Future Diagnostics for Clinical Trials in Neuropsychiatry

National Academies of Science/Institute of Medicine

Neuroscience Trials of the Future: A Workshop

March 3-4, 2016

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UCLA

UCLA Semel Institute

Translational Research Center for Neuropsychiatry

Disclosures

- **Consultant:** Forum Pharmaceuticals; Lumos Labs, Inc.; Maven Research; Neurocog Trials Inc.; OMDUSA, LLC; Snapchat; ThinkNow Inc.
- **Research Support:** NIH/NIMH; John Templeton Foundation

U.S. Food and Drug Administration

Drug Approval Process

What is a drug as defined by the FDA?

A drug is any product that is intended for use in the diagnosis, cure mitigation, treatment , or prevention of disease; and that tis intended to affect the structure or any function of the body.

PRE-CLINICAL

Drug Sponsor's Discovery and Screening Phase

Drug Developed

Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

Animals Tested

Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

IND Application

The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from intial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.

IND REVIEW

FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.

FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.

The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.

CLINICAL

Drug Sponsor's Clinical Studies/Trials

PHASE 1

20-80

The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

PHASE 2

100's

The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

FDA DRUG SPONSOR

PHASE 3

1000's

The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

"The goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition."

Problems (now)

- P1: Diseases/conditions lack validity
- P2: Psychometric approach to defining categories or dimensions is probably wrong
- P3: Categorical approach is mostly (~86%) wrong
- P4: External validators (genetics, neuroimaging, cognitive function) prove heterogeneity within and overlap across syndromes
- P5: Biomarkers are part of complex manifolds; still need to explicate relations to drug target and clinically meaningful problem

Solutions (next 5-10 years)

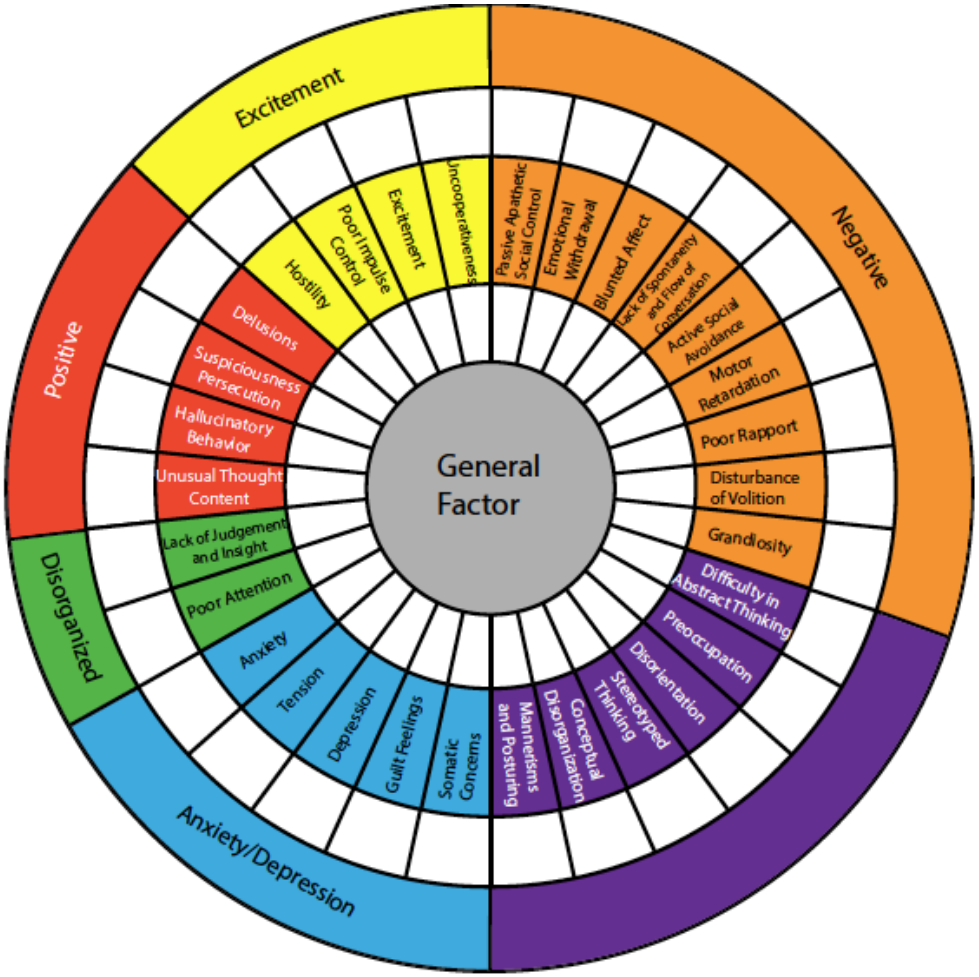
- S1: Do better psychometrics
- S2: Go beyond psychometrics to causal models
- S3: Sample behavior beyond the DSM, measure dimensions that span diagnostic entities
- S4: Go beyond symptoms and biomarkers, validate mediating processes across levels
- S5: industry-academia collaboration on mechanisms, knowledgebases, while protecting proprietary molecular entities and data

Kendler: symptom selection and diagnosis of MDD

- Reviewed 19 texts from 1900-1960 for clinical descriptions of major depression (or melancholia)
- Conclusions: DSM uses only a subset of symptoms
  - DSM criteria "reasonable but incomplete"
  - "…it is problematic when we focus our teaching, clinical work and research solely on DSM criteria which would lead to the neglect of important dimensions of depressive symptoms and signs."
- Not covered in DSM: volition/motivation, speech, anxiety, depersonalization/derealization, other physical symptoms
- S: go beyond diagnosis and diagnostic rating scales

Under review AJP

Modern Psychometric Approach: Bifactor model for PANSS



Ariana Anderson[1]*, Stephen Marder[1], Steven P. Reise[4], Hearee Chung[2], Qingqin Li[3], Marsha Wilcox[3], Giacomo Salvadore[3], Jennifer Zhou[1], Robert M. Bilder[1,4]

Janssen/UCLA

R03MH106922: Modeling RDoC Dimensions Across Levels of Analysis (Anderson)

