The NIMH RDoC Initiative:
What Does it Mean for Psychiatric Nosology?

Thomas McCoy, MD

Roy Perlis, MD MSc

Disclosures

"My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:"

Roy H. Perlis, MD, MSc

- **Psy Therapeutics (equity) - Founder/SAB member**
- **Outermost Therapeutics (equity) – Founder/SAB member**
- **Belle Artificial Intelligence (equity) – Founder/advisor**
- **Vault Health (consultant fee) - advisor**
- **Genomind (consultant fee) - SAB member**
- **RID Ventures (consultant fee) – advisor**
- **Takeda (consultant fee) – advisor**
- **Burrage Capital (consultant fee) - advisor**

April 29, 2013

In a few weeks, the APA will release its new edition of the DSM. ...

Symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have understood that symptoms alone rarely indicate the best choice of treatment. ...

Patients with mental disorders deserve better. ... **Going forward, we will be supporting research projects that look across current categories – or sub-divide current categories – to begin to develop a better system.**

https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis.shtml

April 29, 2013

Context

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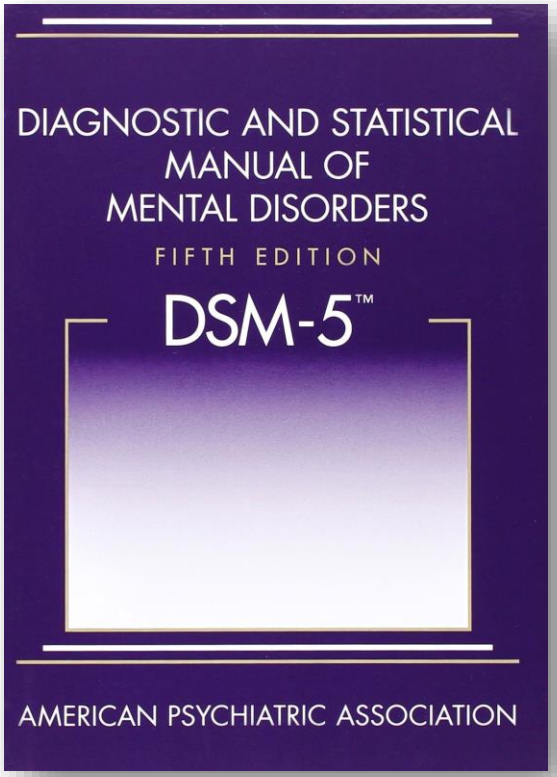
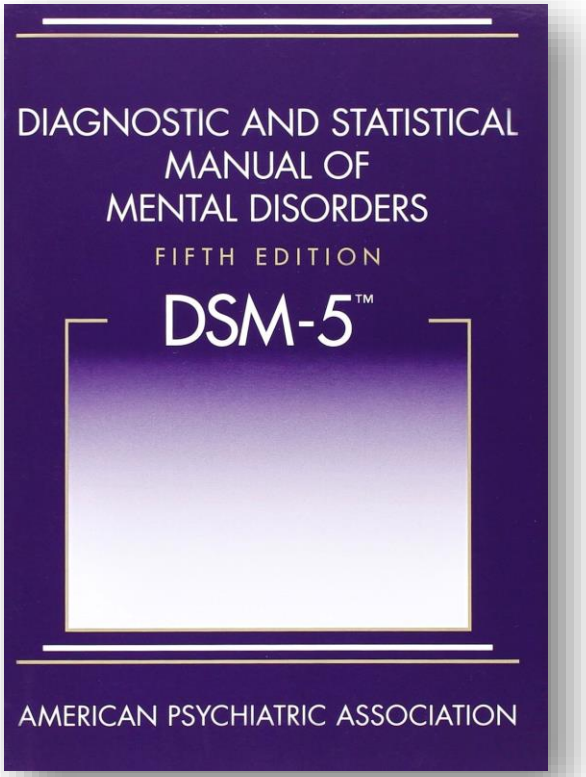
What

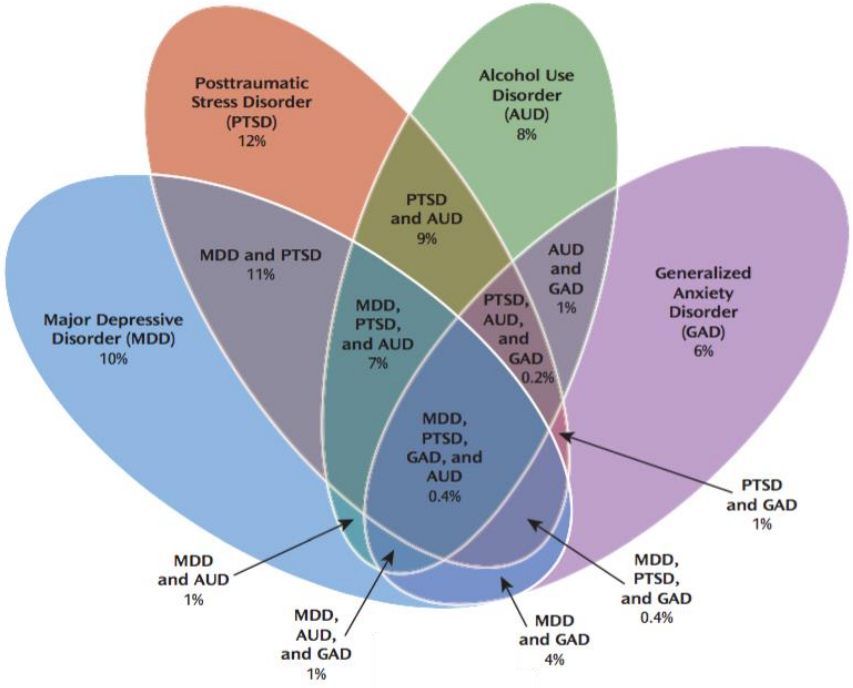
https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis.shtml

