Specificity vs Transdiagnostic Concepts of Diagnostic Entities: Genetic Epidemiologic Approaches

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Intramural Research Program

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National Institute of Mental Health

Disclosure

- This work was supported by the National Institute of Mental Health Intramural Research Program.
- The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the U.S. Government.

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Aims

- Evidence and challenges in evaluating specificity of diagnostic classes
- Role of Genetic Epidemiology
- Future Strategies and Implications

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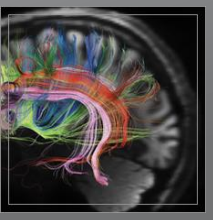

Specificity of Diagnostic Entities

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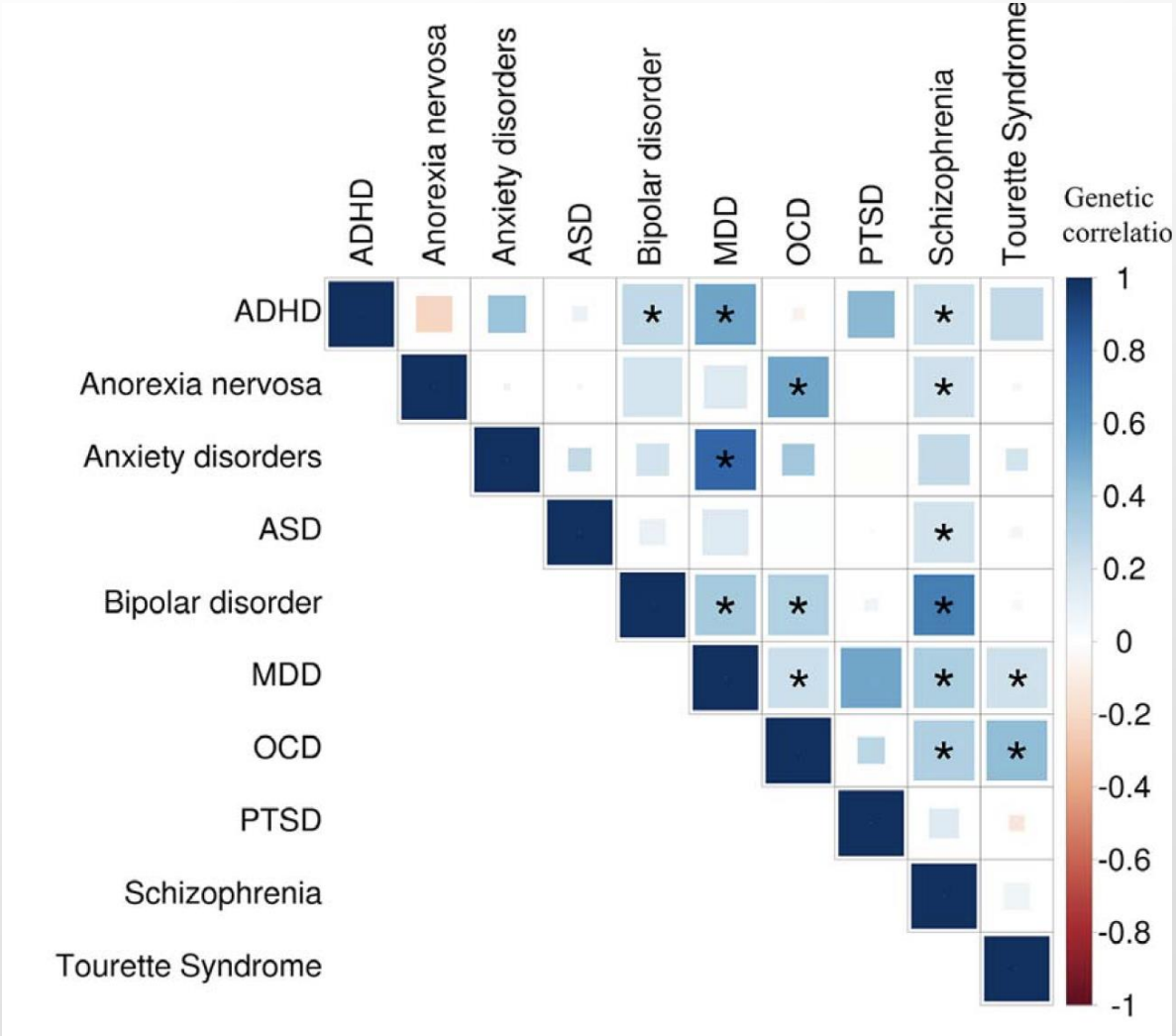
Shared Heritability in Common Brain Disorders



The Brainstorm Consortium, *Science* **360**, eaap8757 (2018) 22 June 2018

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Many studies of GWAS and Registries show a Lack of Specificity of Major Diagnostic Categories

Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Chen M-H *et al* (2019). Risk and coaggregation of major psychiatric disorders among first-degree relatives of patients with bipolar disorder: a nationwide population-based study. *Psychological*

Risk and coaggregation of major psychiatric disorders among first-degree relatives of patients with bipolar disorder: a nationwide population-based study

Mu-Hong Chen[1,2], Ju-Wei Hsu[1,2], Kei-Lin Huang[1,2], Tung-Ping Su[1,2,3], Cheng-Ta Li[1,2], Wei-Chen Lin[1,2], Shih-Jen Tsai[1,2], Chih-Ming Cheng[1,2], Wen-Han Chang[1], Tai-Long Pan[4,5,6], Tzeng-Ji Chen[7,8] and Ya-Mei Bai[1,2]

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…And many others show Specificity of Major Categories

J Clin Psychiatry. 2021 Sep 7;82(5):20m13810. doi: 10.4088/JCP.20m13810.

