



NIMH Updates and Research Priorities

ASCP Annual Meeting

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of Mental Health

Disclosure of Affiliations

No conflicts of interest or disclosures

Agenda

- NIH and NIMH Updates
- NIMH Intervention Development: Priorities and Opportunities

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.

Consolidated Appropriations Act of FY 2018

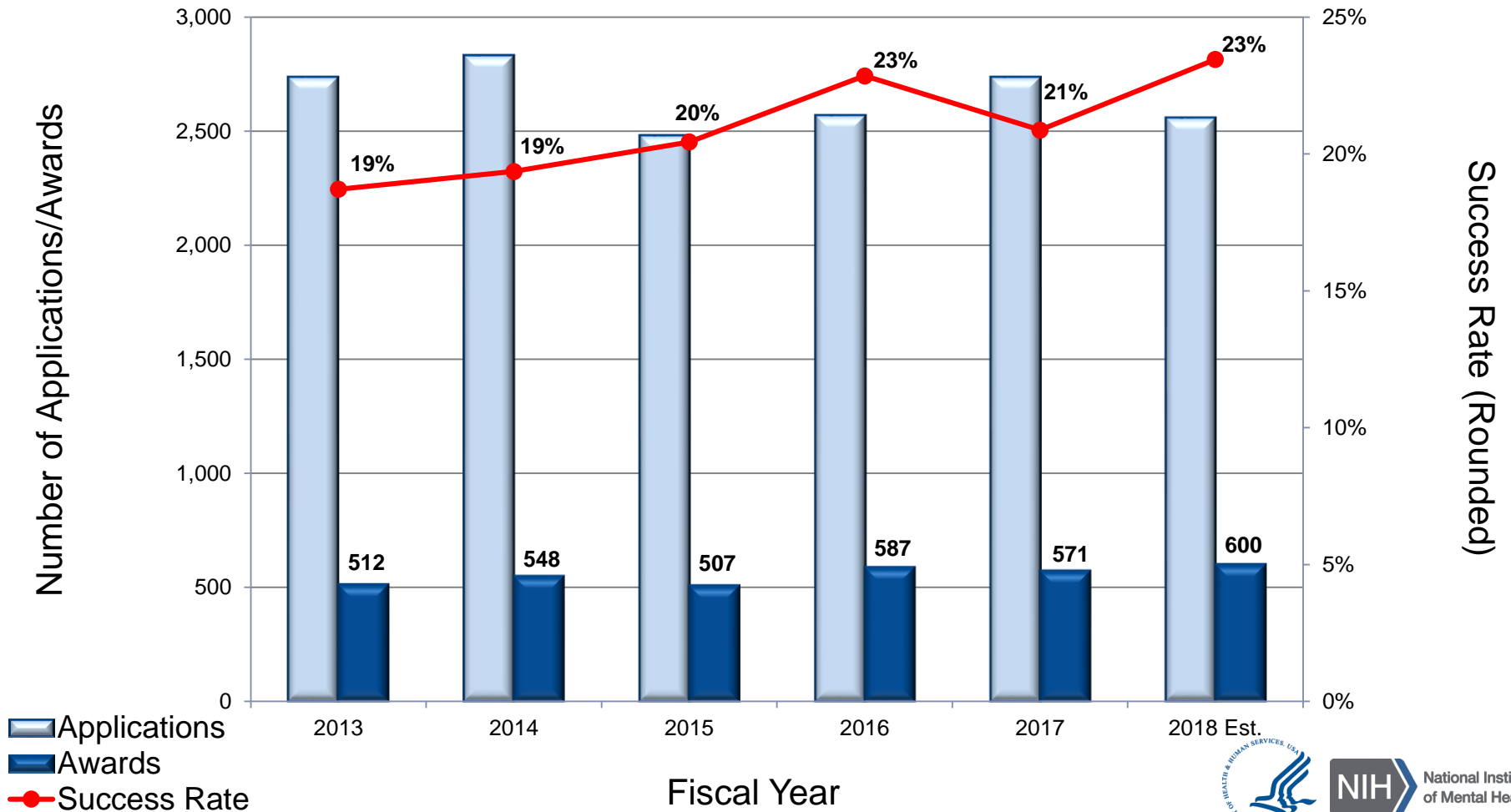
- HHS total \$78 billion
- NIH total \$37 billion
- Specific increases for NIH Initiatives:
 - **BRAIN Initiative: \$400 million (+ \$140M)***
 - All of Us: \$290 million (+ \$60M)*
 - Regenerative Medicine: \$10 million (+ \$8M)*
 - Universal Flu Vaccine Research: \$100 million (+ \$40M)
 - Combating Antibiotic-Resistant Bacteria: \$351 million (+ \$17M)
 - Clinical and Translational Science: \$543 million (+27 M)
 - Institutional Development Awards: \$351 million (+\$17M)

