Lecture 3
Bipolar Disorder

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Outline

A. Introduction
   - A brief history of bipolar (BP) disorder
   - Core clinical features
   - Diagnosis, clinical course and management
   - Epidemiology and societal burden
   - Famous individuals with BP disorder

B. Causes of BP disorder: pharmacology, neurobiology, environment, genetics
   - Current drugs therapies
   - Brain regions implicated in BP disorder
   - Environmental risk factors
   - Genetics

C. Developing new therapies to treat BP disorder
   - Novel therapeutic approaches and prevention

D. References, internet resources, additional slides
A. Introduction
Brief history of bipolar disorder
(aka manic-depressive illness, manic-depressive psychosis)

- Ancient sources describe psychological states of mania and melancholia, but these were not considered to be aspects of a single underlying disorder.

- Emil Kraepelin (1893) distinguished “manic-depression” and “dementia praecox” as distinct disorders, with the former characterized by recurring bouts of mania and depression without progressive cognitive decline and the later characterized by psychosis and progressive dementia.

- John Cade (1949) demonstrated that lithium salts are effective in treating mania, the first effective drug for the treatment of a mental illness.

- Karl Leonhard (1957) introduced the term “bipolar disorder” to describe disorders containing both mania and depression.

- Morens Schou (1960s) carried out systematic studies on the effectiveness of lithium salts in treating bipolar disorder.

Emil Kraepelin  
(1956-1926)  
German psychiatrist  
Heidelberg and Munich Universities

John Cade  
Australian psychiatrist  
(1912-1980)

Mogens Schou  
Danish psychiatrist  
(1918 -2005)  
Psychiatric Research Institute  
Aarhus University, Denmark
## Core Symptoms

(National Institute of Mental Health)

<table>
<thead>
<tr>
<th>Symptoms of mania or a manic episode include:</th>
<th>Symptoms of depression or a depressive episode include:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood Changes</strong></td>
<td><strong>Mood Changes</strong></td>
</tr>
<tr>
<td>• A long period of feeling &quot;high,&quot; or an overly happy or outgoing mood</td>
<td>• An overly long period of feeling sad or hopeless</td>
</tr>
<tr>
<td>• Extreme irritability</td>
<td>• Loss of interest in activities once enjoyed, including sex.</td>
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<tr>
<td><strong>Behavioral Changes</strong></td>
<td><strong>Behavioral Changes</strong></td>
</tr>
<tr>
<td>• Talking very fast, jumping from one idea to another, having racing thoughts</td>
<td>• Feeling tired or &quot;slowed down&quot;</td>
</tr>
<tr>
<td>• Being easily distracted</td>
<td>• Having problems concentrating, remembering, and making decisions</td>
</tr>
<tr>
<td>• Increasing activities, such as taking on new projects</td>
<td>• Being restless or irritable</td>
</tr>
<tr>
<td>• Being overly restless</td>
<td>• Changing eating, sleeping, or other habits</td>
</tr>
<tr>
<td>• Sleeping little or not being tired</td>
<td>• Thinking of death or suicide, or attempting suicide.</td>
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<tr>
<td>• Having an unrealistic belief in one's abilities</td>
<td></td>
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<tr>
<td>• Behaving impulsively and engaging in pleasurable, high-risk behaviors</td>
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</tbody>
</table>
DSM-5 BP spectrum disorders

- Bipolar I Disorder
- Bipolar II Disorder
- Cyclothymic Disorder

- Substance/Medication-induced bipolar and related disorder
- Bipolar and Related Disorder due to Another Medical Condition
- Other Specified Bipolar and Related Disorder
- Unspecified Bipolar and Related Disorder

Also: schizoaffective disorder, bipolar type
Mood changes over time with BPI, BPII and unipolar depressive disorder

“Life-charts” are important tools for the diagnosis and treatment of BPD

Figure 1: Life chart showing progression of bipolar disorder
Recording mood changes on a life chart can help clinicians to monitor and manage patients with bipolar disorder. According to severity, manic and hypomanic symptoms are registered above the state of euthymia (normal mood state) whereas depressive symptoms are depicted below.
“Manic” symptoms (DSM-5):

1) Inflated self-esteem or grandiosity
2) Decreased need for sleep
3) More talkative than usual or pressure to keep talking
4) Flight of ideas or subjective experience that thoughts are racing
5) Distractibility, as reported or observed
6) Increase in goal-directed activity or psychomotor agitation
7) Excessive involvement in activities that have a high potential for painful consequences
“Depressive” symptoms (DSM-5):

1) Depressed mood, most of the day nearly all day
   (In children and adolescents, can be irritable mood.)