Risks of Coaggregation of Major Psychiatric Disorders Among First-Degree Relatives of Patients With Bipolar I and Bipolar II Disorder: Evidence From a Nationwide Population-Based Study

Chih-Ming Cheng [1 2 3 4], Mu-Hong Chen [1 2 3 4], Wen-Han Chang [1 5], Chia-Fen Tsai [1 2 3], Shih-Jen Tsai [1 2], Ya-Mei Bai [1 2], Tung-Ping Su [1 2 3 6], Tzeng-Ji Chen [7], Cheng-Ta Li [1 2 3 8]

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Challenges in Interpretation

- Diagnostic Methods:
  - ✓ Direct Structured Interview
  - ✓ Electronic Health Records
  - ✓ Registry
  - ✓ Ancillary Informants
- Timing in Course of Illness and across Life Span
- Comorbidity: Manifestation or Consequence?
- Sample Ascertainment: Registries
  - ✓ Unknown biases
  - ✓ Greater severity
  - ✓ Cross sectional
  - ✓ Current state
  - ✓ Under-estimation of comorbidity

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Diagnostic Classification

ELSEVIER

Journal of Psychiatric Research

Volume 21, Issue 1, 1987, Pages 55-91

The impact of diagnostic misclassification on the pattern of familial aggregation and coaggregation of psychiatric illness

Kenneth S. Kendler

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Timing of Diagnosis is Central Issue: Manifestations of Bipolar Disorder across the Life Span

Precursors

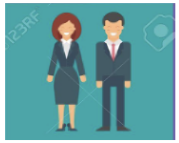
- ❑ Attention deficit
- ❑ Social Anxiety
- ❑ Reduced and more variable motor activity

Onset & Manifestations

- ❑ Mania, social anxiety
- ❑ < Energy, attention problems
- ❑ < Motor activity
- ❑ Later peak activity & sleep onset
- ❑ Dysregulation of reactivity/ cross system homeostasis

Consequences

- ❑ Substance Disorders
- ❑ Cardiovascular Disease
- ❑ Functional Impairment
- ❑ Cognitive Difficulties
- ❑ Suicide attempts



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PERSPECTIVE

What is a representative brain? Neuroscience meets population science

Emily B. Falk[a,b,c,1], Luke W. Hyde[d,e,f,1], Colter Mitchell[e,g,1,2], Jessica Faul[e,3], Richard Gonzalez[b,d,h,3], Mary M. Heitzeg[i,3], Daniel P. Keating[d,e,i,j,3], Kenneth M. Langa[e,k,l,3], Meghan E. Martz[d,3], Julie Maslowsky[m,3], Frederick J. Morrison[d,3], Douglas C. Noll[n,3], Megan E. Patrick[e,3], Fabian T. Pfeffer[e,g,3], Patricia A. Reuter-Lorenz[d,e,o,3], Moriah E. Thomason[p,q,r,3], Pamela Davis-Kean[b,d,e,f,4], Christopher S. Monk[d,e,f,i,o,4], and John Schulenberg[d,e,f,4]

Review > Proc Natl Acad Sci U S A. 2013 Oct 29;110(44):17615-22.

doi: 10.1073/pnas.1310134110. Epub 2013 Oct 22.

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PERSPECTIVE

What is a representative polygenic risk score? Molecular genetics meets genetic epidemiology

Kathleen R Merikangas[1] and colleagues[2-???] In preparation.

PERSPECTIVE

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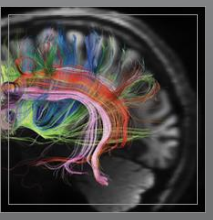