*Total includes funds from 21st Century Cures Act



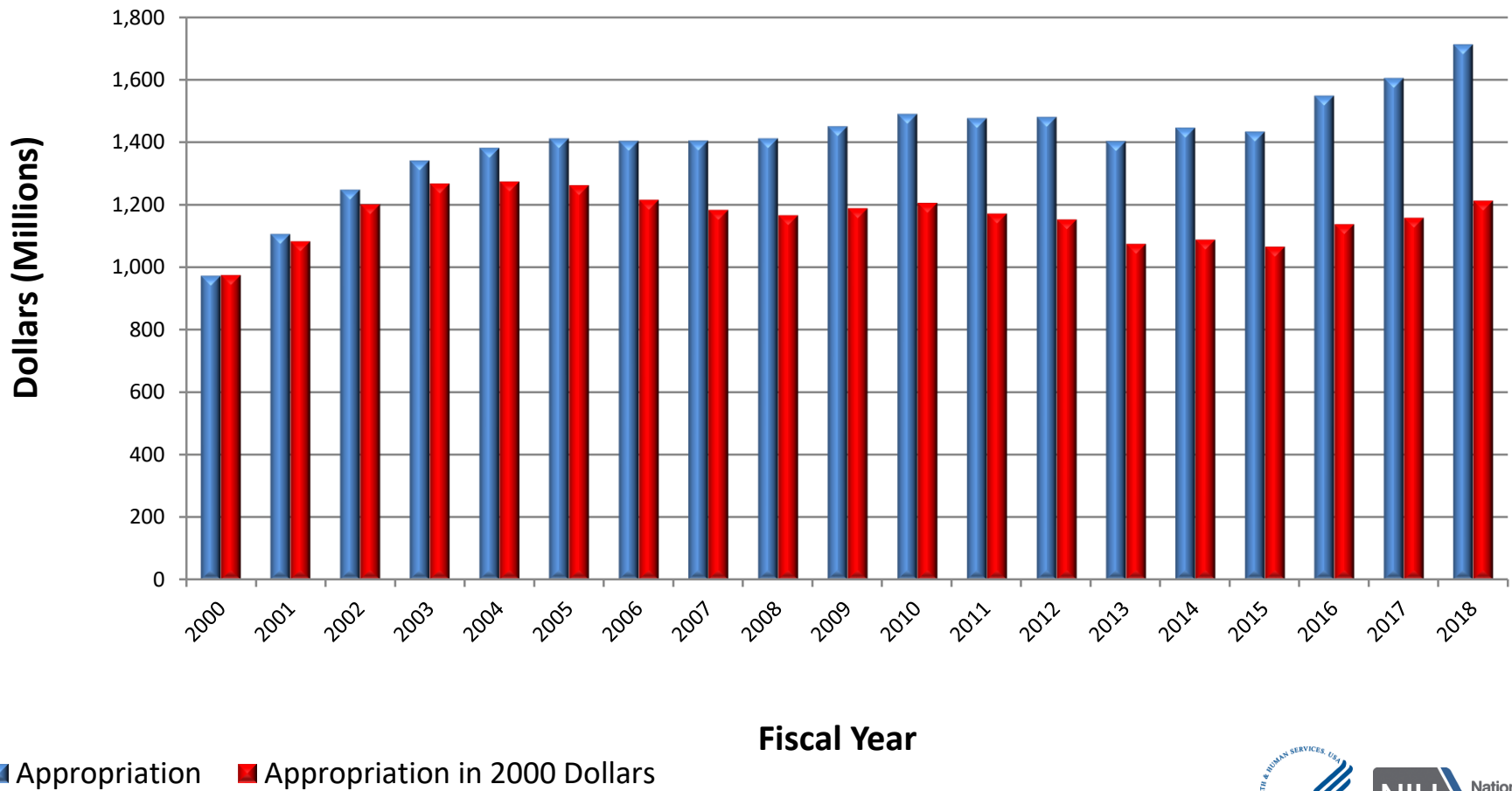
NIMH Budget Update

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



NIMH Budget Update

NIMH Program Level in Appropriated Dollars and Constant 2000 Dollars



Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

- 4th annual BRAIN Initiative Investigators Meeting
- Advisory Committee to the Director BRAIN Initiative Working Group 2.0:
 - Review BRAIN Initiatives activities and progress
 - Suggest changes to the goals outlined in BRAIN 2025
 - Identify new opportunities for research and technology



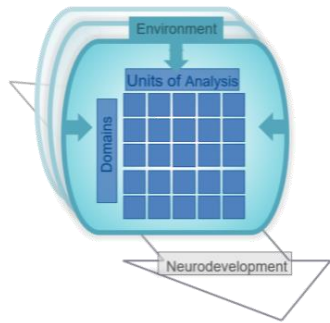
NAMHC Genomics Workgroup Report



Principal Recommendations from the Genomics Workgroup

- Appropriate and rigorous statistical methods
- Unbiased genetic association studies
- All types of genetic variation for disease association
- Genetic association efforts beyond the DSM
- Genetic and phenotypic variation across diverse populations.
- Develop and share research resources
- Robust genome-wide significance to select genes for further study

Research Domain Criteria (RDoC) Changes to the Matrix Workgroup Update



- RDoC Changes to the Matrix Workgroup Charge
 - Standardize submission for suggested revisions
 - Evaluate proposed changes
 - Make recommendations to the NAMHC
- Proposed Reorganization of Positive Valence Domain
 - Move some constructs to sub-constructs
 - Add concepts

Agenda

- NIH and NIMH Updates
- NIMH Intervention Development: Priorities and Opportunities

Experimental Therapeutics Approach to Intervention Development

Intervention
as tool to
validate or
engage the
target



**Target
Engagement**
informs “go/no-
go” decision



Clinical Trial
value
optimized
regardless of
clinical effect



Experimental Therapeutics Approach to Intervention Development

Why?

- Address if and how interventions work
- Elucidate therapeutic change mechanisms
- Inform decision about whether to invest in further development (positive results) or redirect (negative results)



Funding Opportunity Announcements

Clinical Trial Pipeline - Phase of Intervention Development

First in Human	Exploratory Experimental Therapeutics	Confirmatory Efficacy	Effectiveness (Prevention, Treatment, Services)
First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01)*			Pilot Effectiveness Trials for Treatment, Preventive and Services Interventions (R34)
	Early Stage Testing of Pharmacologic or Device-based Interventions for the Treatment of Mental Disorders (R61/R33) and (R33)*	Confirmatory Efficacy Clinical Trials of Non-Pharmacological Interventions for Mental Disorders (R01)	Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (R01)
	Development of Psychosocial Therapeutic and Preventive Interventions for Mental Disorders (R61/R33) and (R33)		Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (Collaborative R01)

