STANLEY CENTER
FOR PSYCHIATRIC RESEARCH
AT BROAD INSTITUTE

Precision Medicine in Neuroscience

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Statement of outside interests

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 therapeutics

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 Medicine in Neuroscience meant to solve?
  - High clinical trials failure rates for psychiatry, neurology, pain; industry investment discouraged
  - Trial-and-error prescribing for many brain disorders (e.g., depression, psychotic disorders, migraine, epilepsy, chronic pain)
  - Unacceptably variable treatment responses; confounding of treatment response with placebo effects (e.g., depression, pain syndromes, movement disorders)
- What are the obstacles?
  - Indistinguishable clinical presentations often mask diverse underlying biological mechanisms
  - Continuing reliance on intrinsically heterogeneous decretive/syndromal diagnoses.
- What is to be done?
  - Discover disease mechanisms that can inform biomarkers and disease relevant treatment targets
  - Biomarkers that identify patients most likely to respond to matched treatments, permit treatment-relevant disease staging, and identify true biological treatment responses.

Precision Medicine-initial success in cancer

- Aspiration: Right treatment for the right patient at the right time
- Scientific Foundation: Insight into disease mechanisms that mean meaningfully inform patient stratification, disease staging, and treatment response independent of placebo.

- Illustration: Gefitinib for non-small cell lung cancers (NSCLC)
- Gefitinib targets the epidermal growth factor receptor (EGFR), which is overexpressed in ~80% of NSCLCs
- Yet initial clinical trials appeared to have failed
- But it was recognized that ~10% of patients were strong responders, who were initially lost in the noise
- NSCLC patients are now stratified by particular EGFR mutations

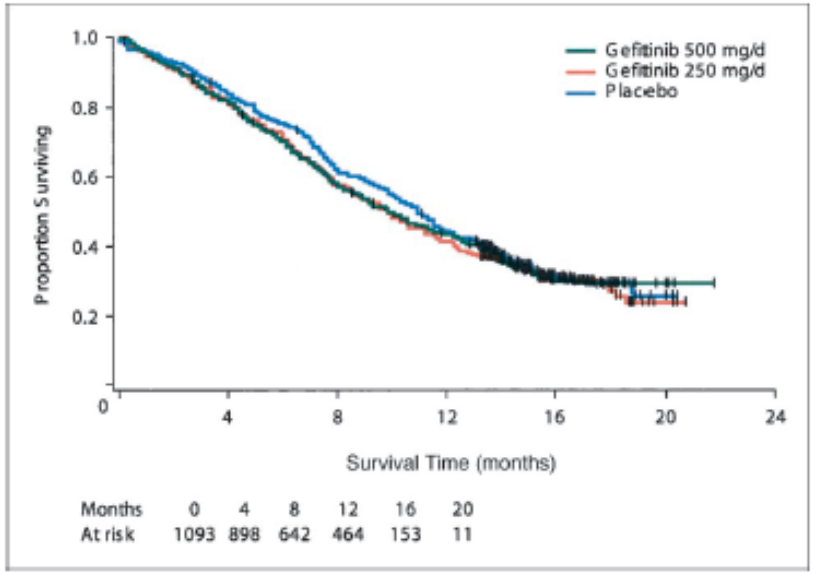


Fig 2. Kaplan-Meier estimates of overall survival in each treatment group. (global ordered log-rank $P = .4560$).

Lynch et al. N Engl J Med 350:2129, 2004

Giaccone et al J Clin Oncol 22:777-784, 2004

Precision Medicine in Neuroscience—Challenges

- Cancer is a hard problem beyond detecting and targeting gene products of penetrant somatic mutations with monoclonal antibodies
  - Additional mutations associated with Rx resistance, tumor microenvironment including vascular and immune cells
- *However, Clinical neuroscience is a harder problem*
  - Complexity and interindividual variability of human brains
  - Highly restricted access to living brain tissue—unlike cancer, other organ pathologies
  - Paucity of veridical animal models of disease
  - Fiendishly complex genetics, environmental risk factors for all psychiatric and most neurologic disorders—excepting some but not all monogenic disorders
  - Overlapping symptoms, genetics and environmental risks for many disorders

Beyond scientific challenges, epistemic obstacles remain critical

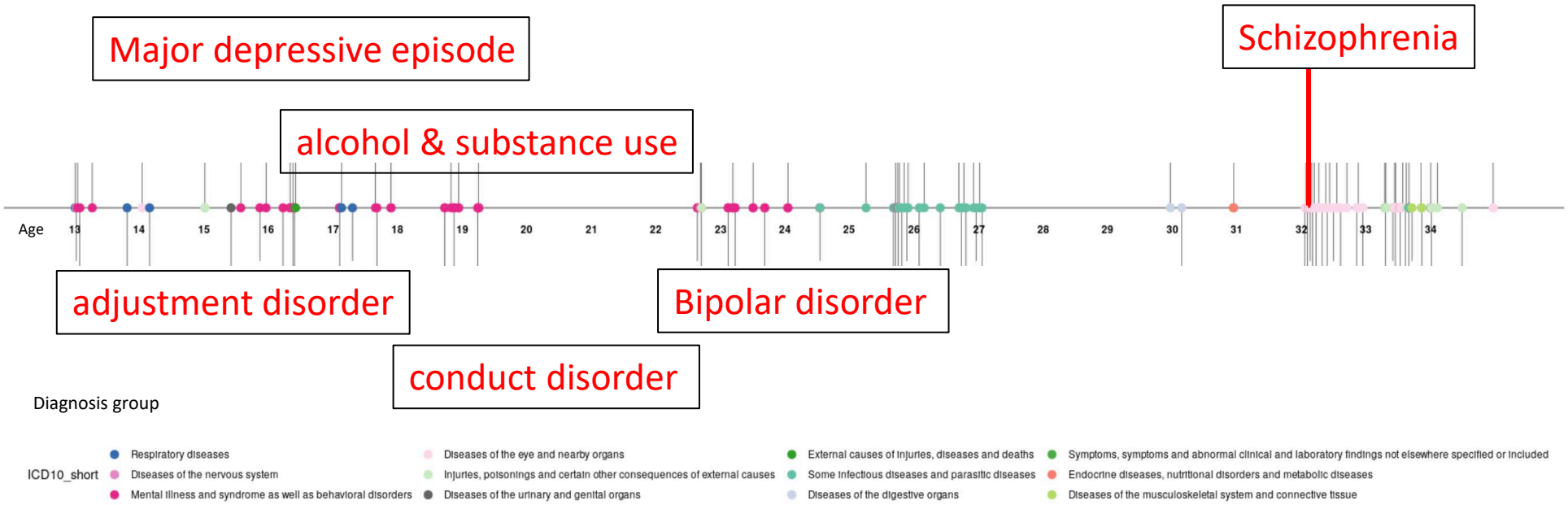
- Disease/Disorder definitions
  - Reliance on descriptive/syndromal diagnoses blind to mechanistic heterogeneity
    - Universal in psychiatry; frequent in neurology even for neurodegeneration after initial biomarker stratification where possble
    - Disease staging poorly accounted for. "Too late" is not rational staging
  - Cryptic heterogeneity of cases leads to small effect sizes & poor replicability in case-control studies—including clinical trials
- Inappropriate use of model organisms: while needed to investigate basic biological mechanisms, rarely if ever yielding veridical disease models
- *This workshop can represent a call to action to prioritize deconstruction of syndromes by mechanism.*