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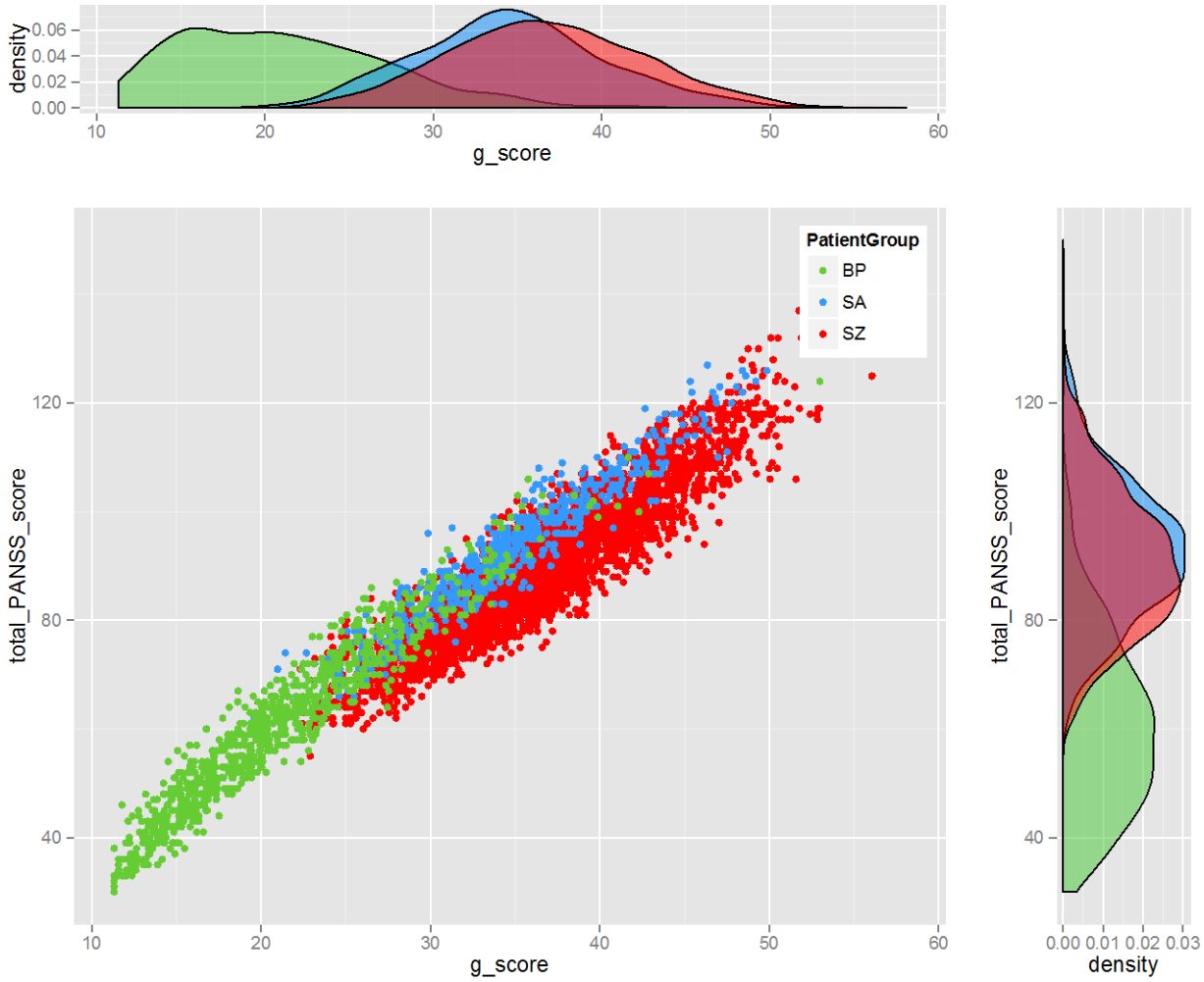
Median schizoaffective disorder patient has higher total PANSS score, but median schizophrenia patient has a higher “misery” g-score



R03MH106922: Modeling RDoC Dimensions Across Levels of Analysis (Anderson)

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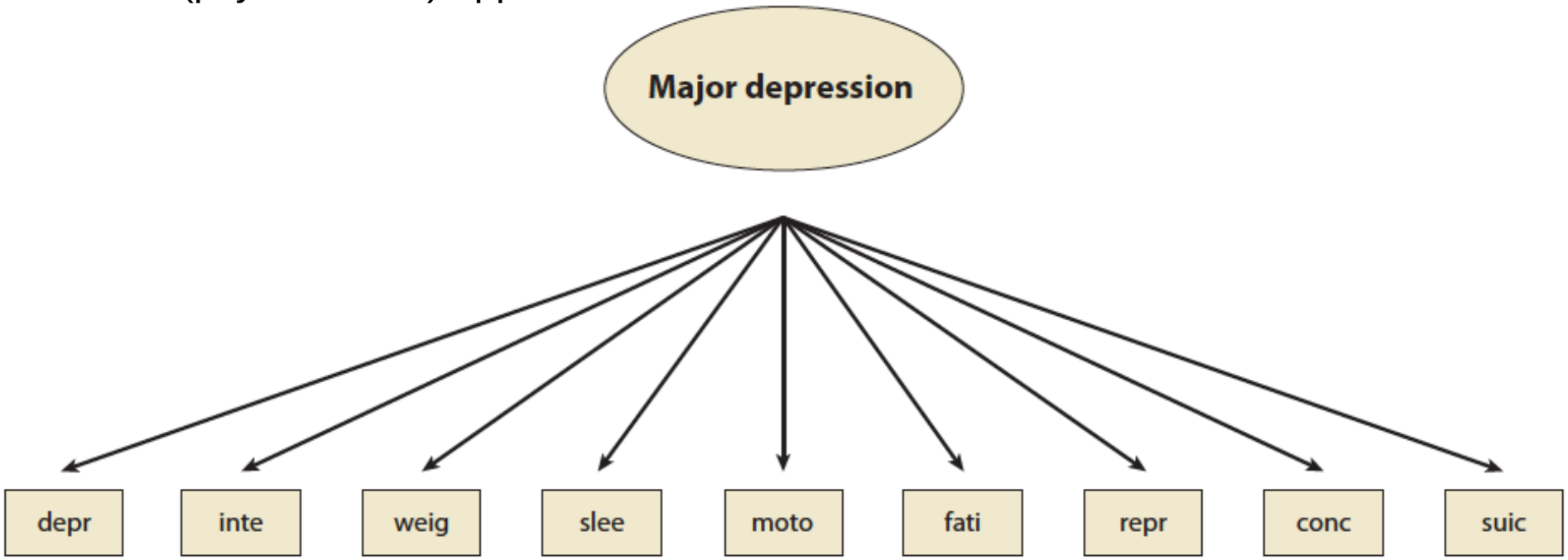
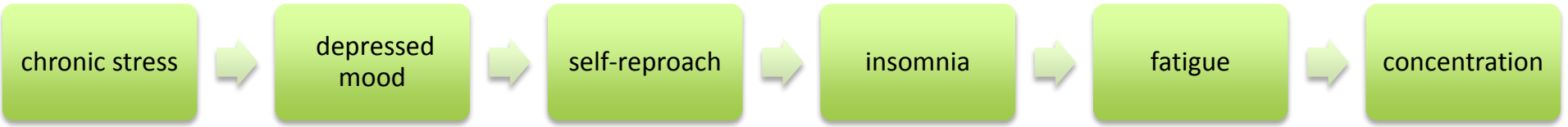
The Psychometric Model

- Disease entities cause symptoms
- We measure symptoms to assess disease
- Symptoms, summed or averaged, comprise the endpoints in clinical trials
- In neuropsychiatric disorders, the disease entities are probably wrong
- Thus assessing sums and averages of symptoms is probably wrong
- S1: to the extent that dimensions are correct, we can be much more efficient using IRT and CAT models
- S2: go beyond psychometric model, consider causal models and symptom networks

