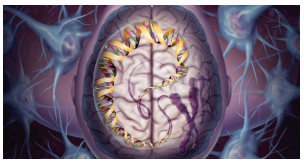
PSYCHIATRIC & NEURODEVELOPMENTAL GENETICS UNIT
CENTER FOR HUMAN GENETIC RESEARCH

Imaging Genetics: Decoding Psychopathology



Jordan W. Smoller, MD, ScD
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Massachusetts General Hospital

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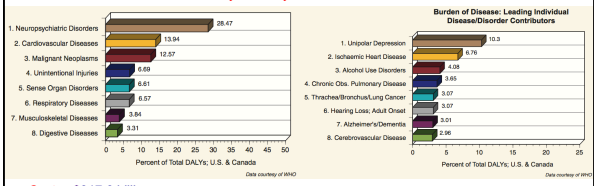
The Burden of Mental Illness

More disability than any other medical disorders:



Costs: $317.6 billion
Lethal consequences:

- Life expectancy of patients with chronic mental illness is shortened by an average of 25 years
- Suicide: 4th leading cause of death--ahead of diabetes, stroke and chronic lung disease

Genetic Epidemiology of Selected Disorders

Disorder	Familial Relative Risk	Heritability
Autism	25-50	60-90%
Schizophrenia	10	85%
Bipolar Disorder	7-10	85%
ADHD	2-6	77%
Alcohol/Drug Addiction	3-8	55%
Eating Disorders	10	55%
OCD	4-10	30-50%
Anxiety Disorders	5	40%
Depression	3	40%

The Usual Suspects

Serotonin Genes · Dopamine Genes · Norepinephrine Genes · GABA Genes · Neuropeptide Genes

ORIGINAL ARTICLES

BIOL PSYCHIATRY 2007;61:1121–1126

Spurious Genetic Associations

Patrick F. Sullivan

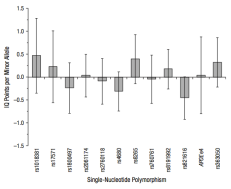
Low prior probability of association and low power

Simulation of *COMT* candidate gene studies:
- 10 polymorphisms, 500 cases and 500 controls
- 97% of simulated case-control analyses produce association at 0.05 level even though data randomly generated

Most Reported Genetic Associations With General Intelligence Are Probably False Positives

Christopher F. Chabris[1], Benjamin M. Hebert[2], Daniel J. Benjamin[3], Jonathan Beauchamp[2], David Cesarini[4], Matthijs van der Loos[5], Magnus Johannesson[6], Patrik K. E. Magnusson[7], Paul Lichtenstein[7], Craig S. Atwood[8], Jeremy Freese[9], Taissa S. Hauser[10], Robert M. Hauser[10], Nicholas Christakis[11,12], and David Laibson[2]

Psychological Science 2012



3 independent samples
Combined N ~10,000

A New Era in Psychiatric Genetics

Before 2008: virtually no specific genetic risk factors identified for common psychiatric disorders

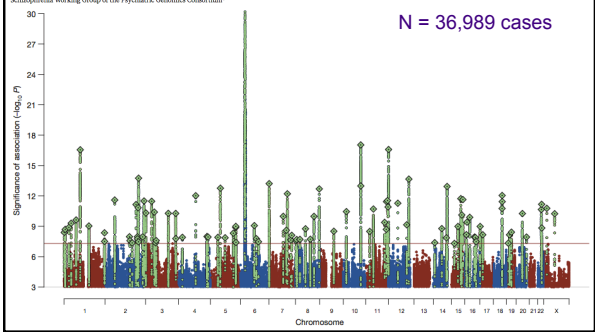
ARTICLE

doi:10.1038/nature13595

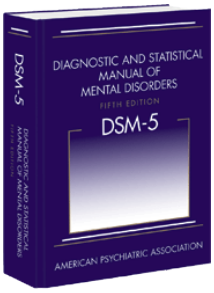
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