Categorical Nosology



(Useful) Syndrome Soup





Regier, D. A. *et al* (2013). DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *AJP*, 170(1), 59-70.

What is RDoC?

- Structure for research
  - Multidimensional & continuous
  - Rooted in neurobiology (gene -> behavior)

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- Explicitly dynamic
  - E.g. Addition of motor domain
- Anticipates precision medicine

What RDoC is **Not**

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  - Does not attempt to cover all conditions
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- Clinical / policy
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- Threshold setting
  - Hopes to move to threshold model but not inherent

Cuthbert and Insel *BMC Medicine* 2013, **11**:126
http://www.biomedcentral.com/1741-7015/11/126

BMC Medicine

DEBATE Open Access

Toward the future of psychiatric diagnosis: the seven pillars of RDoC

Bruce N Cuthbert[1,3*] and Thomas R Insel[2,3]

“ Develop, for <u>research</u> purposes, new ways of classifying mental disorders based on <u>dimensions</u> of observable behavior <u>and</u> neurobiological measures”

Research Domain Criteria

ORIGIN STORY

RDoC Origin

2008: NIMH Strategic Plan – Strategy 1.4

- Initiate a process for bringing together experts in clinical and basic sciences to jointly identify the fundamental behavioral components that may span multiple disorders (e.g., executive functioning, affect regulation, person perception) and that are more amenable to neuroscience approaches.
- Determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological.
- Develop reliable and valid measures of these fundamental components of mental disorders for use in basic studies and in more clinical settings.
- Integrate the fundamental genetic, neurobiological, behavioral, environmental, and experiential components that comprise these mental disorders.

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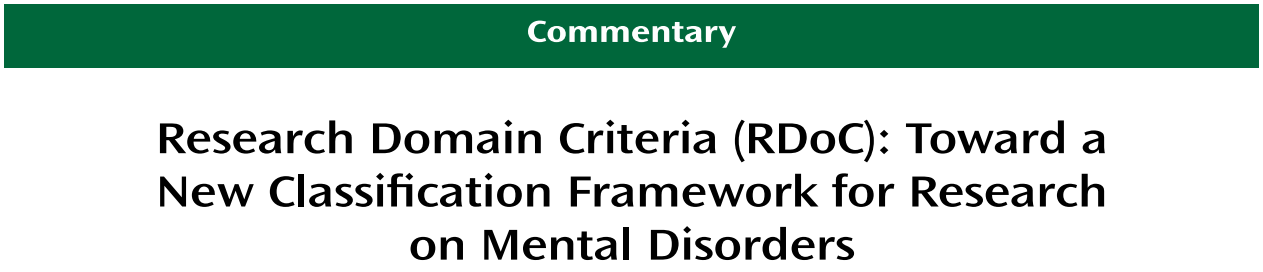

Insel T, Cuthbert B, Garvey M, et al. *AJP*. 2010;167:748-751.

RDoC Origin

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2010: Named RDoC

2010-2012: Committee process

Journal of Abnormal Psychology
2010, Vol. 119, No. 4, 631–639

0021-843X/10/$12.00 DOI: 10.1037/a0020909

Developing Constructs for Psychopathology Research: Research Domain Criteria

Charles A. Sanislow
Wesleyan University

Daniel S. Pine, Kevin J. Quinn, Michael J. Kozak, Marjorie A. Garvey, Robert K. Heinssen, Philip Sung-En Wang, and Bruce N. Cuthbert
National Institute of Mental Health, Bethesda, Maryland

RDoC Origin

2008: NIMH Strategic Plan – Strategy 1.4

2010: Named RDoC

2010-2012: Committee process

1. Clinical ***and*** basic evidence of valid behavioral function
2. Evidence that a neural circuit implements the function

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2010-2012: Committee process

2012: Release concept matrix (v1)

State of the art

Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior

Sarah E. Morris, PhD; Bruce N. Cuthbert, PhD

The Matrix

	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social communication								
Perception/understanding of self								
Perception/understanding of others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

~~Five~~ **Six** Domains

- Negative Valence
- Positive Valence
- Cognitive Systems
- Social Processes
- Arousal/Modulation
- *Sensorimotor (Jan '19*)*

