

Affective Disorders (Mood Disorders)

1. Depression
2. Bipolar Disorder (Manic - Depression)
3. Unipolar disorder (typically Depression)

Epidemiology of Affective Disorder

- 1. About 1-5% of general population**
- 2. Slightly more females than males**
- 3. Familial component**

DSM IV : Bipolar Disorder

- 1. At least one manic episode**
- 2. Usually followed by depressive episode**
- 3. May cycle between manic and depressive episodes**

DSM IV Diagnostic Criteria for Manic Episode

- A. Period of abnormally elevated, expansive or irritable mood
- B. During period of mood disturbance, at least 3 of the following
 1. Inflated self esteem or grandiosity
 2. Decreased need for sleep (3 hrs may suffice)
 3. Highly talkative
 4. Thoughts are racing
 5. Distractable
 6. Increased goal directed activity or psychomotor agitation
 7. Buying sprees, sexual promiscuity, foolish investments
- C. Mood disturbance impairs work or social relationships
- D. Not schizophrenia or other psychosis
- E. Not induced by substance

DSM IV Diagnostic Criteria for Depression

- A. At least 5 of the following for at least 2 weeks
 1. Depressed mood most of the day nearly every day
 2. Diminished interest in daily activities
 3. Significant weight loss or gain (appetite change)
 4. Insomnia or hypersomnia every day
 5. Psychomotor agitation or retardation every day
 6. Fatigue or energy loss every day
 7. Inability to think or concentrate, indecisiveness
 8. Recurrent thoughts of death
 9. Feelings of worthlessness
- B. Not caused by an organic factor (drug or injury)
- C. Not in response to death of a loved one (bereavement)
- D. No evidence of hallucinations, delusions (schizophrenia)

Mode of inheritance affective disorder:

1. One or more genes of major effect: affected person has higher probability of producing an affected child than seen in schizophrenia. From 25% to 50%, depending on the study.
2. May show reduced penetrance (not every individual with the gene or genes exhibits the condition).

Drug therapy for depression

Tricyclics: Elavil, Anafranil, Norpramin, Sinequan
Tofranil, Pamelor, Vivactil, Surmontil

Heterocyclics: Asendin, Wellbutrin, Ludlomil, Desyrel

Selective serotonin re-uptake inhibitors SSRIs: Prozac,
Paxil, Luvox, Celexa, Zoloft, Lexapro

Other compounds: Remeron, Serzone, Effexor

Monoamine oxidase inhibitors (MOIs): Nardil, Parnate

Implications of drug therapy effectiveness for understanding the genetic basis of psychiatric conditions

1. The two major psychoses respond to entirely different classes of therapeutic drugs

Different sets of genes underlie vulnerability to each condition

2. Among patients with the same diagnosis, there are differences in the responsiveness to different drugs.

A given condition, such as schizophrenia, exhibits genetic heterogeneity. The same phenotype may be caused by alleles at different genetic loci.

GENETICS OF ADDICTION

1. Defining addiction

2. Heritabilities of addictions to various substances

A. At least 3 of the following:

- 1. Substance often taken in larger amounts or over longer periods than the person intended**
- 2. Persistent desire or one or more unsuccessful efforts to cut down or control use**
- 3. A great deal of time spent in activities necessary to obtain the substance or recover from its use**
- 4. Frequent intoxication or withdrawal symptoms when expected to fulfill obligations at work, school or home or drives while intoxicated**
- 5. Important social, occupational or recreational activities curtailed or reduced because of either intoxication or withdrawal**
- 6. Continued use of substance despite knowledge of having a recurrent problem made worse from its use**
- 7. Marked tolerance: need for markedly increased amounts of the substance to achieve the desired effect, OR markedly diminished effect when using the same amount of the substance**
- 8. Characteristic withdrawal symptoms**
- 9. Substance taken to relieve or avoid withdrawal symptoms**

B. Some symptoms persisted for at least one month or repeatedly over time

DSM IV withdrawal symptoms

- A. Cessation or reduction of use produces several of the following:
 1. Coarse tremor of hands, tongue or eyelids
 2. Nausea or vomiting
 3. Malaise or weakness
 4. Autonomic NS activity tachycardia, sweating, hypertension
 5. Anxiety
 6. Depressed mood or irritability
 7. Transient hallucinations or illusions
 8. Headache
 9. Insomnia

- B. Symptoms not due to some other physical or mental disorder.

