Center for
Precision Psychiatry
MGH Department of Psychiatry

TOWARD PRECISION PSYCHIATRY:
TIME TO RETIRE THE DSM AND BEGIN AGAIN

Steven E Hyman, MD

Broad Institute of MIT and Harvard

Harvard University

DISCLOSURES

Industry

- Director, Voyager Therapeutics
- Director, Cyclerion Therapeutics
- Director, Vesalius Therapeutics
- Scientific Advisory Board, J&J Innovative Medicines
- Scientific Advisory Board, F-Prime Capital
- Co-founder, Emugen

Nonprofit organizations

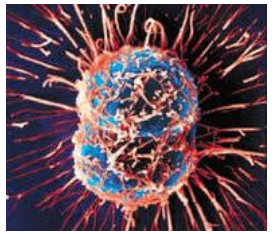
- Director (Chair), Charles A Dana Foundation, New York
- Director (co-Chair), Wyss Center for Bio- and Neuroengineering, Geneva, Switzerland

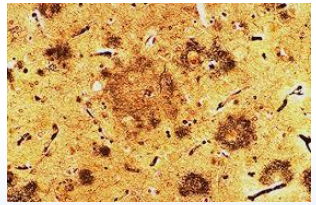
PRECISION MEDICINE ASPIRES TO IDENTIFY *THE RIGHT TREATMENT FOR THE RIGHT PATIENT AT THE RIGHT TIME*

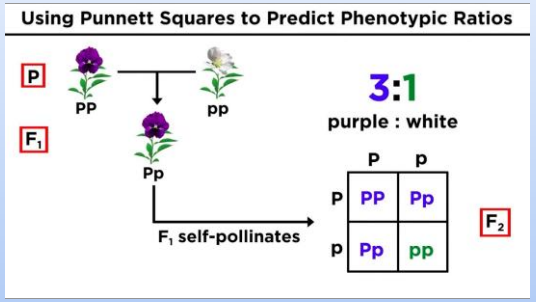
- What problems is Precision Psychiatry meant to solve?
  - High failure rates in clinical trials that leaves industry skeptical and psychiatry with limited treatment options
  - Need for trial-and-error prescribing; unacceptably variable treatment responses
- Why these problems?
  - Indistinguishable clinical presentations often mask diverse underlying biological mechanisms
- What must we discover to succeed?
  - Disease mechanisms and treatment targets that beneficially modify those mechanisms
  - Biomarkers that identify the patients likely to respond to those treatments (metaphorically we do not want to administer antibiotics to treat a cough caused by a viral infection or cancer)

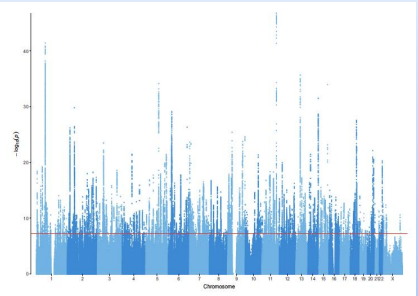
PSYCHIATRY WAS HISTORICALLY TECHNOLOGY-LIMITED IN ITS ABILITY TO CONFRONT NATURE'S CHALLENGES

- The human brain is arguably the most complex object of scientific investigation
  - In addition, healthy human brains exhibit vast background variability in gene expression, structure, physiology, and outputs such as cognition and behavior, further complicating study
  - Mechanisms of any common psychiatric disorder are also highly heterogeneous
- Unlike cancer or other organ pathologies that are routinely biopsied, access to living human brain tissue is highly restricted for medical and ethical reasons
- Psychiatric pathophysiology is subtle. No ground truth-like biological 'anchors' such as amyloid, tau, α-synuclein in neurodegenerative disorders
- Fiendish complexity of psychiatric genetics. Our brains are not like Mendel's peas
- No veridical animal models of psychiatric disorders









FOR PSYCHIATRIC RESEARCH NATURE'S OBSTACLES ARE REAL, BUT HUMAN CLASSIFICATION MADE MATTERS WORSE

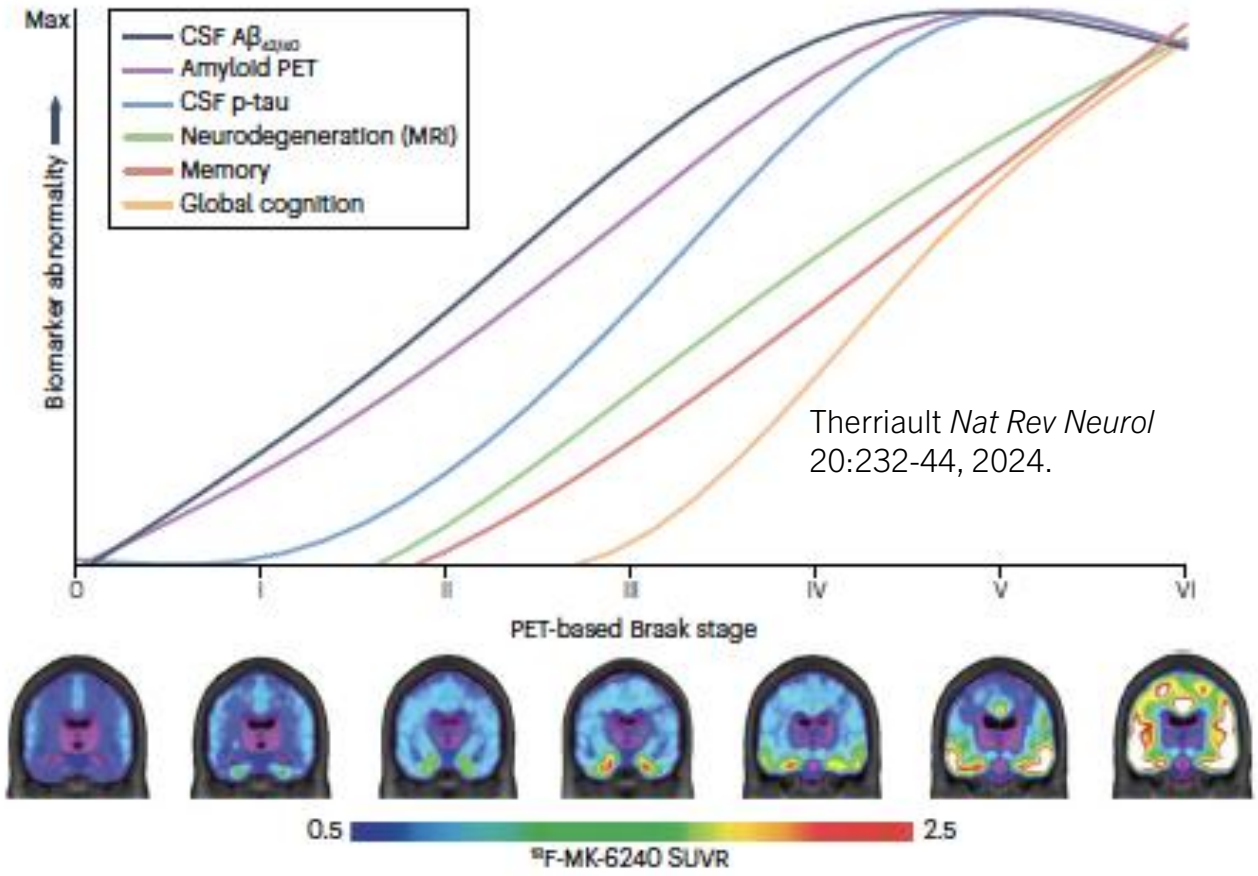
- Psychiatry has long been **technology limited**, lacking the tools to investigate healthy and pathological brain function, behavior, cognition, and emotion
  - The technological revolution of the 21st century has changed our scientific prospects:
  - Genomic and computational tools, single cell transcriptomics and epigenomics, brain cell atlases, connectomes, human IPSCs and organoids, advances in proteomics, AI/ML, etc.
- Psychiatry is now arguably **epistemically limited**, still focused on DSM categories
- A classification is a cognitive schema imposed on data to increase their intelligibility and utility for specific purposes. They are necessary but have risks
  - Classifications may reify named constructs and blind observers to novel or ill-fitting data
  - Despite disclaimers about validity, the DSM is widely embraced, required for many purposes,
  - As a result, investigation and clinical treatment tends to stay within the boxes and fails to see the anomalies and problems

