



Diagnosis and Patient Identification: The RDoC approach

Sarah Morris, Ph.D.

Acting Director, NIMH RDoC Unit

Program Officer, Schizophrenia Spectrum Disorders

March 3, 2016



National Institute
of Mental Health

RDoC: Background



The screenshot shows the NIMH Director's Blog page for Tom Insel, M.D. The page features a navigation bar with categories like Health & Education, Outreach, Research Priorities, Funding, Labs at NIMH, News, and About Us. Below the navigation bar is a header section with a photo of Tom Insel, his name, and a 'Subscribe to RSS Feed for Blog' button. The main content area is titled 'Director's Blog: Transforming Diagnosis' and includes a recent post by Thomas Insel on April 29, 2013, discussing the release of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The post text reads: 'In a few weeks, the American Psychiatric Association will release its new edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This volume will tweak several current diagnostic categories, from autism spectrum disorders to mood disorders. While many of these changes have been contentious, the final product involves mostly modest alterations of the previous edition, based on new insights emerging from research since 1990 when DSM-IV was'. The page also features a 'Recent Posts' sidebar with three entries: 'Farewell' (October 29, 2015), 'New hope for treating psychosis' (October 20, 2015), and 'Look who is getting'. There are also sections for 'Publications by the Director' and 'Science News'.

“We need to begin collecting the genetic, imaging, physiologic, and cognitive data to see how all the data – not just the symptoms – cluster and how these clusters relate to treatment response. That is why NIMH will be re-orienting its research away from DSM categories. 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.”

RDoC: Background

“Schizophrenia...was effectively the disease that responded to antipsychotics, depression became the disease that responded to antidepressants, anxiety was a disease that responded to anxiolytics, and bipolar disorder was the disease that responded to lithium therapy.”

Yee & Miller
JAMA Psychiatry
2015

RDoC: Background

“Schizophrenia-control comparisons are... weakened...since only a proportion of the experimental cohort will have the pathophysiologic process in question. This causes Type II (false negative hypothesis test) errors and inconsistency in replication studies. Negative results cannot be decisive if study cohorts are not composed of valid subjects.

The propositions put forward in this article are not proposed as unique to the study of schizophrenia. Rather, the intent is to shift the focus of investigation to clinicopathologic correlations of specific psychopathologic domains with discrete neural circuits. This contrasts sharply with common practice. Schizophrenia is usually studied as a unitary problem... Asserting that theory predicts functional or structural disruption in a circuit combined with systematic evaluation of that circuit with converging methods provides an opportunity for strong inference research and theory falsification in schizophrenia.”

Carpenter et al.,
Arch Gen Psychiatry, 1993
(emphasis mine)





RDoC: Background

“The tendency has always been strong to believe that whatever received a name must be an entity or being, having an independent existence of its own.

And if no real entity answering to the name could be found, men did not for that reason suppose that none existed, but imagined that it was something peculiarly abstruse and mysterious.”

John Stuart Mill (1843)
(cited by Hyman, *Annu Rev Clin Psychol*, 2010)

