Research Domain Criteria (RDoC): Integrating genetics, imaging, & cognitive science to transform mental health diagnosis and treatment

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No Disclosures

NIH National Institute of Mental Health

Drug hunters' challenges in developing better treatments

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

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Int J Neuropsychopharmacol. 2010 Oct;13(9):1269-84. Epub 2010 Aug 18.

"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."

Precision Medicine in the Age of RDoC

Brain disorders? Precisely

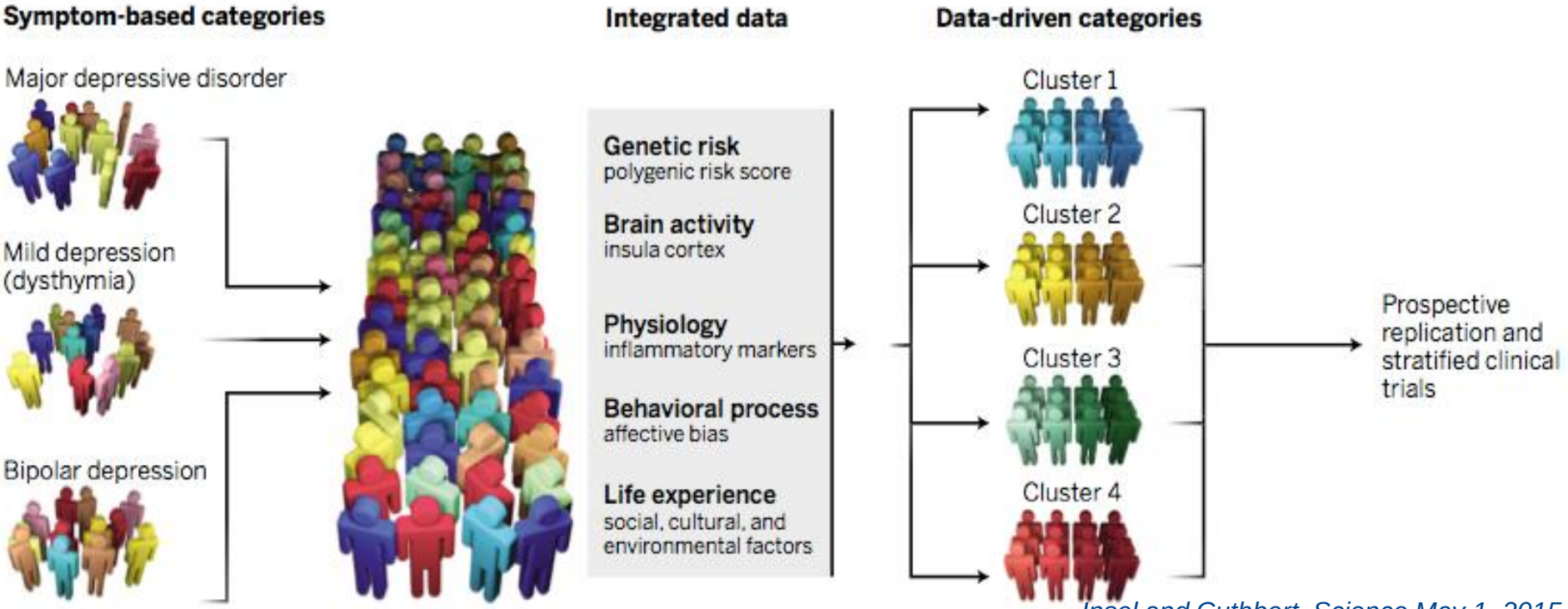
Precision medicine comes to psychiatry

Science

AAAS

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.



Insel and Cuthbert, Science May 1, 2015

Genesis of RDoC

- Current approaches: DSM (Diagnostic and Statistical Manual for Mental Disorders) and the ICD (International Classification of Diseases)
- For *research*, current approaches to psychiatric diagnosis are no longer optimal in the era of precision medicine.
- Diagnosis remains restricted to symptoms and signs.
- ***Problem: While sufficient for current clinical use, DSM/ICD categories also drive the entire research system (psychopathology, journals, trials, FDA).***

Toward the Future

- Changing viewpoints based on the concepts of modern research — neural, cognitive, and behavioral science.
- Shift the discovery paradigm from a diagnosis based purely on symptoms, to one based upon the relationships between neural systems, behavior/cognition, and symptoms.
- Experimental designs: studies based upon dimensions of functional systems rather than disease categories

