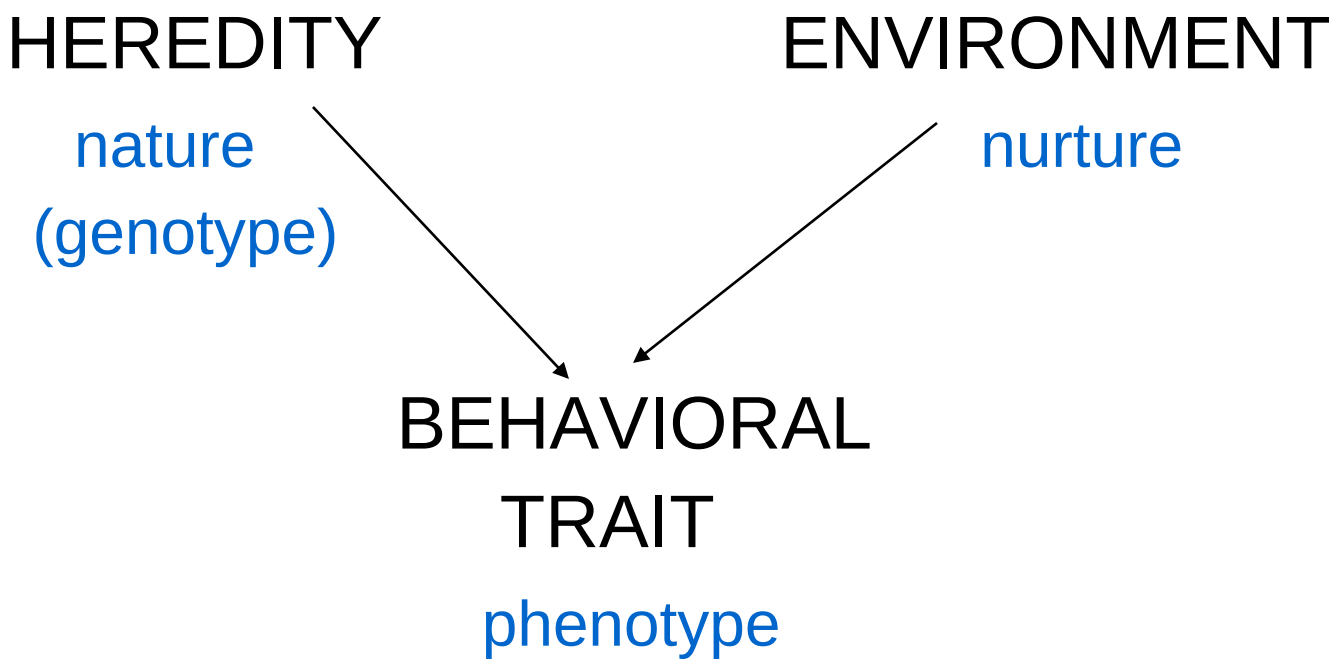
Psych 3102
Introduction to Behavior Genetics

Lecture 9

Methodology in Behavior Genetics

Animal studies



quantitative genetics → presence & nature of genetic influences

molecular genetics → locating and identifying specific genes in the genome

Animal Breeding Studies

Simple genetic breeding experiments used to demonstrate presence of genetic influence on behavior:

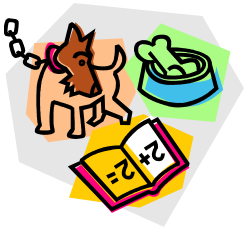
1. selection studies - animals bred together to try to influence level of a trait (artificial selection not natural selection)

   a successful selection study proves genetic influence on the trait

2. inbred line studies - develop inbred lines (strains) test the lines to see if they differ (by chance) for level of the trait of interest

   existence of differences between inbred lines for a trait proves genetic influence on that trait


DOGS




Canis familiaris sub-species = breeds

All breeds of dogs have been produced by artificial selection, a demonstration of the power of this method for bringing about change

Wolf-like ancestor domesticated ~50,000 ya, guarded camps, removed vermin

Ancestral dog selective breeding began ~ 14.000 ya

- original animals subjected to thousands of years of selective breeding by humans to produce present-day breeds, then inbred within the breed (breed = inbred line)

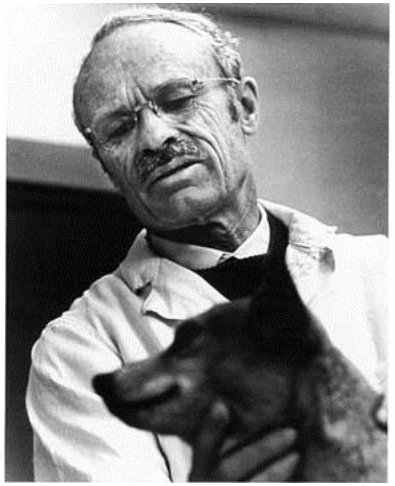
- breeds differ for many traits:

  physical appearance size intelligence temperament
  emotionality activity level aggressiveness

all of these traits must show some genetic influence for them since they breed-true, even after cross-fostering and varying environments

genetic component of variance

Research by Scott & Fuller (1965)



