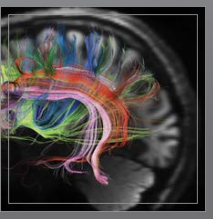


Diagnosis and Patient Identification: The RDoC approach

Sarah Morris, Ph.D.

Acting Director, NIMH RDoC Unit

Program Officer, Schizophrenia Spectrum Disorders

March 3, 2016

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RDoC: Background

"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."

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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

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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)

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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)

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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

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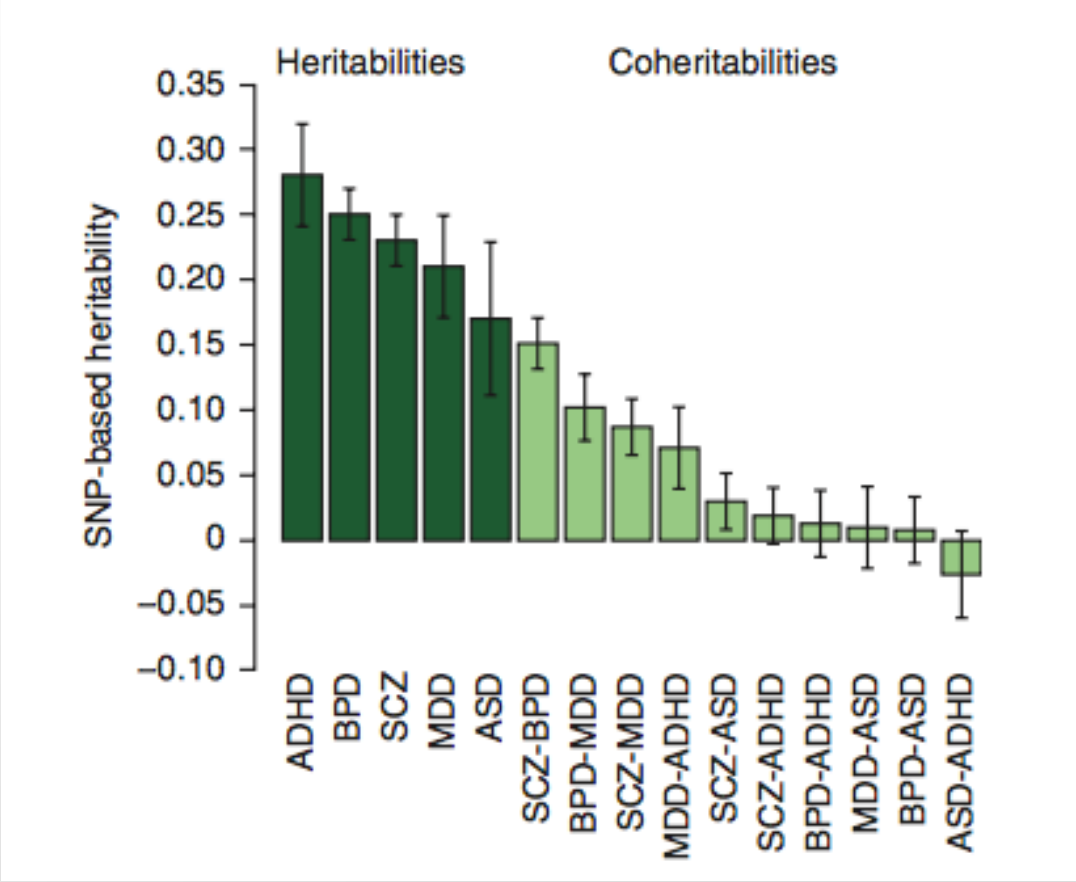
RDoC: Background