EARLY EXAMPLES OF PRECISION MEDICINE FROM CANCER

- Breast cancer
  - A subset of aggressive breast cancers overexpress the Human Epidermal Growth Factor Receptor 2 (HER2).
  - HER2 biomarkers identify cancer cells that overexpress that protein and indicate HER2 directed treatments. These have no benefit for HER2 negative cancers
- Lung Cancer
  - Initial division of lung cancer into cell types e.g., small cell; non-small cell lung cancer (NSCLC)) and then further subdivided according to specific mutations in specific genes
  - Drugs for NSCLC initially declared failures (Iressa and Tarceva) were found to have extraordinary benefit to a subset (~11%) later identified by specific biomarkers
  - A standard workup now includes a panel of genetically defined biomarkers
- Tissue of origin (traditional cancer classification) is less important in treatment decisions than driver mutations. A given mutation may cause cancer in different tissues, e.g., BRAF mutations can cause melanoma, colorectal carcinomas, thyroid cancers and others

MECHANISM-BASED BIOMARKERS REVOLUTIONIZED CLINICAL TRIALS FOR ALZHEIMER DISEASE

- Lacking biomarkers, clinical dementia experts selecting for clinical trials failed to distinguish AD (amyloid, tau) from other causes of dementia (eg Lewy bodies) ~30% of the time based on autopsies
- Biomarkers are now required for AD clinical trials with amyloid-β and p-tau directed antibodies



Therriault *Nat Rev Neurol* 20:232-44, 2024.

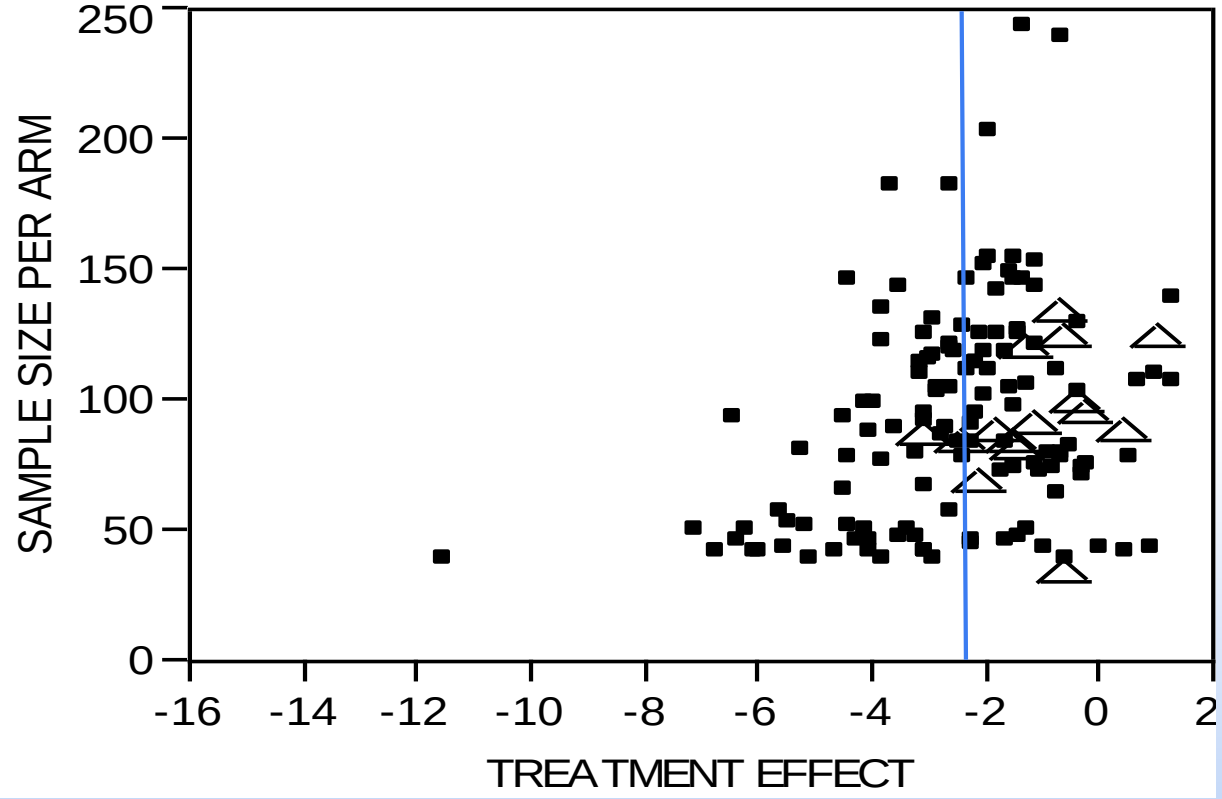
- Neurodegenerative disorders yield ground-truth-like biochemical clues :
  - Aβ & tau in Alzheimer's disease, α-synuclein in Parkinson's, Lewy body dementia
  - Current biomarkers for neurodegenerative disorders provide initial stratification, but significant progress is still needed

PRECISION MEDICINE REQUIRES KNOWLEDGE OF DISEASE MECHANISMS, TARGETS, AND WELL VALIDATED BIOMARKERS

- To Identify the right patient:
  - *Diagnostic biomarkers*
  - *Stratification biomarkers* (identify mechanism-based subgroups within a syndrome such as dementia or lung cancer)
- To ensure the right medicine at the right time
  - *Tracking* or *staging biomarkers to provide* objective measures disease progression
- To measure treatment efficacy
  - *Target engagement*
  - *Pathway modification*
  - *To identify and quantify biological treatment responses*
- Biomarkers can be genomic, proteomic, metabolomic, physiological, or imaging *so long as they are robust, replicable across labs, and ideally, quantitative*

LIFE WITHOUT BIOMARKERS: ANTIDEPRESSANT CLINICAL TRIALS IN COHORTS SELECTED FOR DSM MAJOR DEPRESSION.