*https://www.nimh.nih.gov/news/science-news/2019/sensorimotor-domain-added-to-the-rdoc-framework.shtml

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Multiple constructs per domain

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Units of Analysis

- *Genes (May '17*)*
- Molecules
- Cells
- Circuits
- Physiology
- Behavior
- Self-reports
- Paradigms

*https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/update-on-genes-in-the-rdoc-matrix.shtml

The Matrix -- Today

Negative Valence Systems

Construct/Subconstruct	Genes Notice	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Acute Threat ("Fear")		Elements	Elements	Elements	Elements	Elements	Elements	Elements
Potential Threat ("Anxiety")		Elements	Elements	Elements	Elements		Elements	Elements
Sustained Threat		Elements	Elements	Elements	Elements	Elements	Elements	
Loss		Elements		Elements	Elements	Elements	Elements	Elements
Frustrative Nonreward		Elements		Elements		Elements	Elements	Elements

Positive Valence Systems

Construct/Subconstruct		Genes Notice	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Reward Responsiveness	Reward Anticipation								Elements
	Initial Response to Reward		Elements		Elements		Elements	Elements	Elements
	Reward Satiation								Elements
Reward Learning	Probabilistic and Reinforcement Learning								Elements
	Reward Prediction Error		Elements		Elements	Elements	Elements	Elements	Elements
	Habit - PVS		Elements	Elements	Elements		Elements	Elements	Elements
Reward Valuation	Reward (probability)								Elements
	Delay								Elements
	Effort		Elements		Elements			Elements	Elements

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml

RDoC Domains and Constructs

http://tiny.cc/rdocdef

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml

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2013: Funding shift

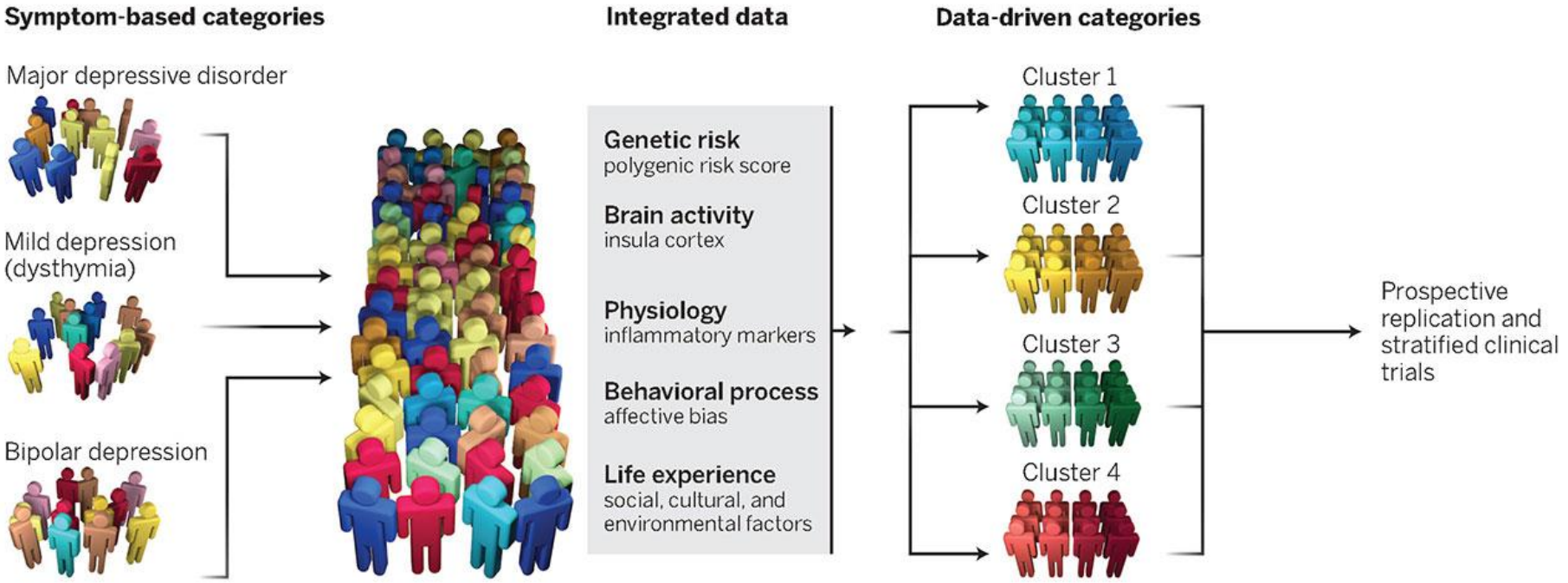
2015: RDoC for more precise medicine

Brain disorders? Precisely

Thomas R. Insel, Bruce N. Cuthbert

Science 01 May 2015:
Vol. 348, Issue 6234, pp. 499-500
DOI: 10.1126/science.aab2358