In the absence of biomarkers, case-control studies including clinical trials—often yield small effect sizes and poor replicability

- In medicine, different mechanisms can produce clinically indistinguishable syndromes
- In biology, convergent evolution often produces morphologically or behaviorally indistinguishable phenotypes, even mimicry
- Descriptive criteria used to select 'cases' in many case-control studies (all in psychiatry) represent a congeries of mechanism & phenocopies
  - **Clinical trials often fail when** using cryptically heterogeneous syndromal inclusion criteria
  - More than 30 years of case-control **MRI studies in psychiatry** have not resulted in clinical utility except to rule out a structural neurologic lesion
  - In **genetics**, well powered studies of syndromes yield statistically significant risk variants, but no insight into how the variants might cluster in meaningfully stratified patient groups

The nightmare of descriptive nosology in psychiatry

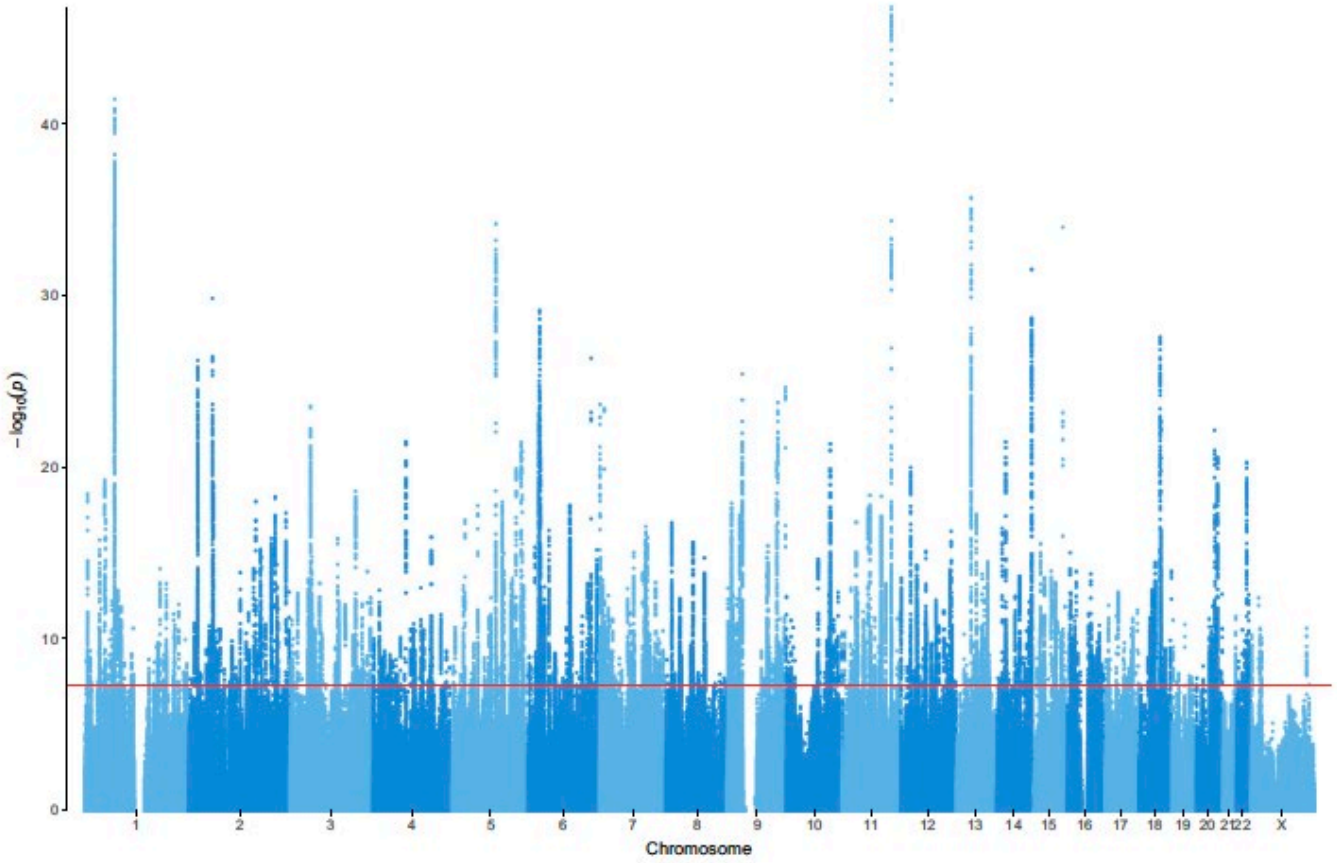
- At age 16 this patient could have been included in a genetics or imaging study of MDD, at 24 of bipolar disorder, and at 32 of schizophrenia—of course with no change in the patient's genome
- Descriptive psychiatry cannot provide insight into the mechanisms that cause this changing clinical picture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



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

Major Depression GWAS: Meta-analysis of case control studies without ground truth or diagnostic anchors: 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



- DSM Major Depression is a mixture of phenocopies
- In addition, shallow phenotyping (e.g., self-report), contaminates results with heritable confounds, obscuring disease relevance, and inflating cross disorder correlations (Cai et al. Nat Genet 2026)

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

Mechanisms that provide traction for discovery of biomarkers and treatments occur at multiple scales in the brain

Biomarkers

- Candidate biomarker measures for brain disorders:
  - Molecular: Fluid biomarkers, e.g., cerebrospinal fluid proteomics
  - Electrophysiology, e.g., EEG, MEG, intracranial recording for DBS
  - Imaging, e.g., structural or resting state MRI, PET
- BEST definition: A "characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" (FDA-NIH Biomarker Working Group 2016)