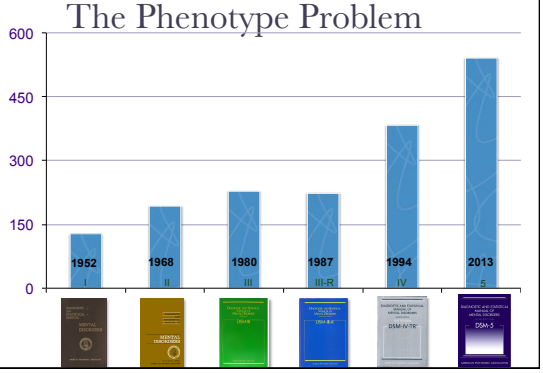
N = 36,989 cases



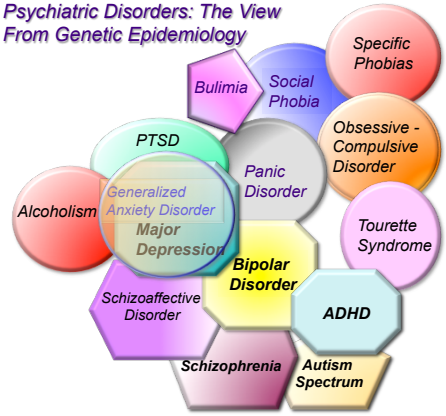
The Book of Phenotypes



Psychiatry's DSM: The Phenotype Problem



Psychiatric Disorders: The View From Genetic Epidemiology



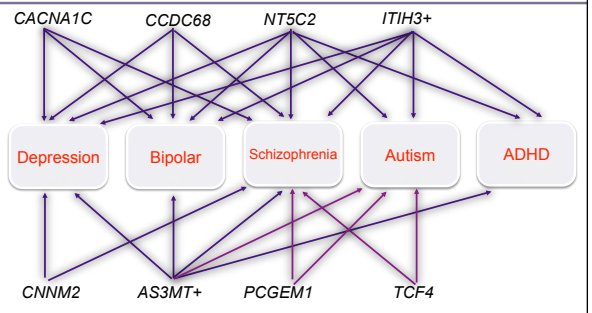
From DSM to DNA: Shared Genetic Risk Factors

THE LANCET

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium*

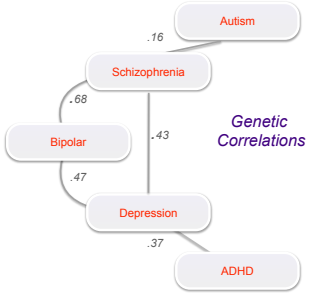
N > 60,000



Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium*

VOLUME 45 | NUMBER 9 | SEPTEMBER 2013 NATURE GENETICS



Common Findings in Neuroimaging of Psychopathology

Disorder	Structural	Functional
Autism Spectrum	• ↑early TBV • ↓corpus callosum volume	• Atypical connectivity of multiple networks
ADHD	• Delayed cortical surface area development • Frontal cortical thinning • Widespread ↓WM integrity	• Disturbed function in attention and inhibitory networks • Reduced reward sensitivity • Atypical DMN and PFC/Nac connectivity
Schizophrenia	• Ventricular enlargement • Accelerated cortical GM loss • Widespread ↓WM integrity	• ↑DMN connectivity; • ↓fronto-parietal connectivity; • altered DLPFC activation (working memory tasks)
Bipolar Disorder	• Widespread ↓WM integrity • ↑deep WM hyperintensities	• Altered cortico-limbic connectivity
Depression	• ↓hippocampal volume	• ↑amygdala & dACC reactivity to negative stimuli • ↓rACC activation to emotional stimuli • ↓ventral striatal activation to positive stimuli
Anxiety Disorders	• Altered amygdala volume • Reduced amygdala-PFC WM integrity	• ↑amygdala, insula, and dACC reactivity to threat;
PTSD	• ↑amygdala volume • ↓hippocampal volume	• ↑amygdala reactivity to threat; • Altered ACC activation to trauma stimuli