Substances for which dependence or abuse may be common:

- 1. Alcohol**
- 2. Nicotine**
- 3. Cannabis (marijuana)**
- 4. Cocaine**
- 5. Hallucinogens**
- 6. Amphetamines**
- 7. Opioids (Heroin and morphine)**
- 8. Inhalants**
- 9. PCPs (phencyclidines)**
- 10. Sedatives**

Evidence from animal studies for a genetic role in alcoholism

1. Differences between inbred strains of mice

- Individuals from given inbred strains of mice are genetically very similar, almost like MZ twins.
- Inbred strains differ in the rates at which they consume alcohol and become dependent (withdrawal)

2. Selection for alcohol consumption in random-bred strains of mice or rats.

- Response to selection: high and low consuming strains
- Response to selection: high and low dependence

3. Preference, tolerance, and withdrawal appear to be under separate genetic control.

Twin studies of heritability of alcoholism

Study	Sex	MZ	DZ	h^2
Kendler	F	+0.54 (590)	+0.36 (440)	0.56
Reed	M	+0.59 (11866)	+0.29 (15101)	0.58
Kendler	M	+0.67 (3185)	+0.41 (5750)	0.54
Heath	M	+0.68 (396)	+0.20 (231)	0.64
Prescott	M	+0.53 (863)	+0.18 (654)	0.52

Between 52% and 64% of the variability observed in human populations for alcoholism is due to genotypic differences among people.

Heritability of dependence on other substances:

1. Nicotine: 60%
2. Cocaine: 79%
3. Hallucinogens: 20%

Potential genetic mechanisms underlying addiction:

1. Receptors for the substances themselves:
2. Transporters of the substances
3. Enzymes that breakdown the substances
4. Secondary signaling messengers

SUBSTANCE



RECEPTOR
+
SUBSTANCE



**ENZYME
DEGRADES
SUBSTANCE**



**SPECIFIC SIGNALING
MOLECULE**



BRAIN REACTION

COMORBIDITY: When having one condition or trait is associated with another condition or trait. When having one condition or trait increases the risk of having another.

COMORBIDITY in human genetics:

A: EXAMPLES

1. Obesity and diabetes
2. Alcohol and nicotine dependence
3. Alcohol dependence and major depression

B: MEANING OF COMORBIDITY

1. Influenced by common environmental factors
2. Influenced by common genetic factors

GENETICS AND HUMAN INTELLIGENCE: LECTURE OVERVIEW

- 1. Early interest in hereditary aspects of intelligence**
- 2. How is intelligence defined?**
- 3. Evidence for the genetic basis of intelligence**

Early studies of intelligence in humans

Sir Francis Galton, father of behavior genetics
(Charles Darwin's second cousin)

1. Developed statistical methods to examine correlations between relatives for different traits of interest: correlation coefficient and regression coefficient.
2. Studied familial components to "eminence" results in a book "Hereditary Genius" 1869

I have no patience with the hypothesis occasionally expressed, and often implied, especially in tales written to teach children to be good, that babies are born pretty much alike, and that the sole agencies in creating differences between boy and boy, and man and man, are steady application and moral effort. It is in the most unqualified manner that I object to pretensions of natural equality. The experiences of the nursery, the school, the University, and of professional careers, are a chain of proofs to the contrary.

Francis Galton,
Hereditary Genius
1869

A shortcoming of Galton's studies was that measures of intelligence were subjective, not standardized. For Galton's study, "achievement" and "prominence" were the "measures" used.

Defining intelligence: What is intelligence?

