



# *Recent Developments in the Epidemiology and Genetics of Bipolar Disorder*

*Kathleen Ries Merikangas, Ph.D.*

NIH

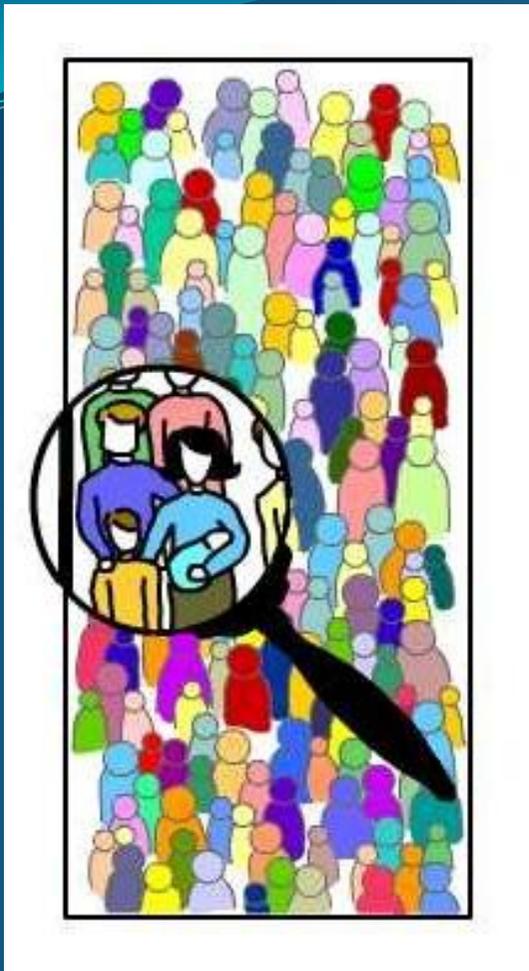
National Institute  
of Mental Health



# Goals

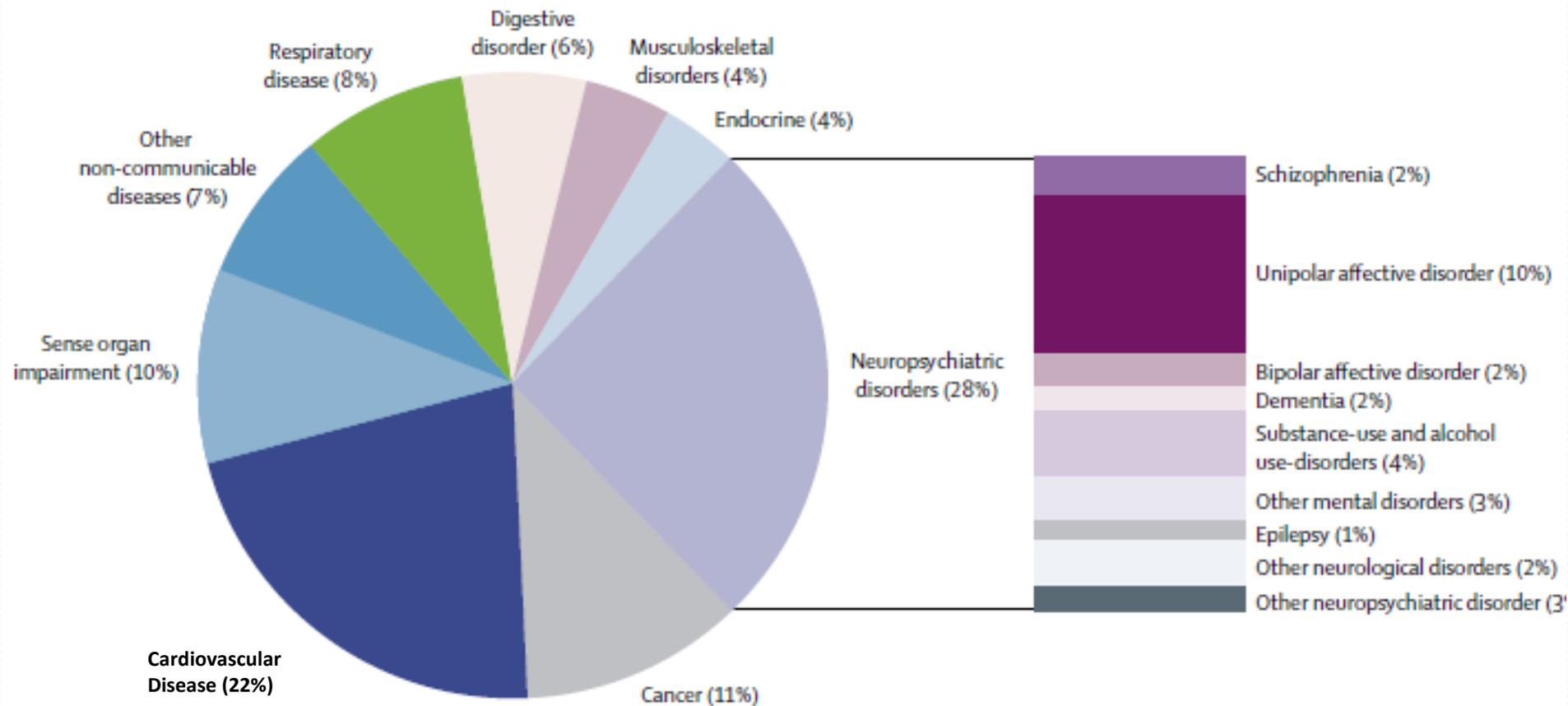
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- ◆ **To summarize evidence from epidemiologic research on bipolar disorder**
- ◆ **To review the genetic epidemiology of mood disorders**
- ◆ **To present findings from the NIMH community family study of comorbidity of mood spectrum disorders**



# Epidemiology of Bipolar Disorder

# No Health without Mental Health: Global Burden of Non-Communicable Diseases



(Disability Adjusted Life Years World-Wide, 2005)

# DSM-V Criteria: Mood Disorders

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## **Bipolar I Disorder:**

- Elevated or irritable mood > 1 wk
- 4/7 symptoms of mania

## **Bipolar II Disorder:**

- Hypomanic episode: Manic symptoms 5 days
- Impairment
- Major depressive episode

## **Major Depression:**

- Depressed or irritable mood
- 2 weeks
- 5/9 symptoms of depression
- Impairment

# WORLD MENTAL HEALTH SURVEYS



Brazil, Colombia, Costa Rica, Mexico, Peru, United States, Nigeria, South Africa, Lebanon, Iraq, Belgium, Bulgaria, France, Germany, Israel, Italy, Netherlands, Northern Ireland, Portugal, Romania, Spain, Turkey, Ukraine, India, China Beijing, China Shanghai, Japan, and New Zealand