Genetic Epidemiology

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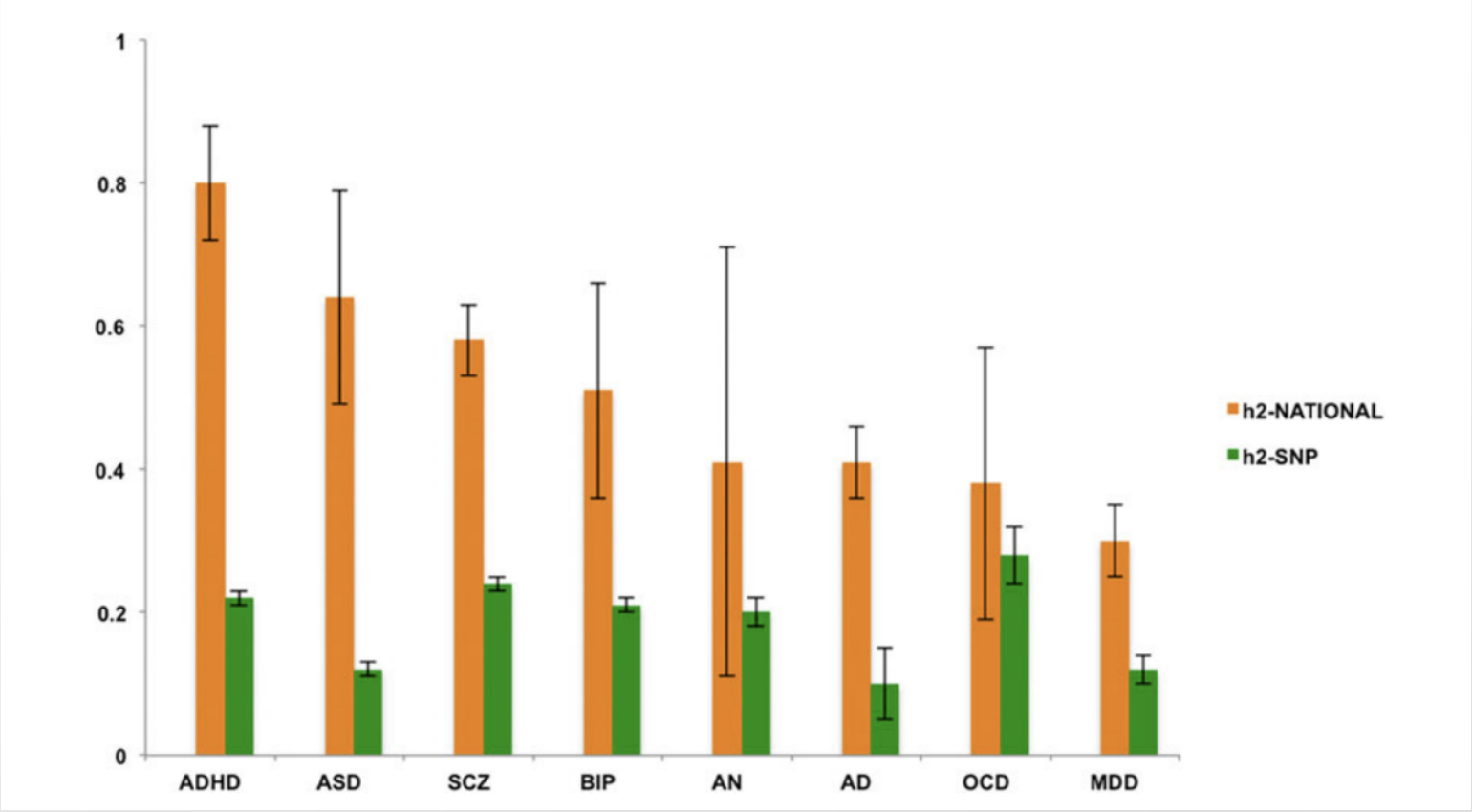
Sibling vs SNP-based heritability



Cite this article: Pettersson E *et al* (2019). Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychological Medicine* **49**, 1166–1173. https://doi.org/10.1017/S0033291718002039

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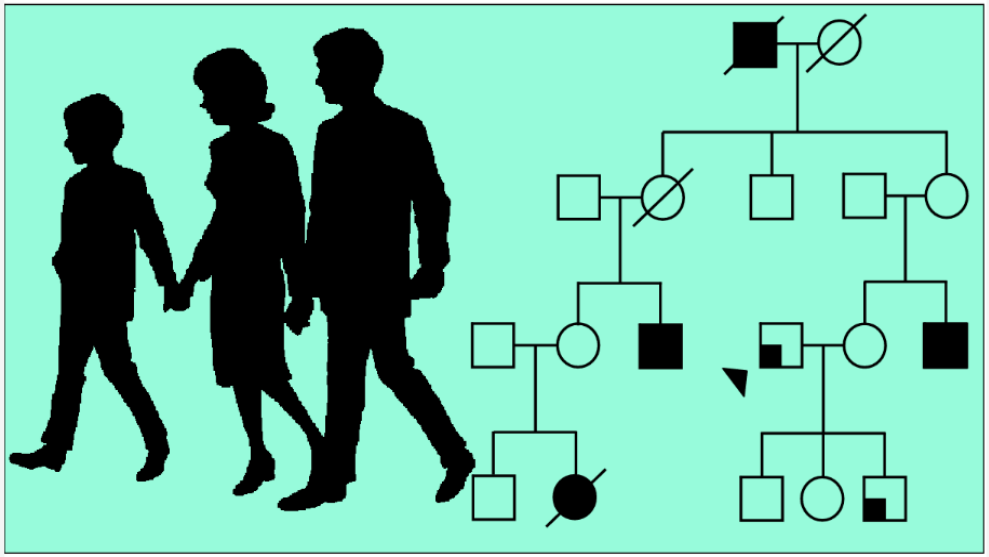
Family history as a risk factor for common, complex disease

An independent, epidemiological assessment of the evidence for familial risk of disease



Public Health Genetics

Adam Butterworth

2007

Family Studies

Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0073-x

REVIEW ARTICLE

Rediscovering the value of families for psychiatric genetics research

David C. Glahn[1,2] · Vishwajit L. Nimgaonkar[3] · Henriette Raventós[4,5] · Javier Contreras[4] · Andrew M. McIntosh[6,7] · Pippa A. Thomson[7,8] · Assen Jablensky[9] · Nina S. McCarthy[9,10,11] · Jac C. Charlesworth[12] · Nicholas B. Blackburn[13] · Juan Manuel Peralta[13] · Emma E. M. Knowles[1] · Samuel R. Mathias[1] · Seth A. Ament[14] · Francis J. McMahon[15] · Ruben C. Gur[16] · Maja Bucan[17] · Joanne E. Curran[13] · Laura Almasy[16,17,18] · Raquel E. Gur[16] · John Blangero[13]

