Psych 3102
Introduction to Behavioral Genetics

Lecture 21

Genetics of mental disorders

Adult psychopathology

High incidence of serious psychological episodes:

- USA 50% report at least one episode/lifetime
  30% report an episode within the last year

Adult psychopathologies studied in behavior genetics:

schizophrenia
affective/mood disorders
substance abuse disorders
personality disorders

Childhood

autism/autistic spectrum disorders
ADHD
conduct disorder

5 limitations of the current diagnoses

1. mental illness is classified into a series of discrete disorders

2. each symptom used to diagnose the disorder is equally weighted

3. multiple diagnoses are possible

4. organization of behavior into multiple 'axes' :
Axis I clinical syndromes & disorders
Axis II personality disorders & mental retardation
Axis III general medical conditions that effect mental health
Axis IV psychosocial problems
Axis V global assessment of functioning

little distinction between some disorders in different axes (eg OCD & OCPD)
alternative model based on phenotypic structure often used in behavior genetics

Review of definitions:

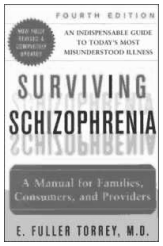
- prevalence
- risk
- proband
- concordance
- correlation
- liability-threshold model
- comorbidity
- latent trait analysis
- endophenotype

Schizophrenia

- long-term psychotic disorder (has to occur for 6 months)
  - delusions, hallucinations (especially auditory)
  - gross impairment in reality-testing, loss of ego boundaries
  - disorganized speech, behavior

- affective flattening, less goal-oriented behavior (avolition)

- marked social, occupational dysfunction



Onset: late adolescence, early adulthood
prognosis worse with earlier onset
episodic but lasts a lifetime

Prevalence: 1% worldwide

Causes: developmental neurological disorder
-deficits in information-processing, stimulus-filtering

- neurological differences later seen in SZ brains
may be present at birth to some extent
upbringing, experiences not causal on own

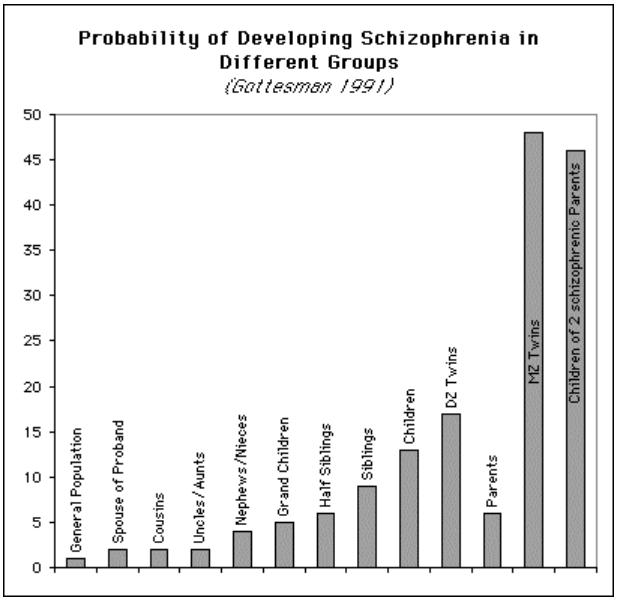
Treatment: antipsychotic drugs, behavioral therapy, support systems now manage most symptoms

Drug treatments indicate 2 systems influence characteristics:
dopamine system ‘hyperactive’ brain component

serotonin system hallucinations

Family studies

40 studies



why is risk lower in parents of SZ patients?

why is spousal risk 2%?

- familial risk could be due to shared genetic factors or shared environmental factors

Twin and adoption studies

- 4 twin studies:
- heritability ~ 80% based on 14 twin studies and liability threshold model
- adoption studies:
  adopted away sibs risk = 11% (same as reared together)
- few pre-natal effects : risk to children is similar whether Mom or Dad had SZ, half-sibling data confirm this
- G x E: at risk offspring had higher risk if adopted into poor-functioning homes

Shared environment seems to be unimportant, unless genetic risk present
Non-shared environment or stochastic events are more important
co-twin control method

birth complications neurological abnormalities
attention problems as children prenatal viral infections