ORIGINAL ARTICLE

# Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative

*Kathleen R. Merikangas, PhD; Robert Jin, MA; Jian-Ping He, MD; Ronald C. Kessler, PhD; Sing Lee, MB, BS, FRCPsych; Nancy A. Sampson, BA; Maria Carmen Viana, MD, PhD; Laura Helena Andrade, MD, PhD; Chiyi Hu, MD, PhD; Elie G. Karam, MD; Maria Ladea, MD, PhD; Maria Elena Medina-Mora, PhD; Yutaka Ono, MD; Jose Posada-Villa, MD; Rajesh Sagar, MD; J. Elisabeth Wells, PhD; Zahari Zarkov, MD*

*Arch Gen Psychiatry. 2011;68(3):241-251*

# National Comorbidity Survey Replication: Adolescent Supplement

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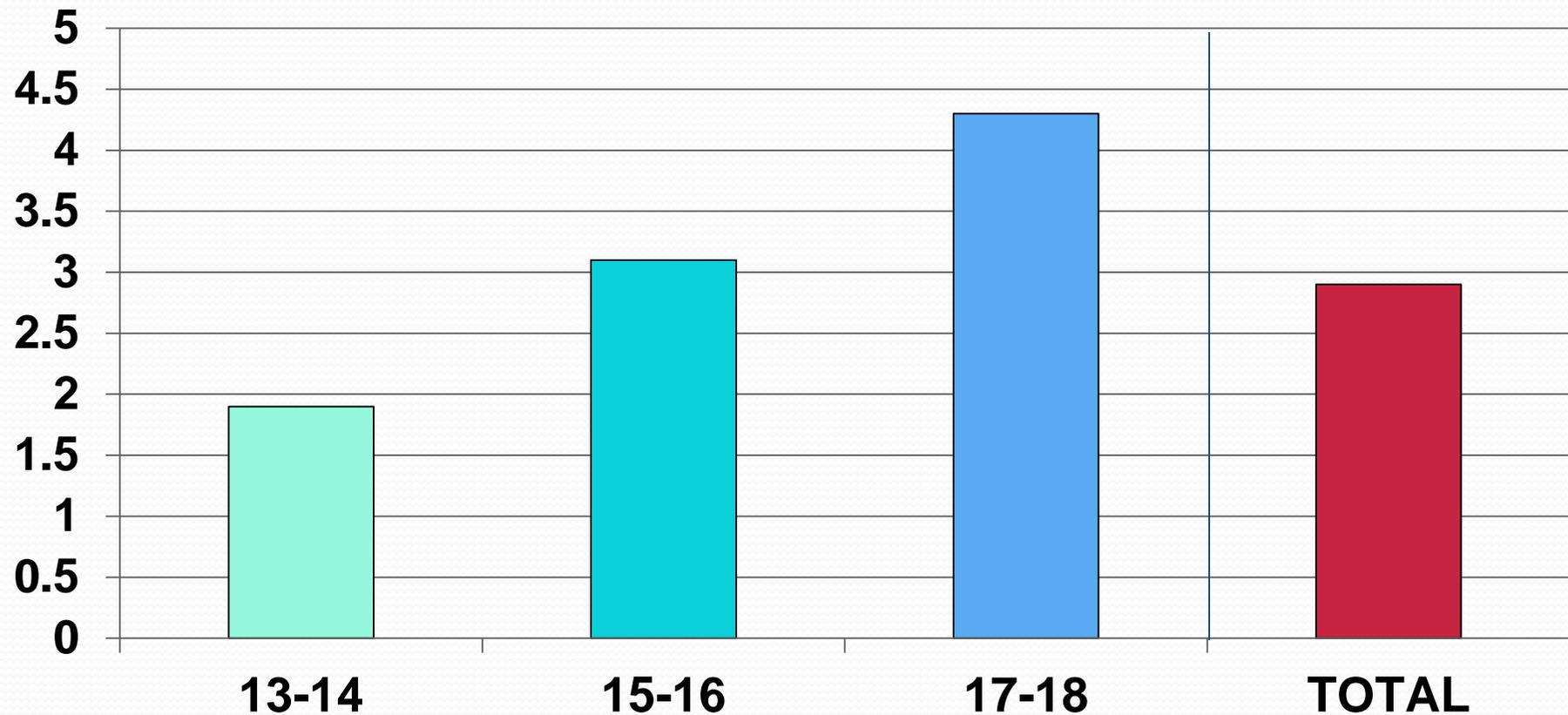
**(N= 10,123 youth ages 13-18)**



# Prevalence of Bipolar Spectrum Disorder in Adolescents by Age

*National Comorbidity Survey Adolescent Supplement*

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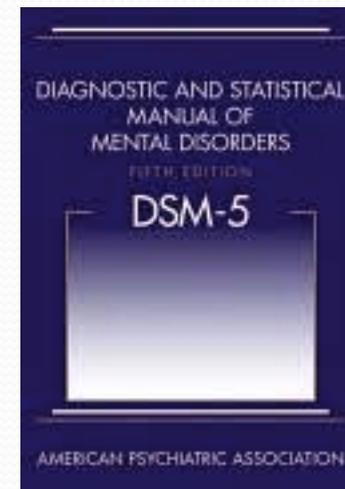
*Merikangas et al., 2010*

# Controversy over DSM-V

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"The weakness is its lack of **validity**. Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a **consensus about clusters of clinical symptoms, not any objective laboratory measure**. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever," he wrote. *Tom Insel, M.D.*