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



Psychiatric Genetics Consortium
Nature Genetics, 2013

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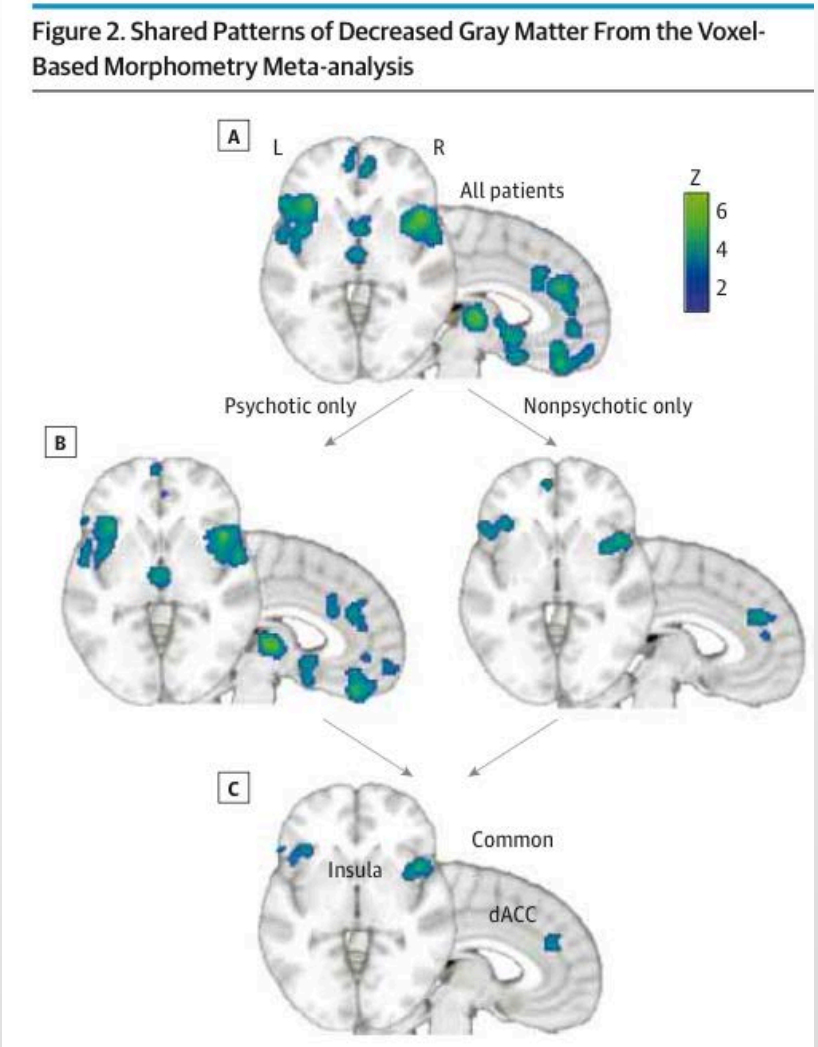
RDoC: Background



Goodkind et al.
JAMA Psychiatry, 2015

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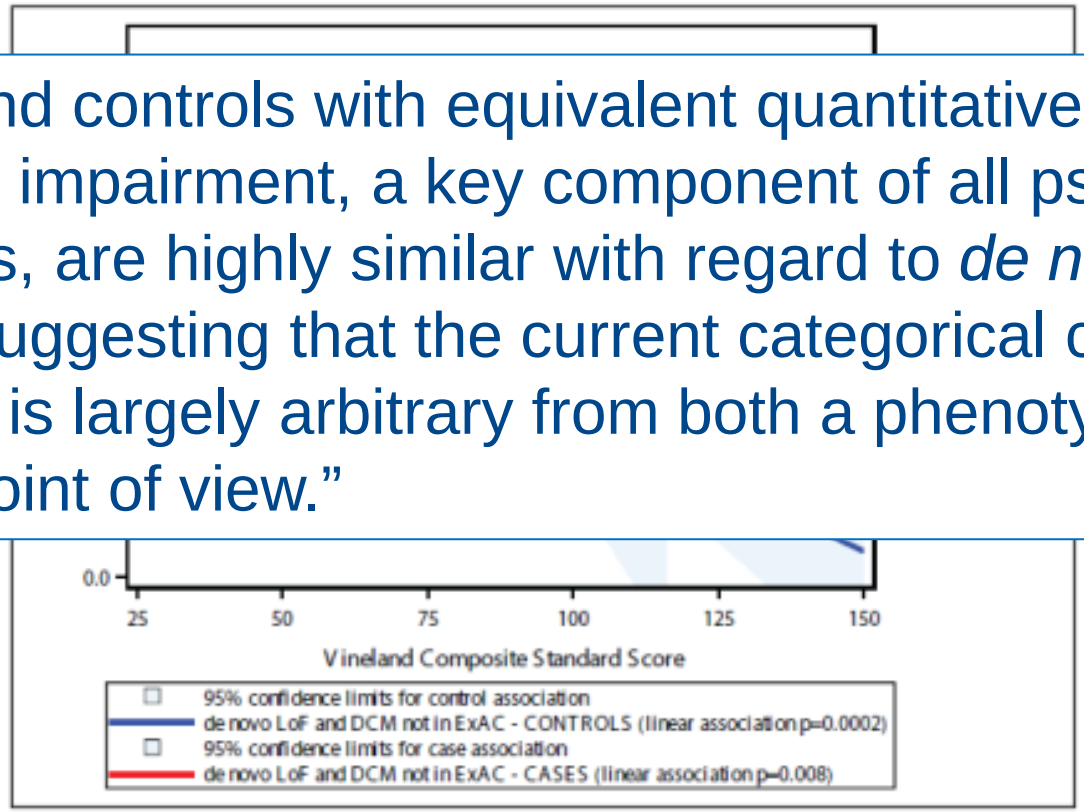
RDoC: Background