2) Markedly diminished interest of pleasure in all, or almost all, activities

3) Significant weight loss when not dieting or decrease or increase in appetite (in children, consider failure to make expected weight gain.)

4) Insomnia or hypersomnia

5) Psychomotor agitation or retardation

6) Fatigue or loss of energy

7) Feelings of worthlessness or excessive or inappropriate guilt

8) Diminished ability to think or concentrate, or indecisiveness nearly

9) Recurrent thoughts of death (not just fear of dying),
   recurrent suicidal ideation without a specific plan.
   Or a suicide attempt of a specific plan for committing suicide.
BP disorder in children and adolescents (Early-onset BP disorder)

**DSM-5 diagnostic category:**
Disruptive mood dysregulation disorder

**Disorders often mistaken for BP disorder:**
Attention Deficit/hyperactivity disorder (ADHD)
Severe mood dysregulation (SMD)

### Symptoms of mania include:

#### Mood Changes
- Being in an overly silly or joyful mood that is unusual for your child. It is different from times when he or she is just being silly and having fun.
- Having an extremely short temper and unusual irritability.

#### Behavioral Changes
- Sleeping little but not feeling tired
- Talking a lot and having racing thoughts
- Having trouble concentrating or paying attention, jumping from one thing to the next in an unusual way
- Talking and thinking about sex more often than usual
- Behaving in risky ways more often, seeking pleasure a lot, and doing more activities than usual.

### Symptoms of depression include:

#### Mood Changes
- Being in a sad mood that lasts a long time
- Losing interest in activities once enjoyed
- Feeling worthless or guilty.

#### Behavioral Changes
- Complaining about pain more often, such as headaches, stomach aches, and muscle pains
- Eating a lot more or less than usual and gaining or losing a lot of weight
- Sleeping or oversleeping when these were not problems before
- Losing energy
- Recurring thoughts of death or suicide.
Epidemiology and societal burden

- Bipolar I: lifetime prevalence = 1% (USA)
  Bipolar II: lifetime prevalence = 1.1%
  Subthreshold symptoms: lifetime prevalence = 2.4%

- Estimated age-standardized rates are similar worldwide: 421 – 492/100,000

- Peak years of onset in late adolescence and early adulthood.

- Bipolar disorder Disability-Adjusted Life Years (DALY), a measure of the burden of disease; one DALY = one year of “healthy” life lost, due to living with disability or early death. (data from WHO)

  = 180 – 186 per 100,000
  = 230 – 235 per 100,000
Modern drug therapy

Mood stabilizers:
  e.g., lithium carbonate

Anticonvulsants:
  e.g., valproic acid, carbamazepine, lamotrigine

Second-generation antipsychotics:
  e.g., quetiapine

Antidepressants:
  e.g., fluoxetine
Comorbidities and long-term issues

- Anxiety disorders: post-traumatic stress disorder (PTSD), social phobia
- Attention deficit/hyperactivity disorder (ADHD)
- Alcoholism and substance abuse
- Suicide
- Physical illnesses: thyroid disease, migraine headaches, heart disease, obesity, diabetes
Famous individuals with bipolar disorder

- Robert Schumann
  German Composer
  Died in mental hospital

- Ludwig Boltzmann
  German Physicist
  Died of suicide

- Sylvia Plath
  American Poet
  Died of suicide

- Graham Greene
  English Author

- Virginia Woolf
  English author
  Died of suicide (1941)

- Kay Redfield Jamison
  American clinical psychologist, Prof
  Johns Hopkins Univ.
B. Causes of BP disorder: pharmacology, neurobiology, environment, genetics
Drugs currently used in the treatment of BP disorders

Mood stabilizers:
- Lithium salts (Li⁺carbonate, Li⁺citrate, Li⁺sulfate)