**Controversial update to psychiatry manual, DSM-5, arrives**



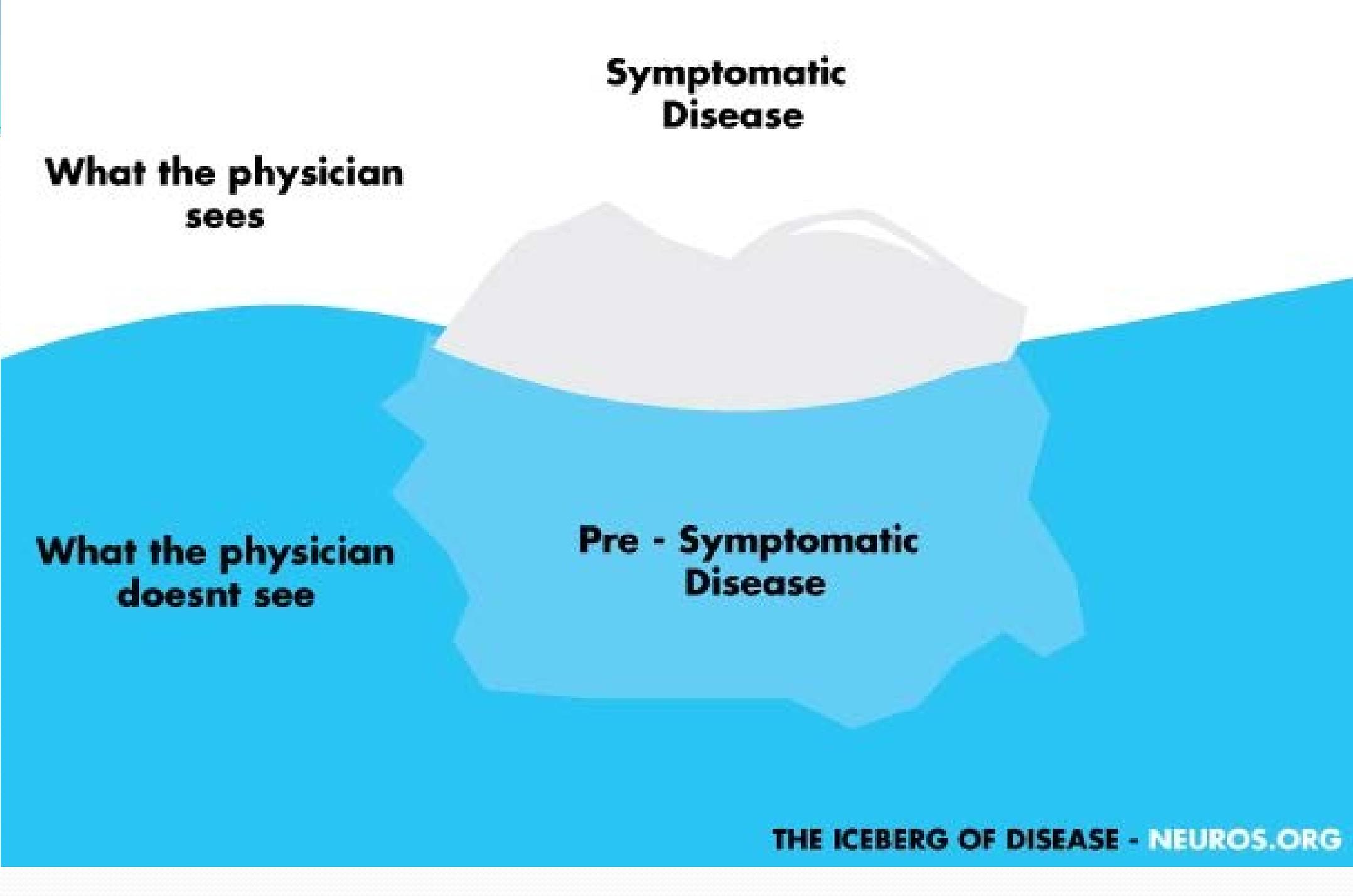
CBS News, June 3, 2013

**Symptomatic  
Disease**

**What the physician  
sees**

**What the physician  
doesn't see**

**Pre - Symptomatic  
Disease**



# Treatment of Mood Disorders in Past Year

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<b>%</b>	<b>Major Dep</b>	<b>Bipolar</b>
<b>Any Service Contact</b>	<b>57.3</b>	<b>50.7</b>
<b>Specialty Mental Health</b>	<b>31.6</b>	<b>29.2</b>
<b>General Medical</b>	<b>27.2</b>	<b>25.4</b>

*National Comorbidity Survey Replication  
Merikangas et al., 2007*

# **“Hidden” mania or hypomania among those with major depression**

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- **Clinical samples of adults: 40-60%**
- **Epidemiologic studies:**
  - Adults: 10% to 20%**
  - Youth: 20% to 40%**

## Article

# The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer

Alexander Viktorin, M.Sc.

Paul Lichtenstein, Ph.D.

Michael E. Thase, M.D.

Henrik Larsson, Ph.D.

Cecilia Lundholm, M.Sc.

Patrik K.E. Magnusson, Ph.D.

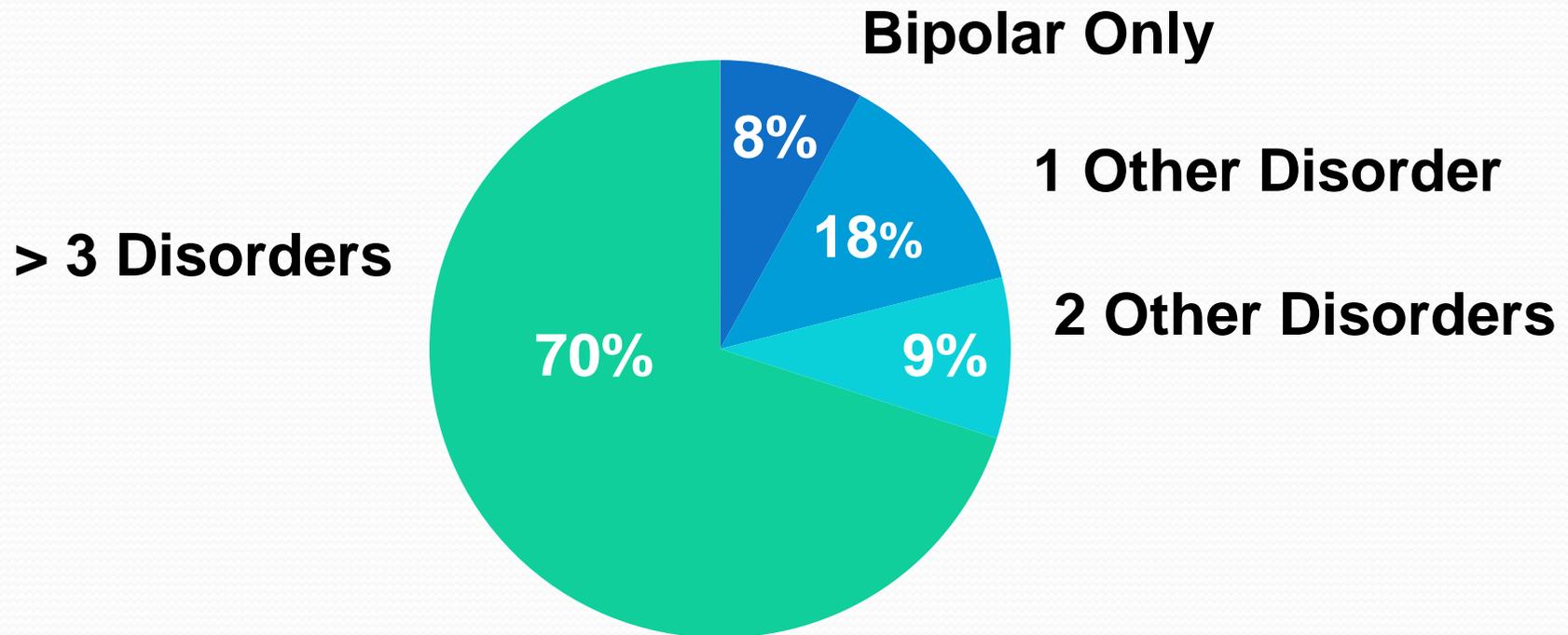
Mikael Landén, M.D., Ph.D.

