

NIMH's Research Domain Criteria (RDoC): Foundations and Future

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Friends of NIMH

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National Institute
of Mental Health

Disclosures

No disclosures to report.

Why RDoC? Patient/Family Problems with Diagnosis



- Patients may receive multiple diagnoses
- Diagnoses provide modest information about prognosis
- Treatment is trial-and-error
- Distress is a major symptom, but varies from day-to-day and can be situationally-dependent

Why RDoC? Scientific Problems with Diagnoses

- Current diagnostic systems remain based on clinical symptoms and signs
- Reliability, at the expense of validity
- Broad syndromes: heterogeneity, co-morbidity, NOS diagnoses
- Disorders are treated as distinct categories; “healthy-sick” dichotomy
- Failure to establish biomarkers
- Diluted treatment effects
- **PROBLEM: Diagnostic categories have driven the entire research & clinical systems (grant review, journals, trials, regulatory approvals)**


636,120 Ways to Have Posttraumatic Stress Disorder

Isaac R. Galatzer-Levy¹ and Richard A. Bryant²

¹New York University School of Medicine; and ²University of New South Wales, Kensington, New South Wales, Australia

Abstract

In an attempt to capture the variety of symptoms that emerge following traumatic stress, the revision of posttraumatic stress disorder (PTSD) criteria in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* has expanded to include additional symptom presentations. One consequence of this expansion is that it increases the amorphous nature of the classification. Using a binomial equation to elucidate possible symptom combinations, we demonstrate that the *DSM-IV* criteria listed for PTSD have a high level of symptom profile heterogeneity (79,794

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Why RDoC? Treatment Discovery

Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective

Erik H. F. Wong¹, Frank Yocca¹, Mark A. Smith² and Chi-Ming Lee³

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“On average, a marketed psychiatric drug is efficacious in approximately half of the patients who take it. One reason for this low response rate is the artificial grouping of heterogeneous syndromes with different pathophysiological mechanisms into one disorder.”