1. Abstract reasoning, problem solving, capacity to acquire knowledge
2. Memory, adaptation to one's environment, mental speed, linguistic competence, mathematical competence, creativity
3. Good decision making, perception

Measuring intelligence:

Important features of any behavioral tests:

1. Validity: does the test measure what it is supposed to measure?
2. Reliability: do people get the same score with repeated testing?
3. "Norms" : How do other people do on the test?
Used for comparing individual scores.
4. Standardization: each test comes with specific rules for administering the test, the tester is supposed to follow the rules

Binet test:

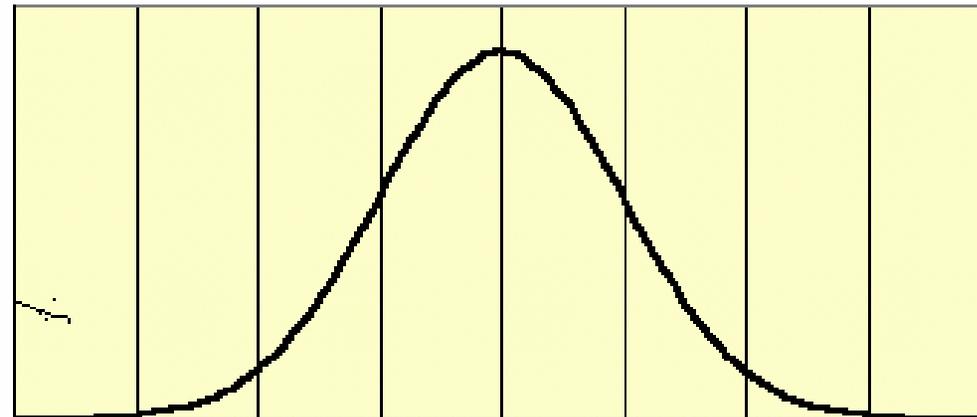
1. Developed in Paris at the turn of the century
2. Mental age/chronological age X 100
3. Imported to US, revised by Terman at Stanford=Stanford-Binet IQ.

Weschler Intelligence Scales for Children

1. Does not rely as heavily on educational experience
2. Also an adult form of the test

IQ Comparison Site
<http://plaza.powersurfr.com/delajara/>
Copyright 2001 Rodrigo de la Jara