The Overarching Goals of RDoC

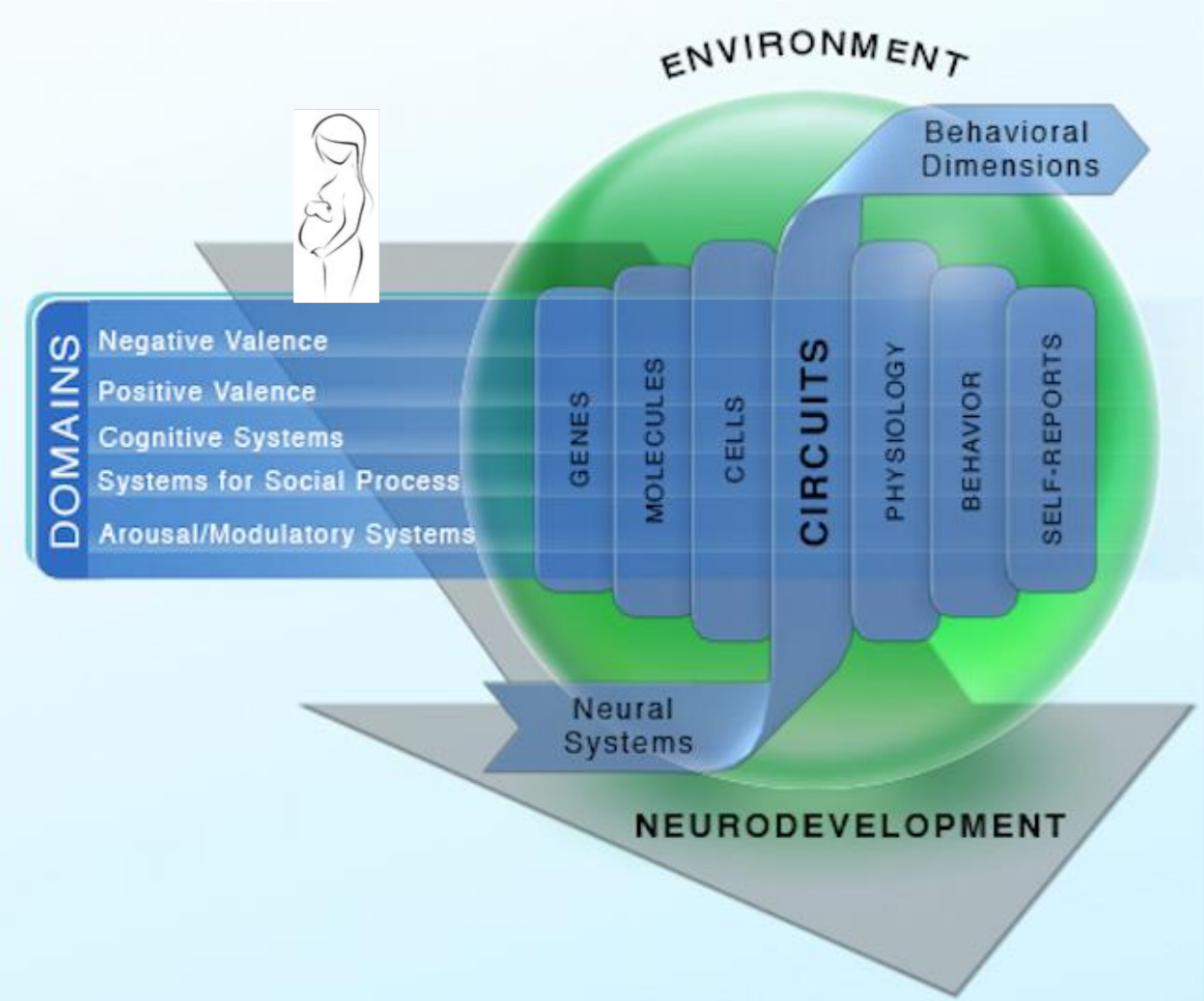
Develop, for research purposes, a framework for studying psychopathology based on dimensions of observable behavior and neurobiological measures.

- Identify 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

Exactly what *does* RDoC involve?