Wong, Int J Neuropsychopharmacol. 2010

Why RDoC? Scientific Problems with Diagnoses

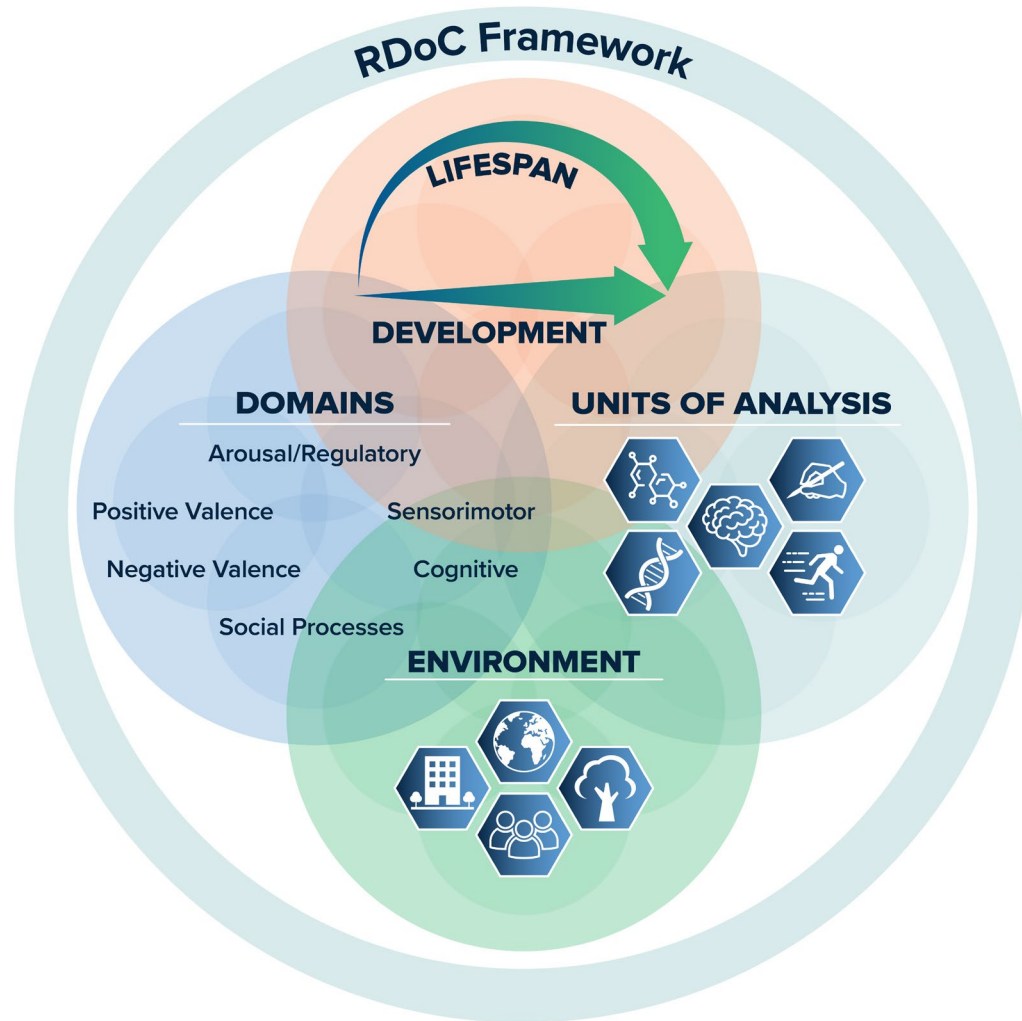


How Does RDOC Relate to Diagnostic Systems?



- RDoC is not intended to curate a comprehensive set of clinical features that encompass the many symptoms and signs for which individuals may seek treatment;
- rather, the aim is to encourage psychopathology research that frames hypotheses in terms of neurobehavioral constructs rather than groupings based on predetermined diagnostic criteria.
- In other words, RDoC is intended to generate a literature that can (among other goals) inform future versions of diagnostic systems rather than create an alternative clinical manual.
- RDoC is sometimes described as an alternative to existing diagnostic systems, but such framing erroneously implies a shared scope and purpose.
- RDoC is narrower in scope than diagnostic systems and serves a specific research purpose. Such research yields novel ways of stratifying, classifying, and clustering psychopathology, and the validity of these can be tested by examining their ability to predict prognosis or treatment response (thus crossing paths with the purpose of diagnosis);
- however, further work would be needed to develop diagnoses informed by these novel characterizations.
- RDoC domains and constructs, in and of themselves, do not necessarily define valid clinical entities for the purposes of clinician communication, drug development, or regulatory processes but the framework serves as a roadmap via which translational behavioral neuroscience research may converge with diagnostic practice.

Research Domain Criteria (RDoC)



Changing the conversation about how research on mental disorders is done

- Diagnosis-agnostic
- Neurobehavioral domains with foundations in basic science
- Integrative measurement approaches
- Incorporating environmental impacts and developmental processes

Toward Precision Diagnosis, Treatment, and Prevention

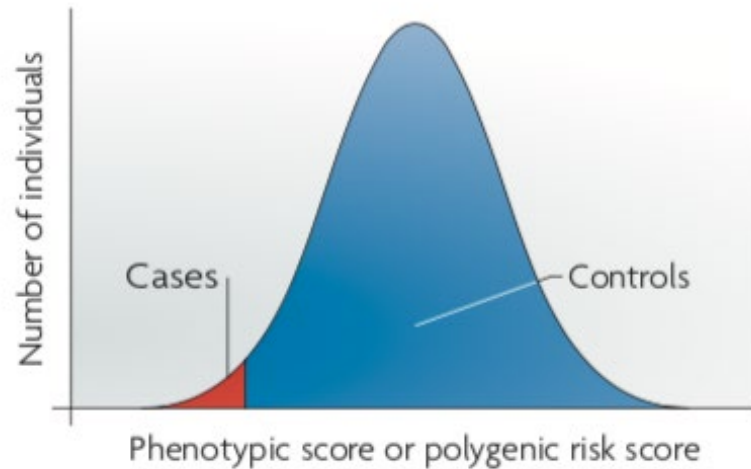
- Long-term goal: Move away from one-size-fits-all diagnoses (heterogeneity, comorbidity) toward dimensional, transdiagnostic mechanisms
- Strategic principles:
 - 1) Invert the usual clinical paradigm: Psychopathology as deviations from normal processes, rather than starting with disease state definitions (direct translation)
 - 2) Normal-to-abnormal dimensions: Study transitions to psychopathology across time and inform early intervention
 - 3) Data-driven functional constructs jointly defined by behavior/cognition and implementing neural circuit or system (address mind-body problems)
 - 4) Computational neuroscience approaches for deriving functional constructs and clinical phenotypes

