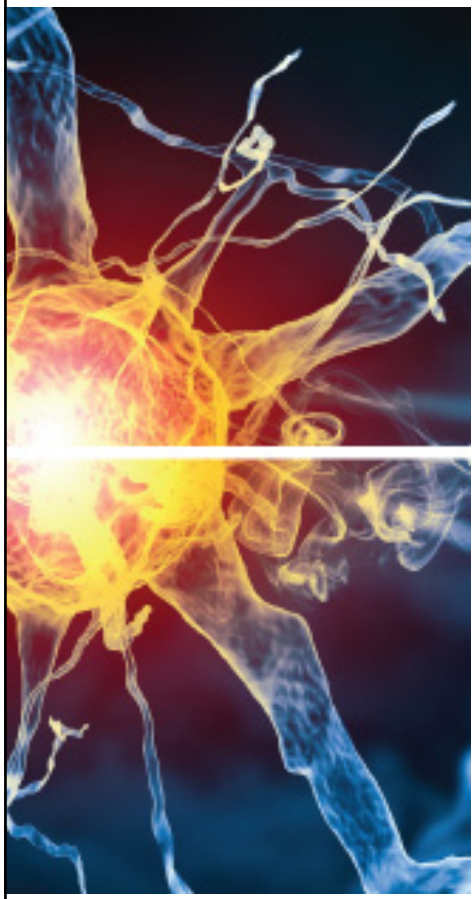
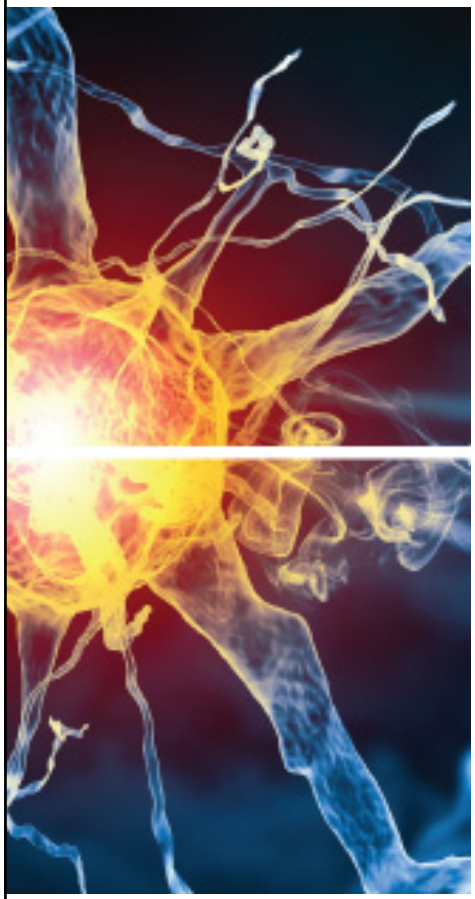


# Treatment of Schizophrenia
# “QUO VADIS”




## Jeffrey A. Lieberman, M.D

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College of Physicians and Surgeons
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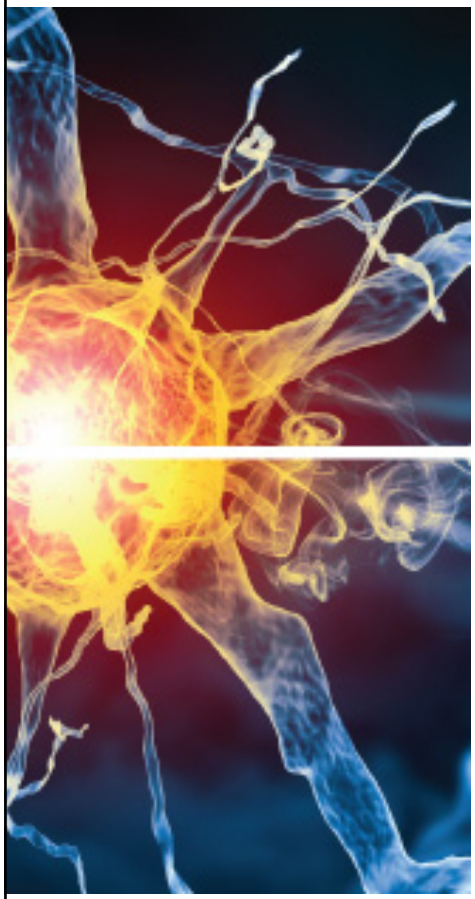
# Jeffrey A. Lieberman, M.D.

## Disclosures

- ***Research/Grants:*** Alkermes*; Eli Lilly and Company/DeNovo Biopharm, LLC*
- ***Advisory Board:*** Intracellular Therapies, Inc.*; Pierre Fabre*
- ***Other Financial or Material Support:*** Repligen Corporation

*Dr. Lieberman received no direct financial compensation or salary support for participating in these research, consulting, or advisory board activities.



# 1 Learning Objective

Review current and emerging treatment targets for the management of patients with schizophrenia.

# Schizophrenia Treatment Update

- Conventional Mechanism Treatments
- New Targets and Novel Treatments
- Neuromodulation
- Genetically Targeted Treatments
- Early Detection and Intervention Models

# Schizophrenia Treatment Update

- Conventional Mechanism Treatments
- New Targets and Novel Treatments
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- Early Detection and Intervention Models

# FDA Approved Antipsychotics

Chlorpromazine - 1957
Perphenazine - 1957
Trifluoperazine - 1959
Fluphenazine* - 1960
Thioridazine - 1962
Haloperidol* - 1967
Thiothixene - 1967
Molindone - 1974
Loxapine - 1975
Pimozide - 1984

Clozapine -1989
Risperidone* - 1993
Olanzapine* - 1996
Quetiapine - 1997
Ziprasidone - 2001
Aripiprazole* - 2002
Paliperidone* - 2006
Iloperidone - 2009
Asenapine - 2009

Lurasidone - 2010
Brexpiprazole - 2015
Cariprazine - 2015
Pimavanserin - 2016
ITI-007 - 2017?
F17464 - 2018?

* Long Acting Injectable Formulation

# Comparison of APDs MOAs

- How do different classes of antipsychotic drugs work ?
  - Sustained full D-2 antagonism
  - Intermittent D-2 antagonism
  - Sustained D-2/3 partial agonism

From: **Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia**

JAMA Psychiatry. Published online June 07, 2017. doi:10.1001/jamapsychiatry.2017.1322

| Treatment | HR (95% CI) |
|---|---|
| LAI paliperidone | 0.51 (0.41-0.64) |
| LAI zuclopenthixol | 0.53 (0.48-0.57) |
| Oral clozapine | 0.53 (0.48-0.58) |
| LAI perphenazine | 0.58 (0.52-0.65) |
| LAI olanzapine | 0.58 (0.44-0.77) |
| LAI risperidone | 0.61 (0.55-0.68) |
| Polytherapy | 0.62 (0.58-0.65) |
| Oral olanzapine | 0.63 (0.59-0.68) |
| LAI haloperidol | 0.64 (0.56-0.73) |
| Oral zuclopenthixol | 0.67 (0.59-0.76) |
| Oral risperidone | 0.71 (0.64-0.78) |
| Oral aripiprazole | 0.73 (0.66-0.81) |
| Oral levomepromazine | 0.76 (0.66-0.89) |
| LAI flupentixol | 0.78 (0.62-0.98) |
| Oral haloperidol | 0.81 (0.71-0.93) |
| LAI fluphenazine | 0.86 (0.35-2.08) |
| Other oral formulations | 0.86 (0.75-0.98) |
| Oral perphenazine | 0.86 (0.77-0.97) |
| Oral quetiapine | 0.91 (0.83-1.00) |
| Oral flupentixol | 0.92 (0.74-1.14) |

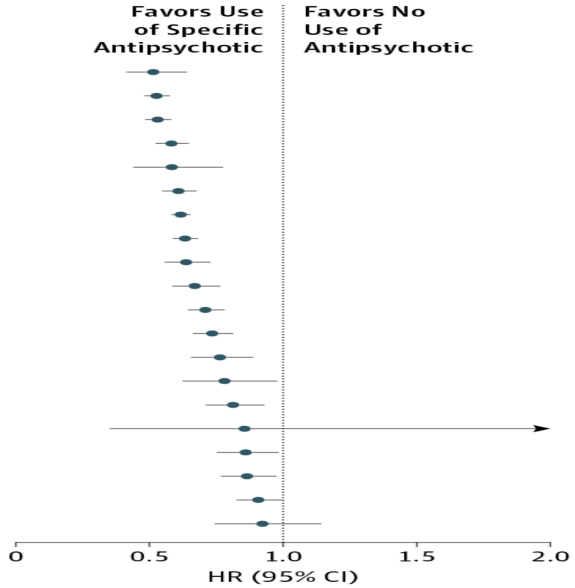



Figure Legend:

Adjusted Hazard Ratios (HRs) and 95% CIs for Psychiatric Rehospitalization During Monotherapy Compared With No Use of Antipsychotic in Within-Individual Analyses in the Prevalent PopulationPaliperidone long-acting injectable (LAI) is a once-monthly injection. The vertical dashed line shows the reference value (no use of antipsychotic). The arrow indicates that the higher end of the 95% CI (2.08) is beyond the scale (up to 2.00).

# Adjunctive Treatments

Efficacy of 42 Pharmacologic Cotreatment Strategies Added to Antipsychotic Monotherapy in Schizophrenia:
Systematic Overview and Quality Appraisal
of the Meta-analytic Evidence

Correll, et al. *JAMA Psychiatry*. Published online May 17, 2017

# ITI-007 for the Treatment of Schizophrenia: Intracellular Therapies

- Pharmacology
  - 5-HT2A Receptor Antagonist
  - Dopamine Phosphoprotein Modulator (DPPM)
  - Glutamatergic Phosphoprotein Modulator (D1/GluN2B)
  - Serotonin Reuptake Inhibitor
- Efficacy
  - Improves sleep quality
  - Enhances antipsychotic and antidepressant activity
  - Antipsychotic efficacy for 'positive' symptoms; reduced agitation
  - negative symptoms and positive' symptoms
  - Improved cognition and improved affect
  - Antidepressant efficacy
  - Pro-social function
- Side Effects
  - Sedation

Lieberman J, et al. *Biol Psychiatry.* 2016;79(12):952-61

# Functional Selectivity

- Selectivity in intracellular signalling pathways

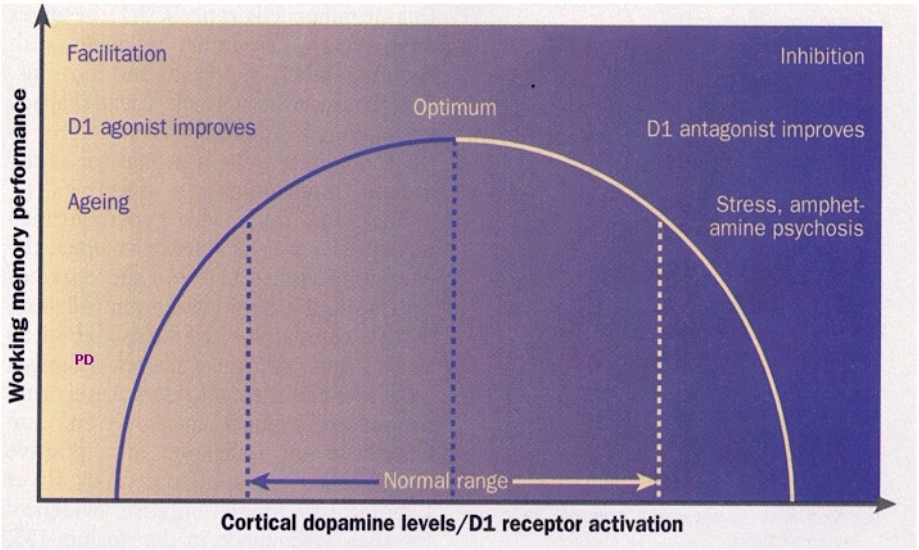
# Schizophrenia Treatment Update

- Conventional Mechanism Treatments
- New Targets and Novel Treatments
- Neuromodulation
- Genetically Targeted Treatments
- Early Detection and Intervention Models