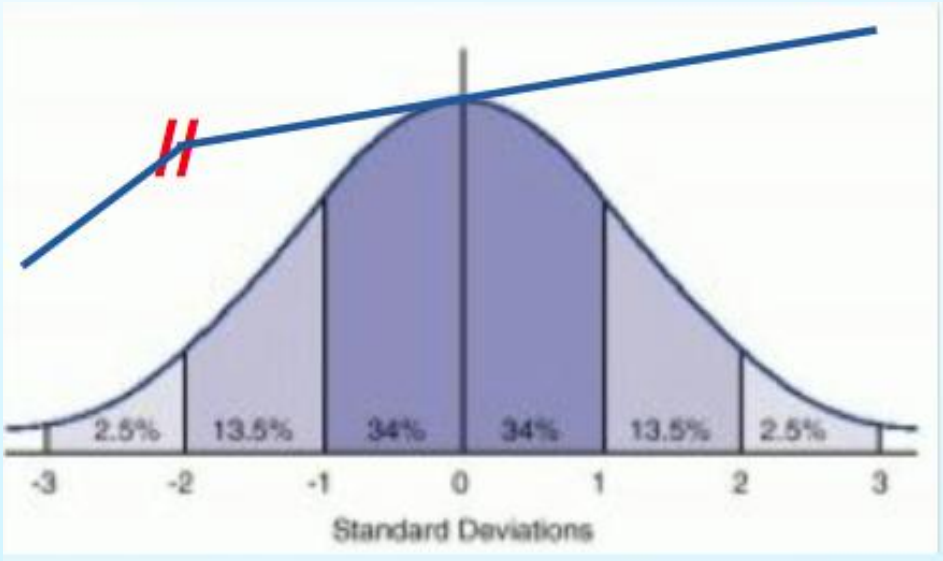
- Focused research initiative moving "toward a new classification system": study and validate trans-diagnostic, dimensional constructs
- Goals:
  1) Deeper understanding of psychological & biological systems related to mental illness ➜
  2) New biomarkers & biosignatures ➜
  3) More homogeneous groupings for new intervention development

The RDoC Framework: Four dimensions



The 5 RDoC Domains: Background

- Translational perspective:
- 1) Start by defining fundamental behavioral/cognitive functions and their implementing neural systems
- 2) Mental disorders as deviations along *normative* dimensions of functioning



The 5 RDoC Domains: Provenance

- Negative Valence: Fear, avoidance, loss
- Positive Valence: reward, pleasure
- Cognitive Systems: A long tradition of study
- Social Processes: Increasingly studied, relevance for human disorders (autism, schizophrenia, Borderline Personality Disorder)
- Arousal/regulatory systems: Important for activation (e.g., alpha-7 nicotinic receptors), sleep, circadian rhythms

RDoC Matrix: Integrative Framework

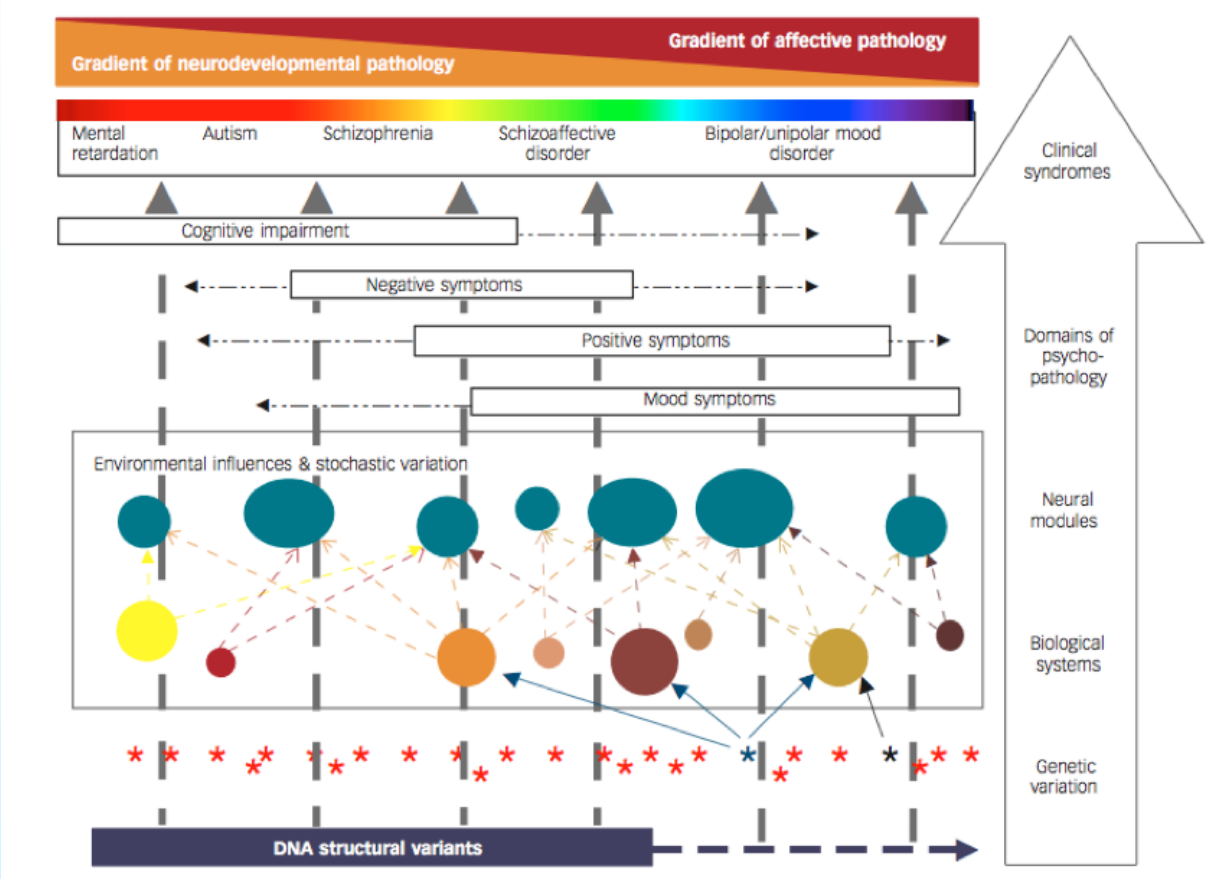
v. 5.1, 07/15/2012	RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
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								
Affiliation/attachment								
Social Communication								
Perception/Understanding of Self								
Perception/Understanding of Others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