Toward Precision Diagnosis, Treatment, and Prevention

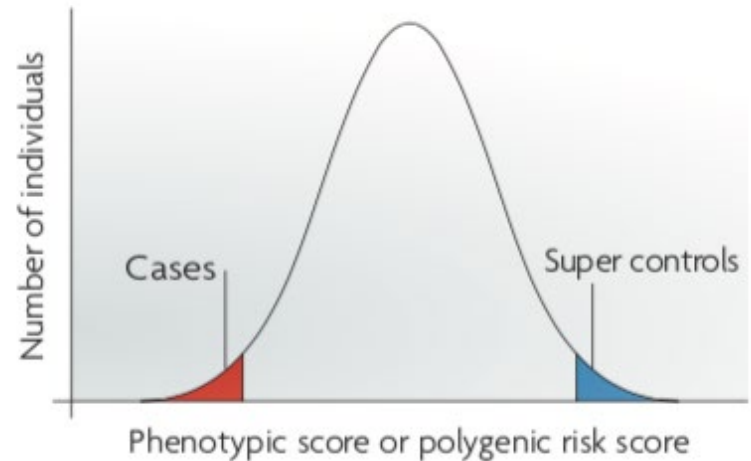
- *Understanding*: Shift the discovery paradigm toward diagnostic constructs based on relationships among neural systems, behavior/cognition, and symptoms
- *Diagnosis and treatment*: Away from broad syndromal treatments to specific, mechanism-based interventions
- *Preempting disorder*: From symptom management to prevention based on quantitative measures of functional and neurodevelopmental trajectories
- *Future research to support clinical service*: Computational neuroscience and big data for models of brain-behavior relationships and classification algorithms for precision interventions

Dimensionality: Quantitative Traits and Research Designs

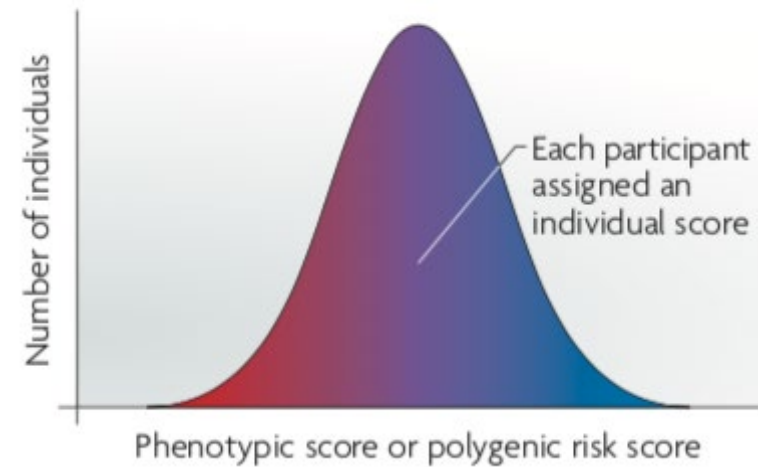
a Case-control



b Extreme selection



c Quantitative measurement

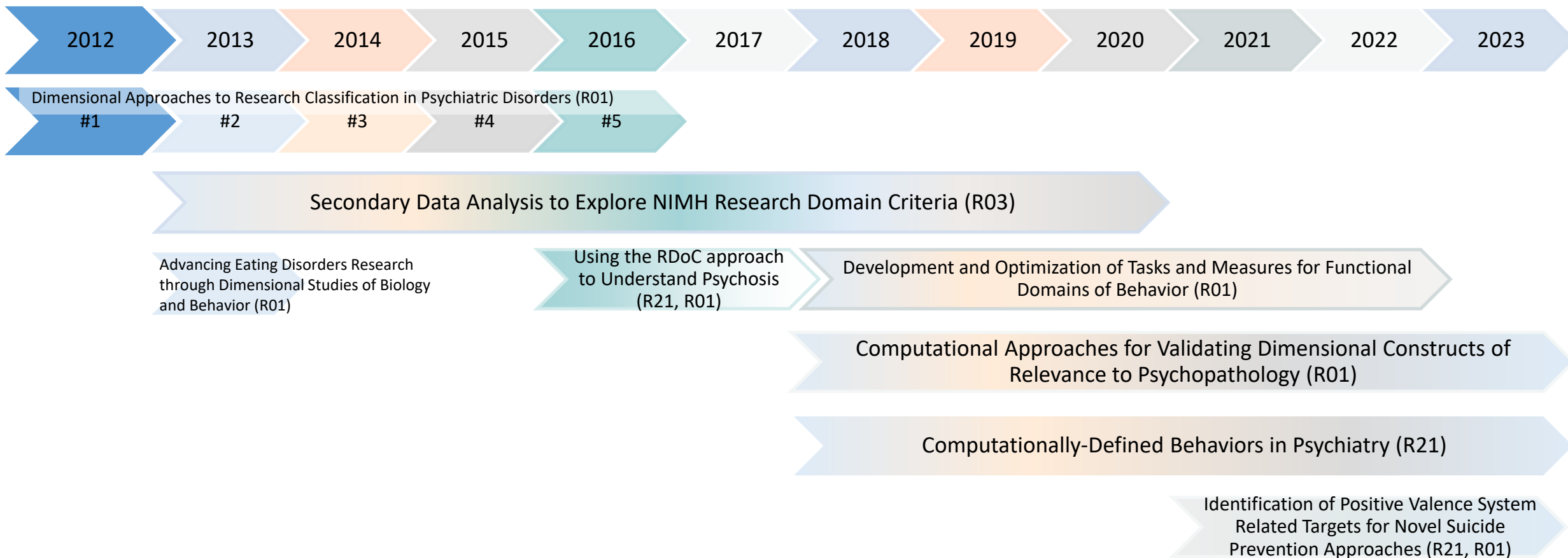


Common disorders are
quantitative traits

Robert Plomin, Claire M. A. Haworth and Oliver S. P. Davis

Nature Rev. Genet. 10, 872-878 (2009)