Treatments

Genes

Molecules

Cells

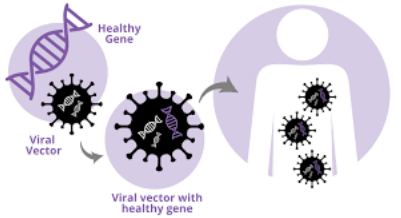
Synapses

Local Circuits

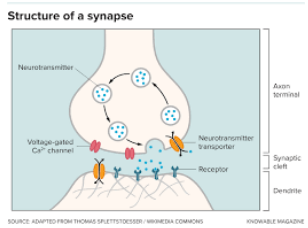
Networks/Computation

Cognition/Behavior

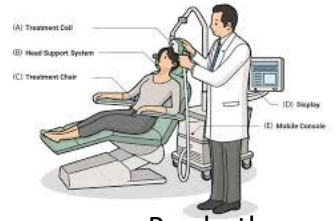
Gene therapy



Pharmacology



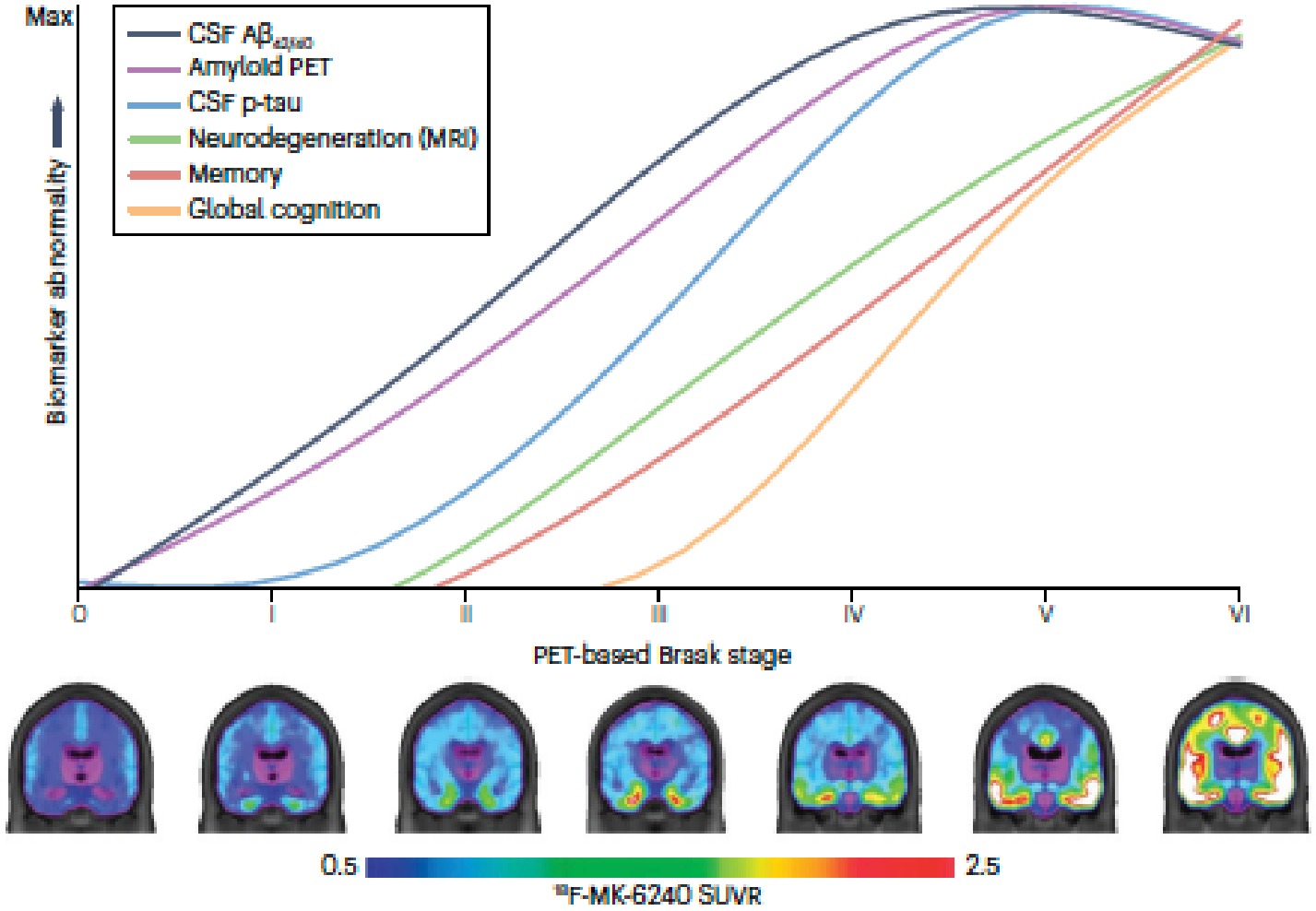
Neuromodulation



Psychotherapy

Proteomic and TET biomarkers have revolutionized diagnosis and treatment for Alzheimer's disease

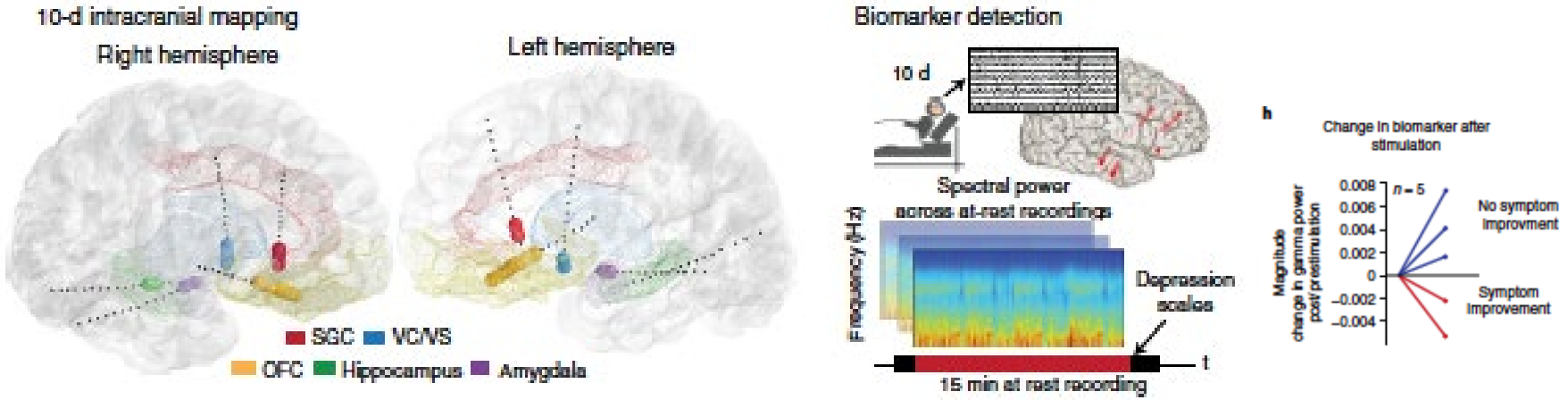
- Prior to biomarker discovery, ~40% of patients enrolled AD clinical trials had no brain amyloid or tau at autopsy
- Brain amyloid (A) and tau (T) provided biochemical clues that anchored the discovery of fluid and PET biomarkers and supported treatment discovery
- Initial AD diagnoses, now based on AT(N) criteria (N=neurodegeneration) is entirely biological
- Beyond AT(N), AD is heterogeneous, motivating a search for biosignatures



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

Systems level biomarkers represent a first steps to personalize DBS for Depression

Closed loop neuromodulation in 36-year-old woman with severe, childhood onset depression unresponsive to multiple medications and ECT



- Multiday intracranial recording and electrical stimulation identified:
  - A *person-specific physiological biomarker* in the amygdala
  - A treatment site in the right ventral capsule/ventral striatum where stimulation produced significant and consistent dose-dependent improvement in symptoms.