Anticonvulsants:
- Sodium valproate, divalproex sodium (Depakote)
- Carbamazepine (Tegretol)
- Lamotrigine (Lamictal)
- Gabapentin (Neurontin)
- Topiramate (Topamax)
- Oxacarbazepine (Trileptal)

Second-generation antipsychotics:
- Olazapine (Zyprexa)
- Aripiprazole (Abilify)
- Quetiapine (Seroquel)
- Risperdone (Risperdal)
- Ziprasidone (Geodon)

Antidepressants:
- Fluoxetine (Prozac)
- Paroxetien (Paxil)
- Sertraline (Zoloft)
- Bupropion (Wellbutrin)
Lithium salts
(Lithium carbonate, lithium citrate, lithium sulfate)

Lithium citrate

Possible Li$^+$ targets:
- Glycogen synthase kinase 3-beta (GSK3β)
- Inositol monophosphatase

Although lithium salts had previously been used in the treatment of mania by physicians in Denmark and the US, the rediscovery of the calming effects of lithium in 1949 is considered to be the beginning of modern neuro-pharmacology. John Cade’s discovery was made by serendipity. While investigating the effects of urine extracts isolated from schizophrenia patients following injection in guinea pigs, he examined the effects of the lithium salt of uric acid as a control, eventually identifying lithium as a calming agent. (Note the importance of experimental controls!) The calming properties of lithium salts were soon confirmed in mentally ill patients.

Systematic and meticulous studies carried out by Mogen Schou firmly established lithium’s effectiveness in preventing episodes of mania. Recent studies indicate that may also be effective in preventing episodes of depression and in reducing the risk of suicide.

Narrow therapeutic window and teratogenic effects prevent use in some patients.
Valproic acid salts  
(sodium valproate, valproate semi-sodium)

Proposed molecular targets (inhibition):
1) GABA transaminase
2) Voltage-gated Na$^+$ channels
3) Voltage-gated Ca$^{2+}$ channels
4) Histone deacetylase

Pierre Eymard (1962) discovered valproic acid’s anticonvulsant properties while screening compounds capable of suppressing pentylenetetrazol-induced seizures. The solvent used for these compounds, valproic acid (a liquid at room temperature), alone was serendipitously discovered to be effective in suppressing seizures (Note again the importance of experimental controls!)

Often used in combination with lithium salts for the treatment of BP disorder.

Note: valproic acid also has tetratogenic properties and is not recommended for use during pregnancy. Autism and low IQ in offspring have also been linked to use of valproic acid salts during pregnancy. Liver, hematopoietic, pancreatic, renal and ovary damage are also possible side-effects.
Carbamazepine (Tegretol)

Used primarily in the treatment of epilepsy, BPI disorder and trigeminal neuralgia

Proposed molecular targets:
1) Voltage-gated Na\(^+\) channels (inhibition)
2) GABA\(_A\) receptors (potentiation)


May cause birth defects if taken during pregnancy. Additional side-effects include potentially fatal Steven-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN), particularly in individuals of South Asian descent who carry the HLA-B*1502 allele.

Oxcarbazepine (Trileptal)
Lamotrigine (Lamictal)

Used primarily in the treatment of epilepsy and BP I disorder

Proposed molecular targets (inhibition):
1) Voltage-gated Na\(^+\) channels (inhibition)
2) Voltage-gated Ca\(^{2+}\) channels (N and P/Q/R-subtypes)

Approved for treatment of BP I in US in 2003 (adults only).

Considered to have low risk to fetus, when take during pregnancy.
Causes serious skin disorders (SJS/TEN) in some individuals.
Brain regions implicated in BP disorder: human emotions

- Goal directed behavior
- Expression
- Subjective experience
- Physiologic responses

↑

- Appraisal
- Arousal

“Affective state” comprising autonomic, neuroendocrine, somatomotor responses, “feelings”

conscious + unconscious processes

response to an “emotive” stimulus

e.g., pursue or run away
Regulation of affective states is required for contextually appropriate behaviors

Brain regions responsible for perception and control of emotions

DLPFC = dorsolateral prefrontal cortex
DMPFC = dorsomedial prefrontal cortex
ACG = anterior cingulate gyrus
VLPFC = ventral lateral prefrontal cortex
Brainstem nuclei: dopamine-, norepinephrine- and serotonin-producing neurons