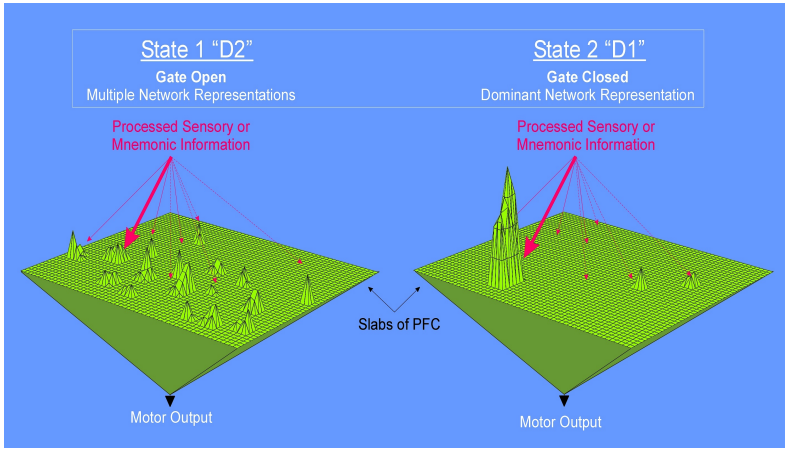
# Targets for Novel Drug Development

- Alpha-7 nicotinic receptor: partial agonists
- D1 receptor: partial agonists (DAR-100A, PF4958242)
- Glutamate
  - NMDA receptor allosteric modulators (glycine, serine, D-cycloserine)
  - Glycine transport inhibitors (bitopertin, sarcosine, BI42580
  - AMPA receptor agonists
  - Metabotropic receptor partial agonists (pomaglumetad)
- M1 muscarinic receptor agonists
- GABA-A R subtype selective agonists
- Nona Peptides (Oxytocin)
- Cannabinoid receptors (CB-1) (Cannabadiol)
- Immunologic – Anti-inflammatory drugs
- Phosphodiesterase Inhibitors (1, 4, 9, 10)

# D-1 Receptor Signaling Treated by D-1 Agonists




Arnsten and Goldman-Rakic. 1986;
Arnsten et al. 1994;
Murphy et al. 1994, 1996 a,b., 1997;
Williams and Goldman-Rakic. 1995;
Verma and Moghaddam. 1996, Goldman
Rakic et al, 2000, *Brain Res Rev*




Girgis RR, et al. *Psychopharmacology (Berl).* 2016; 233(19-20):3503-3512.
Seamans JK, et al. *J Neurosci.* 2001;21(10):3628-38.

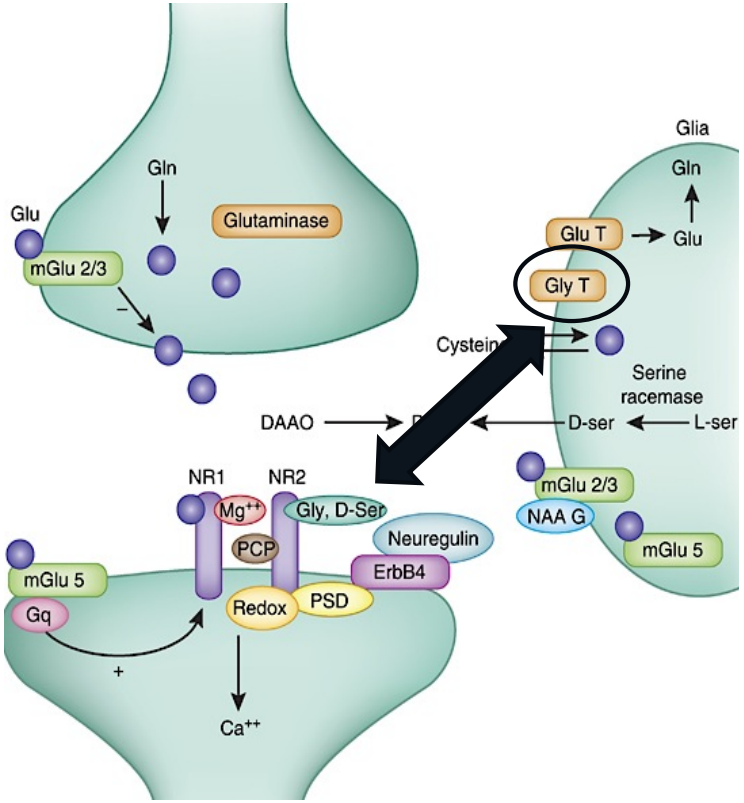
# DAR-0100 (Dihydrexidine) A Potent Selective D1 Agonist Tested in Schizophrenia

- Randomized Clinical Trial of Adjunctive Rx with D-1 agonist
- No treatment effects:
  - fMRI hemodynamic response
  - WM Tasks
  - PANSS
  - CDRS
  - SANS

George MS, et al. *Schizophr Res*. 2007;93(1-3):42-50.

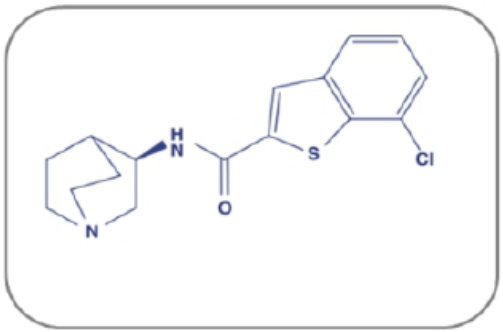
# Glutamate Based Treatments

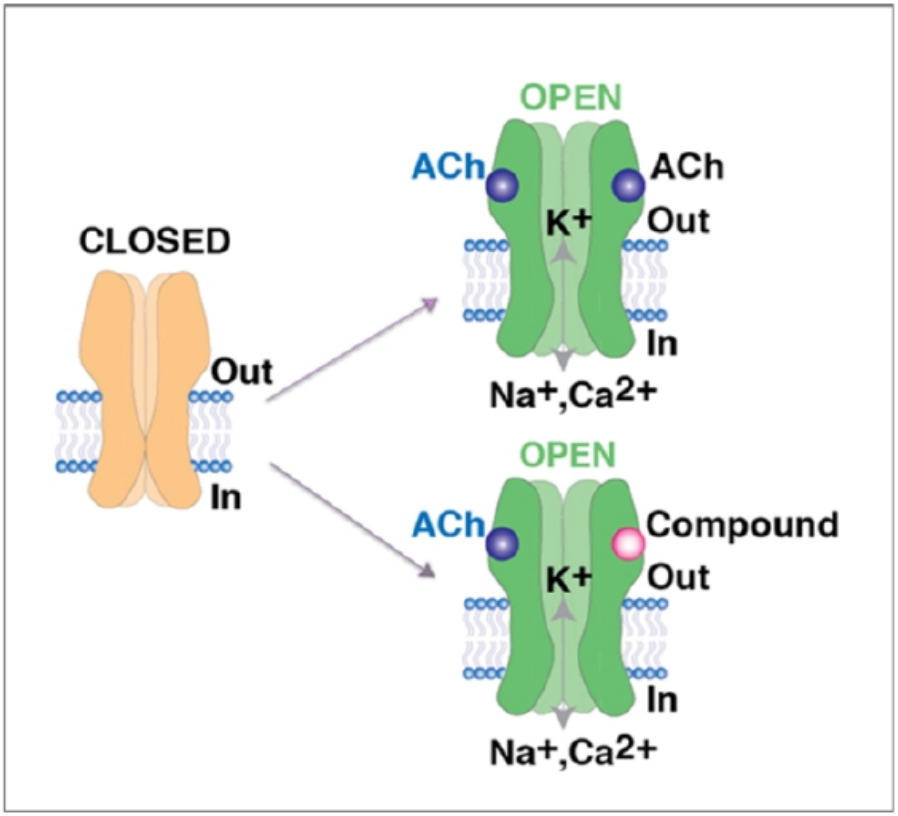
- Rationale
- NMDA allosteric modulators: Glycine, D-Serine, GlyT inhibitors
- Glutamate modulators: Pomaglumetad, Gabapentin, Pregabalin, NAC, Benzoate
- mGluR-5 modulators
- AMPA potentiators




Moghaddam B, Javitt D. *Neuropsychopharmacology.* 2012;37(1):4-15.

# Encenicline, An Investigational α7 Nicotinic Acetylcholine Receptor Partial Agonist, for Cognitive Impairment in Patients with Schizophrenia



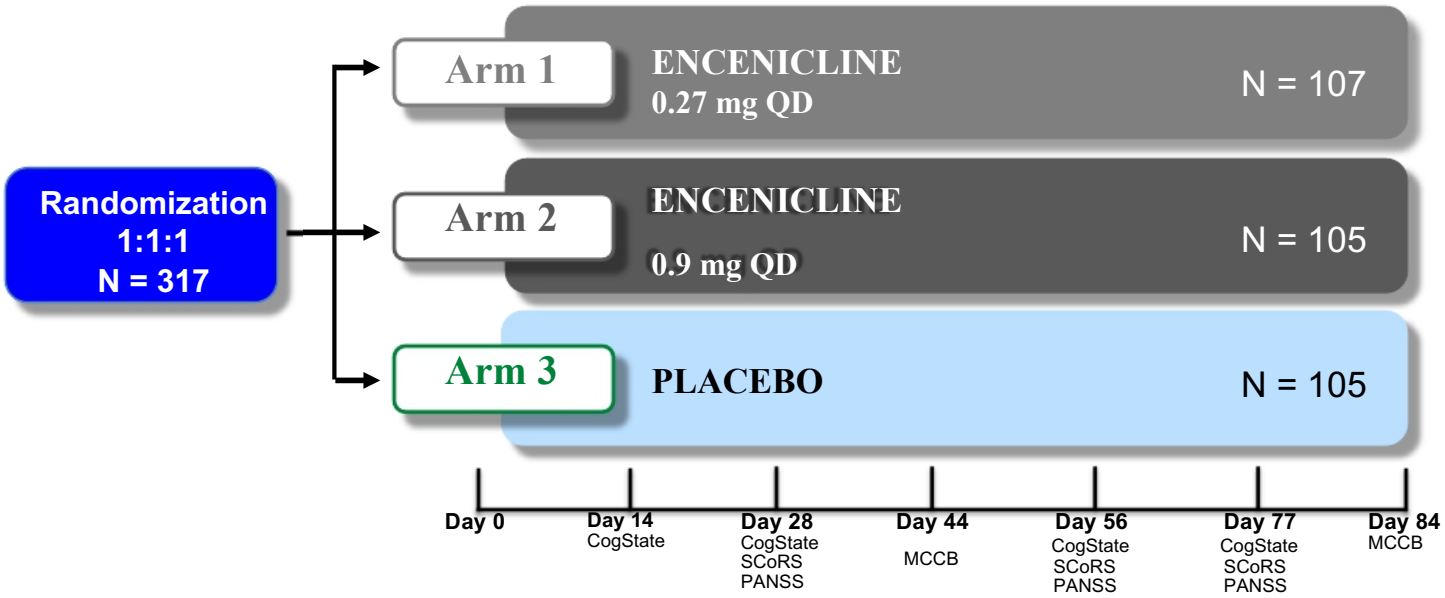




This agent is not approved by the US FDA for schizophrenia.

# Phase IIb Schizophrenia Study

## Study Design

12-week, randomized, double-blind, placebo-controlled study in patients with schizophrenia receiving stable atypical antipsychotic treatment




***Note: MCCB administered in United States only due to unavailability of validated translated test battery***

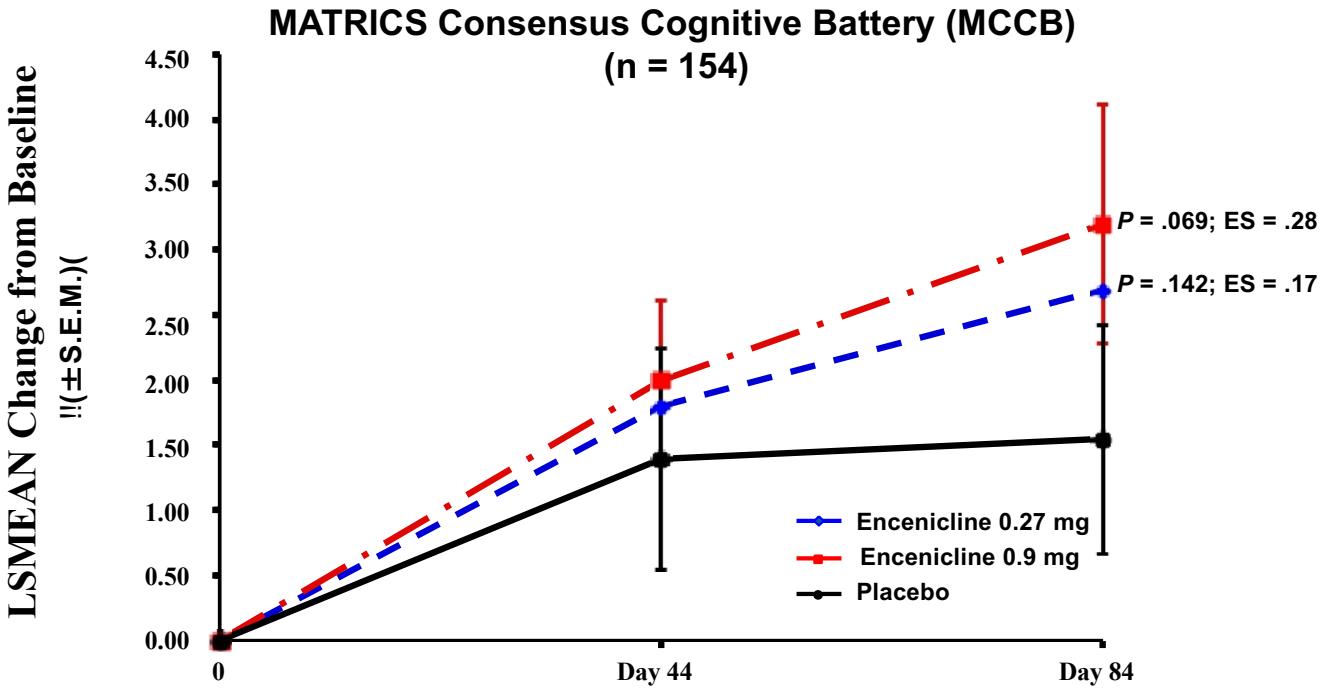
The dose represented is the free base form. Encenicline HCl 0.27 mg is equivalent to 0.3 mg and encenicline HCl 0.9 mg is equivalent to 1.0 mg

Not approved by US FDA for schizophrenia.

