Agenda

• Re-examining Our Frameworks
• A Framework for the Future
• How Can We Get There?
Agenda

• Re-examining Our Frameworks
  • Theory-Driven vs Data-Driven
    • Diagnoses \(\rightarrow\) Symptoms

• A Framework for the Future

• How Can We Get There?
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Andrew T Drysdale1-3, Logan Grosenick4,5, Jonathan Downar6, Katharine Dunlop6, Farrokh Mansouri6, Yue Meng1, Robert N Fetcho1, Benjamin Zebley7, Desmond J Oathes8, Amit Etkin9,10, Alan F Schatzberg9, Keith Sudheimer9, Jennifer Keller9, Helen S Mayberg11, Faith M Gunning2,12, George S Alexopoulos2,12, Michael D Fox13, Alvaro Pascual-Leone13, Henning U Voss14, BJ Casey15, Marc J Dubin1,2 & Conor Liston1-3
Patterns of Resting State Connectivity

Drysdale et al., *Nature Medicine*, 2017
Clustering Patients Based on Connectivity

Dyrdale et al., Nature Medicine, 2017
Subtypes Differ in Responsivity to Prefrontal Cortex Repetitive Transcranial Magnetic Stimulation

Drysdale et al., *Nature Medicine*, 2017
Theory-Driven Approaches to Clinical Psychiatry

JAMA Psychiatry | Original Investigation

Association of Neural and Emotional Impacts of Reward Prediction Errors With Major Depression

Robb B. Rutledge, PhD; Michael Moutoussis, PhD; Peter Smittenaar, PhD; Peter Zeidman, PhD; Tanja Taylor, PhD; Louise Hryniewicz, BSc; Jordan Lam, BSc; Nikolina Skandali, MSc; Jenifer Z. Siegel, MSc; Olga T. Ousdal, MD, PhD; Gita Prabhu, PhD; Peter Dayan, PhD; Peter Fonagy, PhD; Raymond J. Dolan, FRS, MD
Breaking Down Behavior

Happiness(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j} CR_j + w_2 \sum_{j=1}^{t} \gamma^{t-j} EV_j + w_3 \sum_{j=1}^{t} \gamma^{t-j} RPE_j

- baseline happiness
- past rewards
- expected values
- reward prediction error
Breaking Down Behavior

ventral striatum

medial prefrontal cortex

Rutledge et al., *JAMA Psychiatry*, 2017
Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies

Hanna Keren, Ph.D., Georgia O’Callaghan, Ph.D., Pablo Vidal-Ribas, M.Sc., George A. Buzzell, Ph.D., Melissa A. Brotman, Ph.D., Ellen Leibenluft, M.D., Pedro M. Pan, M.D., Ph.D., Liana Meffert, B.Sc., Ariela Kaiser, B.A., Selina Wolke, M.Sc., Daniel S. Pine, M.D., Argyris Stringaris, M.D., Ph.D.

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Reward Processing in Depression
Combining Theory- and Data-Driven Approaches

Symptom-based categories:
- Major depressive disorder
- Mild depression (dysthymia)
- Bipolar depression

Integrated data:
- Genetic risk
  - polygenic risk score
- Brain activity
  - insula cortex
- Physiology
  - inflammatory markers
- Behavioral process
  - affective bias
- Life experience
  - social, cultural, and environmental factors

Data-driven categories:
- Cluster 1
- Cluster 2
- Cluster 3
- Cluster 4

Prospective replication and stratified clinical trials
Agenda

• Re-examining Our Frameworks
  • Theory-Driven vs Data-Driven
  • Diagnoses → Symptoms

• A Framework for the Future

• How Can We Get There?
Traditional Diagnostic Framework

Disease

Depression

Symptoms

Mood, Energy, Concentration, etc.
Research Domain Criteria (RDoC) Framework

Disease

Transdiagnostic Phenotypes

Symptoms

Depression

Mood, Energy, Concentration, etc.
Diagnosis as Outcome

Disease

Transdiagnostic Phenotypes

Symptoms

RDoC
Research Domain Criteria Initiative

Diagnosis

Mood, Energy, Concentration, etc.