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Characteristics of Research on Diagnostic Entities

Professor Jules Angst
Zurich Switzerland

- **Sampling** from general population to supplement clinic-based studies
- **Prospective research** to track dynamics of disorders
- **Multisystem evaluation** that included psychologic/psychiatric as well as somatic systems
- **Phenomenologic approach** that supplements the "committee-based" diagnostic conventions

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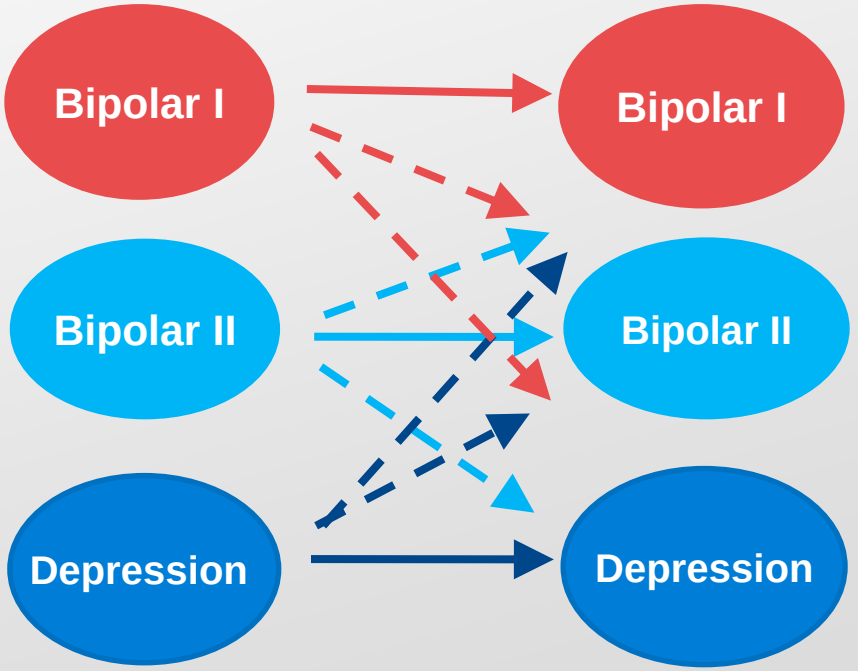
NIMH Family Study of Affective Spectrum Disorder: Familial specificity and co-aggregation

Sample and Sites

- Household screening of local area & enrichment for mood disorders
- Sample: 610 probands
  - ✓ 200 Bipolar
  - ✓ 193 MDD
  - ✓ 60 Anxiety, no mood
  - ✓ 150 Controls
- 1157 relatives (339 offspring age 7-55)
- n= 624 Clinical Center

Colaus, Lausanne, CH

Specificity of Familial Transmission of Mood Disorder Subtypes



Merikangas et al, 2014

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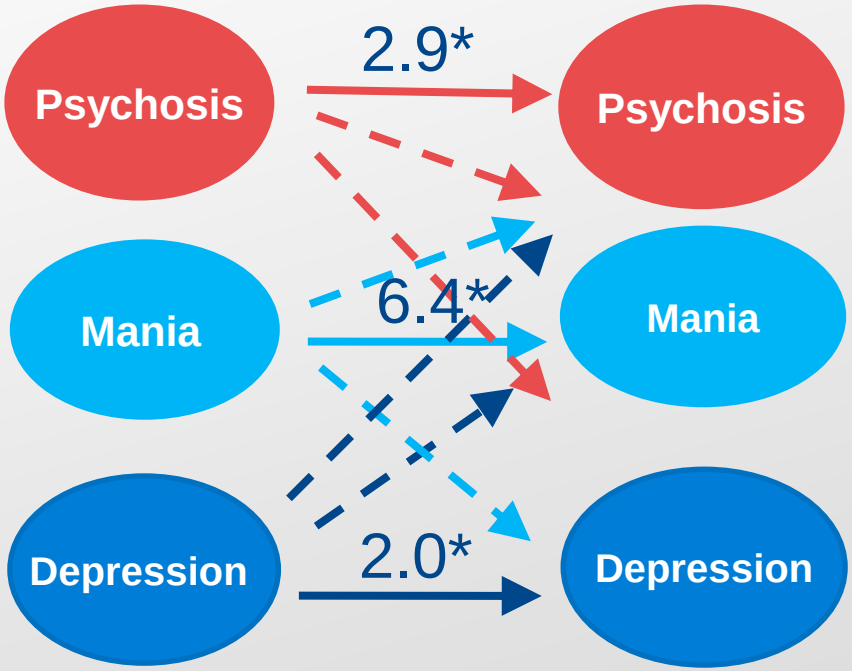
Colaus Specificity of Mood Disorder Subtypes

Probands

Relatives



Molecular Psychiatry (2013), 1–5
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www.nature.com/mp

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Specificity of Major Diagnostic Categories