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

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RDoC: Background

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

Erik H. F. Wong[1], Frank Yocca[1], Mark A. Smith[2] and Chi-Ming Lee[3]

[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."

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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?

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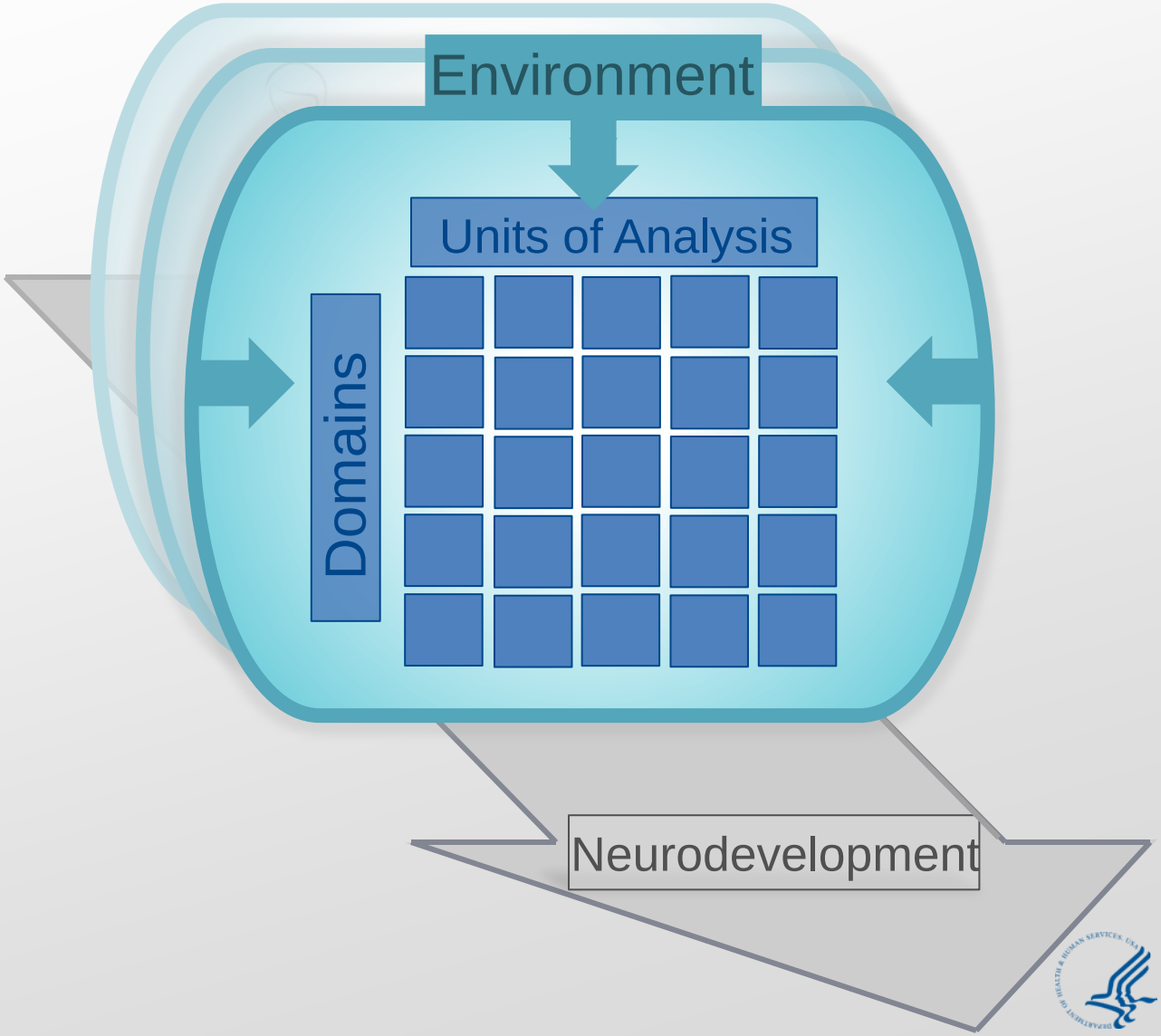
What is RDoC?