- 20 years of study into dog behavior

5 breeds of dog:

fox terrier

cocker spaniel

basenji

beagle

Shetland sheepdog

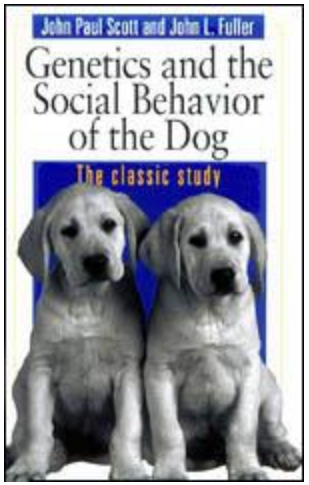
variance between breeds much greater than variance within breeds

Methods of study use the following:

- variance within breeds what does this tell us?
- comparisons between breeds what can this tell us?
- crosses between breeds to form F_1 hybrids

what can this tell us? would we expect the F1 animals to vary much? what about F2 animals?

- cross-fostering to test for maternal effects on behavior (an environmental effect)
- behavioral traits: emotionality, trainability, problem-solving, sexual behavior, sociability



For each measured trait:

variance within breeds = a measure of environmental variance

variance between breeds

= a measure of genetic + environmental variance

variance between – variance within = measure of genetic variance

ANOVA analysis of variance

Detour test

MICE and RATS

Selection studies

- successful selection for a trait provides evidence the trait is heritable
  = under the influence of genes

  high line bred for high level of expression of the trait

  low line bred for low level of expression

  control line unselected animals, randomly mated within the line
  (animals originally from same population as selected lines)

Examples

response to alcohol : ethanol sleep time

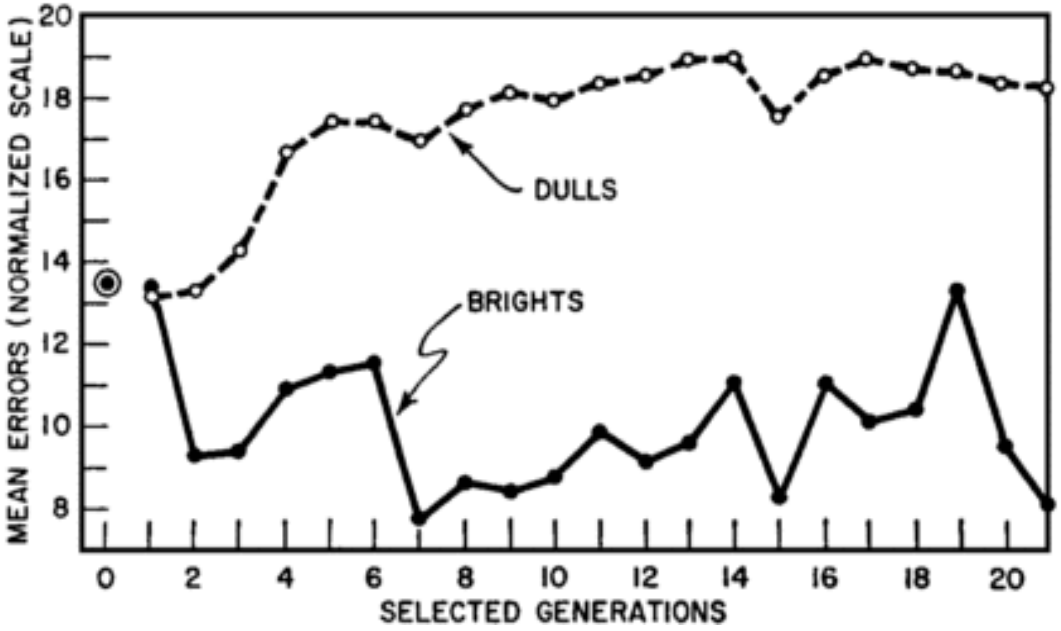
learning: maze-learning ability

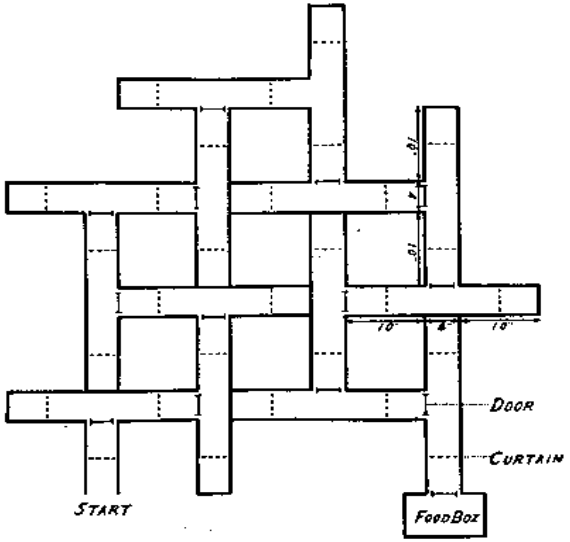
emotionality (anxiety) level : open field behavior

Response to selection for maze-learning in rats

Tolman & Tryon

Selection began 1920's





Plan of maze
14-Unit T-Alley Maze

FIG. 1

(From M. H. Elliott, The effect of change of reward on the maze performance of rats. *Univ. Calif. Publ. Psychol.*, 1928, 4, p. 20.)