Keefe RS, et al. *Neuropsychopharmacology*. 2015;40(13):3053-3060.

# Phase IIb Schizophrenia Study

## MATRICSconsensus cognitive battery (MCCB)*




*p* values vs. placebo. All data presented as mean ±SEM. ES = Cohen's d effect Size

*The MCCB was performed only in the United States. Not approved by US FDA for schizophrenia.

Keefe RS, et al. *Neuropsychopharmacology*. 2015;40(13):3053-3060.

# The Bad News

**WALTHAM, Mass.** – March 24, 2016 - FORUM Pharmaceuticals Inc. today announced topline results from two Phase 3 clinical trials in patients with cognitive impairment in schizophrenia (CIS). While encenicline (FRM-6124) demonstrated a favorable safety and tolerability profile in both studies, neither study met its co-primary endpoints based on effect on cognitive function and patient function.

“These results are not what we might have hoped for on behalf of patients. We wish to thank over 1,500 patients who participated as well as the investigators at more than 200 clinical sites,” said Deborah Dunsire, MD, President and CEO of FORUM.

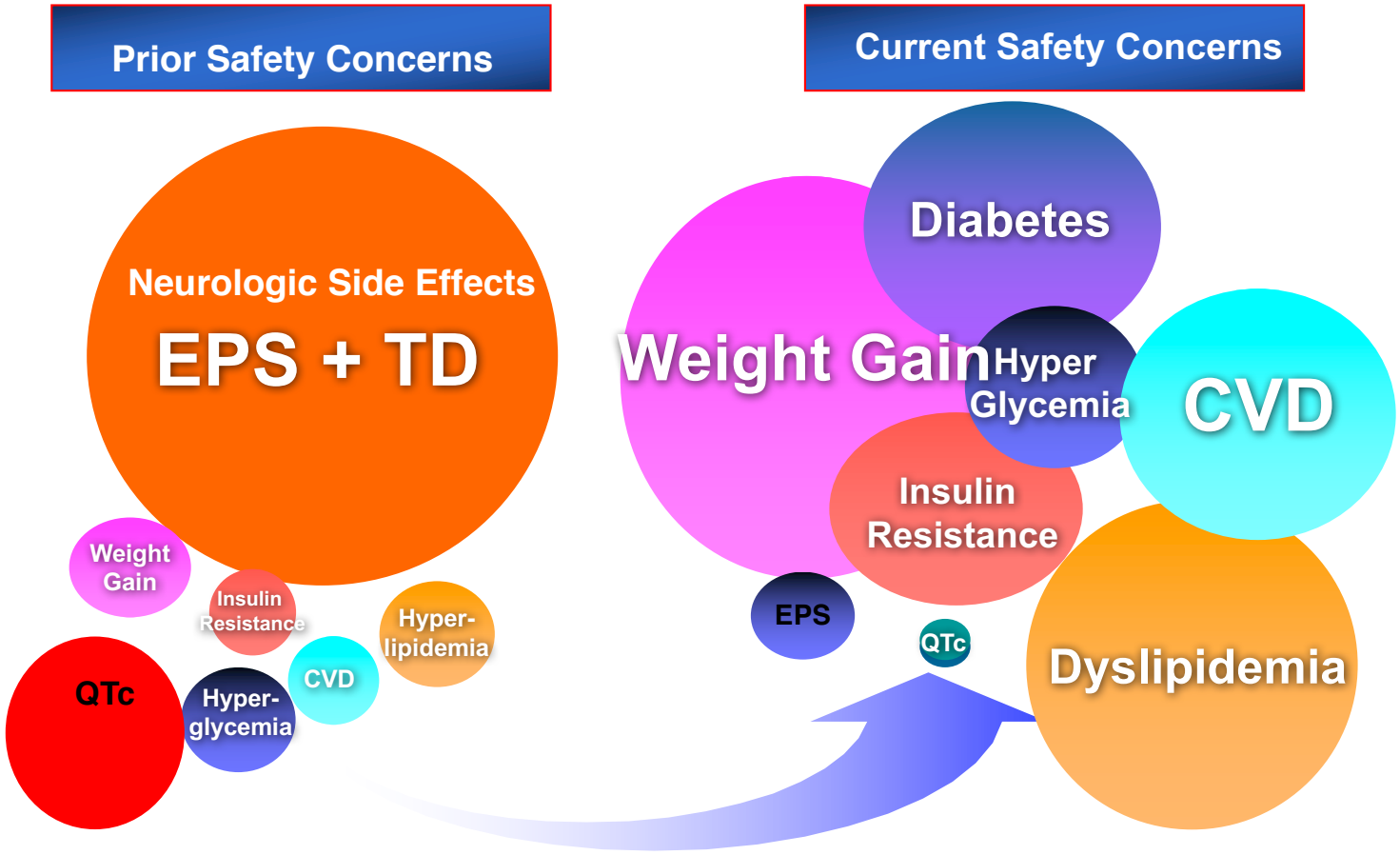
An unexpectedly high placebo response was observed in both trials. Activity was observed across certain sub-groups and secondary endpoints, and these results are being further analyzed.

# Nicotinic Positive Allosteric Modulators (PAMs)

- AVL-3288 is a small molecule, investigational drug developed by the University of California Irvine and the New York State Psychiatric Institute with support by NIMH. AVL-3288 differs from direct α7nAChR agonists, increases receptor activity only in the presence of the endogenous ligand, retaining proper temporal pattern of activation and the retention of native kinetics.

Gee KW, et al. *J Psychopharmacol.* 2017;31(4):434-441

# Side Effects of Atypical Antipsychotics: Shift in Risk Perception



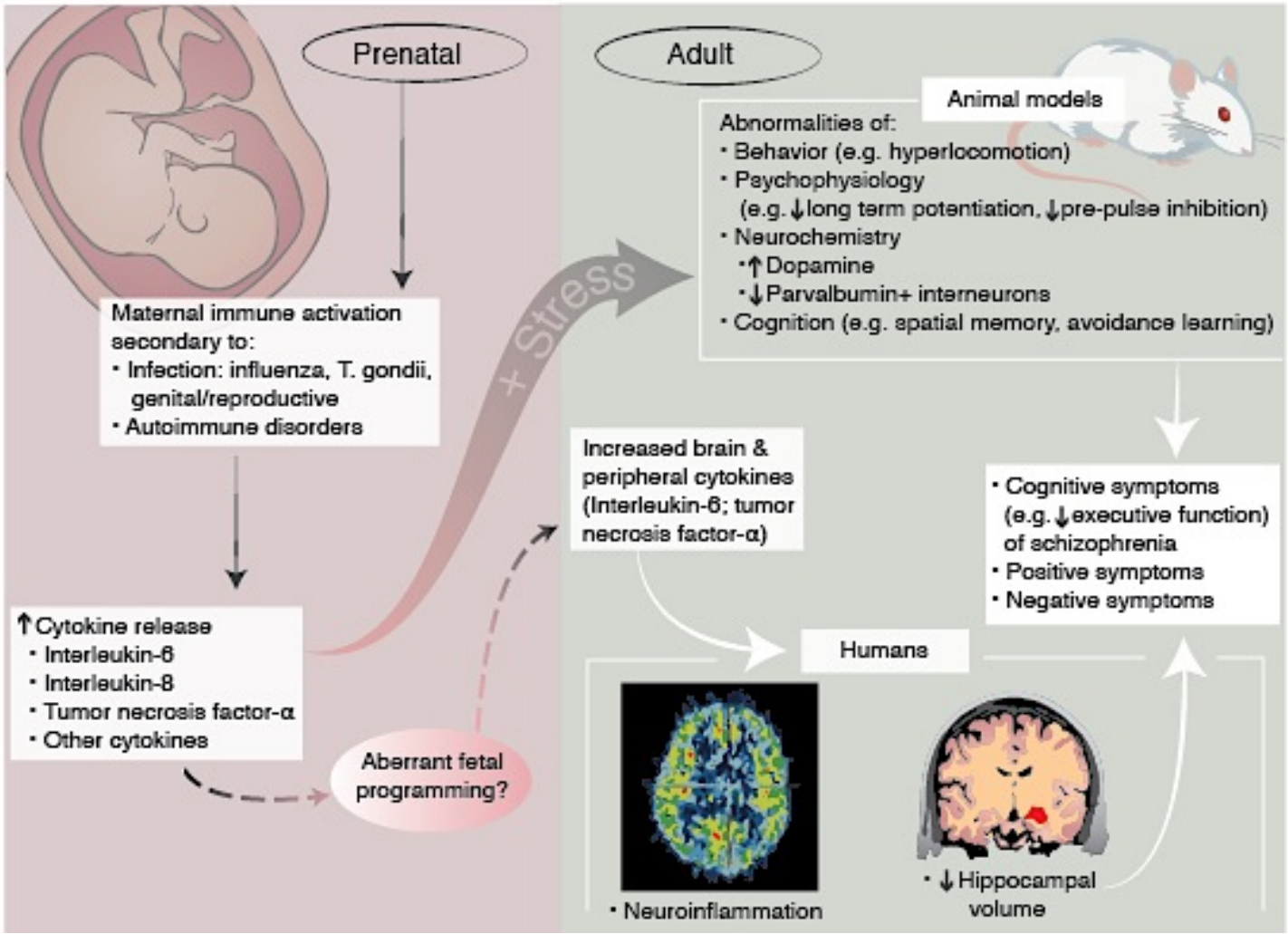

# Metformin for Antipsychotic-induced Weight Gain in Schizophrenia

- 16 week double blind RCT comparing MET to PBO in patients with BMI > 30
- Any APD or combination
- Patients received interventions for diet and exercise
- 146 patients enrolled
- Target dose of metformin 2000 mg/day
- 3 kg weight loss on metformin vs. 1 kg weight loss on placebo
- Metformin well tolerated

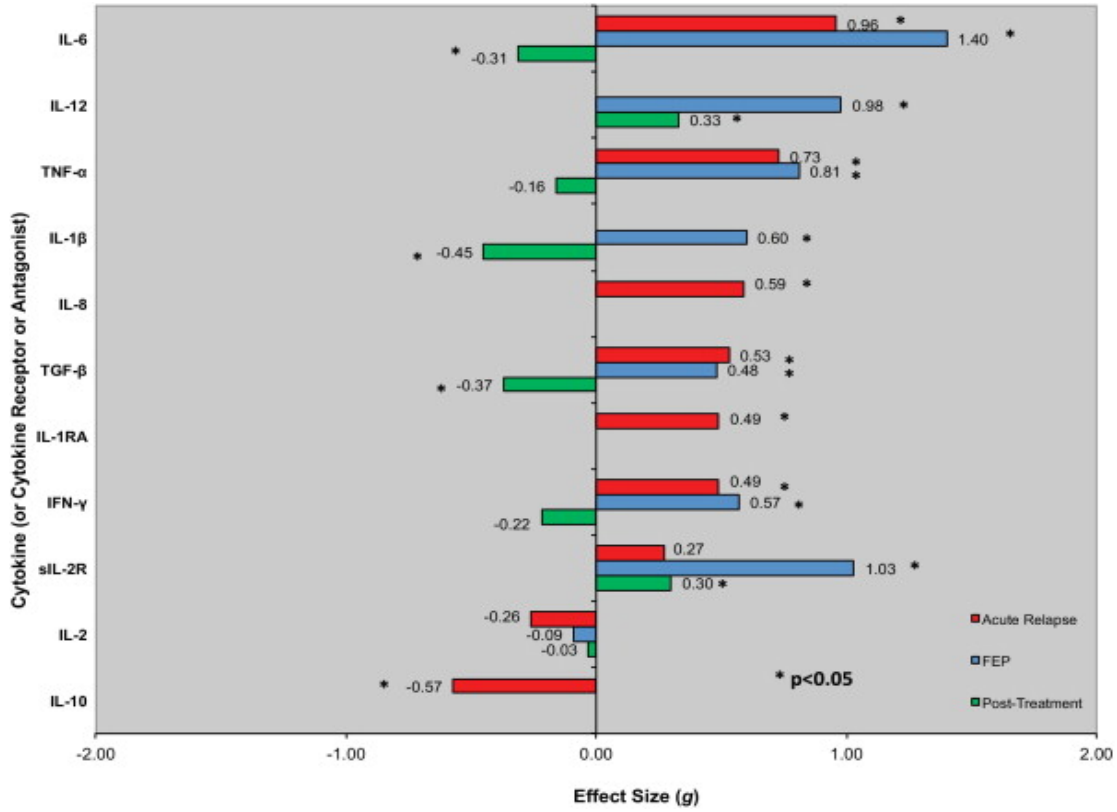
Jarskog LF, et al. Am J Psychiatry. 2013;170(9):1032-1040.