“Dorsal” System:
Selective attention
Planning
Effortful regulation

“Ventral” system:
Assessment of “salience”
Generation of affective states
Regulation of autonomic response

Philips ML et al, Biological Psychiatry 54, 2003
Proposed changes in “dorsal” and “ventral” system regulatory circuits in BP disorder

related to decreased volume and activity of PFC?

related to enlarged amygdala?

mood swings irritability emotional lability

Philips ML et al, Biological Psychiatry 54, 2003
Consistent abnormalities in BPD detected by fMRI imaging

• Abnormal activation (usually increased) or function of the amygdala in both manic and depressed states; also observed in unaffected relatives of BP patients (i.e., abnormal activation of ventral system).

• Decreased activation in the lateral and medial ventral PFC independent of mood state (i.e., decreased activity in dorsal system); some prefrontal recovery may occur in euthymia to compensate for over-active amygdala.

• Reduced functional connectivity between ventral PFC and amygdala detected in both manic and depressed states (detected as reduced temporal co-activation).

• Abnormal activation and connectivity with amygdala has also been observed in the anterior cingulate cortex.

Strakowski et al, Bipolar Disorders 14, 2012
Environmental risk factors

- Childhood trauma, including physical, sexual or emotional abuse and emotional neglect, are risk factors for the development of BP disorder in adults.

- In particular, childhood trauma is associated with earlier onset of the illness, a rapid cycling course, more psychotic features, higher number of lifetime mood episodes, as well as suicide ideation and attempts.

- Life events are also often triggers for manic or depressive episodes in adolescents and adults. Hypomania triggers include: falling in love, recreational stimulant use, starting a creative project, late night partying, going on vacation and listening to loud music. Depression triggers include: stressful life events, general stress, fatigue, sleep deprivation, physical injury or illness, menstruation and decreases in physical exercise.
Evidence for a genetic component in BP disorder

- BP disorder is known to “run in families” sometime in conjunction with schizophrenia or major depression. Risk declines with genetic relatedness to proband.

- Lifetime risk of narrowly defined BP disorder = 0.5-1.5%; first degree relative = 5 - 10 (\(\lambda_s\) = relative risk to sibling of affected individual compared with risk in general population = 8); monozygotic co-twin = 40 - 70% (\(\lambda_{MZ}\) = 60); estimated heritability from twin studies: ~90%.

- Genes are important, but not the “whole story.”
Results of family-based “linkage” and population-based genetic “association” studies

• A very large linkage study (972 pedigrees) failed to identify any chromosomal loci strongly associated with BP disorder.

• Likewise, hundreds of small-scale “candidate gene” population-based case-controls studies have yielded inconsistent results and no proven gene that contributes to BP disorder.

• By contrast, large-scale whole genome association studies (GWAS), which examine associations between allele frequencies and/or genotypes for several hundred thousand to more than one million genetic markers (usually SNPs: single nucleotide polymorphisms) has identified several robust and replicable candidate BP disorder genes.
**Genome-wide significant association in European-origin samples for BP disorder**