Scangos et al. *Nature Medicine* 27:1696-1700, 2021

Psychiatric Biomarkers Network

Goals

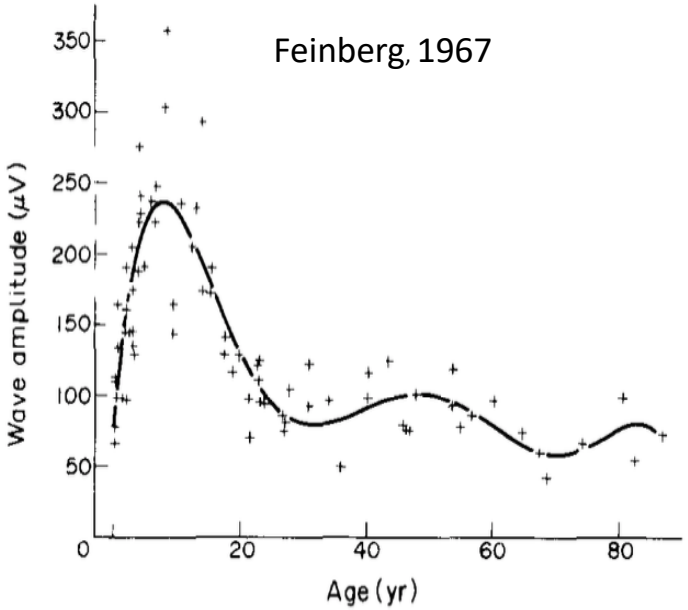
- **Biorepository** Enable fluid biomarker discovery by collecting and sharing high quality samples associated with genotypes and clinically meaningful phenotypes, eschewing DSM/ICD diagnostic silos

- Discover biomarkers for patient stratification, tracking, and treatment response based on:

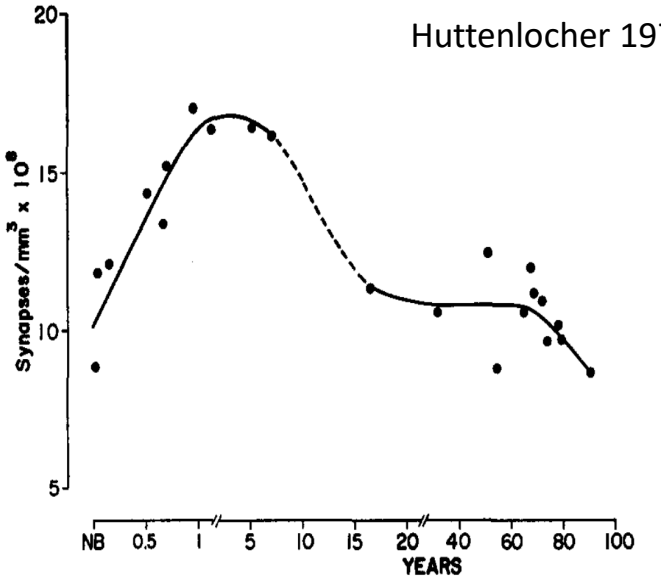
  - Hypotheses based on genetics, neurobiology

  - Unbiased proteomics of paired cerebrospinal fluid and blood samples

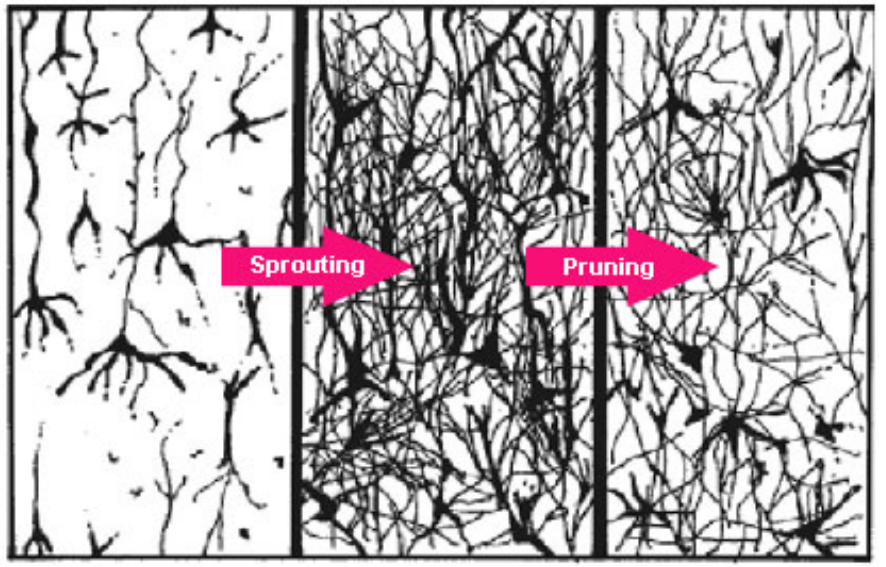
Feinberg (1982): Schizophrenia results from excessive and inappropriate synaptic pruning during adolescent development-but no mechanism identified