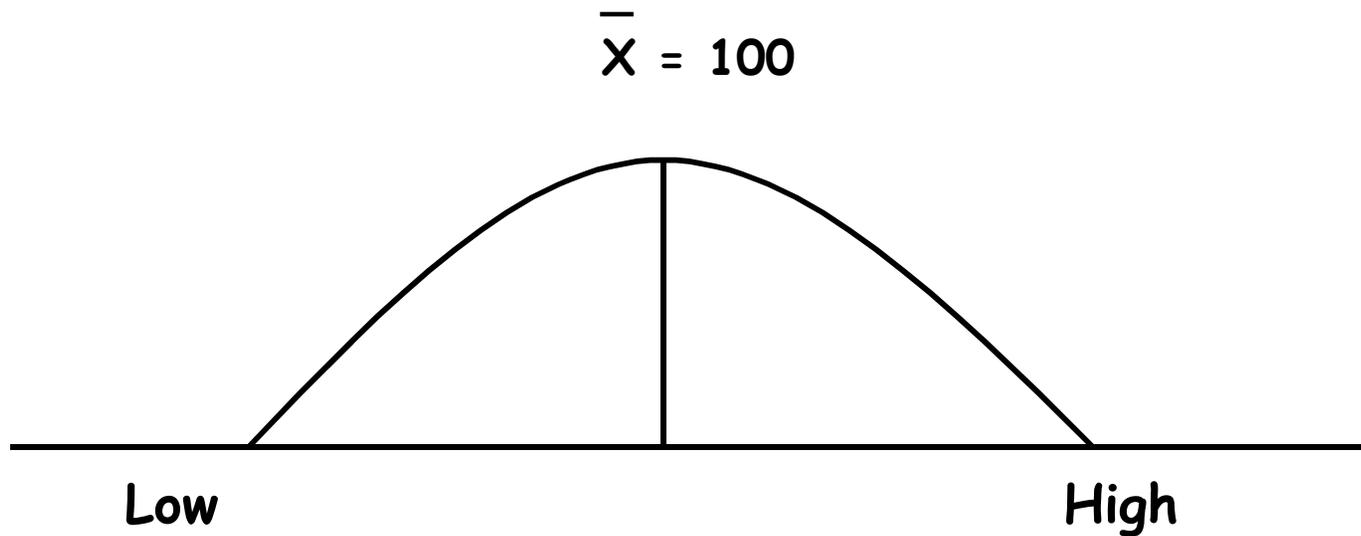
IQ Normal Curve



Standard Deviations	-4	-3	-2	-1	0	1	2	3	4
Wechsler IQ	40	55	70	85	100	115	130	145	160
Stanford-Binet IQ	36	52	68	84	100	116	132	148	164
Cumulative %	0.003	0.135	2.275	15.866	50.00	84.134	97.725	99.865	99.997

Cognition (information processing, or intellectual abilities)

1. Verbal skills: ability to understand and express meaning
2. Spatial abilities: perceive and draw spatial relationships
3. Mathematical-logical skills: reasoning
4. Musical abilities
5. Motor skills
6. Interpersonal: respond appropriately in social situations
7. Intrapersonal: self understanding, use of understanding to guide one's own behavior



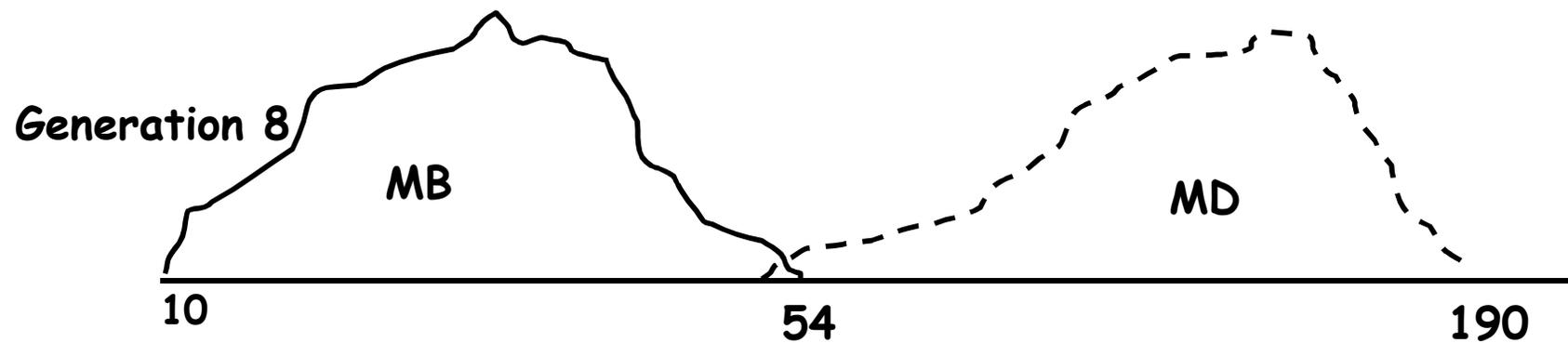
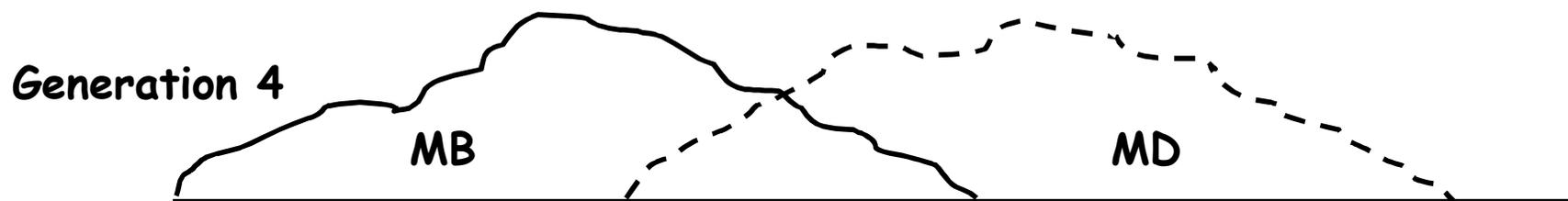
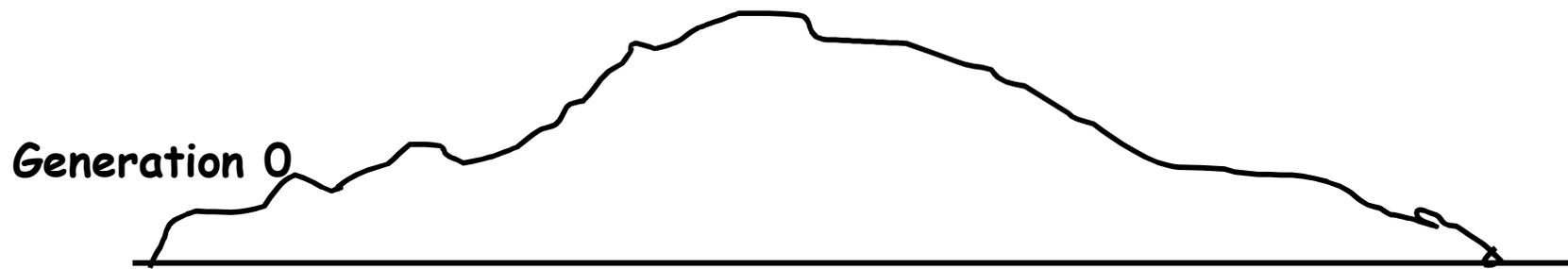
Distribution of IQ scores