Classic (psychometric) approach



Network (causal modeling) approach

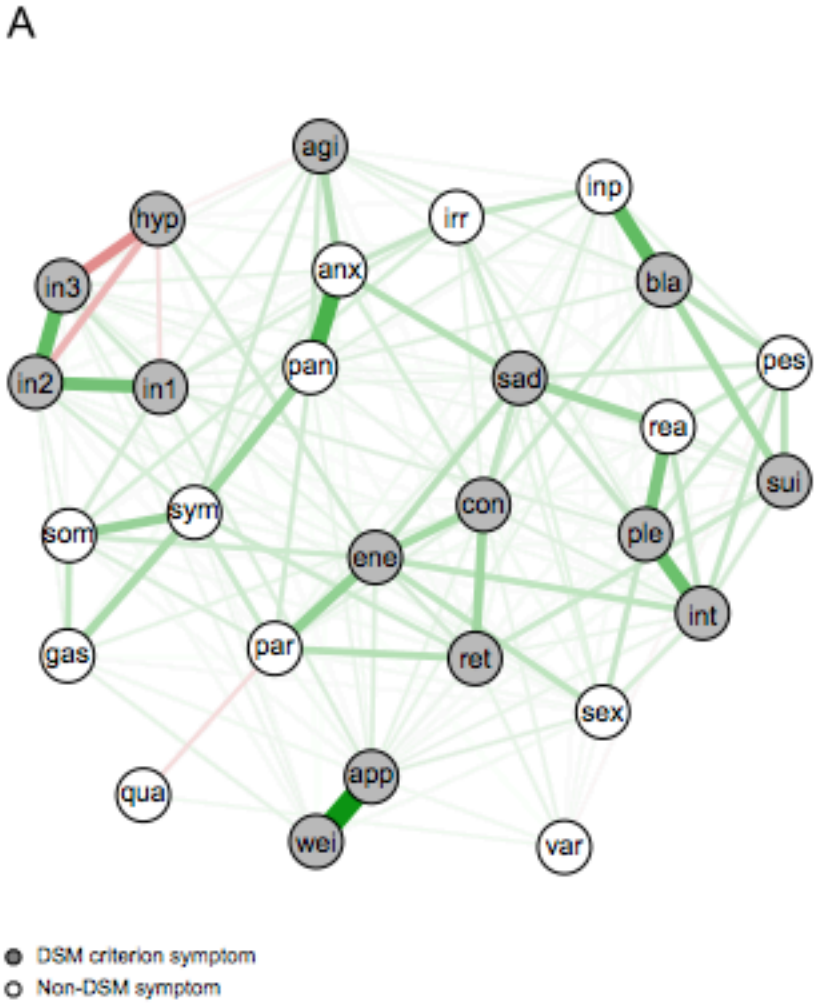


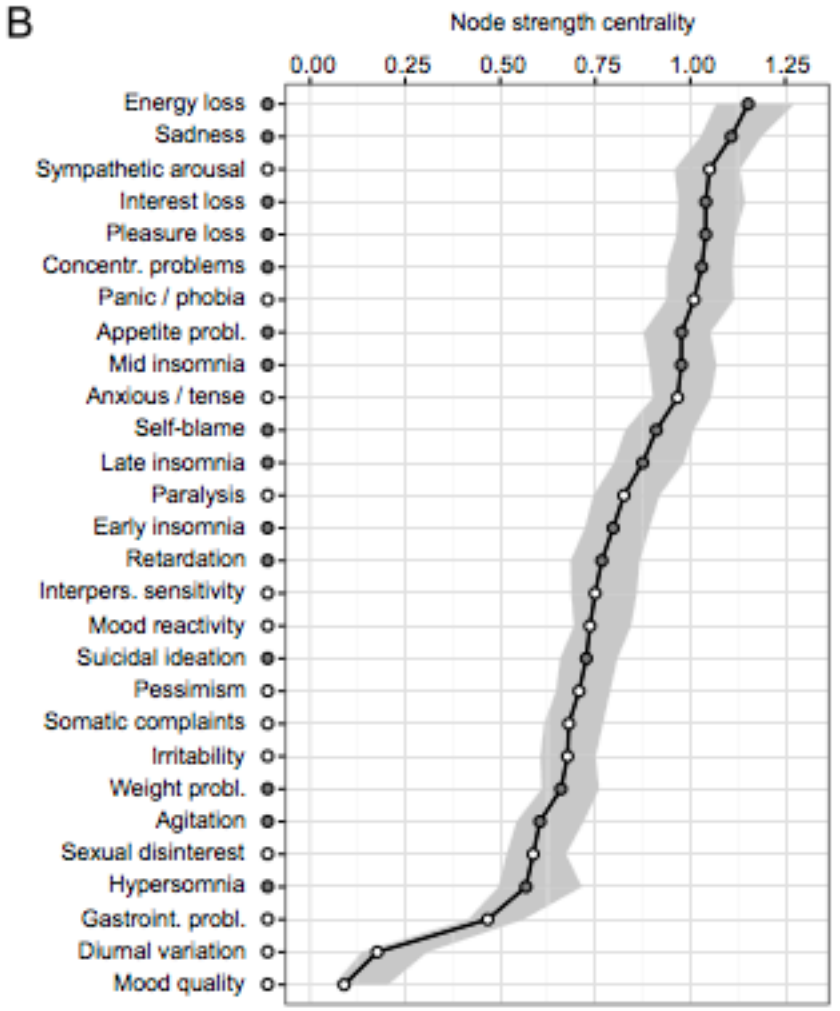
Borsboom & Cramer 2013 Annual Rev Psychology

"In sum, not only do we not know that symptoms are caused by mental disorders, but it is in fact extremely unlikely that they are."

Borsboom & Cramer 2013 Annual Rev Psychology

S: Consider network models of symptoms or other measurable phenomena





Fried et al 2016 J Affective Disorders

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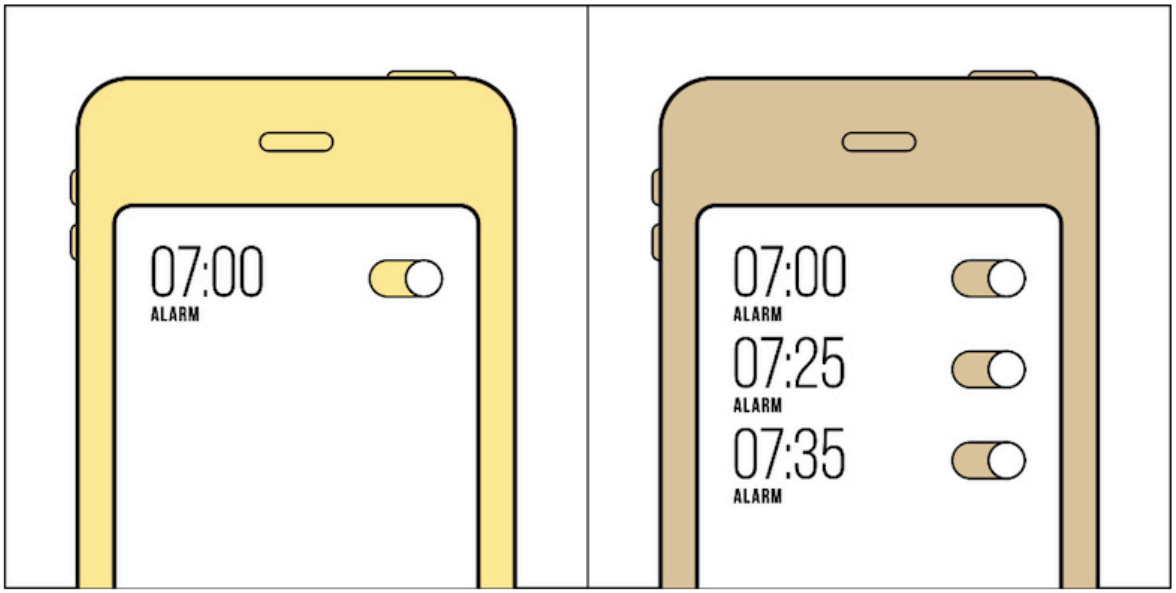
There are two kinds of people in the world…



- Those who split the world into two kinds of people, and…
- Those who don't.

Psychological Medicine (2012), **42**, 903–920. © Cambridge University Press 2011
doi:10.1017/S0033291711001966

REVIEW ARTICLE

Categories *versus* dimensions in personality and psychopathology: a quantitative review of taxometric research

N. Haslam[1]*, E. Holland[1] and P. Kuppens[2]

[1] *Department of Psychology, University of Melbourne, Parkville, Victoria, Australia*
[2] *Faculty of Psychology and Educational Sciences, University of Leuven, Belgium*

- Reviewed 177 articles, 311 findings, 533,377 participants
- 14% of findings were "taxonic" (despite categorical sampling)
- Personality, mood, anxiety, eating externalizing disorders not taxonic
- Promising, not definitive evidence for taxonic structure in:
  - Schizotypy
  - Substance use disorders
  - Autism
- MOST latent traits are dimensional

International Journal of Methods in Psychiatric Research
Int. J. Methods Psychiatr. Res. 16(S1): S8–S15 (2007)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/mpr.211

DSM categories and dimensions in clinical and research contexts

HELENA CHMURA KRAEMER

Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

Kraemer 2007

- Proposes adding dimensions to categories
- When is a dimensional diagnosis unneeded or impossible? The brief answer: virtually never.
- S: Every categorical diagnosis can be made dimensional by using symptom counts, symptom duration, symptom severity, degree of impairment, certainty of diagnosis, consensus of multiple diagnoses, and more…

Biological Validity

- Consider large genetic correlations (categories and dimensions have shared genetic contributions)
- Consider population-based “disease” associations, even greater overlap implying shared G+E contributions
- S: consider common dimensions and clusters of categories as targets (measures and patient groups); need subgroups within AND across syndromal boundaries