PROBAND	RELATIVES (n=1157, Adjusted Risk Ratio)						
	BPI	BPII	MDD	ANX	SUB	ADHD	EATING
BPI	**6.7**	0.6	1.7	1.2	0.8	0.6	1.2
BPII	4.1	**3.3**	1.0	0.8	0.9	0.4	0.7
MDD	0.8	1.1	**2.0**	0.7	1.1	1.0	1.3
ANX	0.6	0.9	0.9	**1.6**	1.0	1.2	1.4
SUB	0.8	1.1	1.0	1.2	**1.8**	1.2	0.5
ADHD	1.2	1.1	0.9	1.3	1.1	**2.2**	0.9
EATING	1.3	1.3	1.0	0.9	1.3	1.3	1.0

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Familial Heritability of Domains associated with BPI

Rhythms

- ↓ Activity (h^2=.44) ↑ Variability
- Later Sleep Midpoint (h^2=.50)
- Later Chronotype (h^2=.29)
- Instability of Subjective Energy & Attention

Reactivity

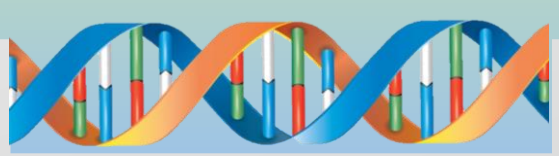
- ↓ Heartrate Nighttime Variability (h^2=.51)
- ↑ Anxiety Reactivity to Positive Events

Neurocognitive Function

- ↑Complex Cognition (h^2=.61)
- ↑Visuospatial (h^2=.41)

Temperament

- ↑ Anxiety Sensitivity (h^2=.35)
- ↑ Sociability (h^2=.31)



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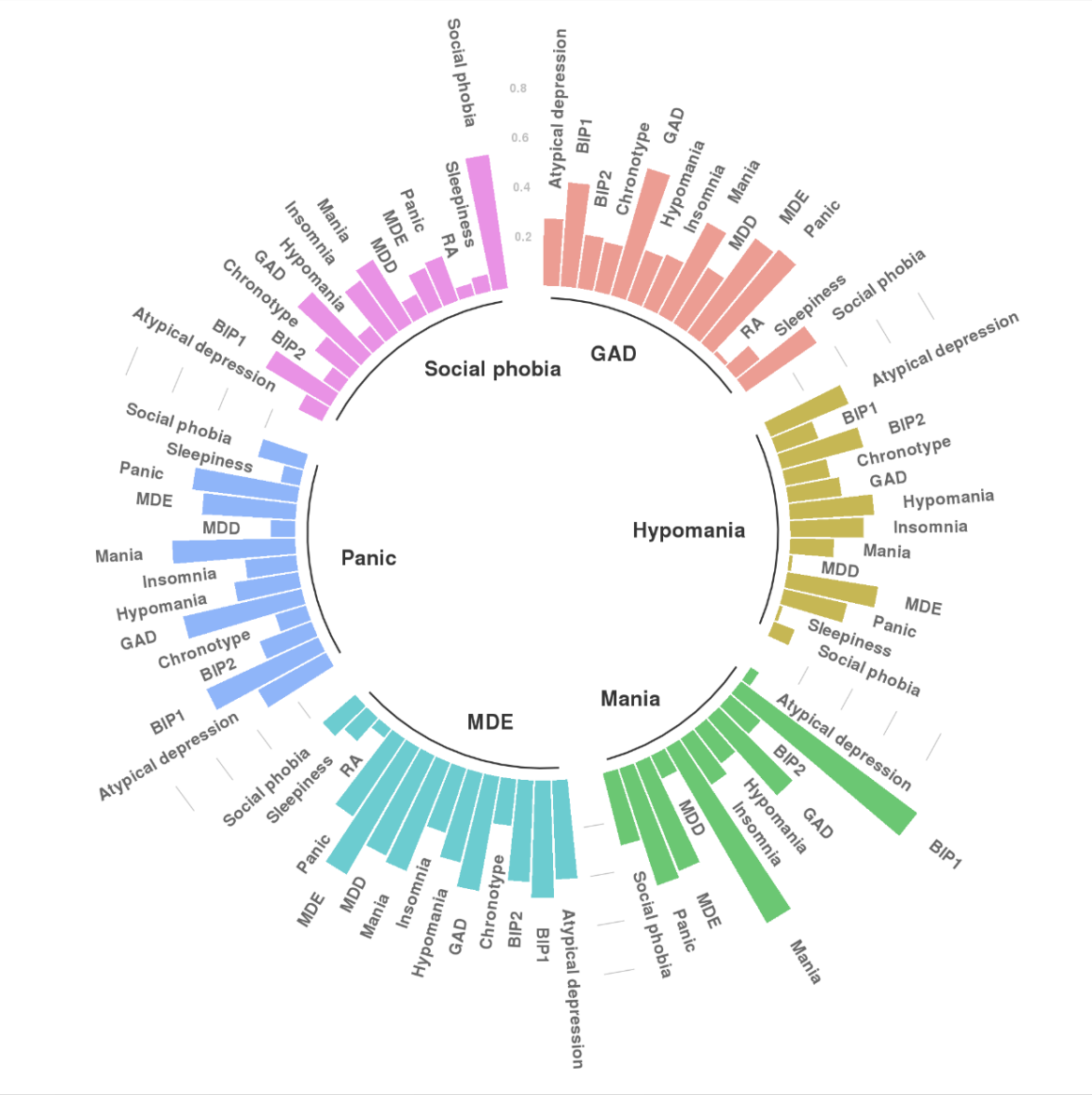
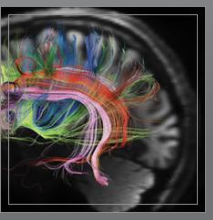
Co- and Cross Heritability of Diagnoses, Subtypes and Core Features