Slow wave sleep EEG showing reduced amplitude with age



Synaptic density across the lifespan determined by electron microscopy

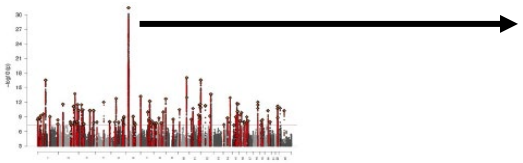


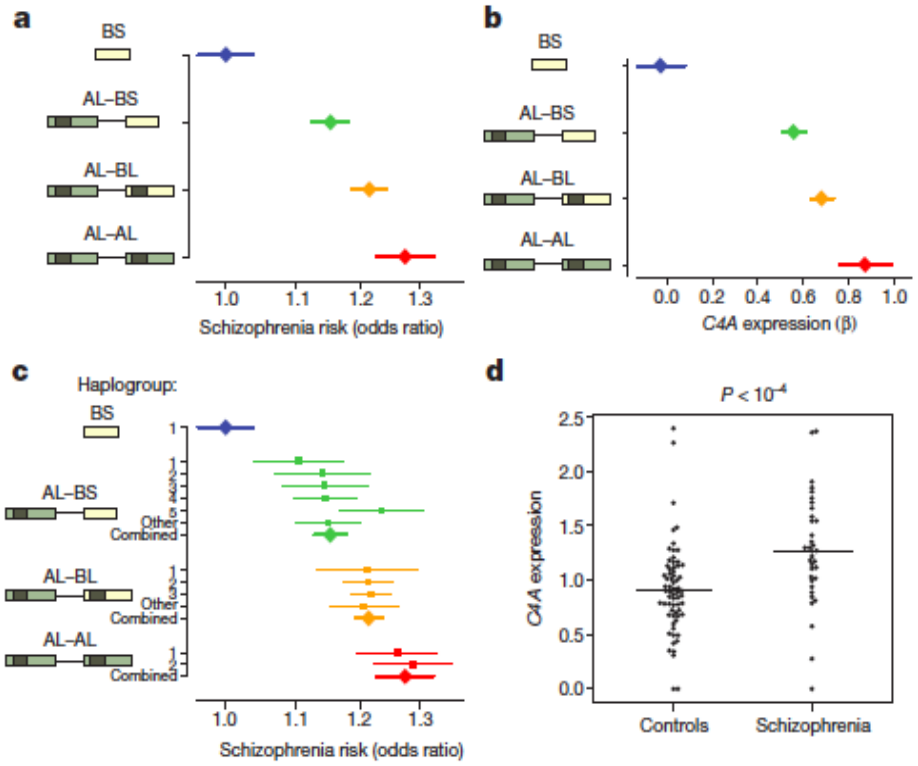
Cartoon of changing synaptic density during normal development

- A major epoch of synaptic reorganization occurs in prefrontal and temporal association cortex from late childhood to adolescence with net synaptic elimination (15-20%).
- Strength of synapses results from experience-dependent plasticity
- Myelination of the associated axons continues into a person's mid-30's.

Association of schizophrenia risk with a structural variant in complement factor C4A gene offered a mechanism for the over-pruning hypothesis

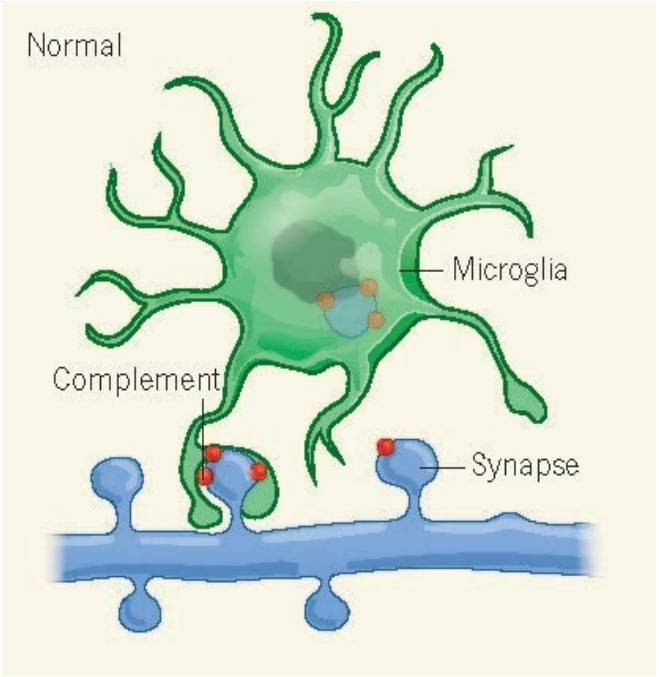
Schizophrenia risk increases with grater number of copies of C4A and higher levels of gene expression





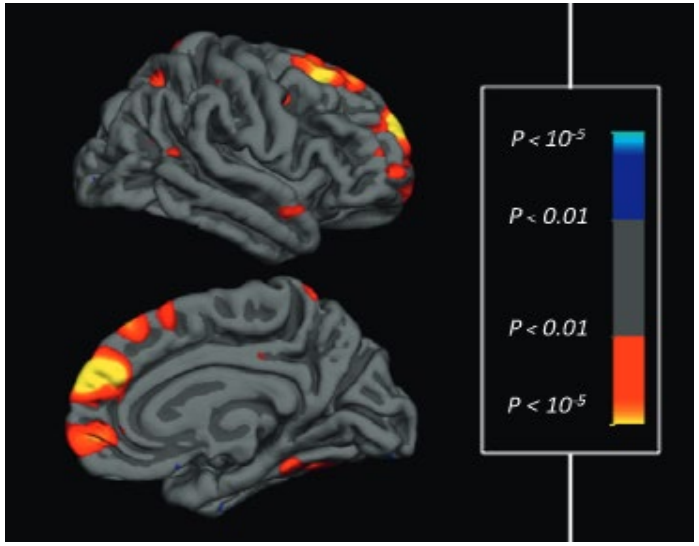
Steve McCarroll

Aswin Sekar



- Complement factor 4A recruits C3 to weak synapses;
- C3 binds to C3A receptor on microglia, leading to engulfment

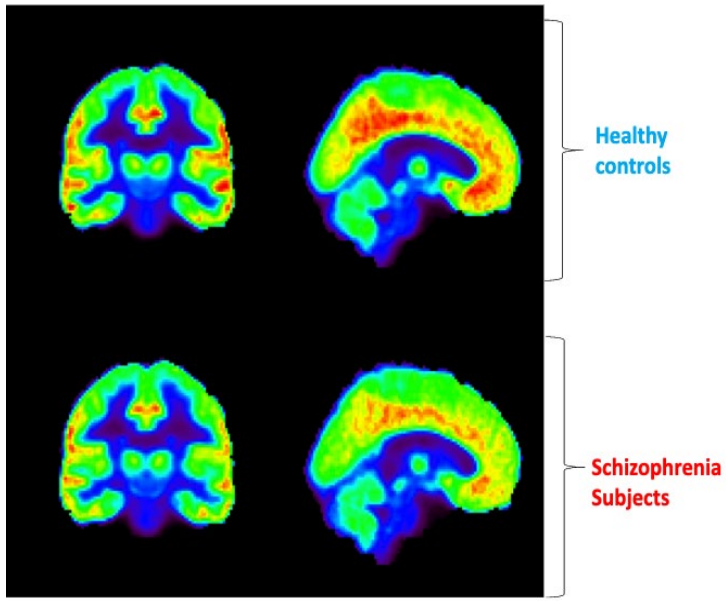
More recent data consistent with the Feinberg over-pruning hypothesis
But what is the mechanism?