LETTER

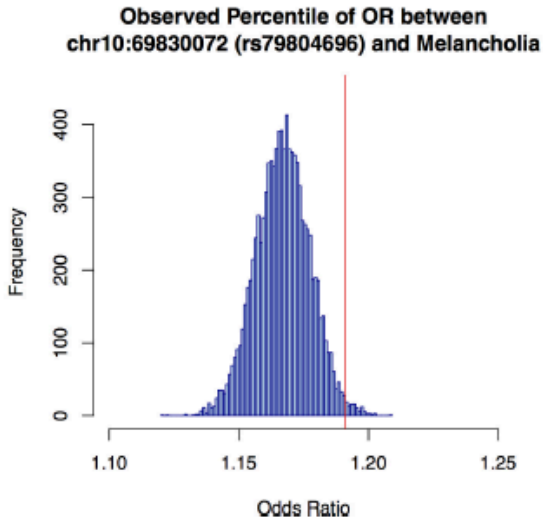
doi:10.1038/nature14659

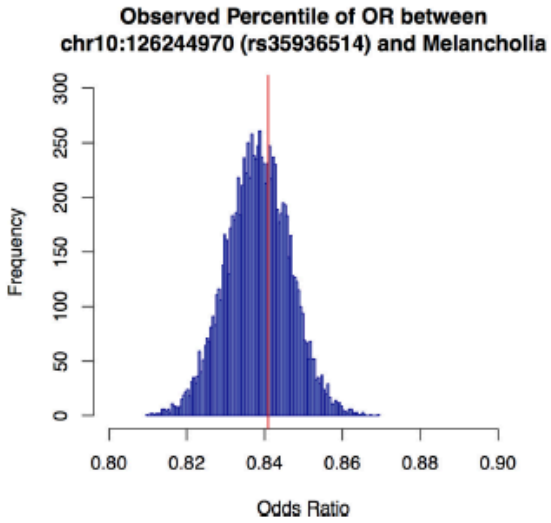
Sparse whole-genome sequencing identifies two loci for major depressive disorder

CONVERGE consortium*

Focus on melancholia increases ORs

RESEARCH LETTER





Extended Data Figure 4 | Empirical estimation of the odds ratio increases due to the removal of cases not falling under the diagnostic class of melancholia from an association analysis with major depression. The figures show the empirical distributions of the odds ratios for association with each of two SNPs (rs79804696, rs35936514), after removing a random set of 796 samples, equal to the number of cases of MDD not diagnosed as being melancholic. The horizontal axis is the odds ratio for each analysis, and the vertical axis the frequency of occurrence of the odds ratio in 10,000 analyses. The vertical red line is the observed odds ratio after removing cases of MDD not diagnosed as melancholic

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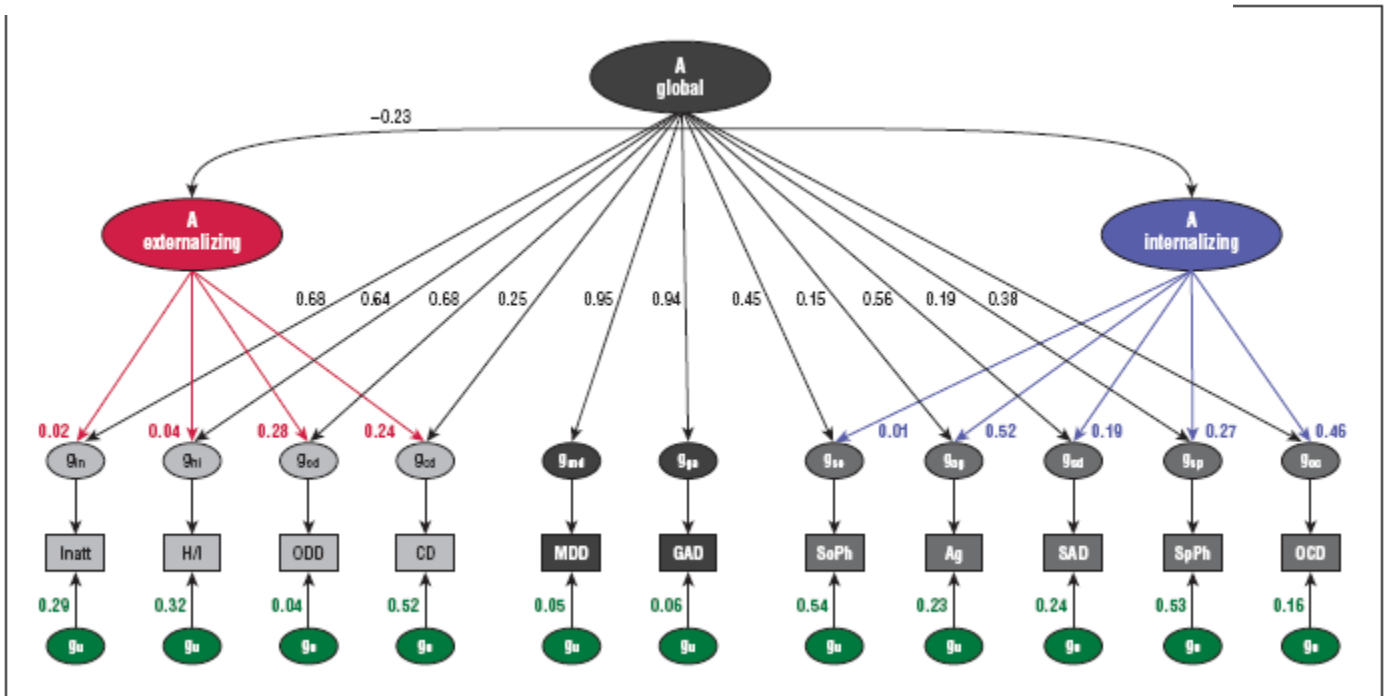
ORIGINAL ARTICLE

Higher-Order Genetic and Environmental Structure of Prevalent Forms of Child and Adolescent Psychopathology

Benjamin B. Lahey, PhD; Carol A. Van Hulle, PhD; Amber L. Singh, PhD; Irwin D. Waldman, PhD; Paul J. Rathouz, PhD

Arch Gen Psychiatry. 2011;68(2):181-189



…dimensions of child and adolescent psychopathology mostly share their genetic liabilities but are differentiated by nonshared experiences.