Building a Valid Nosology



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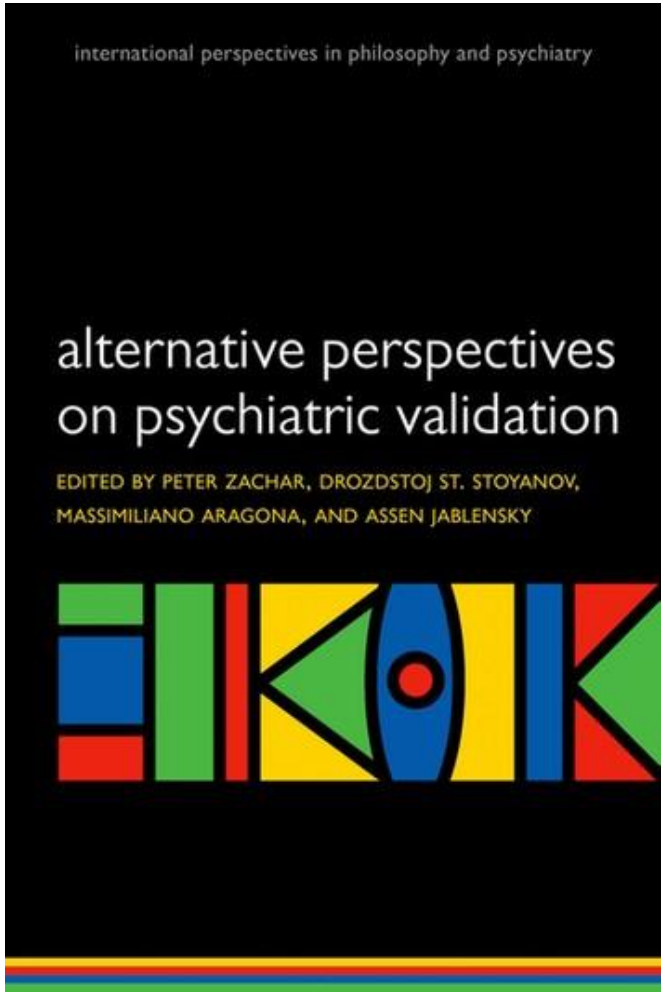
“Valid” Nosology



RDoC for an ICD/DSM World

F32.2 + F10.221 ← ???

" 22 y/o male with intentional GSW in ctx of breakup and new unemployment now s/p 3wk SICU stay admitted to ILOC reporting 6 mo decline in mood and self worth, increased irritability, social isolation (left soccer team and lost job), and marked increase in EtOH use w/ family Hx of suicide and BPAD… "

Deploying RDoC

Techniques and Methods

Biological Psychiatry

High Throughput Phenotyping for Dimensional Psychopathology in Electronic Health Records

Thomas H. McCoy Jr., Sheng Yu, Kamber L. Hart, Victor M. Castro, Hannah E. Brown, James N. Rosenquist, Alysa E. Doyle, Pieter J. Vuijk, Tianxi Cai, and Roy H. Perlis

ABSTRACT

BACKGROUND: Relying on diagnostic categories of neuropsychiatric illness obscures the complexity of these disorders. Capturing multiple dimensional measures of neuropathology could facilitate the clinical and neurobiological investigation of cognitive and behavioral phenotypes.

METHODS: We developed a natural language processing–based approach to extract five symptom dimensions, based on the National Institute of Mental Health Research Domain Criteria definitions, from narrative clinical notes. Estimates of Research Domain Criteria loading were derived from a cohort of 3619 individuals with 4623 hospital admissions. We applied this tool to a large corpus of psychiatric inpatient admission and discharge notes (2010–2015), and using the same cohort we examined face validity, predictive validity, and convergent validity with gold standard annotations.

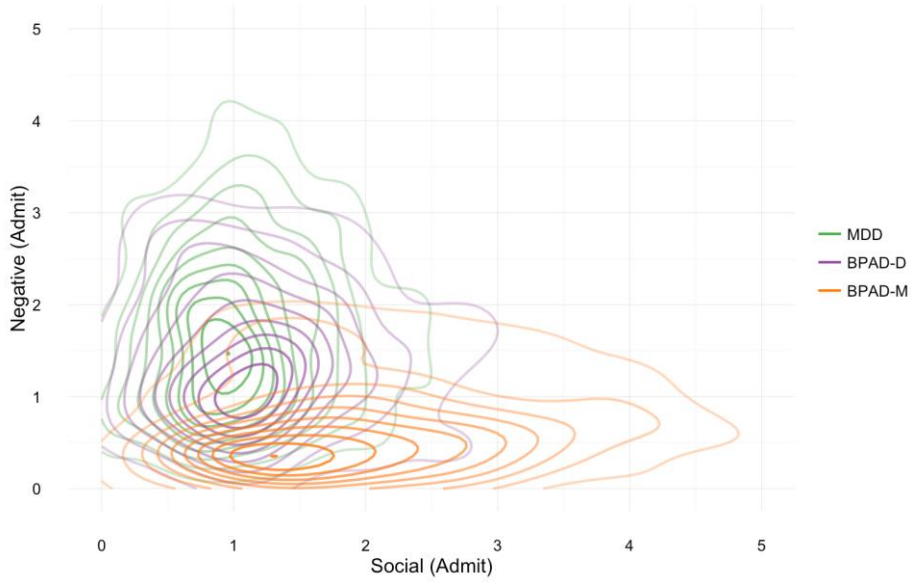
RESULTS: In mixed-effect models adjusted for sociodemographic and clinical features, greater negative and positive symptom domains were associated with a shorter length of stay ($\beta = -.88$, $p = .001$ and $\beta = -1.22$, $p < .001$, respectively), while greater social and arousal domain scores were associated with a longer length of stay ($\beta = .93$, $p < .001$ and $\beta = .81$, $p = .007$, respectively). In fully adjusted Cox regression models, a greater positive domain score at discharge was also associated with a significant increase in readmission risk (hazard ratio = 1.22, $p < .001$). Positive and negative valence domains were correlated with expert annotation (by analysis of variance [$df = 3$], $R^2 = .13$ and .19, respectively). Likewise, in a subset of patients, neurocognitive testing was correlated with cognitive performance scores ($p < .008$ for three of six measures).