*Am J Psychiatry* Viktorin et al.; *AiA*:1–7

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# Comorbidity in Bipolar Spectrum Disorder in the U.S. General Population of Adults

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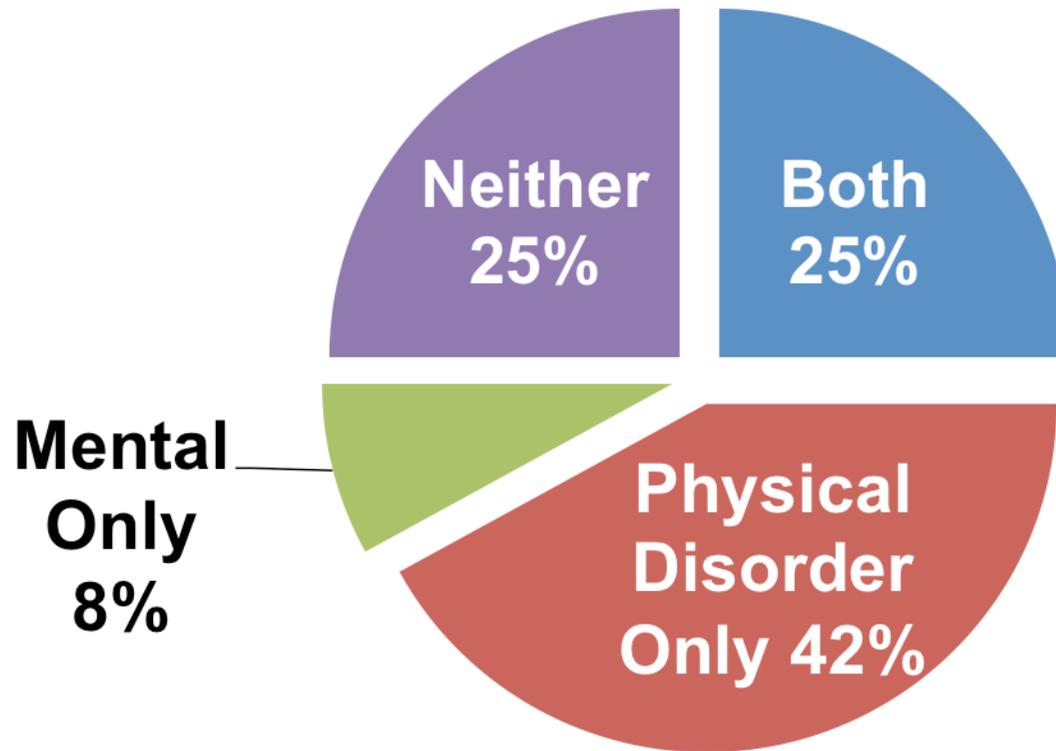


*National Comorbidity Survey Replication  
Merikangas et al., 2007*

# Mental-Physical Comorbidity in the US General Population

## *National Comorbidity Survey Replication*

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# Impact of Comorbid Mental & Physical Conditions

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- **Increased mortality (*Benton et al., 2007*)**
- **Greater health care costs (*Unutzer et al., 2009*)**
- **Poorer treatment response (*Teesson et al., 2011*)**
- **More functional impairment (*Katon et al., 2003*)**