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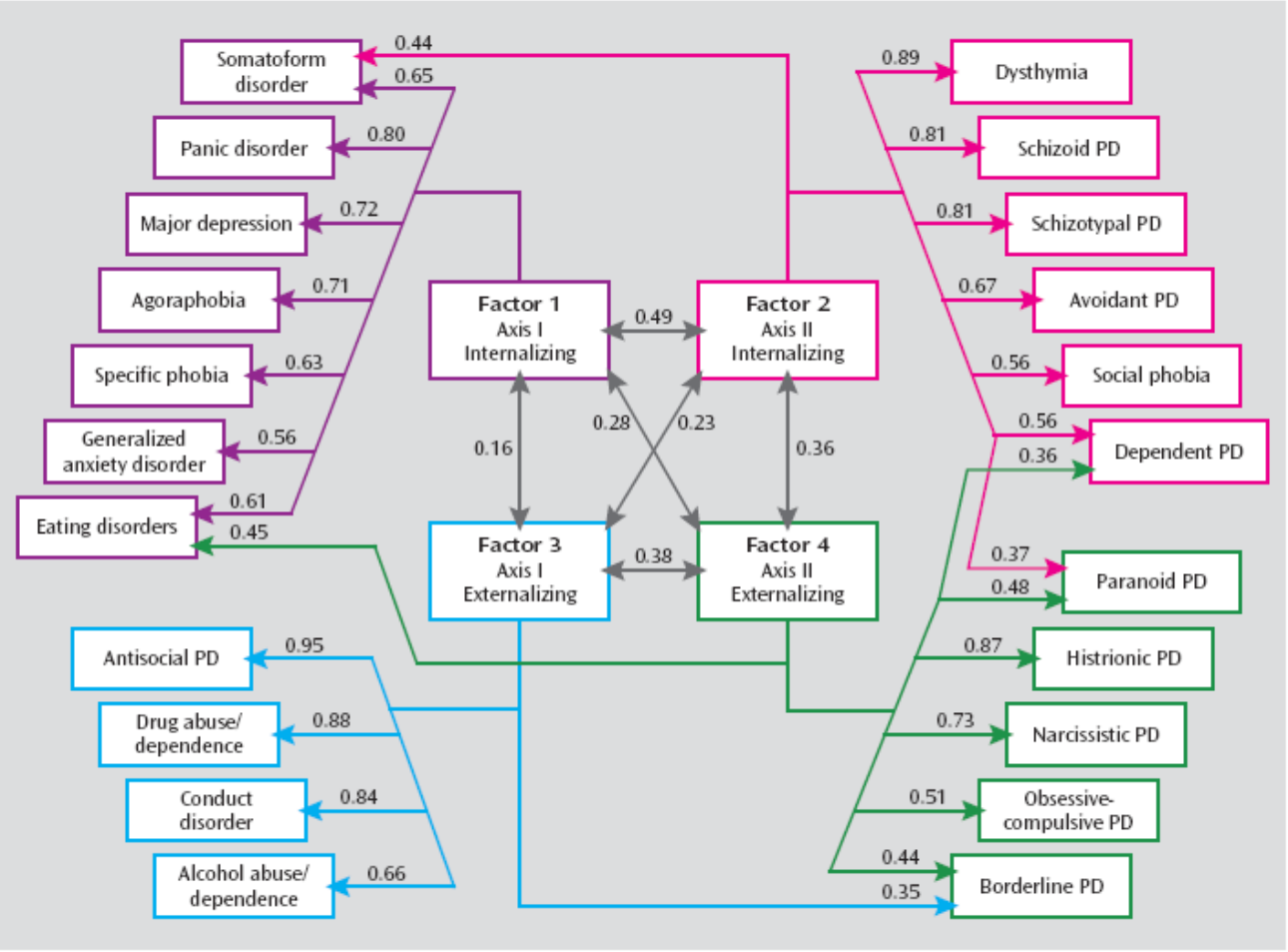
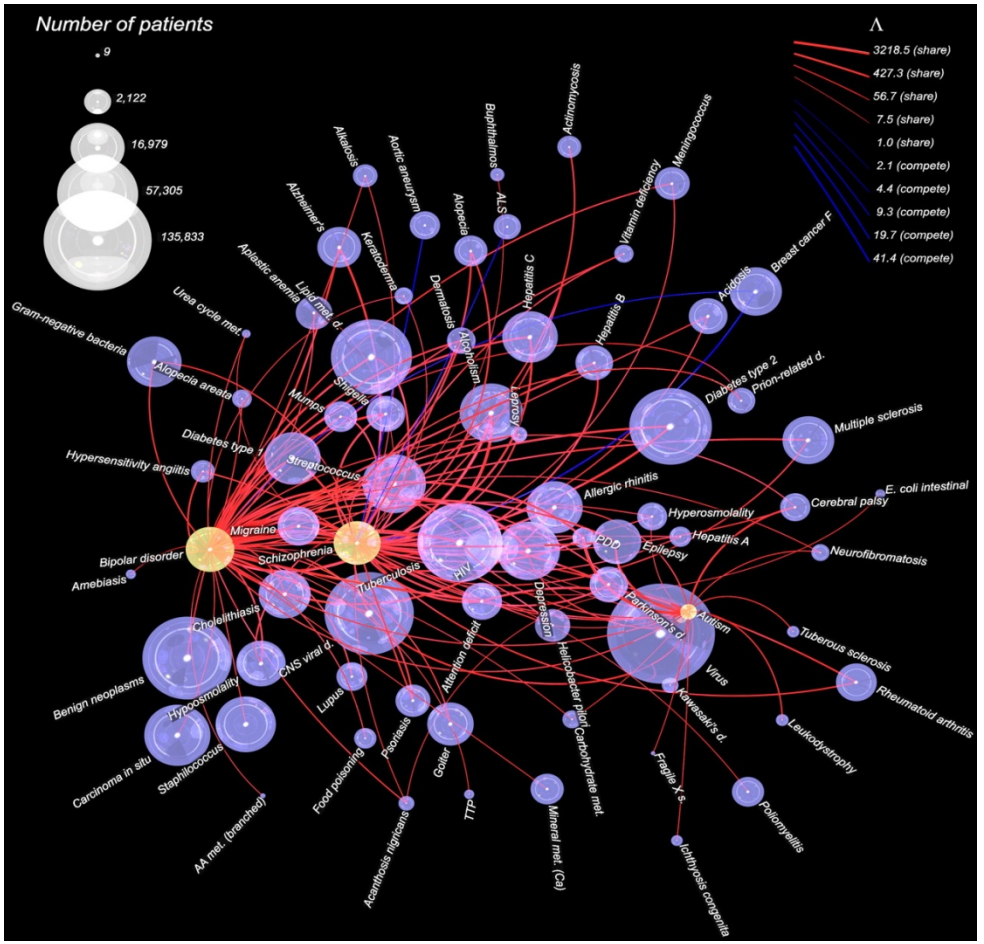
The Structure of Genetic and Environmental Risk Factors for Syndromal and Subsyndromal Common DSM-IV Axis I and All Axis II Disorders



Kendler et al. Am J Psychiatry 2011; 168:29–39

Significant correlations (that we interpret as genetic overlap) among three neurodevelopmental disorders (autism, bipolar disorder, and schizophrenia; corresponding nodes are shown in yellow) and all other disorders in our data set (blue nodes)