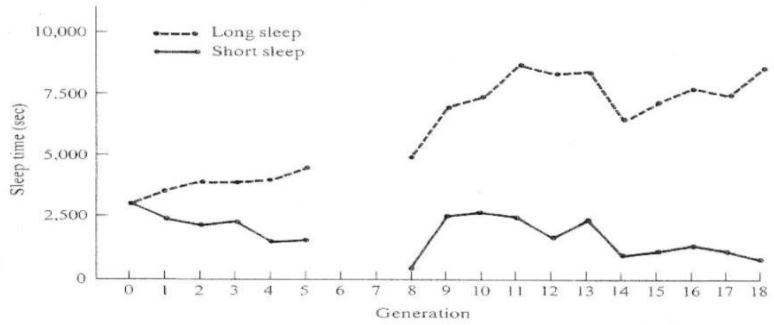


Figure 10.21
Results of ethanol sleep-time selection study. Selection was suspended during generations 6 through 8. (From McClearn, unpublished.)

Selection for ethanol sleep time

Began in 1960's

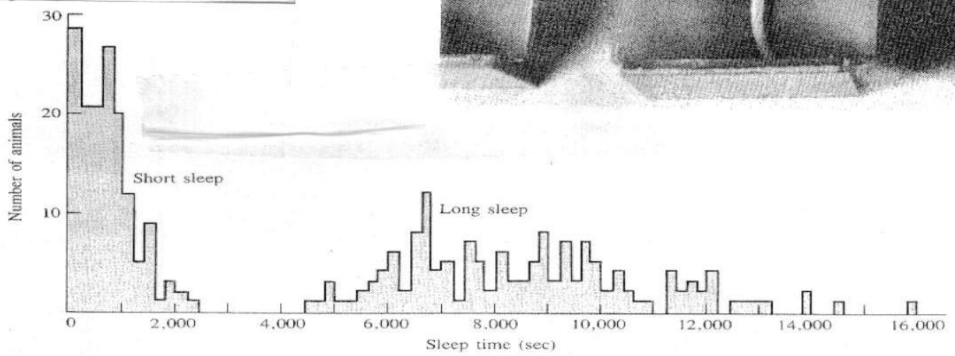


Figure 10.22
Distributions of ethanol sleep time after 15 generations of selection. (From McClearn, unpublished.)

Open field behavior in mice

- mouse placed in brightly-lit box for 6-minute trials

Fearful mouse

freezes or shows low activity levels

defecates a lot urinates a lot

stays close to sides of box (+ve thigmotaxis)

Non-fearful mouse

explores, shows higher activity levels

defecates less urinates less

ventures into middle of arena

Selection for activity level

high line : mate together highest scoring mice for activity in the open field each generation