Robert Wood Johnson Foundation

## THE SYNTHESIS PROJECT

NEW INSIGHTS FROM RESEARCH RESULTS

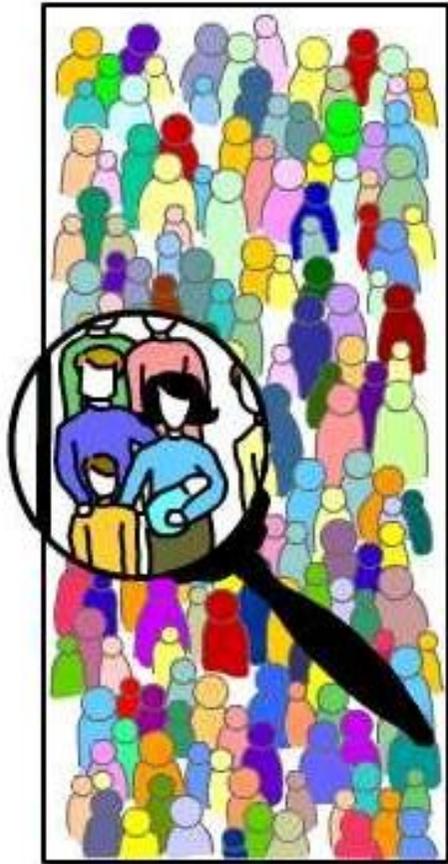
ISSN 2155-3718

**Benjamin G. Druss MD, MPH**  
Rosalynn Carter Chair and Professor  
of Health Policy and Management  
Emory University

**Elizabeth Reisinger Walker,**  
**MAT, MPH**  
Doctoral Candidate  
Emory University

RESEARCH SYNTHESIS REPORT NO. 21  
FEBRUARY 2011

# Mental disorders and medical comorbidity



# Genetic Epidemiology

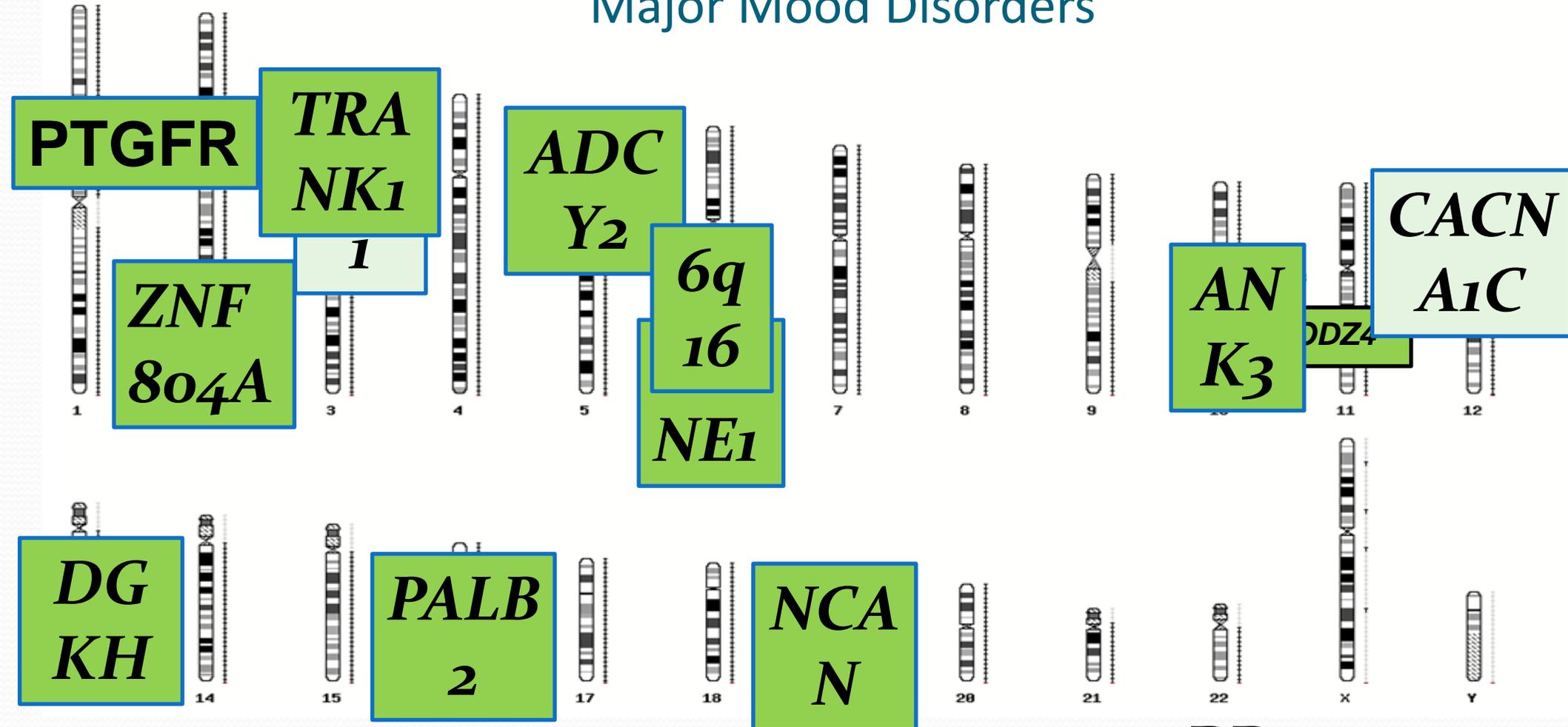
# Familial Risk and Heritability of Mood Disorders

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Disorder	Risk Ratios	Heritability
Bipolar Disorder	7-10	0.60–0.95
Major Depression	2-3	0.28–0.40

# Significant GWAS Findings as of 2/14

## Major Mood Disorders



Courtesy F. McMahon

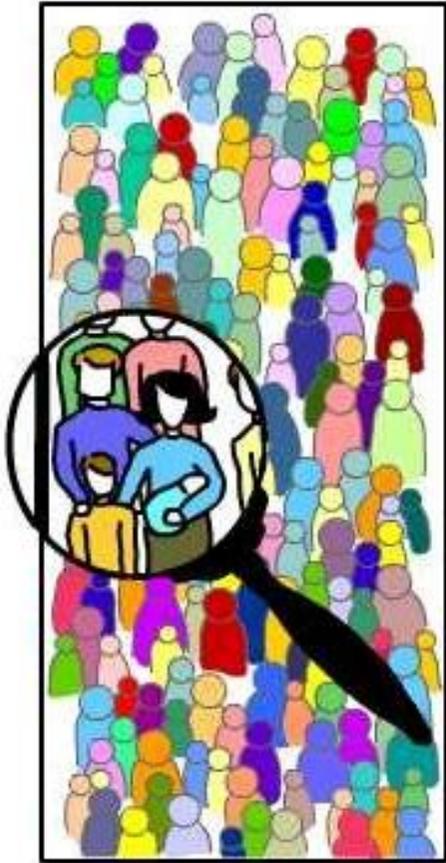
BP+  
BP MDD

# Recent findings on familial factors and mental disorders

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- **Some shared genetic and environmental risk factors in family and high risk studies** (*Lichtenstein et al., 2011, Rasic et al., 2013*)
- **Some evidence for common heritability between schizophrenia and bipolar disorder based on shared molecular markers, GCTA** (*Visscher et al., 2008, Yang et al., 2011*)
- **Specificity of mood and psychotic disorders** (*Maier et al., 1992;2002; Steinhausen et al., 2013; Vandeleur et al., 2013*) **the core dimensions underlying mood disorder subtypes** (*Merikangas et al., 2013*)

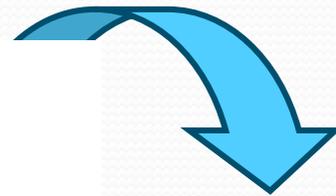
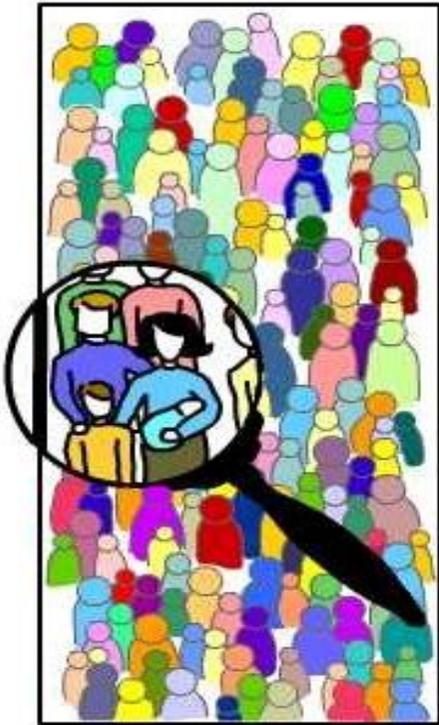
# NIMH Family Study of Comorbidity of Mood Spectrum Disorders