<table>
<thead>
<tr>
<th>Single nucleotide polymorphism</th>
<th>Study</th>
<th>p value</th>
<th>Odds ratio</th>
<th>Nearest gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD rs12576775</td>
<td>PGC-BD[^13]</td>
<td>$4.4 \times 10^{-8}$</td>
<td>1.14</td>
<td>ODZ4</td>
</tr>
<tr>
<td>BD rs4765913</td>
<td>PGC-BD[^13]</td>
<td>$1.5 \times 10^{-8}$</td>
<td>1.14</td>
<td>CACNA1C</td>
</tr>
<tr>
<td>BD rs1064395</td>
<td>Cichon et al[^30]</td>
<td>$2.1 \times 10^{-9}$</td>
<td>1.17</td>
<td>NCAN</td>
</tr>
<tr>
<td>BD rs7296288</td>
<td>Green et al[^15]</td>
<td>$9.0 \times 10^{-9}$</td>
<td>0.90</td>
<td>RHEBL1, DHH</td>
</tr>
<tr>
<td>BD rs3818253</td>
<td>Green et al[^15]</td>
<td>$3.9 \times 10^{-8}$</td>
<td>1.16</td>
<td>TRPC4AP</td>
</tr>
<tr>
<td>BD rs9371601</td>
<td>Green et al[^18]</td>
<td>$2.9 \times 10^{-8}$</td>
<td>1.10</td>
<td>SYNE1</td>
</tr>
<tr>
<td>BD+SZ rs1344706</td>
<td>O’Donovan et al[^19]</td>
<td>$4.1 \times 10^{-13}$</td>
<td>1.11</td>
<td>ZNF804A</td>
</tr>
<tr>
<td>BD+SZ rs2239547</td>
<td>PGC SZ[^40]</td>
<td>$7.8 \times 10^{-9}$</td>
<td>1.12</td>
<td>ITIH3-ITIH4</td>
</tr>
<tr>
<td>BD+SZ rs10994359</td>
<td>PGC SZ[^40]</td>
<td>$2.4 \times 10^{-8}$</td>
<td>1.22</td>
<td>ANK3</td>
</tr>
<tr>
<td>BD+SZ rs4765905</td>
<td>PGC SZ[^40]</td>
<td>$7.0 \times 10^{-9}$</td>
<td>1.11</td>
<td>CACNA1C</td>
</tr>
<tr>
<td>BD+SZ rs4583255</td>
<td>Steinberg et al[^41]</td>
<td>$6.6 \times 10^{-11}$</td>
<td>1.08</td>
<td>MAPK3</td>
</tr>
<tr>
<td>BD+RUD rs2251219</td>
<td>McMahon et al[^42]</td>
<td>$3.63 \times 10^{-8}$</td>
<td>0.87</td>
<td>PBRM1</td>
</tr>
</tbody>
</table>

We used the significance threshold $p<5 \times 10^{-8}$. Odds ratio refers to the risk of bipolar disorder conferred by each risk allele at the locus. BD=bipolar disorder. PGC-BD=Psychiatric Genome-Wide Association Study Consortium Bipolar Disorder Working Group. PGC SZ=Schizophrenia Psychiatric Genome-Wide Association Study Consortium. SZ=schizophrenia. RUD=recurrent unipolar depression.

*Cradock and Sklar, Lancet, 2013*
Schizophrenia and bipolar disorder share genetic determinants

A epidemiological study of SCZ and BP disorder in 2 million families (> 9 million individuals in Sweden)

Narrow-sense heritability ($h^2$):
  Schizophrenia = 0.64
  Bipolar disorder = 0.59

(Lichtenstein P et al., *Lancet*, 2009)
C. Developing new therapies to treat BP disorder
Diagnosing psychotic and affective disorders

Figure 1: Principles underlying the main distinction between affective psychosis (eg, bipolar disorder and psychotic depression) and non-affective psychosis (eg, schizophrenia and schizophreniform disorder).

Van Os and Kapur S, Lancet, 2009
Figure 2: Three hypothetical typical patients diagnosed with a combination of categorical and dimensional representations of psychopathology

Categorical diagnoses of schizophrenia (blue), bipolar disorder (green), and schizoaffective disorder (violet) are accompanied by a patient’s quantitative scores (connected by red lines) on five main dimensions of psychopathology.
Defining BP disorder subtypes in terms of neurobiological characteristics instead of clinical symptoms may provide a more powerful approach to elucidation the underlying genetics and molecular mechanisms of these disorders.

Is there an identifiable progression towards BP-I disorder that may allow early intervention and prevention?
Psychosocial therapies for BP disorder

1. Cognitive behavioral therapy (CBT) helps people with bipolar disorder learn to change harmful or negative thought patterns and behaviors.

2. Family-focused therapy includes family members. It helps enhance family coping strategies, such as recognizing new episodes early and helping their loved one. This therapy also improves communication and problem-solving.

3. Interpersonal and social rhythm therapy helps people with bipolar disorder improve their relationships with others and manage their daily routines. Regular daily routines and sleep schedules may help protect against manic episodes.