Prospective Studies of Offspring

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Collaborative Offspring Studies of Mood Disorders and Circadian Rhythms

NIMH Family Study of Affective Spectrum
K Merikangas, PhD

- ❑ Parents with Mood, Anx, SUD, Controls
- ❑ N=339 offspring (ages 7-55)
- ❑ N=174 < age 18

Lausanne Family/High Risk
Martin Preisig, MD, MPH

- ❑ Parents: BPI, BPII, MDD, Controls
- ❑ N=449 Offspring, Ave age 10.1, study entry
- ❑ 13.2 year follow up

Chinese Bay Area
Jihui Zhang, MD PhD

- ❑ Parents BPD, Controls
- ❑ N=402 offspring (ages 6-21)

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Specificity of Mood Disorder Subtypes in Offspring

Rates/100	Proband Mood Disorder			
	Bipolar I	Bipolar II	MDD	Controls
N =374	44	35	128	167
Mania/ Bipolar I	**25.0**	**2.9**	3.1	0.0
Bipolar II/ Hypomania	15.9	**25.7**	9.4	6.5
Major Depression	20.5	31.4	**37.5**	22.6

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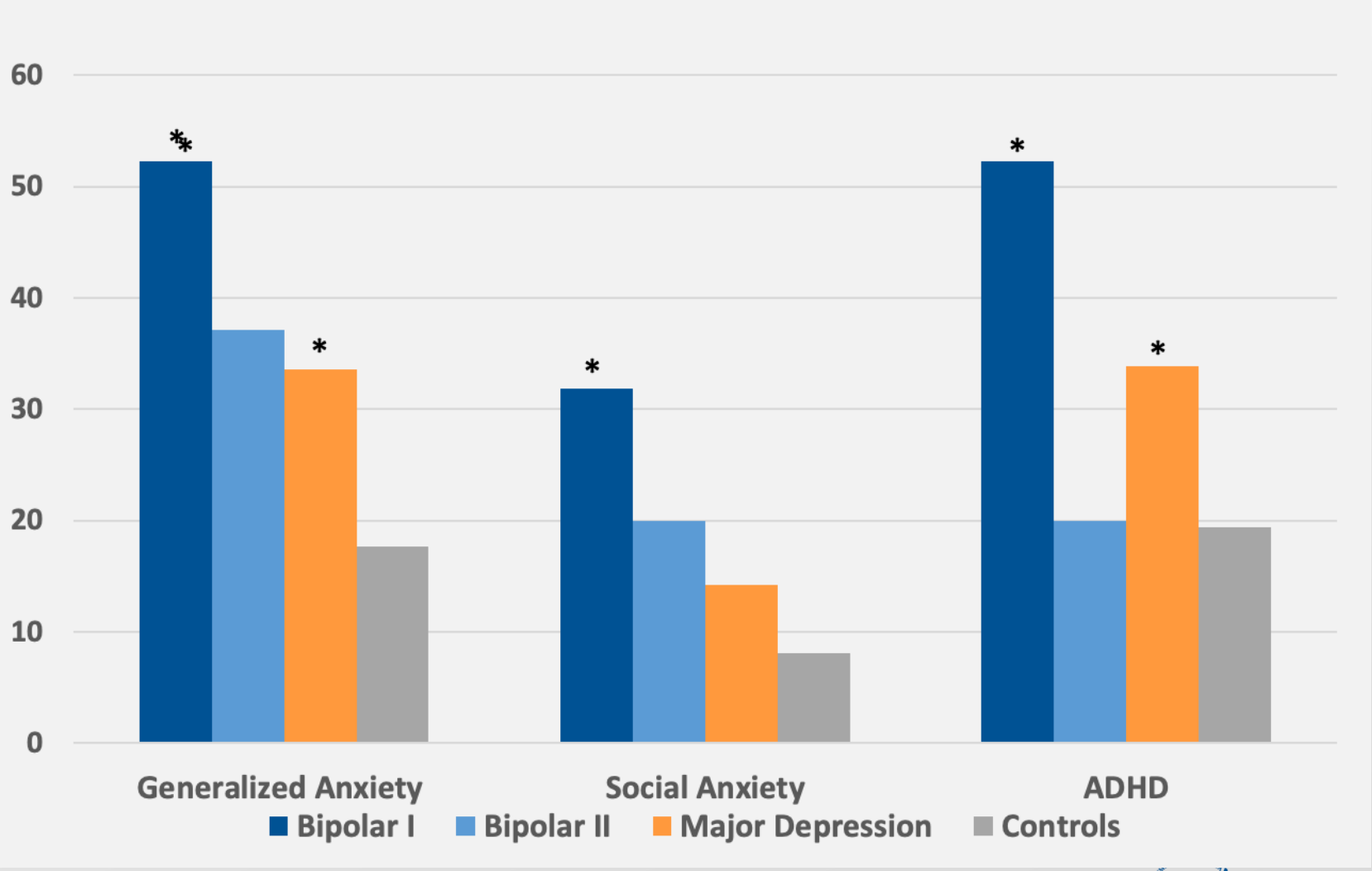
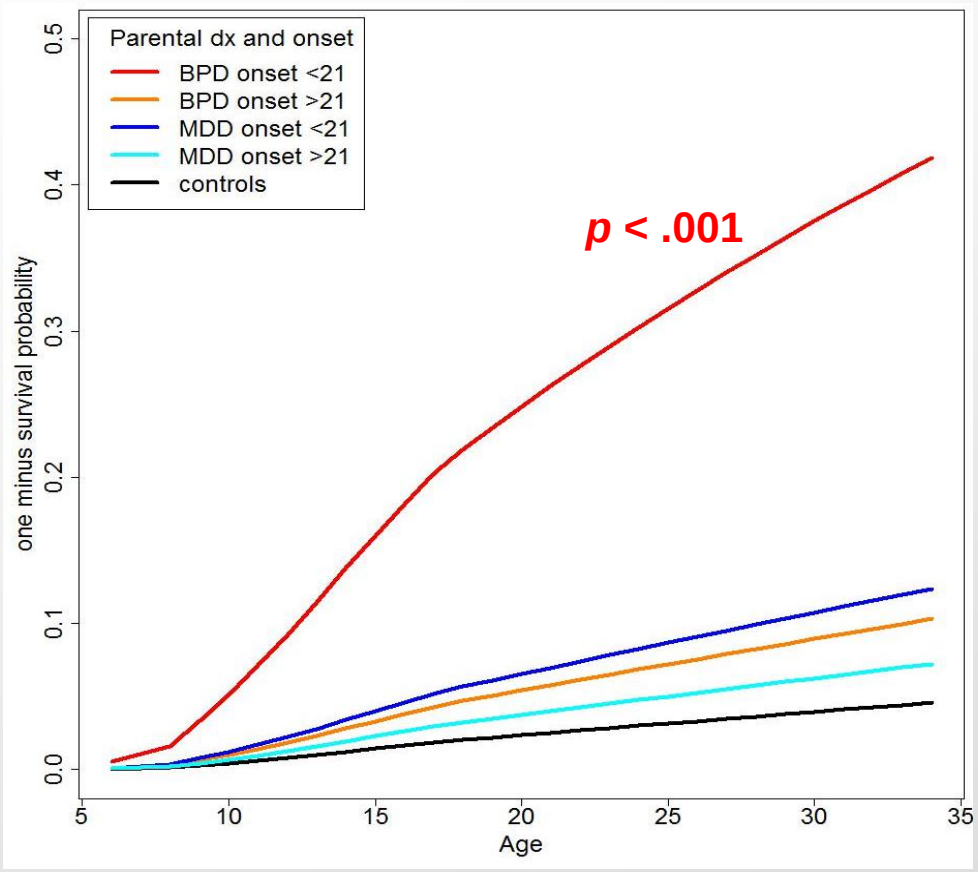
Other Disorders in Offspring by Parent Diagnosis



