Clinical Point of View: Current Practices, Challenges, and Needs

Biomed21

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26 June 2017

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NIMH: Clinical Challenges to New Treatments

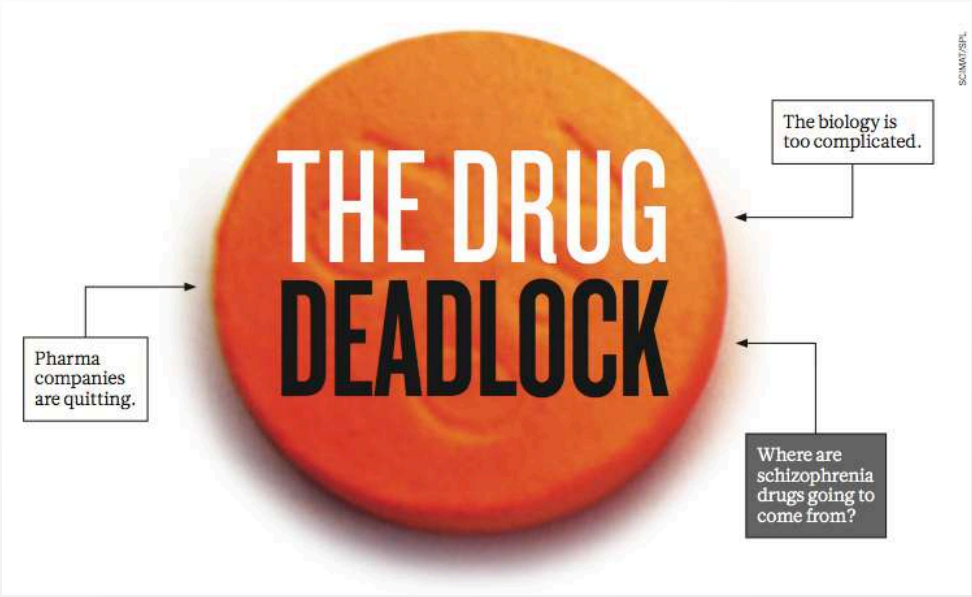
- (1) Clinical trials approaches
- (2) Clinical phenotypes
- (3) Messaging

The standard approach to drug development has not worked

1. Hypothesize a link between a mechanism and a disorder (schizophrenia, depression)
2. Propose a compound that might impact the mechanism, & test in pre-clinical models
3. Design a trial in humans: estimated dosing, small sample size, efficacy as primary outcome
4. **Negative results are typically uninterpretable:**
5. Small N; wrong dose; wrong patient population; wrong hypothesis? ~~ no way to know
6. Positive results are misleading, often fail to replicate
7. Phase II failure = $2-4M and 5 years lost

New treatments in the pipeline are rare

G. Miller, *Science*, *329*: 481-596, July 30, 2010



A. Abbott, *Nature*, *468*: 158-159, November, 2010

NIMH Priority: Experimental Medicine, Fast-Fail Trials

Fast-Fail: Learn ***why*** a proof-of-concept trial failed, to move forward in a systematic way

- Move rapidly into humans
- Focus on Phases 0 – 2a, and on mechanisms of action
- First step: demonstrate target engagement and mechanisms rather than efficacy: intervention as a probe
- “Wins”: relationship of target engagement to early signs of efficacy