Registration trials for major depression; all approved antidepressants. In this figure, treatment effects of all participants in each trial are averaged



Squares vs rectangles represent differently powered trials

Khin et al, *J Clin Psychiatry* 2011

Drug – Placebo differences on Hamilton rating scale:
Average gives and insignificant ~2 point change

DSM-based Major Depression in the absence of biomarkers

FDA *Individual–level data*: drug vs. placebo responses for DSM-diagnosed major depression (in registration trial for all approved antidepressants)

Distribution	Mean change from baseline	SEM	SD	Estimated proportion of overall population			
				Active drug	95% CI	Placebo	95% CI
Large	-16.00	0.22	4.22	24%	20% to 29%	10%	6% to 13%
Minimal	-1.68	0.11	2.99	12%	10% to 14%	21%	19% to 24%
Non-specific	-8.94	0.15	6.96	63%	58% to 69%	69%	65% to 73%

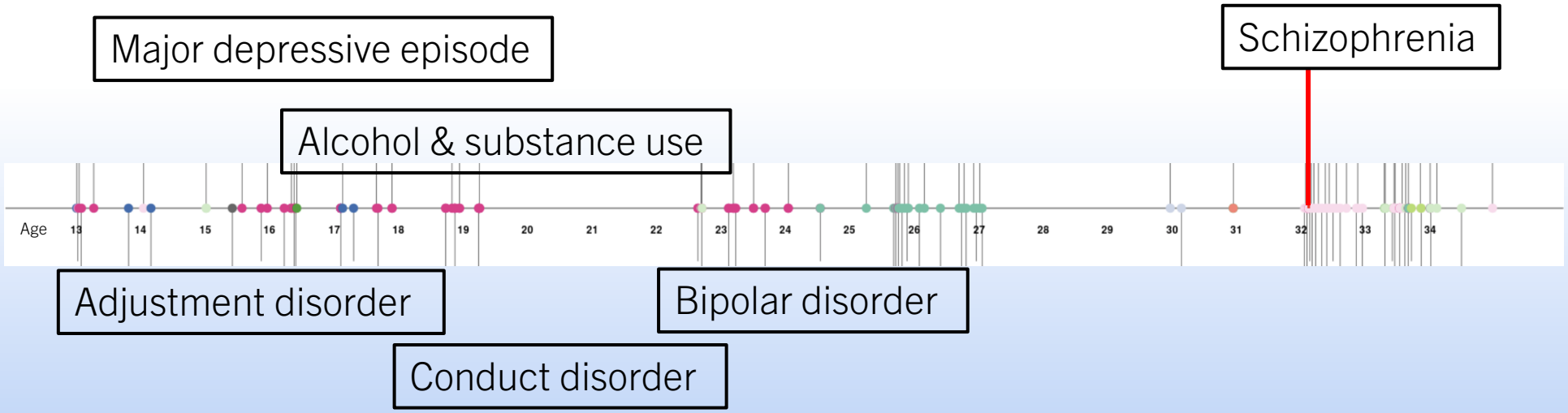
Change measured by HAMD17+Hamilton rating scale for depression.

- The patient cohorts identified by DSM criteria show high heterogeneity of response
- Only ~24% have large drug-placebo responses (consistent with STAR*D trial)
- The non-specific category contains highly confounded drug and placebo responses and shows lower benefit, consistent with different underlying mechanisms

Stone et al. BMJ 2022; 378:eo67606

DSM/ICD CATEGORIES CONFOUND BOTH TREATMENT DECISIONS AND CLINICAL RESEARCH

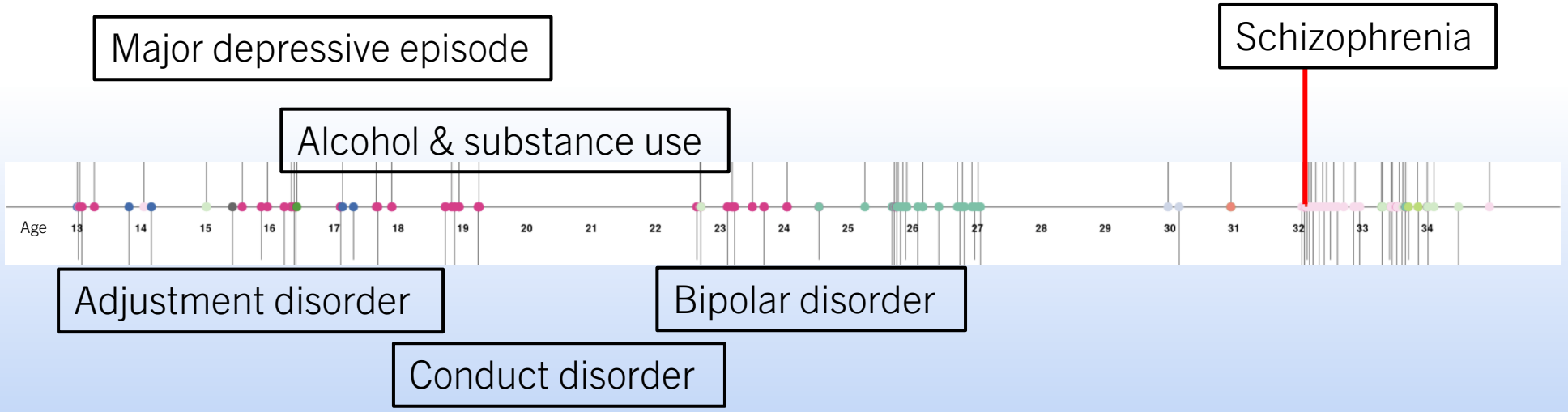
- At age 16 this patient could have been included in a genetics or imaging study of MDD, at 24 of bipolar disorder, and at 32 of schizophrenia—of course with no change in the patient's genome
- Descriptive psychiatry cannot provide insight into the mechanisms that cause this changing clinical picture, evolving in the context brain development and new environmental exposures
- Descriptive psychiatry—literally box by box—condemns patients to symptomatic, trial-and-error Rx



Patient enrolled in Finland SUPER Study
Acknowledgment: Anders Kämpe, Aarno Palotie, Finnish Institute of Molecular Medicine

PROGRESS TOWARD PRECISION REQUIRES EXCLUSION OF THE DSM FROM RESEARCH DESIGNS

- The categories named in the boxes do not identify coherent, mechanistically homogeneous diseases. Is this a patient with at least 6 categorically independent comorbidities?
- DSM categories have arbitrary thresholds and boundaries with no correspondence to human biology
- It would be a fool's errand to search for subtypes or biomarkers within these arbitrarily drawn boxes
- Research must begin anew with the patient, not the boxes to discover stratification and tracking biomarkers



Other possible diagnoses excluded for simplicity:

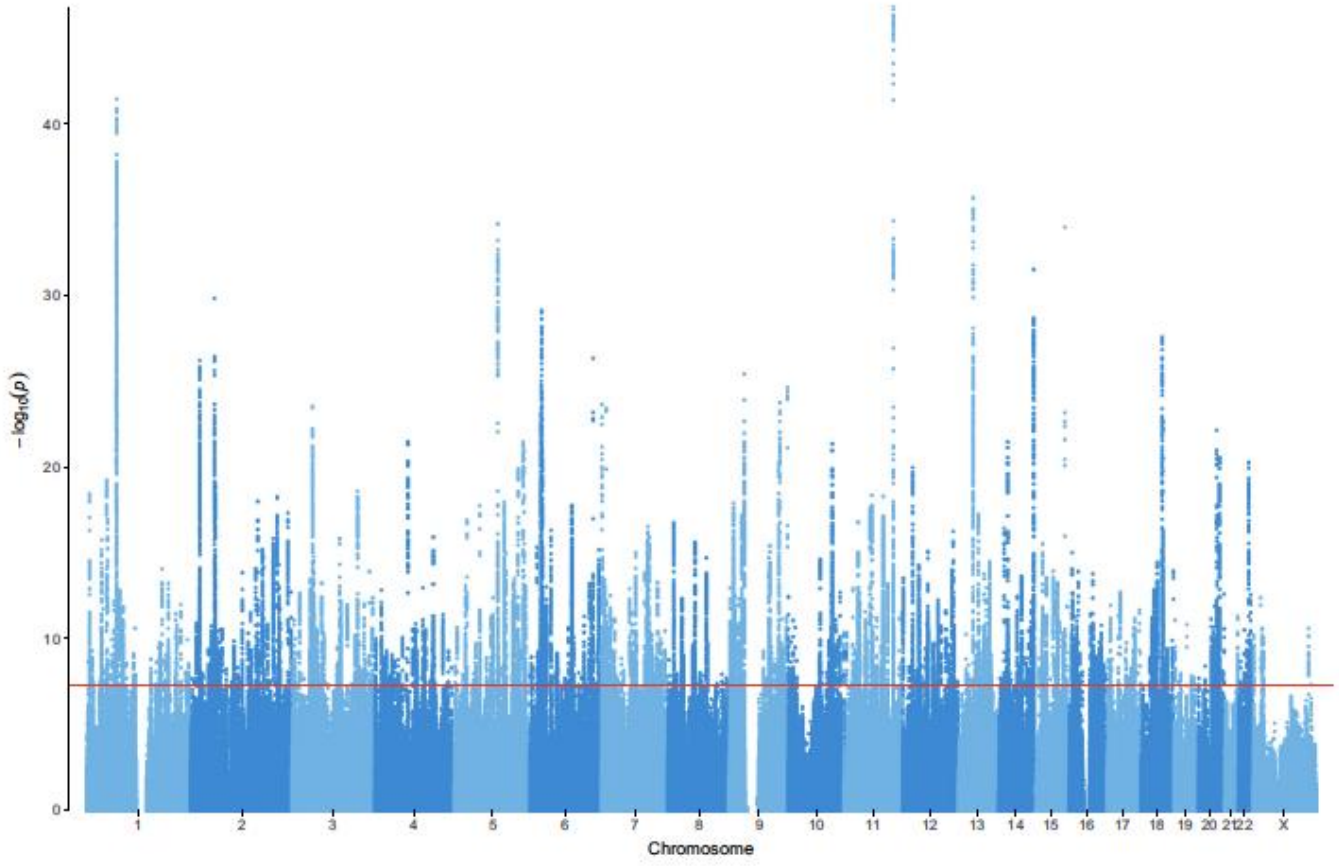
- Schizophreniform
- Schizotypal
- Schizoaffective
- Other schizophrenia spectrum disorder
- Other psychotic disorder

Patient enrolled in Finland SUPER Study

Acknowledgment: Anders Kämpe, Aarno Palotie, Finnish Institute of Molecular Medicine

MAJOR DEPRESSION GWAS: CASE CONTROL WITH NO BIOMARKERS: HOW MANY DIFFERENT MECHANISMS?

Participants selected by descriptive DSM/ICD or simpler criteria for Major Depression GWAS meta-analysis of 688,808 cases and 4,364,225 controls yielding 635 significant loci



A useful concept: the 'phenocopy' was originally defined as an environmentally caused mimic of a genetic phenotype—but usefully expanded in era of complex genetics to indicate different mechanistic bases for indistinguishable phenotypes

- Major Depression is a congeries of phenocopies
- How can the risk variants be clustered into distinct or overlapping mechanisms?
  - Surface level phenotyping cannot help
  - Mechanism-base biomarkers are needed to connect patient-level genotypes with disorder phenotypes.

McIntosh, A. & Major Depressive Disorder Working Group of the Psychiatrics Genomics Consortium. *Cell*, 188: 2025

OUR BRAINS ARE NOT LIKE MENDEL'S PEAS

- Psychiatric disorders are extremely polygenic, influenced by thousands of common genetic variants (alleles) of small effect distributed across the genome.
- Given that risk variants, everyone likely has some degree of loading relevant to all psychiatric disorders, sometimes significant loading for multiple disorders as now diagnosed. (Despair proponents of eugenics.)
- An affected individual has a stochastic grab bag of risk alleles above some threshold, together with pathogenic exposures (which like many risk alleles are shared across disorders) and bad luck during development
- Given sharing of alleles across disorders (DSM schizophrenia and bipolar disorder have a genetic correlation of 0.7), and shuffling of widely distributed risk alleles at meiosis, multiple disorders occur within pedigrees, symptoms vary widely within and between families, and symptoms are shared within single putative disorders.

A REASONABLE BUT UTTERLY FAILED ATTEMPT TO GROUND DIAGNOSIS IN PHENOMENOLOGY: ROBINS AND GUZE (1970)

- The work of the descriptive psychiatrists, Robins, Guze, and colleagues, was foundational to the paradigm-setting DSM-III,
- Robins and Guze argued (1970) that reliable and valid diagnoses would result from the convergence of:
  - *Clinical description*
  - *Laboratory studies*
  - *Delineation of one disorder from another* (as Kraepelin attempted for schizophrenia and bipolar disorder—and ultimately doubted that he could distinguish them)
  - *Follow-up studies* (stability of diagnosis over the life course)
  - *Family studies* (prediction that disorders would 'breed true' within families)
- These proposed validators do not converge on unitary valid disorders; putative disorders are not distinct from each other, share risk alleles and exposures, share neurobiology, and do not breed true
- Extreme polygenicity and diverse exposures yield mechanistically heterogeneous syndromes.

THE PARADIGM SETTING DSM-III WAS RIDDLED WITH ERRORS BEYOND ITS NECESSARY RELIANCE ON PHENOMENOLOGY

- Discontinuous categories have never been empirically justified
  - Symptoms are normally distributed in populations- no bright lines in nature
  - Common DNA variants that explain most genetic risk for psychiatric disorders are also normally distributed as illustrated by polygenic scores.
  - Diagnostic thresholds are arbitrary and do not account for developmental stage or context
- DSM categories manage to be both *too broad* (combining heterogeneous conditions) and *too narrow* with unjustified, rampant splitting into ~300 categories.
  - Remarkably high rates of comorbidity; In the National Comorbidity Study Replication, >50% of people with a any DSM diagnosis had two or more diagnoses
  - DSM disorders show significant sharing of both common and rare alleles (e.g., schizophrenia and bipolar disorder share ~70% of their common variants and ultrarare, high impact variants such as AKAP11

INITIAL SUMMARY: PSYCHIATRY'S CURRENT PREDICAMENT

- Heterogeneous disease mechanisms, opaque to current DSM descriptive diagnoses

  Descriptive psychiatry (DSM/ICD/HiTOP) cannot deconvolute heterogeneity because different genetics, exposures, or pathophysiologic processes can produce *indistinguishable phenotypes*.

  Even Kraepelin, at the end of has career doubted whether he had separated dementia praecox from manic depressive insanity based on his method of careful description

- Because DSM is blind to underlying mechanistic differences. it has hobbled case-control research designs, including clinical trials, genetics, and imaging studies

  Industry has disinvested in new psychiatry research because of clinical trials failures

  <30 years of MRI imaging has not been able to contribute to diagnosis

- Descriptive psychiatry, reified and disseminated by the DSM system, saddles psychiatric research with putative disorders comprised of an unknown number of 'phenocopies.'