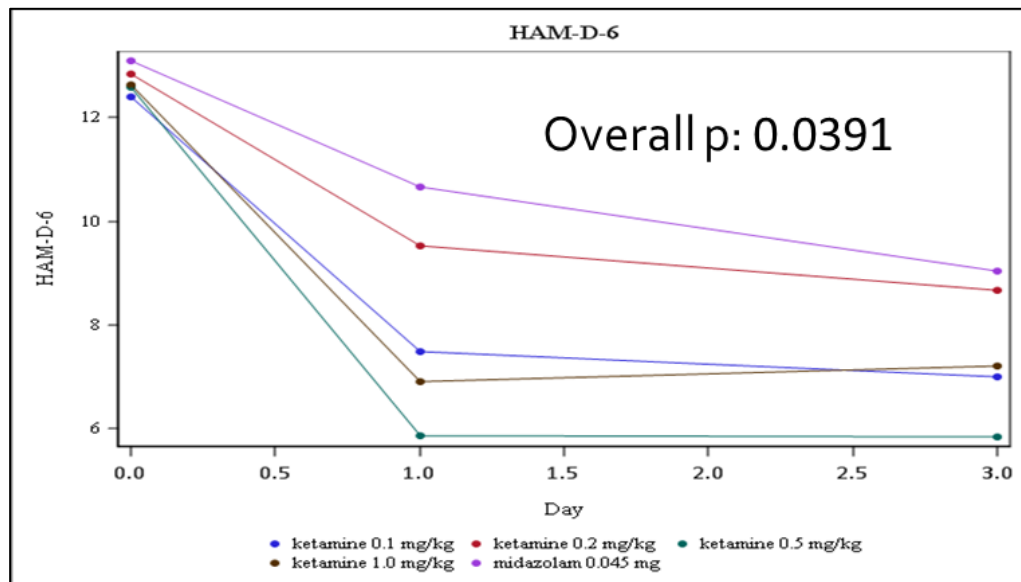
FAST-RAPID Contracts

- **Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID)**
 - **Goal:** Efficient evaluation of candidate treatments
 - *PI: Maurizio Fava, M.D., MGH*
- **Experimental Medicine Studies: Fast-Fail Trials (FAST)**
 - **Goal:** Develop reliable and rapid set of early phase methods for evaluation of compounds designed to act on prioritized neurobiological targets
 - FAST-PS: Psychotic Spectrum (*PI: Jeffrey Lieberman, M.D., RFMH*)
 - FAST-MAS: Mood and Anxiety Spectrum (*PI: Andrew Krystal, M.D., Duke University*)
 - FAST-AS: Autism Spectrum (*PI: James McCracken, M.D., UCLA*)

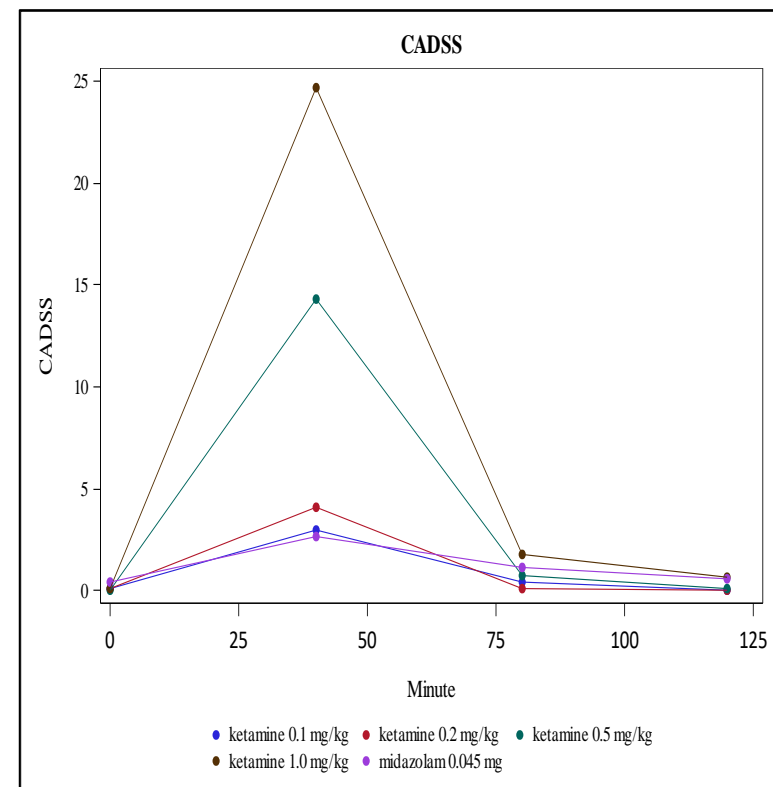
RAPID: Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in Treatment-Resistant Depression