Steps for Fast-Fail Trials

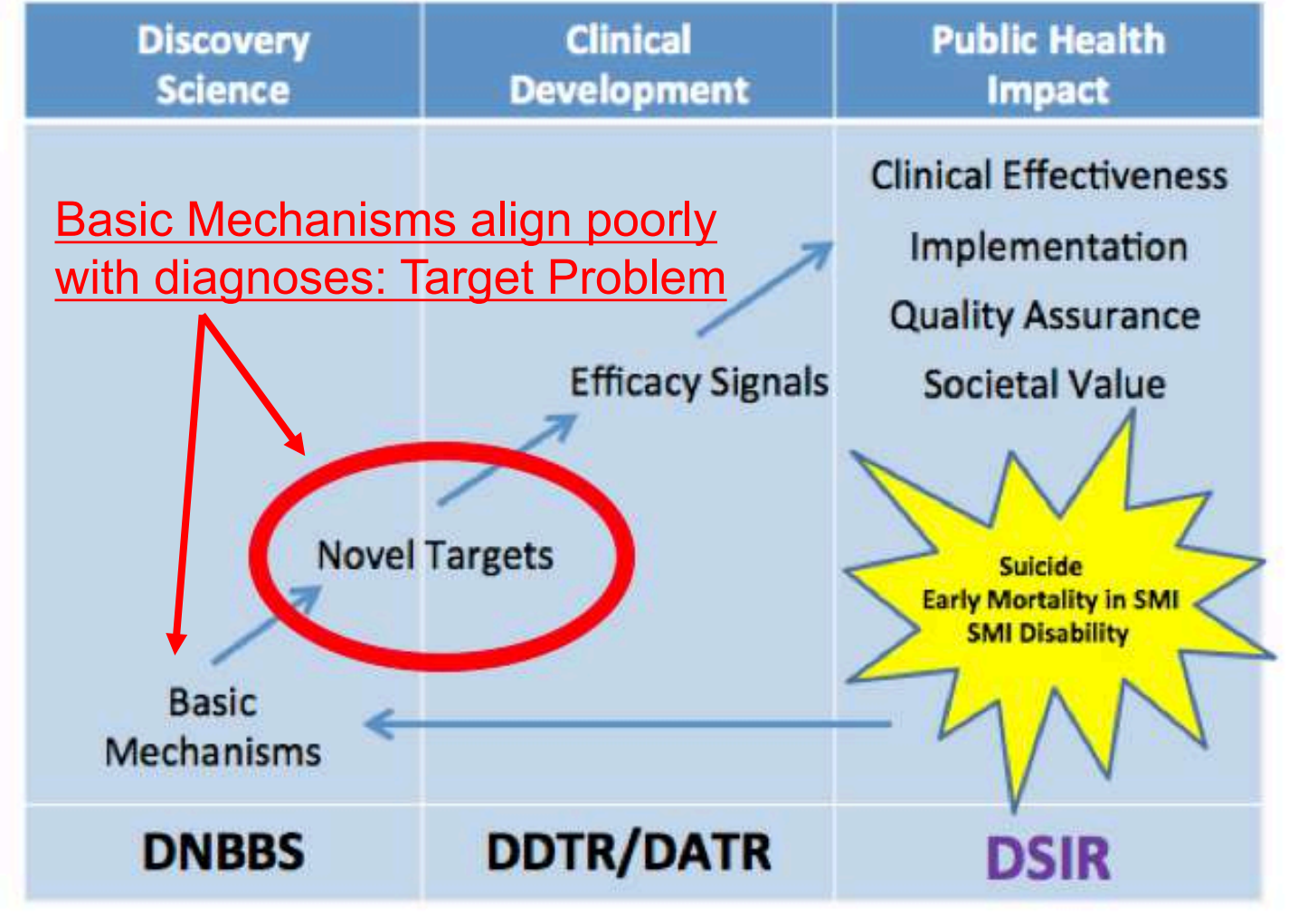
Test a hypothesis about the treatment's mechanism of action:

1. Show that the treatment reaches the target, establish optimal dose (e.g., receptor occupancy, # of sessions)
2. Show that the treatment 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)