low line : mate together lowest scoring mice

Selection for defecation level

high line : mate together highest defecators

low line : mate together lowest defecators

Results

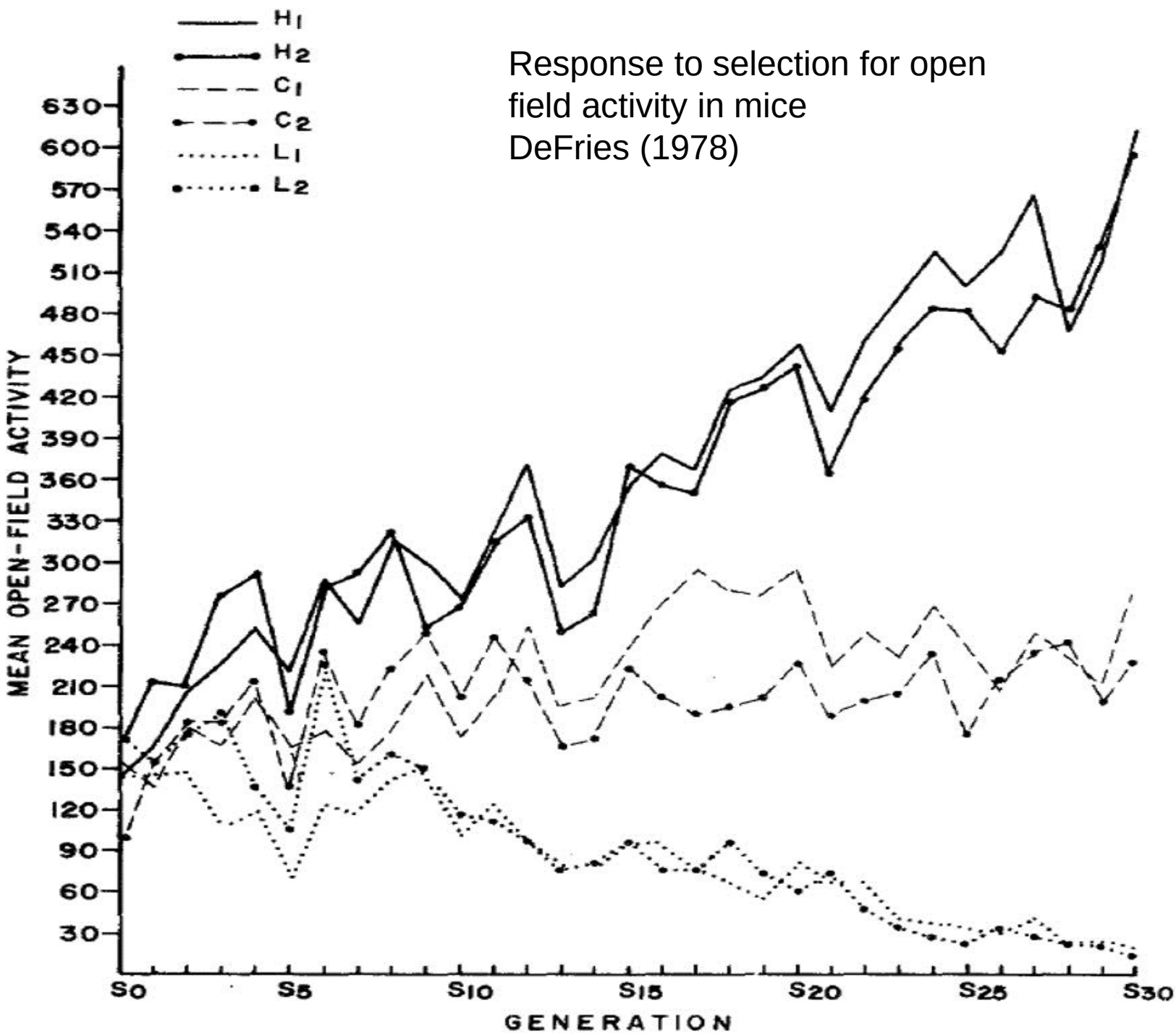
after 30 generations of selection (separately for each trait)

for activity: 30-fold difference between high and low lines

for defecation : 7-fold difference between high and low line

no overlap in scores between high and low line

Response to selection for open field activity in mice
DeFries (1978)

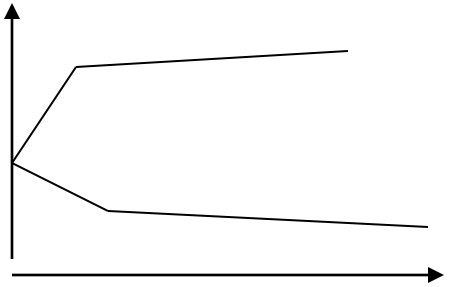


What else can a successful selection study tell us?

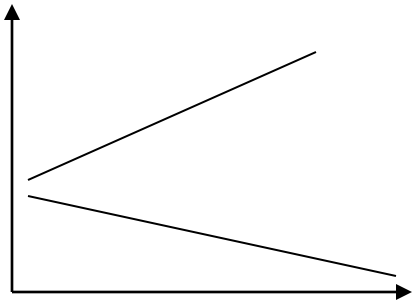
- by analyzing response to selection over the generations:
  1. can get an estimate of number of genes influencing the trait
  2. can get idea about nature of gene action

Examples:

large initial difference between lines
in a few generations then leveling
off of response indicates fewer genes,
possibly non-additive gene effects



smaller differences between lines
continuing for many generations
indicates more genes, additive gene effects