RDoC Status Update: Funding Opportunity Announcements



RDoC Status Update: Funding Opportunity Announcements

Research Funded by NIMH Research Conducted at NIMH (Intramural Research Program) Priority Research Areas Research Resources

RDoC

Research Domain Criteria Initiative

Home > Research > Research Funded by NIMH > Research Domain Criteria (RDoC)

RDoC Funding Opportunities

Part of the [Research Domain Criteria \(RDoC\)](#) initiative, these funding opportunities seek research grant applications designed to develop innovative ways of understanding mental disorders in clinical studies on the basis of neuroscience, and behavioral measures rather than traditional diagnostic categories.

Types of RDoC Grants:

As with all NIH grant applications, RDoC grant applications can be submitted as part of:

- Investigator Initiated Applications:**
NIMH welcomes applications on projects of interest to RDoC without a current RDoC FOA. Please contact the NIMH RDoC Unit at RDoCAdmin@mail.nih.gov for more information.
- Funding Opportunity Announcements (FOAs):**
Here, applications are solicited on specific topics, in this case RDoC. For a listing of previous and current RDoC FOAs, see below.
 - Currently Active RDoC Funding Opportunity Announcements**
 - PAS-21-264: Computationally-Defined Behaviors in Psychiatry (R21)
 - PAS-21-263: Computational Approaches for Validating Dimensional Constructs of Relevance to Psychopathology (R01)
 - Previous (Expired) RDoC Funding Opportunity Announcements**
 - PAR-18-930: Development and Optimization of Tasks and Measures for Functional Domains of Behavior
 - PAS-21-216: Identification of Positive Valence System Related Targets for Novel Suicide Prevention Approaches (R01)
 - PAS-21-215: Identification of Positive Valence System Related Targets for Novel Suicide Prevention Approaches (R21)
 - RFA-MH-19-240: Computationally-Defined Behaviors in Psychiatry
 - RFA-MH-19-242: Computational Approaches for Validating Dimensional Constructs of Relevance to Psychopathology
 - PAR-17-158: Secondary Data Analyses to Explore NIMH Research Domain Criteria (R03)
 - PAR-16-136: Using the NIMH Research Domain Criteria (RDoC) Approach to Understand Psychosis (R01)
 - PAR-16-135: Using the NIMH Research Domain Criteria (RDoC) Approach to Understand Psychosis (R21)
 - RFA-MH-16-510: Dimensional Approaches to Research Classification in Psychiatric Disorders (R01)
 - RFA-MH-15-500: Dimensional Approaches to Research Classification in Psychiatric Disorders
 - RFA-MH-14-050: Dimensional Approaches to Research Classification in Psychiatric Disorders
 - RFA-MH-14-030: Advancing Eating Disorders Research through Dimensional Studies of Biology and Behavior
 - PAR-14-008: Secondary Data Analyses to Explore NIMH Research Domain Criteria (R03)
 - RFA-MH-13-080: Dimensional Approaches to Research Classification in Psychiatric Disorders (R01)
 - RFA-MH-12-100: Dimensional Approaches to Research Classification in Psychiatric Disorders (R01)

A list of grants funded under these RDoC Funding Opportunity Announcements is available [here](#).

Paradigm Shift



**SCHIZOPHRENIA
BULLETIN**
The Journal of Psychoses and Related Disorders

Schizophrenia Bulletin vol. 42 no. 4 pp. 863–864, 2016
doi:10.1093/schbul/sbw050
Advance Access publication May 18, 2016

EDITORIAL

Shifting Paradigms and the Term Schizophrenia

William T. Carpenter

Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD

Schizophrenia Bulletin, since its inception in 1969, has played a central role in the dissemination of hypothesis-driven research findings relating to the causes and treatments of schizophrenia. Original research reports and reviews combined with cover art work, first person accounts, and special features have advanced the field while creating a strong sense of community among researchers, clinical care providers and recipients of care.