WHAT IS TO BE DONE?

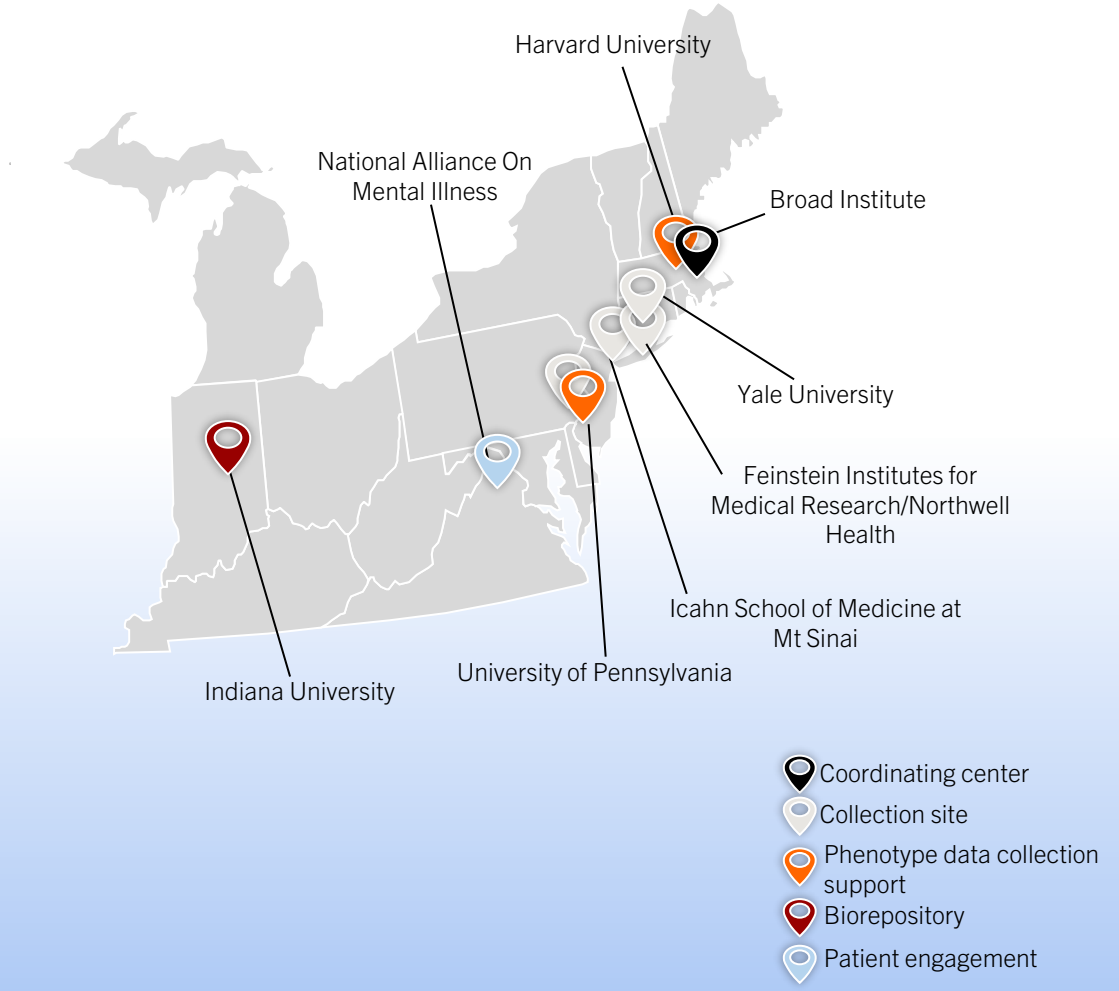
- Start anew. Eschew individual diagnoses and begin new studies with broad spectra
  - Shared genetics and rates of comorbidity as employed by HiTOP can help with design
  - Psychosis spectrum (inclusive of bipolar 1 disorder); Depression-anxiety spectrum
- The ADNI model from neurodegeneration research may be one good place to begin:
  - Longitudinally collect and bank CSF, blood, cells, DNA along with appropriate phenotyping
  - Rigid standards and quality control; need fully independent replications & different populations
  - Given complexity of correlations AI will help, but rigorous statistics and skepticism are critical
- For mood disorders and OCD, neurophysiology in the service of personalized closed loop deep brain stimulation is another place to start
- As research progresses, develop and validate measurement scales, propose and test diagnostic and treatment thresholds working with FDA and EMA
- Address diagnostic families one at a time, replacing DSM definitions only as mechanisms, scales, and biomarkers are validated.
- Involve multiple disciplines, countries, sectors-–including those with lived experience

THE PSYCHIATRIC BIOMARKERS NETWORK (PBN)

Fluid Biomarker Discovery for the Psychosis Spectrum

- Inspired and advised by ADNI investigators
- Broad inclusion anchored by traditional schizophrenia and bipolar 1 disorder
- Repository of cerebrospinal fluid (CSF), peripheral blood (serum, plasma), frozen cells, and DNA collected under rigorously standardized protocols in patients and unaffected controls, longitudinally with deep phenotypes
- Importance of paired CSF and blood for eventual clinical translation
- Test both genetically informed hypotheses (e.g., excessive synapse elimination) and facilitate unbiased proteomics to identify new biomarker candidates
- Key partnerships: Industry (J&J) and patient groups National Alliance on Mental Illness
- Communication and harmonization with independent groups in Europe

PBN study sites, July 2021-present



LONGITUDINAL PROSPECTIVE STUDY PROTOCOL

https://psychiatricbiomarkers.org

Collected at baseline and at 6M intervals

Collected at baseline and at 12M intervals

Participant Populations

Schizophrenia Spectrum Disorders

Bipolar I Disorder

Healthy Controls

Clinical Assessments

Socio-demographics
Medical & psychiatric history
C-SSRS
NetSCID, PANSS
GF Role/Social, SOFAS
YMRS, QIDS-C, ACES, PSQI, MEQr
PNC substance use

Cognitive Assessments

Penn Neurocognitive Battery (WebCNP)