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

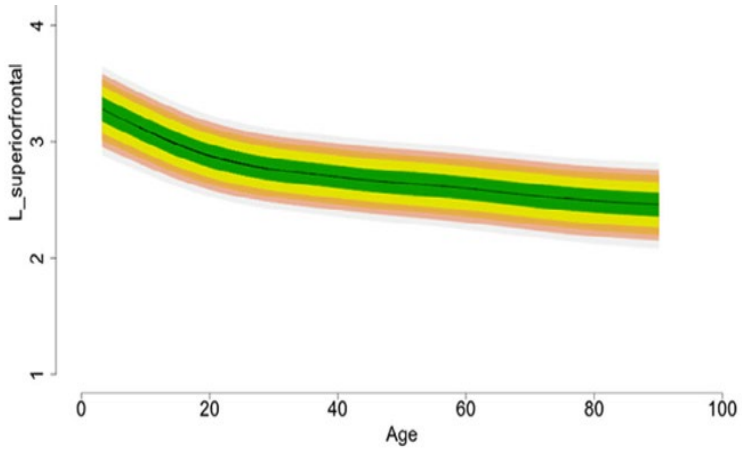
Cannon et al., 2015

- Excessive cortical thinning demonstrated by structural MRI
- Consistent with post-mortem loss of dendritic spines and synapses without cell death



Radhakrishnan et al, 2021

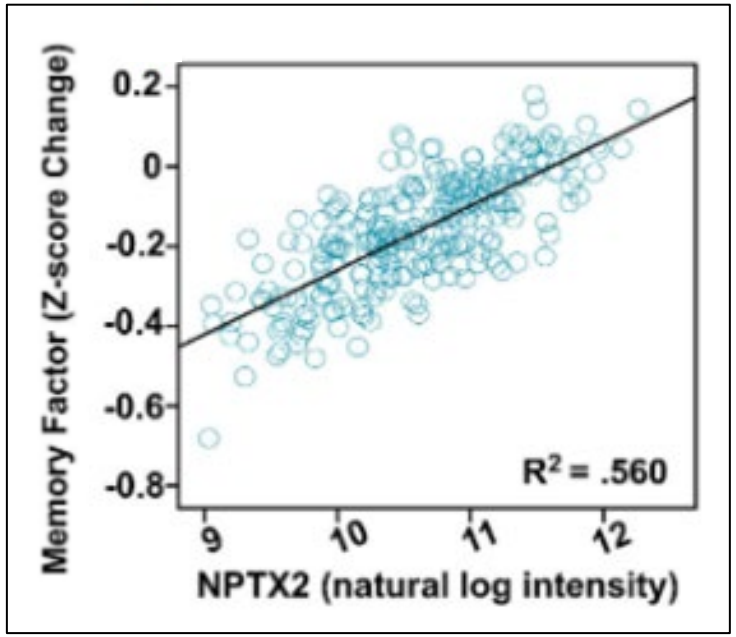
- Synaptic Vesicle Glycoprotein 2A (SV2A) Positron Emission Tomography, a presynaptic marker, is consistent with fewer synapses in schizophrenia

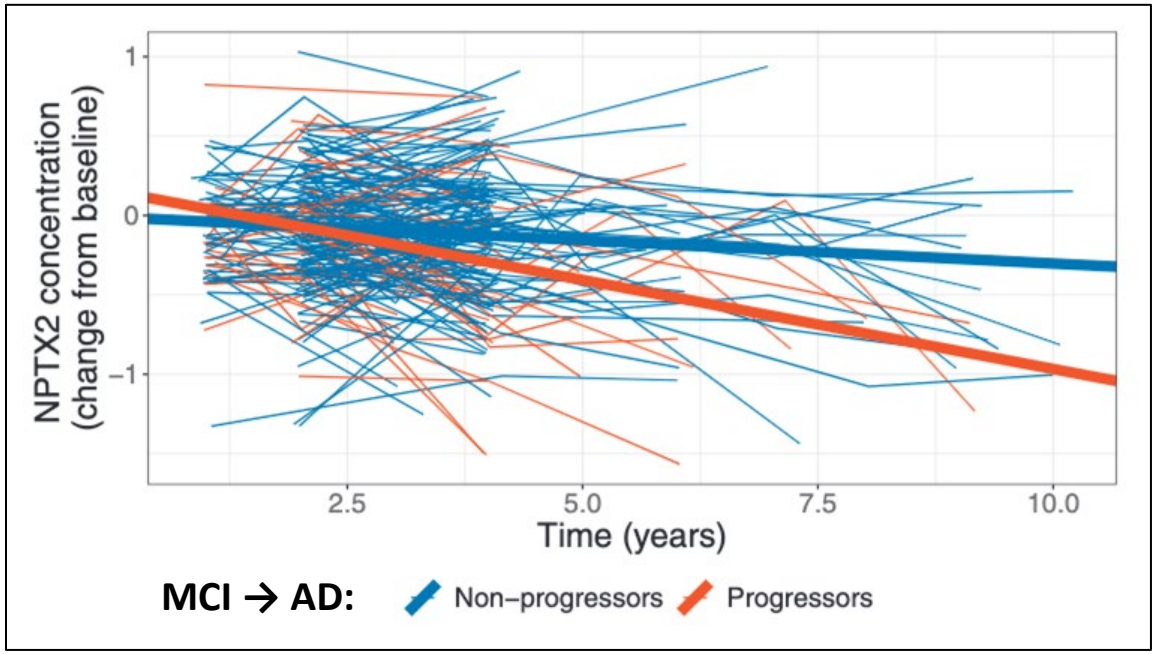


Frangou et al., 2021

- Frontal grey matter thickness, structural MRI of ~17,000 healthy individuals

Decreased NPTX2 in CSF from MCI and AD patients correlates with cognitive decline over time