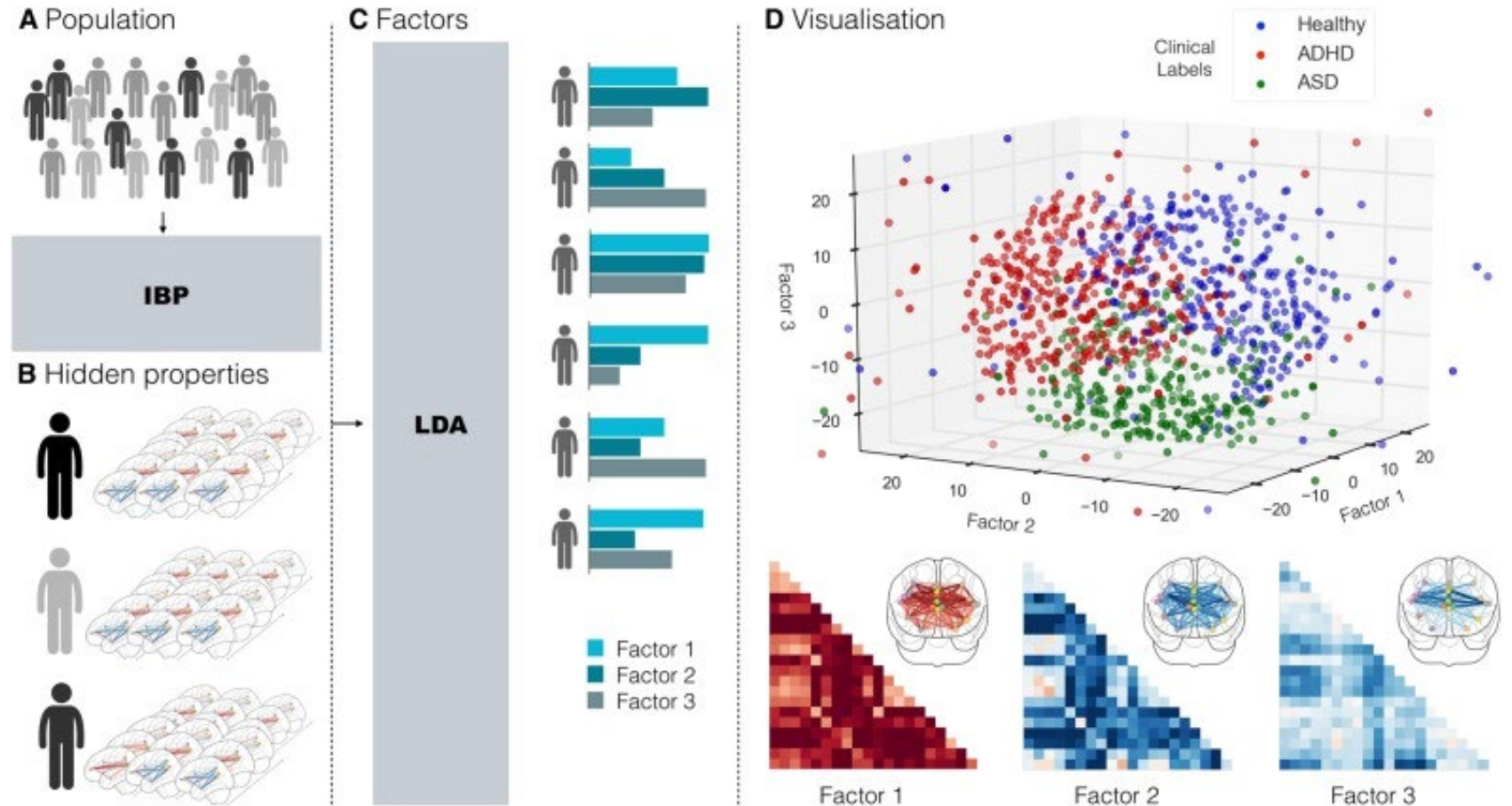
In this context, we considered a title change for the *Bulletin* represented by these approximate options:

1. Psychosis Bulletin
2. The Bulletin: The Journal of Psychoses and Related Disorders; or
3. Schizophrenia Bulletin: The Journal of Psychoses and Related Disorders.

“We can see the field rapidly changing concepts and methods but we cannot yet see the eventual reformulation of nosology and clinical application. We hope the modest change associated with title will make clear that we embrace advancing knowledge within and across current diagnostic boundaries.”

