Psych 3102
Introduction to Behavior genetics

Lecture 11

Methodology continued

Human studies

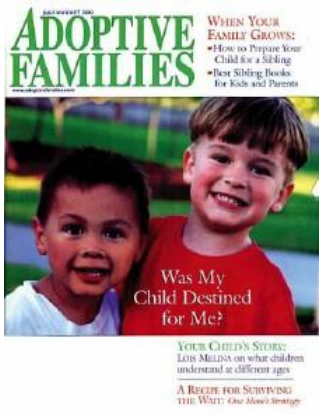
Problems with human studies

- no direct breeding studies possible – methods are therefore not as powerful or as direct as animal studies
- genetically defined populations not available
- environment cannot be controlled

Family studies

provide data on similarities between relatives but genetic and shared environmental influences are confounded

- separated by addition of twin and adoption data



Influences on variation (variance components)

For family, twin and adoption studies

•Genetic

1.Additive genetic
2.Nonadditive genetic

} produce similarities and differences between biological relatives, differences between nonbiological family members

•Environmental

1.Nonshared environmental – produces individual differences within families whether biological and nonbiological

2.Shared environmental – produces similarities within families whether biological or nonbiological

Differences measured by variance

Similarities measured by covariance (standard form = correlation)

Family studies
with twins and adoptions

Components of variance and covariance

RELATIONSHIP	(resemblances) Covariance source	(differences) Variance source
Biological *parent/offspring* *sib/sib, DZ twins* *MZ twin pairs*	shared genes + shared environment	segregating genes + nonshared e. non-shared e only
Adoptive (nonbiological) *p/adoptive child* *sib/adoptive sib*	shared environment only	segregating genes + nonshared e.
Adopted away (biological) *p/adopted away child* *sib/adopted away sib*	shared genes only	segregating genes + nonshared e.

- we can get some estimates of genetic and environmental variance components

Model-fitting

- using variance and covariance data from family, twin, adoption studies
- constructing an explanation in the form of a model that describes the observed data

1. models are constructed by hypothesizing that certain variables (eg additive genetic influence, shared e, non-shared e) are present at certain levels of influence
2. expected variance and covariance values are computed and compared to observed data
3. model with the fewest parameters that best fits the data is chosen

path analysis visual way of analyzing the model and discovering which variable parameters best explain the data

paths = lines drawn to represent statistical effect one variable has on another, independent of all other variables (partial regression coefficients)

variables = trait measurements (shown inside squares)
and latent variance components (shown inside circles)