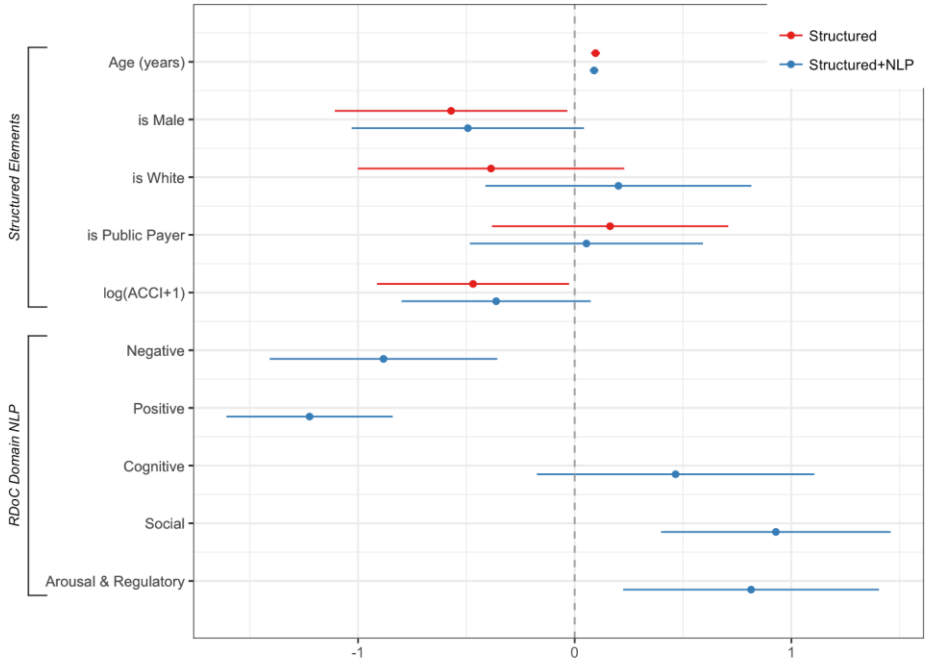
CONCLUSIONS: This shows that natural language processing can be used to efficiently and transparently score clinical notes in terms of cognitive and psychopathologic domains.

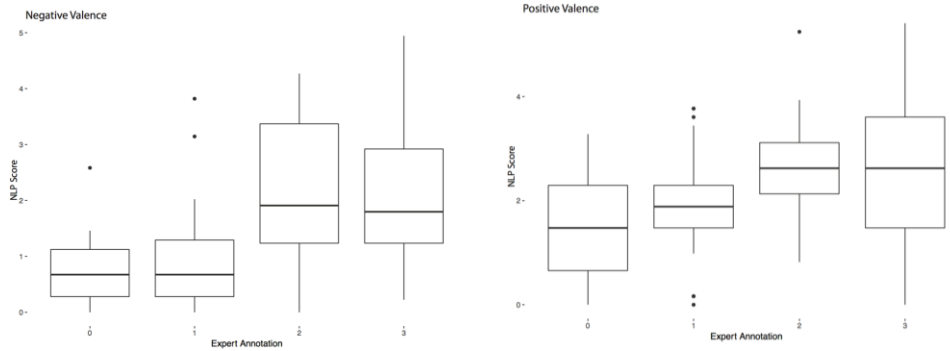
Keywords: Computed phenotype, Electronic health record, Natural language processing, Research Domain Criteria, Topic modeling, Transdiagnostic