- **Goal:** Establish optimal anti-depressant dose of single administration of ketamine in TRD
- **Study design:** RCT, Single administration of i.v. ketamine (0.1-1.0 mg/kg) or active placebo (0.45 mg/kg) in 99 TRD patients

Differences in HAM-D-6 Scores Between Ketamine and Midazolam



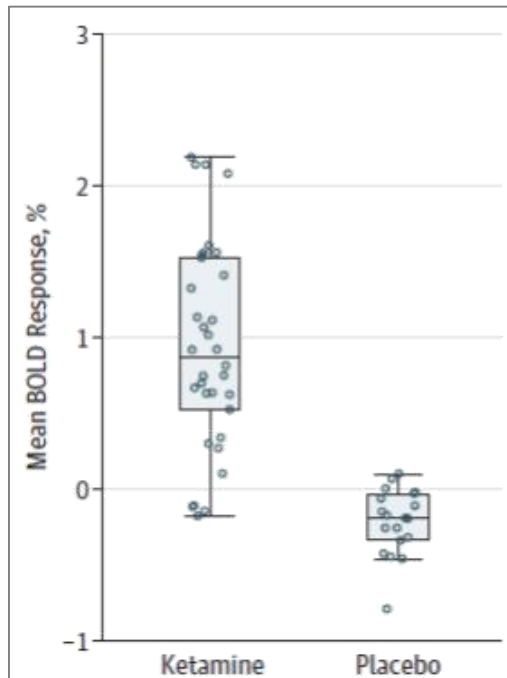
CADSS Scores During the Infusion



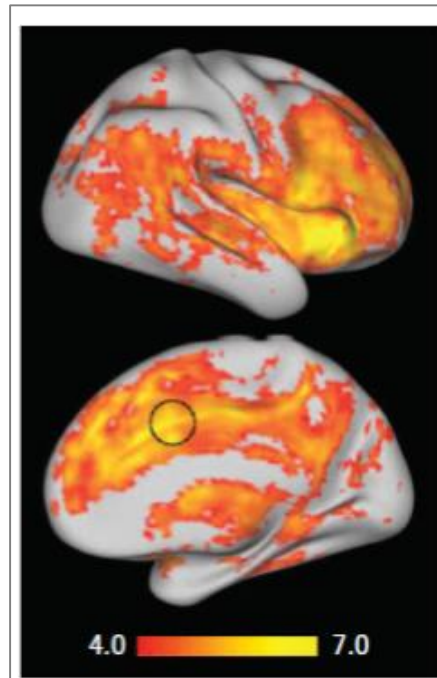
FAST-PS: Biomarker for Target Engagement Validation Study

- **Goal:** Refinement and comparison of imaging-based biomarkers for glutamatergic hyperactivity
- **Study Design:** RCT in 53 healthy volunteers receiving either i.v. ketamine (1 minute-bolus followed by 59 minutes of infusion) or placebo

