Update on Drug Development Efforts at NIMH

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NIH BRAIN Initiative Team B: Neural Recording and Modulation Technologies

BRAIN Initiative

National Institute of Mental Health

Disclosures

- The views expressed are my own and do not necessarily reflect the views of the NIH, DHHS, or the US Federal Government
- Patent on TMS technology, not licensed, no royalties
- Equipment loan from Magstim Company
- Past (>4 yrs ago) grant support from St Jude/Abbott, Neuronetics, Neosync, Cyberonics, Brainsway

National Institute of Mental Health

Outline

- NIMH Overview, Strategic Plan, and Budget
- Challenges in Psychiatric Drug Development
- NIMH Support for Drug Trials
- Advisory Council Working Groups on Drug Development
- Responding to COVID-19

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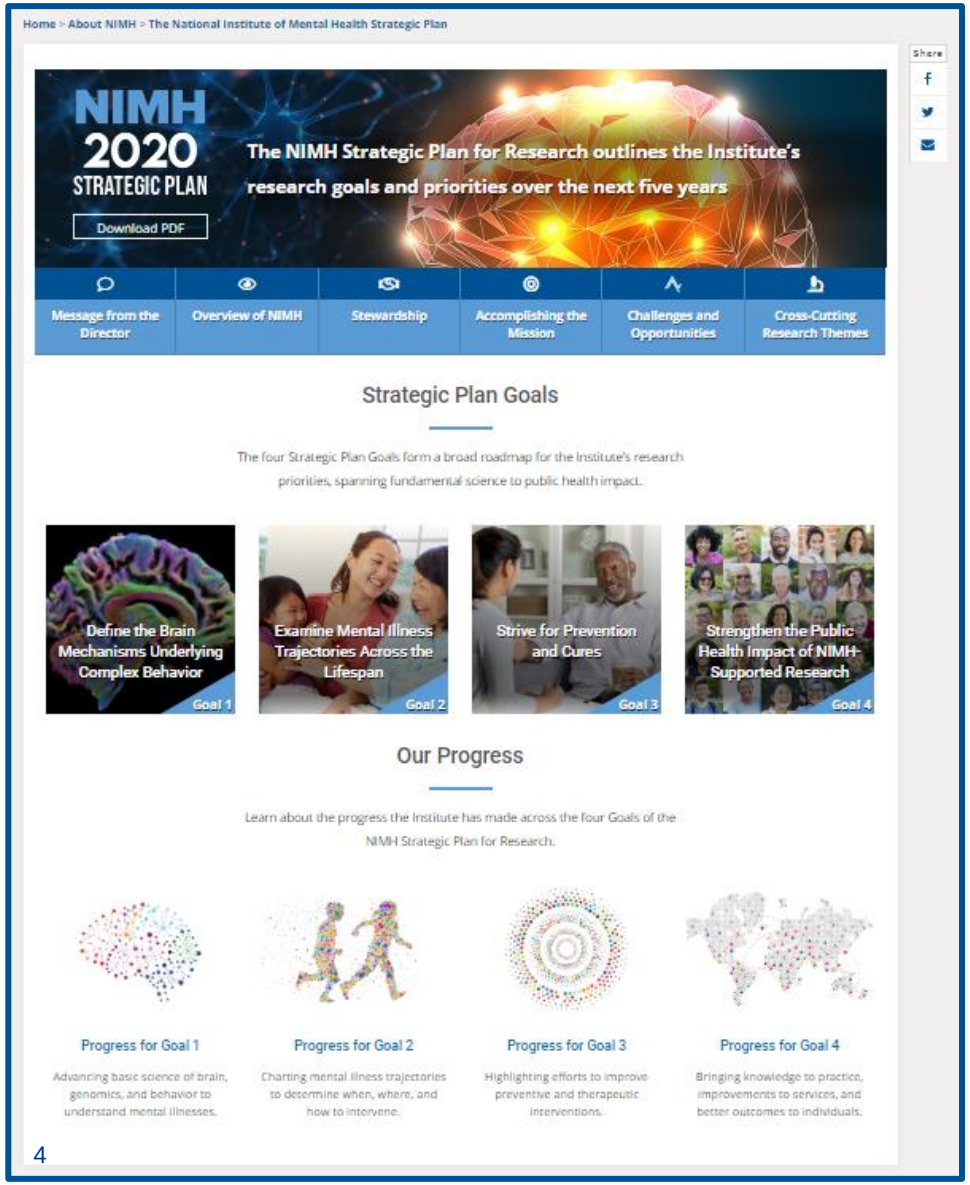
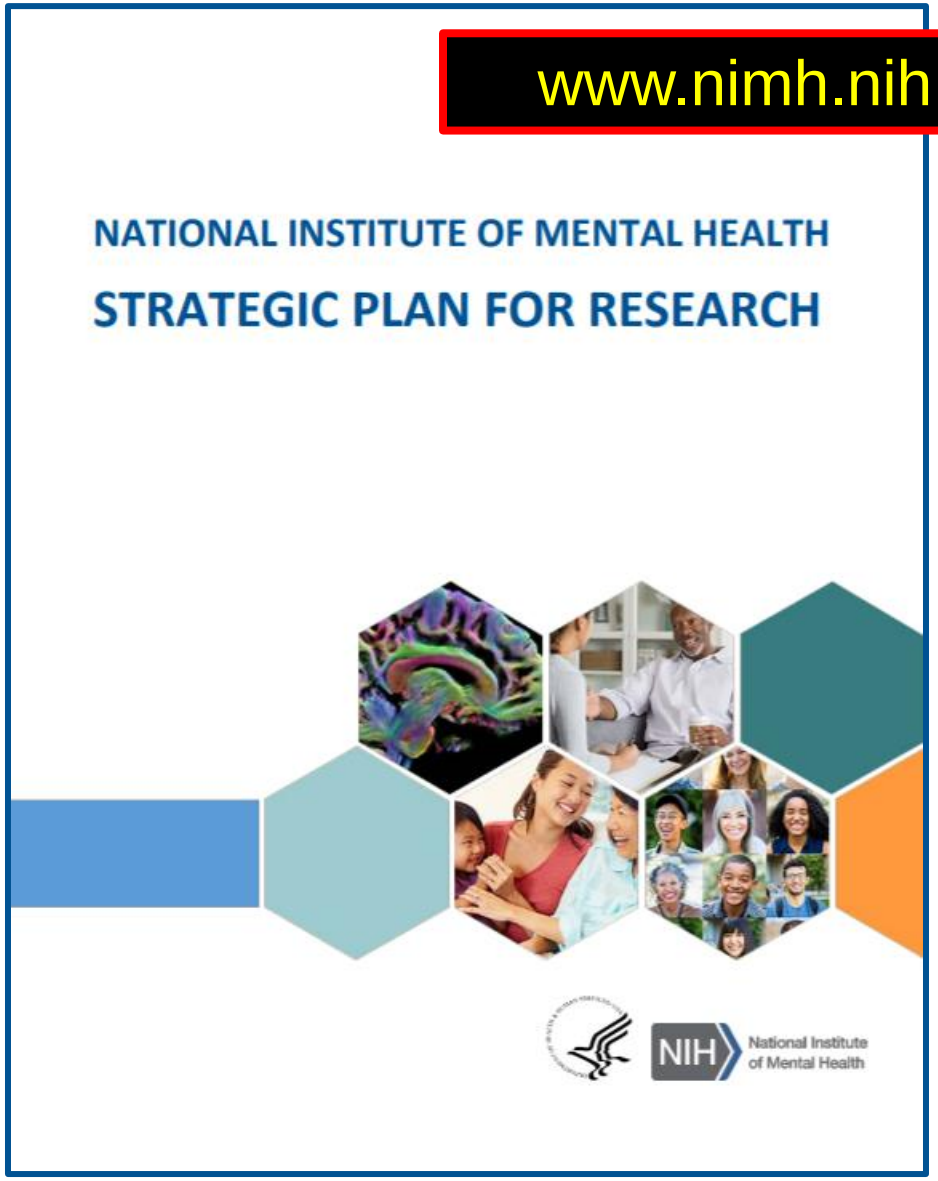
NIMH Strategic Plan for Research