ACE model

most commonly used model in behavior genetics

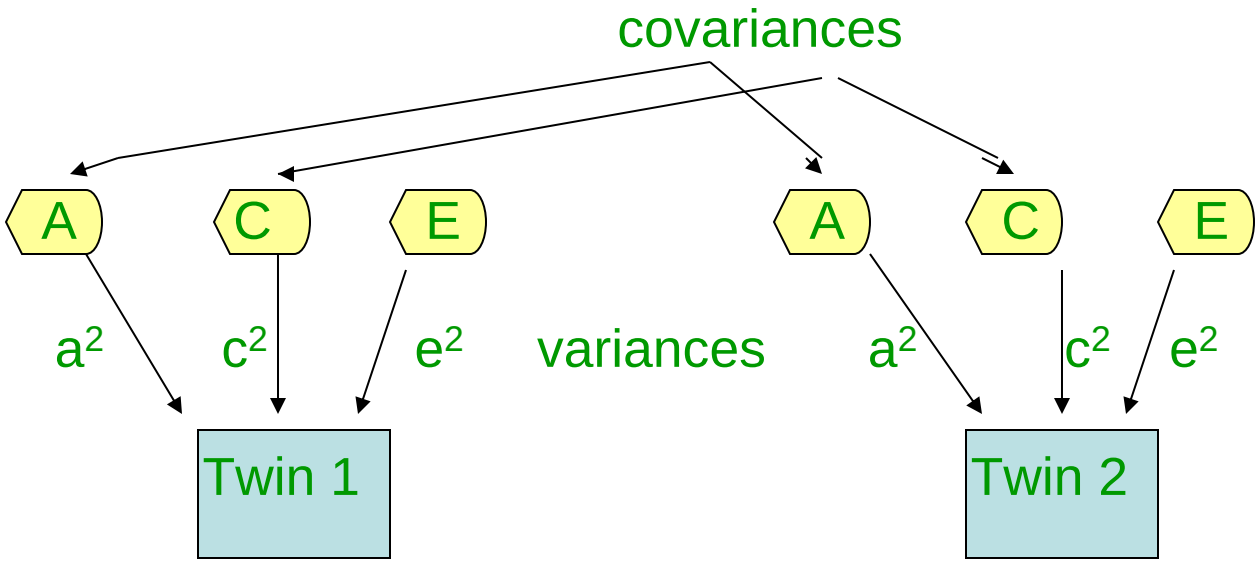
A = additive genetic effects

C = common (shared) environment effects

E = non-shared (individual-specific) environmental effects

$$V_{(P)} = V_{G_A} + V_{E_C} + V_{E_E}$$

ACE path diagram for twin data



measured trait

latent variance component

SUMMARY Sources of variation in human family studies

Genetic influences G

A = additive genetic influences

a^2 = variance due to additive effects of genes

D = dominance effects

d^2 = variance due to dominance effects of genes

I = epistasis

i^2 = variance due to epistasis (interaction between genes

nonadditive

Environmental influences

E = non-shared environmental influences

e^2 = variance due to individual experiences

C = shared (common) environmental influences

c^2 = variance due to environmental differences between families

Problems with adoption studies

1. many fewer adoptions than in the past

current US adoption rate: 15,000 per year

(total 135,000 but a lot of these are foster or step parent)

2010: 11,000 foreign child adoptions

1970: 1% of all babies born, around 175,000, 19.3% of unmarried moms

76,000 babies born by assisted reproductive technology

3. may be unknown prenatal influences

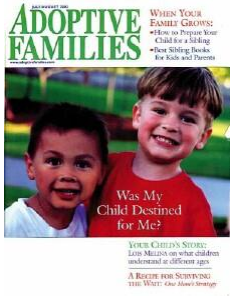
data on both biological parents needed as well as adoptive parents

4. selective placement

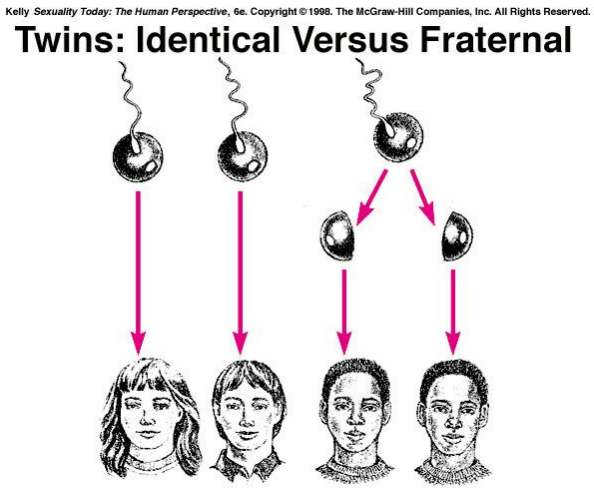
attempts are made to place children in adoptive homes that are similar to the biological parents' homes

data on bio and adoptive parents needed to assess this

may produce correlations between biological home and adoptive home



Twin Studies



monozygotic (MZ) twins identical

dizygotic (DZ) twins fraternal

MZ similarities >DZ similarities for any phenotype influenced by genes, assuming equal environments

Twin births = 1 in 85 live births (1 in 5 conceptions)

All twins
- 1/3 MZ
- 2/3 DZ
  - 1/3 same sex
  - 1/3 opposite sex

comparison of these is best

MZ twinning is independent of maternal age & fertility treatments - both of which increase DZ twinning