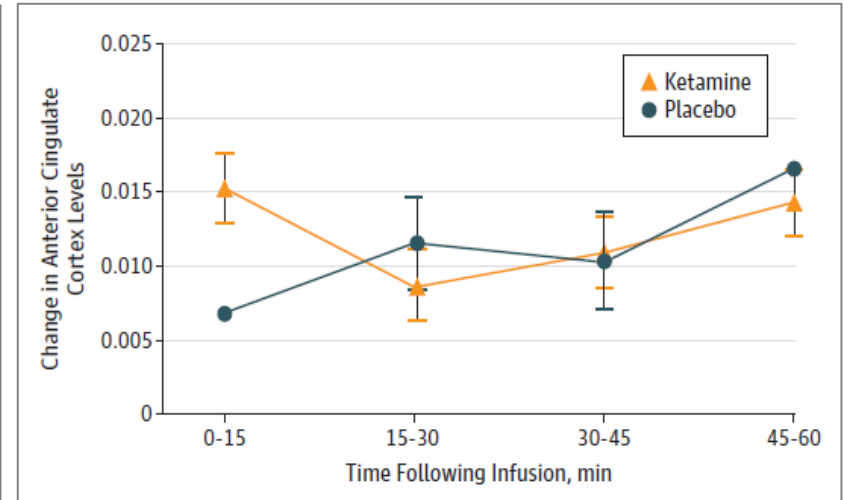
Δ in \bar{x} BOLD response



Activation maps



MRS response



FAST-PS: Assessment of mGluR2/3 Agonist Activity in Brain

- **Goal:** Assess whether higher doses of mGluR2/3 agonist might better inhibit ketamine-induced glutamate effects
- **Study design:** RCT, daily mGluR2/3 agonist LY2140023 (40 and 160 mg) or placebo for 10 days; i.v. ketamine administration (1 minute-bolus followed by 59 minutes of infusion) and pharmacobOLD fMRI on Day 1 and Day 10
- **Status:** Study enrollment completed and data analysis in progress

FAST-MAS: KOR JNJ-67953964 Antagonist Phase 2a Study in Anhedonia

- **Goal:** Assess if antagonism of the kappa opioid receptor (KOR) engages key neural circuitry related to hedonic response
- **Study design:** Eight-week RCT, 10 mg JNJ-67953964 daily, in 89 patients with anhedonia.
- **Results:**
 - Significant Group x Time interaction in reward gain anticipation, consistent with relatively greater ventral striatal activation during anticipation of both gain and loss in the study drug group post-treatment
 - JNJ-67953964 was not associated with any serious adverse events and was generally well tolerated

FAST-AS: EEG Effects in Clinical Trial of Subtype Selective GABA_A Receptor α 2,3 Positive Modulator (AZD 7345)