https://doi.org/10.1016/j.biopsych.2018.01.011

RDoC Validation







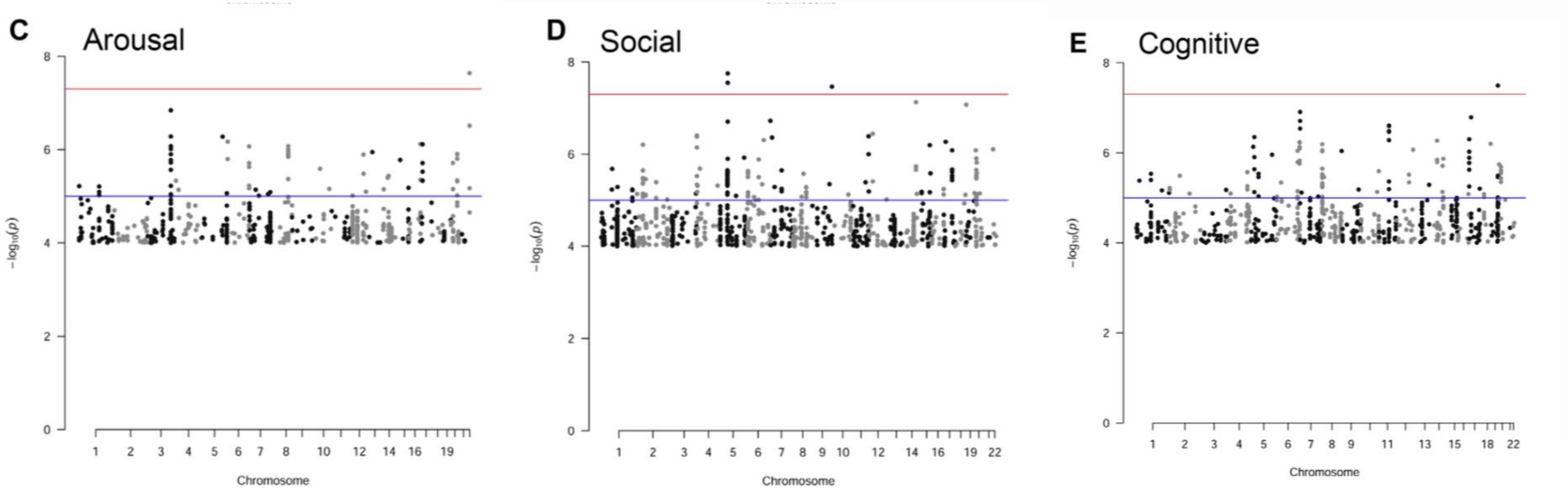
RDoC Biology

Priority Communication

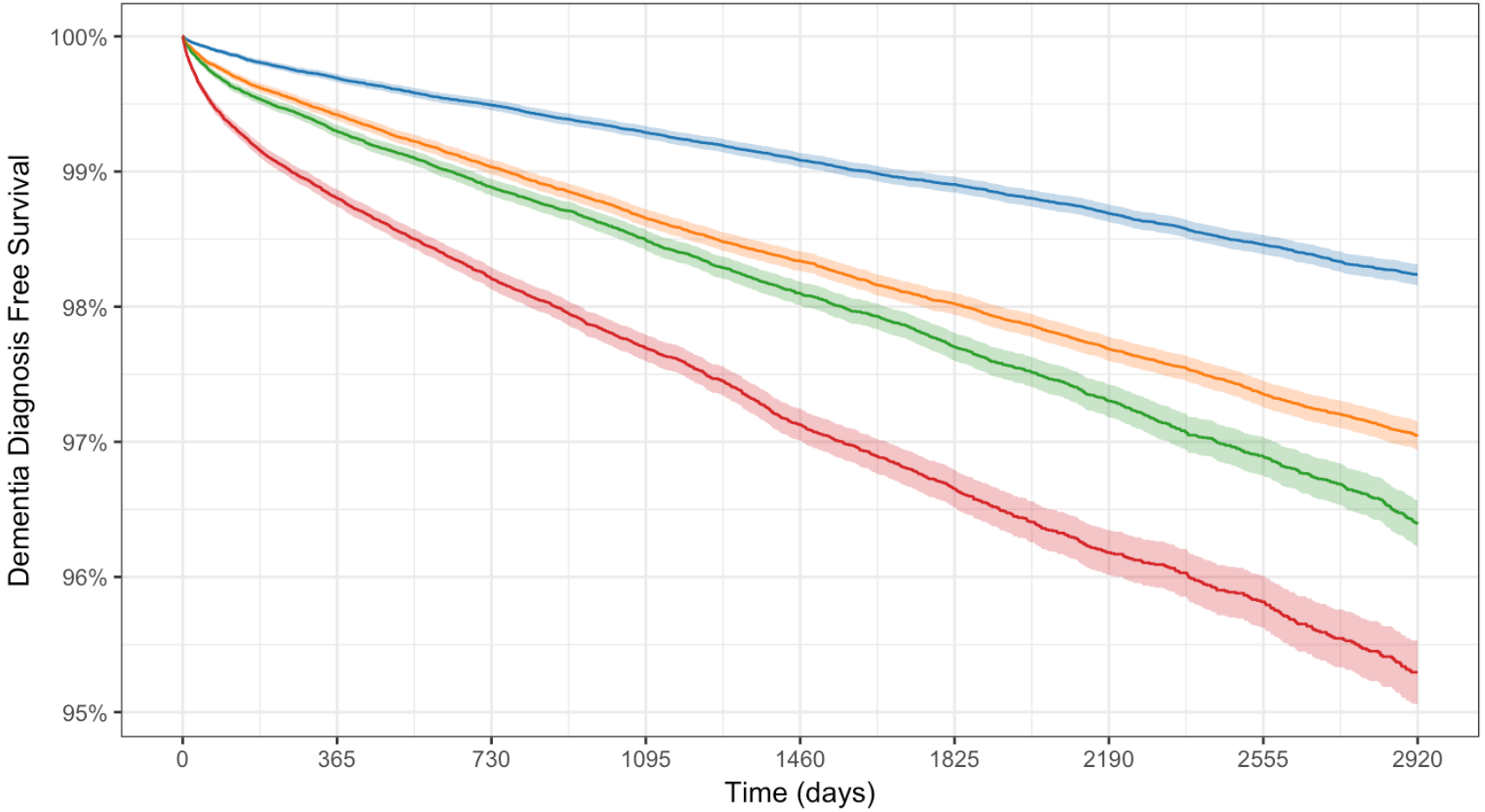
Biological Psychiatry

Genome-wide Association Study of Dimensional Psychopathology Using Electronic Health Records

Thomas H. McCoy Jr., Victor M. Castro, Kamber L. Hart, Amelia M. Pellegrini, Sheng Yu, Tianxi Cai, and Roy H. Perlis