Neuroimaging

T1/2, diffusion, and brief resting state functional MRI

Blood Collection

Plasma
Serum
Blood for DNA & RNA
PBMCs *(optional)*

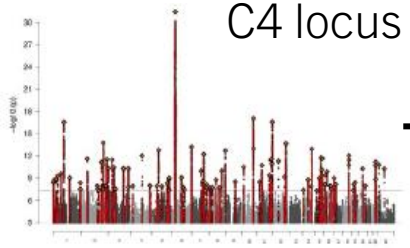
Lumbar Puncture

CSF cells
CSF aliquots

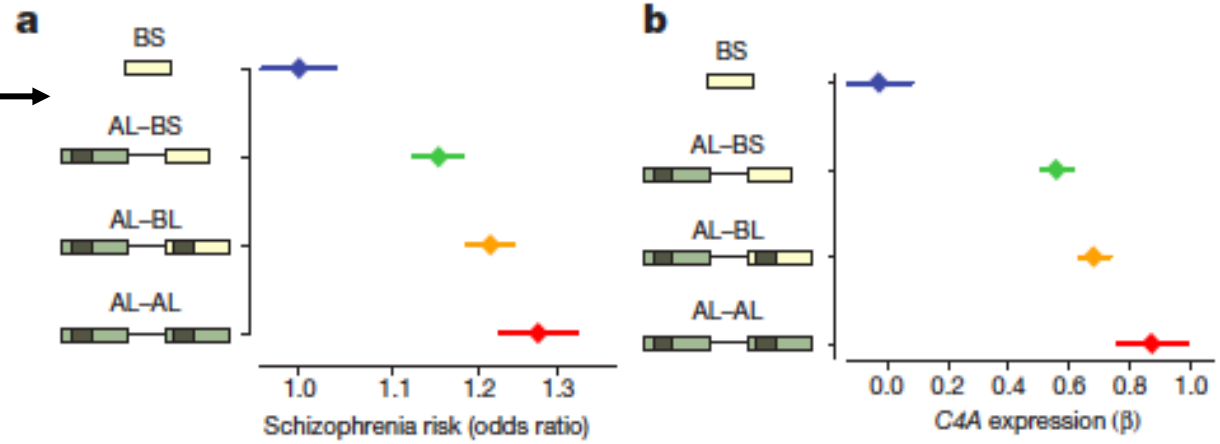
- Biological samples are sent to the **Indiana University Genetics Biobank** for processing, storage, and further distribution to analysis labs
- All data collected and generated from samples is **aggregated at the Broad Institute** in a cloud-based database for collaborator access

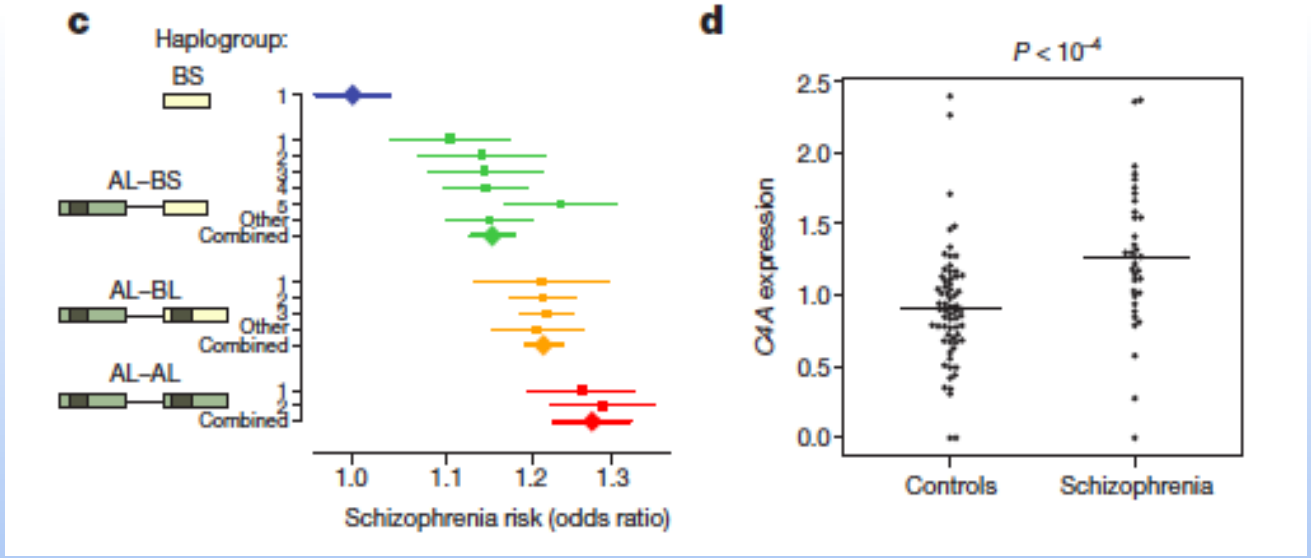
Terra

Association of Complement factor C4A gene with schizophrenia revitalized interest in synapse elimination hypotheses



C4 locus





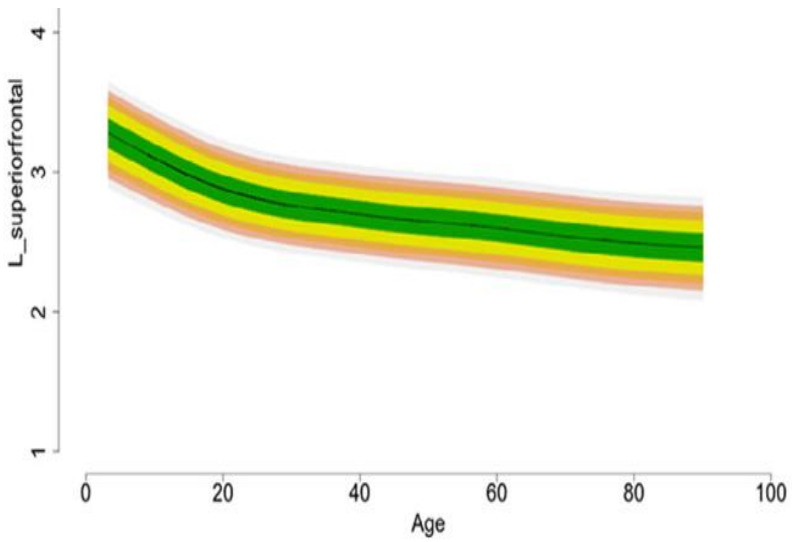
Schizophrenia risk increases with number of copies of C4A and higher levels of brain C4A RNA

C4A protein level is elevated in post-mortem brains in schizophrenia *after normalizing for genotypes*

Steve McCarroll

Aswin Sekar

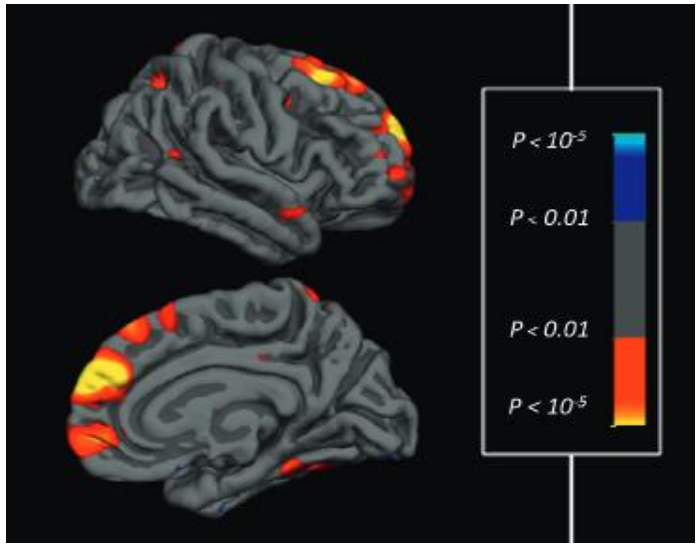
NEUROBIOLOGICAL DATA SHOWING NORMAL AND PATHOLOGICAL SYNAPSE LOSS IN SCHIZOPHRENIA