Types of MZ twins

Whilst all DZ twins have separate chorionic and amniotic sacs,

MZ twins may have one of 3 types of arrangements *in utero :*

1.Dichorionic MZs (DC-MZ) 32% of all MZ

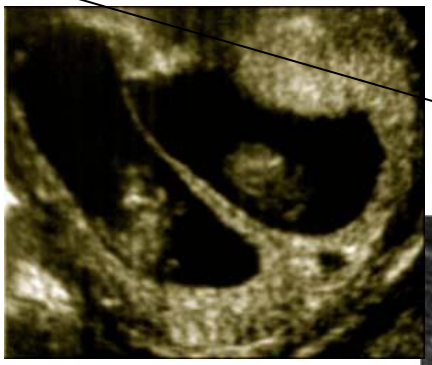
separate placentas, amnions, chorions

zygote splits before Day 4 after fertilization (before implantation)

2 .Monochorionic/diamniotic (MC-DA MZ) 66%

separate amnions but share the same chorionic sac and placenta

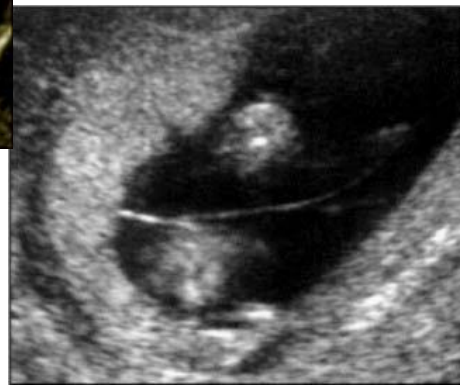
zygote splits between Day 4 and Day 7 (after implantation)



3. Monochorionic/monoamniotic (MC-MA MZ) 2-3%

share amnion, chorionic sac and placenta

zygote splits after Day 8



Effects of uterine environment:

- death rate 6 times higher in twins than singletons
  12% in MC-MZs compared with 2.5% in DC-MZs
- birth weight highest in DZs lowest in MC-MZs
- sex ratio fewer male MZs than expected
  MC-MZ males/female ratio 0.23
- congenital deformities more common in MC-MZs

seems like MZ and DZ twins may not have equally similar uterine environments

BUT does this effect behavioral traits ?

is the equal environments assumption violated?

- cognitive and personality traits, several studies

DC-MZs are less similar to each other than MC-MZs

but effects are very small, may be transient

Jacobs et al (2001) Behavior Genetics Wechsler tests

Behavior Genetics, Vol. 31, No. 2, 2001

Heritability Estimates of Intelligence in Twins: Effect of Chorion Type

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This study investigates the basic assumption of homogeneity of monozygotic (MZ) twins: are there differences according to the timing of the zygotic splitting, early in dichorionic (DC) and later in monochorionic (MC) pairs? We assessed the IQ of 451 same-sexed twin pairs of known zygosity and chorion type with the Wechsler Intelligence Scale for Children-Revised (WISC-R). The variances of within-pair differences were compared for monochorionic (MC), dichorionic monozygotic (DC-MZ) and dizygotic same-sexed (DZ) twins and structural equation modeling was applied. High heritability estimates were found for almost all subscales and IQ-scores. A significant effect of chorion type was found: the MC twins resembled each other more than the DC-MZ twins on the subscales Arithmetic and Vocabulary. The effect accounts for respectively 14% and 10% of the total variance.

KEY WORDS: Twins; chorion type; heritability; intelligence; prenatal environment.