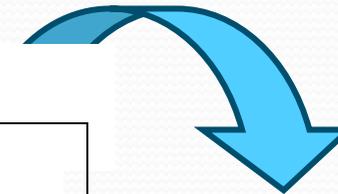
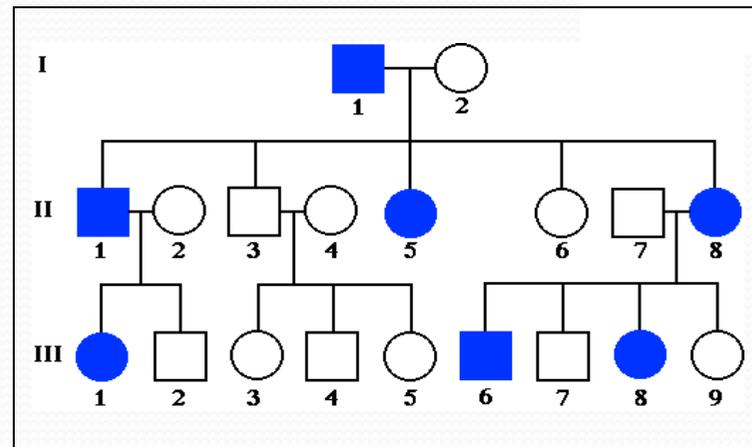
# *NIMH Family Study of Affective Spectrum*

**GOAL:** to identify the core features of affective disorders and their biologic underpinnings

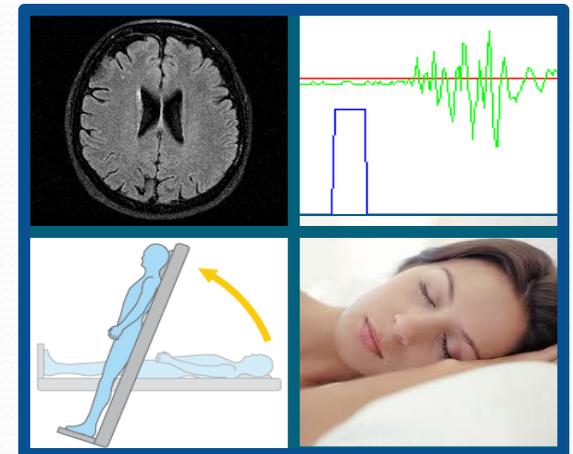
General Population



Extended Families



Biologic Measures



# What runs in families?

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# Unique Features of NIMH Family Study

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- ◆ Sample ascertainment of adults (mean age = 48) from *local community cohort and non clinical settings*
- ◆ Inclusion of *children under age 18*
- ◆ Diagnostic interview that *captures core features and dimensions of psychiatric disorders*
- ◆ Assessment of *both mental and physical disorders*
- ◆ Inclusion of *biologic measures* in families

# NIMH Family Study of Affective Spectrum Disorder: Sample

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<b>Probands</b>	<b>485</b>
<b>Mania/Hypomania</b>	<b>145</b>
<b>Major Depression</b>	<b>278</b>
<b>Anxiety</b>	<b>181</b>
<b>Other/None</b>	<b>116</b>
<b>Relatives</b>	
<b>Interviewed</b>	<b>1112</b>
<b>Children &lt; 18</b>	<b>189</b>
<b>ALL</b>	<b>3535</b>

# Association between Mood Disorder Subtypes in Probands (n=475) and Relatives (n=2082)

Probands

Relatives

**Mania**

**8.3 (3.8, 17.9)\*\***  
—————→  
 **$h^2=.83$**

**Mania**

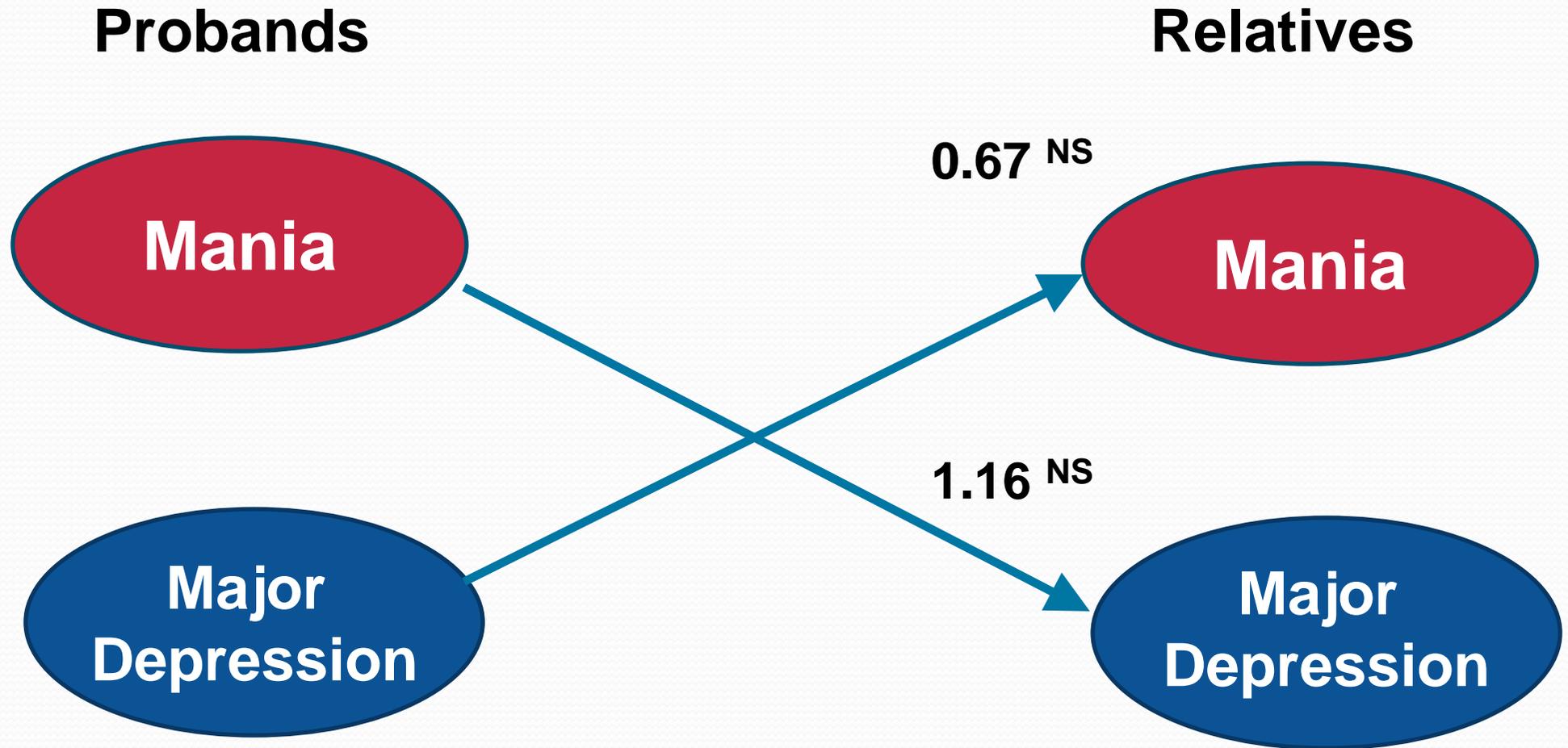
**Major  
Depression**

**2.5 (1.7, 3.6)\*\***  
—————→  
 **$h^2=.54$**

**Major  
Depression**

# Association between Mood Disorder Subtypes in Proband and Relatives

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# Lausanne Family Study of Mood Disorders (n=287 probands; 1726 relatives)