- 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



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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

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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

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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.

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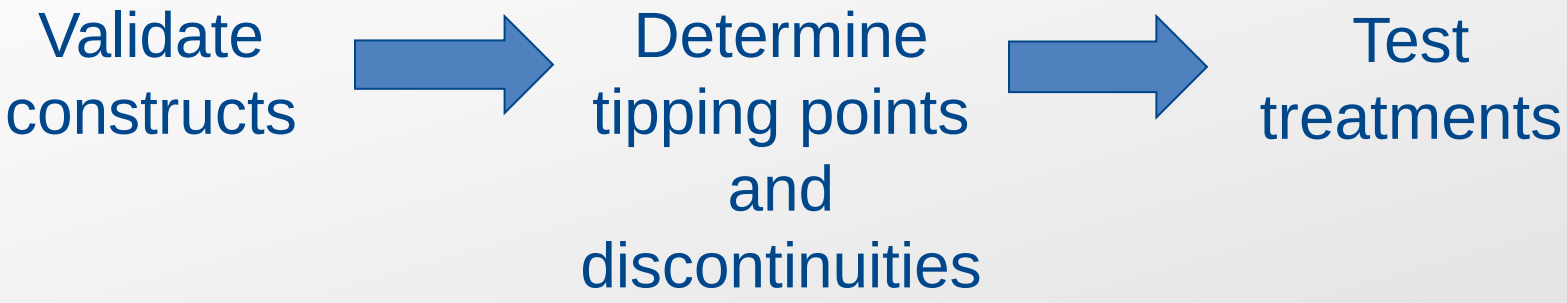
RDoC in neuroscience trials of the future



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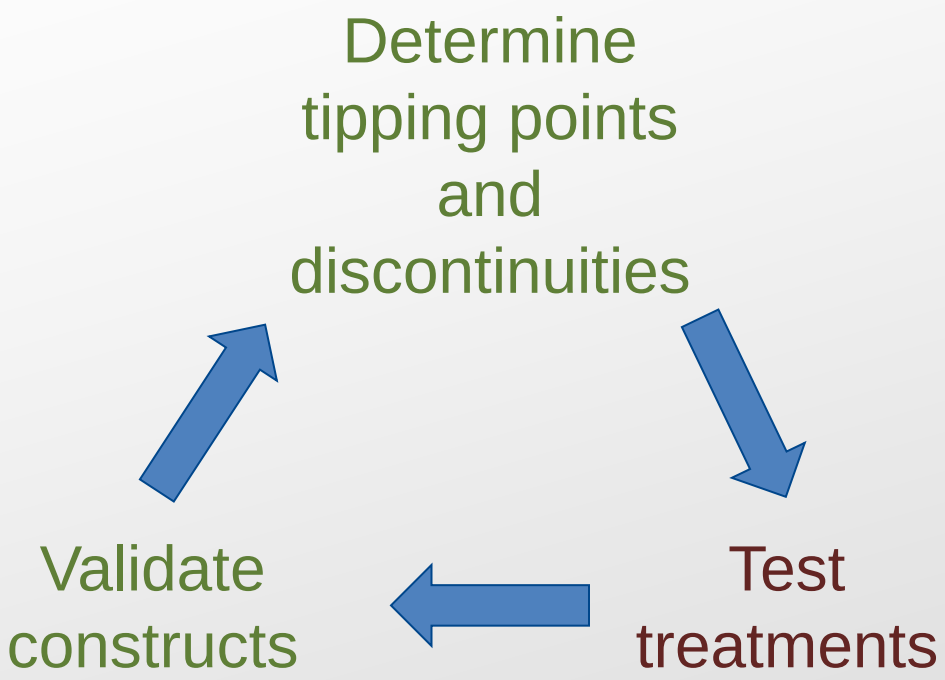
RDoC in neuroscience trials of the future