Depression
Agenda

• Re-examining Our Frameworks
• A Framework for the Future
• How Can We Get There?
A Bayesian Approach To Precision Psychiatry

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A Novel Framework for Improving Psychiatric Diagnostic Nosology

Shelly B. Flagel, Daniel S. Pine, Susanne E. Ahmari, Michael B. First, Karl J. Friston, Christoph Mathys, A. David Redish, Katharina Schmack, Jordan W. Smoller, and Anita Thapar
Diagnoses as Observations

- Causes
- Hidden (Physiological) States
- Latent Constructs
- DSM Diagnoses

Causation

Interpretation from observation
Integrating RDoC

Causation

Interpretation from observation

Causes

Hidden (Physiological) States

Latent Constructs

RDOC Behaviors

DSM Diagnoses
Bayesian Approach

Causes

\( C = C_1, C_2, \ldots C_{(Nc)} \)  
\( T(t) = T_1(t), T_2(t), \ldots T_{(Nt)}(t) \)

Hidden (Physiological) States

\( X(t) = X_1(t), X_2(t), \ldots X_{(Nt)}(t) \)  
\( X(t+1) = f(X(t), C, T(t)) \)

Latent Constructs

\( LV(t) = LV_1(t), LV_2(t), \ldots LV_{(NLV)}(t) \)  
\( LV(t) = g(X(t)) \)

RDoC

M = instrumental measurements, brain scans, tests, ...  
S = symptoms

DSM Diagnoses & Clinical Course

D = diagnoses  
P = prognoses

\( p(S \mid LV) \)  
\( p(M \mid LV) \)  
\( p(LV \mid P, S, D, M) \)  
\( p(D \mid LV) \)  
\( p(P \mid LV) \)
Example: Obsessive-Compulsive Disorder

Causes

Hippocampal Size, Hip; Time since Trauma, T(t)

Hidden (Physiological) States

Altered Neural Plasticity, PL; Functional Connectivity, FC

Latent Constructs

Deficits in extinction, Ex; cognitive control, CC

\[ p(\text{Ex}(t)) \mid \text{Hip}, T(t), PL, FC; p(\text{CC}(t)) \mid T(t), PL, FC \]

Diagnosis

\[ p(\text{PTSD}) \mid CC, Ex \]

Prognosis

\[ p(\text{Chronic}) \]

\[ p(\text{Rx Response}) \]

Symptoms

\[ p(\text{intrusive}) \]

\[ p(\text{reactivity}) \]

\[ p(\text{nightmares}) \]

Mental Health RDoC

\( p(S \mid LV) \)

\( p(RDoC \mid LV) \)
Agenda

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Integrating RDoC

Causes

Hidden (Physiological) States

Latent Constructs

RDOC Behaviors

DSM Diagnoses; Clinical Course

Interpretation from observation
All of Us

• The NIH All of Us Research Program is an historic effort to advance precision medicine by collecting and studying data from one million or more people living in the United States

https://allofus.nih.gov
NIMH and *All of Us*: New Tasks and Measures
NIMH and *All of Us*: New Tasks and Measures

• The *All of Us* cohort provides a variety of other data (genetics, health records, scores on self-report measures) that could be **combined with behavioral tasks** to assess the utility of psychological constructs.

• In line with this goal, NIMH is collaborating with *All of Us* to develop and deploy behavioral tasks focused on:
  • emotion identification;
  • sustained attention;
  • reward responsiveness/reward learning;
  • risky decision-making; and,
  • response inhibition.
NIMH and *All of Us*: Advancing Computational Psychiatry

- **Data-driven Validation**: Test the relationships between and within RDoC domains/constructs
- **Theory-driven Computational Phenotypes**: Develop parameterized, mathematically formalized behavioral descriptions and associated tests and measures
The All of Us cohort enables **testing and validating psychological constructs** with very large samples.

In line with this goal, NIMH has launched several funding opportunities, focused on:

- using computational approaches to test the validity of constructs in the NIMH Research Domain Criteria (RDoC) matrix ([PAR-21-263](#))
- applying computational approaches to develop behavioral assays across mental-health relevant domains of function ([PAR-21-264](#))
- developing and optimizing tasks and measures for constructs pertaining to functional aspects of behavior or cognitive/affective processes ([PAR-18-930](#))
NIMH Vision and Mission

**VISION**

NIMH envisions a world in which mental illnesses are prevented and cured.

**MISSION**

To transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.
Questions