[Symptoms]

- Altered Stress Reactivity
- Problems with emotion regulation
- Lack of pleasure in usual activities
- Lack of energy for productive tasks
- Impulse control
- Problems with executive function
- Social withdrawal
- Poor relationships
- Problems with arousal-modulating systems
- Sleep problems

Contemporaneous Dimensional Approaches to Diagnosis

"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)



High Priority: Experimental Medicine, Fast-Fail Trials

Test the hypothesis about the drug's mechanism of action:

1. Show that the drug reaches the target, establish optimal dose (receptor occupancy)
2. Show that the drug causes a change in relevant brain activity or mental process in the hypothesized direction (mechanism of action)
3. Correlate change in mechanism with change in clinical signal (proof of concept)

RDoC's role in clinical trials

RDoC considerations for early phase clinical trials:

1. Focus on a novel mechanism relevant to a clinical problem regardless of DSM diagnosis (e.g., anhedonia, working memory)
2. Enroll patients based on deficits in the mechanism, not DSM diagnosis
3. Both the experimental medicine paradigm and RDoC require trial outcomes that reflect the target mechanism

Fundamental regulatory challenge to endorsing an alternative to DSM classification of psychiatric illness

- Need to provide a rationale for alternative approach
- True whether
  - Phenomenological domain
  - Biomarker-defined subgroup
  - RDoC construct
- Key regulatory issue: Pseudo-Specificity

Regulatory agencies initial rejection of claim as "pseudo-specific" might be considered a "straw man" position

- Objection may be overcome with arguments and data to show validity and value of targeting a particular domain or biomarker-defined subgroup

Thomas Laughgren, MD (former FDA Psychiatry head), ISCTM 2014

Example: FAST-MAS, An RDoC-inspired Clinical Trial

Kappa opioid receptor antagonist for Anhedonia, a PoC trial

PI: Andrew Krystal, MD, Duke University

RDoC Study Design Features:

- **Inclusion:** enroll patients based on anhedonia measure
  - DSM diagnoses across the mood and anxiety spectrum
- **Outcomes:**
  - Capture multiple aspects of anhedonia (anticipation, experience, motivation)
  - Use objective measures of brain function (fMRI, behavioral task performance)
- **Regulatory path:** include traditional clinical depression and anxiety measures to explore correlations

FAST-MAS Outcome Measures (Phase IIa Trial)

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Choice of Outcomes: Reverse of Traditional Approach