NIMH RDoC RFAs and investigator-initiated grants

NIMH clinical trials RFAs

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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*."

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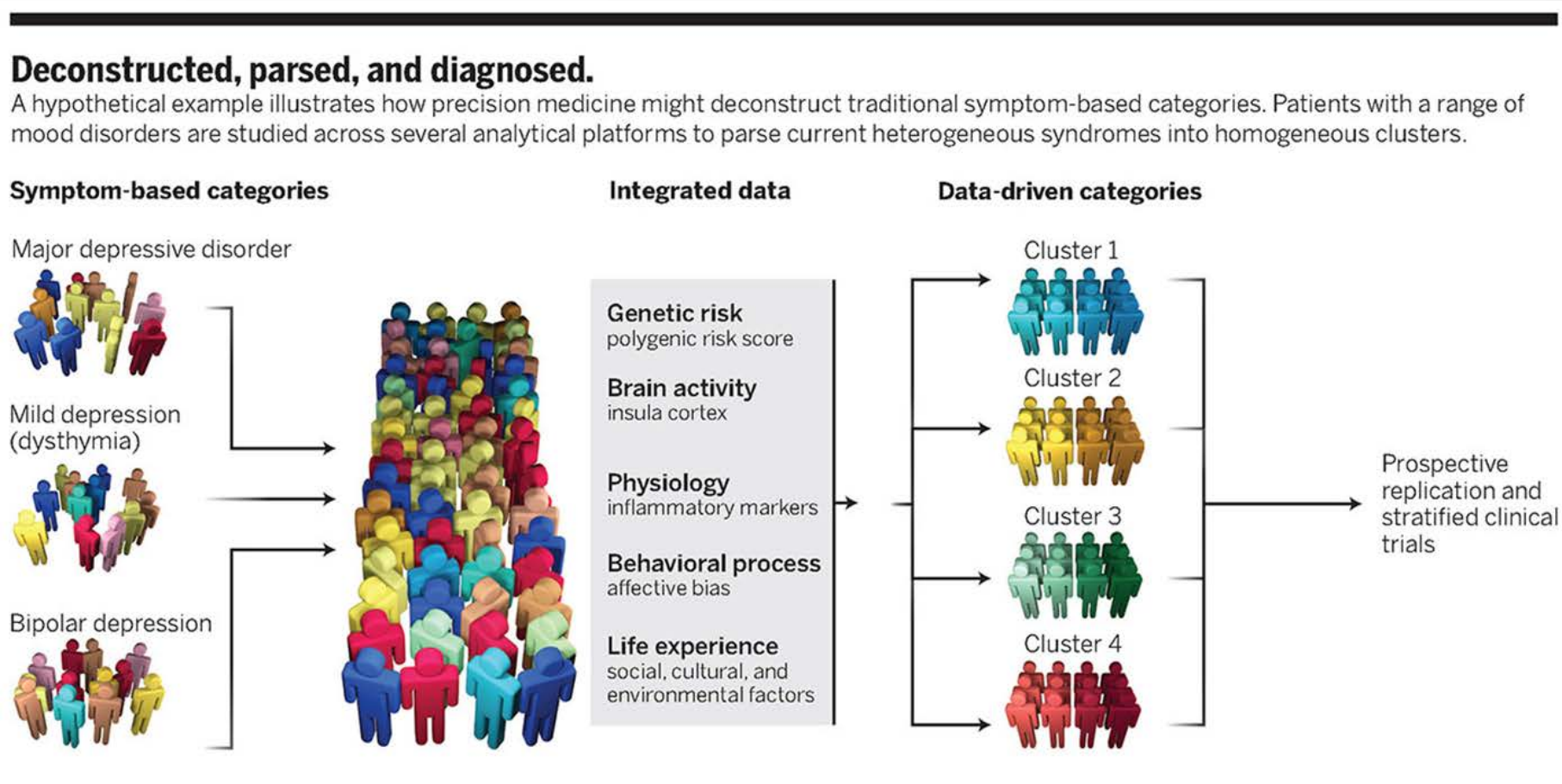
RDoC in neuroscience trials of the future