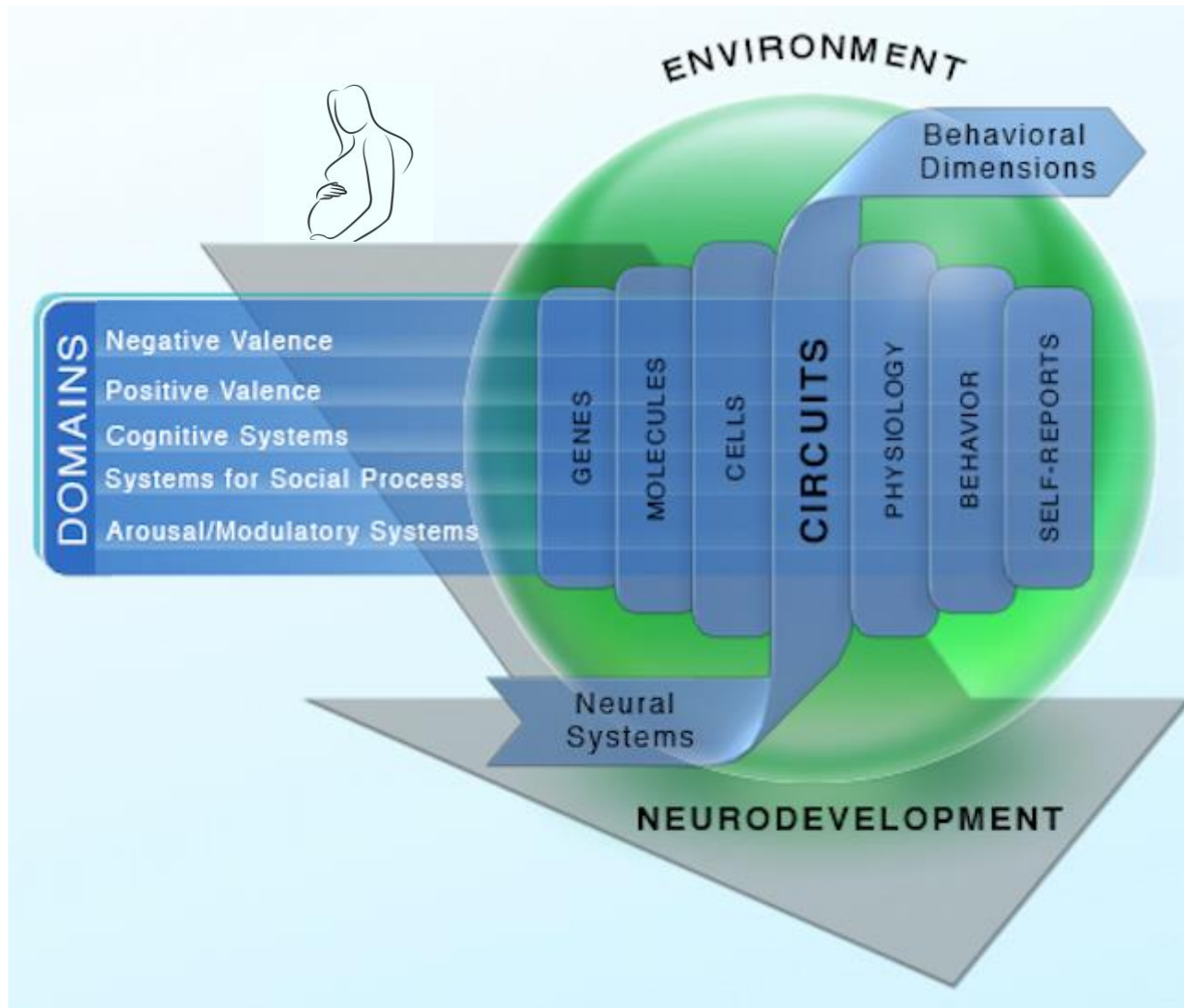
- **Goal:** Explore potential of EEG to stratify adults with ASD and assess pharmacodynamics of AZD 7345 following single and multiple doses
- **Study design:** a) Pilot control vs ASD study to generate EEG entry criteria for drug study; b) 6 week double-blind drug vs placebo with EEG pre and post acute and chronic dosing
- **Results:** Modest reduction in relative delta power consistent with earlier healthy volunteer studies and unexpected increase in theta power on drug vs placebo in absence of sedative, other side effect or any clinical efficacy group differences

