The NIMH Research Domain Criteria (RDoC) Project : Overview

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Problems in current psychopathology diagnosis

- Defined by clusters of signs & symptoms, but not primary aspects of behavior or brain functioning
- Poor validity: A system created for reliability
- Heterogeneity of DSM/ICD categories (polythetic criteria sets)
- Extensive co-morbidity: Multiple mechanisms
- Result: difficult to relate diagnoses to genes, particular brain circuits, or basic behavioral mechanisms;
- AND: our diagnostic system drives research grants, journal publications, clinical trials, and regulatory agencies

Sample Problem 1: Depression

- Any 5 out of 9 symptoms required for DSM diagnosis
- Several opposites:
  - psychomotor retardation, hypersomnia, weight gain, vs.
  - Agitation, poor sleep, weight loss
- This causes problems for research, and treatment
- Symptoms have low intercorrelations, and different heritabilities

Problems with Depression Diagnosis

- Many milder cases remit without specific treatment, suggesting that they are responses to life stress
- Depression can may be a toxic reaction to drugs or result from disorders such as Cushing's syndrome
- 5 forms of major depression? (Goldberg, 2011, *World Psychiatry*)
  1. Depression presenting with somatic symptoms
  2. Depression with panic attacks
  3. Depression in people with obsessional traits
  4. Depression accompanying known physical illnesses
  5. Pseudo-demented depression, in older people

Sample Problem 2: Schizophrenia

- Criteria for diagnosis can be met in the following cases:
  - Disorganized speech and behavior, inappropriate affect, poor self-care
  - Hallucinations, paranoia, agitation
  - Apathy, social withdrawal, flat affect, delusions
- Are these the same condition?
- Should we expect all 3 symptom profiles would respond the same to medication or psychological therapies?

NIMH Strategic Plan: Goal 1.4

- "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures."
  - Identify fundamental components that may span multiple disorders (e.g., executive function, affect regulation)
  - Develop reliable and valid measures of these fundamental components for use in basic and clinical studies
  - Determine the full range of variation, from normal to abnormal
  - Integrate genetic, neurobiological, behavioral, environmental, and experiential components

3 Guiding Principles of RDoC

- It is a dimensional system spanning the range from normal to abnormal, similar to how dimensions are used in other areas of medicine (e.g., blood pressure, cholesterol)
- RDoC is agnostic about current disorder categories. The intent is to generate classifications stemming from basic behavioral neuroscience, rather than starting with an illness definition and seeking its neurobiological underpinnings
- RDoC uses several different units of analysis in defining constructs for study (e.g., imaging, physiological activity, behavior, symptoms).

Avoiding Reification

- Trying to get away from a mindset where the diagnosis “causes” things to go wrong.
- RDoC focuses on what’s going wrong

RDoC: Candidate Domains/Constructs and Units of Analysis (v. 1.0)

v. 3.1, 6/30/2011	DRAFT RESEARCH DOMAIN CRITERIA 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								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/Regulatory Systems								
Arousal & regulation (multiple)								
Resting state activity								

Construct: A concept summarizing data about a specified functional dimension of behavior (and implementing genes and circuits).

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Acute threat ("fear")							
Potential threat ("anxiety")							
Sustained threat							
Loss							
Frustrative nonreward							

Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	Paradigms
Visual perception	Dysbindin/ NRG1/ Neuroligin/ Neurexin	Glutamate, GABA. NMDA, Serotonin, Ach, Catechola mines, peptides	Magno (non-linear gain control). Parvo. "Frame and fill". Pyramidal, parvalbumin positive interneurons.	**Subcortical:** magnocellular, parvocellular, koniocellular. **Cortical:** dorsal/ventral streams; cortico-cortical connections into supra- and infra-granular layers.. **Non-retinogeniculate:** Superior colliculus, Suprachiasmatic nucleus. **Local circuitry** implicated in contextual fields and association fields (responsible for the influence of spatial context on target processing): lateral interactions; top-down interactions	Oscillations (scalp EEG, LFP, and single/multi-unit). ERP components: All of the sensory evoked potentials (from stimulus onset through N1), Ncl, ssVEP, tVEP. BOLD (activation) of cortical regions. Adaptation/habituation.	Stimulus detection. Discrimination, identification and localization. Perceptual priming. Visual acuity. Reading. Perceptual learning.	Perceptual anomalies of schizophrenia and depression.	<u>Scheme I. Stages of Vision.</u> <u>Early vision</u> retinotopic representations, local computations. <u>Intermediate vision</u> Nonloca properties of images, transformations beyond retinotopic representations (e.g., surface properties of the object independent of light, head position). <u>Late vision</u> Representations of external objects (e.g., object identification, classification, visually guidec action). <u>Scheme 2. Commonly Used Research Paradigms</u> Vernier discrimination; Object recognition/perceptual closure /perceptual organization; object perception; contour integration/interpolation; face identification; emotion expression identification; Parallel/serial search; Reading; contrast sensitivity lateral facilitation; biological motion processing; coherent motion; bistability; multistability; figure ground;

Ascertaining Samples in RDoC:

1) Different units of analysis can be independent variables:

v. 2.1, 4/1/2011	DRAFT RESEARCH DOMAIN CRITERIA 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	IV				IV	DV	DV	
Frustrative nonreward								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior	DV			DV		IV		
Cognitive (effortful) control								

2) Dimensional approach (translation of basic dimensions)
3) Agnostic to current DSM/ICD categories –
   Recognizes that in the end, some may go away
   and some may remain useful

Matrix Elements (cont.)

- Would prefer elements that are important to the main circuits or behavior relevant to the construct
- E.g., norepinephrine (LC) is important for arousal and thus could be relevant for WM, but is it central?
- Matrix elements can be specified as simple lists, within each Unit of Analysis

The Translational Bridge

- A translational research effort: The starting point is a basic-science perspective….
- **But** with clinical symptoms, and classification, in mind
- Necessity for compromise to produce a product
- Importance of noting issues and priorities for research
- RDoC: a **framework** for organizing translational research
- I.e., the matrix is not a definitive end-product, rather a framework for organizing research

Process

- Draft specifications by NIMH working group
- Initial workshop for each domain with researchers from the field to clarify the domain & its constructs, identify particular targets and systems ….
- Followed by continuing commentary on web
- On-line criterion specification for each domain & construct
- Define a mechanism and criteria for changes to the domain specifications (e.g., N replicated studies)

Phases of RDoC

- Initial construct validation : 5-10 years
- “Develop reliable and valid measures of these fundamental components for use in basic and clinical studies”……
- Selection of particular methods for measuring constructs
- Develop & evaluate tasks and paradigms for reliability and validity as measures suitable for trials and practical clinical use (years 5-15); cf. CNTRACS
- Regulatory agency approvals: ?

Implications of RDoC

- Change in perspectives on psychopathology
- Inform future versions of psychiatric diagnosis
- Personalized medicine
- New treatment development focused on behavioral/brain mechanisms: Pharmacological, behavioral, devices, and combined

Scope of Domains, Constructs

- Changes in Domains: possible
- Changes to constructs: yes
- “Sweet spot” for the “grain size” of constructs
- Metaphor: Major factors from a “Principal Components Analysis” of the data

Conclusions

- Research Domain Criteria (RDoC) approach should lead to:
  - A better understanding of psychiatric symptoms
  - More personalized treatment
  - More homogeneous groups for research, and therefore advances in understanding the causes of psychiatric conditions