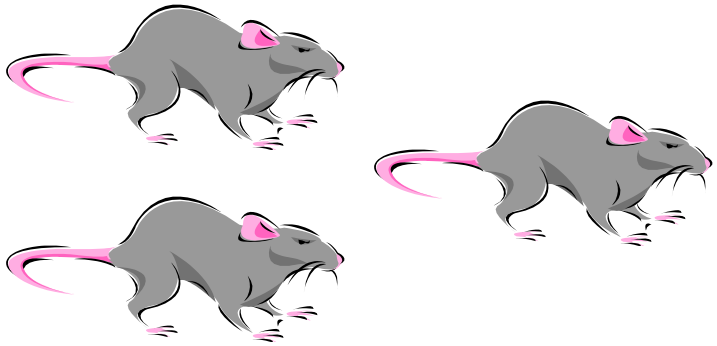


Web Page: http://rhodeslab.beckman.illinois.edu/publications/publications.htm>>

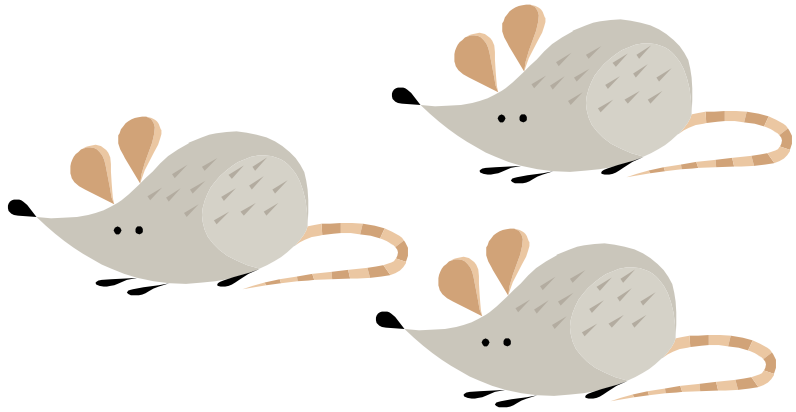
Selective breeding of house mice has been used to study the evolution of locomotor behavior.

4 replicate lines selectively bred for high voluntary wheel running (High-Runner)
4 bred randomly (Control).

Major changes in High-Runner lines appear to have taken place in the brain rather than in capacities for exercise. Neurobiological profile resembles human attention deficit hyperactivity disorder (ADHD) and is also consistent with high motivation for exercise as a natural reward. Both ADHD and motivation for natural rewards (such as food and sex), as well as drugs of abuse, have been associated with alterations in function of the neuromodulator dopamine, and High-Runner mice respond differently to dopamine drugs. In particular, drugs that block the dopamine transporter protein (such as Ritalin and cocaine) reduce the high-intensity running of High-Runner mice but have little effect on Control mice. In preliminary studies of mice exercised on a treadmill, brain dopamine concentrations did not differ, suggesting that changes in the dopamine system may have occurred downstream of dopamine production (e.g., receptor expression). Brain imaging by immunohistochemical detection of c-Fos identified several key regions (prefrontal cortex, nucleus accumbens, caudate, lateral hypothalamus) that appear to play a role in the differential response to Ritalin and increased motivation for running in High-Runner mice. The activation of other brain regions, such as the hippocampus, was closely associated with the running itself. Running also increased the production of new neurons to apparently maximal levels in the hippocampus, but impaired learning in High-Runner mice.



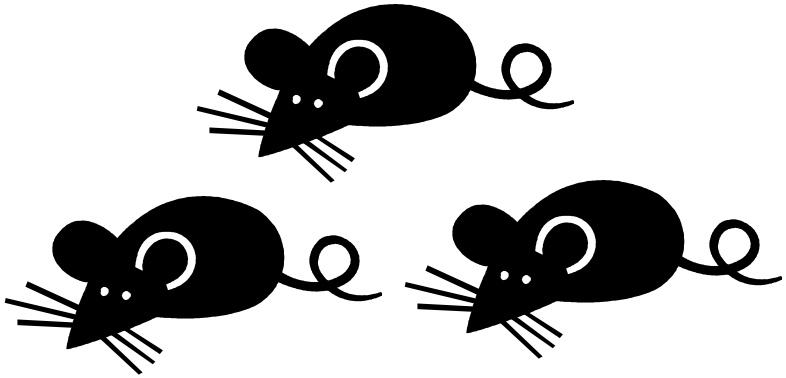
Strain A



Strain B

INBRED STRAINS

Strain C



Inbred strain studies

inbred strain (line)

- a population of animals produced by mating related individuals together for many generations