4. Psychoeducation teaches people with bipolar disorder about the illness and its treatment. This treatment helps people recognize signs of relapse so they can seek treatment early, before a full-blown episode occurs. Usually done in a group, psychoeducation may also be helpful for family members and caregivers.
Neuroprogression and long-term management of BPD
D. References, internet resources, additional slides
References (1)

- Benazzi F Bipolar disorder—focus on bipolar disorder II and mixed depression, *Lancet* 369, 935-945, 2007
- Price JL and Drevets WC, Neurocircuitry of mood disorders, *Neuropsychopharmacology Reviews* 35, 192-216, 2010
References (2)

• Singh N et al, A safe lithium mimetic for bipolar disorder, *Nature Communications*, July 1, 2013


• Phillips ML et al., Neurobiology of emotion perception II: implications for major psychiatric disorders, *Biological Psychiatry* 515-528, 2003


References (3)


• Larsson et al, Patterns of childhood adverse events are associated with clinical characteristics of bipolar disorder, *BMC Psychiatry* **13**, 97, 2013

• Psychiatric Genomics Consortium, Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs, *Nature Genetics*, 2013


Background:

Research Journal:
Additional Reading

NIH-Bipolar Disorder in Children and Adolescents

NIH-Bipolar Disorder in Adults


Internet resources

• National Institute of Mental Health

• National alliance on Mental Illness (NAMI)
  http://www.nami.org

• The Balanced Mind Foundation (family resources for our kids with mood disorders)
  http://www.thebalancedmind.org

• DBgene: A genetic database for bipolar disorder and its overlap with schizophrenia and major depressive disorder
  http://bdgene.psych.ac.cn
Additional slides
Bipolar disorder subtypes (DSM-IV and ICD-10)

Panel 1: Bipolar disorder subtypes

Diagnostic and Statistical Manual for Mental Disorders fourth edition (DSM-IV) criteria

- Bipolar disorder type I
  - At least one episode of full-blown mania or mixed episode (manic and depressive symptoms). Usually has at least one depressive episode
- Bipolar disorder type II
  - Several protracted depressive episodes and at least one hypomanic episode, but no manic episodes
- Cyclothymic disorder
  - Several periods of hypomanic and depressive symptoms. Depressive symptoms do not meet criteria for depressive episodes
- Bipolar disorder not otherwise specified
  - Depressive and hypomanic-like symptoms and episodes that might alternate rapidly, but do not meet the full diagnostic criteria for any of the above disorders

International Classification of Diseases 10th edition (ICD-10) criteria: differences from DSM-IV

- ICD-10 does not discriminate between bipolar disorder types I and II
- ICD-10 requires two discrete mood episodes, at least one of which must be manic, for a bipolar disorder diagnosis. In DSM-IV, one episode of mania (or mixed mood), or one episode of hypomania plus a major depressive episode, suffice for a BD diagnosis

**Bipolar I disorder (DSM-5)**

**Manic episode:**

A) A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting **at least one week** and present most of the day, nearly every day.

B) During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior.

1) Inflated self-esteem or grandiosity
2) Decreased need for sleep
3) More talkative than usual or pressure to keep talking
4) Flight of ideas or subjective experience that thoughts are racing
5) Distractibility, as reported or observed
6) Increase in goal-directed activity or psychomotor agitation
7) Excessive involvement in activities that have a high potential for painful consequences

C) The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D) The episode is not attributable to the physiological effects of a substance or another medical condition.
Major Depression Episode

A) Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

1) Depressed mood most of the day, nearly every day as indicated by either subjective reports or observations made by others. (In children and adolescents, can be irritable mood.)
2) Markedly diminished interest of pleasure in all, or almost all, activities most of the day, nearly every day
3) Significant weight loss when not dieting or decrease or increase in appetite nearly every day. (In children, consider failure to make expected weight gain.)
4) Insomnia or hypersomnia nearly every day.
5) Psychomotor agitation or retardation nearly every day
6) Fatigue or loss of energy nearly every day
7) Feelings of worthlessness or excessive or inappropriate guilt
8) Diminished ability to think or concentrate, or indecisiveness nearly every day.
9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan. Or a suicide attempt of a specific plan for committing suicide.

B) The symptoms cause clinically significant distress or impairment in social, occupational or other areas of functioning.

C) The episode is not attributable to the physiological effects of a substance or another medical condition.
Hypomanic Episode:

A) and B) Same as for manic episode, but lasting or only at least 4 days, instead of at least one week.

C) The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D) The disturbances in mood and the change in functioning are observable by others.