But is it Heritable? Twin Studies

STRUCTURAL	
Phenotype	**Heritability**
Mean cortical thickness	65%-82%
Anterior cortical thickness	80%-100%
Corpus callosum white matter density	80%
Total cortical unmyelinated white matter volume	85%
Intracranial volume	71%-91%
Amygdala volume	49-83%
Lateral ventricle volume	31%-92%
Caudate volume	90%
Accumbens	49%
Corpus callosum volume	85%-92%
Hippocampal volume	77-79%
Thalamus volume	74-88%
White matter integrity (various regions)	40-80%
FUNCTIONAL	
Working memory task-related brain activation	~40%-65%
Resting state functional local connectivity	46-89%
Resting state functional global connectivity	37-62%

Two General Approaches

- Discovery: Identify loci that influence neuroimaging endophenotypes
- Characterization: Characterize neural expression of established genetic risk factors

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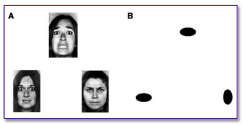
Endophenotypes

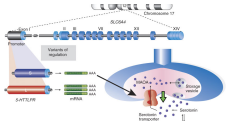
- Neurocognitive and Neural Phenotypes are
  - ➢ linked to major neuropsychiatric disorders
  - ➢ highly heritable
  - ➢ more direct expression of gene effects?

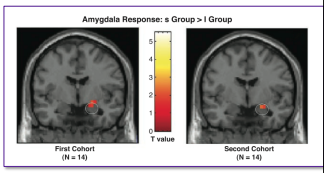
Genes/ Proteins → Biological Processes → Brain Systems → Behavior/ Cognition → Psychiatric Illness

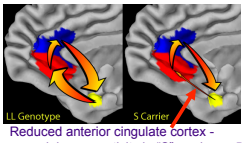
Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Ahmad R. Hariri,[1] Venkata S. Mattay,[1] Alessandro Tessitore,[1] Bhaskar Kolachana,[1] Francesco Fera,[1] David Goldman,[2] Michael F. Egan,[1] Daniel R. Weinberger[1]*









Reduced anterior cingulate cortex - amygdala connectivity in "S" carriers Pezawas et al. Nature Neurosci, 2005

The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: a meta-analysis

SE Murphy[1], R Norbury[2], BR Godlewska[1], PJ Cowen[1], ZM Mannie[1], CJ Harmer[1] and MR Munafò[3]

[1]*Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK;* [2]*University of Oxford Centre for Clinical Magnetic Resonance Research (OCMR), John Radcliffe Hospital, Oxford, UK and* [3]*School of Experimental Psychology, University of Bristol, Bristol, UK*

	k	g	95% CI		P-value	I^2 (%)	P_{diff}
All studies	34	0.21	0.00	0.43	0.050	70	NA
Published							
Yes	29	0.35	0.15	0.55	0.001	60	0.008
No	5	−0.66	−1.38	0.06	0.073	80	

- Modest but significant effect
- Larger when only published studies considered
- Significant heterogeneity of effects across studies
- Variance explained ~1% compared to ~30% in original studies
- No study was adequately powered to detect this effect

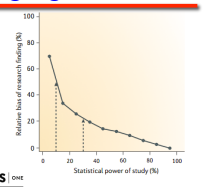
Bias: Winner's Curse, Selective Reporting, Data-dredging, etc

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[5] and Marcus R. Munafò[1]

NATURE REVIEWS | NEUROSCIENCE | VOLUME 14 | MAY 2013 | 365

Median power:
Neuroimaging studies: 8%
Animal studies: 31%

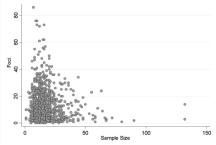


OPEN ACCESS Freely available online PLOS ONE

Potential Reporting Bias in fMRI Studies of the Brain

Sean P. David[1,2,3]*, Jennifer J. Ware[3,4], Isabella M. Chu[1], Pooja D. Loftus[1], Paolo Fusar-Poli[3], Joaquim Radua[3], Marcus R. Munafò[2], John P. A. Ioannidis[5]

