in almost all such studies. However, if it were crucial for the particular behaviors we measured, we might have expected to see more frequent effects of sex, as agonistic behavior is generally more pronounced in male than in female mice. Unlike common practice with laboratory rats, mice are typically housed with like-sexed individuals in small groups, usually with littermates in those laboratories that maintain breeding colonies. Thus, group housing is the standard protocol in most mouse laboratories. Group-housed and isolated male mice differ in the dynamics of the patterns of their dominance hierarchies, as well as in their aggressive behavior, and these differences are strain-dependent (1). Moreover, individual housing can lead to increased anxiety-like behavior in an elevated plus maze (2). Just how housing practices might interact with laboratory site to affect strain differences is not readily predictable from literature of which we are aware, nor for our data were there differences in housing—all mice were grouped.

Dawson *et al.* agree that multiple tests using different approaches should be used to solidify inferences about the genetic structure of behavior, although they are hardly unique in adopting this practice. They imply without directly asserting that the fact that our measures were unconditioned, as well as ill defined, may have led us to be unable to isolate small genetic differences reliably. Only some behavioral domains are best tapped with conditioned responses, and we avoided these in our study for practical reasons. We do not agree that our responses were ill defined. For example, on our water escape task, group differences were not particularly large (multiple $R^2 = 0.18$), but the intertrial consistency of behavior, as indicated by Cronbach's coefficient alpha, was reasonably high ($\alpha = 0.81$ over the first four trials). Such consistency is not the hallmark of ill-defined tasks. They also err in their assertion that “the main source of variation...in one laboratory was where the experimenter was highly allergic to mice.” We offered this as an example of a laboratory difference, but there are no data suggesting it was the “main source of variation”—this appears to be Dawson *et al.*'s opinion. There was probably ultrasound emitted from the motor of the Racal Airmate 1 device strapped to the small of the back of the Edmonton experimenter at waist level. However, this was a constant: the experimenter wore the unit whenever working with the mice, from the day they arrived in the colony until the end of testing, and there was ample time for habituation. Whether wearing the Airmate apparatus had any effect on mouse behavior in standard tests can only be addressed with a controlled study using people not allergic to mice who wear or do not wear the filter unit. Data relevant to this question are needed before the effects can be called “profound.”

Hen notes that his knockout mouse colony has been maintained on a genetic background involving multiple 129 substrains. This, we suspect, is true for many other knockout colonies as well. To explain the loss of alcohol drinking phenotype in the 5-HT_{1B} knockouts over time, he proposes that an increasing influence of modifier genes from the 129/SvEvTac strain reduces alcohol preference. This hypothesis can be tested definitively by rederiving cryopreserved embryos from the original population. The stability of reduced alcohol-induced ataxia in the knockouts suggests that the effects of such modifier genes are trait-specific, which is consistent with our other findings. Hen elaborates a breeding strategy that can protect against such modifier gene effects; maintaining knockouts on fully inbred rather than segregating populations also will accomplish this.

Tordoff *et al.* suggest our results may have been influenced by differences among labs in the composition of Purina diets. This is quite feasible because there were modest but statistically significant differences among our three labs in mouse body and brain weights. We agree that it would be interesting to run further experiments of this nature using rigorously defined semisynthetic diets. Our study rigorously equated the behavioral test apparatus and testing protocols, and we sought to restrict variation in many aspects of the lab environment. We did not seek to *equate* the lab environment, however. We wanted to know whether commonplace variations in lab environments would modify the pattern of genetic effects, and we found that for certain behaviors they did, whereas other behavioral tests yielded substantially the same results in all three labs, despite the differences among diets and drinking water. It is doubtful that differences between labs can be explained by a single environmental factor; instead, both the environmental and genetic contributions are probably multifactorial and complex.

References

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