# Metformin in Longevity Study

- Metformin enhances glucose metabolism.
- Animal studies show effects on metabolic and cellular processes of aging
  - inflammation,
  - oxidative damage,
  - diminished autophagy,
  - cell senescence
  - apoptosis.
- Metformin may retard aging


Prenatal
Adult
Animal models
Abnormalities of:
• Behavior (e.g. hyperlocomotion)
• Psychophysiology
(e.g. ↓long term potentiation, ↓pre-pulse inhibition)
• Neurochemistry
• ↑Dopamine
• ↓Parvalbumin+ interneurons
• Cognition (e.g. spatial memory, avoidance learning)
+ Stress
Maternal immune activation secondary to:
• Infection: influenza, T. gondii, genital/reproductive
• Autoimmune disorders
Increased brain & peripheral cytokines (Interleukin-6; tumor necrosis factor-α)
• Cognitive symptoms (e.g. ↓executive function) of schizophrenia
• Positive symptoms
• Negative symptoms
↑Cytokine release
• Interleukin-6
• Interleukin-8
• Tumor necrosis factor-α
• Other cytokines
Aberrant fetal programming?
Humans
• Neuroinflammation
• ↓Hippocampal volume

# Inflammatory Targets




Targets: Elevations in cytokines, especially TNF-α (trait) and Interleukin-6 (state), are robust and replicated findings in schizophrenia

Miller AM, McInnes IB. *Curr Pharm Des*. 2011;17(1):1-8.

# Potential Inflammatory Agents

- Non Specific Anti-Inflammatory Agents:
  - Celecoxib
  - Aspirin
- DMARDs:
  - TNF, IL-1, IL-6, T Cell, B Cell, JAK-STAT inhibitors
- Minocycline

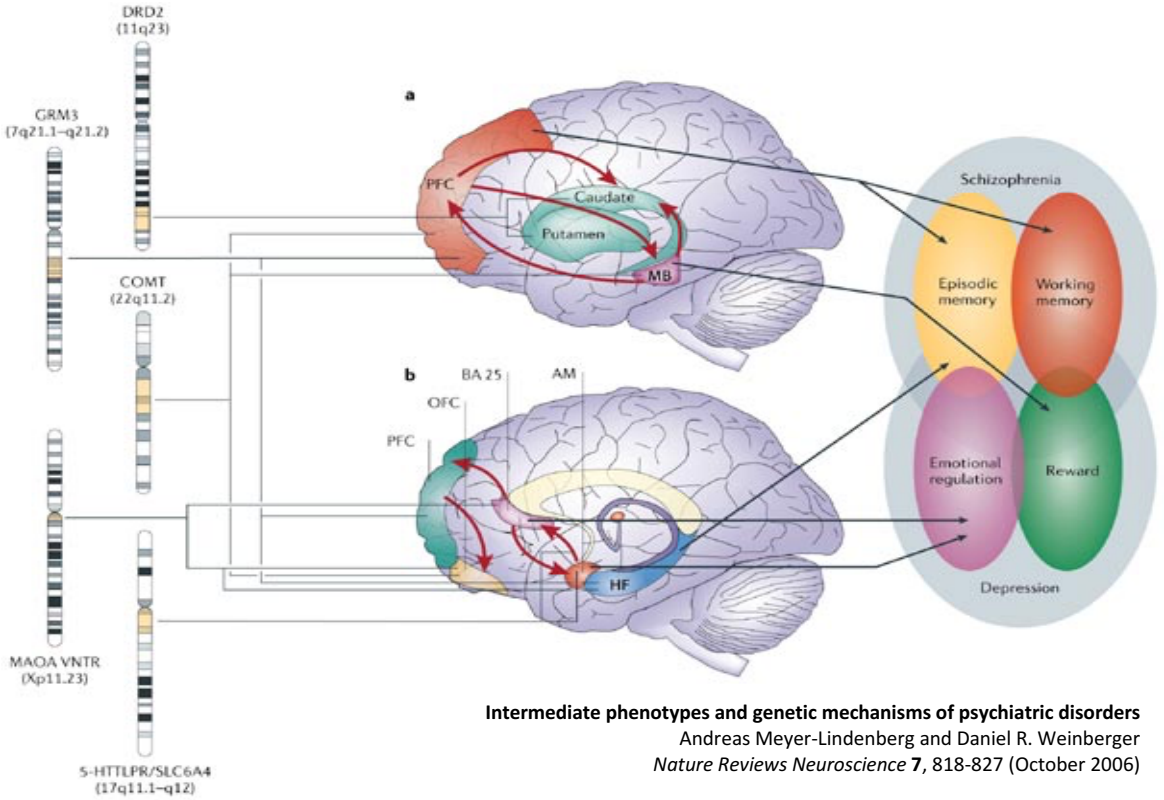
DMARDs = Disease modifying anti-rheumatic drugs

JAK-STAT = Janus Kinase-Signal Transducer and Activator of Transcription

# Schizophrenia Treatment Update

- Conventional Mechanism Treatments
- New Targets and Novel Treatments
- Neuromodulation
  - rTMS, DCTS, DBS
- Genetically Targeted Treatments
- Early Detection and Intervention Models

# The Complex Path from Genes to Behavioral and Disease Phenotype: Mediation Through Brain Circuitry




**Intermediate phenotypes and genetic mechanisms of psychiatric disorders**
Andreas Meyer-Lindenberg and Daniel R. Weinberger
*Nature Reviews Neuroscience* **7**, 818-827 (October 2006)



Meyer-Lindenberg A, Weinberger DR. *Nat Rev Neurosci.* 2006;7(10)818-827.

# Schizophrenia Treatment Update

- Conventional Mechanism Treatments
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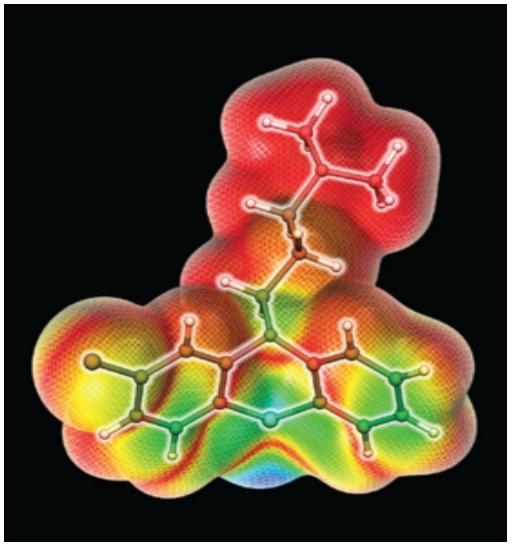
# Massive Study Reveals Schizophrenia's Genetic Roots

## The largest-ever genetic study of mental illness reveals a complex set of factors

Now the biggest-ever genetic study of mental illness has found 128 gene variants associated with schizophrenia, in 108 distinct locations in the human genome.



Collaboration of 300 scientists from 35 countries, in the Psychiatric Genomics Consortium compared whole genomes of nearly 37,000 people with schizophrenia with more than 113,000 people without the disorder, in a genome-wide association study (GWAS).

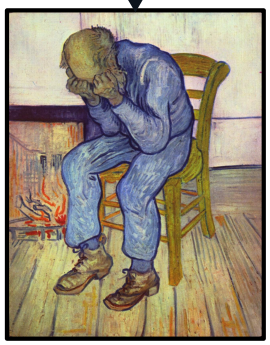
Makin S. Scientific American https://www.scientificamerican.com/article/massive-study-reveals-schizophrenia-s-genetic-roots/. Published November 1, 2014. Accessed June 11, 2018

Original article: Nature 2014;511(7510):421-427.

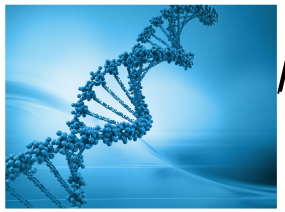
**Level 1: Identify genetic etiology**

**Level 2: Model Systems – Biological Targets and Novel Treatments**

**Level 3: Clinical Trials**

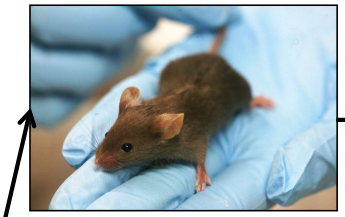


Phenotype

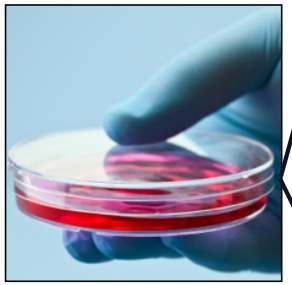


Genetic mutation

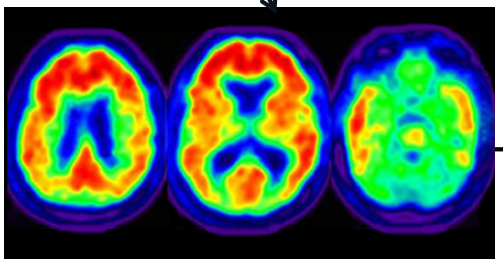
Clinical research



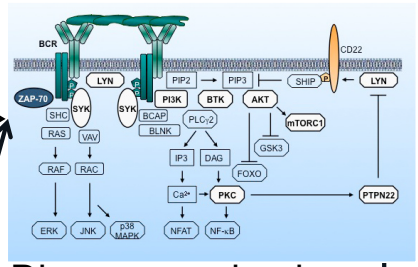
Animal models



Stem cell research



Biomarker studies




Disease mechanism

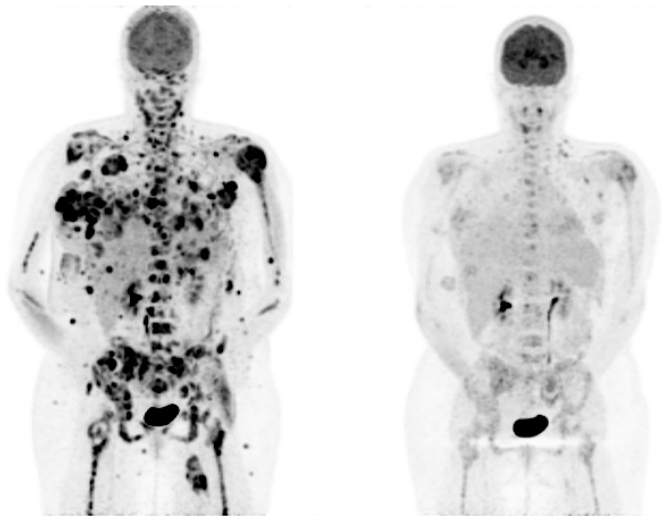
Drug screening

**Small, targeted clinical trials and treatment services for genetic isolate populations**

**Targeted Mechanistic Clinical Studies**

The New York Times

- Early 2010 study on experimental drug PLX4032 for melanomas
- Enrolled terminally ill patients with metastasized cancer
- Subset of patients with a specific genetic mutation
- Drug tailored to specific mutation
- Patients experienced dramatic improvements