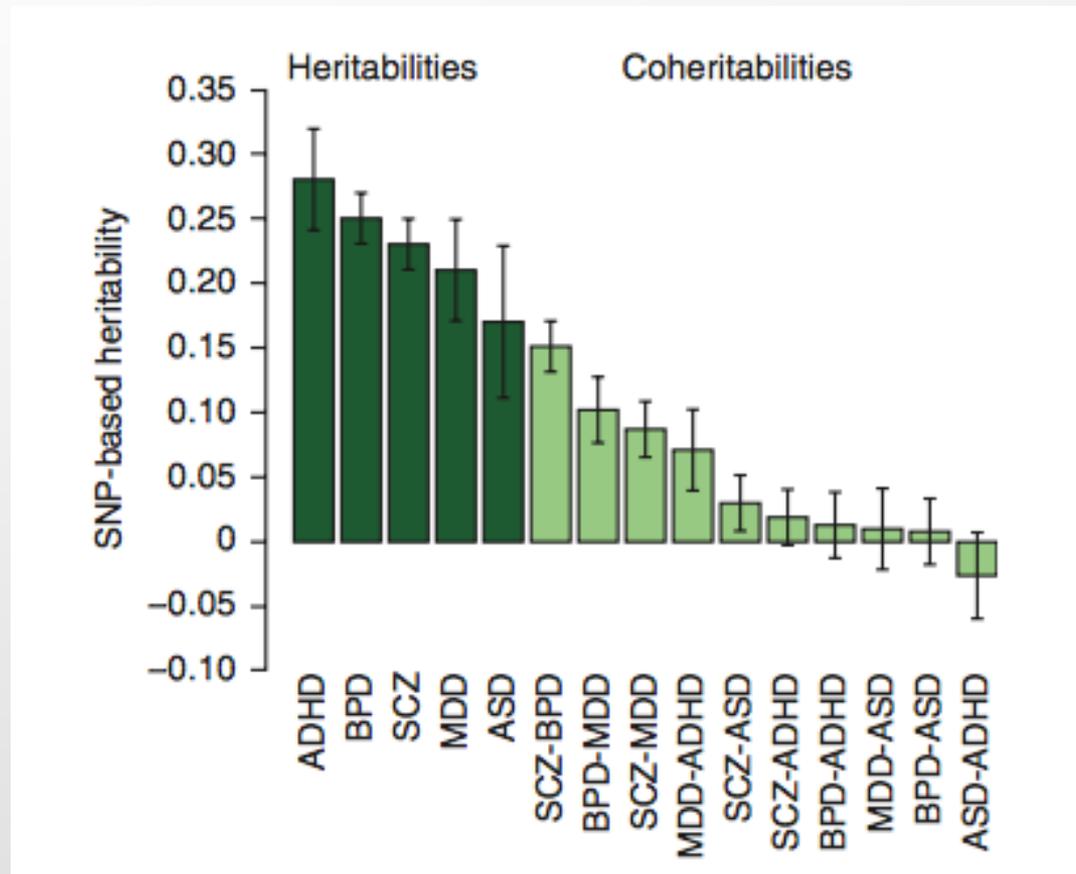


RDoC: Background

- Reliability at the expense of validity
- Heterogeneous, overlapping categories:
 - Many symptoms occur across diagnostic categories (e.g., sleep disruption, hallucinations)
 - For example: Major Depression: 5 of 9 symptoms required
 - There are 126 different possible combinations

RDoC: Background

Nature tells us that these disorders aren't fully distinct.