INTRODUCTION

Monozygotic twins (MZ) arise from the division of a single fertilized ovum and are therefore genetically identical. According to differences in the antenatal development, three types of MZ twins can be distinguished. Approximately 32% of the MZ twins are dichorionic, where each fetus has its own chorion and amnion. Because the choriogenesis takes place around the fourth day after conception, dichorionic MZ twins (DC-MZ) probably have originated by a cleavage before the fourth day. Nearly 66% of the MZ twins are monochorionic-diamnionic (MC-DA). These twins share a common chorion, but have their own amnion. The separation must have taken place after the choriogenesis, but before the amniogenesis, which occurs after the seventh day of gestation. So separation probably occurred between the fourth and the seventh day of the gestation. Finally 2 to 3% of the MZ twins are monochorionic-monoamnionic (MC-MA), the two fetuses sharing one chorion and one amnion. In this case, the separation must have taken place after the amniogenesis, so after the eighth day (Leroy, 1991). The assumption that the division of the zygote occurs stepwise later in respectively DC-MZ, MC-DA and MC-MA pairs, has been recently demonstrated to be highly probable by studying X-inactivation in MZ female pairs: X-inactivation is totally symmetrical in MC-MA pairs, almost symmetrical in MC-DA pairs and asymmetrical in DC-MZ pairs (Monteiro *et al.*, 1998; Puck, 1998; Chitnis *et al.*, 1999). All dizygotic twins (DZ) - who result from the fertilization of two different eggs by two different spermatozoa - are dichorionic.

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No mean differences between groups

Variance differences for vocab, arithmetic accounting for 10-14% of variance

Compare with size of genetic variances ranging from 29-83% for various tasks

Effects of Chorion Type on Genetic and Environmental Influences on Height, Weight, and Body Mass Index in South Korean Young Twins

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The present study examined the effects of chorionicity of twins on variations of height, weight, and body mass index (BMI) during childhood in the classical twin design. Mothers of 81 pairs of monochorionic monozygotic (MCMZ), 47 pairs of dichorionic monozygotic (DCMZ), and 457 pairs of dizygotic (DZ) twins drawn from the South Korean Twin Registry reported their children's height and weight. Twins' age ranged from 1.9 to 8.7 yrs, with a mean of 4.0 yrs and SD of 1.7 yrs. We computed maximum likelihood twin correlations and performed model-fitting analyses. In correlational and model-fitting analyses, we treated age and sex as covariates to control their main effects. Maximum likelihood MCMZ, DCMZ, and DZ twin correlations were, respectively, .96, .92, and .74, for height, .88, .91, and .57 for weight, and .93, .92, and .61 for BMI. The pattern of these twin correlations suggested very modest chorion effects on body measures. Model-fitting analyses confirmed the observations from twin correlations. Whereas genetic and shared environmental influences were significant for all three body measures, chorion effects attained statistical significance only for height (4%), and those for weight and BMI were zero. These findings indicate that genetic and environmental estimates for height, weight, and BMI during childhood are biased little by the chorion type of MZ twins, supporting the validity of the equal prenatal environment assumption in the classical twin design.

The classical twin method compares similarities between monozygotic (MZ) and dizygotic (DZ) twins. One of the crucial assumptions of the classical twin design is that MZ and DZ twins experience similar degrees of prenatal environment. Due to the variation in placental anatomy, however, MZ and DZ twins experience different environments during the prenatal period, and if these substantially influence the trait under study, the classical twin study will yield biased estimates of genetic and environmental factors.

As the zygotes of DZ twins implant individually in the uterus, each embryo develops its own placenta and chorion. Unlike DZ twins, MZ twins vary in their placentation, according to the timing of division of the inner cell mass. If MZ twins are divided at, or before, the morula stage, that is, around the fourth day of gestation, then each twin will develop an individual chorion and amnion like DZ twins. These twins are known as dichorionic MZ (DCMZ) twins. If the division occurs between the fourth and the seventh day of the gestation, then these twins will share a common chorion, known as monochorionic MZ (MCMZ) twins. Finally, if the division takes place after the eighth day, then the two fetuses will share a common amnion as well as a common chorion. These twins are called monochorionic monoamnionic (MCMA) MZ twins.

Approximately a third of MZ twins are DCMZ and two thirds are MCMZ. Only 2% to 3% of the MZ twins are MCMA twins (Bulmer, 1970). The sharing of a chorion and a placenta, and the presence of vascular anastomoses between the circulations of the two fetuses allow exchange of blood, hormones, oxygen, and other substances like alcohol and viruses between both members of the twin pair (Machin et al., 1996). For this reason, MCMZ twins may resemble each other more than DCMZ twins in postnatal development. Critics of twin studies argue that MCMZ twins should be removed from twin analyses to minimize biases in estimation of heritability (Phillips, 1993).