The RDoC Approach: Trans-Diagnostic Example

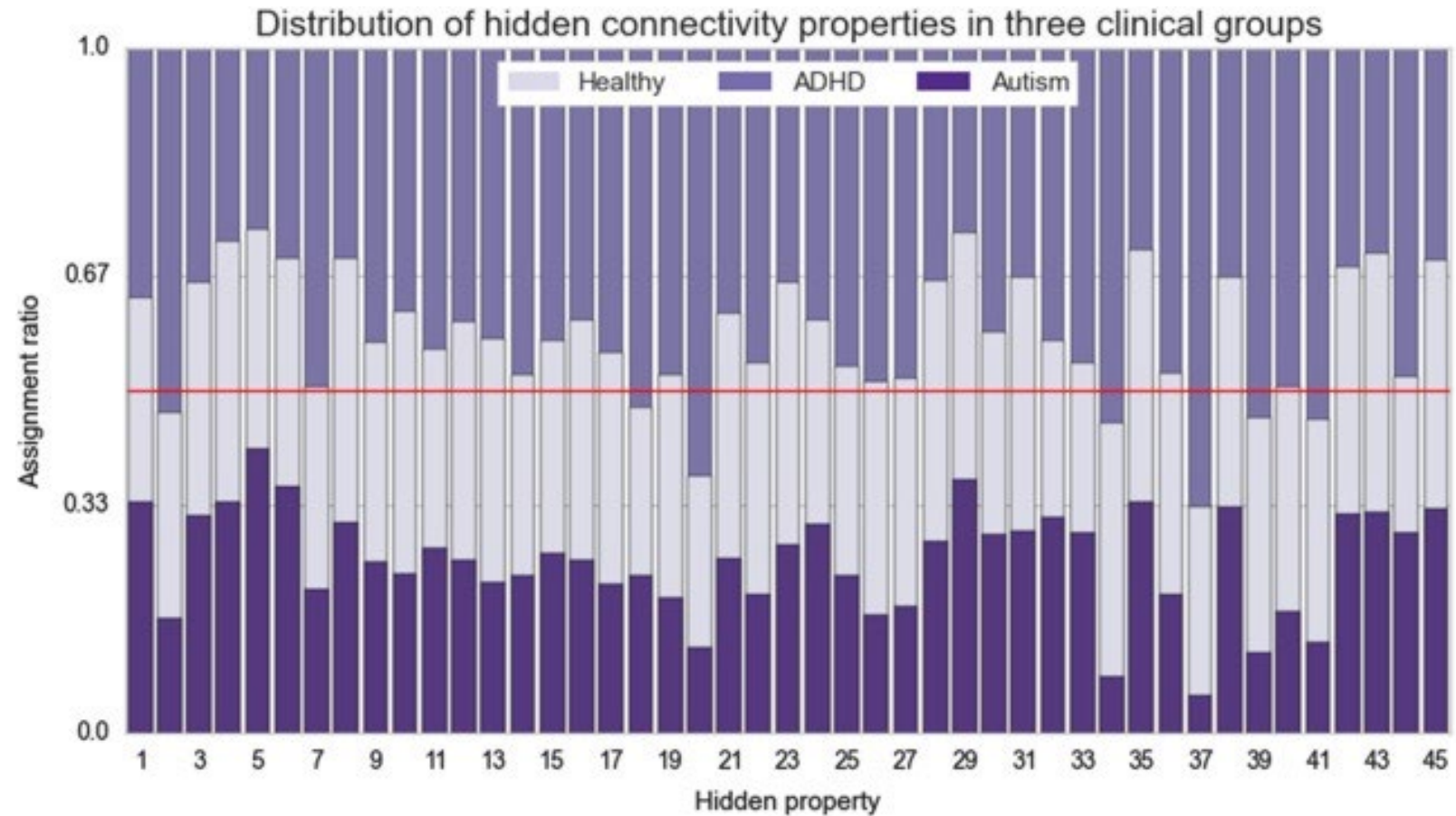
- Autism Spectrum Disorder (ASD)
- Attention-Deficit/Hyperactivity Disorder (ADHD)
- Healthy comparison participants
- Derived factors based on connectivity properties



Kernbach JM, et al., 2018, *Transl Psychiatry*. PMID: PMC6050263.

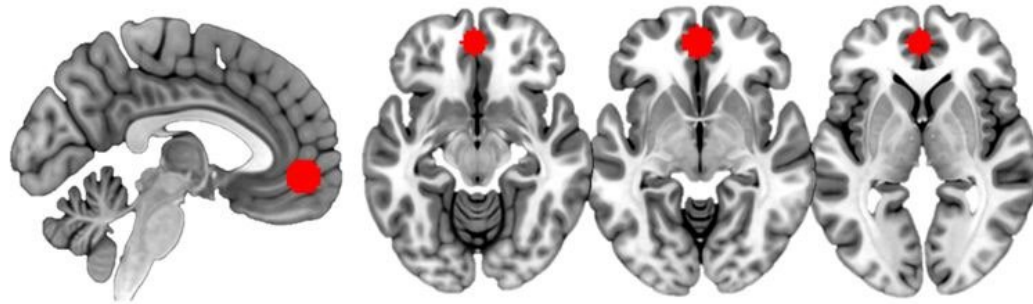
The RDoC Approach: Trans-Diagnostic Example