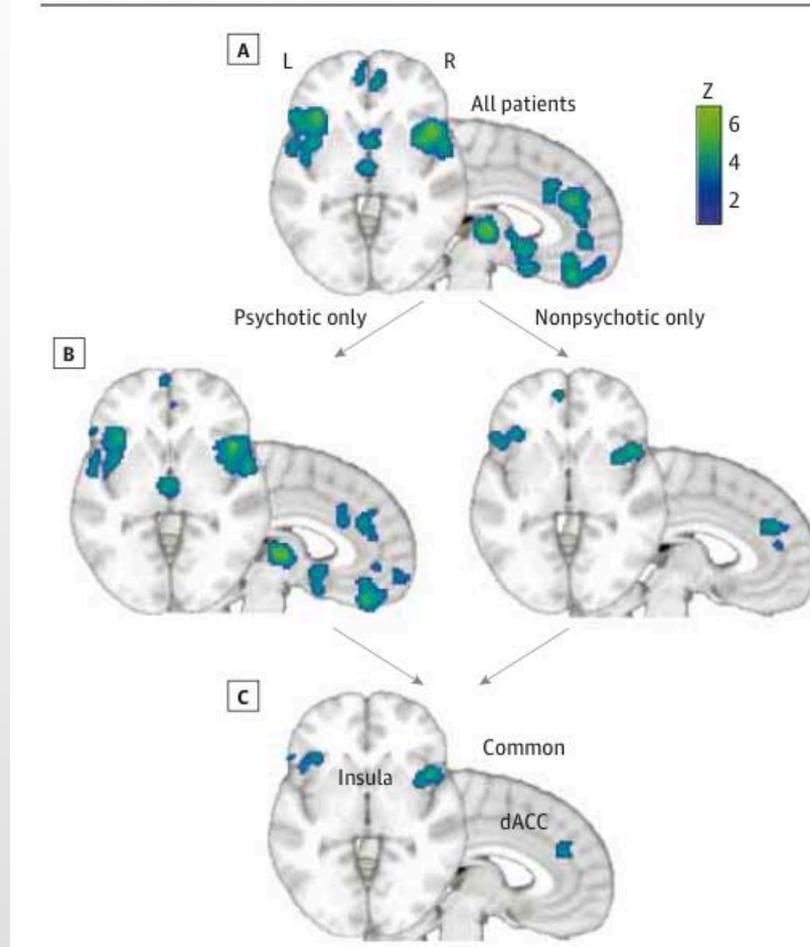


Psychiatric Genetics Consortium
Nature Genetics, 2013



RDoC: Background

Figure 2. Shared Patterns of Decreased Gray Matter From the Voxel-Based Morphometry Meta-analysis

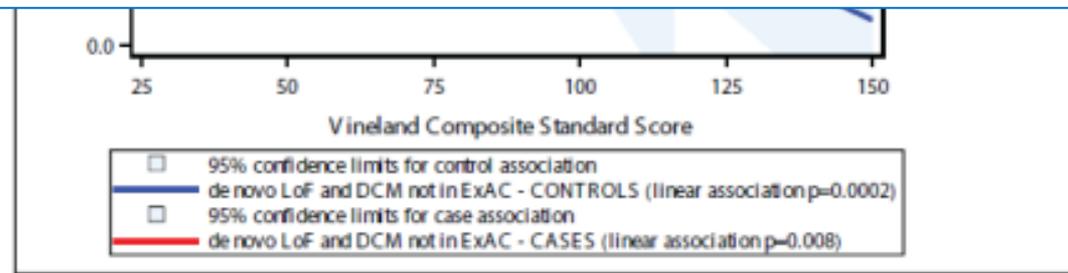


Goodkind et al.
JAMA Psychiatry, 2015

RDoC: Background

Relationship between *de novo* variant burden and daily functioning in children with and without autism

“Cases and controls with equivalent quantitative levels of functional impairment, a key component of all psychiatric diagnoses, are highly similar with regard to *de novo* variant burden, suggesting that the current categorical clinical threshold is largely arbitrary from both a phenotypic and genetic point of view.”



Robinson, et al.
Nature Genetics, in press



RDoC: Background

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

¹*CNS & Pain Discovery Research, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

²*Early Clinical Development, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

³*Translational Science, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

“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.”