In twin studies of chorion effect, so far, more attention has been given to personality and cognitive abilities than to other traits, perhaps because some of personality traits and cognitive abilities have been shown to be related to hormonal influences

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Determination of zygosity

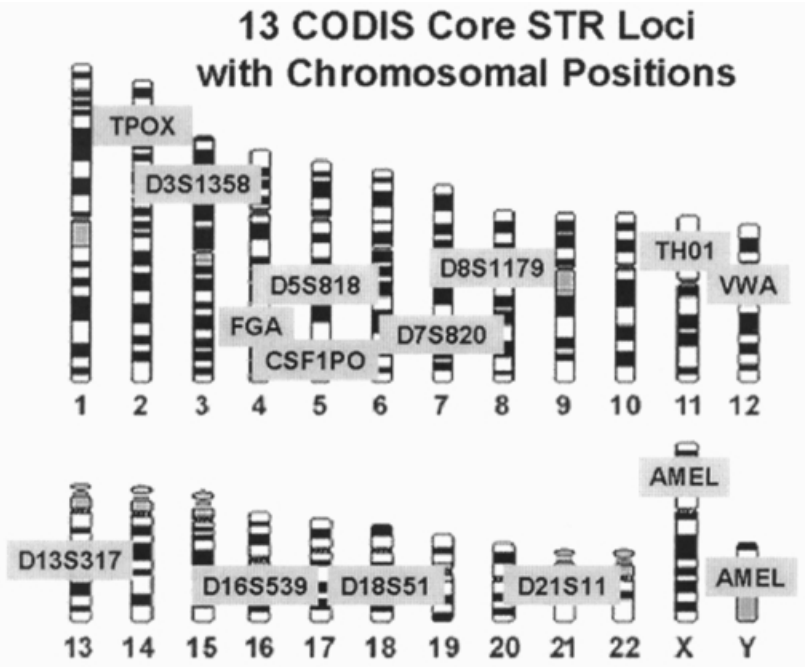
- visual appearance 90% accurate

- use of DNA markers 100% accurate

CODIS panel

(COmbined DNA Index System)

14 VNTR (STR) markers, each with multiple alleles



Physical similarity and twin zygosity in children

Measured or asked of mother	% of twins "exactly similar" (or "yes" responses)	
	MZ	DZ
"Is it hard for strangers to tell them apart?"	100	8
Eye color	100	30
Hair color	100	10
Facial appearance	49	0
Complexion	99	14
Weight	46	6
"Do they look alike as 2 peas in a pod?"	48	0
"Does either mother or father ever confuse them?	79	1
"Are they sometimes confused by others?"	93	1
Height	56	13
Number of pairs	181	84

Cohen et al (1975) Archives of General Psychiatry,13,1373

However

identical genotypes at conception may not result in identical genetic outcomes

expression pattern differences (epigenetics)