Probands

Relatives

Psychosis

2.9 (1.1-7.7)\*

Psychosis

Mania

6.4 (2.2-8.7)\*\*

Mania

Major Depression

2.0 (1.5-2.7)\*

Major Depression

# Disorders in Offspring by Parental Mood Disorder Subtypes



Offspring	Bipolar	Major Depression	Controls	Bipolar	Major Depression
	Lifetime Risk (%)			Relative Risk	
Bipolar	33.3	16.4	12	2.8	1.4
Major Depression	72.2	50.8	32.0	2.3	1.6

## NEWS AND COMMENTARY

### Independence of Mania and Depression

# Evidence for separate inheritance of mania and depression challenges current concepts of bipolar mood disorder

IB Hickie

*Molecular Psychiatry* advance online publication, 24 December 2013; doi:10.1038/mp.2013.173

Two new family studies<sup>1,2</sup> that demonstrate independent patterns of inheritance for mania and depression challenge the current conceptualization of bipolar mood disorder. The implications for genetic association and other neurobiological studies are profound.

distinction between unipolar and bipolar depression draws heavily on earlier family study data.

The clinical concept of bipolar disorder is based on the notion that mania and depression are opposite ends of a single mood dimension—varying from elated to profoundly depressed states. An alternative conceptualization, recognizes increased activation as the core feature of mania and decreased activation as characteristic of some but not all depressed states. Critically, within this alternative model, the ‘bipolar’ dimension is one of motor and psychic activation, not mood. Consequently, it may vary from high to low states independently of mood. By contrast

# Activity as Core Feature of Mania

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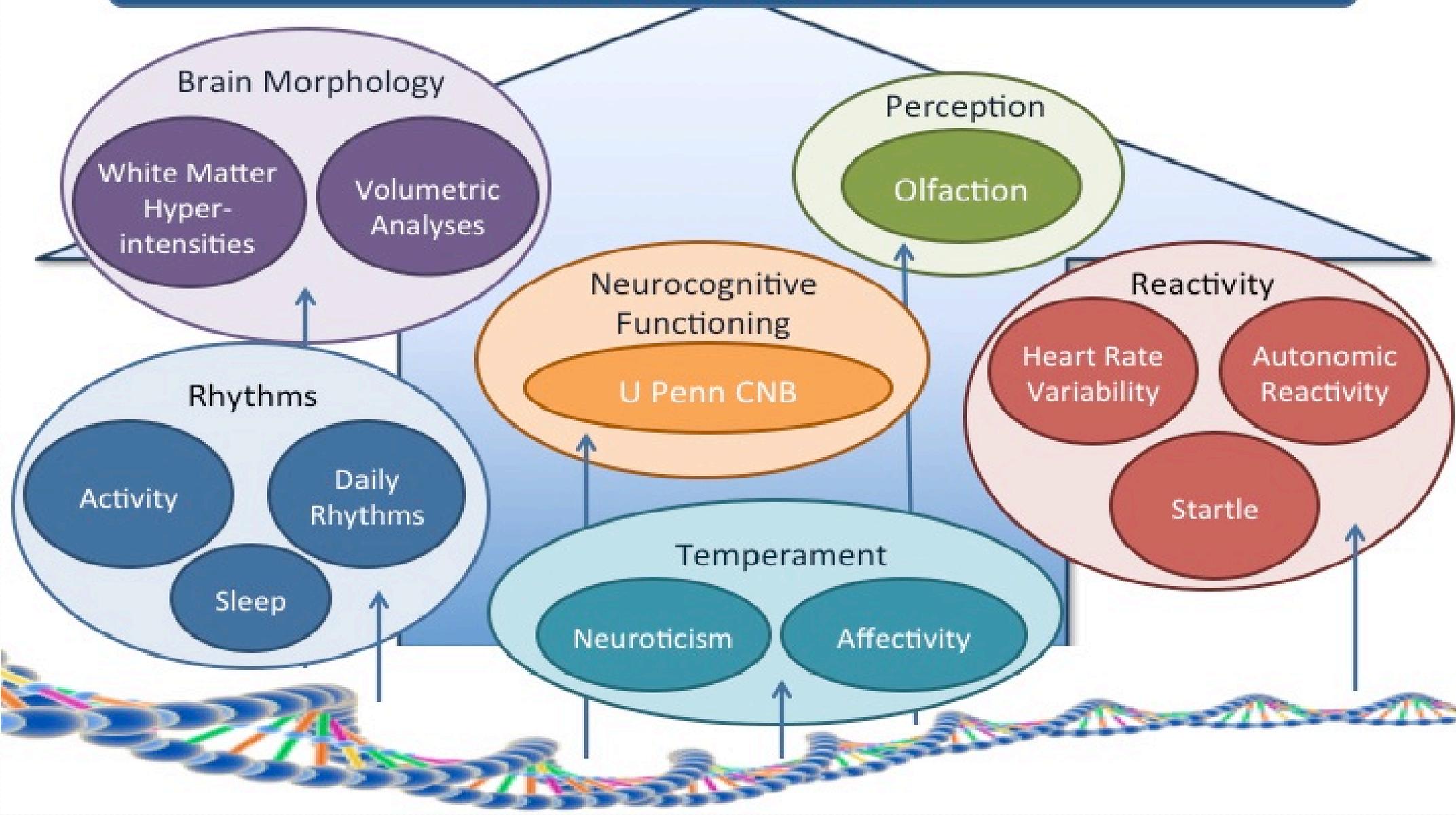
**“ functional disturbance of brain with increased excitability”  
manifest by increased speed of all processes...mood  
change not core feature....**