Incidence of Bipolar Disorder in Offspring across 12 years



Research report

The specificity of the familial aggregation of early-onset bipolar disorder: A controlled 10-year follow-up study of offspring of parents with mood disorders

Martin Preisig [a], Marie-Pierre F. Strippoli [a], Enrique Castelao [a], Kathleen Ries Merikangas [b], Mehdi Gholam-Rezaee [a], Pierre Marquet [a], Jean-Michel Aubry [c], Caroline L. Vandeleur [a,*]

Journal of Affective Disorders 190 (2016) 26–33

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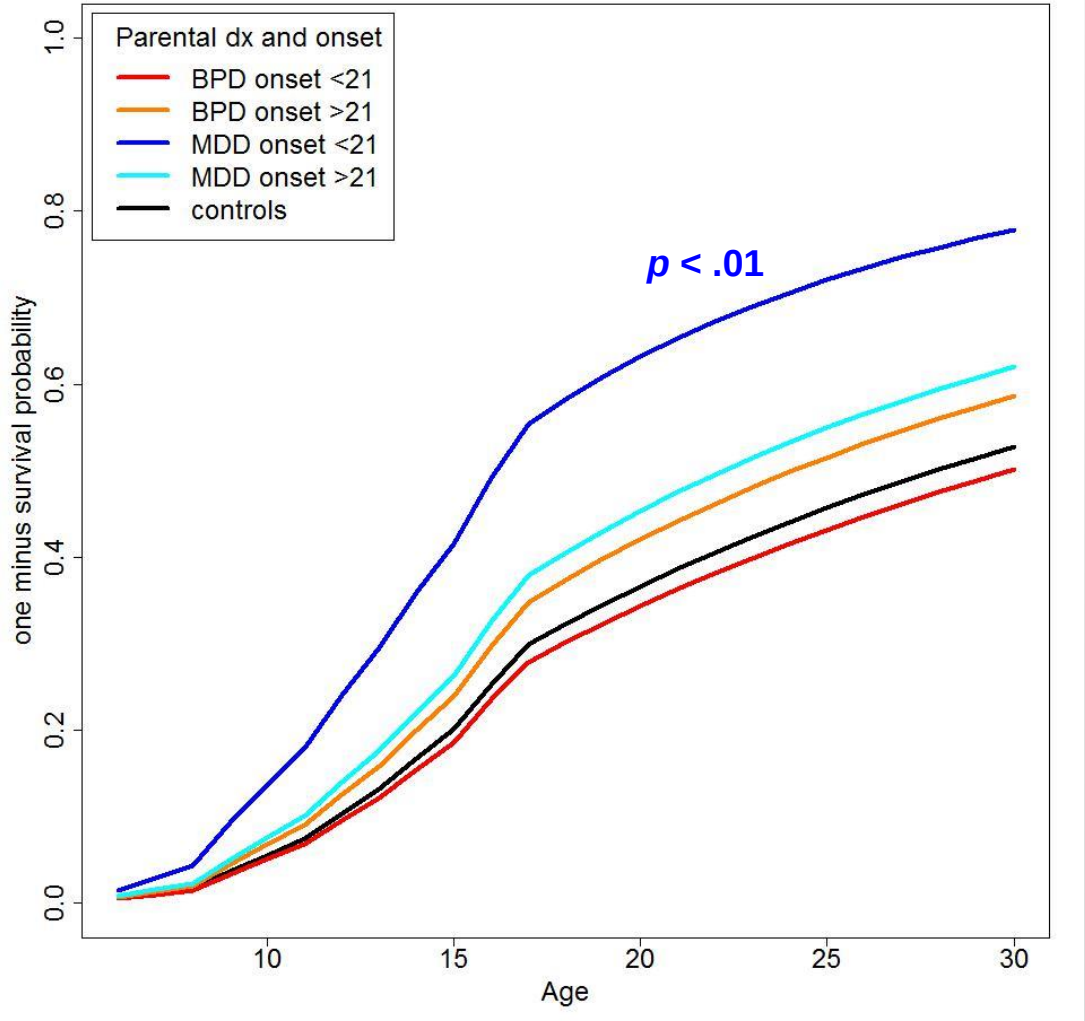
Incidence of MDD in offspring by parental mood disorders