*What if this is the rule rather than the exception…?*

Harman A. http://www.nytimes.com/2010/09/19/health/research/19trial.html. Published September 8, 2010. Accessed June 11, 2017

# N of One Studies


*The actress Glenn Close has been open about the fact that there is serious mental illness her family. Her sister, Jessie, and nephew, Calen, have psychotic disorders. They were in a research study at McLean. The research team found that Calen and Jessie shared a rare genomic copy number variant resulting in extra copies of the gene for glycine decarboxylase. This gene encodes the enzyme that degrades glycine, a key modulator of the NMDA receptor, which has been implicated in psychosis. When Calen and Jessie were given glycine the response was like giving insulin to a person with diabetes—their psychiatric symptoms largely resolved. When the drug was stopped, their symptoms returned. When they received glycine again under non-blind conditions, the same improvements were observed.*

# Schizophrenia Treatment Update

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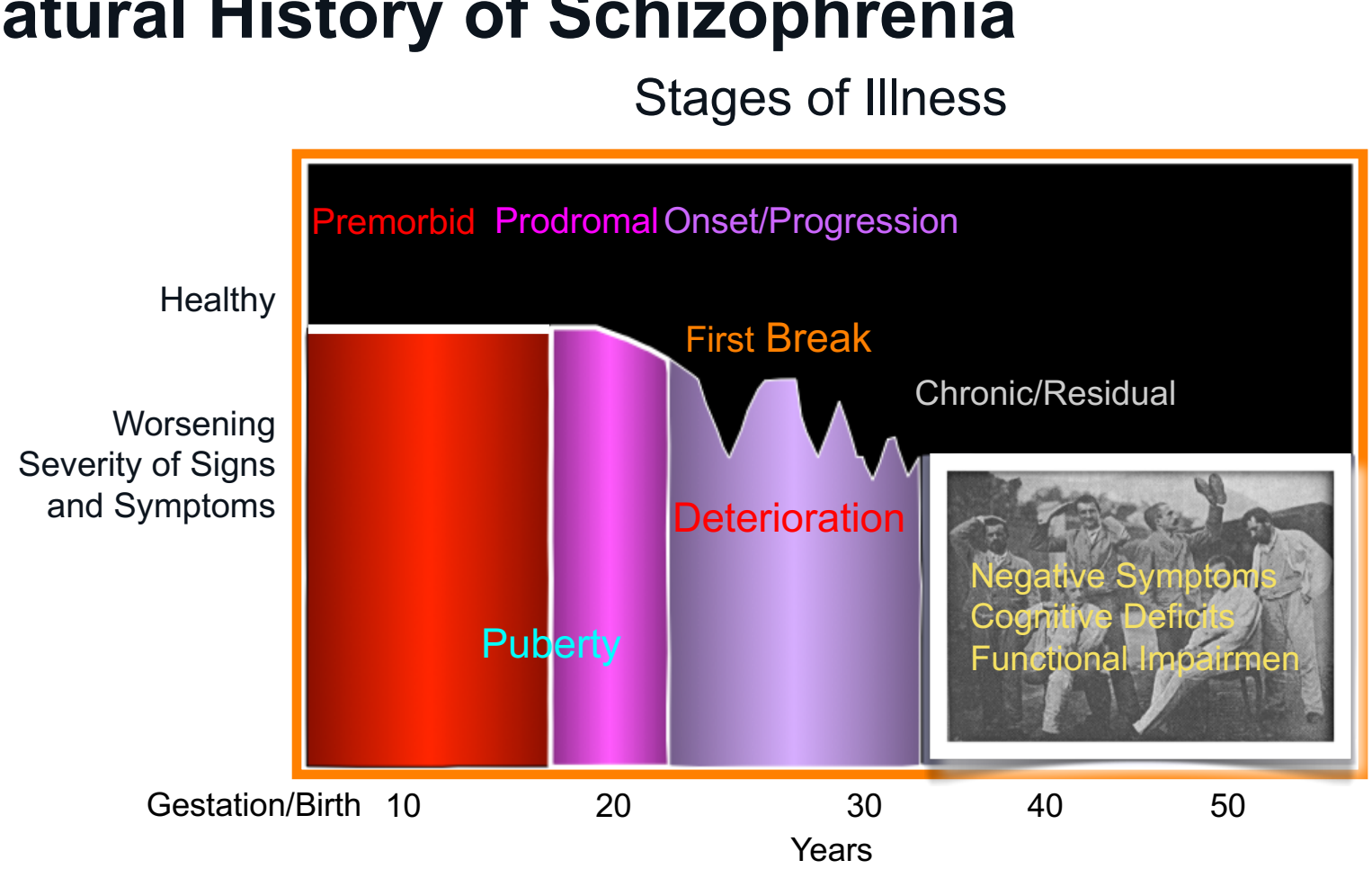
# End Stage of Schizophrenia (Dementia Praecox)

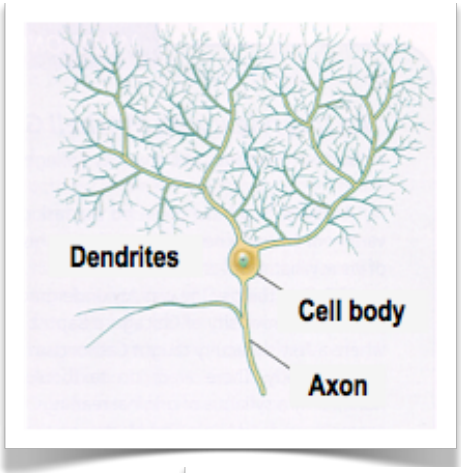
E. Kraepelin 1919

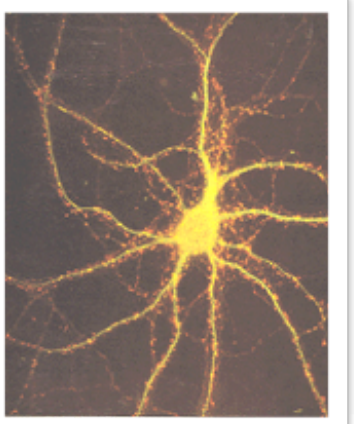
# Natural History of Schizophrenia

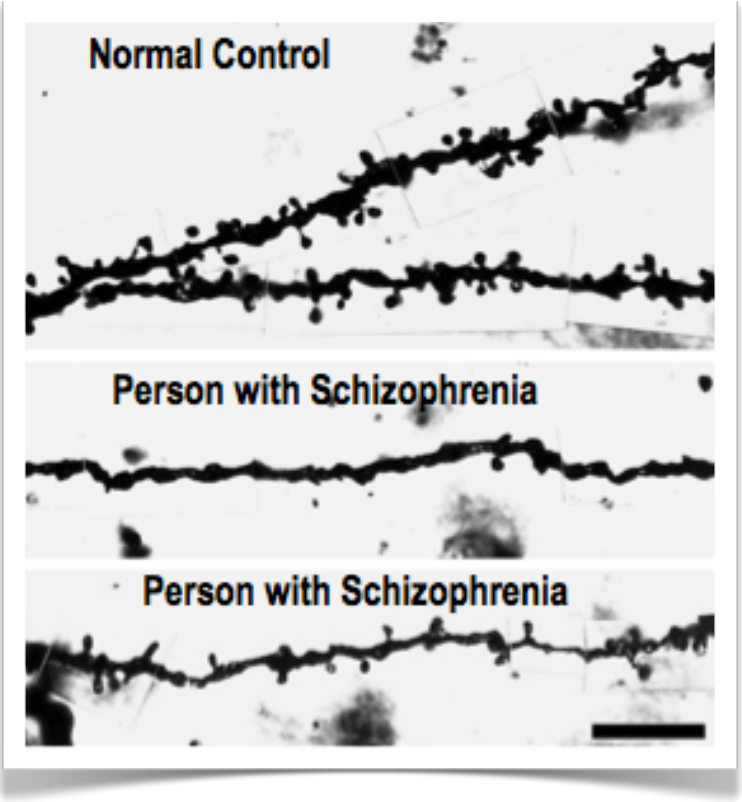



Lieberman JA, et al. *Biol Psychiatry*. 2001;50(11):884-897.

# Pathophysiology and Neuropathology of Schizophrenia

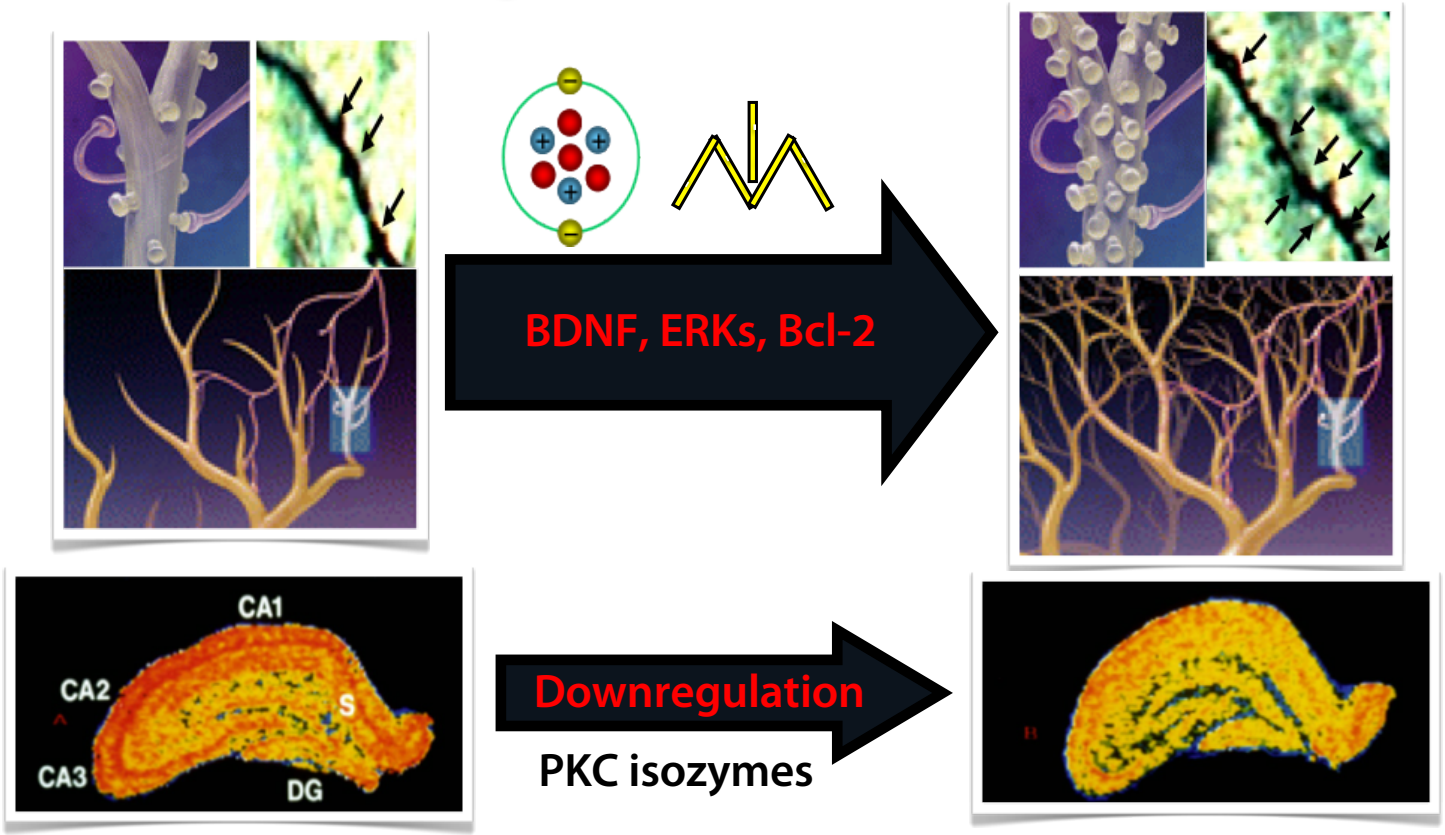


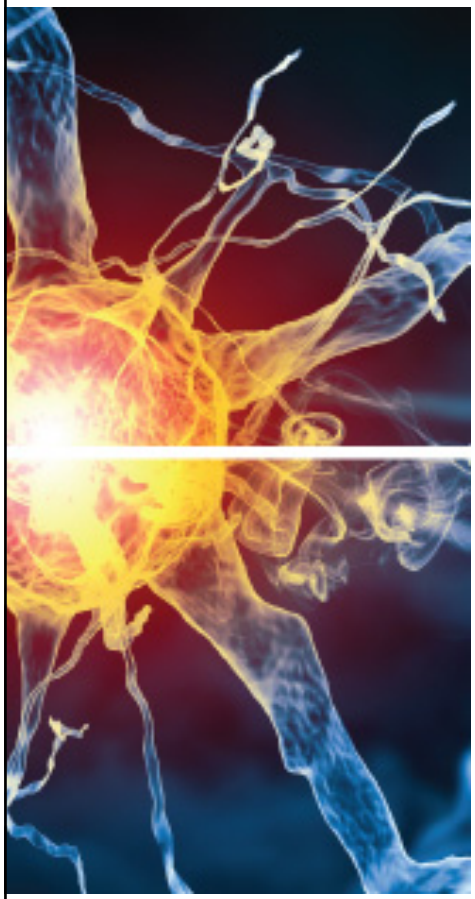




Adapted from Glantz LA, Lewis DA. *Arch Gen Psychiatry.* 2000;57(1):65-73.