None of the connectivity properties were specific to one of the study groups

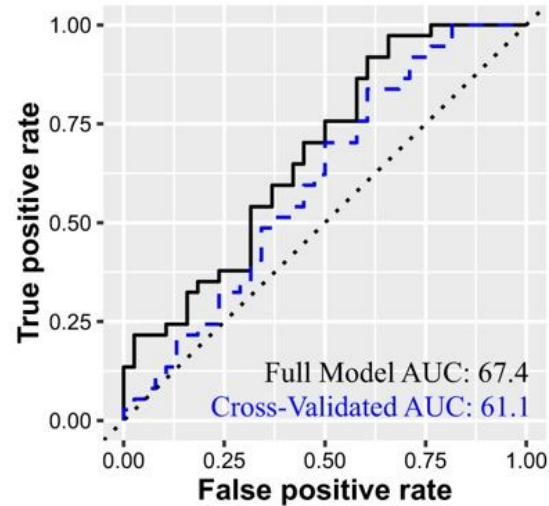


The RDoC Approach: Dissecting Heterogeneity within a Diagnosis

A. Neurosynth Derived ACC/mPFC Mask

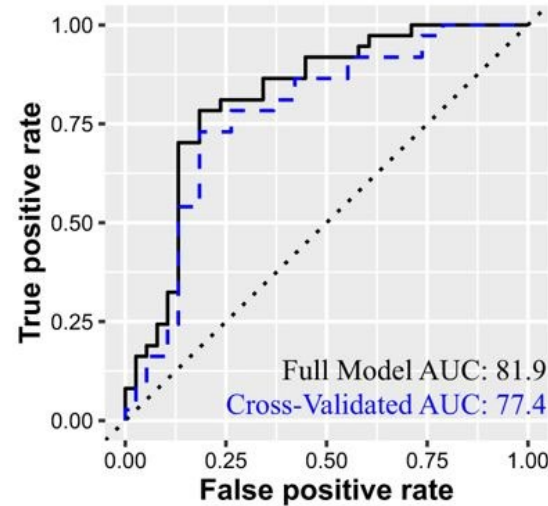


B. Covariate Model



Without connectivity measure:
Predictive accuracy = 61%

C. FC Model ACC/mPFC Mask



With connectivity measure:
Predictive accuracy = 82%

— Full sample - - - Leave-one-out cross-validated ····· Chance performance

Novel Treatment Indications

The screenshot shows a web browser window with the URL `investors.cerevel.com/news-releases/news-release-details/cerevel-therapeutics-announces-fast-track-designation-granted-us`. The page features the Cerevel logo and a navigation menu with links for 'About Cerevel', 'Our Programs', 'Our Science', 'Investor & Media', 'Careers', and 'Contact Us'. The main content area is titled 'Press Release Details' and contains the following text:

Cerevel Therapeutics Announces Fast Track Designation Granted by the U.S. FDA to CVL-871 for the Treatment of Dementia-Related Apathy

June 15, 2021 at 7:00 AM EDT

CAMBRIDGE, Mass., June 15, 2021 (GLOBE NEWSWIRE) -- Cerevel Therapeutics (Nasdaq: CERE), a company dedicated to unraveling the mysteries of the brain to treat neuroscience diseases, announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to CVL-871, a D1/D5 partial agonist in development for the treatment of dementia-related apathy. [Download PDF](#)

"Apathy is a strong predictor of dementia progression and can lead to decreased quality of life, increased morbidity and mortality, early institutionalization, and significant caregiver burden," said Raymond Sanchez, M.D., chief medical officer of Cerevel Therapeutics. "We believe that CVL-871 could be a potential treatment to address the constellation of symptoms represented by dementia-related apathy, such as social disengagement, diminished initiative and interest and loss of emotion, and we look forward to our continued collaboration with the FDA to advance the development of this important program through the Fast Track process."

Fast Track is an FDA process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The designation allows for early and more frequent communication and meetings with the FDA regarding the development of CVL-871 for the treatment of dementia-related apathy. A candidate that receives Fast Track designation is also eligible for rolling review, and potentially priority review, of the marketing application.