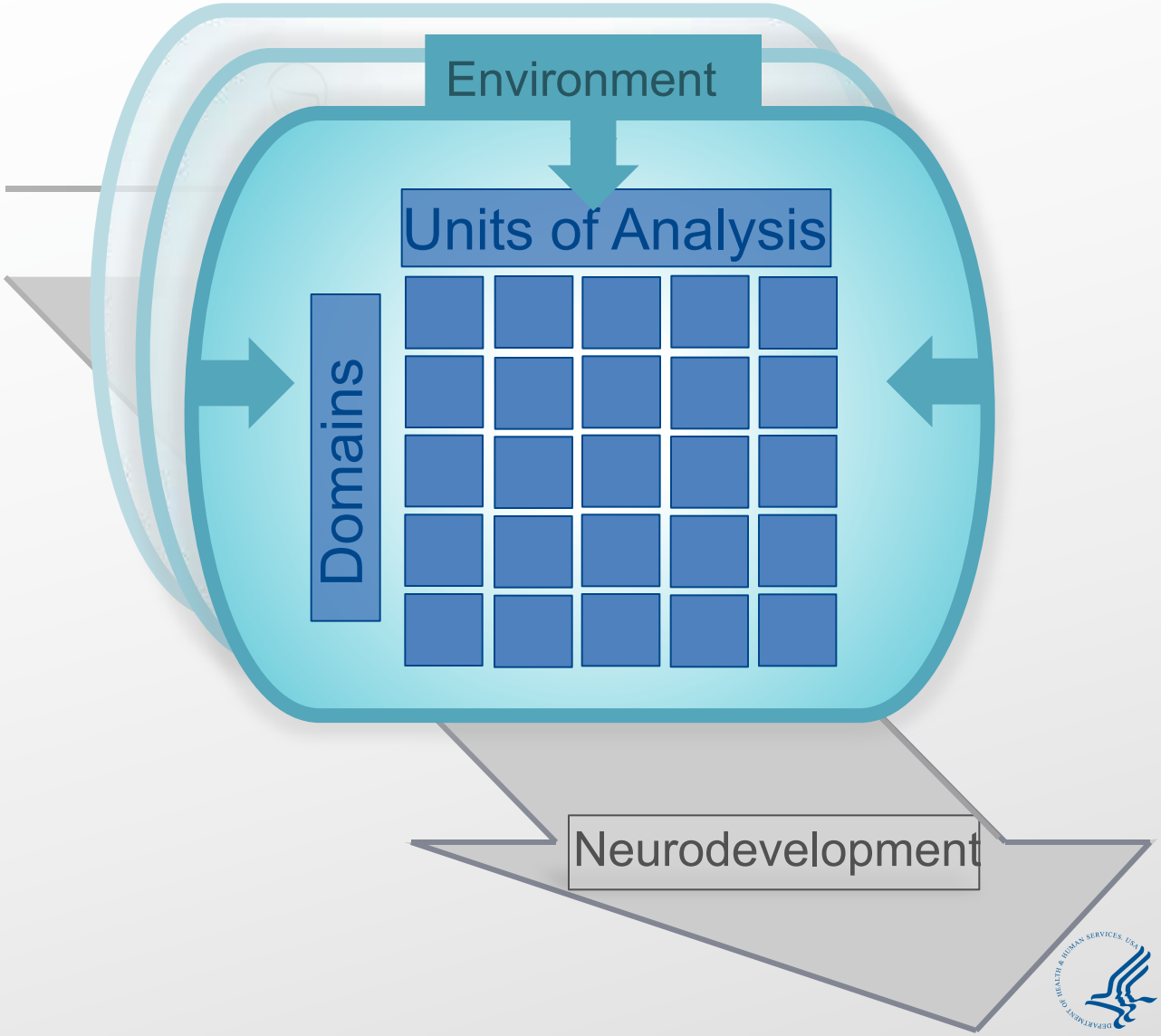
2. Challenges with clinical phenotypes

- Problems with symptom-based (DSM, ICD) systems for contemporary research
- Disorders are broad syndromes; heterogeneity, co-morbidity
- Not specific disease entities: but, have become reified
- Almost all disorders are dimensional in severity
- ***Problem: Diagnostic categories drive the entire research system (research grants, journals, trials, regulatory agencies)***

