Research Domain Criteria (RDoC): Toward Future Psychiatric Diagnosis

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Unremitting public health burden of mental disorders

Current practices in clinical diagnosis (DSM, ICD) are no longer optimal for contemporary research.

Diagnosis remains restricted to symptoms and signs, disorders are broad syndromes.

Symptom-based approach hampers prevention.

**Problem:** While sufficient for current clinical use, DSM/ICD categories also drive the entire research system (research grants, journals, trials, regulatory).
• Changing viewpoints based on the concepts of modern research — neural, cognitive, and behavioral science.

• Shift the discovery paradigm from diagnostic constructs based purely on symptoms, to those based upon the relationships among neural systems, behavior/cognition, and symptoms.

• Experimental designs: studies based upon dimensions of functional systems rather than disease categories.
The Overarching Goals of RDoC

Develop a **framework** for studying psychopathology based on dimensions of observable behavior and neurobiological measures.

- Posit **fundamental components** that may span multiple disorders (e.g., executive function, affect regulation)
- Determine the **full range of variation**, from normal to abnormal
- Integrate genetic, neurobiological, behavioral, environmental, and experiential components
- Develop reliable and **valid measures** of these fundamental components for use in basic and clinical studies
Dimensional Psychiatry: Shift from (categorical) infectious disease model to …
Complex Trait Model (full distribution)

Empirically-based cutpoints for (e.g.) mild, moderate, severe levels of dysfunction
Dimensional Psychosis Phenotype

Kaymaz and van Os, *Psychological Medicine*, 2010
Exactly what does RDoC involve?

• Focused research initiative moving “toward a new classification system”: study and validate trans-diagnostic, dimensional constructs

• Concept:

  1) Deeper understanding of psychological & biological systems related to mental illness ➔

  2) New “biomarkers” & biosignatures ➔

  3) More homogeneous groupings for psychopathology/pathophysiology ➔

  4) new intervention development
The RDoC Framework: Four dimensions
## RDoC Matrix: Integrative Framework

(Workshops July 2010 – June 2012)

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Dynamic: Always “Under Construction”

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- Altered Stress Reactivity
- Emotion regulation problems
- Lack of pleasure in usual activities
- Lack of energy for productive tasks
- Language delays
- Executive function problems
- Social withdrawal
- Poor relationships

- Problems with arousal-modulating systems
- Sleep problems
Potential New RDoC Constructs/Domains

• Motor construct or domain
• Resting state/default network (function?)
• Neuroimmune factors: Construct (row) or Unit of Analysis (column)?
• Overlaps between impulsivity and executive function?
Misunderstandings: RDoC Myths (1)

• “NIMH does not accept DSM/ICD applications”
• A: Over half our clinical applications are DSM/ICD.
• “RDoC ignores the environment and development”
• A: Wrong. About half our RDoC grants involve children.
• “The RDoC matrix blocks my research because the construct that I want to study is not listed”
• A: We encourage the study of new constructs – they are needed to grow the matrix.
• “I can’t study interactions among the constructs”
• A: We encourage studies among 2 or more constructs.
• “RDoC is reductionistic and ignores psychology and/or experiential factors”
• RDoC is integrative, not reductionistic.
• “You must study multiple DSM/ICD disorders to do RDoC”
• A: Wrong. We encourage transdiagnostic studies, but accept those using a single DSM/ICD diagnosis.
Substantive Hazards/Challenges

- “Grain size”: e.g., cognition vs executive function vs working memory
- Measurement: new instruments, techniques
- Relating lab/task measures to clinical symptoms, outcomes
- Assessing symptoms versus functioning
- Determining cut points for continuous phenomena
Examples of RDoC-compatible data

- (1) Anxiety disorders
- (2) Psychotic disorders
- (Neither incorporate normal-to-abnormal dimension)
Anxiety: Divergence among response measures

McTeague & Lang, Int’l Society for Traumatic Stress Studies, 2013
“Psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain.” Craddock & Owen, *Br J Psych* (2010)
Example: BSNIP*, parsing the schizophrenia-bipolar spectrum

* Bipolar-Schizophrenia Network on Intermediate Phenotypes
Example: BSNIP*, parsing the schizophrenia-bipolar spectrum

Composite cognitive score

Sweeney et al., SOBP Symposium, 2012

Schizobipolar scores strongly inversely correlated with BACS composite scores \( r = .35; \ p = <.0000 \)

* Bipolar-Schizophrenia Network on Intermediate Phenotypes
BSNIP: Sz-bipolar spectrum (DSM analysis)

A significant DSM effect does not indicate meaningful differences at the individual level!

Sweeney et al., 2012
BSNIP: Sz-bipolar spectrum (RDoC approach)

Sweeney et al., 2012

Schizobipolar scores strongly inversely correlated with BACS composite scores $r = .35; \ p = <.0000$
BSNIP “Biotypes: (1) Cognitive Control, (2) Sensorimotor Reactivity

Clementz, …. & Tamminga, Am J Psychiatry, in press
Schizo-bipolar scores by Biotype and Diagnosis

More Sz-like

Bio 1

Bio 2

Bio 3

More Bipolar-like

BSNIP: Gray Matter Loss by Biotype: Probands and Relatives

BSNIP biotypes, but not DSM, predict schizophrenia (Sz) polygene risk

Sz Polygene score (Sz workgroup of PGC, Nature 2014)

Clementz, Keshavan, Pearlson, Sweeney, & Tamminga, ICOSR, 2013, shared by permission
Toward Indicated Prevention: Early (pre-clinical) signs of psychosis risk

Pennsylvania Neurodevelopmental Cohort (N = 4,642): Gur et al., *JAMA Psychiatry*, 2014
Ongoing RDoC Activities

• Curation and development of tasks & instruments
• RDoCdb (database): common data elements, data sharing
• Data mining: discovering relationships in large cohorts
• RDoC Forum for online discussions
• Regulatory agencies: (FDA/EMA)
Summary: Contemporary Directions for Mental Disorders

- Need to move from symptom management toward cure, pre-emption, and prevention
- RDoC: Flexible, dimensional research framework that includes neurodevelopment, environment
- Dimensional approach to mental disorders
- Big data, common data elements, different sampling frames
- Computational neuroscience: Identify new dimensions/subgroups rather than seeking correlates of current disorders
- The future: toward precision treatment and prevention for CNS disorders, consistent with other areas of medicine
Nigg et al.: Attention-Deficit Hyperactivity disorder
ADHD deconstructed in terms of temperament traits:
1) Negative valence systems (fear, anxiety, stress)
2) Positive valence systems (reward, approach)
3) Cognitive/effortful control (cognition)

“To better parse heterogeneity … [look] beyond existing symptom lists toward phenotypic measures that can be represented dimensionally and have well-theorized relationships with neurobiological systems. …. Phenotypic measures that retain clinical applicability are desirable.”
Type 1: “Mild” ADHD (but meet DSM criteria)

“Effortful Control” (impulsivity) scores
[more impulsive is upward on the graph]

Karalunas, … & Nigg, JAMA Psychiatry 2014
Types 2 and 3: Temperament Differentiation

Type 2: “Surgent” (assertive, pleasure-seeking, activity)

Type 3: “Negative emotion”: (anger, discomfort, fear, sadness)

“… revising the nosologic criteria in the case of ADHD is tractable and will be biologically meaningful.”

Karalunas, … & Nigg, *JAMA Psychiatry* 2014