RDoC: Background

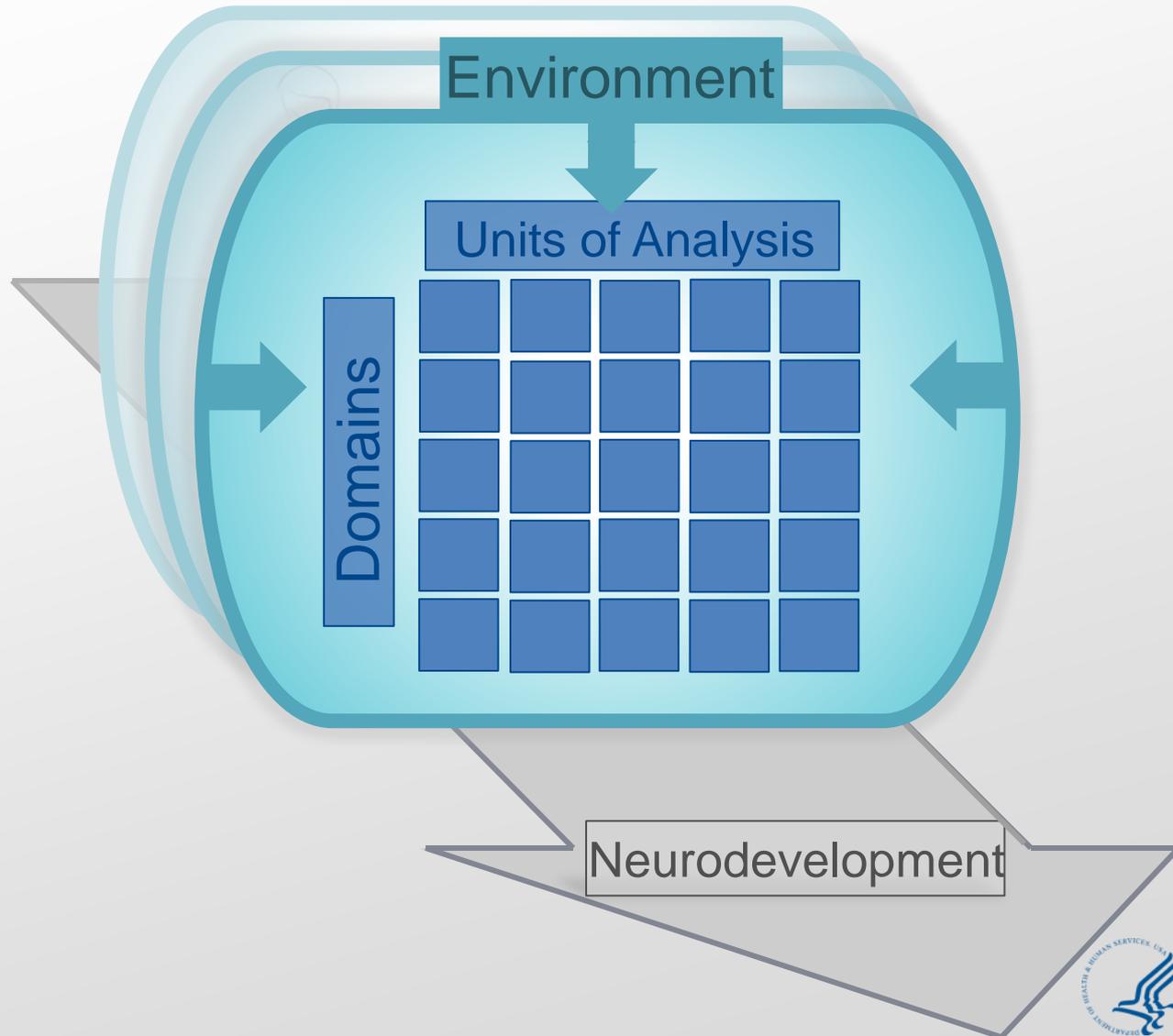
What do we mean by “validity”?

- Does diagnosis predict prognosis?
- Does diagnosis predict treatment response?
- Are genetic, neural, physiological, experiential and behavioral features convergent and discriminatory?

What is RDoC?

- The Research Domain Criteria (RDoC) initiative is an NIMH-led effort to change how patients (and non-patients) are identified and classified for research purposes.
- Instead of grouping patients into heterogeneous diagnostic groups, RDoC provides a framework for classifying participants on the basis of neurobehavioral constructs based on our understanding of brain and behavior.