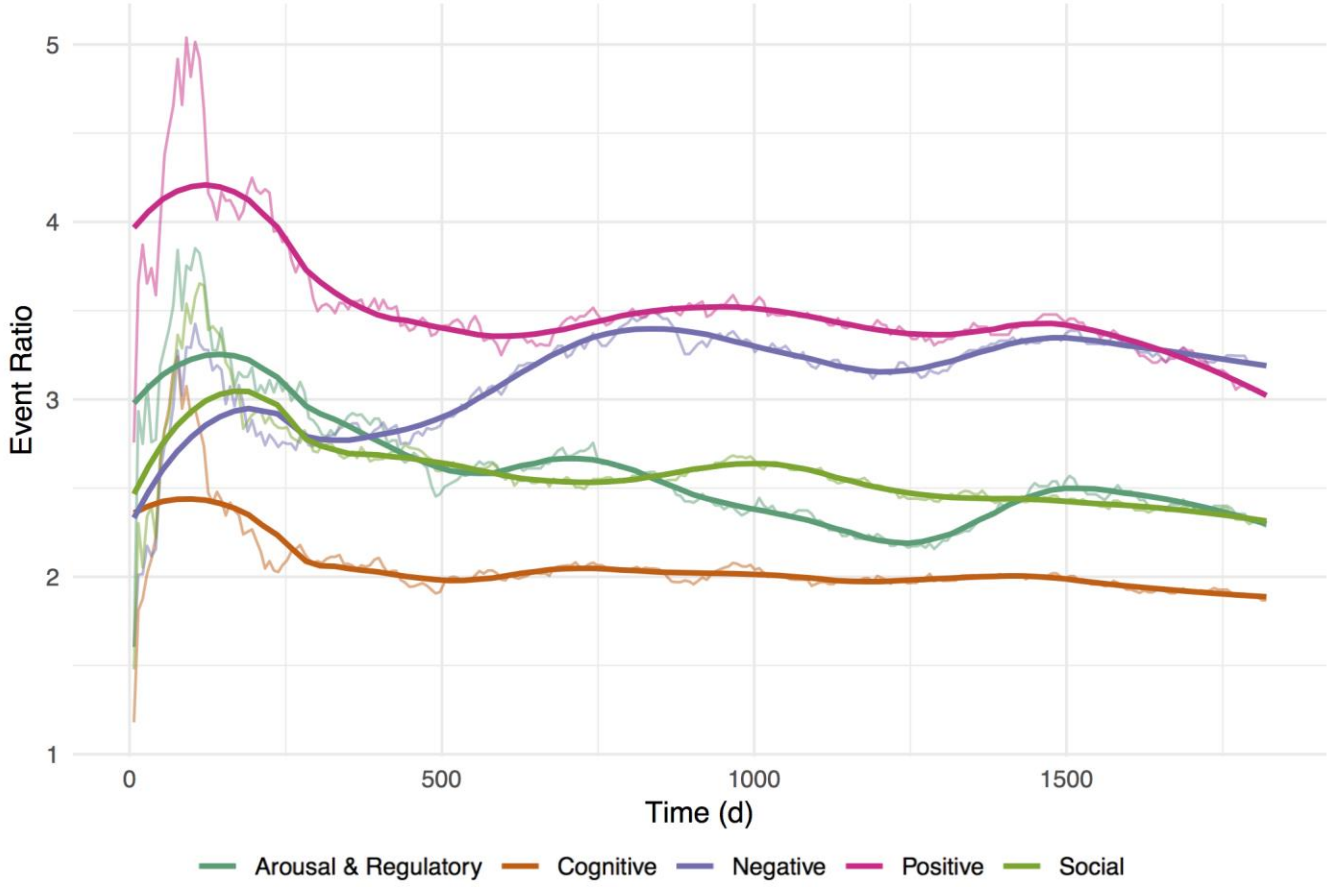


RDoC Stratification of Cognition



Dementia | $X^2=378.8$; p <.000001

RDoC Stratification of Suicide



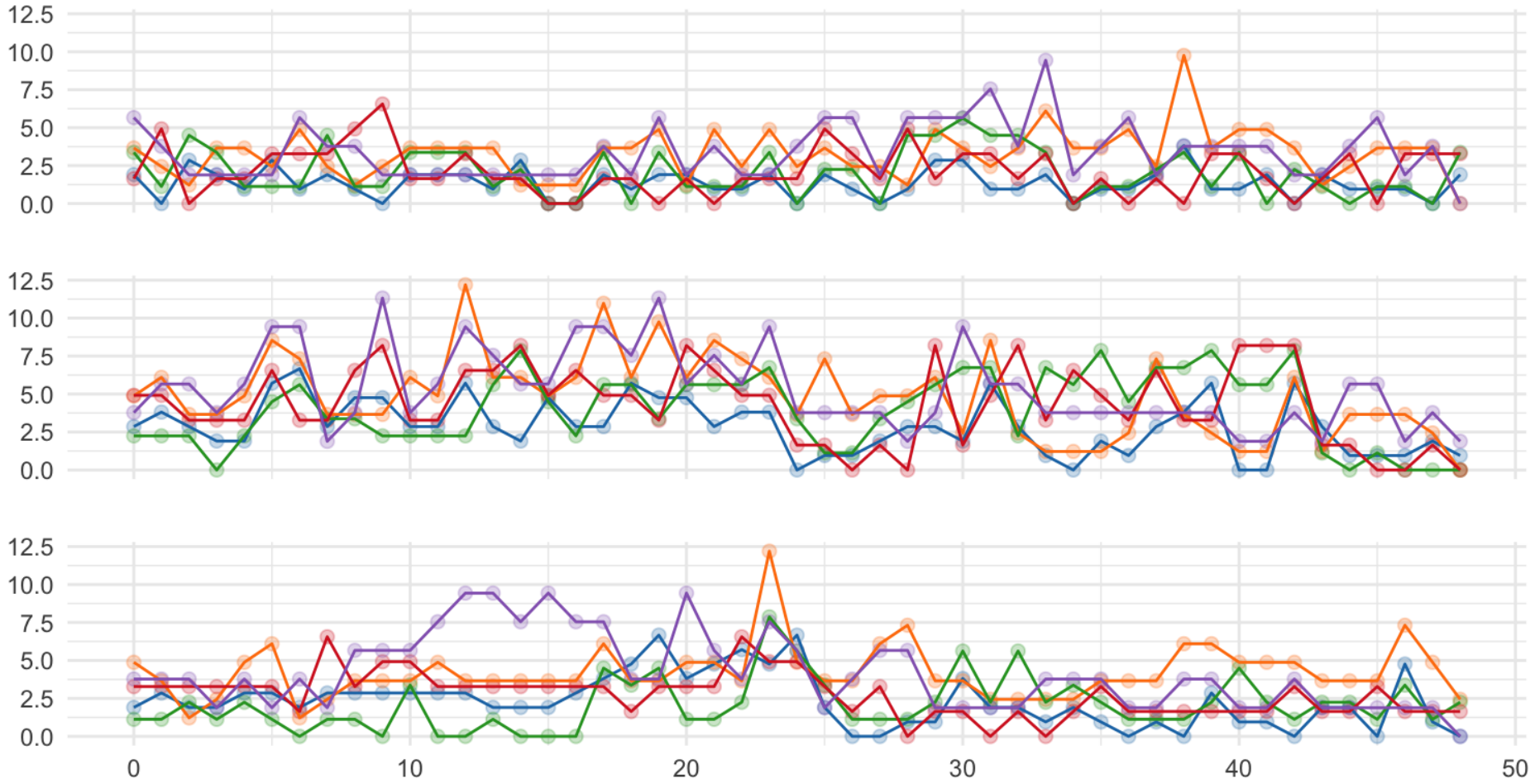
Received: 9 October 2018 | Revised: 10 December 2018 | Accepted: 12 January 2019
DOI: 10.1002/da.22882

RESEARCH ARTICLE

WILEY ADAA ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

Research Domain Criteria scores estimated through natural language processing are associated with risk for suicide and accidental death

RDoC in Time


12.5
10.0
7.5
5.0
2.5
0.0
12.5
10.0
7.5
5.0
2.5
0.0
12.5
10.0
7.5
5.0
2.5
0.0
0
10
20
30
40
50

RDoC is …

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  - Addition of motor domain
  - Removal of specific genes
- Structure for future research
  - Multidimensional & continuous
  - Rooted in neurobiology (gene -> behavior)
- Anticipates precision medicine

Thank You

MGH CQH

Thomas McCoy

Victor Castro

Kamber Hart

Funders

NIMH

NSF