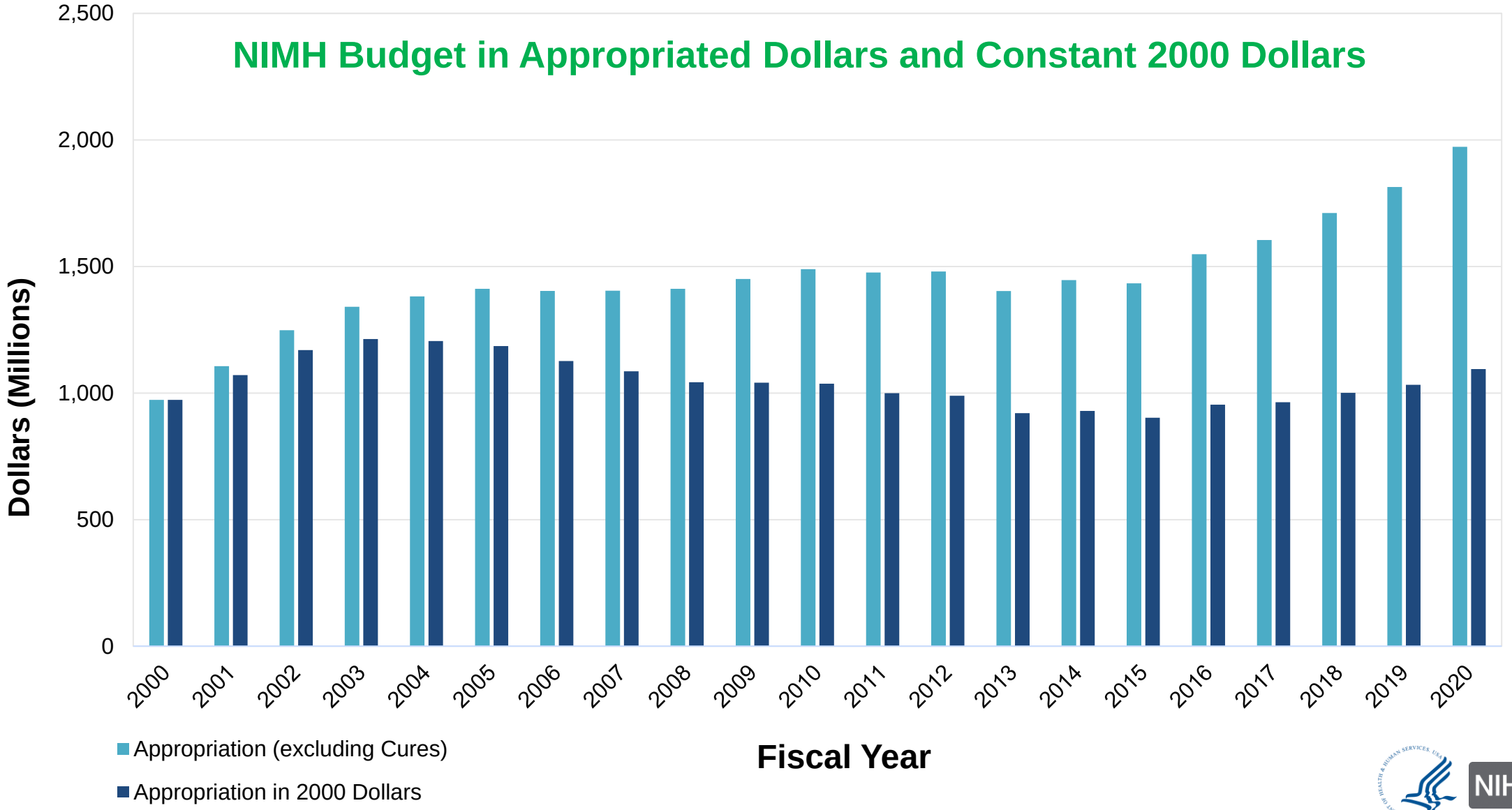


www.nimh.nih.gov/strategicplan

Newly launched online as a living document

NIH National Institute of Mental Health

NIMH Budget Update



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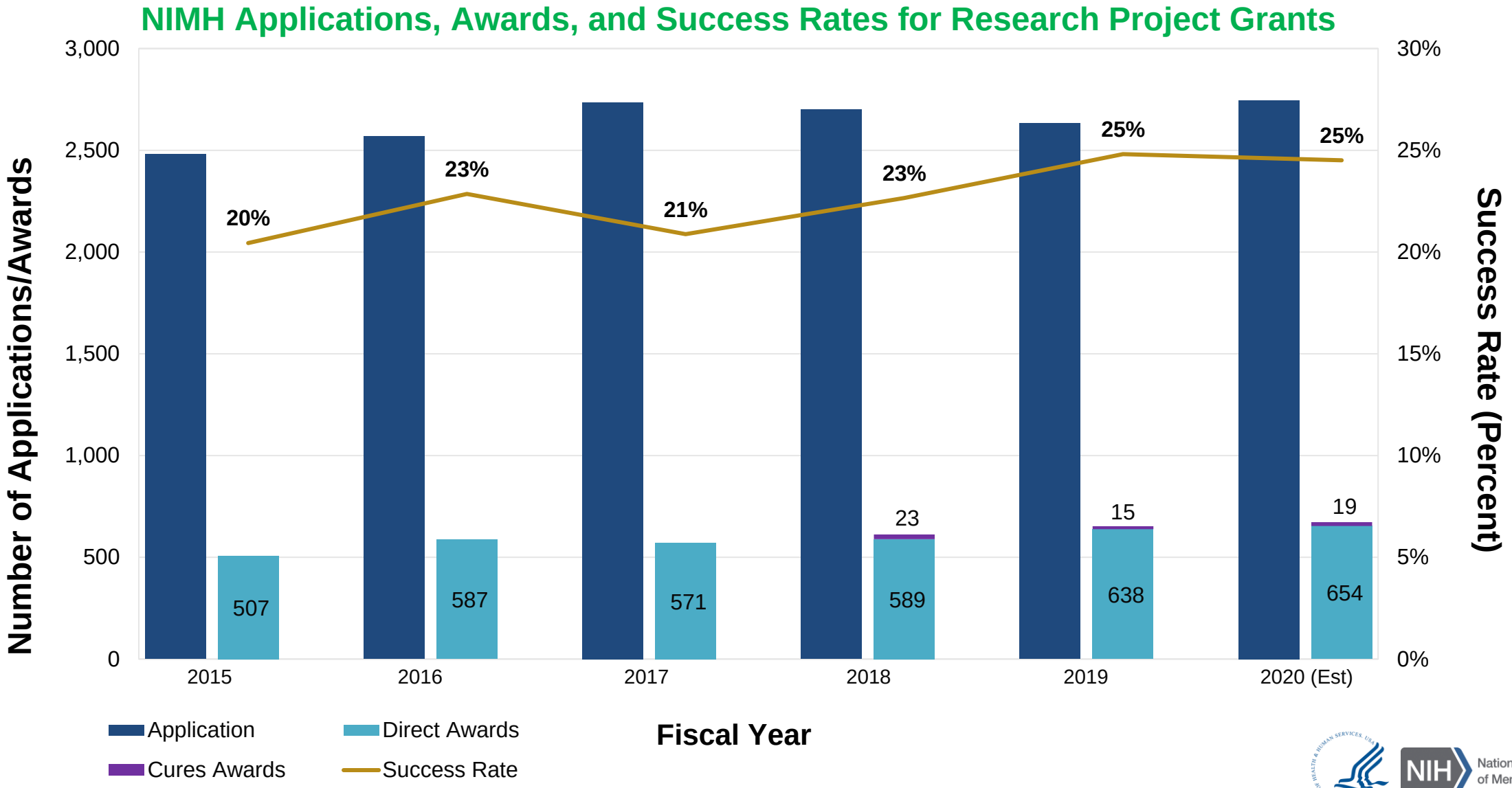
NIMH Budget Update



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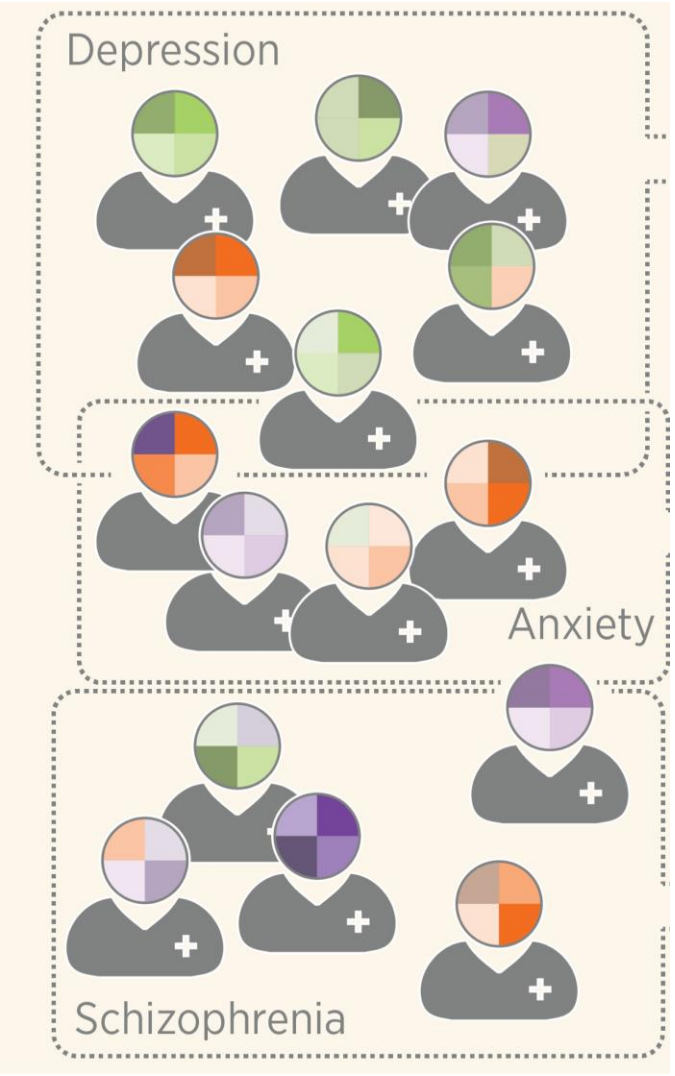
Challenges in Psychiatric Drug Development