Smaller sample size → more significant foci



ONLINE FIRST

Excess Significance Bias in the Literature on Brain Volume Abnormalities

John P. A. Ioannidis, MD, DSc

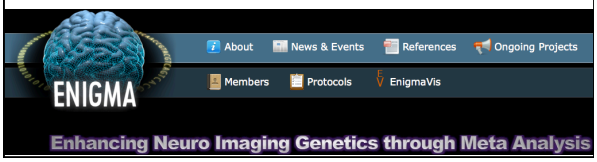
2-4 fold excess of significant findings

Genomewide Approaches

- Do not rely on prior genetic hypotheses
- Proven success for complex traits
- But…
  - Typical effect sizes: allelic OR < 1.2
  - Multiple testing requires stringent correction (typically $p < 5 \times 10^{-8}$)
  - Most imaging genetic studies vastly underpowered

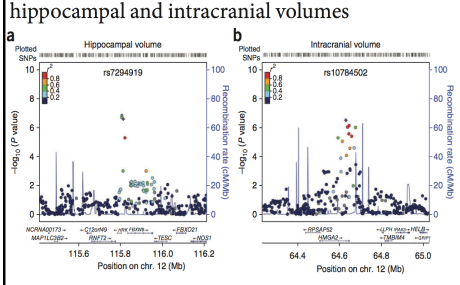
How to Achieve Power?

- Consortia and meta-analysis
- Example: ENIGMA
  - 50 cohorts worldwide, 125 institutions
  - N ~30,000
  - Harmonized image analysis and QC



nature genetics

Identification of common variants associated with human hippocampal and intracranial volumes



- ↓Hippocampal volume in MDD, PTSD,BPD, SCZ
- ENIGMA consortium (N = 7794; replication including CHARGE ~10K):
  - Hippocampal volume 12q24.22; P=2.56x10^{-17}
  - Intracranial volume: 12q13.3, P=3.45x10^{-11}

Implications

- Common genetic variants underlying brain structural phenotypes can be found
- Neural "endophenotypes" may not be less complex than disorder
- Usual suspects nowhere to be seen

Another Challenge: What's the Phenotype?

- Prior imaging/disease studies provide leads
- But endophenotype concept implies these relationships must be genetically mediated
- But, the search space could be huge
- How to select high-yield brain phenotypes?
- Need screening methods

High Dimensional Endophenotype Ranking in the Search for Major Depression Risk Genes

David C. Glahn, Joanne E. Curran, Anderson M. Winkler, Melanie A. Carless, Jack W. Kent Jr., Jac C. Charlesworth, Matthew P. Johnson, Harald H.H. Göring, Shelley A. Cole, Thomas D. Dyer, Eric K. Moses, Rene L. Olvera, Peter Kochunov, Ravi Duggirala, Peter T. Fox, Laura Almasy, and John Blangero

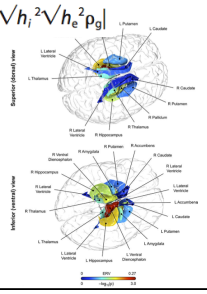
BIOL PSYCHIATRY 2011;

Endophenotype ranking value: $ERV_{ie} = |\sqrt{h_i}^2 \sqrt{h_e}^2 \rho_g|$

Generate genetic covariance between disorder and endophenotype using:

- Square root of disorder heritability
- Square root of endophenotype heritability
- Genetic correlation between them

Derived from pedigree or twin data



Genomic Complex Trait Analysis (GCTA)

- Estimate heritability due to common variants directly from genotypes ("SNP-chip heritability")
- Measure genetic similarity of unrelated individuals and its linear relationship to phenotype similarity
- Genetic relationship matrix (GRM)
- Estimate heritability using residual maximum likelihood analysis from a linear mixed model
- Larger sample sizes reduce standard error
- Rank putative endophenotypes

Massively Expedited Genomewide Heritability Analysis (MEGHA)

- Problem: massive number of potential phenotypes
- GCTA unfeasible for screening
- MEGHA (Ge et al.) uses same GRM but computes efficient variance component score test (kernel machine methods)
- Can compute permuted p values

Poster Talk (Group 1): Ge et al. Fast Heritability Analysis Using Genome-Wide Data via Kernel Machines

Two General Approaches

- Discovery: Identify loci that influence neuroimaging endophenotypes
- Characterization: Characterize neural expression of established genetic risk factors

GENETICS

Editor: Jordan W. Smoller, MD, ScD

A New Role for Endophenotypes in the GWAS Era: Functional Characterization of Risk Variants

Mei-Hua Hall, PhD, and Jordan W. Smoller, MD, ScD

Harv Rev Psychiatry 2010;18:67–74.