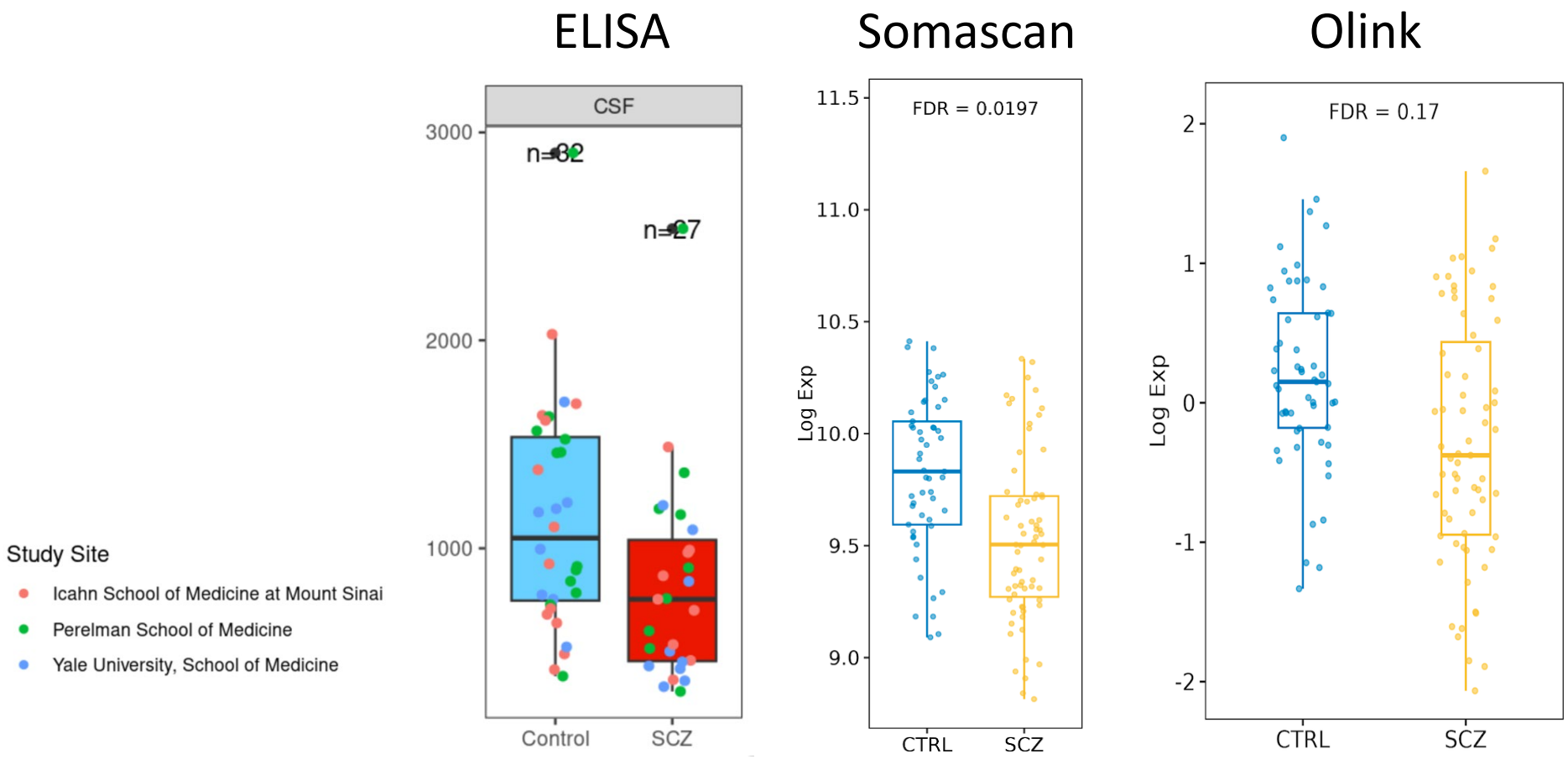




Left, AD patients' **baseline** CSF NPTX2 levels correlated with change in memory score at 2-year follow-up. (Swanson & Willette/**ADNI** 2016)

Right, **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 reduced in CSF in PBN pilot study by targeted assay and two proteomic platforms

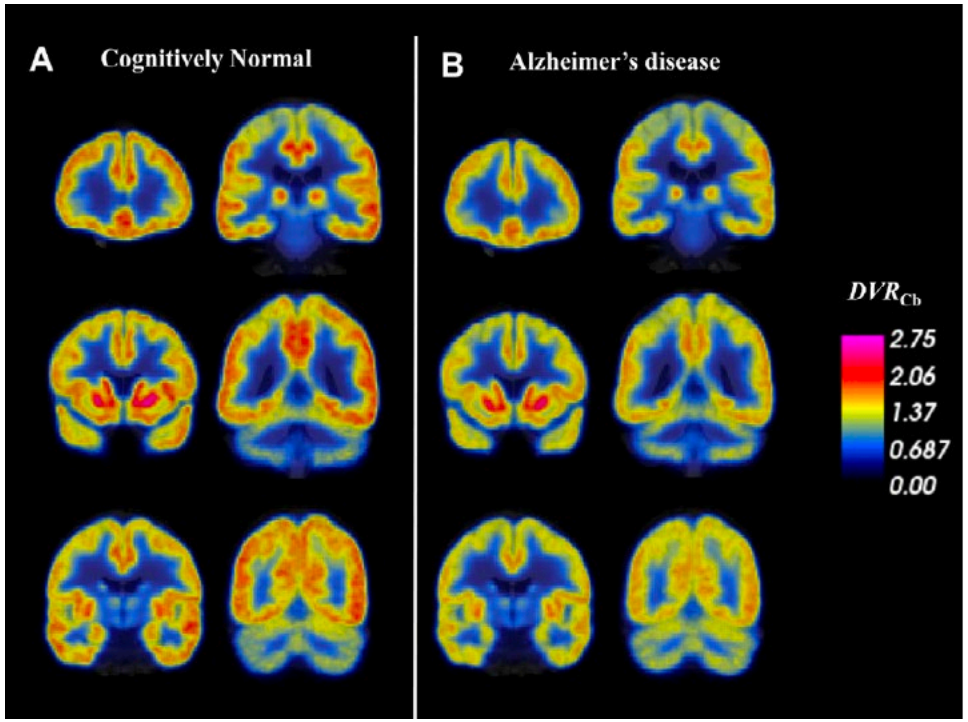


Correlation with cognitive measures currently being analyzed

J&J Innovative Medicine

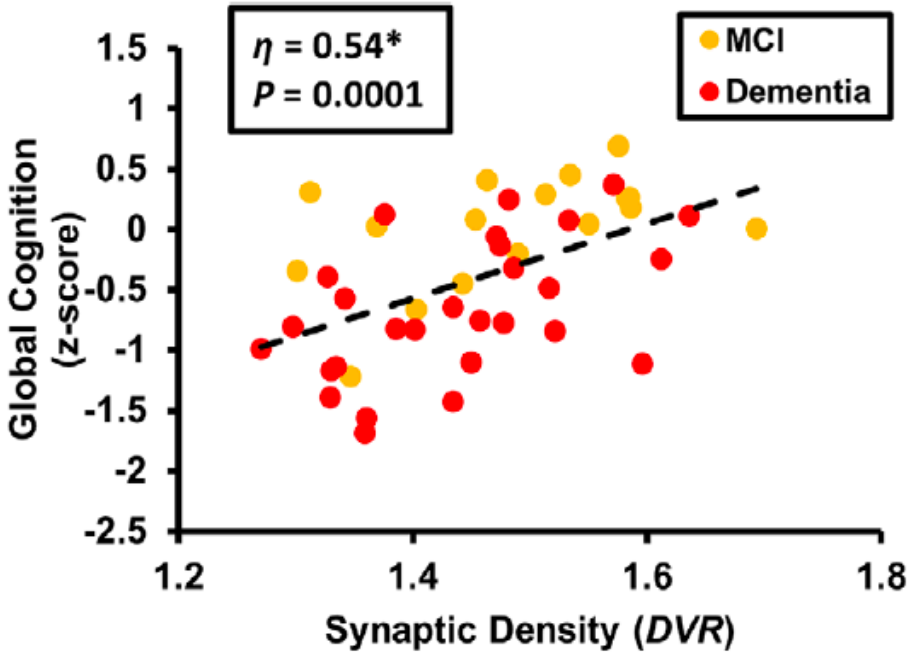
Relationship of synaptic density to cognition in measured by Synaptic Vesicle Glycoprotein 2A SV2A PET with [11C]UCB-J in Alzheimer's disease