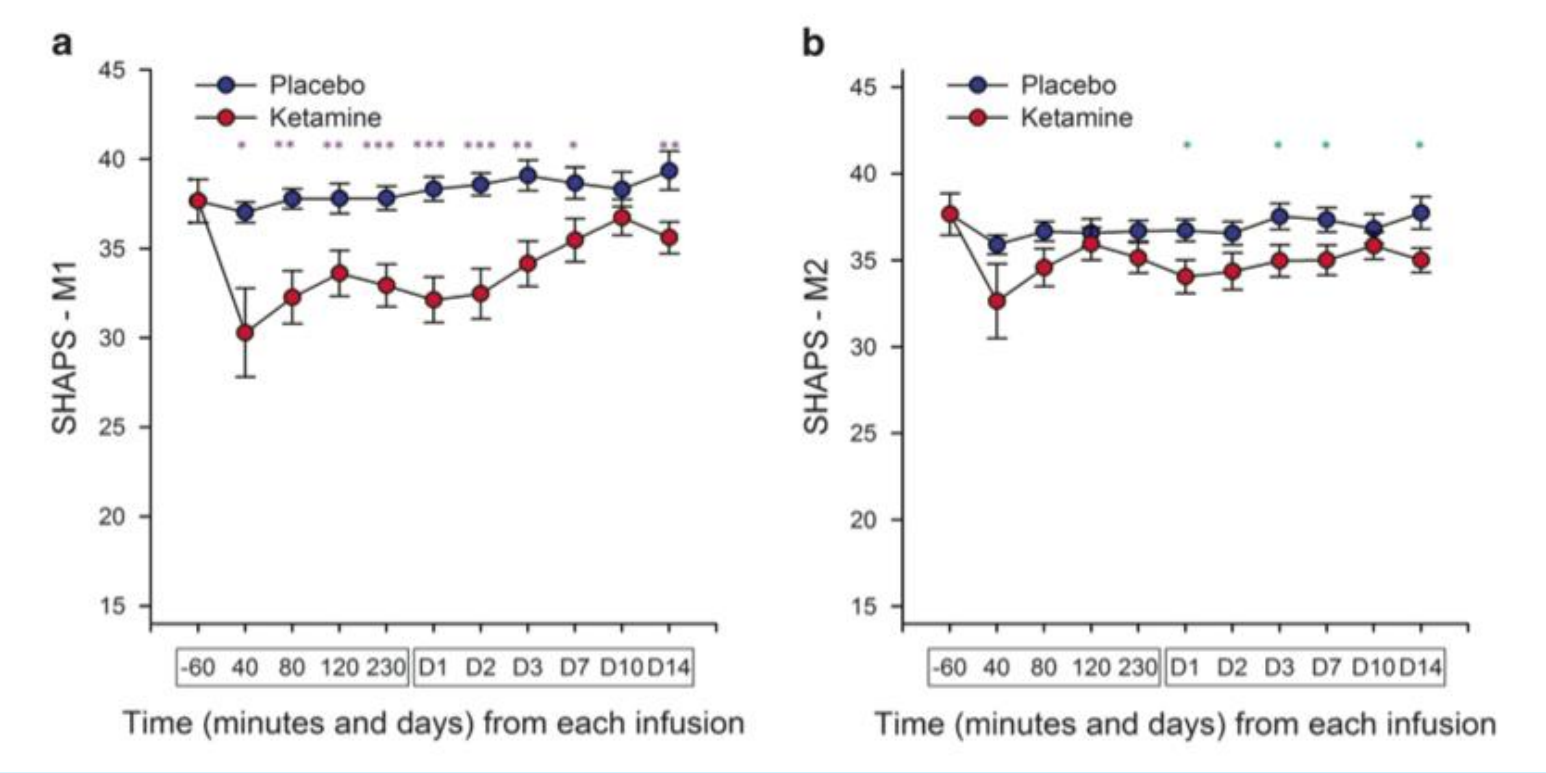
~ A. Krystal, ISCTM, 2013

- Primary
  - Circuit measure of expected effect of drug on the brain Primary outcome is measure of engaging circuitry related to hedonic experience/response
- Key Secondary
  - Behavioral intermediate phenotype assessment (more closely linked to neural circuitry than clinical outcome but also linked to clinical outcome)
    - Probabilistic Reward Task assesses capacity to learn based on reward
  - Clinical Outcome: Measured with a clinical scale that has been demonstrated to be sensitive to treatment effects in depressed patients treated SSRI/SNRI
    - Snaith-Hamilton Pleasure Scale (SHAPS)
- Exploratory
  - Additional circuit measure
    - QEEG measure of cingulate activity
  - Additional Behavioral Measure
    - Effort Expenditure for Rewards Task assesses the degree to which one is motivated by reward as demonstrated by effort
  - Additional Self-report scale
    - Temporal Experience of Pleasure Scale (TEPS)
  - HAM-D, HAM-A