DNA methylation profiles may differ between identical twins

- research shows much less difference within twin pair than was suspected

– DZ methylation pattern differences are greater than MZ

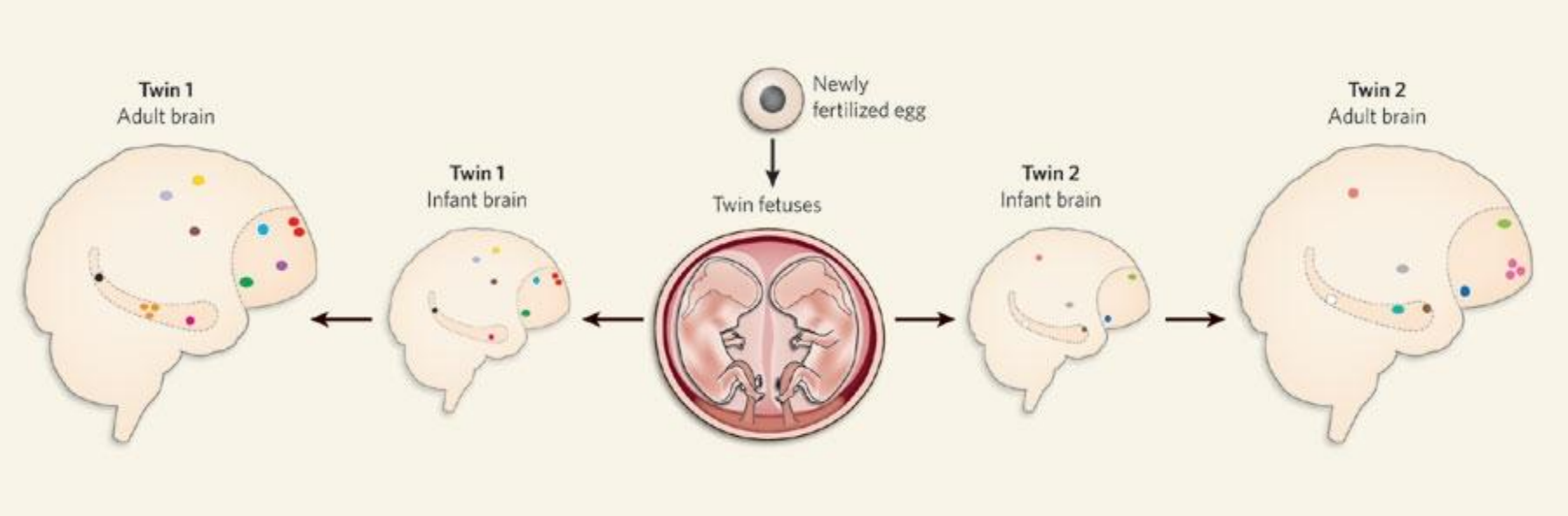
changes in sequence after conception

retrotransposon-induced changes

mutations introduced during DNA replication before mitosis

Human brain variation by retrotransposon

from Coufal et al (2009), Nature 460)



Twins that are genetically identical at conception may later show brain cell genetic differences at birth because of new Line1 (retrotransposon) insertions that take place during the development of the nervous system in the fetus.

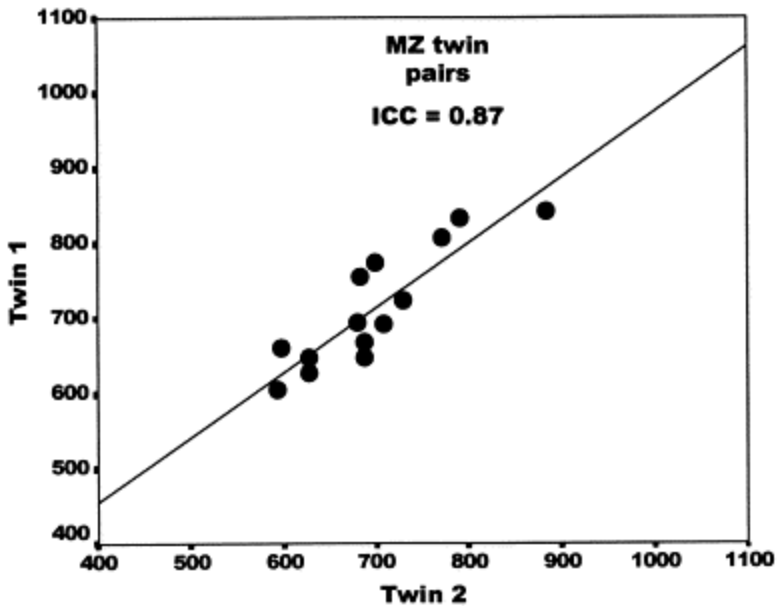
Ongoing retrotransposition in neural progenitor cells will further diversify the genetic makeup of their brains in adulthood. Depending on the target genes and neurons affected, the twins may differ in brain function or dysfunction