*Mendel, 1855*

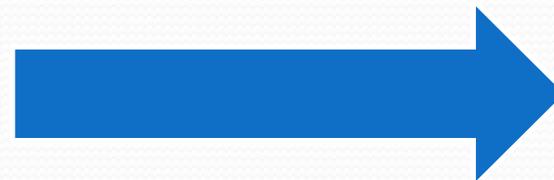
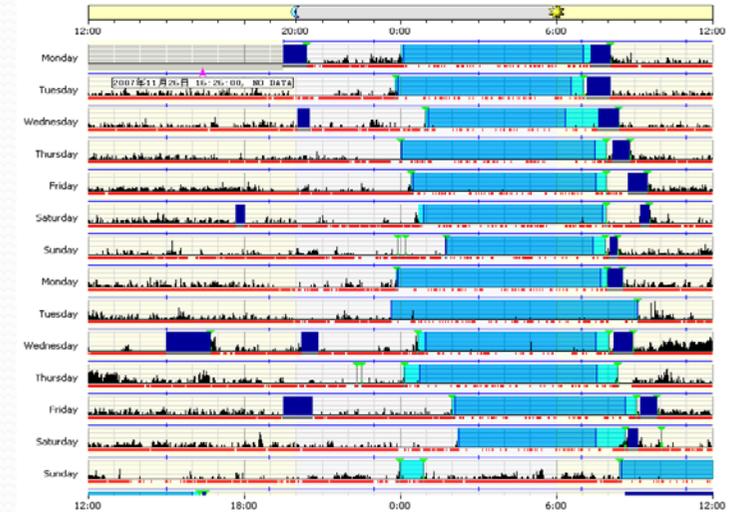
# NIMH Family Study Biologic Measures



## BIPOLAR DISORDER



# Measure of activity rhythm: 2 weeks



4 epochs per day

- Mood
- Activity
- Energy
- Reactivity
- Food intake
- Stress
- Headache attacks

# Findings: Activity, Sleep and Mood

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- ◆ **Bipolar disorder is associated with greater variability in sleep, activity and energy than other affected subgroups and controls**
- ◆ **There is a circadian shift in activity to later in the day among those with bipolar disorder**
- ◆ **Links between emotions, activity and sleep are potentiated among those with bipolar disorder, suggesting greater susceptibility to perturbations in homeostatic regulatory systems.**

# Summary

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- **Bipolar Disorder exists on a spectrum and has major impact on morbidity and mortality**
- **Comorbidity with both mental and medical disorders is pervasive**
- **The onset of mania tends to occur in late childhood and increases monotonically with age thereafter**
- **Bipolar disorder is strongly heritable but identification of genetic pathways is still elusive**

# Significance



- ◆ Importance of *dissecting the key components* of mood disorders and *their associations with other mental and medical disorders*
- ◆ Value of careful phenotypic characterization of *large non-clinical samples*
- ◆ Need for evaluation at *emergence of symptoms/disorders at adolescence*
- ◆ *Value of the modern family study* in identifying sources of heterogeneity in the core features of mood disorders
- ◆ *Objective measures of activity, sleep and mood regulation* may provide insight into underlying biologic and genetic pathways

# Collaborators: NIH

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**Activity, Sleep**

**Wallace Duncan, Ph.D., NIMH**

**Autonomic Nervous System**

**David S. Goldstein, M.D., Ph.D., NINDS**

**Cardiovascular Markers**

**Alan Remaley, M.D., PhD, Clinical Center**

**Clinical/Biomarkers**

**Carlos Zarate, M.D. NIMH**

**Epidemiology**

**Shelli Avenevoli, Ph.D. Extramural**

**Ben Vitiello, M.D., Extramural**

**Genetics**

**Yin Yao, Ph.D., NIMH**

**Francis McMahon, M.D., NIMH**

**Neuroimaging**

**Allison Nugent, Ph.D.**

**Nicholas Patronas, M.D., Clinical Center**

**Neurology**

**Karin Nelson, M.D., NINDS, Child**

**Psychophysiology**

**Christian Grillon, Ph.D., NIMH**

# Collaborators: Outside NIH



## **Actigraphy**

**Ciprian Craniceanu, Ph.D., Johns Hopkins**  
**Vadim Zippunikov, Ph.D., Johns Hopkins**  
**Judy Cameron, Ph.D., University of Pittsburgh**

## **Autonomic Nervous System**

**Mitchel Kling, M.D., U Penn**

## **Clinical/Epidemiology**

**Jules Angst, M.D., U of Zurich, Switzerland**  
**Martin Preisig, M.D., M.P.H., U Lausanne, Switzerland**  
**Susan Gau, M.D., Ph.D., National University Taiwan**

## **Genetics**

**Neil Risch, Ph.D., UCSF**

## **Momentary Sampling**

**Joel Swendsen, Ph.D., Bordeaux, France**

## **NeuroCognitive Function**

**Ruben Gur, Ph.D., Raquel Gur, M.D., Ph.D.,**  
**Monica Calkins, Ph.D., U Penn**

## **Neurology**

**James Merikangas, M.D., GWU, Adult**  
**William McClintock, M.D., CNMC, Child**

## **Olfaction**

**Paul Moberg, Ph.D., Bruce Turetsky, M.D., U Penn**

## **Sleep**

**Emmanuel Mignot, M.D., Ph.D., Stanford**  
**Ruth Benca, M.D., U of Wisconsin**

# Genetic Epidemiology Research Branch



## Branch

Katheen R Merikangas Ph.D.  
Sabrina Rodriguez

Senior Investigator, Genetic Epidemiology  
Lab Manager

## Clinical Team

Francesca Belouad, M.A.  
Susan Goo, M.S.N.  
Tarannum Lateef, M.D., M.P.H.  
Erin Nakamura, M.P.H.  
Catherine Roca, M.D.

Psychologist  
Nurse Clinician  
Pediatric Neurologist  
Coordinator/ Public Health  
Psychiatrist

## Biostatistics/Analytic

Lihong Cui, M.Sc.  
Jianping He, M.Sc.  
Jaclyn Dozier, B.A.

Biostatistician  
Epidemiology  
Data Manager

## Training

Diana Paksarian, Ph.D.  
Nicole Jameson, B.S.  
Diane Lameira, B.A.  
Brooke Sheppard, M.Sc.  
Haochung Shou, B.S.

Postdoctoral Fellow , Epidemiologist  
Post Bac IRTA  
Post Bac IRTA  
Predoctoral Fellow (Johns Hopkins)  
Predoctoral Fellow (Johns Hopkins)



**Thank you!**