How much of this variation is due to genotypic differences among individuals? What is the heritability ?

Maze learning in rats:

**selection for maze “bright” and “dull” strains of rats
(R.C. Tryon 1942)**

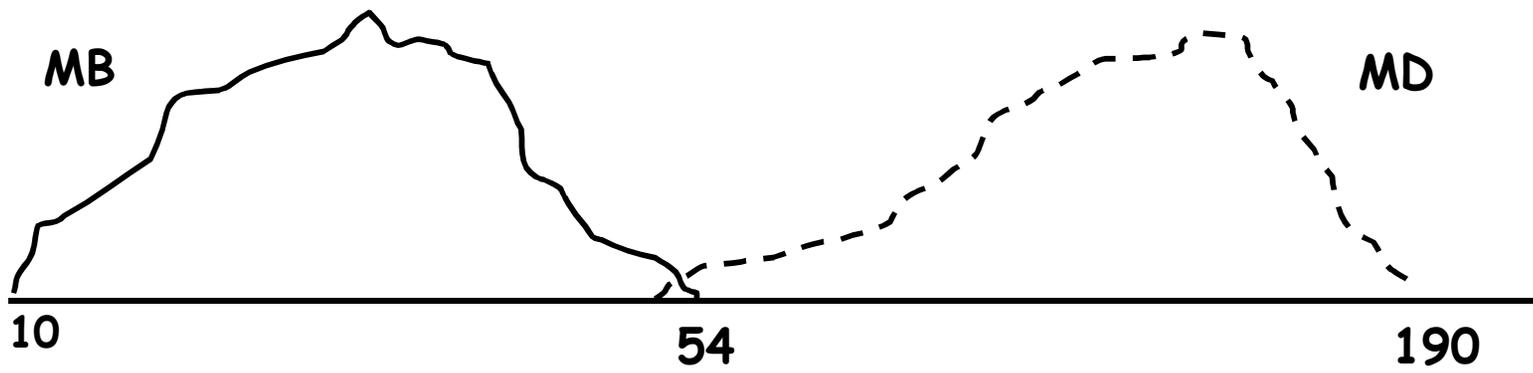
- 1. Used a 17 unit (multiple “T”) maze**
- 2. Counted up the number of errors made across multiple trials in the maze (19 trials)**
- 3. Errors were counted as number of entries in a blind alley**
- 4. Rats making the fewest errors were mated among themselves; rats making the most errors were mated among themselves**