1. Clinical heterogeneity within and across diagnoses
2. Clinical trial designs that result in uninformative failures

Challenge #1: Clinical Heterogeneity



- Heterogeneity
  - Within diagnoses
  - Comorbidities across diagnoses
- Need ways to select and stratify patients going into trials

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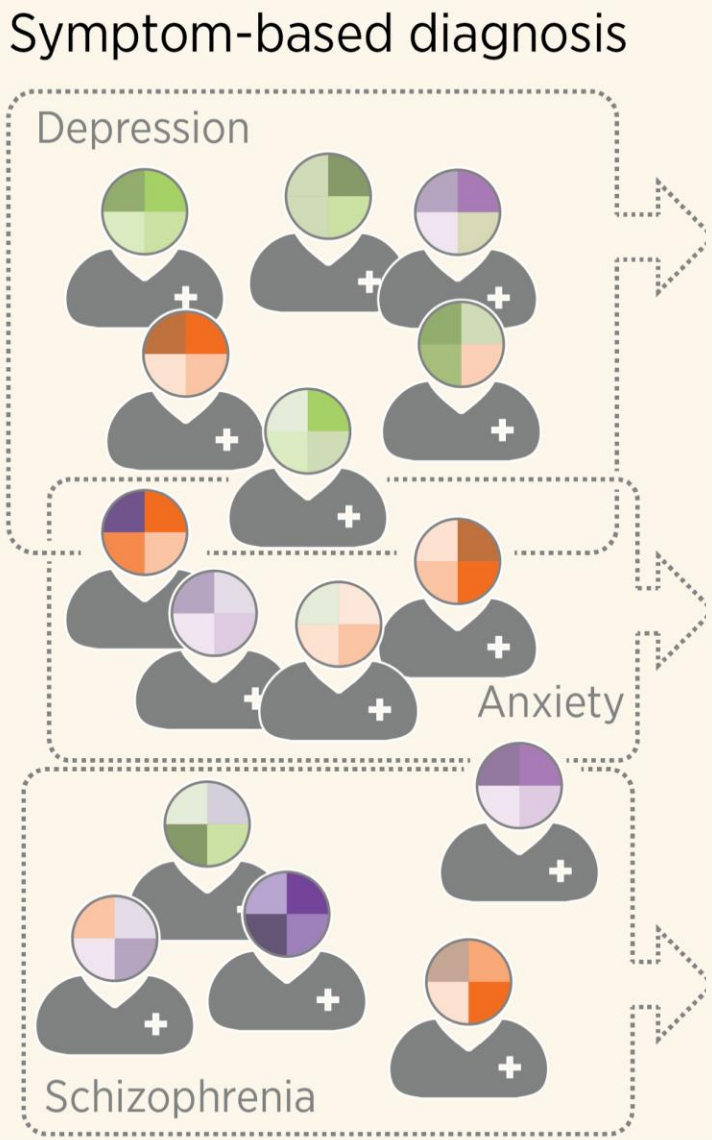
Challenge #1: Clinical Heterogeneity



Research Domain Criteria Approach (RDoC)

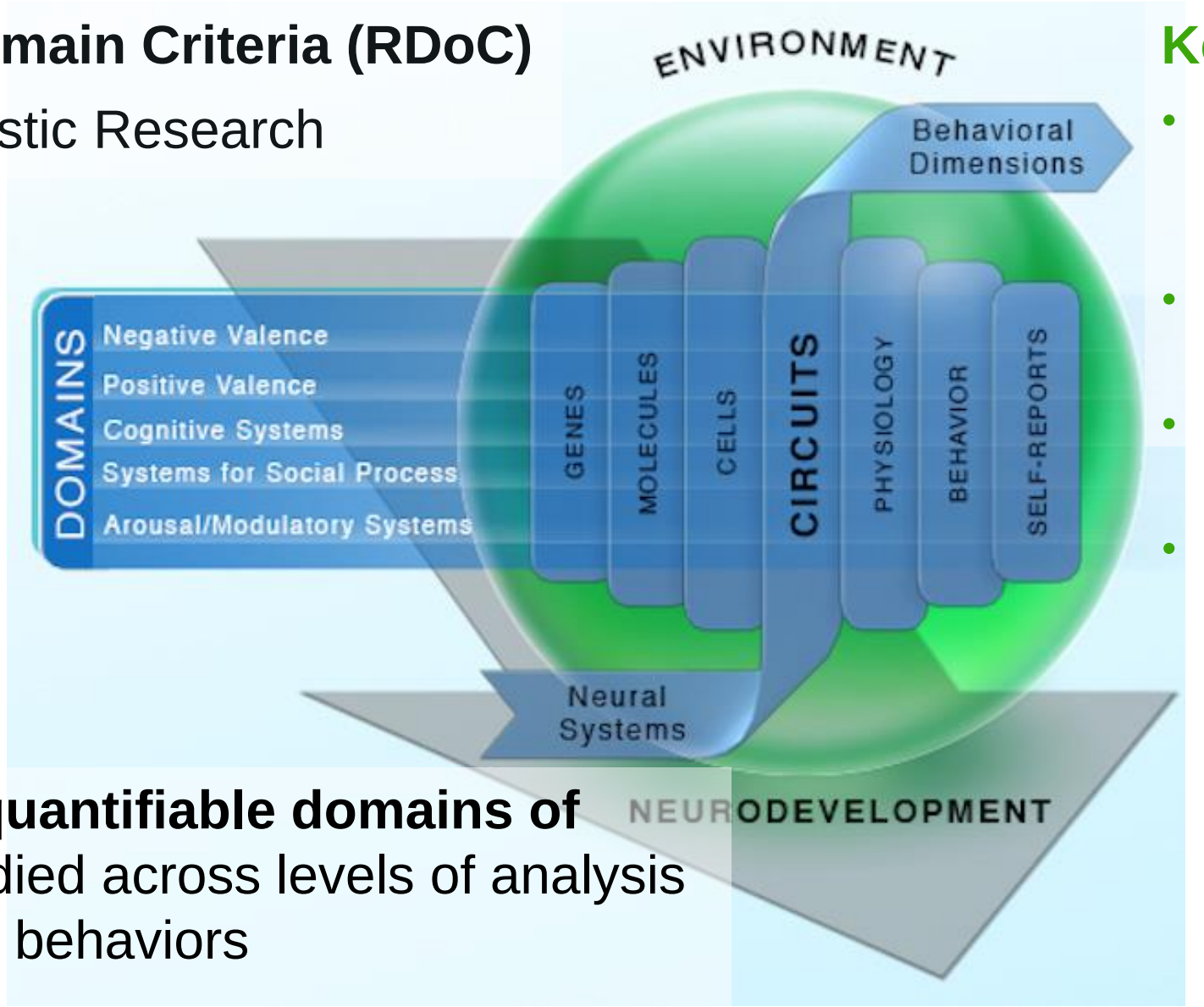
Biotyping

Source: Zhi-De Deng, modified from Insel and Cuthbert. Science. 2015; 348: 499

Strategies to Address Heterogeneity

Research Domain Criteria (RDoC)

Trans-Diagnostic Research Framework



Objectively quantifiable domains of function, studied across levels of analysis from genes to behaviors

Key Deliverables

- Biotypes to characterize heterogeneity & stratify samples
- Mechanisms across units of analysis
- Putative therapeutic targets
- Quantify target engagement

Example:

- Targeting Anhedonia transdiagnostically via FAST-FAIL

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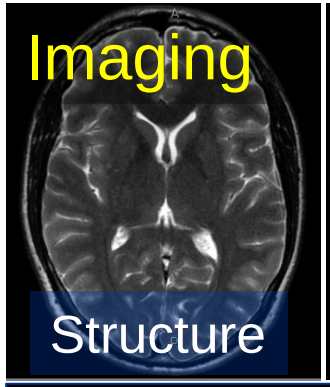
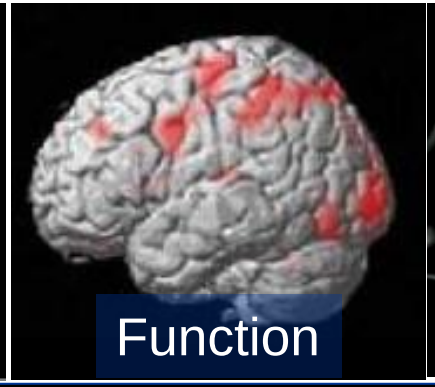
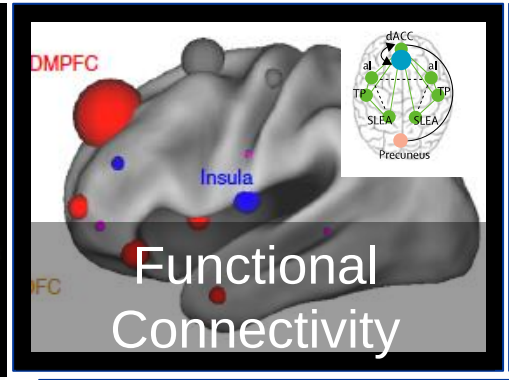
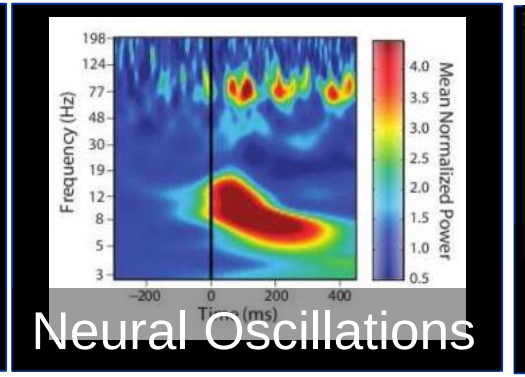
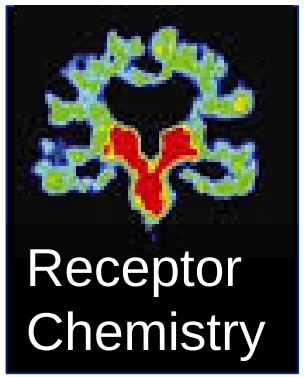
Multi-Modal Biotyping – Data Science Opportunities and Challenges



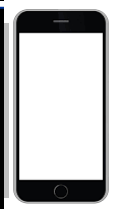


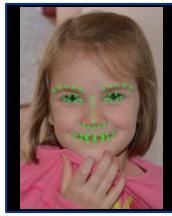


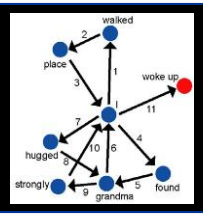




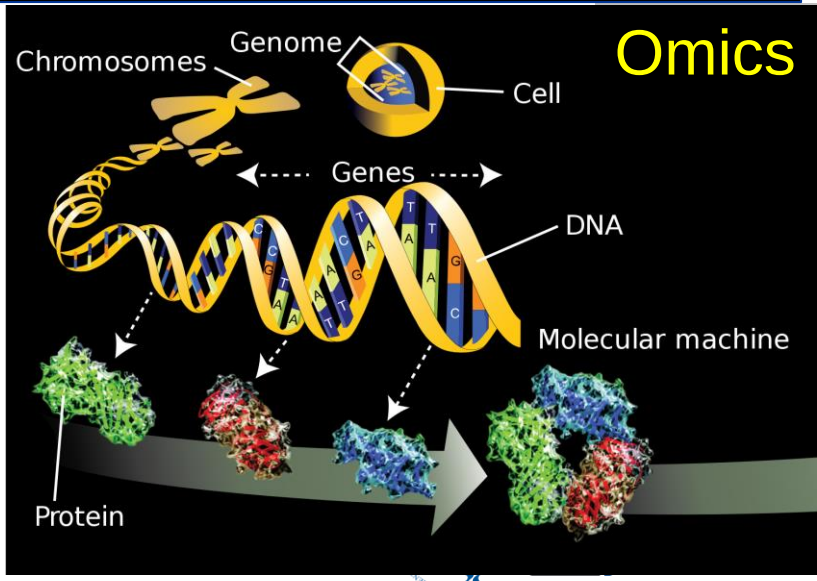
Smart phones / smart watches / mobile trackers







Speech / Language / Facial Expression



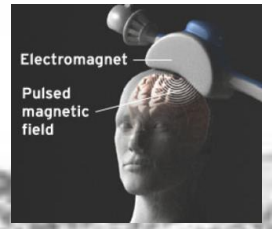
Challenges in Psychiatric Drug Development

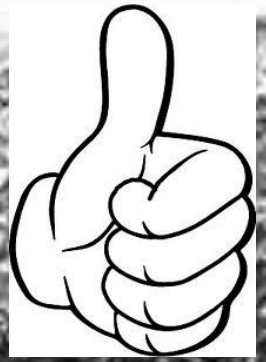
1. Clinical heterogeneity within and across diagnoses
2. Clinical trial designs that result in uninformative failures

Conventional Intervention Development Trial Design

Intervention → Conventional RCT → Clinical Sx

Valley of Death





Uninformative Failures

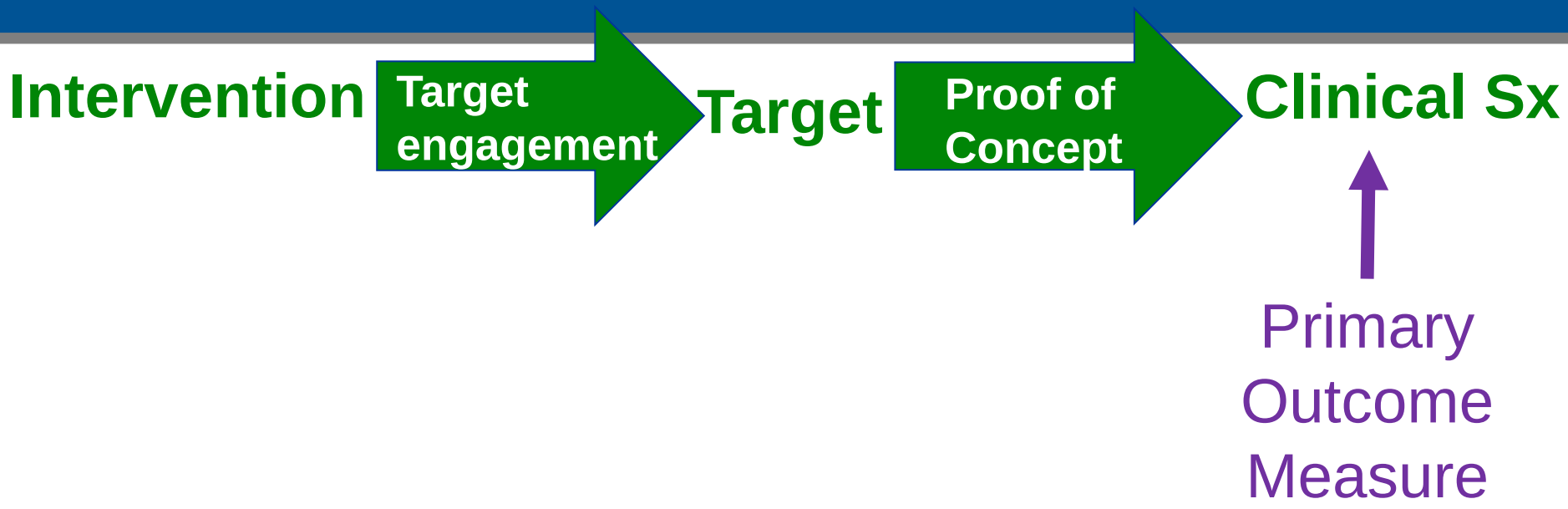
Unknown whether intervention reached intended target.

Unknown adequacy of dosing.

