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Review

The use of norms of reaction to analyze genotypic and environmental influences on behavior in mice and rats

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Abstract

Norms of reaction (NoRs) represent the phenotypic values of genotypes as functions of environmental parameters and permit the visualization of differences in phenotypic response of different genotypes. NoR graphs can be used to analyze interactions between genotypic and environmental factors during development to produce phenotypes in inbred strains of rats and mice. We describe the main features of NoRs, the history of their use in this context, and discuss several applications in behavioral neuroscience. In addition, we give a test for determining whether distinct strains have different NoRs.

Keywords: Norm of reaction; Reaction norm; Strain differences; Mice; Rats; Inbred strains; ANOVA

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1. Introduction

Inbred rodent lines differ over a range of phenotypes. Some of these strain differences are in the arena of behavioral neuroscience. For example, commercially available mouse strains vary with respect to nociception (Mogil et al., 1996; Kest et al., 1999); the speed and duration of forced exercise (Lerman et al., 2002); the neuroregulatory role of steroids (Phan et al., 2002); the effect of anxiety on learning (Dockstader and van der Kooy, 2001); the anxiolytic effects of benzodiazepines (Griebel et al., 2000), etc. In rats, strain differences have been found in responses to anxiogenic stimuli, as measured by the emergence test (Pare et al., 2002), the open field test (Ramos et al., 2002), and the plus maze test (Ramos et al., 2002). Strain differences also have been reported in the effects of neonatal handling (Aguilar et al., 2002) and environmental enrichment (Fernandez-Teruel et al., 1997) on exploratory behavior; and in prepulse inhibition (PPI), the amount that an auditory prepulse reduces startle magnitude (Swerdlow et al., 2000; Swerdlow et al., 2001; Faraday, 2002). If data such as these are to be used profitably, new tools must be developed for analyzing and visualizing strain differences (Crawley et al., 1997; Anagnostopoulos et al., 2001; Abbott, 2002; Abbott and Knight, 2002). The norm of reaction (NoR), a graphical method that has long been used by researchers without being analyzed systematically (but see Platt and Sanislow, 1988), can serve as one such tool.

We believe that the inferential power of NoRs continues to be underappreciated in behavioral biology in general and behavioral neuroscience in particular. Though we focus on rodent data from which NoRs can be constructed published since Platt and Sanislow's (1988) review, we mention an earlier experiment that illustrates the role of NoRs (van Oortmerssen et al., 1987) but was not discussed in that review. The genotypes we will consider here are inbred rodent (mouse and rat) strains that were produced by 15 or more generations of sibling matings; different alleles are assumed to be fixed in each strain (Silver, 1995).

This review first outlines the history of NoRs with an emphasis on mouse and rat research (see below). We next show how to test the hypothesis that different genotypes have distinct NoRs. This method is relevant to all contexts in which NoRs are used, and is not limited to rodent genetics. We then show how NoRs can be used to evaluate qualitatively the sensitivity of a phenotype to environmental manipulations and genetic factors. We suggest ways in which NoRs may be of use in behavioral neuroscience, from the study of differences between inbred strains and transgenics to research on the effects of androgens and estrogens.

2. The norm of reaction

Norm of reaction (NoR) graphs are two-dimensional graphs depicting data on phenotypes (morphological or behavioral traits) collected in experimental studies, those in which the investigators manipulate the level of the independent variable (Glantz, 2002). A NoR graph shows several curves, each of which represents the response of a particular genotype to an environmental treatment. We call the curves NoRs and the graph containing the curves the NoR graph. The shapes of the NoRs, for instance, whether they are parallel or intersect, can be used to infer important information about genotype-environment ($G \times E$) interactions. Thus, NoRs provide a method for studying the relative importance of genes, environmental factors, and $G \times E$ interactions during individual development.

NoR graphs have five general features that are relevant to the analysis presented here (Fig. 1):

(i) The *x*-axis of the graph measures the environmental parameter to which the organism is exposed. This parameter can be categorical in nature such as repetitions of a task. (As experience accumulates, the subject may react differently to iterations of a test.) It may also be an ordinal unit such as the dosage of a drug. Most commonly, it is an environmental factor that can be varied continuously.
(ii) The *y*-axis of a NoR graph shows the value of the phenotype subjects display in response to each environmental manipulation.
(iii) The slope of a NoR shows the strength of the phenotypic response (of a genotype) to a change in an environmental parameter, with greater slopes representing enhanced sensitivity.
(iv) Analyses based on NoRs require at least three, and preferably more, experimentally determined values for the phenotype. Unless there at least three points, the question as to whether a NoR is linear becomes vacuous. If the phenotypic response is not linear, it can be approximated by a linear NoR.
(v) To use a NoR graph for inferential purposes, the responses of at least two genotypes must be plotted in the graph, so as to compare their phenotypic reactions to the different experimental regimes. Each data point on the curve represents the mean phenotypic value of a group of animals of the same genotype tested at that level of the environmental manipulation. Different data points that make up the curve representing one genotype may have different error bars because phenotypic sensitivities at different levels of the experimental parameter are likely to vary.

In a previous review, Platt and Sanislow (1988) compared the NoR to a related concept, the 'reaction range'. Sinnott et al. (1950) designated the 'reaction range' as 'the potentially possible or actually realizable phenotypes