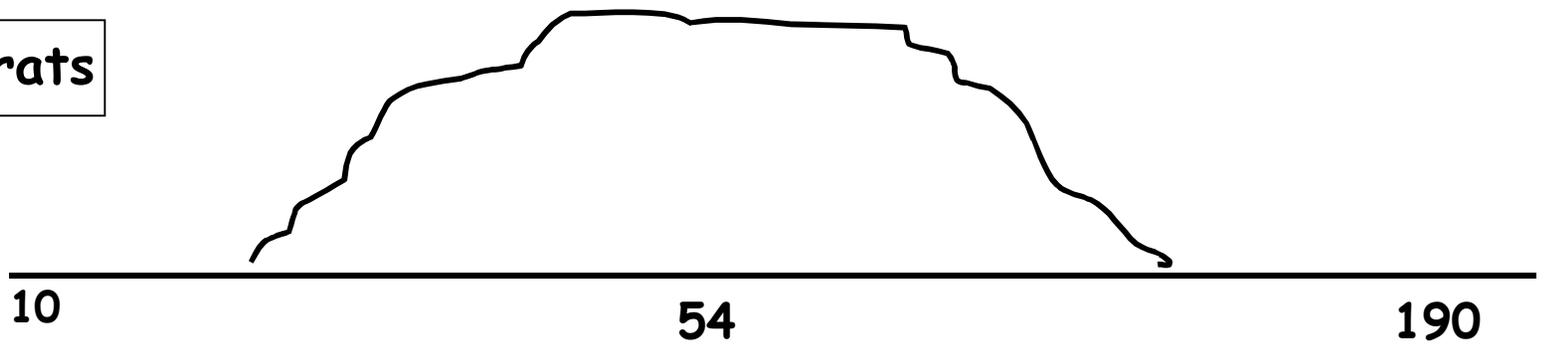
Number of errors in maze test

The response to directional selection for maze learning indicates that the heritability of maze learning is above zero

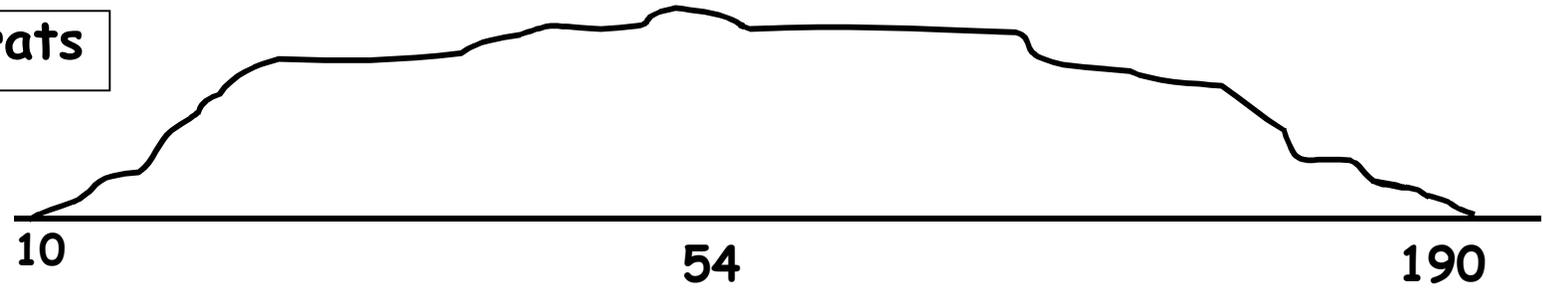
What is the mode of inheritance of individual differences in maze learning?



