NIMH Updates and Precision Medicine Activities

ASCP Annual Meeting
May 30, 2019
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Head, RDoC Unit, NIMH
Disclosure of Affiliations

No conflicts of interest or disclosures
Agenda

- NIH and NIMH Updates
- NIMH Precision Medicine Activities and Priorities
NIMH Vision & 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.
Appropriations Update

- On May 8, the House Appropriations Committee advanced the FY 2020 Labor, Health and Human Services, Education, and Related Agencies funding bill.

- The bill includes:
  - $99 billion for HHS
  - $41.1 billion for NIH
  - $1.89 billion for NIMH

- The bill continues to support several research initiatives, including:
  - $3.2 billion for HIV/AIDS research
  - $2.4 billion for Alzheimer’s disease research
  - $500 million for the All of Us precision medicine research initiative
  - $411 million for the Brain Research through Application of Innovative Neurotechnologies (BRAIN) initiative
  - $25 million for firearm injury and mortality prevention research
NIMH Budget Update

NIMH Applications, Awards, and Success Rates for Research Project Grants

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Application</th>
<th>Direct Awards</th>
<th>Cures Awards</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>2,885</td>
<td>1,530</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>2015</td>
<td>2,545</td>
<td>1,280</td>
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<td>20%</td>
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<tr>
<td>2016</td>
<td>2,770</td>
<td>1,450</td>
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<td>23%</td>
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<td>2017</td>
<td>2,890</td>
<td>1,530</td>
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<td>21%</td>
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<tr>
<td>2018</td>
<td>2,815</td>
<td>1,460</td>
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<td>23%</td>
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<tr>
<td>2019</td>
<td>2,930</td>
<td>1,570</td>
<td></td>
<td>26%</td>
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</table>
NIMH Budget in Appropriated Dollars and FY 2000 Dollars

Dollars (Millions)

Fiscal Year


Appropriation
Appropriation in 2000 Dollars
• 5th annual BRAIN Investigators Meeting
  • Over 1,500 BRAIN Initiative awardees, representatives, and investigators

• Ongoing BRAIN 2.0 Advisory Committee to the Director (ACD) meetings and public feedback continue to guide the refresh of *BRAIN 2025: A Scientific Vision*

• The ACD Working Group on BRAIN 2.0 Neuroethics Subgroup welcomes public comment on findings and analysis detailed in the *BRAIN Initiative Neuroethics Roadmap*
Translating CNS Science to Drugs: The Pipeline Problem

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Development</th>
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<tbody>
<tr>
<td>Target ID</td>
<td>IND</td>
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<tr>
<td>Target to Hit</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Hit to Lead</td>
<td>Phase 2</td>
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<tr>
<td>Lead Optim.</td>
<td>Phase 3</td>
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<tr>
<td>Pre-Clinical</td>
<td>Market</td>
</tr>
</tbody>
</table>

- **6 years**
  - Success rate < 1%
  - Success rate: 0-<5%*

**Total cost >$2B & Rising**

*No novel schizophrenia or depression target taken through process*
If >90% will fail, the path to success is: fail fast and fail often

- Move quickly into humans
- Focus on Phase 0 – Phase 2a
- Focus on target engagement
- Require replication
- Precompetitive partnerships
- Share data – failures must be public
Why Precision Psychiatry? ~ Changing perspectives on mental disorders

• Traditional disorders: Syndromes
• Heterogeneity, co-morbidity, over-specification
• Marked advances in understanding:
  • (1) Major brain circuits ….
  • (2) And functions they implement (fear, reward, memory)
• Instead of continuing with symptom-based approaches…
• Can we understand mental disorders as deviations from normal functioning of behavioral/brain systems?
• Research Domain Criteria (RDoC): An implementation strategy
RDoC: Continually Evolving Framework
Precision Medicine for Psychiatry: An International Effort

The new field of ‘precision psychiatry’

Brisa S. Fernandes, Leanne M. Williams, Johann Steiner, Marion Leboyer, André F. Carvalho, and Michael Berk

BMC Medicine

OPINION

CrossMark

NIH
National Institute of Mental Health
A Possible Strategy Agnostic to Dx

• Prioritize Targets
  ■ Neuroscience evidence of effects on brain circuits
  ■ “Tool” compounds available that will test the function of target in the human brain
  ■ If “functionated” then explore therapeutic potential

• Expand Partnerships with industry to access compounds that have desired properties for testing effects of quantitatively determined degrees of target engagement
Elements of “Functionating” Strategy

• **Compound Characteristics**: Data on target engagement (e.g., PET ligand), off target effects, and strategies for assessing target effects on circuits

• **Circuit Biology**: Evidence that the specific molecular target modifies a clinically meaningful circuit