E) The episode is not sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F) The episode is not attributable to the physiological effects of a substance or another medical condition.
Major Depression Episode

A) Five or more of the “depressive” symptoms listed above have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

B) The symptoms cause clinically significant distress or impairment in social, occupational or other areas of functioning.

C) The episode is not attributable to the physiological effects of substance or another medical condition.
Bipolar I specifications:

With:
- anxious distress
- mixed features
- rapid cycling
- melancholic features
- atypical features
- mood-congruent psychotic features
- mood-incongruent psychotic features
- catatonia
- peripartum onset
- seasonal pattern
Bipolar II disorder (DSM-5)

A) Criteria have been met for at least one hypomanic episode (Criteria A-F, above) and at least one major depressive episode (Criteria A-C, above).

B) There has never been a manic episode.

C) The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
Bipolar II specifications:

Current or most recent:
- hypomanic
- depressed

With:
- anxious distress
- mixed features
- rapid cycling
- mood-congruent psychotic features
- mood-incongruent psychotic features
- catatonia
- peripartum onset
- seasonal pattern

Course if full criteria for mood episode are not currently met:
- in partial remission
- in full remission

Severity if full criteria for mood episode are currently met:
- mild
- moderate
- severe
Cyclothymic disorder (DSM-5)

A) For at least 2 years (at least 1 year in children and adolescents) there have been numerous periods with hypomanic symptoms that do not meet criteria for hypomanic episode and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode.

B) During the above 2-year period (at least 1 year in children and adolescents), the hypomanic and depressive periods have been present for at least half the time and the individual has not been without the symptoms for more than 2 months at a time.

C) Criteria for a major depressive, manic or hypomanic episode have never been met.

D) The symptoms in Criterion A are not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

E) The symptoms are not attributable to the physiological effects of a substance or another medical condition.

F) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specification: with anxious distress.
Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN) rare, a but dangerous side effect of anticonvulsant drugs (carbamazepine and lamotrigine) used in the treatment of BP disorder

The basolateral nuclei of the amygdala attach emotional significance to stimuli.

The central nuclei of the amygdala mediate emotional responses

The cortical medial nuclei of the amygdala play a role in behavior responses to olfactory stimuli

Neuroanatomy: Brodmann areas
The insula plays roles in: i) awareness of body states (including pain and dyspnea), ii) Basic emotions (including anger, fear, disgust, happiness and sadness) and iii) social emotions (including empathy.)
Figure 2. Approximate boundaries of the putative affect and cognitive divisions of the anterior cingulate gyrus. The affective division (A) is a ventral region of the anterior cingulate cortex comprising subgenual anterior cingulate gyrus (Brodmann area 25), Brodmann area 33, and pregenual anterior cingulate gyrus (rostral regions of Brodmann area 24). This division is outlined in the figure. Brodmann areas 25 and rostral area 24 are also labeled. The cognitive division of the anterior cingulate gyrus (C) comprises caudal and dorsal regions, including Brodmann areas 24b’-c’ and 32’, and is outlined in the figure. The corpus callosum (CC) and cingulate sulcus (CS) are also indicated on the figure.
Neuroanatomy: ventrolateral prefrontal cortex (vlPFC) and ventromedial prefrontal cortex (vmPFC)

vlPFC: BA10, BA47

vmPFC: BA11

Note: BA11 comprises the orbitofrontal cortex
Calculation of relative risks (RR) for relatives for schizophrenia and BP disorder in a Swedish sample comprising > 2 million families with > 9 million individuals (Lichenstein P, et al, Lancet 373, 2009)