Broader Goal: Building Pharmacology in Child Psychiatry

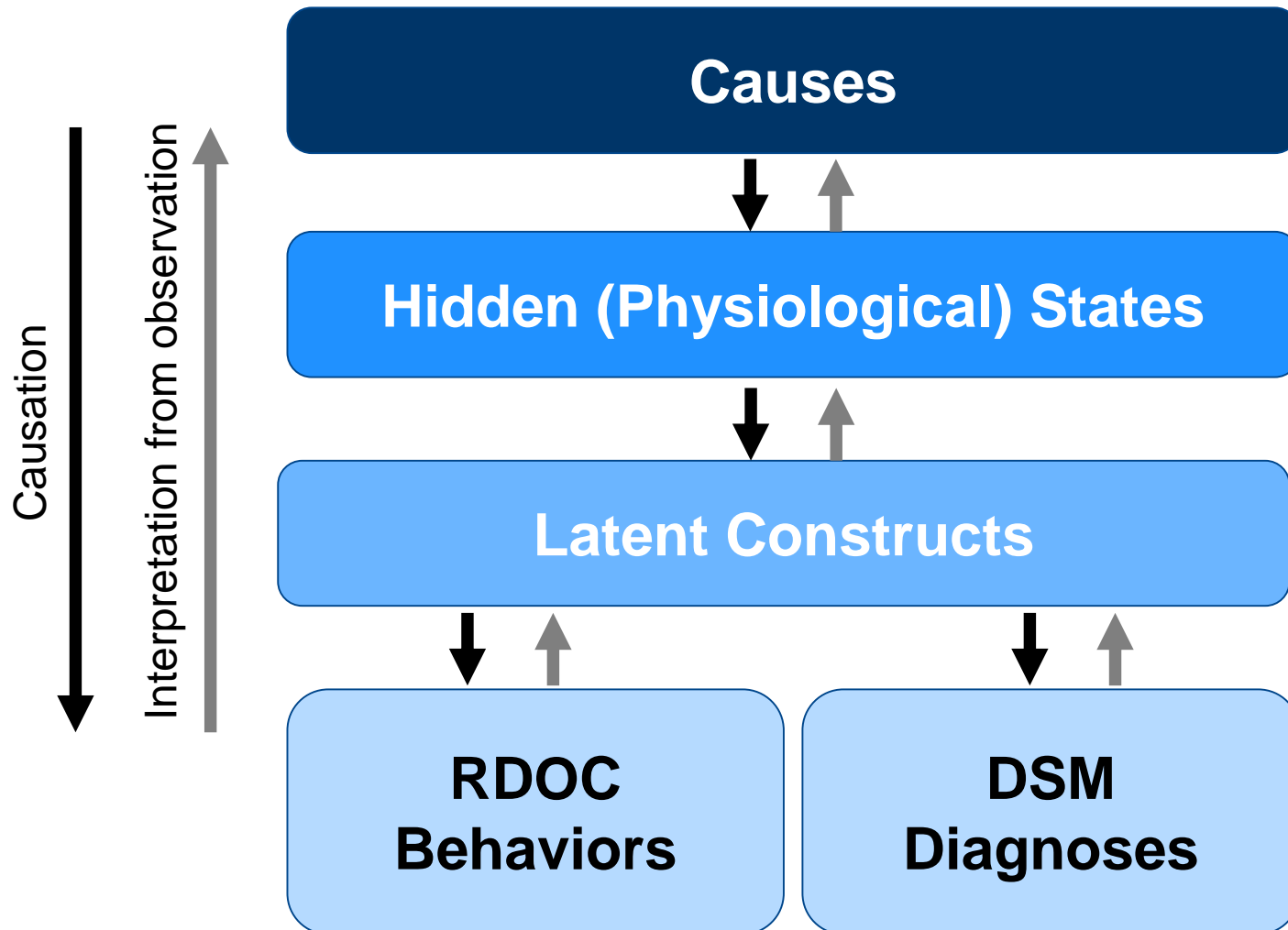
Prior to Efficacy, Trials Establish Safety and Appropriate Doses:

- Establish pediatric trial model for safely testing drug candidates
- Establish framework that brings together relevant expertise
- Assess novel mechanism of action of drug candidates by quantifying immediate brain effects
 - Pharmacokinetic/pharmacodynamic bridging design
 - Registration quality data that could be used in a regulatory approval package
- Support the development of pharmacodynamic measures
- Train the next generation of pediatric psychiatrists in clinical pharmacology

RDoC Framework: Flexible, Evolving



A Computational Approach to RDoC



All of Us

- 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



Recent NIMH Notices and Funding Initiatives

- Ongoing RFAs to Address the Safety, Efficacy, and Effectiveness of Preventive, Therapeutic, and Services Interventions
- ALACRITY P50 Transdisciplinary Research Centers
- Notice on Harnessing Technology to Enhance MH Assessment, Detection, Intervention, and Service Delivery
- RFAs for Early Stage Testing of Pharmacologic or Device - Based Interventions for the Treatment of Mental Health Disorders
- PA for Research to Support the Reduction and Elimination of Mental Health Disparities
- PARs for Early Stage Drug/Device Treatment Development for Psychiatric Disorders



NIMH's Mission

MISSION

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

www.nimh.nih.gov

Research = Hope