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 (e.g. 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
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?

- hyperactivity 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

prepulse inhibition
P50 sensory gating deficit
gene on chromosome 15 mouse model
α7 nicotinic receptor gene promoter 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):

<table>
<thead>
<tr>
<th></th>
<th>Severe depression</th>
<th>Bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relatives</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Unrelated (prevalence)</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Relative with bipolar</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Relative with depression</td>
<td></td>
<td>1%</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ</td>
<td>43%</td>
<td>55%</td>
</tr>
<tr>
<td>DZ</td>
<td>28%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- confirms evidence from family studies for genetic influence

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• 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)

<table>
<thead>
<tr>
<th>For depressive symptoms</th>
<th>N(pairs)</th>
<th>Correlation (tetrachoric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td>590</td>
<td>0.44</td>
</tr>
<tr>
<td>DZ</td>
<td>440</td>
<td>0.19</td>
</tr>
</tbody>
</table>

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?
  -
  -
  -
  -
  -

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% Caucasians have risk-allele (short allele)