Experimental Therapeutics Approach to Trial Design

Intervention → Conventional RCT → Clinical Sx

Experimental Therapeutics Approach to Trial Design



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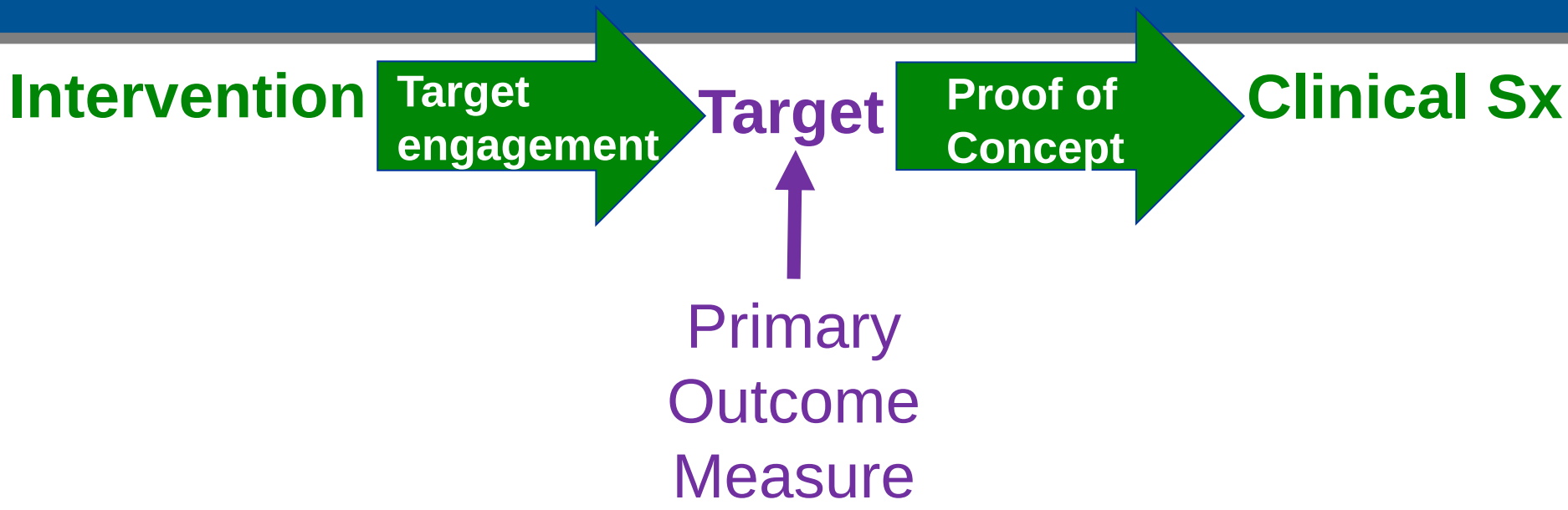
Experimental Therapeutics Approach to Trial Design



- Measures that link to the action of the therapeutic target
  - Impact on circuits function and/or circuit dynamics,
  - domains of function,
  - other measures linked to the target (whether peripheral or central, biological or psychological)

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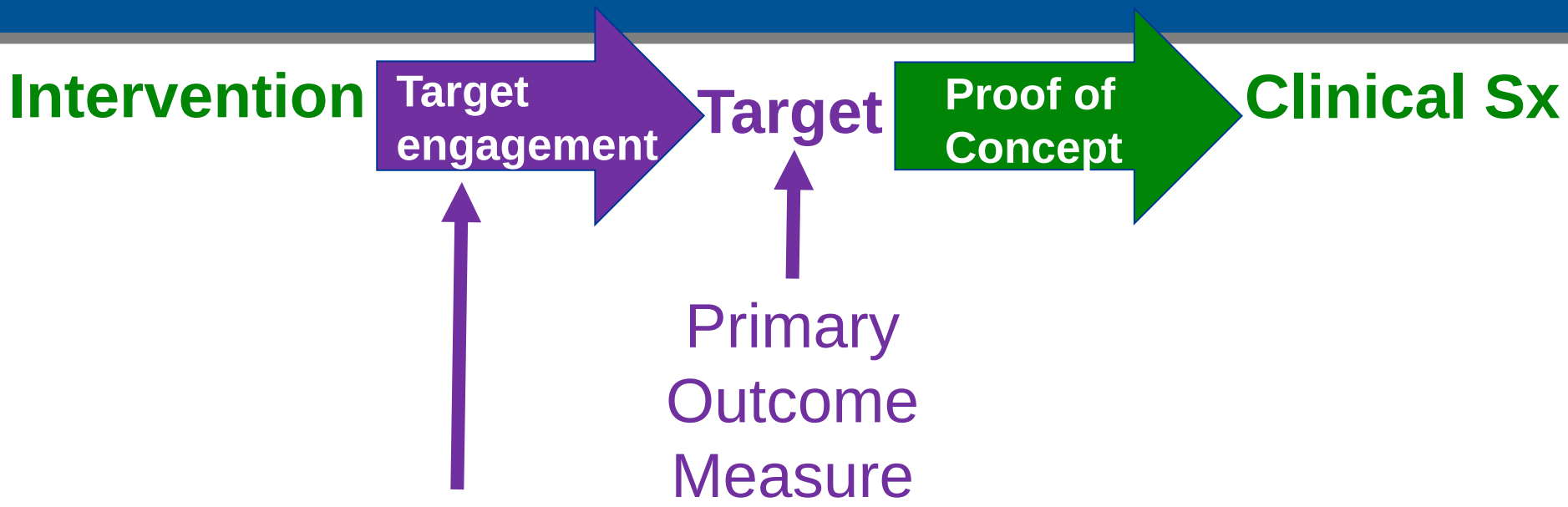
Experimental Therapeutics Approach to Trial Design



- Show that intervention
  - reaches target
  - causes change in target in hypothesized direction (mechanism of action)
  - dose-dependent effects on target

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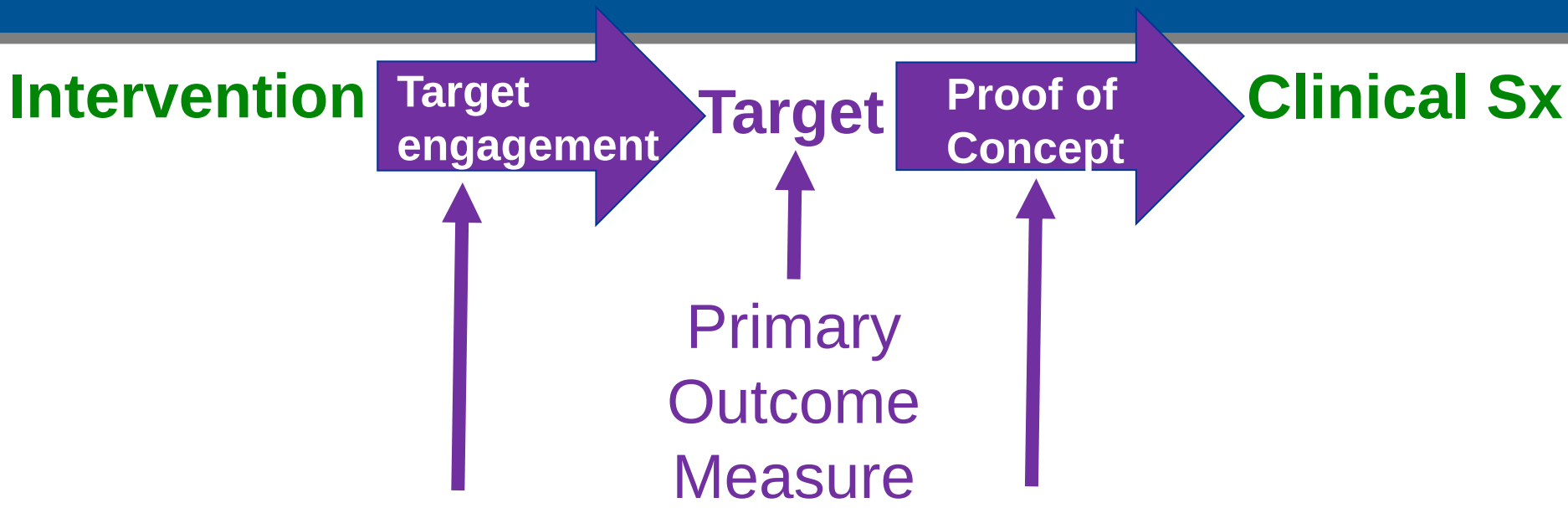
Experimental Therapeutics Approach to Trial Design



- Show that intervention
  - reaches target
  - causes change in target in hypothesized direction (mechanism of action)
  - dose-dependent effects on target

- Show that changing target
  - changes clinical signal (proof of concept)
  - is safe and tolerable

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- NIH-Wide Research Initiatives
- Responding to COVID-19

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NIMH Clinical Trials Pipeline

First in human & early stage clinical trials of novel drugs/devices U01

Early stage testing of drug/device R61/33

Development of psychosocial & preventative intervention R61/33

Confirmatory efficacy trials of non-drug intervention R01

Pilot effectiveness of treatment, prevention, & services interventions R34

Clinical trials testing effectiveness of treatment, prevention & services interventions R01

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Redirecting the revolution: new developments in drug development for psychiatry

Linda S. Brady, William Z. Potter & Joshua A. Gordon

- FDA Safety and Innovation Act created Breakthrough Therapy designation to expedite review of promising drugs for serious conditions
- FDA guidance on drug development tools and biomarker qualification program
- Esketamine and brexanolone – newly approved rapidly acting antidepressants
- Mechanistically new compounds for schizophrenia, autism, PTSD
- Emerging roles for consortia and public/private partnerships to de-risk drug development
  - Autism Biomarkers Consortium
  - Clinical High Risk Network

Expert Opinion on Drug Discovery, 2019: 14:12

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Addressing Clinical Heterogeneity