# Regenerative Drugs that Restore and Enhance Neural Connectivity




Adapted from H. Manji.

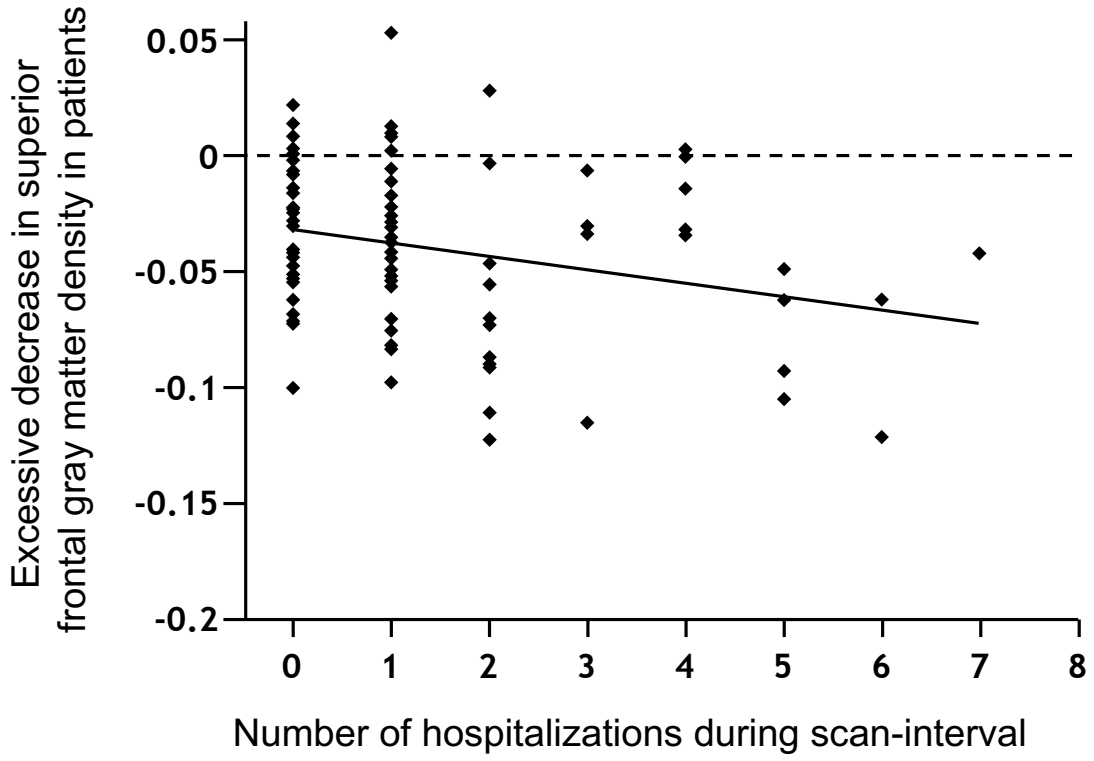


# Neurodevelopmental Versus Neurodegenerative

Can we change the course or prevent the illness?

Symptom Improving vs. Disease Modification

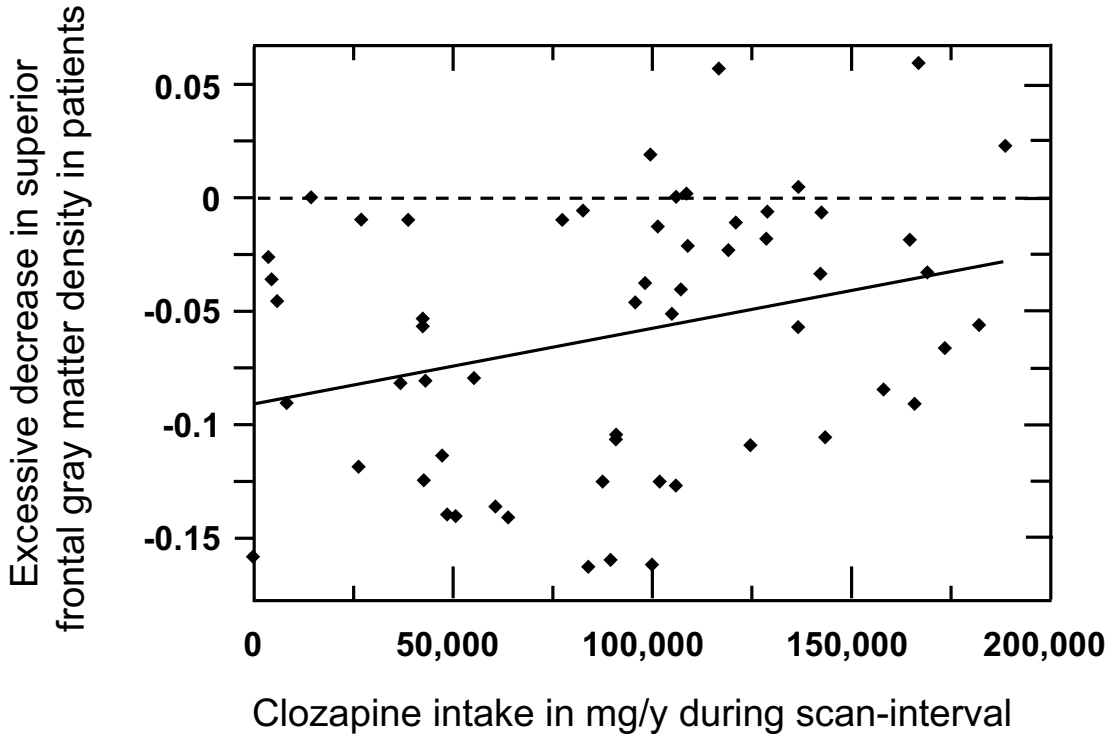
# Regression of Excessive Gray Matter Density Change on Number of Hospitalizations in Patients




N = 96
*P* = .03.

van Haren NE, et al. *Neuropsychopharmacology*. 2007;32(10):2057-2066.

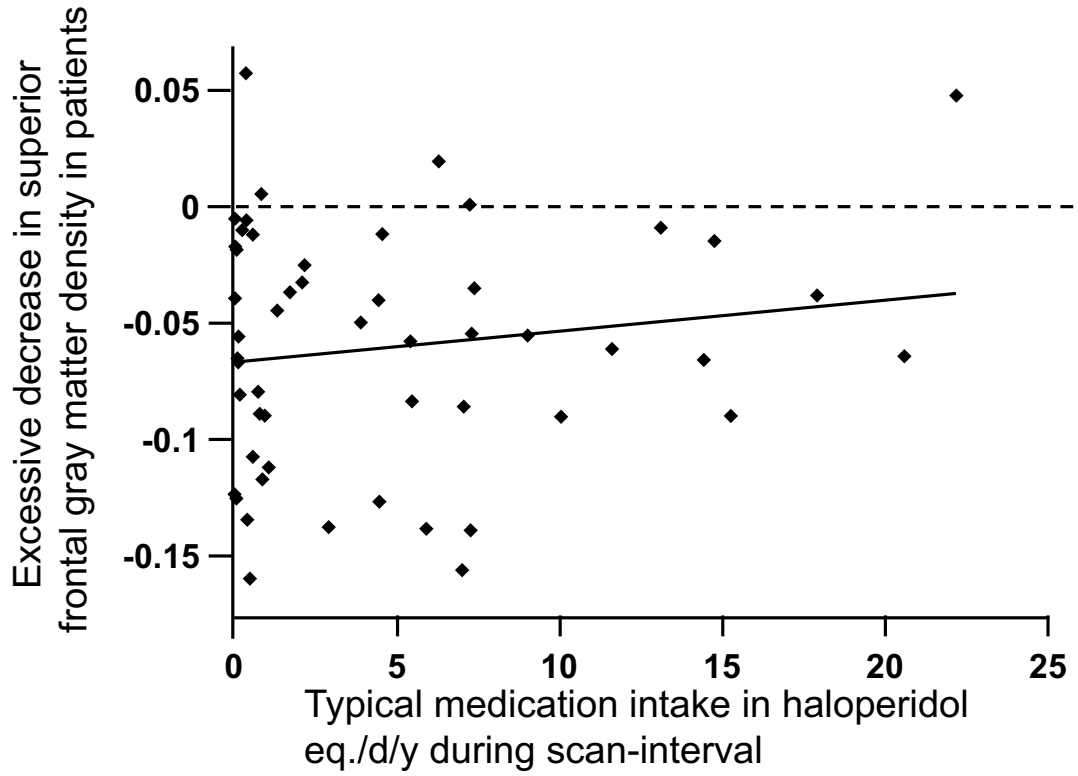
# Regression of Excessive Gray Matter Density Change on Cumulative Clozapine Intake (mg/y) During Scan-Interval




N = 58
*P* = .02

van Haren NE, et al. *Neuropsychopharmacology*. 2007;32(10):2057-2066.

# Regression of Excessive Gray Matter Density Change on Cumulative Typical Medication Intake (Haloperidol eq./d/y) During Scan-Interval




N = 53
*P* = .14

van Haren NE, et al. *Neuropsychopharmacology*. 2007;32(10):2057-2066.

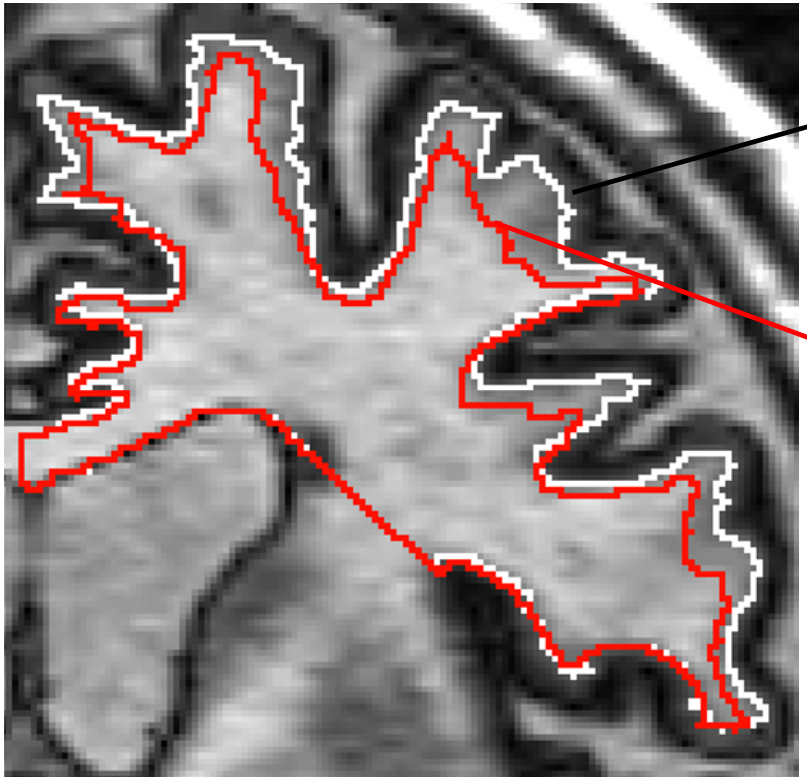
# UCLA First Episode Psychosis Study

- 12-month RCT of comparing oral to LAI risperidone with psychosocial treatment in FEP patients at the UCLA Aftercare Research Program
- LAI risperidone: N = 2 of 40 (5.0%)
- Oral risperidone: N = 14 of 43 (32.6%)
- $\chi 2\ (1) = 11.1,\ p < .001$

Subotnik KL, et al. *JAMA Psychiatry*, 2015;72(8):822-829.