Genes/ Proteins → Biological Processes → Brain Systems → Behavior/ Cognition → Psychiatric Illness

Neuroimaging Dissection of Established Risk Variants

Influence of *ZNF804a* on Brain Structure Volumes and Symptom Severity in Individuals With Schizophrenia

Thomas H. Wassink, MD; Eric A. Epping, MD, PhD; Danielle Rudd, BA; Michael Axelsen, BA; Stephen Ziebell; Frank W. Fleming; Eric Monson, BA; Bong Choon Ho, MD; Nancy C. Andreasen, MD, PhD

ORIGINAL ARTICLE

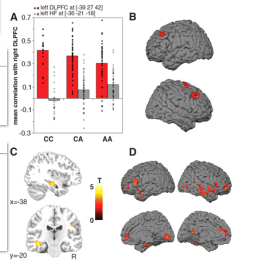
Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task

ORIGINAL ARTICLE

Genetic Variation in *CACNA1C* Affects Brain Circuitries Related to Mental Illness

Kristin L. Bigos, PhD; Venkata S. Mattay, MD; Joseph H. Callicott, MD; Richard E. Straub, PhD; Radhakrishna Vakkalanka, PhD; Bhaskar Kolachana, PhD; Thomas M. Hyde, MD; Barbara K. Lipska, PhD; Joel E. Kleinman, MD, PhD; Daniel R. Weinberger, MD

Neural Mechanisms of a Genome-Wide Supported Psychosis Variant



SCIENCE VOL 324 1 MAY 2009

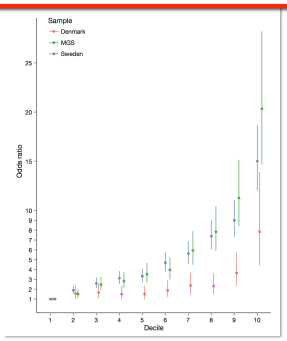
Polygene Risk Scores

- For polygenic phenotypes, many loci of modest effect will not reach GWS
- Can capture polygenic effects in single score
- Derive in discovery sample and apply in test sample

$$PRS = \Sigma_{j=1} x_j * \log(OR_{ij}),$$

where x_j = number of risk alleles (0, 1, or 2) *i*th individual carries at the *j*th SNP; OR_{ij} is the allelic odds ratio for *j*th SNP for individual *I*

Genetic Risk Profiles Predict Schizophrenia



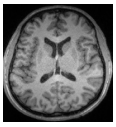
PGC-SCZ, Nature, 2014

MGH Brain Genomics Superstruct

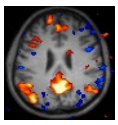
With Randy Buckner, Josh Roffman, MGH Psychiatry, MIT, McLean