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Clinical High Risk (CHR) for Psychosis Research Network and Data Processing, Analysis, and Coordination Center

- Clinical heterogeneity in CHR is a substantial challenge for intervention development
- Addressing heterogeneity requires the development of tools to
  - define a core set of clinical and functional outcomes beyond onset of psychosis, including affective, cognitive, and negative symptom domains and functional outcomes;
  - prospectively stratify CHR individuals into more homogeneous risk subtypes to predict the likelihood of clinical outcomes.
- >30 clinics in the U.S. study and/or treat CHR individuals
- NIH Accelerating Medicines Partnership program encourages public-private partnerships to leverage CHR risk prediction and biomarker findings to support future clinical trials (Dolgin, *Nat Rev Drug Discov* 2019)

RFA-MH-20-340 / RFA-MH-20-341

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Clinical High Risk (CHR) for Psychosis Research Network and Data Processing, Analysis, and Coordination Center

- Goal: to establish multi-site CHR network(s):
  - to recruit large numbers of CHR participants and
  - to employ a common set of biomarker and clinical outcome measures to predict differential outcomes.
- Expected outcome: set of validated tools, including biomarkers, biomarker algorithms, and outcome measures:
  - for selection of help-seeking/CHR subjects for enrollment in future clinical trials to address a variety of outcomes,
  - to serve as potential readouts of early treatment effects,
  - and/or to monitor disease progression and clinical and functional outcomes.

RFA-MH-20-340 / RFA-MH-20-341

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Addressing Informative Trial Design

Experimental Therapeutics Paradigm

- Rationale
  - If >90% of compounds will fail, the path to success is to fail fast and fail often
- Goal
  - Develop reliable set of early phase methods for evaluation of compounds designed to act on prioritized neurobiological targets
    - Fail Fast: test feasibility before a large investment
    - Fail Smart: learn from results, regardless of outcome
- Necessary elements
  - A molecular target implicated in the disorder (or RDoC domain of function)
  - A target-selective, CNS penetrant, IND ready compound
  - A target-specific measure of brain function to monitor target engagement
- Clinical trial design requirements
  - Determine a dose that adequately engages the target
  - Look for correlations between target engagement and clinical outcomes

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Experimental Therapeutics Paradigm

- FAST Contracts initiated in 2012
  - Identified targets of interest, then searched for high quality compounds to test
  - Focused on experimental designs using quantitative pharmacodynamic (PD) readouts
- R61/R33 was initiated in 2014
  - Enabled investigator initiated CTs to test compounds/drugs they identified, sourced on their own
  - Phased approach, to enable stops if results were negative
  - Target engagement, PD designs
  - Primarily repurposed drugs were selected to study
    - Oxytocin, Ondansetron (5-HT3 antagonist), L-DOPA (2 studies), AZD6765 (low-trapping NMDA R antagonist), ezogabine (v-gated K channel opener; withdrawn from market in 2017), tetrahydrocannabinol (THC, cannabinoid agonist), Pomaglumetad methionil, Levetiracetam (synaptic vesicle protein 2A inhibitor)

NIMH Funded FAST-Fail Trials (FAST)

- FAST-AS: Autism Spectrum
  - EEG validation and proof-of-mechanism study of GABA-A a2/a3 selective positive modulator (AZD7325) in adults ASD
- FAST-MAS: Mood and Anxiety Spectrum
  - Kappa Opioid Receptor antagonist (JNJ-67953964) Phase IIa study to assess key neural circuitry related to hedonic response.
- FAST-PS: Psychotic Spectrum
  - Develop imaging biomarkers to assess mGluR2/3 target engagement in the brain (Pomaglumetad methionil)

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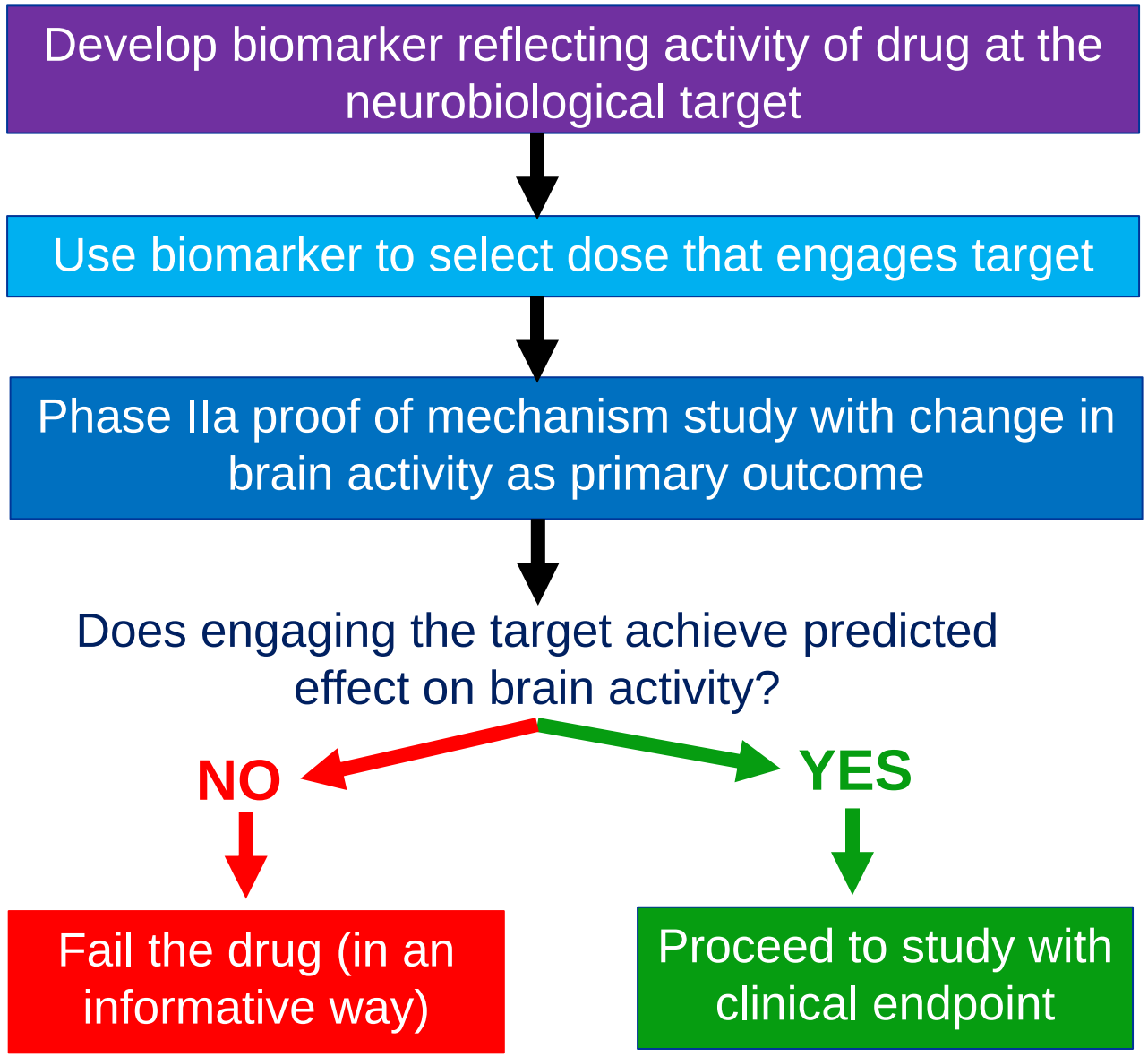
FAST-FAIL Approach



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FAST-MAS Trial Design

Biomarker: Kappa opioid receptor – PET ligand

↓

Selected dose with robust KOR antagonism

↓

Phase IIa POM study: inc ventral striatum activation during reward anticipation primary outcome

↓

Does engaging the target achieve predicted effect on brain activity?