# Quantification of Intracortical Myelination (ICM)

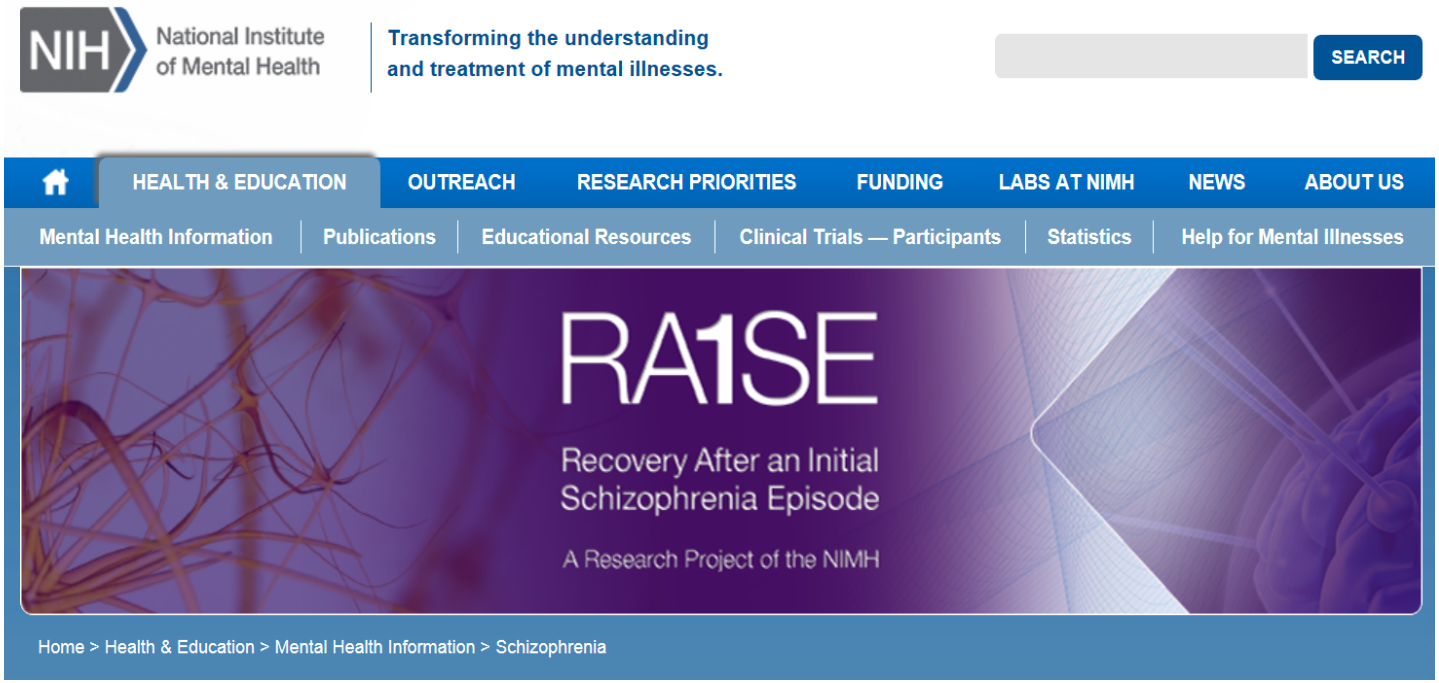
*Difference Between IR and PD → ICM*




Bartzokis G, et al. *Schizophr Res.* 2009;113(2-3):322-331.

# Factors Influencing Outcome and Prognosis

- Duration of Active Illness (DUP)
- Relapses
- Drug Effects: Therapeutic or Adverse
  - Wunderink
  - Vita
  - Lewis
- Goff et al AJP 2017




*The "Recovery After an Initial Schizophrenia Episode" initiative seeks to fundamentally alter the trajectory and prognosis of schizophrenia through coordinated and aggressive treatment in the earliest stages of illness.*

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# RAISE Connection Program:

## Preliminary Findings from New York and Maryland Governing Principles

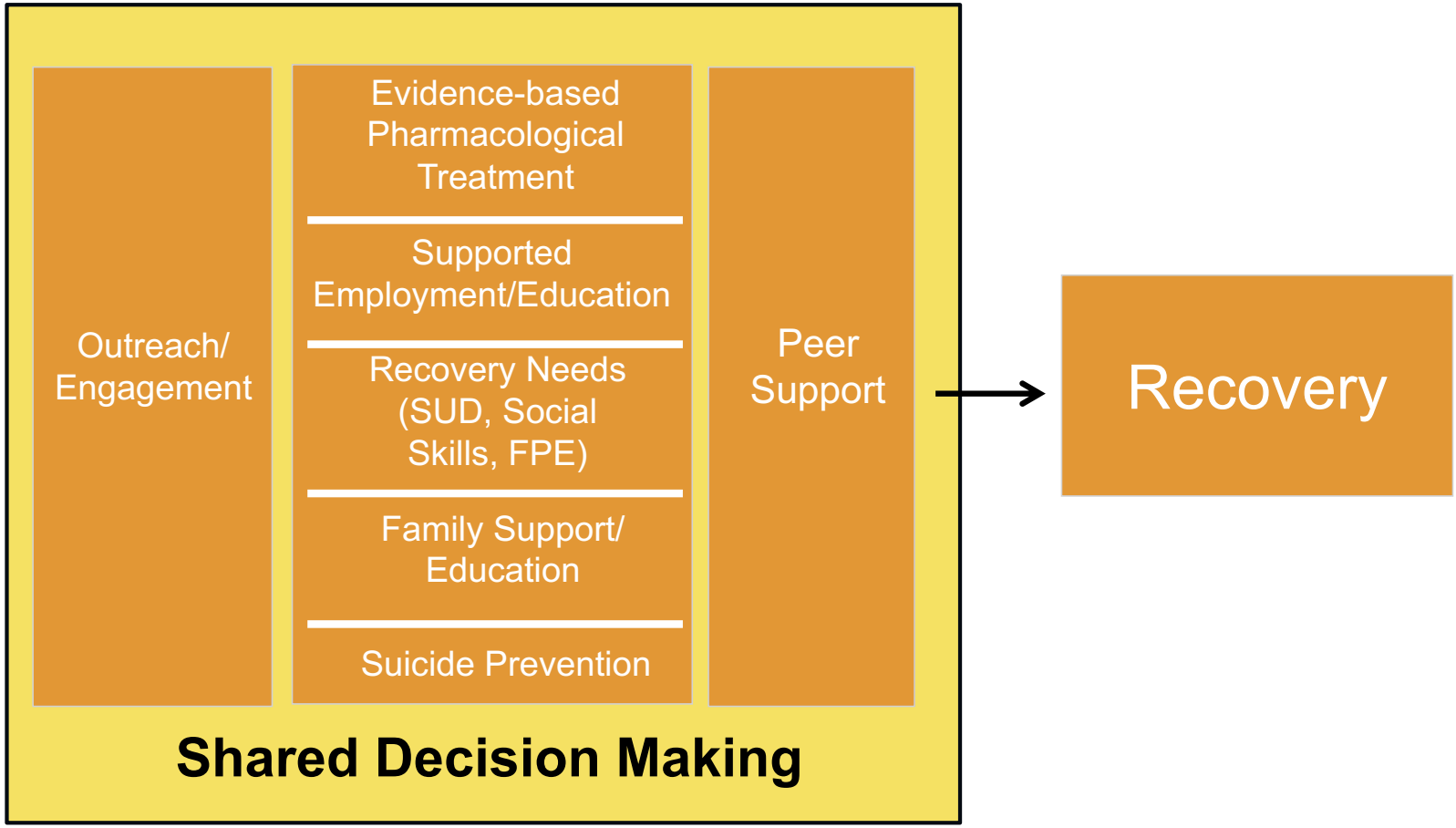
- **Disability**: Limiting disability is the central focus; disability influenced by treatment and environment
- **Recovery**: Core value of empowerment and a personal journey in which the individual acquires the skills and personalized supports necessary to optimize recovery
- **Shared decision-making**: Shared decision-making facilitates recovery and provides a framework within which the preferences of consumers can be integrated with provider recommendations for available treatments

Marino L, Nossel I, Choi JC, Neuchterlein K, Wang Y, Essock S, Bennett M, McNamara K, Mendon B, Dixon L. *J Nerv Ment Dis*. 2015;203(5):365-371.

# Optimized Intervention and Team

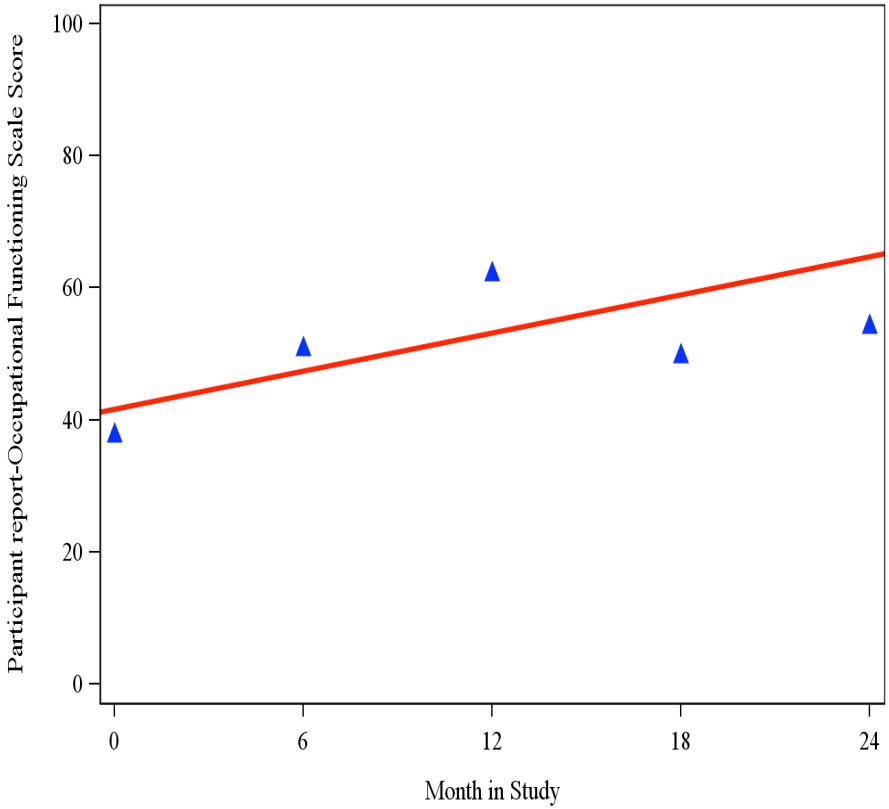
- Multi-element (e.g., psychiatric care and medications, supported education/ employment, skills and substance abuse treatment, family support, suicide prevention)
- Multi-disciplinary team
  - FT Team Leader (Master's-level clinician)
  - FT Supported employment/supported education specialist
  - 0.5 FTE FT Recovery Coach (self-management, substance abuse, family)
  - .20 Psychiatrist
- Individualized approach
- Developmentally flexible

# Connection Team Interventions




http://www.nimh.nih.gov/health/topics/schizophrenia/raise/coordinated-specialty-care-for-first-episode-psychosis-resources.shtml

# MIRECC GAF Occupational Functioning Score Over Time



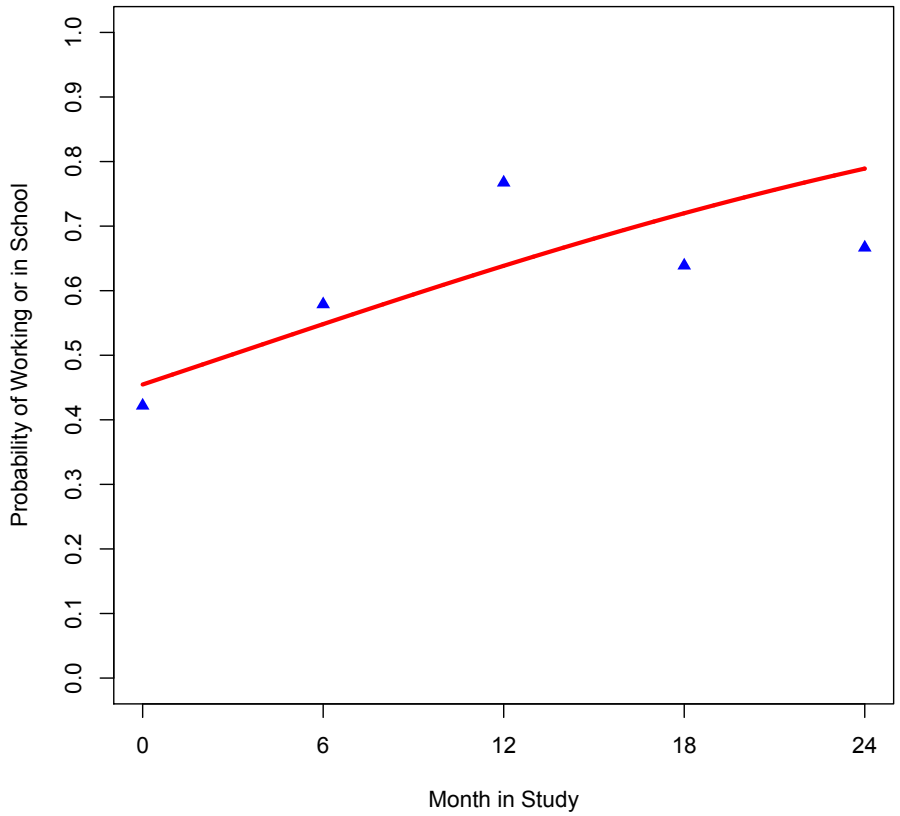

On average MIRECC GAF occupational functioning score increases by 0.96 points (CI: 0.60, 1.32, $p < 0.0001$) every month.