• **Functional Behavior**: Measurement of functional behavior for a construct related to the circuit
(1) Clinical trials: target engagement, experimental medicine

Enroll patients based on measurable impairment in a specific mechanism (e.g., excessive fear, working memory deficit, effort valuation): often transdiagnostic

Outcome measures based on change in these functions

(2) More emphasis on (quantifiable) functioning than (self-reported) symptoms

E.g., EMA and FDA approval for cognition as an indication in depression (following the same for schizophrenia)
NIMH FAST-Fail Trials (FAST)

- FAST-AS: Autism Spectrum
  - EEG validation and proof-of-mechanism study of a GABA-A subtype selective partial agonist in adults with ASD.

- FAST-MAS: Mood and Anxiety Spectrum
  - Eight-week KOR antagonist Phase IIa study to assess key neural circuitry related to hedonic response.

- FAST-PS: Psychotic Spectrum
  - Study to evaluate potential imaging biomarkers, using a ketamine challenge procedure, to assess mGluR2/3 target engagement in the brain.
Developing Tasks & Measures

• NIMH NAMHC “Tasks and Measures” workshop, 2016

• FOA for developing & optimizing RDoC tasks:

• FOA for computational approaches to validate dimensional constructs (e.g., RDoC):
Parametrically-defined behavioral assays in humans

Classify and quantify behavioral variance in human subjects

Explain and predict human behavioral constructs (e.g., RDoC), such as social processes
• NIH officially launched the All of Us Research Program
• Recruiting one million individuals (currently, age 18 and older)
• Thousand of potential studies to inform precision medicine
  - Electronic health records
  - Surveys
  - Biological data
  - Wearable devices
Reward and Anhedonia

Neuroscience of apathy and anhedonia: a transdiagnostic approach

Masud Husain and Jonathan P. Roiser

Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review

Marianne Destoop, Manuel Morrens, Violette Coppens and Geert Dom

Translational Assessments of Reward and Anhedonia: A Tribute to Athina Markou

Andre Der-Avakian and Diego A. Pizzagalli

Nat. Rev. Neurosci., 2018

Front. In Psychiat., 2019

Biol. Psychiat., 2018
# RDoC Positive Valence (Reward) Domain

## Positive Valence Systems

<table>
<thead>
<tr>
<th>Construct/Subconstruct</th>
<th>Genes Notice</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Report</th>
<th>Paradigms</th>
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<tbody>
<tr>
<td>Reward Responsiveness</td>
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<td>Initial Response to Reward</td>
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<td>Reward Learning</td>
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<td>Probabilistic and Reinforcement Learning</td>
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<td>Reward Prediction Error</td>
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<td>Habit - PVS</td>
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<td>Reward (probability)</td>
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<td>Elements</td>
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Reward Task Optimisation Consortium

- Aim: to qualify a battery of tasks measuring different reward processing domains to support drug development
- Funding from 5 pharma partners (Blackthorn, Boehringer Ingelheim, Janssen, Lundbeck, Roche)
- Multi-centre European software deployment trial supported by:
  - Members of the ECNP Experimental Medicines Network
    - P1vital Products Ltd
    - BioTrial
    - Maastricht University, Netherlands
    - University Hospital Frankfurt, Germany
    - Institut Hospital del Mar, Barcelona, Spain
    - Aristotle University of Thessaloniki, Greece
Computational Psychiatry

- Test links across multiple levels of analyses (genetic, molecular, cellular, circuit, behavior)
- Formalize behavioral analysis, defining underlying algorithms and facilitating neurobiological and clinical studies
- Provide quantitative assessment of utility of biomarkers
- Enhanced understanding of brain mechanisms

Data Mining
Biophysical Modeling
Computational Modeling
Computational Phenotyping
BSNIP “Biotypes: (1) Cognitive Control, (2) Sensorimotor Reactivity

Clementz, .... & Tamminga, Am J Psychiatry, 2016
Pre-clinical animal studies of mechanisms: “For,” not “of,” psychopathology

Basic Neurodevelopmental Biology of Circuits and Behavior (R01 Clinical Trial Not Allowed) PAR-19-027

This FOA encourages projects, using in vivo measures in awake, behaving rodents and non-human primates, to:

1) Examine the developmental trajectories of neural circuits associated with cognitive, emotional, and social behaviors;
2) Implement new approaches to study changes in these networks across developmental trajectories; AND/OR
3) Investigate, in animals, processes that been associated with dysfunctions in mental-health behaviors in humans.
Broad Goal: Transform Culture for New Therapeutics

Academia

Foundations

Standardization
Integration

Data/Reagent/Tissue Sharing

Industry

Government