This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

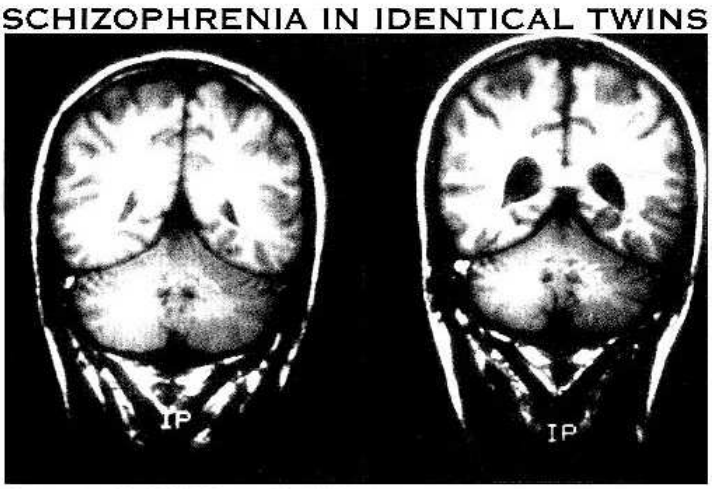


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

Defining schizophrenia

- is it one disorder or a heterogeneous set of disorders?

1. 'classical' subtypes:

catatonic (passive, motor symptoms)
paranoid (active, psychotic symptoms)

- not supported by evidence from genetic studies

2. more severe forms are more heritable:

Type I best prognosis, active symptoms only (hallucinations), responds well to drug treatment

Type II worse prognosis, more severe, active and passive symptoms (withdrawal) , less treatable

- fits well with liability-threshold model for the disorder

Biological basis - what is known?

- hyperactiviity of brain dopaminergic systems
-

- serotonin system
-

- cognitive deficits in information-processing and stimulus-filtering (do not allow filtering of most sensory & cognitive stimuli)
-

- social-interaction impairments

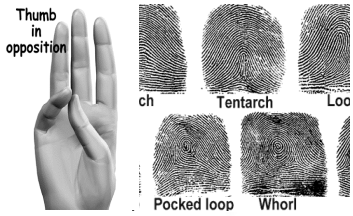
Predicting liability and finding genes

- early diagnosis, predicting those at greatest risk seems important:

finding reliable predictors will also aid in the search for genes

- locating liability genes will further aid diagnosis and treatment

hence the search for endophenotypes – behavioral 'markers' that predict liability:



Neurobiological signs

poor tandem walk

poor finger/thumb opposition

dermatoglyphic asymmetry differences

Childhood IQ tests - poor attention

need all 3 for best prediction

poor verbal working memory

poor gross motor skills

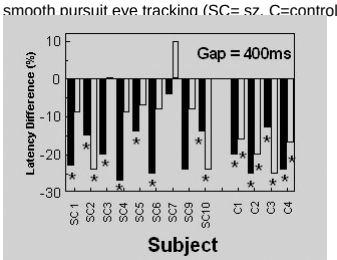
- neurobiological signs & childhood tests indicate problems in neurodevelopment

What causes them?

- all causative factors must be common and global

More promising endophenotypes:
smooth-pursuit eye tracking

smooth pursuit eye tracking (SC= sz, C=control)



prepulse inhibition
P50 sensory gating deficit
gene on chromosome 15 mouse model
α7 nicotinic receptor gene promotor variants

Other genetic risk factors:

- microdeletions on chromosome 22q11 – highest known genetic risk factor, 25-30% of people with this deletion have SZ

- 5HTR2a serotonin receptor chr 13
- RGS4 chr 1 GABA & glutamine signaling

- dysbindin gene chr 6
- neuregulin 1 chr 8

20 genomewide linkage scans – few replicated results. Why?

-
-
-

Mood disorders

- severe swings of mood
- lifetime risk of suicide 19%

2 categories studied in behavior genetics:

major depressive disorder

bipolar disorder

Depressive disorder WHO : #1 cause of disability in US

depressed mood – onset over weeks/months, lasts several months, dissipates slowly

- loss of interest in usual activities sleep and appetite disturbances

- energy loss thoughts of death, suicide

Prevalence = 17% females: 25-30% males: 12-15%

US teenage girls ~16% 4-8% US children

significant upward trend + earlier onset since WWII

Bipolar disorder

- cycles between periods of depression and mania

Mania: euphoria inflated self-esteem sleeplessness racing thoughts

talkativeness distractibility hyperactivity reckless behavior

- begins & ends more suddenly than depressive phase

- episode duration varies (days to months)

