Research Domain Criteria: What They Are and Why They Matter

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Our Mission

"We will develop and apply methods in pursuit of the determinants of mental health and mental illness."
Our Vision

"We will discover determinants of mental health and mental illness, and develop interventions founded on those discoveries."
Value of the DSM

✧ As a diagnostic framework, DSM has a function and value:

• Reliable recognition of mental disorders

• Consistent characterization in a controlled vocabulary

• Permits diagnoses that enable treatment, reimbursement

• Informs treatment options
On the Weakness of the DSM

The weakness is its lack of validity. Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever.

Thomas Insel, M.D., NIMH Director’s Blog, April 29, 2013
Further Challenges to DSM

- Genetic and environmental risk factors are shared by disorders
- Comorbidity in patients and families is the rule, not the exception
- Dimensional nature of disorders, symptoms distributed along spectra
The DSM Paradigm

- Gene Expression (TRANSCRIPTOMICS)
- Protein Expression (PROTEOMICS)
- Genes & Environment
- Brain Structure and Function
- Neuropsychological Functioning
- Behavioral and Emotional Symptoms

Adapted from Ozdemir et al., *Nature Biotechnology*, 2006
On the Weakness of the DSM

"Patients with mental disorders deserve better"

Thomas Insel, M.D., NIMH Director’s Blog, April 29, 2013
Enter, Research Domain Criteria

- Measurement approach based on biology and symptoms not constrained by DSM categories

- Focus on brain circuits regulating domains of cognition, emotion, or behavior

- DSM disorders are one expression of a set of dysregulated circuits

- Mapping circuits at psychological, neurobiological, and genetic levels will yield new and better treatment targets
The RDoC Approach

Genes & Environment

Gene Expression (TRANSCRIPTOMICS)

Protein Expression (PROTEOMICS)

Brain Structure and Function

Neuropsychological Functioning

Behavioral and Emotional Symptoms

Clinical Phenomena

Adapted from Ozdemir et al., Nature Biotechnology, 2006
RDoC Domains

- RDoC Domains represent major areas of functioning, reflecting contemporary thinking about motivation, cognition, and social behavior.

- Five Domains have been posited:
  - Negative Valence Systems (*e.g.*, aggression)
  - Positive Valence Systems (*e.g.*, reward regulation)
  - Systems for Social Processes (*e.g.*, attachment)
  - Arousal/Regulatory Systems (*e.g.*, circadian rhythms)
  - Cognitive Systems (*e.g.*, working memory)
RDoC Constructs

Represent the fundamental units of analysis

I) Included Constructs for which “a particular brain circuit or area could reasonably be specified”.

II) Attempted to keep list “tractable”, maintain a reasonable “grain size”

III) Constructs are based on neurobehavioral data.
Units of Analysis

✓ RDoC Constructs can be assessed by different classes of variables (units of analysis)

✓ Seven such classes have been specified:
  1. Genes
  2. Molecules
  3. Cells
  4. Neural circuits
  5. Physiology
  6. Behaviors
  7. Self-reports
## Constructs & Units -> RDoC Matrix

### Research Domain Criteria Matrix

<table>
<thead>
<tr>
<th>Domain</th>
<th>Units of Analysis</th>
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<tbody>
<tr>
<td>Construct</td>
<td>Genes</td>
</tr>
<tr>
<td></td>
<td>Molecules</td>
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<tr>
<td></td>
<td>Cells</td>
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<td>Paradigms</td>
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### Negative Valence Systems
- Acute threat ("fear")
- Potential threat ("anxiety")
- Sustained threat
- Loss
- Frustrative nonreward

### Positive Valence Systems
- Approach motivation
  - Reward valuation
  - Effort valuation / Willingness to work
## RDoC Matrix