Insel & Cuthbert
Science, 2015

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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)

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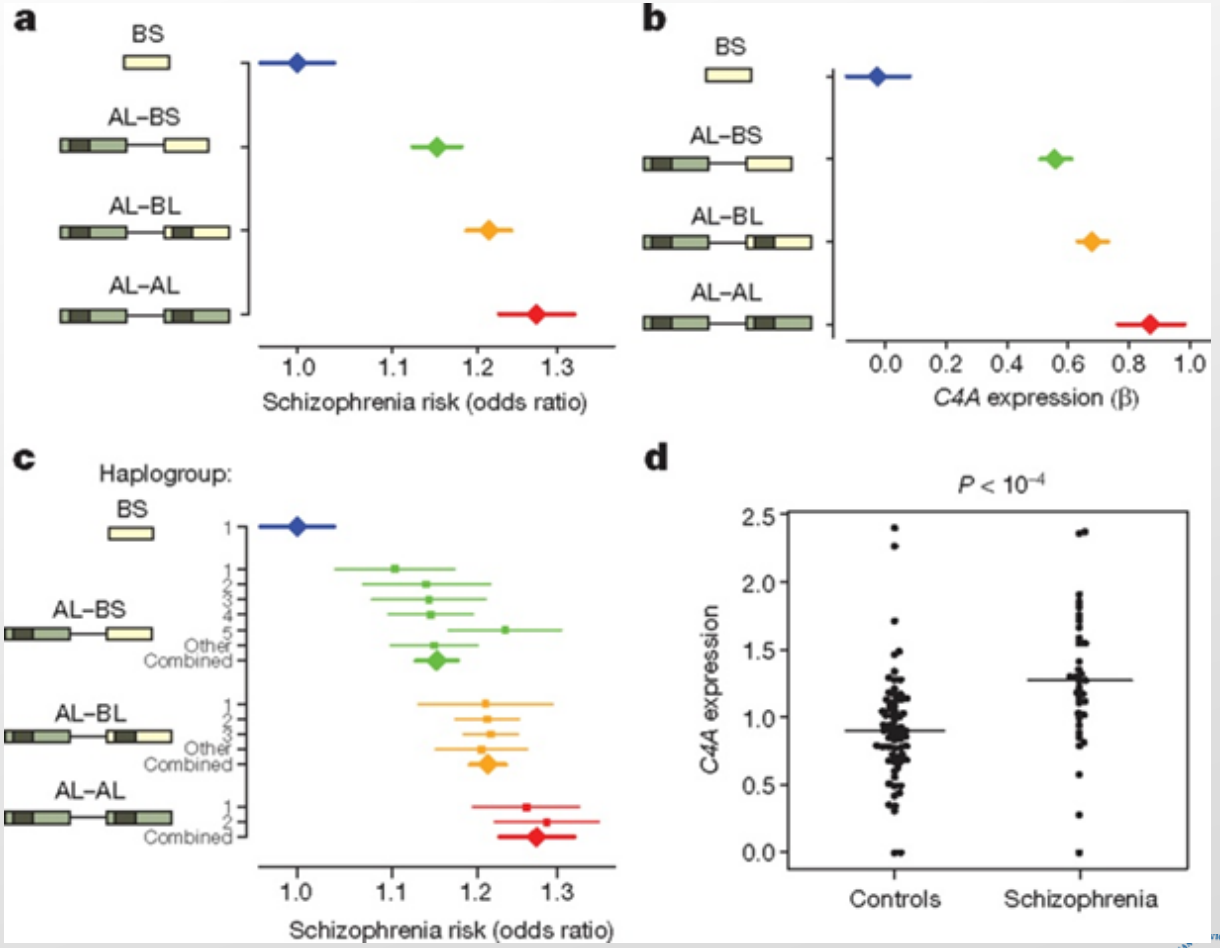
RDoC in neuroscience trials of the future

Identify trial participants via genotype?