Preisig M et al (2016) J Aff Disorders 190:26-33

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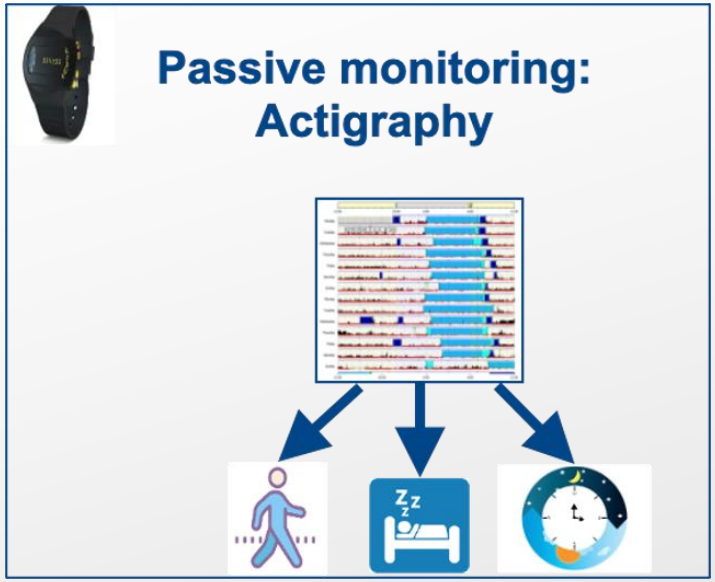
Chinese Bay Area Study: Study of Chronobiology in Offspring of Parents with Bipolar Disorder



- Offspring < age 12
  - ↑ ADHD
  - ↑ Social Anxiety
- Offspring > age 12
  - ↑ Major Depression
  - ↑ Hypomania
- No differences in chronotype, sleep parameters, or insomnia between high and low risk youth
- Decreased average and variability of motor activity emerged at adolescence
- Dampened melatonin increase

Jihui Zhang, Hongliang Feng

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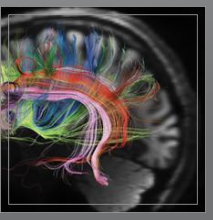

Summary and Future Directions

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Cross Diagnostic Phenomena

- Attention disturbances
- General impairment
- Impaired cognitive function
- Psychosis
- Lower motor activity levels
- Sleep difficulties or patterns
- Social communications
- Substance Use, particularly smoking
- Variability in homeostatic rhythms

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Interpretation of Research on Psychiatric Diagnostic Groups and Subgroups

- Sample ascertainment:
  - ✓ Enhance information about sample characteristics
  - ✓ Build in ancillary measures of syndromic conditions
  - ✓ Identify characteristics of treated samples in defined population
  - ✓ Expand clinical information beyond diagnostic billing codes
  - ✓ Employ developing methods for non probabilistic sampling
- Characterize timing at diagnosis or study entry across life course and phases of illness (state vs trait), particularly with prospective follow up
- Collaborative efforts to harmonize diagnostic and underlying domains, measures, and build in opportunities for cross-replication and generalizability

With Appreciation to

External Collaborators

Jules Angst, M.D., Zurich

Ian Hickie, M.D., Sydney

Martin Preisig, M.D., M.P.H., Lausanne

Peter Szatmari, M.D., Toronto

Phyllis Zee, M.D., Ph.D., Northwestern

Jihui Zhang, M.D., Ph.D., Hong Kong

Vadim Zipunnikov, Ph.D., Johns Hopkins

NIH

Samer Hattar, Ph.D., NIMH

Nora Volkow, M.D., NIDA

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Genetic Epidemiology Resarch Branch, NIMH