NO → Fail the drug (in an informative way)

YES → Proceed to study with clinical endpoint

The first implementation of the NIMH FAST-FAIL approach to psychiatric drug development

Andrew D. Krystal, Diego A. Pizzagalli, Sanjay J. Mathew, Gerard Sanacora, Richard Keefe, Allen Song, Joseph Calabrese, Andrew Goddard, Wayne Goodman, Sarah H. Lisanby, Moria Smoski, Richard Weiner, Dan Iosifescu, John Nurnberger Jr, Steven Szabo, James Murrough, Anantha Shekhar and William Potter

Nature Reviews: Drug Discovery 2019; 18:82

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FAST-MAS Results

Application of the "Fast-Fail" Approach to Evaluating the Potential of Selective Kappa Opioid Antagonism as a Treatment for Anhedonia: A Randomized Proof of Mechanism Trial Assessing Effects on the Ventral Striatum

Andrew D. Krystal*[1,2], Diego A. Pizzagalli[3], Moria Smoski,[2] Sanjay J. Mathew[4,5], John Nurnberger Jr[6], Sarah H. Lisanby[7], Dan Iosifescu[8], James W. Murrough[9], Hongqiu Yang[10], Richard D. Weiner[2], Joseph R. Calabrese[11], Gerard Sanacora[12], Gretchen Hermes[12], Richard S. E. Keefe[2], Allen Song[2], Wayne Goodman[4], Steven T. Szabo[2,13], Alexis E. Whitton[3,14], Keming Gao[11], and William Z. Potter[7]

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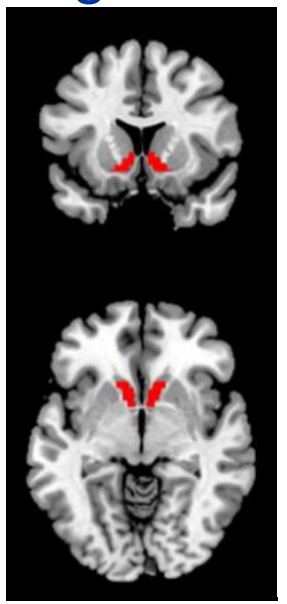
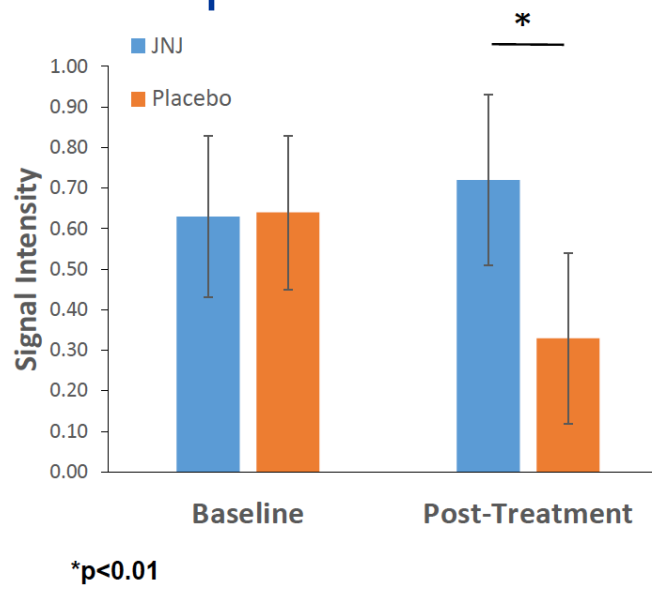
- Met go-criterion on primary outcome: inc fMRI ventral striatum activation during reward anticipation





Nature Medicine, 2020

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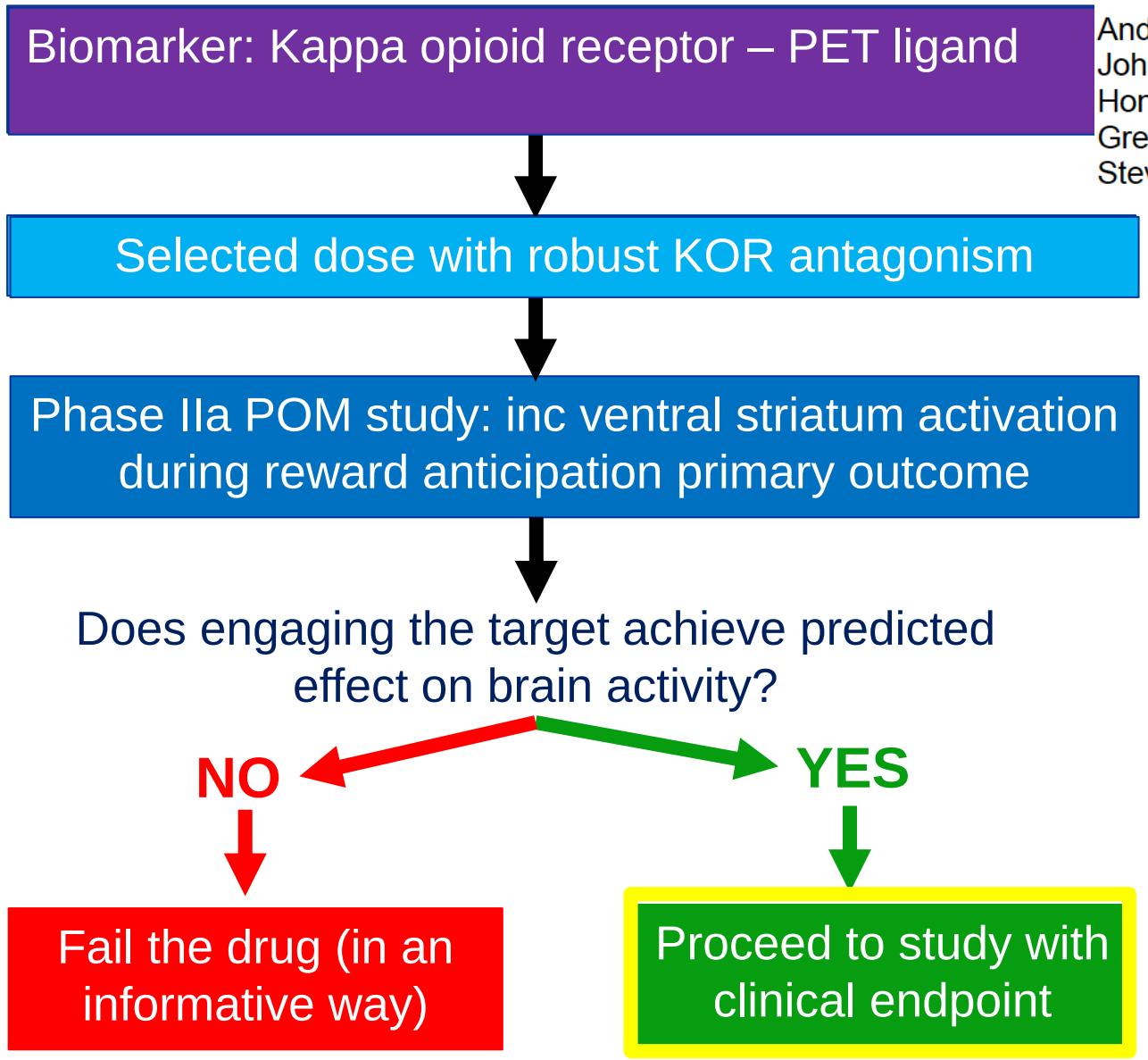

- Met go-criterion on primary outcome: inc fMRI ventral striatum activation during reward anticipation
- Proof of mechanism – engaging target impacted brain circuitry implicated in hedonic response

Nature Medicine, 2020

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FAST-MAS Results

Selective Kappa Opioid Antagonism Ameliorates Anhedonic Behavior: Evidence From the Fast-Fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS)

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Biomarker: Kappa opioid receptor – PET ligand

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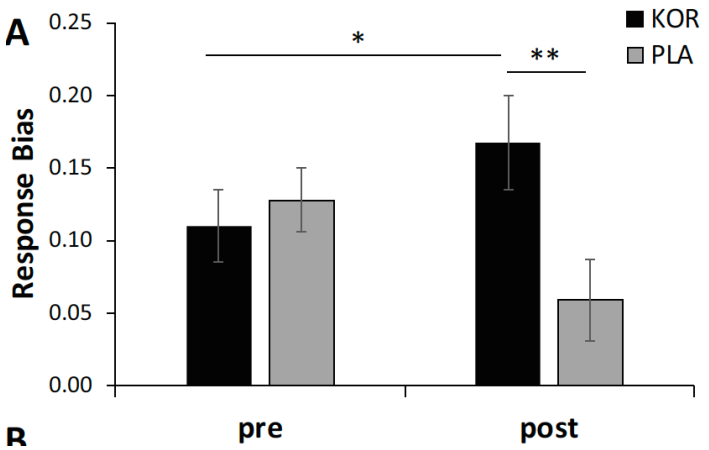
YES → Proceed to study with clinical endpoint



- Proof of concept – engaging target impacted anhedonic behavior

Neuropsychopharmacology. In Review

NIH National Institute of Mental Health

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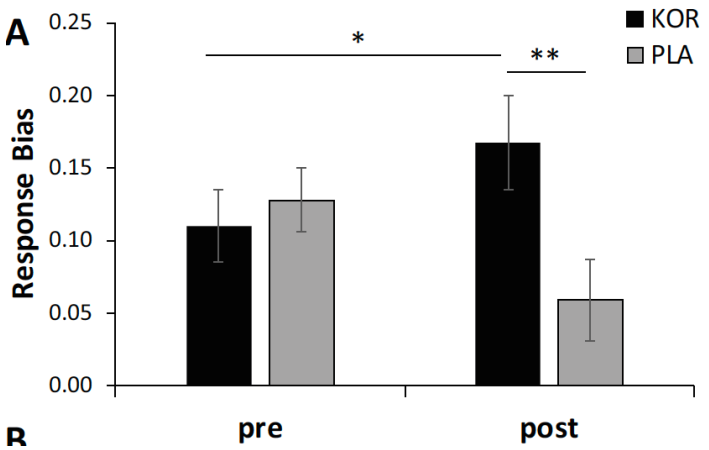