Sekar *et al.*
Nature, 2016

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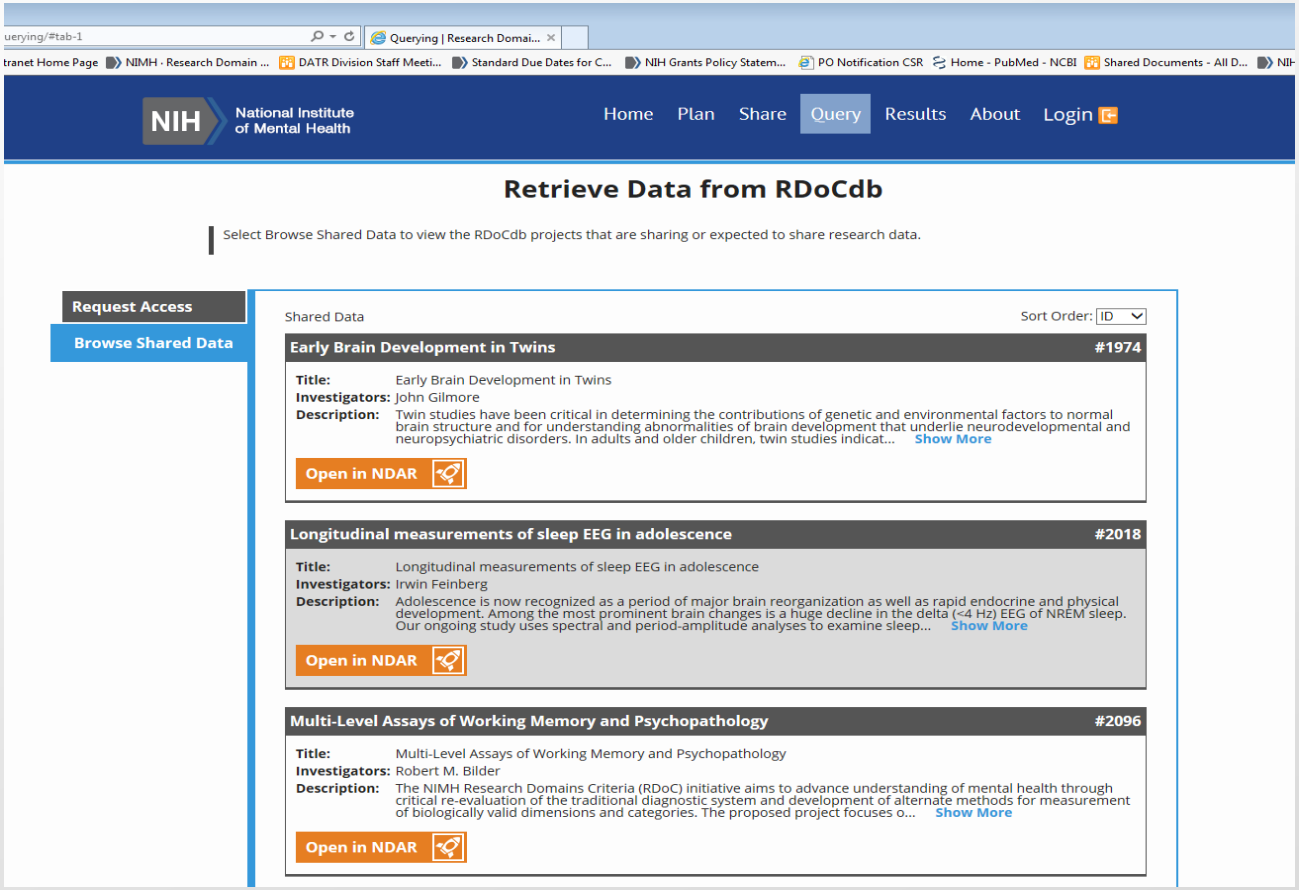
RDoC in neuroscience trials of the future

Data repositories as a resource for hypothesis-generating analyses



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)

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