### Negative Valence Systems Matrix Specifications

<table>
<thead>
<tr>
<th>Units of Analysis</th>
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<th>Paradigms</th>
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<tbody>
<tr>
<td>Construct: Acute Threat (&quot;Fear&quot;)</td>
<td>BDNF, 5HT/5HTRs, CRF, FKB5, GABAARs, Glutamate system, NMDARs, Opioid system, COMT, Cannabinoid system, Dopamine, DAT, Cam kinase, MAP kinase, PI-3 kinase, PKA, PKC, Acetylcholine, Norepinephrine, Strathmin, Pkap, TRBC5</td>
<td>NMDAR, Glutamate, Dopamine, Serotonin, BDNF, GABA, Cortisol/ Corticosterone, Endogenous cannabinoids, orexin, NPY, CRF family, FGF2, Oxytocin, Vasopressin, CCK, Neuropeptides, Neurosteroids</td>
<td>Neurons, Glia, Pyramidal cells, GABAergic cells</td>
<td>Central Nucleus, BasAmyg, LatAmyg, vPAG, dPAG, v-hippocampus (post), d-hippocampus (ant), latPFC/insula, vmPFC (ll), dmPFC (pl), OFC, Hypothalamus, dorsal ACC, rostral/vent ACC, ICMS, Medial Amyg, PAG, RPVM, Pons, autonomic nervous system, insular cortex, LC</td>
<td>Fear Potentiated Startle, Context Startle, Skin Conductance, Heart Rate, EMG, BP, Eye Tracking, Response accuracy, facial EMG, Respiration, pupillometry</td>
<td>Freezing, Response time, Avoidance, Response inhibition, Open field, Social approach, Analgesia, approach (early development), Risk assessment, Facial expressions</td>
<td>Fear survey schedule, BAI, STAI, SUDS, Fear Questionnaire, Trait Fear Inventory, Eilam Ethogram, Structured Diagnostic and Assessment scales, Albany Panic &amp; Phobia</td>
<td>Fear conditioning, viewing aversive pictures or films, emotional imagery</td>
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Our New NIMH-Funded RDoC Research Project
“Longitudinal Family/Molecular Genetic Study to Validate Research Domain Criteria”

PIs: Stephen V. Faraone and Stephen J. Glatt

U.S. DHHS/NIH/NIMH grant R01MH101519

Runs for five years
– From June 25, 2014 to May 31, 2019

IRB-approved and ramping up
Specific Aims

1. Are Constructs in the PVS Domain homogenous?
2. Are PVS Constructs familial?
3. Do PVS Constructs predict psychopathology and impairment?
4. Are PVS Constructs associated with genes?
   - Construct candidate genes
   - Genome-wide significant cross-disorder candidate genes
   - Cross-disorder polygenic scores
5. Track families and plan longitudinal follow-up
## Acknowledgments

### Co-Investigators

<table>
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<tr>
<th>Name</th>
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### Testing/Analysis/Support Team

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### Supporters

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<td>Gail DePalma</td>
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### Sponsors

- [Department of Health & Human Services](#)
- [National Institutes of Health](#)
- [National Institute of Mental Health](#)
How You Can Help

✧ This is a new and collaborative effort designed to benefit the research community at Upstate and beyond.

✧ Data and biomaterials will be banked for other scientists to study.

✧ We are now seeking families of unmedicated subjects (ages 6-12) for our study.
Exclusion Criteria

- Adopted children
- Major sensorimotor disabilities (e.g., deafness, blindness)
- Neurological conditions or a history of head injury and loss of consciousness > 10 min
- Inadequate command of the English language or otherwise unable to understand test directions and/or respond to questions
Study Costs and Benefits

✧ Approximately 2.5 hours per subject
✧ Flexible scheduling
✧ Parking/bus fare is reimbursed
✧ Snacks and beverages provided
✧ At completion, each individual receives a $50 honorarium
✧ CBCL results can be shared with child’s clinician
Advertisements

Brochure for Families

FAMILIES NEEDED FOR A RESEARCH STUDY ON CHILD BEHAVIOR

This study will take place in the Clinical Research Unit at Upstate Medical University.

**Location:**
Institute for Human Performance
505 Irving Ave.
Syracuse, NY 13210

**Principal Investigators:**
Stephen Faraone, PhD
Stephen Glatt, PhD

**If interested, please contact:**
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- or -

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Letter for Clinicians
How to Refer Potential Subjects

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