NIMH Intervention Development Pipeline



Research Domain Criteria (RDoC) Framework: Four Components



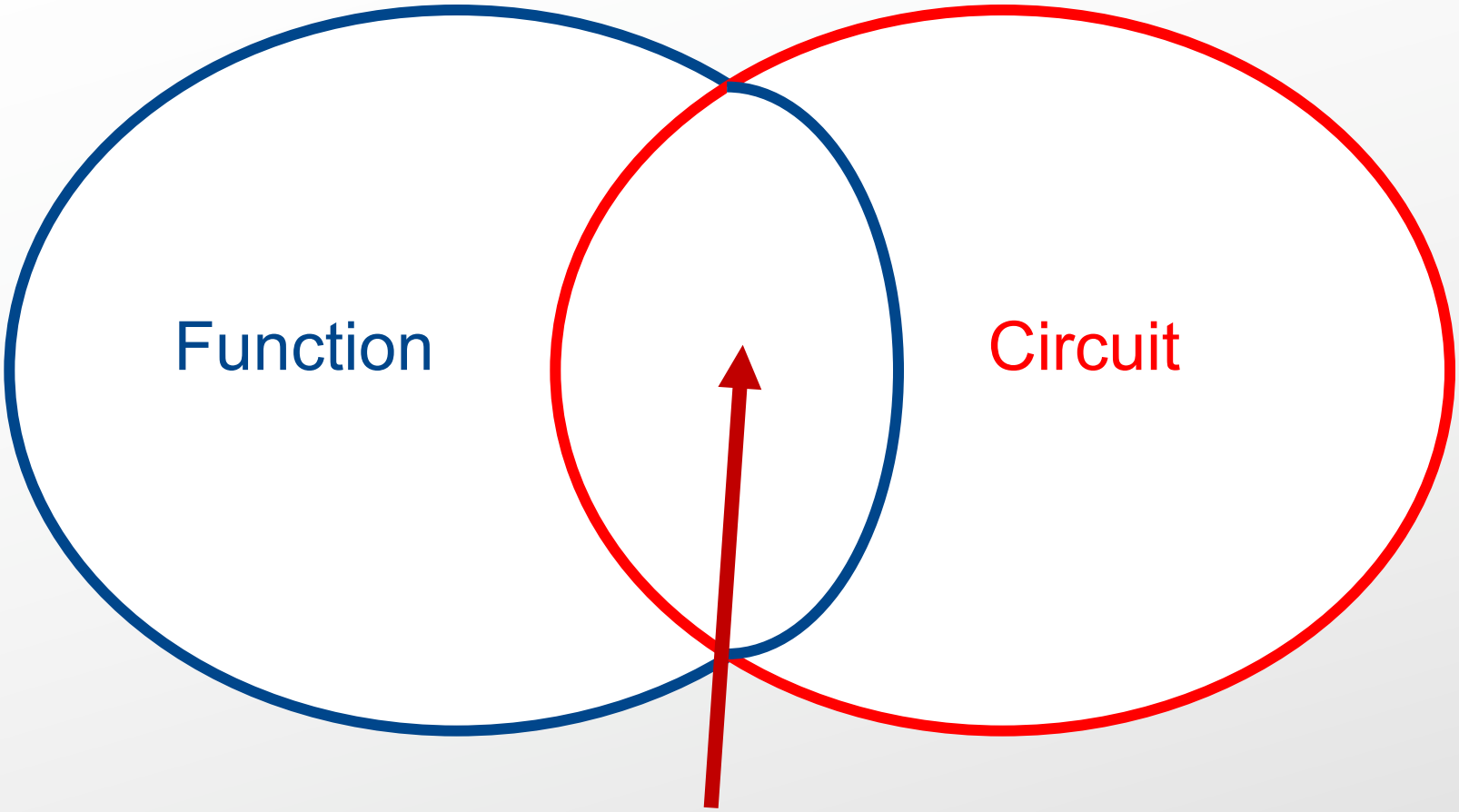
RDoC Matrix: Integrative Framework Domains/Constructs X Units of Analysis