About Dementia-Related Apathy

Apathy has been reported as the leading neuropsychiatric symptom in patients with dementia. The social disengagement and loss of emotion in apathy can lead to impaired decision-making, lack of empathy or concern, loss of interest in personal well-being and

The Next Decade of RDoC

The question is not: *Will RDoC give us useful information compared to a clinical syndrome approach?*

The question is: *What kinds of analyses and tests will provide*

- 1. Precision assessment across the full range of pathology,*
- 2. Prescriptive assignment to treatment based on valid case formulation, and*
- 3. Preventive interventions targeting early vulnerability mechanisms?*

The Next Decade of RDoC: NIH All of Us Research Program

All of Us
RESEARCH PROGRAM

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Join the largest and most inclusive health research initiative of its kind. You could help researchers find answers to the most pressing health questions.

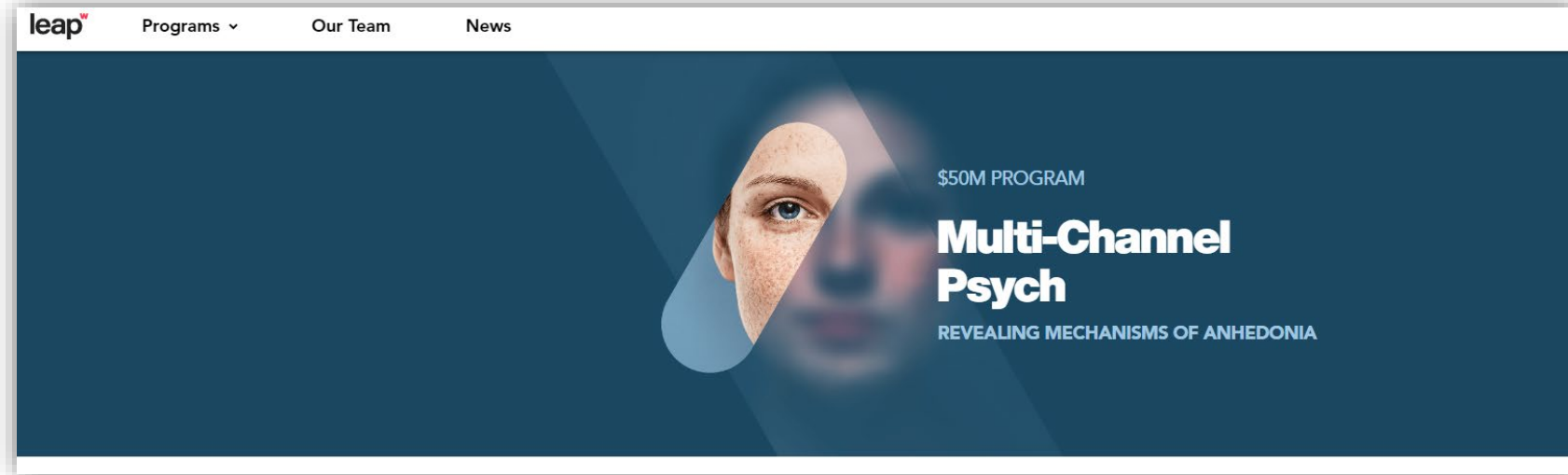
JOIN ALL OF US

Join over 511,000 people and counting.

All of Us, a research program from the National Institutes of Health (NIH), aims to have one million or more volunteers who reflect the diversity of the United States. Researchers will use the participant data collected to study many different health conditions, including common chronic diseases...

<https://allofus.nih.gov/>

The Next Decade of RDoC



Program goals.

- 1. Rapid patient stratification and treatment matching:** Develop an integrated model of anhedonic depression capturing both internal biological factors and externally-manifested and quantifiable symptom-correlated biometrics and behavioral measures. This model should stratify people into those who will be treatment sensitive and those who will be treatment resistant with 80% accuracy, consistent with the current 20% false negative rate for mammograms. The model should also be sufficient to match responsive patients to their appropriate treatment regimen rapidly, including novel or existing behavior modification, psychotherapy, medication, and neurostimulation options. Currently 33% of depressed people have significant symptom reduction with the initial treatment selected, while an additional 21-33% of people require between 2-4 treatment trials to achieve remission. Our goal is to **double the number of people who receive an effective treatment on the first try.**

Individually Measured Phenotypes to Advance Computational Translation (IMPACT)

Goal: This concept aims to encourage research using novel behavioral measures to foster a new generation of clinical signatures, leading toward precision assessment, prognosis, and treatment of mental disorders. The initial focus will be to (1) develop or optimize behavioral tasks that measure individual differences and demonstrate added utility for clinical prediction when combined with standard clinical diagnosis; and (2) form a data infrastructure that can support computational approaches to build tools for clinical decision making. This research will involve one or more longitudinal cohorts established either through new data collection or by leveraging extant cohorts that have appropriate data structures.

Full text of concept can be found at: <https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2022/individually-measured-phenotypes-to-advance-computational-translation-impact>

Thank you

www.nimh.nih.gov/rdoc

Twitter: @NIMH_RD0C