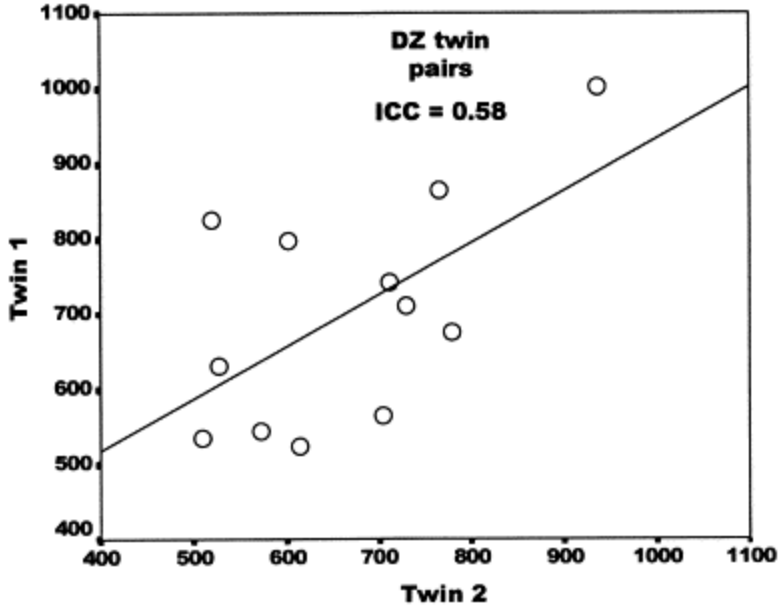
Each unique insertion is represented by a different color. Darker shaded areas highlight brain regions more likely to be affected after birth.(hippocampus,frontal lobe

Behavior genetic analysis of family, twin and adoption studies

1. If the MZ correlation is greater than DZ correlation, genetic variance is present

- this would be untrue if MZs shared more environment than DZ and were more similar as a result (violation of equal environments assumption





Size of corpus callosum

2. Results from family twin and adoption studies are applicable to the general population from which they come

- this would be untrue if samples were not representative of the general population

3.Correlations between adoptive family members are due to shared e only

- this would be untrue if there was selective placement

4. Correlations between adopted apart relatives are due to shared genes only

- this would also be untrue if there was selective placement

Assumptions underlying methodology

1. Equal environments assumption (twin studies)

do MZs and DZs have equally similar environments?

why does the answer to this matter?

if MZs have more similar environments than DZs, MZ correlation will be inflated, gene effects over-estimated

To test the assumption, for behavioral traits

- look for effects of intrauterine environments (chorion arrangements)
- twin-mislabelling studies - look for evidence that treatment has an effect on similarities
- look for effects of differential treatment
- look for effects of having more similar physical appearance

Consider: more sharing of environment *in utero* actually produces greater DISsimilarities eg. birth weight differences MZ>DZ

Overall – equal environments assumption holds up

2. Samples are representative of the general population

why does this matter?

if not, results may not apply to general population

For twin studies

twins are generally born prematurely (3-4 weeks)

- weigh less than singletons (30% less)
- show delayed language development
- early verbal ability test scores are slightly lower
- suffer more obstetric complications

But – do these effects influence the trait being studied?

how can we test if the individuals used in a study are representative of the general population to which they belong?

3. Selective placement (adoption studies)

- attempts are made by adoption agencies to match biological and adoptive homes
- matching is mainly on basis of physical characteristics

  height hair/eye color ethnicity
- some matching for parental education, religion
- selection against extreme poverty, serious psychopathology

  alcoholism, criminal behavior, psychosis, drug abuse

Again – do these factors influence resemblance for behavioral traits?

Selective placement can be accounted for in analysis if data on biological parents is available – look for correlations between traits measured in bio parents and adoptive parents

Effects found to be mostly small or non-existent for behavioral traits

Colorado Adoption Project

Adoptive families

- Caucasian
- No known disabilities
- Adoptees placed in foster homes on release from hospital
- Placed in adoptive homes within 1 month of birth
- No selective placement for educational attainment, socioeconomic status, cognitive ability

- Control families matched to adoptive families on basis of

  sex of proband

  number of children in family

  father's age, years of education

  rating of family on occupational scale

  SES and educational attainment of whole family