Synaptic density measured by SV2A PET



Cognitively normal Alzheimer's disease

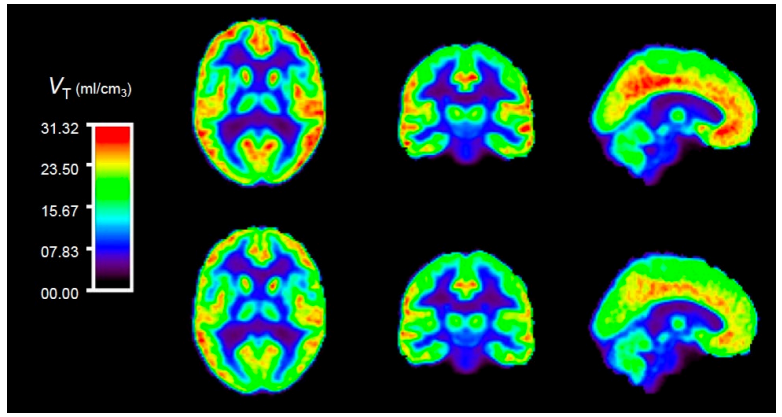
Mecca et al, *Alzheimer's and Dementia*, 2020



Correlation of global cognition with synaptic density measured by SV2A PET in composite AD-affected regions (DVR)

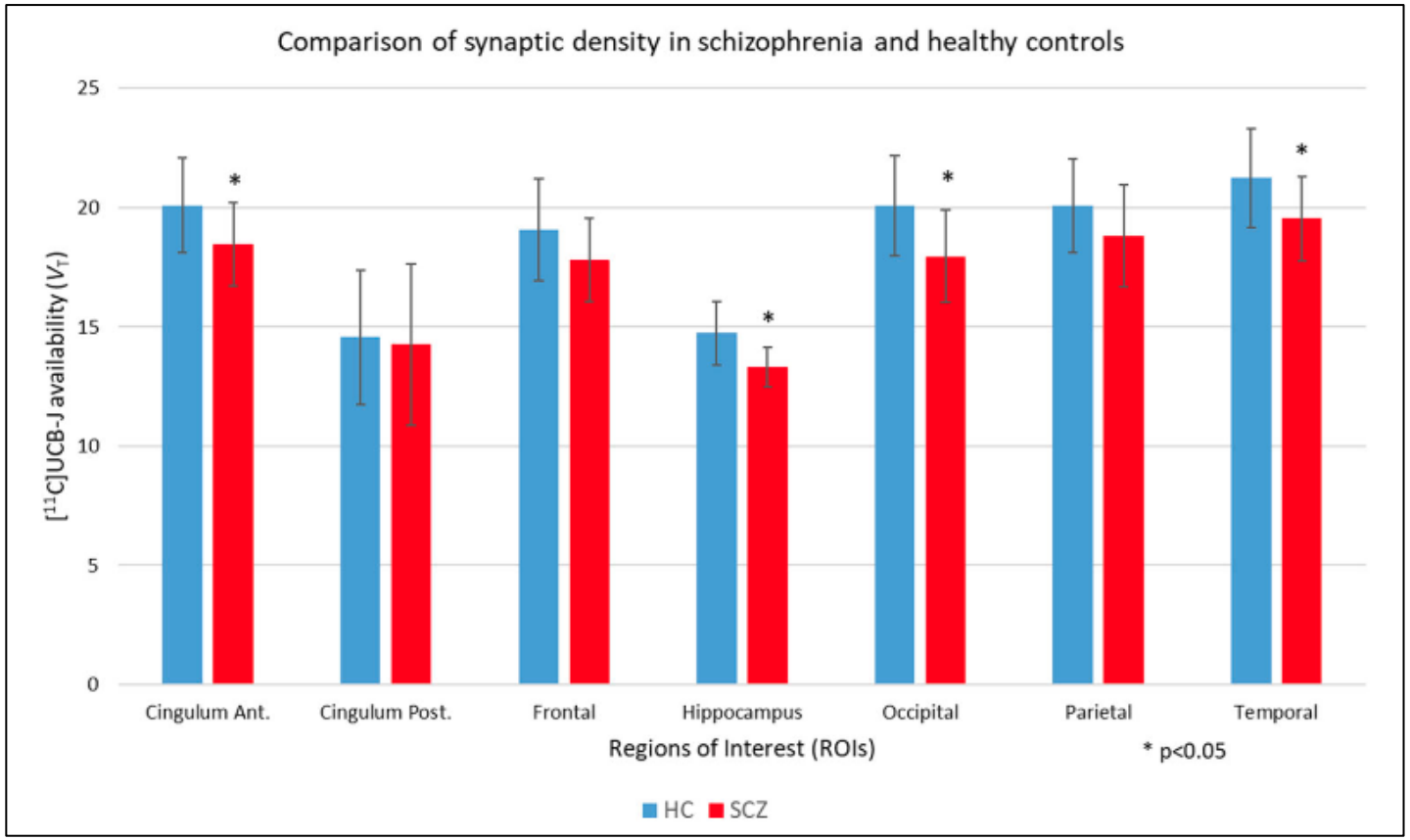
Mecca et al, *Alzheimer's and Dementia*, 2022

[11C]UCB-J Binding in Schizophrenia Vs Unaffected Controls
SV2A PET as a candidate synaptic density marker



Unaffected

Schizophrenia



Radhakrishnan et al., 2021

What is to be done?

- Start anew. Eschew individual diagnoses and begin with broad spectra to be reanalyzed based on biological findings and phenotypes
- In psychiatry comorbidity studies and cross-disorder genetics nominate large spectra for reanalysis, e.g., Grotzinger et al 2025
  - Schizophrenia-Bipolar (psychosis spectrum)
  - Internalizing spectrum
  - Neurodevelopmental (ASD, ADHD)
  - Compulsive
  - Externalizing/Substance Use Disorders (SUDs)
- Reanalyze diagnostic grouping from the bottom up based on genome sequenced, well phenotyped cohorts recruited as early in life as feasible
- Don’t give up on CSF measures
- Data repositories and for future-proofing—UKB is a model, but recruitment was too late