Rapid Acquisition Imaging on Multiple Matched Scanners

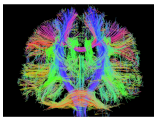
Structural



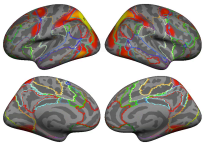
Functional



Web-based cognitive and behavioral tests



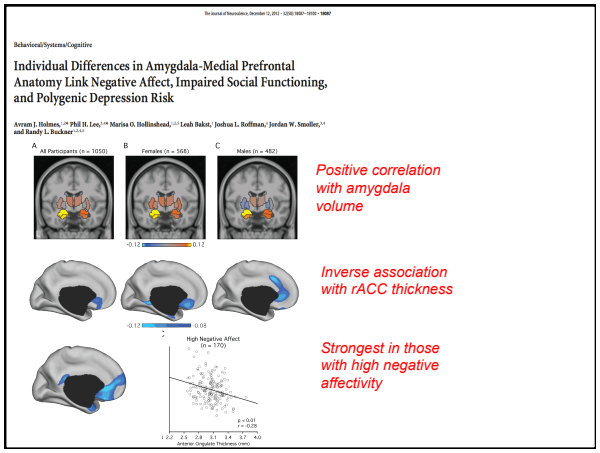
White Matter



Functional Connectivity

GWAS/Exome Analysis

> 4000 participants



Behavioral/Systems/Cognitive

Individual Differences in Amygdala-Medial Prefrontal Anatomy Link Negative Affect, Impaired Social Functioning, and Polygenic Depression Risk

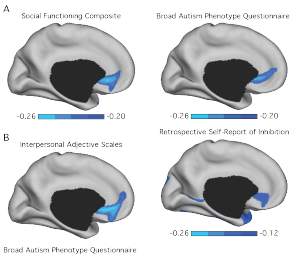
Avram J. Holmes,[1,2*] Phil H. Lee,[1,3*] Marisa O. Hollinshead,[1,2] Leah Bakst,[1] Joshua L. Roffman,[1] Jordan W. Smoller,[1,3] and Randy L. Buckner[1,2,4,5]

Positive correlation with amygdala volume

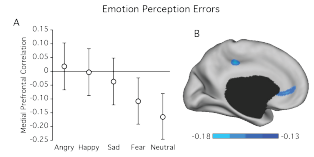
Inverse association with rACC thickness

Strongest in those with high negative affectivity

Dimensions of Social Cognition



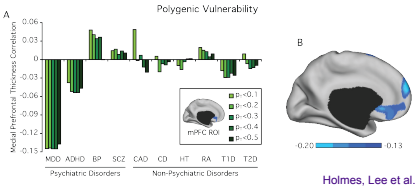
Emotion perception



Holmes, Lee et al. J Neurosci, in press

Polygenic Score for Depression is Associated with ACC thickness

- Completed GWAS of 470 individuals
- Calculated polygene score using data from Psychiatric GWAS Consortium (N = 61,220)
- Question: Are polygenic influences on MDD associated with rACC thickness



Holmes, Lee et al. J Neurosci, 2012

Summary

- Psychiatric disorders are complex and highly polygenic
- A growing catalogue of risk variants – but disorders are clinical constructs with fuzzy boundaries and mechanisms from gene➔brain➔illness are poorly understood
- Imaging genetics offers crucial tool for addressing this
- Two approaches:
  - Discovery: need large samples
  - Characterization
- Directions and Gaps:
  - Increasing Power: larger samples, consortia (e.g. PGC-ENIGMA)
  - Methods for addressing high dimensionality

Acknowledgements

Psychiatric Genomics Consortium

165 scientists from 68 institutions in 19 countries

Workgroup	Chair(s)
SCZ	***Mick O'Donovan***
BPD	Pamela Sklar/John Kelsoe
MDD	***Patrick Sullivan***
ASD	Mark Daly/Bernie Devlin
ADHD	***Steve Faraone***
Analysis	Mark Daly
Cross-Disorder	***Jordan Smoller/Ken Kendler***
CNV	Jonathan Sebat

Thomas Lehner

PGC Cross-Disorder Genetics Group: Jordan Smoller, Ken Kendler, Nick Craddock, Shaun Purcell, Ben Neale, Mike Neale, Pat Sullivan, Marcella Rietschel, John Nurnberger, Roy Perlis, Thomas Schulze, Anita Thapar, Susan Santangelo

PGC Cross-Disorder Genetics Analyses: Stephan Ripke, Ben Neale, Phil Lee, Ken Kendler, Shaun Purcell, Mark Daly

SNP-based genetic correlation analyses: S. Hong Lee, Naomi Wray

Brain Genomic Superstruct: Randy Buckner, Josh Roffman, Phil Lee, Avram Holmes, Marisa Hollingshead, Mert Sebancu,, others