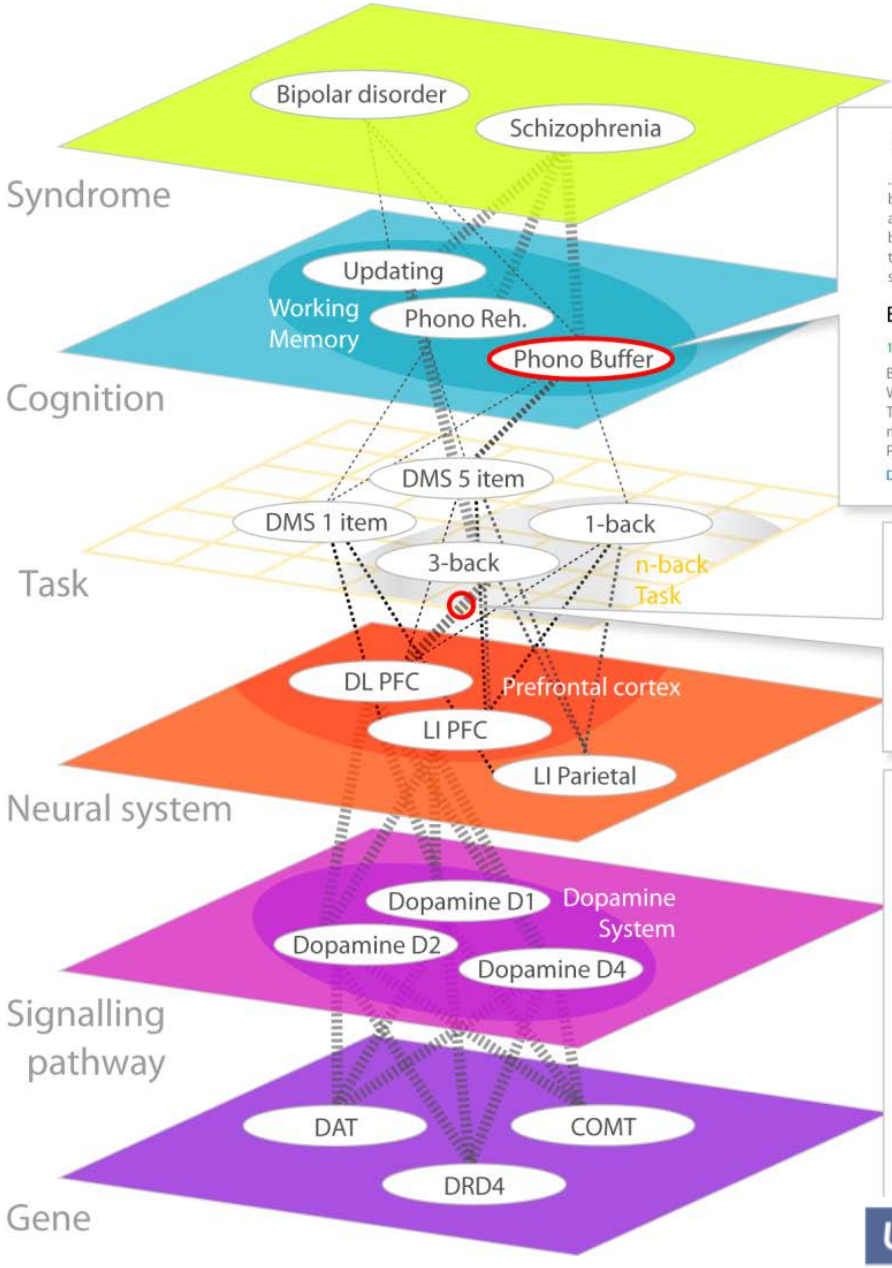


Rzhetsky A et al. PNAS 2007;104:11694-11699

The Level Problem

- Syndromes defined by symptoms
- Drugs act on molecules
- From molecules to symptoms spans a lot of messy biology
- S1: validate biomarkers and “intermediate phenotypes” to flesh out cross-level links from molecular entity to condition entity
- S2: develop multi-level composite endpoints (compare CEPs in T2DM; Einarson et al 2014)

Cognitive Atlas



Phonological Buffer

Edit this page Discuss History

...auditory verbal information is assumed to enter automatically into the phonological buffer. Visually presented language can be transformed into phonological code by silent articulation and thereby be encoded into the phonological buffer. The phonological buffer acts as an 'inner ear', remembering speech sounds in their temporal order, whilst the articulatory process acts as an 'inner voice' and repeats the series of words (or other speech elements) on a loop to prevent them from decay.

Evidence For

14 of 15 people found this convincing

Baddeley, A.D., & Hitch, G. (1974). Working memory. In G.H. Bower (Ed.), The psychology of learning and motivation. New York: Academic Press.

Discuss (14 comments)

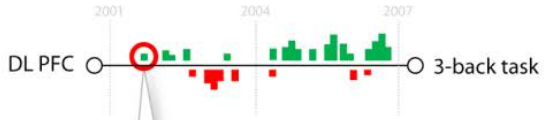
Evidence Against

4 of 6 people found this convincing

Jones, D. M., Macken, W. J., & Nicholls, A. P. (2004). The phonological store of working memory: is it phonological and is it a store? Journal of Experimental Psychology: Learning, Memory, and Cognition, 30, 656-674

Discuss (7 comments)

Evidence linking DL PFC to the 3-back task



Edit this page Discuss History

Evidence supporting: DL PFC correlated with 3-back task

28 of 30 people found this convincing

Cohen, JD et al., 1997. *Temporal dynamics of brain activation during a working memory task.* Nature 386: 604-8.

studies in non-human primates suggest that dorsolateral regions of the prefrontal cortex may also be involved in active maintenance. We have used functional magnetic resonance imaging to examine brain activation in human subjects during performance of a working memory task. We used the temporal resolution of this technique to examine the dynamics of regional activation, and to show that prefrontal cortex along with parietal cortex appears to play a role in active maintenance.

This evidence is also linked to:

- Prefrontal cortex
  - Dorsolateral prefrontal cortex
- Working memory
- fMRI
- n-back task

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Table 1

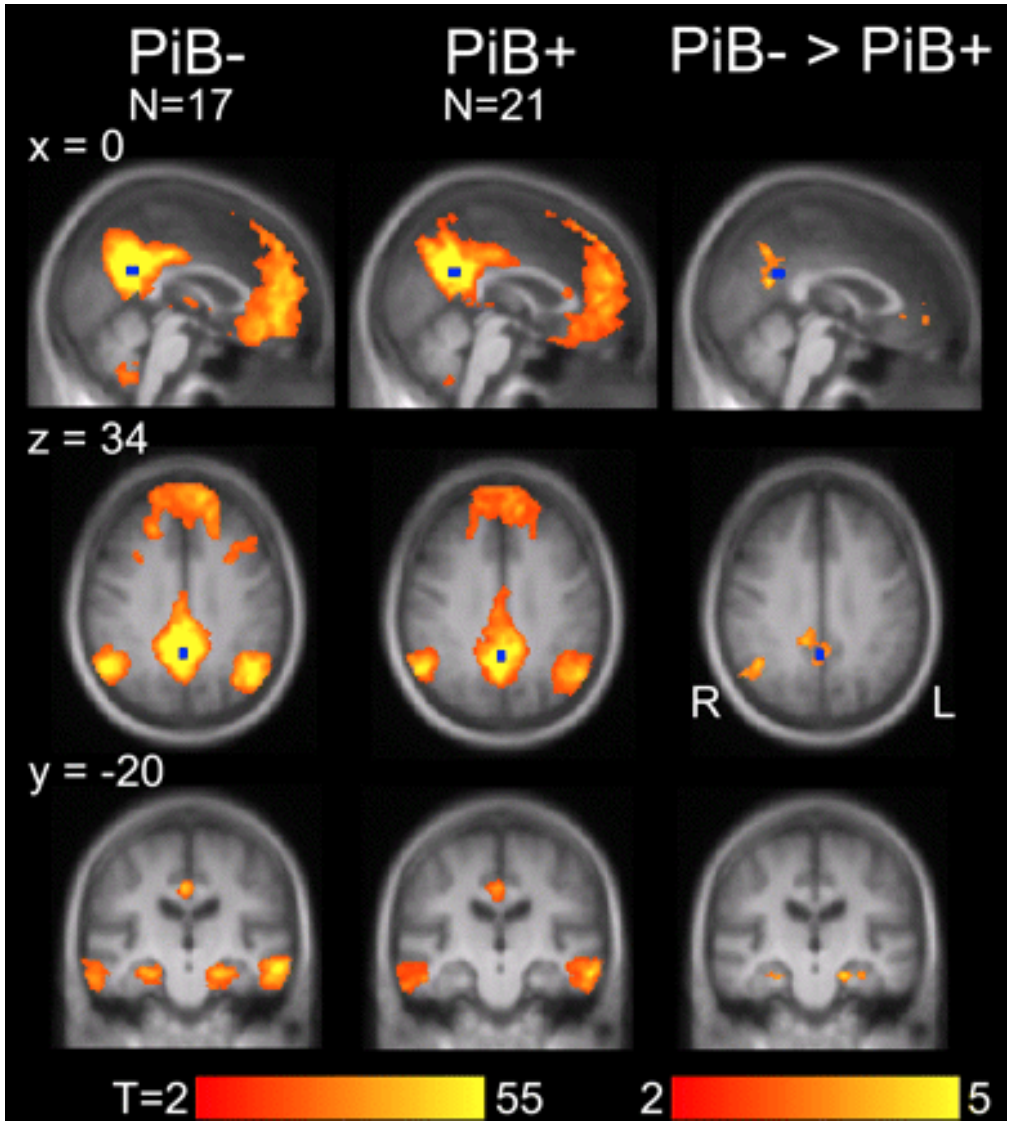
Examples of Ontologies or Descriptive Systems Used to Represent Concepts and Relations Among Concepts for Levels of Analysis From the Syndrome to the Genome

Level of analysis	Example ontologies/descriptive systems
Syndrome	Diagnostic and Statistical Manual of Mental Disorders
Symptom	Measurement models with latent symptom constructs based on rating scales, interview schedules
Cognitive	Measurement models with latent cognitive constructs based on psychometric test scores
Neural system/circuit	NeuroML; CocoMac; Xanat
Cellular systems/ signaling pathways	Ingenuity Pathways Analysis; Gene Ontologies biological processes; KEGG Pathway
Proteins	Entrez Protein; UniProt/SwissProt; NextProt
Genes and gene expression	Gene Ontologies; Entrez Gene, Gene Expression Omnibus

Bilder, Howe & Sabb, 2013
Journal of Abnormal Psychology

Amyloid burden is associated with disruption of the default mode network…

… but neither amyloid burden nor disrupted DMN are associated with cognitive impairment.