<table>
<thead>
<tr>
<th>Relation to proband</th>
<th>Risk for schizophrenia when proband has schizophrenia</th>
<th>Risk for bipolar disorder when proband has bipolar disorder</th>
<th>Risk for schizophrenia when proband has bipolar disorder</th>
<th>Risk for bipolar disorder when proband has schizophrenia</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
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<td><strong>Biological relationships</strong></td>
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<tr>
<td>Parent</td>
<td>Offspring</td>
<td>9.9</td>
<td>8.5-11.6</td>
<td>6.4</td>
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<td>Maternal half-sibling</td>
<td>3.6</td>
<td>2.3-5.5</td>
<td>4.5</td>
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<tr>
<td>Sibling</td>
<td>Paternal half-sibling</td>
<td>2.7</td>
<td>1.9-3.8</td>
<td>2.4</td>
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<tr>
<td><strong>Adoptive relationships</strong></td>
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<td></td>
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<tr>
<td>Biological parent</td>
<td>Adopted away offspring*</td>
<td>13.7</td>
<td>6.1-30.8</td>
<td>4.3</td>
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<tr>
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<td>Adopted away biological sibling</td>
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<td>0.7-87.8</td>
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<tr>
<td>Adoptive parent</td>
<td>Adoptee</td>
<td>..</td>
<td>..</td>
<td>1.3</td>
</tr>
<tr>
<td>Sibling</td>
<td>Non-biological sibling</td>
<td>1.3</td>
<td>0.1-15.1</td>
<td>..</td>
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</tbody>
</table>

RR—relative risk. *Adopted children whose biological parents have disease.

Table 2: Recurrence risks for schizophrenia and bipolar disorders

Prevalence*:
Schizophrenia = 0.4%
BP disorder = 0.45%

*Based on ICD-based diagnoses for two inpatient hospital admission
Calculation of genetic heritabilities from relative risks (RR) among relatives

probability. Our model specified R as the sum of several effects, including family-member type (father, mother, or children), additive genetic ($A_{sz}, A_{bp}$), adult shared environmental ($F_{sz}, F_{bp}$), and childhood shared environmental ($C_{sz}, C_{bp}$) effects, along with a common non-shared environmental effect for both schizophrenia and bipolar disorder (E). For schizophrenia and bipolar disorder, our models were:

$$R_{sz} = \beta_{szf} I_f + \beta_{szm} I_m + \beta_{szc} I_c + A_{sz} + F_{sz} + C_{sz} + E$$

$$R_{bp} = \beta_{bpf} I_f + \beta_{bpm} I_m + \beta_{bpc} I_c + A_{bp} + F_{bp} + C_{bp} + E$$

where $I_f, I_m,$ and $I_c$ are indicator variables for father, mother, and children; $\beta_f, \beta_m,$ and $\beta_c$ are fixed variables associated with disease prevalence for respective family members. The random effects $A, F, C,$ and $E$ are assumed to be normally distributed, with mean zero and a unique variance component for each term. Thus, we have variance components $\sigma^2_{sz}, \sigma^2_{bpf}, \sigma^2_{szf}, \sigma^2_{bpc}, \sigma^2_{sze},$ and $\sigma^2_{bpe}$. The non-shared effect $E$ is normal, with mean zero and variance $\sigma^2_e$.

<table>
<thead>
<tr>
<th></th>
<th>Additive genetic effects (A)</th>
<th>Childhood shared environmental effects (C)</th>
<th>Non-shared environmental effects (E)</th>
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</thead>
<tbody>
<tr>
<td>Non-hierarchical diagnoses</td>
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<tr>
<td>Schizophrenia</td>
<td>64.3% (61.7%–67.5%)</td>
<td>4.5% (4.4%–7.4%)</td>
<td>31.1% (25.1%–33.9%)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>58.6% (56.4%–61.8%)</td>
<td>3.4% (2.3%–6.2%)</td>
<td>38.0% (32.0%–41.2%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>63.4% (62.0%–64.9%)</td>
<td>5.9% (4.0%–6.8%)</td>
<td>30.6% (28.7%–32.3%)</td>
</tr>
<tr>
<td>Hierarchical diagnoses*</td>
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<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>64.3% (61.5%–72.2%)</td>
<td>2.5% (1.9%–6.6%)</td>
<td>33.2% (21.2%–36.7%)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>55.1% (50.8%–60.7%)</td>
<td>2.8% (1.9%–7.2%)</td>
<td>42.1% (32.1%–47.3%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>91.7% (85.2%–100.0%)</td>
<td>8.3% (0.6%–8.3%)</td>
<td>..</td>
</tr>
</tbody>
</table>

Data are parameter estimates (95% CI). *When hierarchical diagnoses were used, non-shared environmental effects did not contribute to comorbidity because an individual could not be diagnosed with both disorders.

Table 3: Estimates of genetic and environmental effects for liability to schizophrenia, bipolar disorder, and their comorbidity