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

Robert M Bilder
Michael E. Tennenbaum Family Professor of Psychiatry & Biobehavioral Sciences and Psychology
Director, Translational Research Center for Neuropsychiatry
UCLA
Disclosures

• **Consultant:** Forum Pharmaceuticals; Lumos Labs, Inc.; Maven Research; Neurocog Trials Inc.; OMDUSA, LLC; Snapchat; ThinkNow Inc.

• **Research Support:** NIH/NIMH; John Templeton Foundation
“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 Anderson1*, Stephen Marder1, Steven P. Reise4, Hearee Chung2, Qingqin Li3, Marsha Wilcox3, Giacomo Salvadore3, Jennifer Zhou1, Robert M. Bilder1,4

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

Janssen/UCLA
Median schizoaffective disorder patient has higher total PANSS score, but median schizophrenia patient has a higher "misery" g-score.
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
There are two kinds of people in the world...

- Those who split the world into two kinds of people, and...
- Those who don’t.
Categories *versus* dimensions in personality and psychopathology: a quantitative review of taxometric research

N. Haslam, E. Holland and P. Kuppens

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

Focus on melancholia increases ORs
...dimensions of child and adolescent psychopathology mostly share their genetic liabilities but are differentiated by nonshared experiences.
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)
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)
Phonological Buffer

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 decaying.

**Evidence For**
- 14 of 15 people found this convincing

**Evidence Against**
- 4 of 6 people found this convincing

Evidence linking DL PFC to the 3-back task

Evidence supporting: DL PFC correlated with 3-back task

28 of 30 people found this convincing


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
### 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**

<table>
<thead>
<tr>
<th>Level of analysis</th>
<th>Example ontologies/descriptive systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>Symptom</td>
<td>Measurement models with latent symptom constructs based on rating scales, interview schedules</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Measurement models with latent cognitive constructs based on psychometric test scores</td>
</tr>
<tr>
<td>Neural system/circuit</td>
<td>NeuroML; CocoMac; Xanat</td>
</tr>
<tr>
<td>Cellular systems/signaling pathways</td>
<td>Ingenuity Pathways Analysis; Gene Ontologies biological processes; KEGG Pathway</td>
</tr>
<tr>
<td>Proteins</td>
<td>Entrez Protein; UniProt/SwissProt; NextProt</td>
</tr>
<tr>
<td>Genes and gene expression</td>
<td>Gene Ontologies; Entrez Gene, Gene Expression Omnibus</td>
</tr>
</tbody>
</table>
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 [11C]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

![Graph showing mean (SD) values for healthy comparison and ultra-high risk groups in different brain regions.]

B

![Graph showing mean (SD) values for healthy comparison and schizophrenia groups in different brain regions.]

C

![Images of brain scans with color bars indicating normalized activity levels.]

* 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 [11C]PBR28 PET images from a participant from each group. * p<0.05, ** p<0.001, *** p<0.005.
Models to Validate Circuit Constructs

GM-ROI → CDA, gamma → Posterior Cortical Localized ROI

FA-SLF → LC → FP

alpha-gamma CFC, CNV → FP

FP → CH

Functional Connectivity PFC-FFA, ↓ DMN → Functional Connectivity FFA-H, H-PFC

FA-CH

Theta-gamma CFC
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
Understanding, preventing and treating the world’s greatest health problem
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)