in mice : 20 generations (5 years) brother/sister, parent/offspring

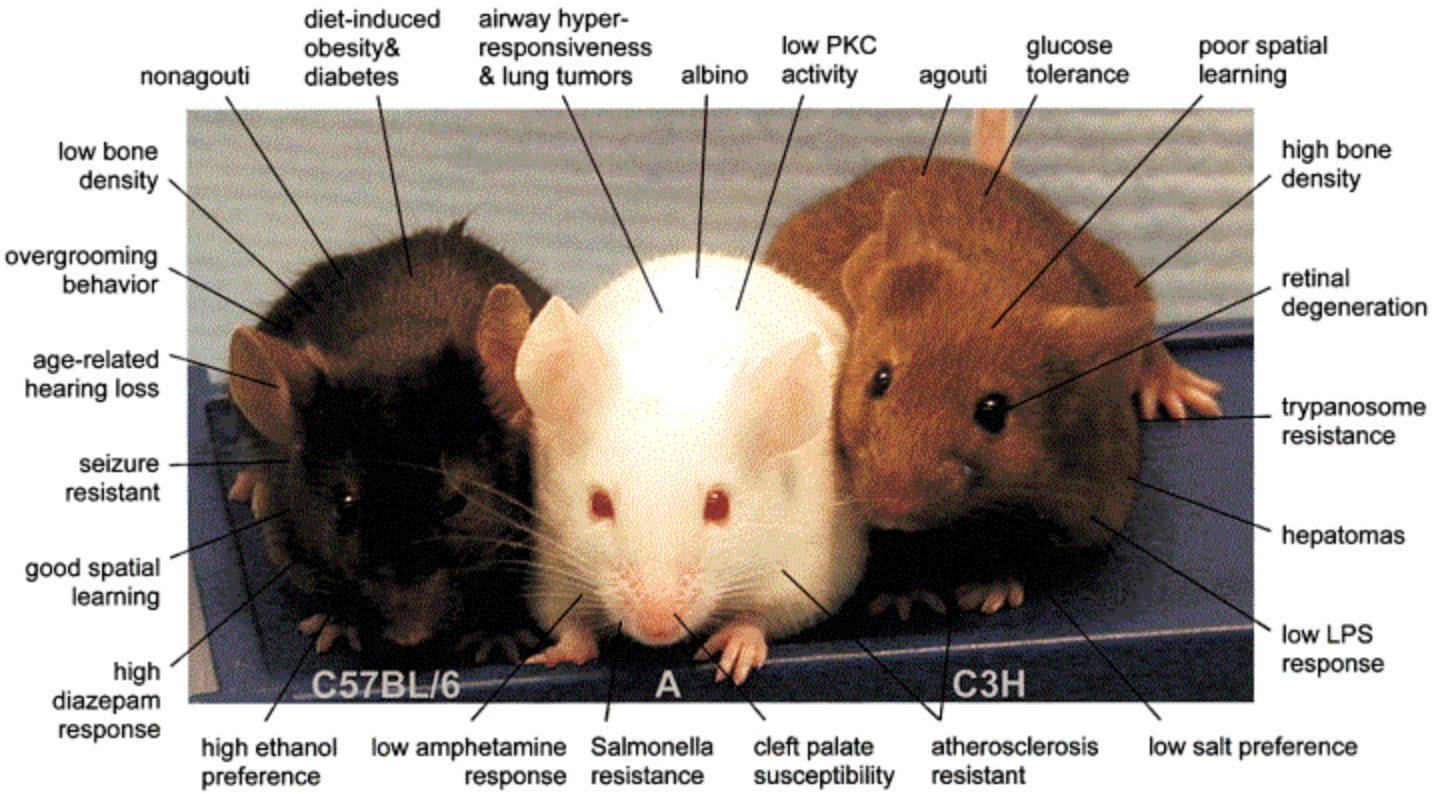
- animals within the strain are homozygous for most segregating loci and are genetically very similar to each other

Different inbred strains may have different alleles fixed at the loci influencing a behavioral trait

Differences in phenotype between strains will reflect these genetic differences between strains if the trait is influenced by genes

Note: alleles (and hence, phenotypes) are fixed at random, there is NO selection involved in producing inbred strains

Inbred Strain Characteristics



PKC = protein kinase C
(signal transduction)

LPS = lipopolysaccharide
(elicits immune response)

What can studies of inbred strains tell us?

1. strain differences in phenotype prove genetic influence on the phenotype

2. genetic and environmental variance can be estimated

   how?

3. crosses between inbred strains will tell us the nature of gene action how?

Examples of traits shown to differ between inbred lines:

avoidance learning

maze learning

open field activity and defecation

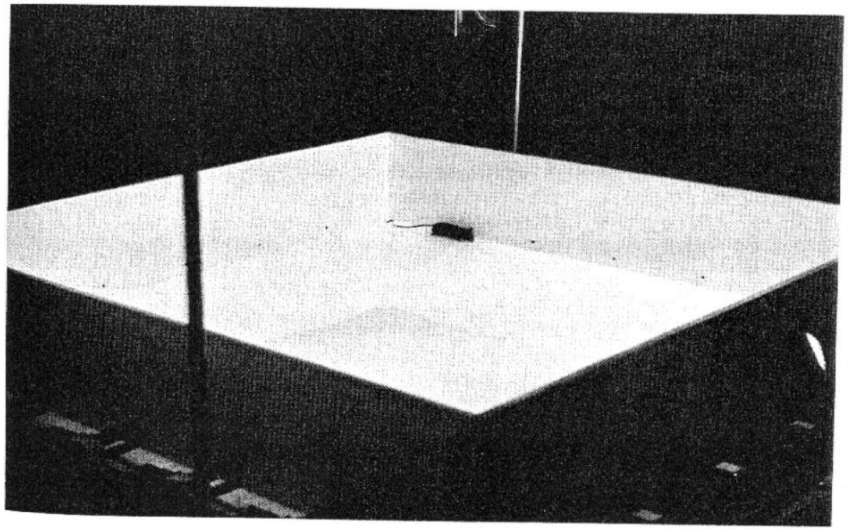


Figure 3.5
Mouse in an open field employed by DeFries et al. (1966). The holes near the floor transmit light beams that electronically record an animal's activity. (Courtesy of E. A. Thomas.)