- Proof of concept – engaging target impacted anhedonic behavior
- Supports further study of KOR antagonism for anhedonia treatment

Neuropsychopharmacology. In Review

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Experimental Therapeutics - Impact

- FAST contract data became available (2018-ongoing)
  - Quality of data generated and collaborative input on project design led to interest from Pharma/biotech
    - NIMH contacted by companies to test their compounds
- NIMH Guide Notices issued to publicize interest in compound targets
  - Pediatric Pharmacologic Trials in Autism Spectrum Disorders, directed at testing selective GABAergic agents (NOT-MH-17-044)
  - Early Stage Clinical and/or Mechanistic Trials in Posttraumatic Psychopathology, Directed at Testing FAAH Inhibitors (NOT-MH-19-055)

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NOT-MH-19-055: Early Stage Clinical and/or Mechanistic Trials in Posttraumatic Psychopathology, Directed at Testing FAAH Inhibitors

- Notice of Special Interest (NOSI) in supporting early stage interventions of fatty acid amide hydrolase (FAAH) inhibitors in posttraumatic psychopathology.
- Hypothesis: endocannabinoid system is relevant to the onset, course, and potentially treatment of neuropsychiatric disorders, including those that occur following trauma exposure.
- FAAH inhibitors are a class of drugs for which there is adequate animal and human data publicly available to consider in designing trials, including relevant safety profiles which vary by compound.
- Interested in supporting early stage testing of FAAH inhibitors using a protocol design where the presumed mechanism(s) of action is adequately tested, to provide meaningful information where target modulation yields a dose-dependent neurophysiological/clinical/behavioral effect.

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Experimental Therapeutics - Impact

- FAST contract data became available (2018-ongoing)
  - Quality of data generated and collaborative input on project design led to interest from Pharma/biotech
    - NIMH contacted by companies to test their compounds
- NIMH Guide Notices issued to publicize interest in compound targets
  - Pediatric Pharmacologic Trials in Autism Spectrum Disorders, directed at testing selective GABAergic agents (NOT-MH-17-044)
  - Early Stage Clinical and/or Mechanistic Trials in Posttraumatic Psychopathology, Directed at Testing FAAH Inhibitors (NOT-MH-19-055)
- Generating new Industry/Academic/NIH collaborations
  - Cooperative Agreement (U01, U19) projects in development
    - Recently awarded project- D1/D5 R agonist collaboration with Cerevel (compound acquired from Pfizer, PF-06412562)

U01MH121766: A Translational & Neurocomputational Evaluation of a D1R Partial Agonist for Schizophrenia

- Dopamine D1R/D5R agonists have pro-cognitive and antipsychotic-like effects, but prior studies could not demonstrate dose-related effects, potentially due to lack of appropriate biomarker and sample heterogeneity
- Multi-center study to characterize dose-related effects of the D1R/D5R partial agonist, PF-06412562 immediate release (IR), on fMRI biomarkers (spatial working memory-related activation, task-based and resting-state functional connectivity), and targets a specific subpopulation of early course schizophrenia patients who may pro-cognitively respond to D1R/D5R agonism.
- Designed and powered for Go/No-Go decision

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Building Pharmacology in Child Psychiatry

- Molecular targets most relevant to the developing CNS may be very different from ones appropriate for adults
- Prior to evaluating efficacy, need to establish safety and appropriate doses by:
  - Establishing a pediatric trial model where drug candidates can be tested safely, even if it has not received formal approval in any adult indication
  - Establishing the framework that brings together the expertise of pediatric clinical pharmacologists, pediatric trial psychiatrists and the regulatory infrastructure support of CTSAs or CROs
  - Assessing novel mechanism of action drug candidates by quantifying immediate brain effects in pediatric populations
    - Pharmacokinetic/pharmacodynamic (PK/PD) bridging design
    - Registration-quality data that could be used in a regulatory approval package
  - Supporting the development of pharmacodynamic measures in pediatric populations, for use in drug testing
  - Training the next generation of pediatric psychiatrists in clinical pharmacology to sustain a future clinical pipeline for testing novel drug candidates

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Outline

- NIMH Overview, Strategic Plan, and Budget
- Challenges in Psychiatric Drug Development
- NIMH-Supported Research Advances
- Advisory Council Working Groups on Drug Development
- Responding to COVID-19

National Advisory Mental Health Council (NAMHC) Workgroup on Drug Development

- Created in 2019 to assess, discuss, and provide recommendations to NIMH on five research topics:
  - Define and evaluate target engagement
  - Address special populations
  - Assess the value of FAST Fail contracts
  - Consider supporting confirmatory efficacy trials
  - Support development of the neuroscience workforce
- Met most recently in May 2020
- Will develop preliminary recommendations into a written report for consideration by the full Council

National Advisory Mental Health Council (NAMHC) Workgroup on Clinical High Risk for Psychosis

- Goal
  - Bring together key public and private stakeholders in early intervention for schizophrenia to advise on initiatives to qualify biomarkers and clinical endpoint measures that reliably predict psychosis and non-psychosis outcomes over periods ranging from 18-24 months
  - Identify tools to improve treatment development for CHR for psychosis populations, for whom there exists a high unmet need
  - Mitigate risk in developing compounds for CHR by developing and validating biomarkers to enable the selection of enriched patient populations for clinical trials, allowing for more efficient testing of targeted interventions
- Charge
  - Review summary statements from applications received in response to:
    - *Clinical High Risk for Psychosis Research Network* RFA-MH-20-340
    - *Clinical High Risk for Psychosis: Data Processing, Analysis, and Coordination Center* RFA-MH-20-341
- Will inform a funding plan that will be provided to the NAMHC in August 2020

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National Institute of Mental Health

NIH and NIMH COVID-19 Guidance

- Information for NIH Applicants and Recipients of NIH Funding
  - NIH Late Application Policy Due to Public Health Emergency for U.S. for COVID-19
- NIMH issued a Notice of Special Interest (NOT-MH-20-047) to support research to strengthen the mental health response to COVID-19 and future public health emergencies
- NIMH is participating in two additional NOSIs:
  - NIMHD; Impact of COVID-19 on Minority Health and Health Disparities (NOT-MD-20-019)
  - NIA; Admin and Revision Supplements on COVID-19 (NOT-AG-20-022)

Coping with COVID-19: NIMH Resources

Coping With Coronavirus: Managing Stress, Fear, and Anxiety

*By **Joshua Gordon** on **March 16, 2020***

Supporting Mental Health During the COVID-19 Pandemic

April 3, 2020 • Institute Update

The outbreak of coronavirus disease 2019 (COVID-19) may be stressful – it can be difficult to cope with fear and anxiety, changing daily routines, and a general sense of uncertainty. Taking steps to care for your mental health can help you manage stress.

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NIMH Mission

www.nimh.nih.gov

Research = Hope

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COVID-19 Guidance

https://www.coronavirus.gov

Coronavirus (COVID-19)

How to prepare and protect yourself ›

What to do if you think you are sick ›

Coronavirus (COVID-19)

Click Here to Subscribe to COVID-19 Updates from NIH

https://www.nih.gov/coronavirus

Resources from NIH

- Information for NIH Applicants and Recipients (Grants & Funding)
- COVID-19 Social Media Resources
- Clinical Trials Related to COVID-19 Listed on ClinicalTrials.gov
- Rising to the COVID-19 Challenge: Rapid Acceleration of Diagnostics (RADx) (NIH Director's Blog)
- Coping with the Collision of Public Health Crises: COVID-19 and Substance Use Disorders
- The Challenge of Tracking COVID-19's Stealthy Spread (NIH Director's Blog)
- Pursuing Safe and Effective Anti-Viral Drugs for COVID-19 (NIH Director's Blog)
- Antibody Points to Possible Weak Spot on Novel Coronavirus (NIH Director's Blog)

News Releases from NIH

- NIH mobilizes national innovation initiative for COVID-19 diagnostics (NIH Office of the Director)
- NIAID strategic plan details COVID-19 research priorities (National Institute of Allergy and Infectious Diseases)
- Expert U.S. panel develops NIH treatment guidelines for COVID-19 (National Institute of Allergy and Infectious Diseases)
- NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options (Office of the Director)
- Antiviral remdesivir prevents disease progression in monkeys with COVID-19 (National Institute of Allergy and Infectious Diseases)
- Investigational chimp adenovirus MERS-CoV vaccine protects monkeys (National Institute of Allergy and Infectious Diseases)
- NIH study validates decontamination methods for re-use of N95 respirators

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