- Trajectory of frontal grey matter thickness by age

Frangou et al 2021

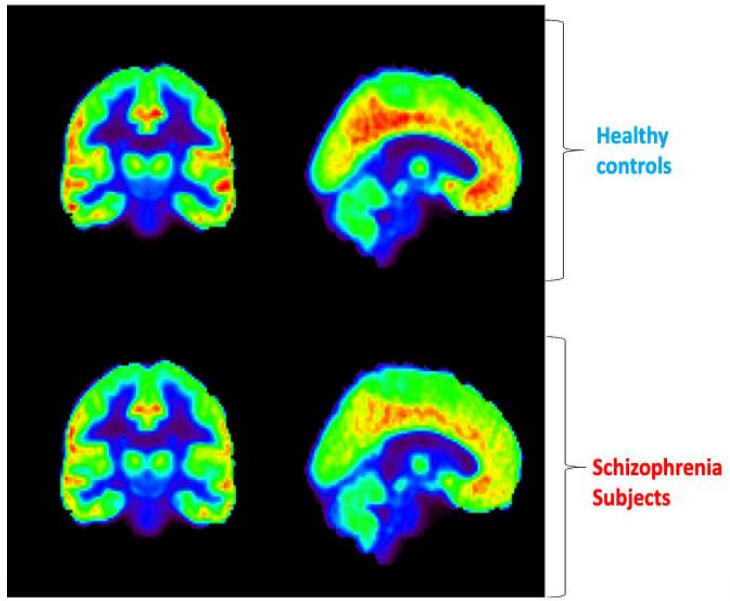
Structural MRI of ~17,000 healthy individuals



Difference in longitudinal *rate of change* in converters to psychosis

Cannon et al., 2015

- Excessive cortical thinning demonstrated by structural MRI
- Consistent with post-mortem finding of loss of dendritic spines and synapses

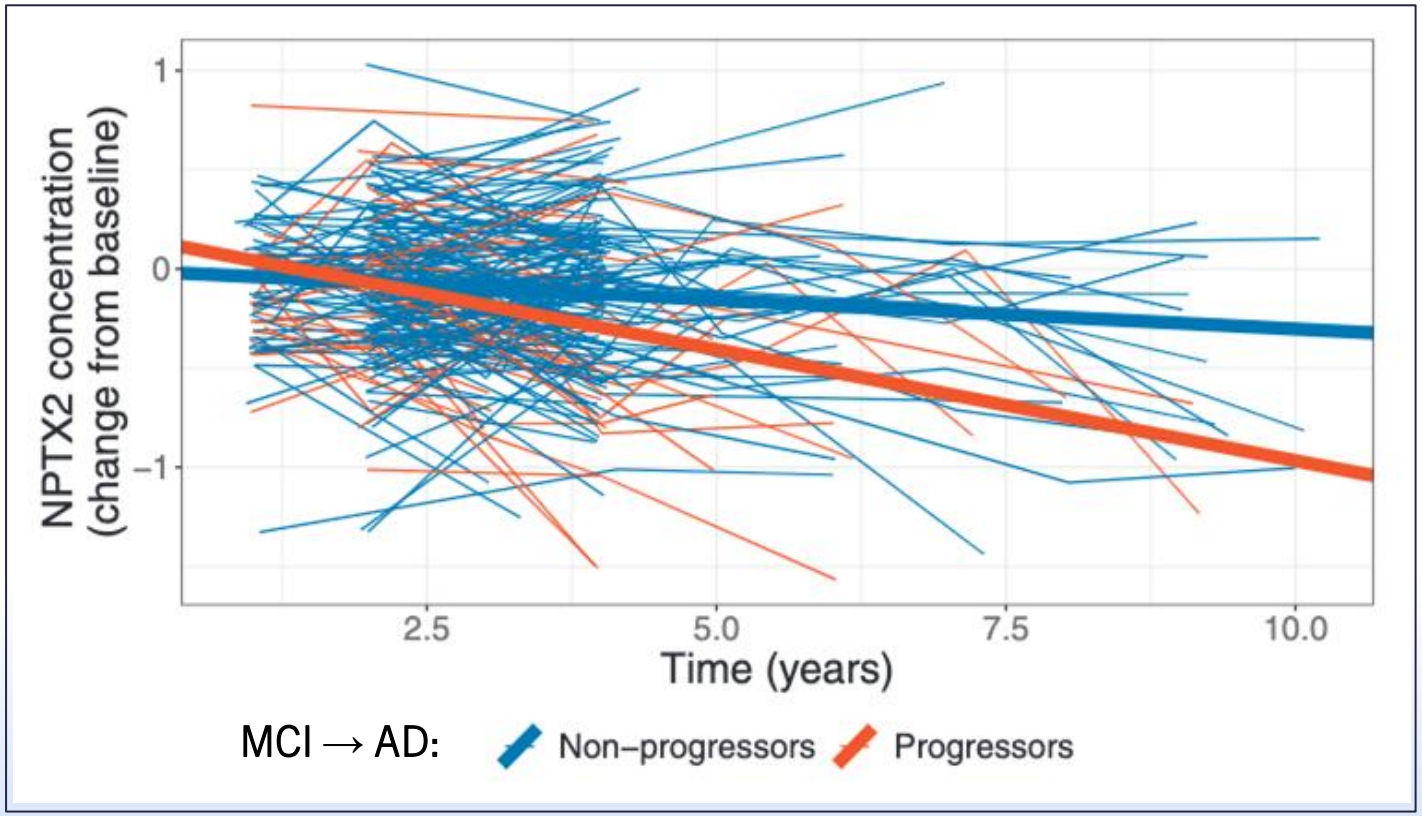


Synaptic Vesicle Glycoprotein 2A (SV2A) PET

Radhakrishnan et al, 2021

- Reduction in SV2A PET signal is consistent with fewer synapses in schizophrenia

Neural Pentraxin 2 (NPTX2) as a prognostic biomarker for cognitive decline in Alzheimer disease



Longitudinal change in CSF NPTX2 levels corresponded to **progression** from mild cognitive impairment to AD over 7-10 years.

Libiger et al./ADNI/FNIH (2021)

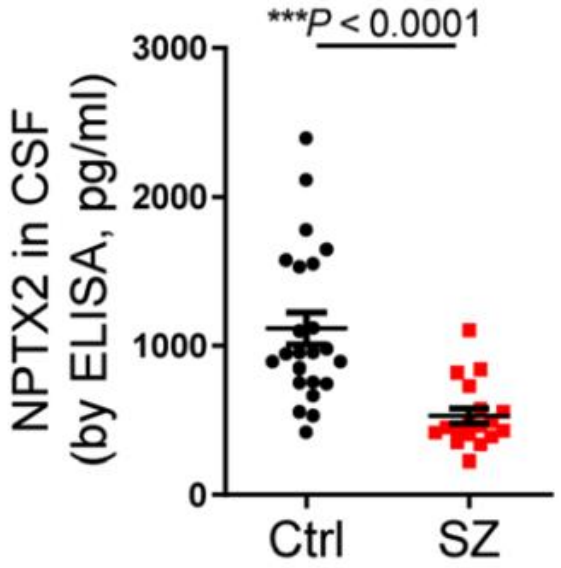
NPTX2 IS ALSO REDUCED IN CSF FROM PATIENTS WITH PSYCHOSIS SPECTRUM DISORDERS

SCIENCE ADVANCES | RESEARCH ARTICLE

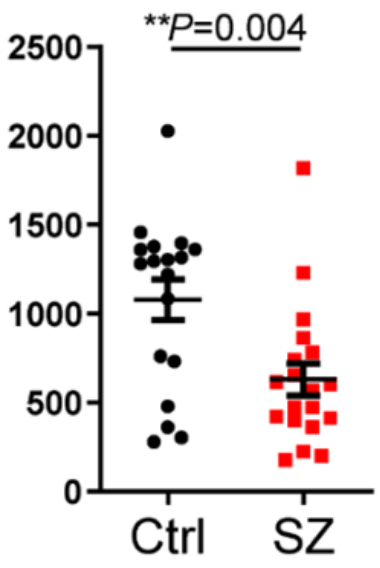
NEUROSCIENCE

A biomarker-authenticated model of schizophrenia implicating NPTX2 loss of function