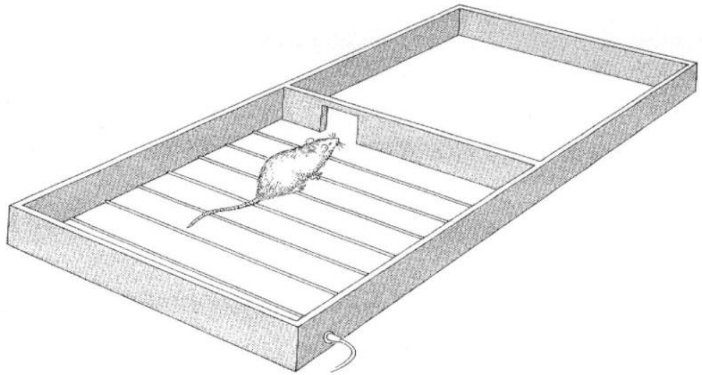


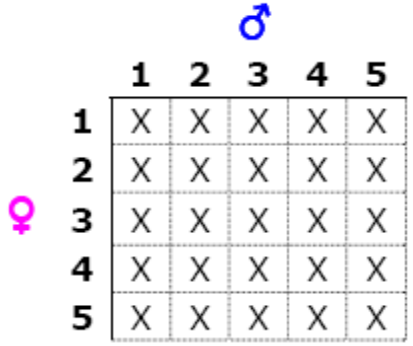
Figure 10.4
Shuttle box used to study avoidance learning in mice. (From *The Experimental Analysis of Behavior* by Edmund Fantino and Cheryl A. Logan. W. H. Freeman and Company. Copyright © 1979.)


C57
BL
♂
4
Wean
4-3-01
DOB
3-1-01

Diallel design

maximizes information from inbred strain studies

- systematic cross-mating
  of several inbred strains,
  with reciprocals



- reciprocal cross differences indicate sex-linkage, prenatal maternal influences

Cross-fostering can separate pre- and post- natal maternal effects

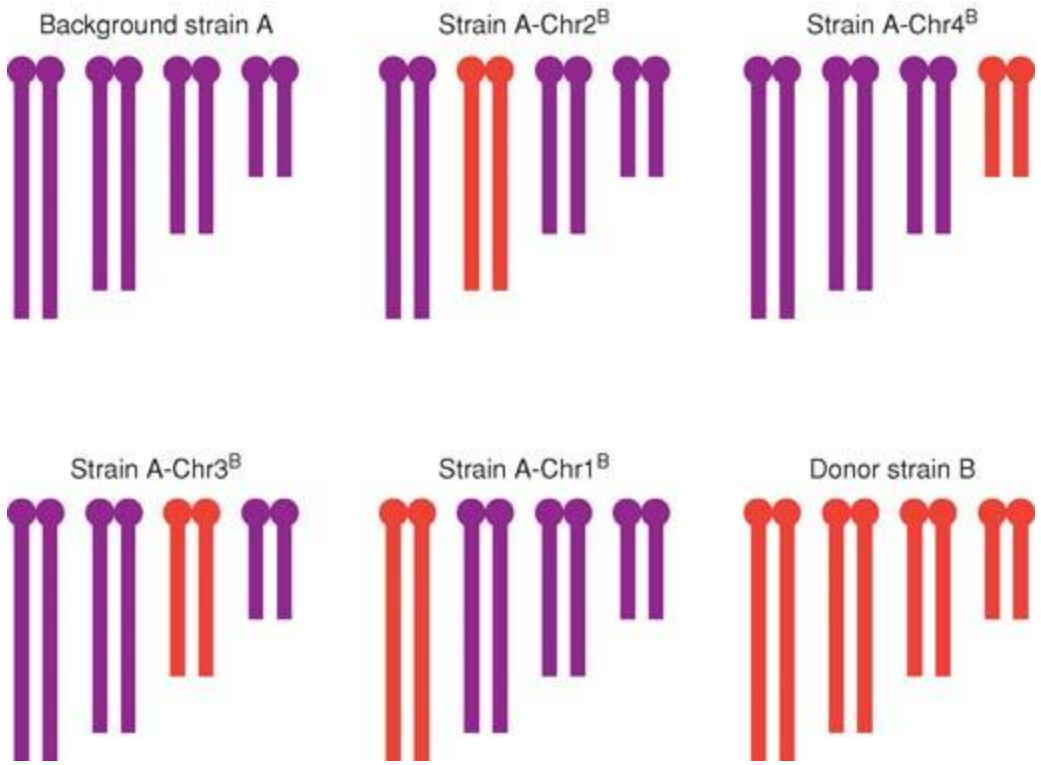
Environment can be manipulated to study environmental effects