RDoC framework



RDoC domains and constructs

Cognitive Systems

- Attention
- Perception
- Declarative memory
- Language behavior
- Cognitive (effortful) control
- Working memory

Negative Valence Systems

- Acute threat (“fear”)
- Potential threat (“anxiety”)
- Sustained threat
- Loss
- Frustrative non-reward

Positive Valence Systems

- Approach motivation
- Initial responsiveness to reward
- Sustained responsiveness to reward
- Reward learning
- Habit

Arousal and Regulatory Systems

- Arousal
- Circadian rhythms
- Sleep and wakefulness

Systems for Social Processes

- Affiliation and attachment
- Social communication
- Perception and understanding of self
- Perception and Understanding of Others

RDoC units of analysis

Genes

Molecules

Cells

Circuits

Physiology

Behavior

Self-
Report

- All on the same level
- None more “basic” or “fundamental” than others
- Each informs and constrains the others
- Integrative and convergent validation
- The matrix is, in essence, a set of hypotheses to be tested

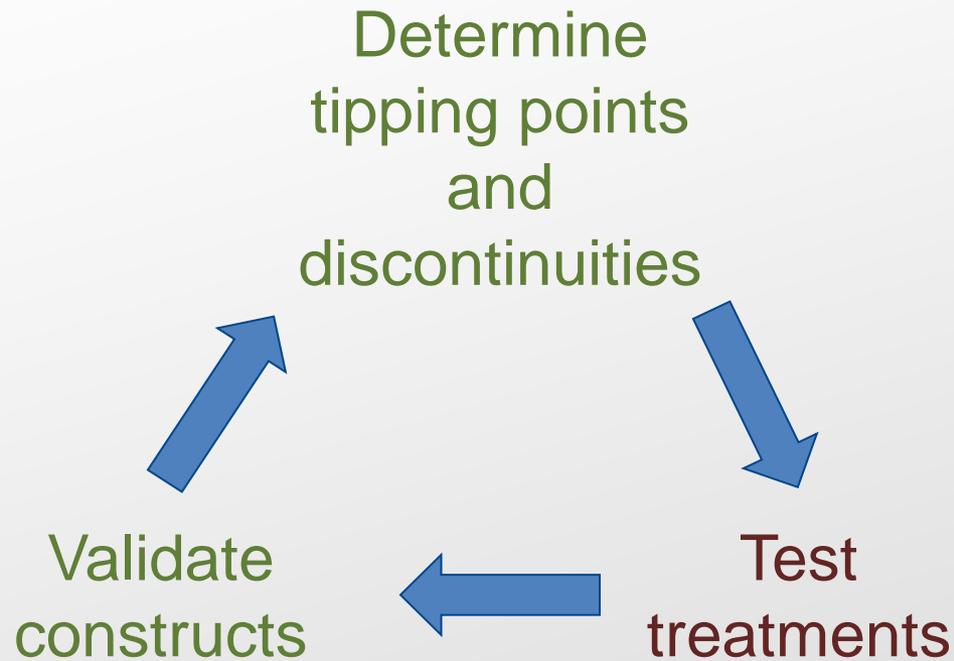
Principles for RDoC research

1. Start with what is known about normal neurobehavioral processes.
2. Focus on narrow clinical problems (instead of heterogeneous diagnoses).
3. Assume dimensionality (among disorders and between illness and health).
4. Self-report of symptoms need not be the “gold standard”; Be integrative.
5. Assume interactions among constructs.

RDoC in neuroscience trials of the future



RDoC in neuroscience trials of the future



NIMH RDoC RFAs and investigator-initiated grants

NIMH clinical trials RFAs

RDoC in neuroscience trials of the future

NIMH Clinical Trials RFAs:

“NIMH is particularly interested in the development of novel interventions that focus on operationally defined, empirically-supported functional domains or symptom(s) of mental disorders as opposed to broad diagnostic categories in which not all subjects may share the same underlying disease process. For example, NIMH Research Domain Criteria (RDoC) constructs may inform mechanism-based hypotheses and the selection of interventions, outcome measures and clinical subjects. Intervention targets related to RDoC constructs are of interest for this FOA, but other, non-RDoC constructs may be suitable as well, especially if they maximize the probability that subjects share the same mechanism of disorder.”