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								

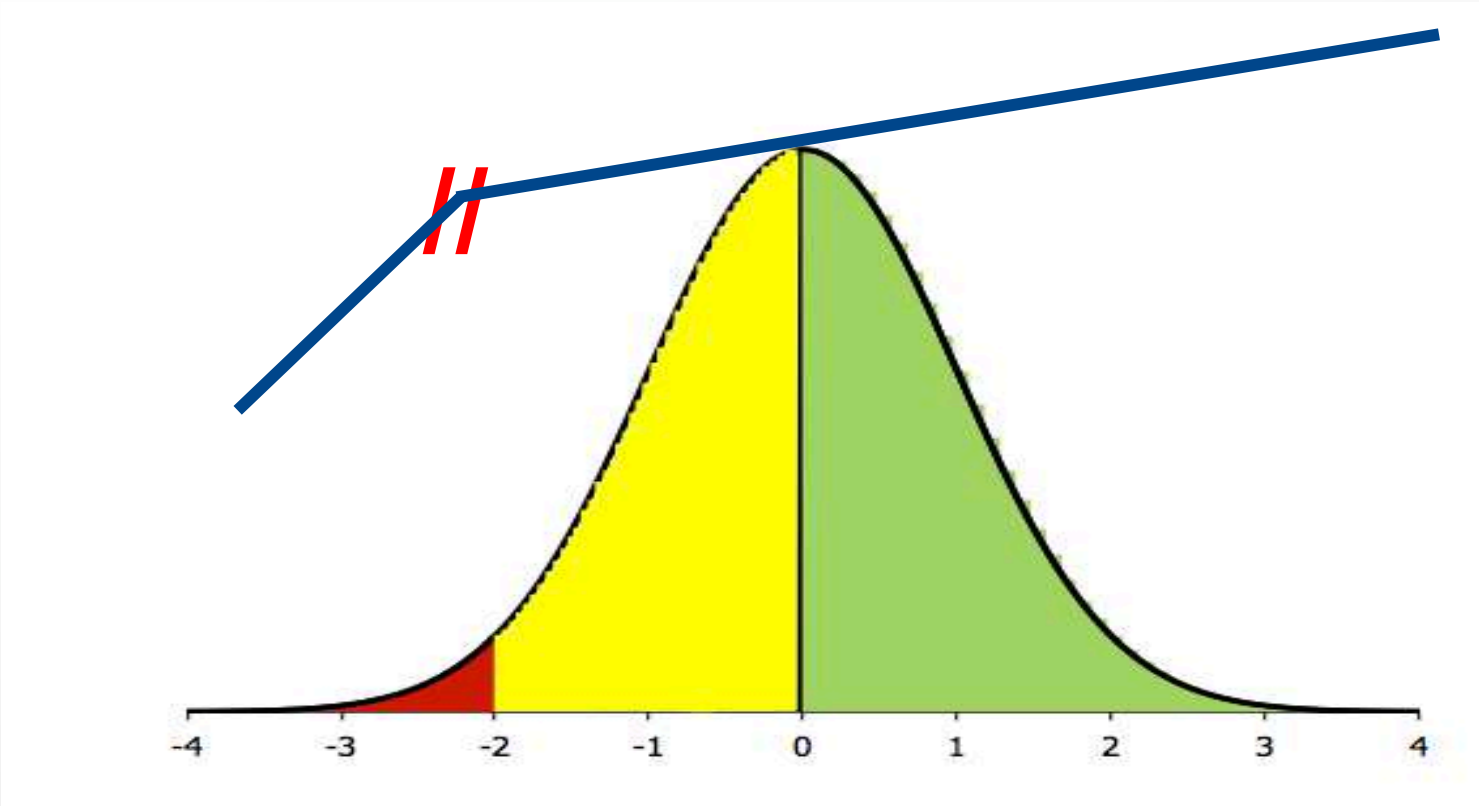
[Symptoms]

- Altered Stress Reactivity
- 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

Constructs: Intersection of “observable behavior and neurobiological measures”



Complex Trait Model (full distribution)



Level of Functioning

Where does RDoC fit into 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

Example: R61MH110540, Sanjay Mathew, PI

- AZD6765 (lanicemine, NMDAR antagonist) as Proof-of-Concept to reduce hyperarousal in post-traumatic stress
- Enrollment criteria: (1) severe PTSD symptoms (may not be PTSD dx), (2) high anxiety-potentiated startle (APS) on NPU test (Neutral, Predictable, Unpredictable contexts)
- Target engagement: Δ in γ-band EEG following drug
- Reduction in APS from visit 1 to 3 = Go/no-go decision for larger trial examining clinical benefit

Similar approaches for other areas

BRAIN
A JOURNAL OF NEUROLOGY

"It is time for a neurological RDoC
(*Rowe*, Brain, *138*, 2015)

- Parkinson's, ALS-frontotemporal dementia, Alzheimer's

Neurological disease models made clear

- " … we would also encourage investigators to discuss their findings within the framework of the NIMH's Research Domain Criteria initiative…" (*21*, 2015)
- NIAAA (alcoholism): "AA-RDoC" (focus on outcome measures for clinical trials) (Litten, … & Koob, *Alcoholism: Clin & Exp Res, 2015*)

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

3. Messaging

"… NIMH will be re-orienting its research away from DSM categories."