Discovery Cohort



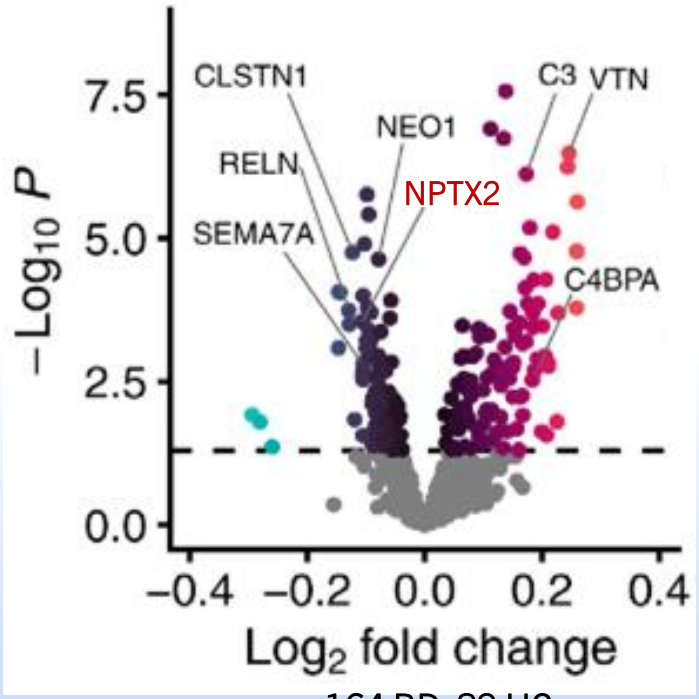
Replication Cohort



Xiao, Roh, …Worley, *Sci Adv* (2021)

Mapping the Cerebrospinal Fluid Proteome in Bipolar Disorder

Andreas Göteson, Jessica Holmén-Larsson, Hatice Celik, Aurimantas Pelanis, Carl M. Sellgren, Timea Sparding, Erik Pålsson, Henrik Zetterberg, Kaj Blennow, Lina Jonsson, Johan Gobom, and Mikael Landén



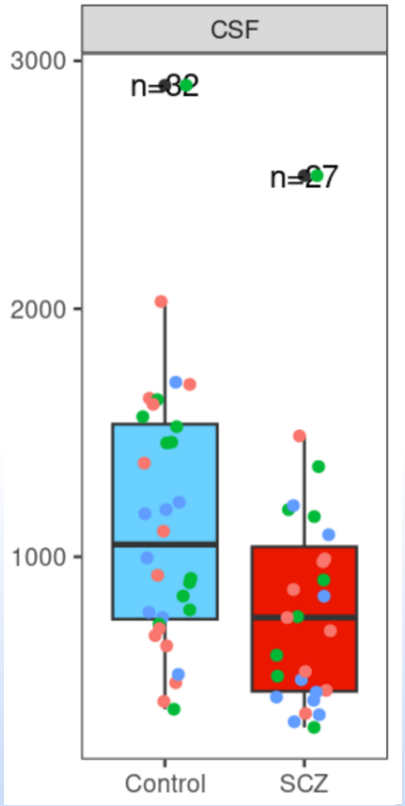
n=164 BD, 89 HC

Goteson et al., *Biol Psychiatry* (2025)

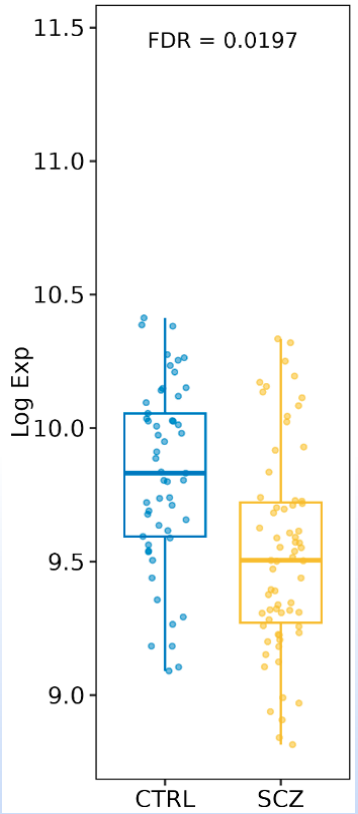
➢ *no cognitive phenotyping, no longitudinal follow-up*

NPTX2 IS REDUCED IN CSF IN THE PBN COHORT OF PSYCHOSIS SPECTRUM PATIENTS

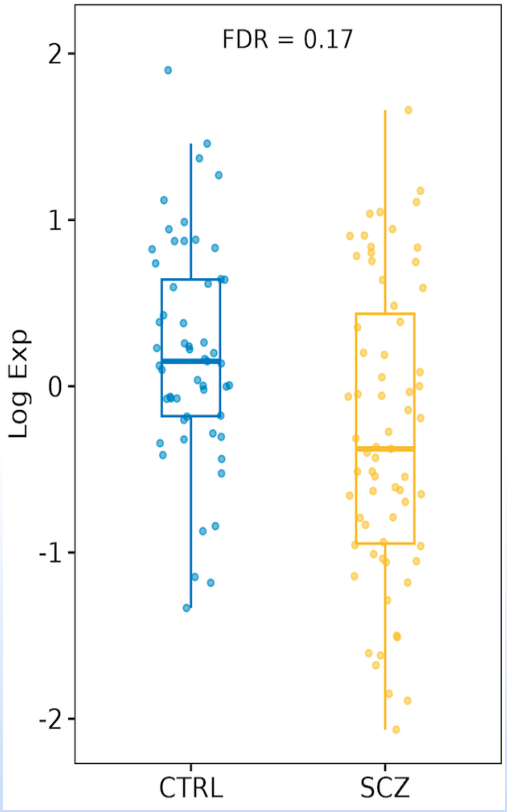
ELISA



Somascan



Olink



Study Site

- Icahn School of Medicine at Mount Sinai
- Perelman School of Medicine
- Yale University, School of Medicine

J&J Innovative Medicine

Gallen Triana-Baltzer and colleagues, J&J; additional analysis by Vishal Sarsani, Stanley Center

FLUID SYNAPTIC MARKERS WORKING GROUP

Partners

Biopharmaceutical: 9 Biotechnology: 4

Nonprofit: 5 Academic: 4

Public: FDA, NIMH, NIA

FNIH

BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

Psychiatric Biomarkers NETWORK

UNMET NEED: PRE-SYMPTOMATIC AND PREDICTIVE SYNAPTIC BIOMARKERS IN AD AND PSYCHIATRIC DISORDERS

AD Synaptic Biomarkers Needed	Psychiatric Biomarkers Lacking	Fluid-Based Synaptic Markers
AD involves synaptic dysfunction and loss, but gold standard biomarkers are lacking; crucial for early intervention.	Biomarkers do not exist for psychiatric disorders like schizophrenia and bipolar disorder. Emerging evidence for synapse dysfunction makes this target area a priority.	Synaptic proteins in CSF and blood show promise as CNS biomarkers, supporting less-invasive tests for synaptic dysfunction and related pathologies.

FNIH