RDoC in neuroscience trials of the future

Deconstructed, parsed, and diagnosed.

A hypothetical example illustrates how precision medicine might deconstruct traditional symptom-based categories. Patients with a range of mood disorders are studied across several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters.

Symptom-based categories

Major depressive disorder



Mild depression (dysthymia)



Bipolar depression



Integrated data

Genetic risk
polygenic risk score

Brain activity
insula cortex

Physiology
inflammatory markers

Behavioral process
affective bias

Life experience
social, cultural, and environmental factors

Data-driven categories

Cluster 1



Cluster 2



Cluster 3



Cluster 4



Prospective replication and stratified clinical trials

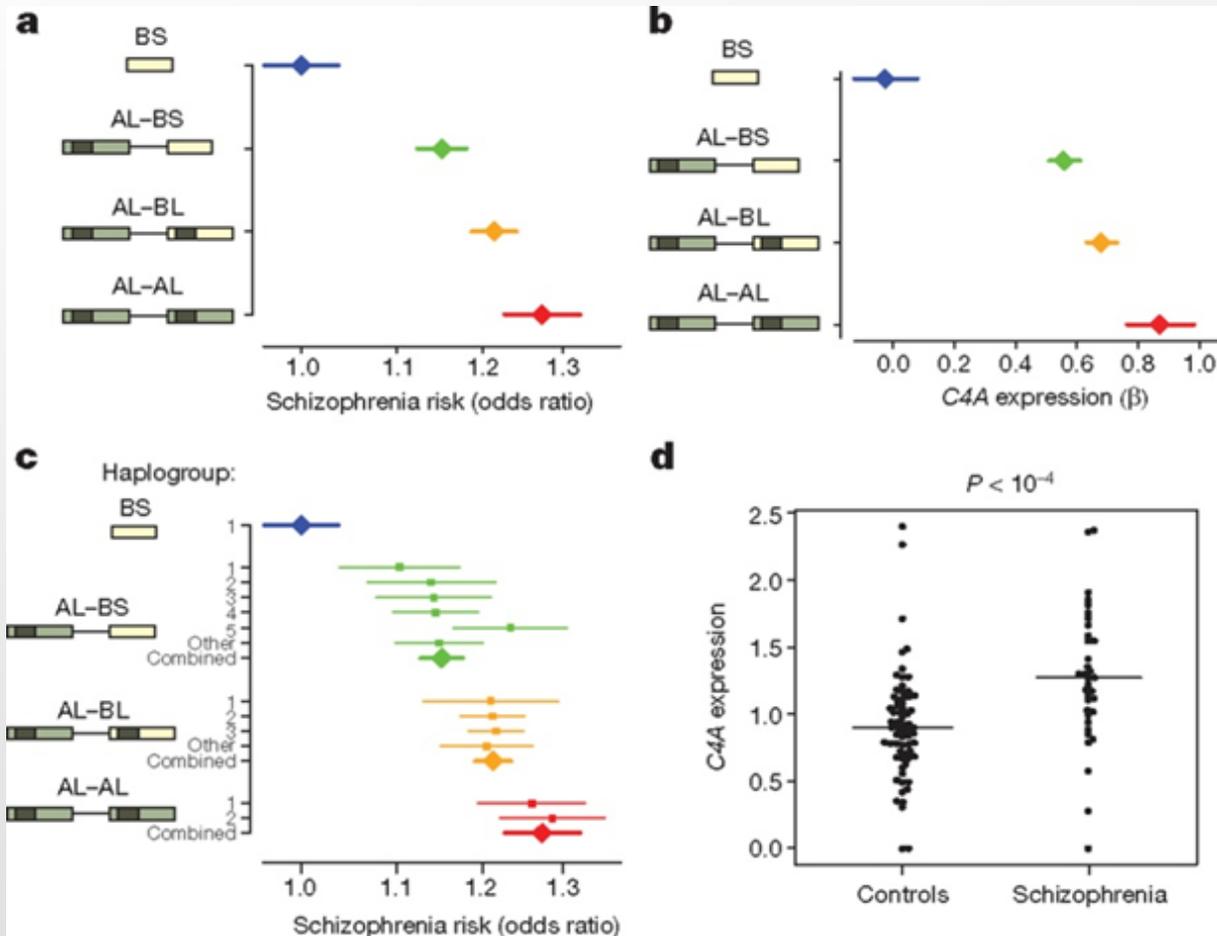
Insel & Cuthbert
Science, 2015

RDoC in neuroscience trials of the future

- Hypotheses
 - Should not be predicated on the assumption that a diagnostic category is unitary or valid
- Participant recruitment
 - Criteria designed to yield a sample that will provide a strong test of the hypothesis
 - Could be completely diagnostically agnostic
 - Could use diagnoses as a proxy (e.g., for psychosis)
 - Examples from funded NIMH clinical trials:
 - People with obsessive-compulsive disorder, Tourette syndrome and/or tic disorder who have elevated scores on Sensory Phenomena Scale
 - People with an enhanced fear response to CO₂ challenge (screened from general population for early treatment development project)

RDoC in neuroscience trials of the future

Identify trial participants via genotype?



Sekar *et al.*
Nature, 2016

RDoC in neuroscience trials of the future

Data repositories as a resource for hypothesis-generating analyses

The screenshot displays the NIH RDoC database interface. At the top, there is a navigation bar with the NIH logo and the text "National Institute of Mental Health". The main heading is "Retrieve Data from RDoCdb". Below this, a message states: "Select Browse Shared Data to view the RDoCdb projects that are sharing or expected to share research data." On the left, there is a sidebar with "Request Access" and "Browse Shared Data" options. The main content area shows a list of shared data projects, each with a title, investigators, and a description. The projects listed are:

- Early Brain Development in Twins** (#1974)
Title: Early Brain Development in Twins
Investigators: John Gilmore
Description: Twin studies have been critical in determining the contributions of genetic and environmental factors to normal brain structure and for understanding abnormalities of brain development that underlie neurodevelopmental and neuropsychiatric disorders. In adults and older children, twin studies indicat... [Show More](#)
Open in NDAR
- Longitudinal measurements of sleep EEG in adolescence** (#2018)
Title: Longitudinal measurements of sleep EEG in adolescence
Investigators: Irwin Feinberg
Description: Adolescence is now recognized as a period of major brain reorganization as well as rapid endocrine and physical development. Among the most prominent brain changes is a huge decline in the delta (<4 Hz) EEG of NREM sleep. Our ongoing study uses spectral and period-amplitude analyses to examine sleep... [Show More](#)
Open in NDAR
- Multi-Level Assays of Working Memory and Psychopathology** (#2096)
Title: Multi-Level Assays of Working Memory and Psychopathology
Investigators: Robert M. Bilder
Description: The NIMH Research Domains Criteria (RDoC) initiative aims to advance understanding of mental health through critical re-evaluation of the traditional diagnostic system and development of alternate methods for measurement of biologically valid dimensions and categories. The proposed project focuses o... [Show More](#)
Open in NDAR

<http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>

Thank you!

Examples of NIMH-funded RDoC grants

Children's Attentional Biases: A Key Component of Negative Valence Systems (Brandon Gibb)

Family Study of Reward and Threat Sensitivity in Internalizing Psychopathology (Stewart Shankman)

RDoC Constructs: Neural Substrates, Heritability, and Relation to Psychopathology (David Zald)

Inflammatory Transcripts, Genes and Positive Valence System Function in Anhedonia (Jerzy Bodurka)

A Twin Study of Negative Valence Emotional Constructs (John Hettema)

From Fear to Anxious Misery: Developing a Defense Circuit Dimensional Classifier (Peter Lang)

Risk and Resilience in Maltreated Children (Joan Kaufman)