Use of rat and mouse consomic strains to identify genes

- consomic strain = inbred strain that has some portion of its genome replaced by homologous genetic material from another inbred strain via a series of marker-assisted backcrosses

- by introducing genetic material in a systematic way, genes that influence a behavior can be discovered

Series of 4 consomic strains, flanked by parental strains A and B (organism has 4 pairs of chromosomes)



Example

Strain A shows high deficit for long-term fear memory

Strain B shows low deficit for long term fear memory

- make a series of consomic strains that introduce 1 chromosome from Strain B at a time into Strain A animals,
- see which chromosome rescues the deficit
- narrow down the search by introducing smaller & smaller pieces of chromosome

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Systematic analysis of emotionality in consomic mouse strains established from C57BL/6J and wild-derived MSM/Ms

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Consomic strains have recently attracted attention as an advantageous method to screen for genes related to developmental, physiological, and behavioral phenotypes. Recently, a new set of consomic strains was established from the Japanese wild-derived mouse strain MSM/Ms and C57BL/6JJcl. By analyzing the entire consomic panel, we were able to identify a number of chromosomes associated with anxiety-like behaviors in the open-field (OF) test, a light–dark box and an elevated plus maze. Detailed observation of the OF behavior allowed us to identify chromosomes associated with those ethological traits, such as stretch attend, rearing, and jumping. Repeated OF test trials have different meanings for animals, and we found that some chromosomes responded to only the first or second trial, while others were consistent across both trials. By examining both male and female mice, sex-dependent effects were found in several measurements. Principal component analysis of anxiety-like behaviors extracted five factors: 'general locomotor activity', 'thigmotaxis', 'risk assessment', 'open-arm exploration' and 'autonomic emotionality'. We mapped chromosomes associated with these five factors of emotionality.

Keywords: Emotionality, consomic mouse strains, wild-derived MSM, genetic mapping, QTL

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Individual differences in most behaviors derive from polygenic influences, rather than Mendelian mutations with large effects (Plomin *et al.* 2001). To date, a vast number of quantitative trait loci (QTL) related to anxiety-like behaviors has been reported in mice and rats by using F2 intercross, N2 backcross, recombinant inbred strains, and heterogeneous stocks (Flint 2002, 2003; Valdar *et al.* 2006). Flint *et al.* (2005) reviewed several QTL studies and found that most QTL have just a small effect size, contributing approximately 6% of the total phenotypic variance for behavioral and physiological phenotypes. Also, extensive genome-wide high-resolution mapping using heterogeneous stock mice revealed 843 QTL for a variety of phenotypes, including behavior, and found that only 10 QTL had effect sizes of greater than 5%, while 109 QTL had less than 2% (Valdar *et al.* 2006). Because of this small effect of each QTL, an enormous amount of effort is required to identify quantitative trait genes (QTGs) for behavior.

Consomic strains, also known as chromosome substitution strains, are a favorable resources for investigating QTG; genotyping to map the chromosome is unnecessary, results are reproducible, QTL detection is statistically significant, and making congenic strains is rapid (Belknap 2003; Nadeau *et al.* 2000). Analysis of consomic strains established from C57BL/6J (B6) and A/J has successfully shown the chromosomes affecting several phenotypes including anxiety-related behaviors (Laarakker *et al.* 2008; Ponder *et al.* 2007; Singer *et al.* 2004, 2005). Recently, a new set of consomic strains was established, dubbed B6-ChrN^{MSM} consomic panel mice, using a different subspecies group of mouse strain MSM/Ms (MSM) (Takada *et al.* 2008). In this panel, each of the MSM chromosomes was introduced into the B6 background to encompass the whole genome. MSM was derived from Japanese wild mice (*Mus musculus molossinus*), and they had not undergone a strong selection history for domestication during breeding. Thus, it was expected that they would retain several behavioral characteristics of wild mice. It is known that several behavioral responses have been changed or sometimes attenuated in standard laboratory strains (Blanchard *et al.* 1998; Fernandes *et al.* 2004; Holmes *et al.* 2000; Koide *et al.* 2000), and thus, wild-derived mouse strains may offer interesting alternatives for behavioral analysis. We previously showed that MSM exhibited higher spontaneous activity in the home cage, reduced novelty-induced activity and increased freezing and grooming in a novel situation, difficulty in habituation to novelty, and reduced pain sensitivity compared to B6 (Koide *et al.* 2000; Takahashi *et al.* 2006). Consomic strains derived from MSM are expected to be useful for identifying genetic loci associated with the widely diverse phenotypes, some of which may have been lost in the laboratory strains. To date,

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