F₁ rats



F₂ rats



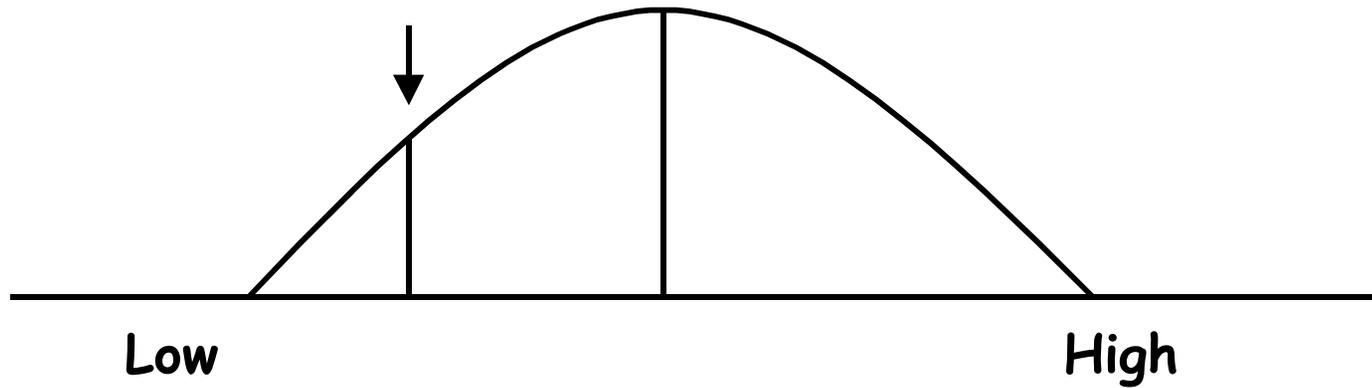
Maze learning appears to exhibit typical complex or polygenic inheritance

Are the maze "bright" and maze "dull" rats good and bad, respectively, at other tasks? In other words is their "intelligence" general or specific?

In three out of five different measures of learning ability, rats of the "dull" strain performed at levels equal to or Superior to rats from the "bright" strain.

Mental
retardation

$$\bar{X} = 100$$



Distribution of IQ scores

MENTAL RETARDATION

DSM4 (Diagnostic and Statistical Manual for Psychiatric Disorders, American Psychiatric Association)

1. Score of 70 or below on a standard IQ (intelligence quotient) test
2. Adaptive functioning: how well the individual meets age and culture specific standards
3. Age of onset before 18

Degrees of severity:

Mild: 55-70

Moderate: 35-55

Severe: 20-35

Profound: below 20

Genetic abnormalities and mental retardation

SINGLE GENE DISORDERS:

1. Phenylketonuria (PKU) used to be the leading single cause of mental retardation
2. X-linked (GDI1, PAK3, Oligophrenin, FMR2)
3. Angelman syndrome
4. Fragile-X syndrome
5. Duchenne muscular dystrophy
6. Picks disease
7. Galactosemia

CHROMOSOMAL DISORDERS

1. Downs syndrome: trisomy 21
2. Turner syndrome: XO
3. Klinefelter syndrome: XXY, XXXY
4. Triplo X syndrome: XXX

Evidence that genetics influences intelligence in man

1. Genetic abnormalities: single gene and chromosomal aberrations are associated with impairments in intelligence
2. Normal variation in intelligence:
Similarities between relatives ?

Demonstrating a genetic component to behavior

1. **Family studies:** Examine similarities between family members. The closer the genetic relationship, the more similar family members are predicted to be
2. **Adoption Studies:** Compares biological with adopted family members. Biologically related individuals are predicted to be more similar than adopted relatives.
3. **Twin studies:** Identical twins compared to fraternal twins. Identical twins predicted to be more similar

Parent-child correlations for IQ in three adoption studies

Study	Adoptive Children		Biological children		Biological mothers and their children adopted by other parents
	Fathers	Mothers	Fathers	Mothers	
Minnesota 1	0.15	0.23	0.39	0.35	
Minnesota 2	0.16	0.09	0.40	0.41	
Texas	0.17	0.19	0.42	0.23	0.32

Conclusion: Despite variability among studies, biological relatives are more similar than adoptive ones.

Test	Twins	Intra-pair Correlation	heritability	
Stanford Binet IQ	MZS (19)	0.69	0.67 \pm 0.13	
	MZT (50)	0.92		
	DZT (50)	0.62		
Otis IQ	MZS (19)	0.73	0.72 \pm 0.10	
	MST (50)	0.92		
	DZT (50)	0.62		
Dominoes IQ	MZS (34)	0.73	0.74 \pm 0.07	
	MZT (37)	0.75		
	DZT (38)	0.69		
<p>MZS Monozygotic raised separately</p> <p>MZT Monozygotic raised together</p> <p>DZT Dizygotic raised together</p>				