- high rate of social dysfunction
- 15% mortality through suicide

Prevalence: 3% same in males and females

Main risk period: 16-25 years median age of onset 20 years

Comorbidity risks (for both depression and bipolar disorder) : anxiety and substance abuse disorders, personality disorders

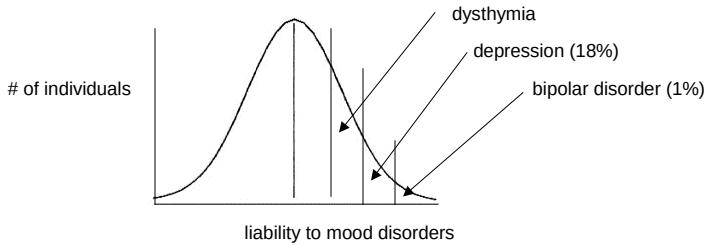
Family studies on mood disorders

Review of many studies (McGuffin & Katz, 1986):

	Severe depression	Bipolar disorder
First degree relatives	9%	8%
Unrelated (prevalence)	3%	1%
Relative with bipolar	14%	
Relative with depression		1%

More recent studies put 1st degree relative risk at 11-16% for bipolar, 67% risk if both parents affected

Evidence points to liability-threshold model for mood characteristics:



- continuum for mood disorders replaces ‘category’ classification : reactive endogenous
- more severe, earlier onset, more recurrent , show higher heritability
- late onset (after age 40) depression is much less heritable
- response to drug-therapy runs in families

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Twin studies

		Depression	Bipolar disorder
Concordances	MZ	43%	55%
	DZ	28%	7%

- confirms evidence from family studies for genetic influence

- to estimate variance components, need some measure of phenotype:

Kendler et al (1992)

female twins population-based sample individual clinical interviews to get symptom counts as measure of disorder

In this study: lifetime prevalence of mood disorder = 29-33%

(DSMIII-R)

For depressive symptoms	N(pairs)	Correlation (tetrachoric)
MZ	590	0.44
DZ	440	0.19

Sources of variance: additive gene effects 42%

non-shared environment 58%

no evidence for shared environment

Bipolar disorder: similar recent studies (McGuffin, 2003)

heritability = 80% no shared e

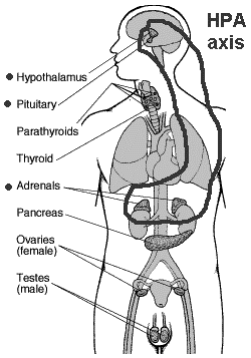
Endophenotypes for mood disorders

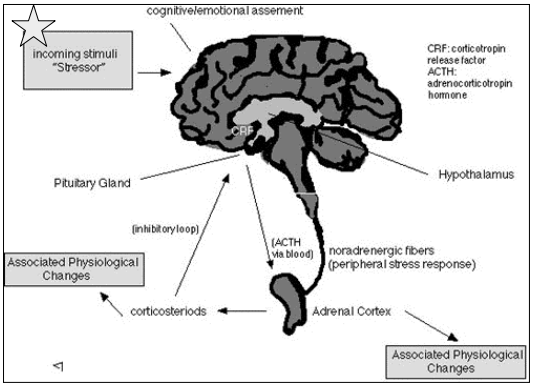
Depression: gray-matter reductions in certain brain regions reported for early-onset depression

Bipolar disorder: same gray-matter reductions

+ poor performance attention, memory tests, even in remission

+ abnormalities in regulation of hypothalamus/pituitary/adrenal axis





Finding genes for mood disorders

- X chromosome?
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  -
  -
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Most success so far for genes for bipolar I - larger effect

Multivariate analyses: reveal co-occurrences of disorders

overlap between genes for bipolar and schizophrenia

are they distinct disorders?

anxiety and depression are essentially the same disorders genetically

Whichever disorder is manifest mainly seems to depend on non-shared e

Genotype/environment interaction

5HTT (serotonin transporter)

depression in response to life events

why do life events cause depression in some but not others?

Caspi et al (Science, July, 2003)

- identified stressful life events known to cause depression

- reaction to the event depends on the genotype of the individual
- functional polymorphism in promotor of serotonin transporter gene associated with risk for depression after stressful event

chr 17 ~50% Causasians have risk-allele (short allele)