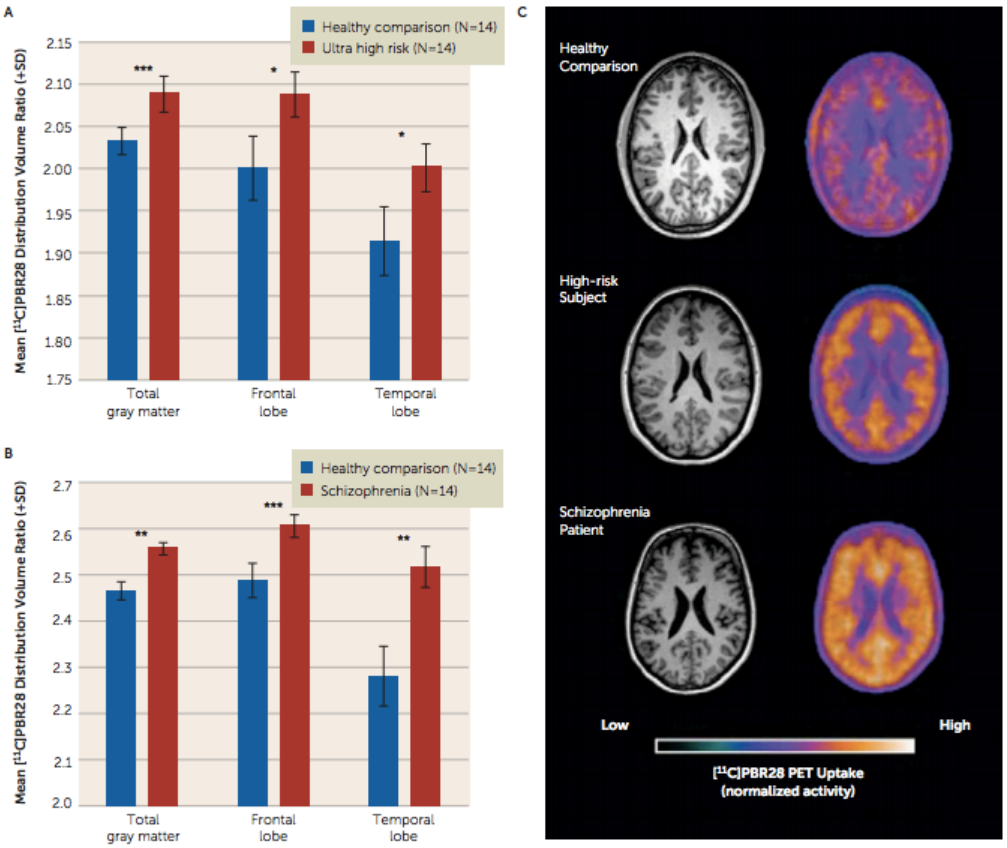


Hedden et al., J Neurosci., 2009

Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [^{11}C]PBR28 PET Brain Imaging Study

Peter S. Bloomfield, M.Sc., Sudhakar Selvaraj, M.D., Ph.D., Mattia Veronese, Ph.D., Gaia Rizzo, Ph.D., Alessandra Bertoldo, Ph.D., David R. Owen, M.D., Ph.D., Michael A.P. Bloomfield, M.D., Ilaria Bonoldi, M.D., Nicola Kalk, M.D., Federico Turkheimer, Ph.D., Philip McGuire, M.D., Ph.D., Vincenzo de Paola, Ph.D., Oliver D. Howes, M.D., Ph.D.

FIGURE 1. Microglial Activity Measured With Positron Emission Tomography (PET) in Ultra-High-Risk Participants, Patients With Schizophrenia, and Matched Comparison Subjects[a]



[a] Significant differences were found between experimental (red) and comparison (blue) groups, according to analysis of covariance (covarying for age and genotype). The images in part C are representative [^{11}C]PBR28 PET images from a participant from each group. * $p<0.05$. ** $p\leq0.001$. *** $p\leq0.005$.

Am J Psychiatry 173:1, January 2016

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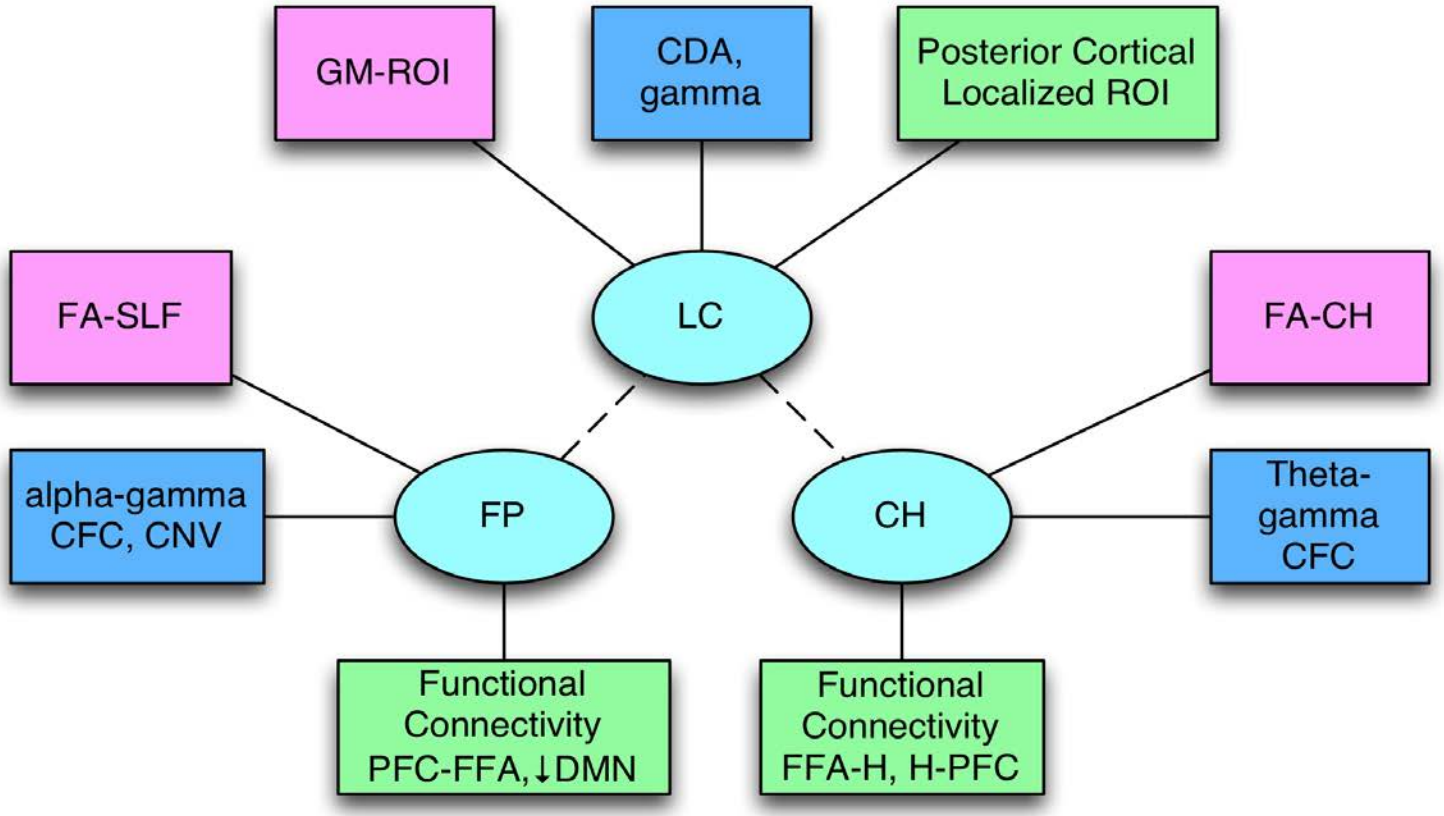
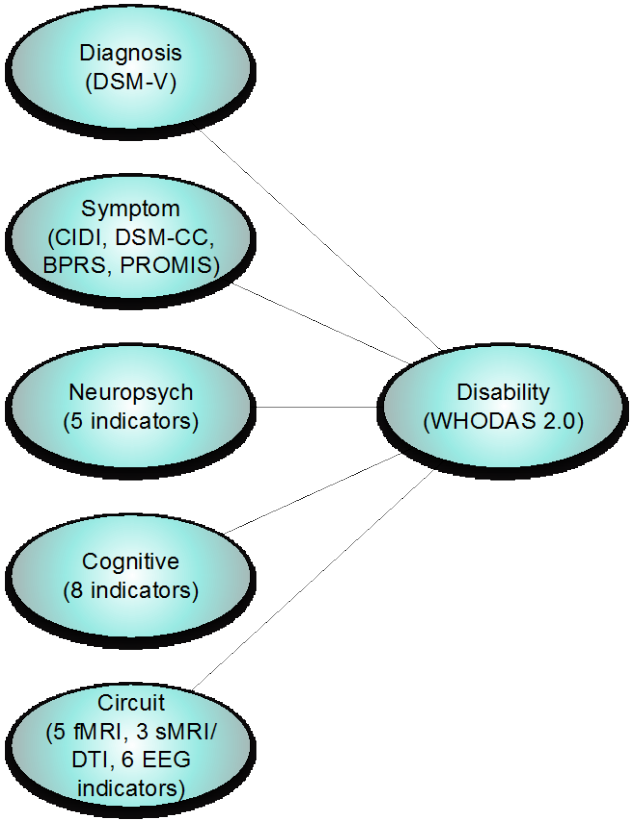
Models to Validate Circuit Constructs