Search: 'Insel transforming diagnosis'

Messaging challenges (1): post hoc fallacy

NATURE | NEWS

US mental-health agency's push for basic research has slashed support for clinical trials

Analysis reveals that the number of clinical trials funded by the National Institute of Mental Health has fallen by 45% since the agency began to focus on the biological roots of disease.

Sara Reardon

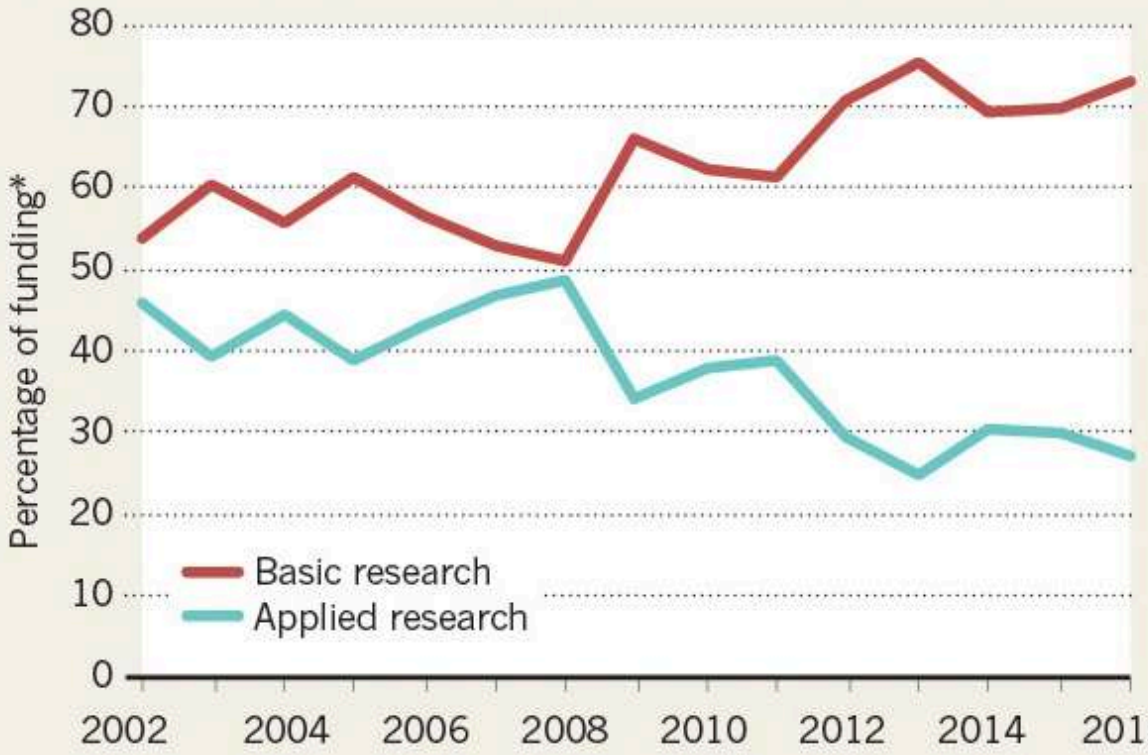
13 June 2017

Messaging challenges (2): Misunderstanding

RETHINKING MENTAL-HEALTH STUDIES

BACK TO BASICS

The NIMH has begun to emphasize basic research on the biological mechanisms underlying mental disorders, rather than applied research on specific illnesses.



Messaging and encouraging change

- Spend time to create simple (tweetable?) messages
- Get thought leaders on board before launch
- Emphasize continuity with current approaches
- Prioritize crosswalks with current practices, even if this means phasing in the main goals
- Try to create/develop early successes to use as exemplars
- Be prepared for sustained engagement with critics