Ketamine in treatment-resistant bipolar depression: A single ketamine dose rapidly reduces anhedonia

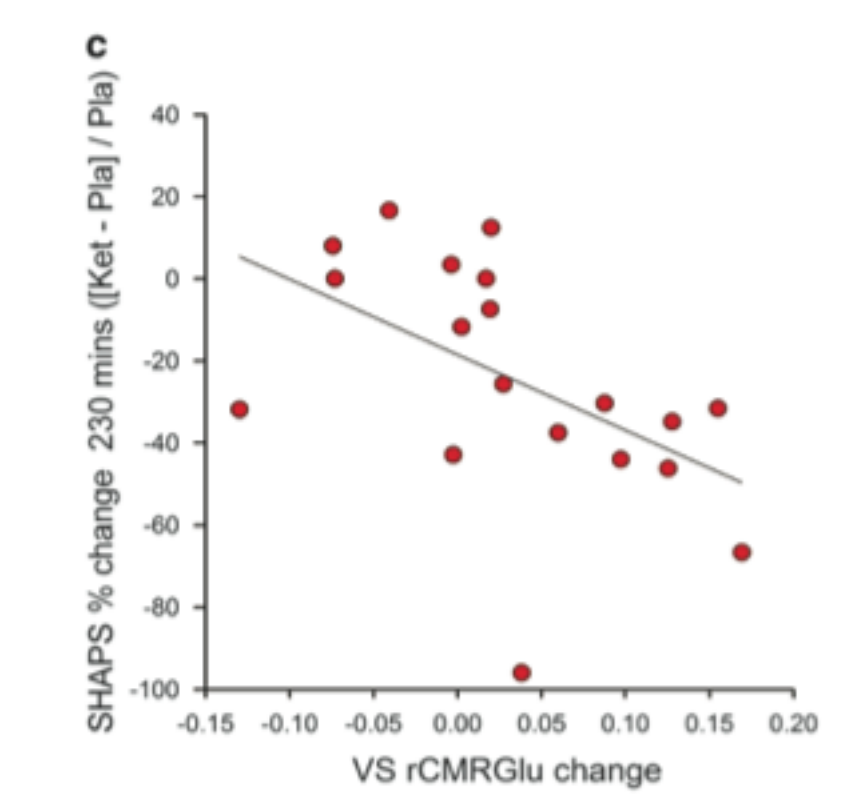
Change in SHAPS score after ketamine infusion

Change in SHAPS score, regressing out MADRS

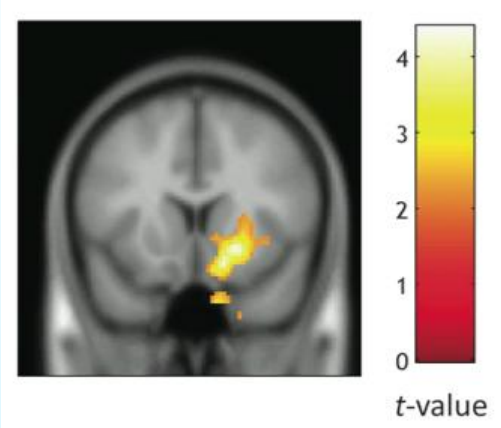


Lally, … & Zarate, *Trans Psychiatry* 2014

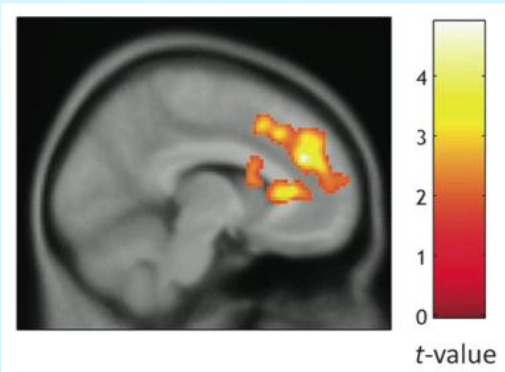
Mechanism: Increased glucose metabolism in ventral striatum ➔ Larger decreases in anhedonia scores



Ventral striatum



Dorsal anterior cingulate



Lally, … & Zarate, *Trans Psychiatry* 2014

RDoC: Summary/Conclusions

- Flexible **framework** for research
- New approaches to experimental-medicine trials
- The future: information commons, data sharing to identify subtypes that form homogeneous groups for treatment
- Toward precision treatments for mental disorders, consistent with other areas of medicine