Mapping to Functional Status

Do symptoms or diagnosis add useful prediction over basic measures of circuit, cognitive or neuropsychological measures?



To avoid extreme group bias, sampling strategy is agnostic to diagnosis, and comprises two groups:

- Care-seeking
- Not Care-seeking

Diagnoses assigned *after* enrollment, as one of the dependent variables under study

Multi-Level Assays of Working Memory and Psychopathology: R01 MH101478

National Institute of Mental Health

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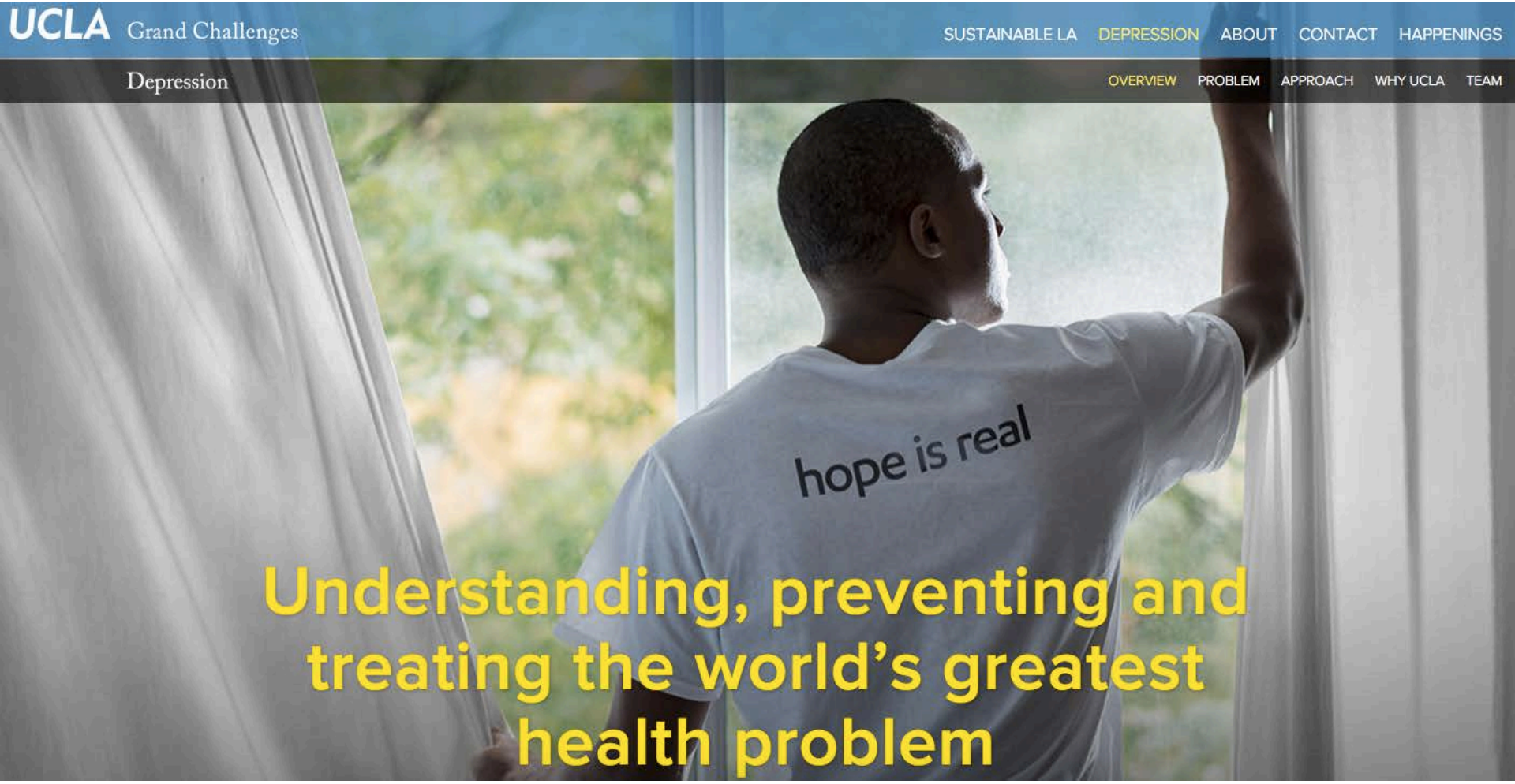

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UCLA Depression Grand Challenge 100K UCLA Risk Sample, WGS

- CAT-MH plus other IRT-based/CAT self reports
  - Computerized adaptive self-reports for dimensions of depression, anxiety, mania, suicidality based on IRT; categorical depression based on random forest models
- Mobile Mood
  - Experience sampling (text, images) + passive monitoring of motion, location, voice, ambient sound, ambient light, app usage, facial affect
- Cognition, imaging, life logs (incl. SLEs), other devices as these mature (sleep staging, EEG, DARPA (Tasso, Leidos) patch for serial blood draw), and other IOT (car, home…)
- Clinical trials: iCBT, fast-acting txs (ECT, ketamine, TSD, others tbd – linked to pharmacogenetic profiles; linked to basic science studies)

Many thanks!

rbilder@mednet.ucla.edu

- R01MH101478: Multi-Level Assays of Working Memory and Psychopathology (Bilder)
- R03MH106922: Modeling RDoC Dimensions Across Levels of Analysis (Anderson)
- C06RR029931: Integrative Phenotyping Center for Neuropsychiatry (Whybrow)
- J&JPRD/UCLA Pharmacogenomics Research Collaborative (Bilder)
- UCLA Depression Grand Challenge (Freimer, Flint, Craske, Bearden, Bilder, Congdon, Narr)

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