Category Fluency was a significant moderator.

PANSS negative symptoms significant predictor.

Schooler N. *Early team based treatment for people with psychotic symptoms. The RAISE early treatment program (ETP) experience*. BBRF Website. https://bbrfoundation.org/sites/bbrf.civicactions.net/files/file-downloads/BBRF%20RAISE-ETP%2020150414%20updated.pdf. Accessed June 11, 2017.

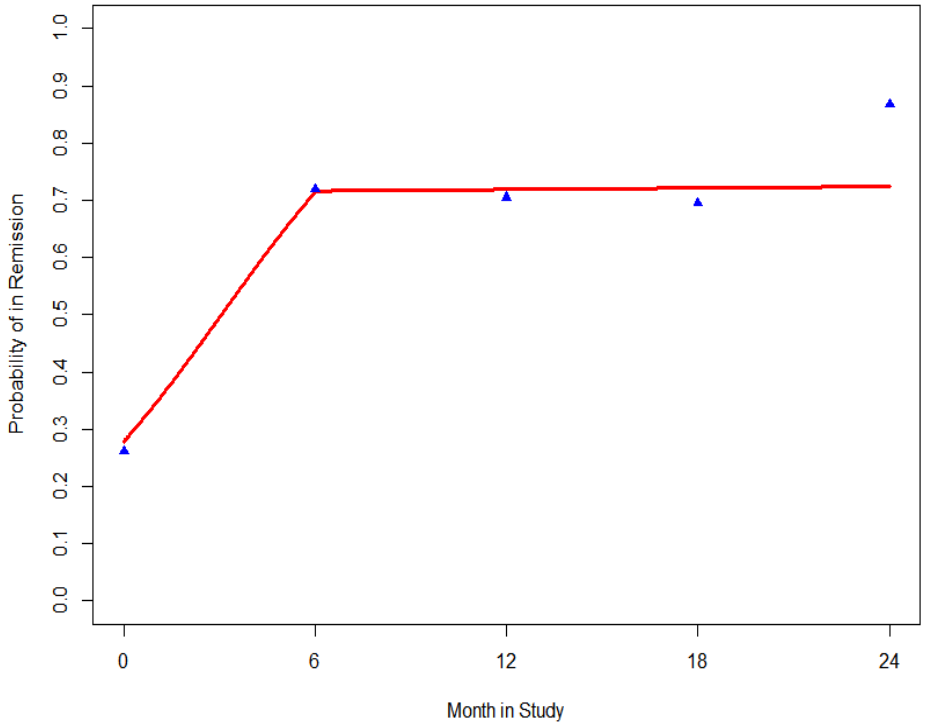
# In Work or School Over Time




For each given subject, the odds of working or receiving education increases by 1.088 times (CI: 1.038, 1.140, $p$ = 0.0006) each month.

Schooler N. *Early team based treatment for people with psychotic symptoms. The RAISE early treatment program (ETP) experience*. BBRF Website. https://bbrfoundation.org/sites/bbrf.civicactions.net/files/file-downloads/BBRF%20RAISE-ETP%2020150414%20updated.pdf. Accessed June 11, 2017.

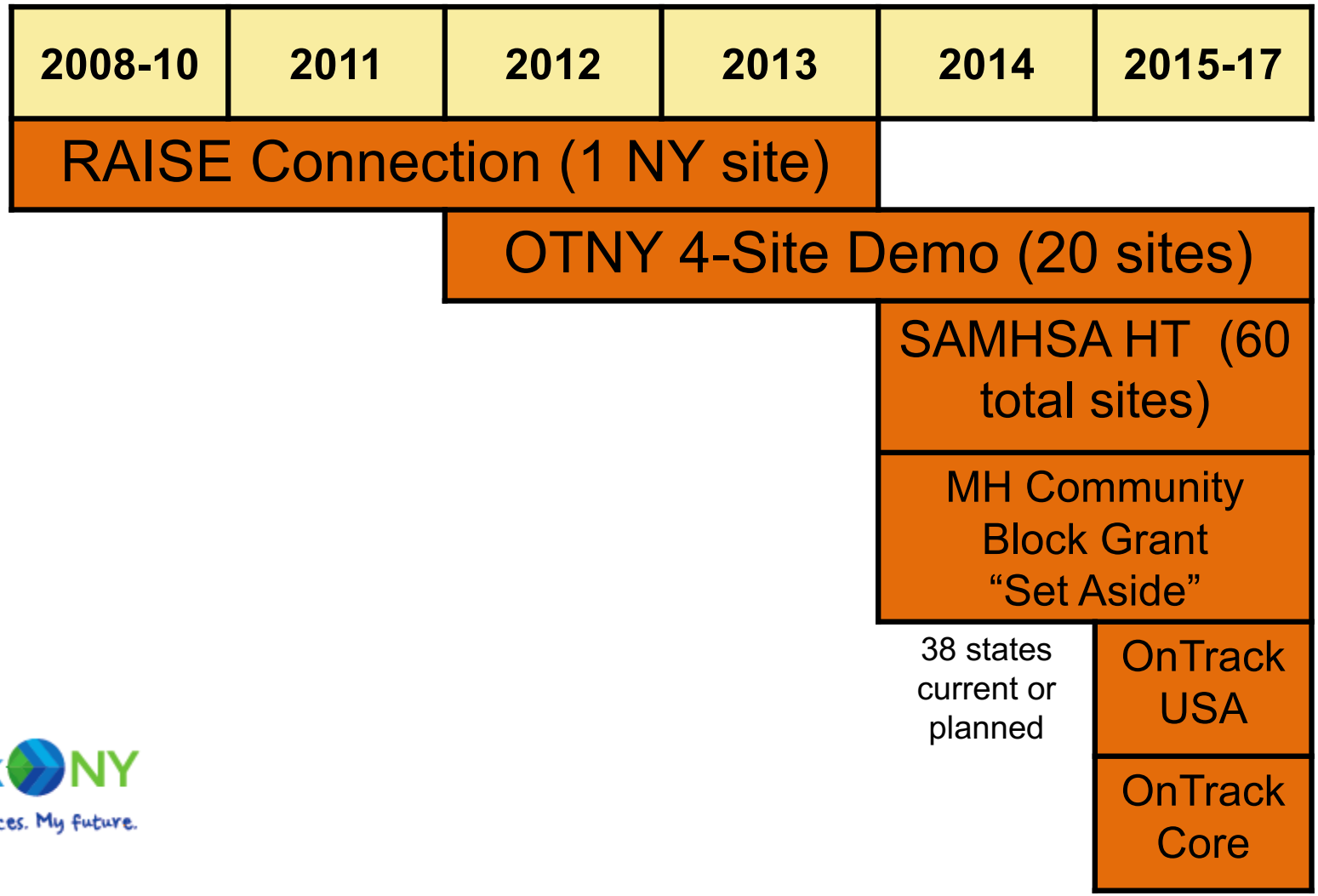
# Remission Over Time




For each given subject, the odds of remission increased by 1.55 times (CI: 1.31, 1.83; $p < .0001$) each month in follow up from baseline to month 6.

Schooler N. *Early team based treatment for people with psychotic symptoms. The RAISE early treatment program (ETP) experience*. BBRF Website. https://bbrfoundation.org/sites/bbrf.civicactions.net/files/file-downloads/BBRF%20RAISE-ETP%2020150414%20updated.pdf. Accessed June 11, 2017.

# Timeline

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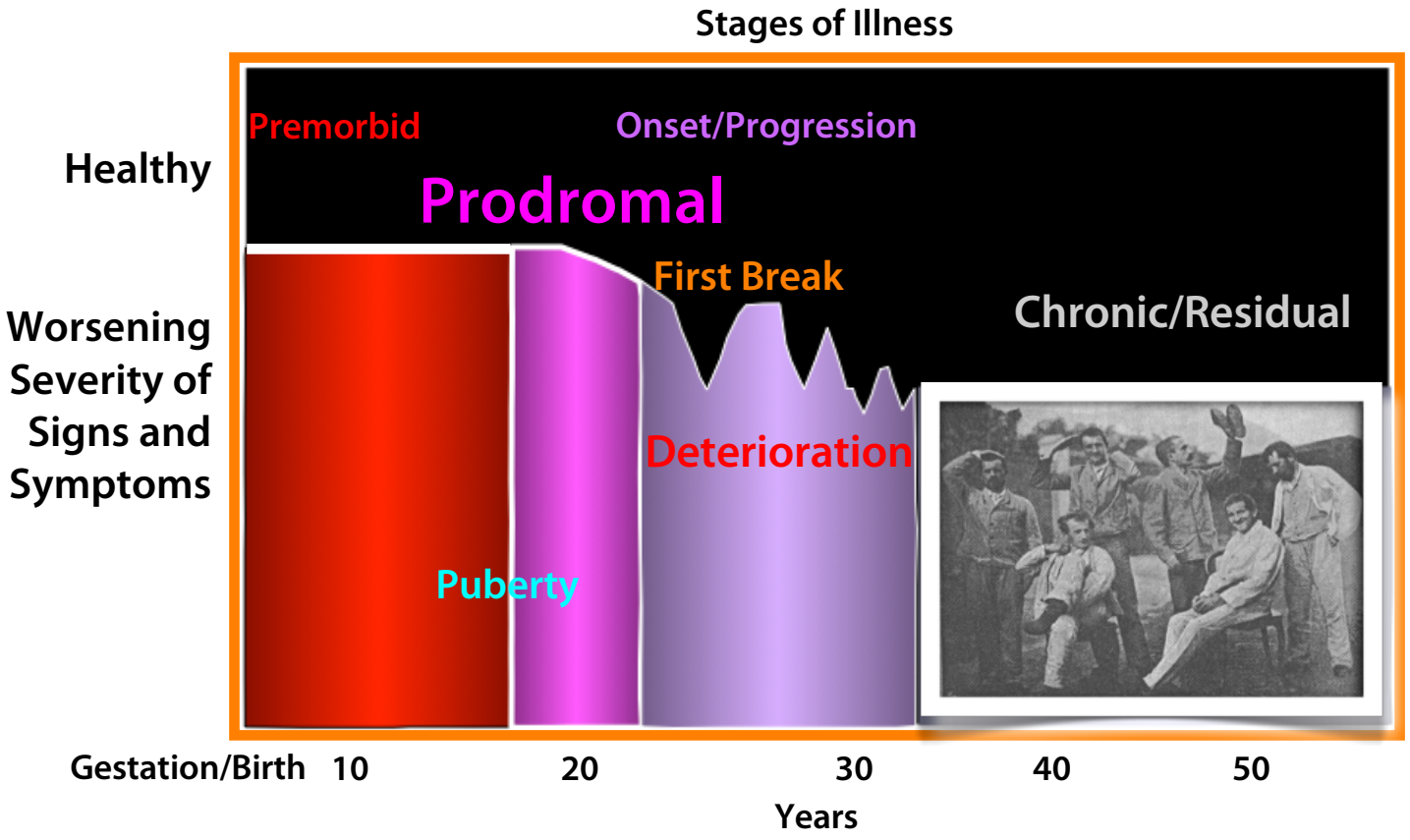
# Can Treatment Prevent the Onset of Mental Illness?

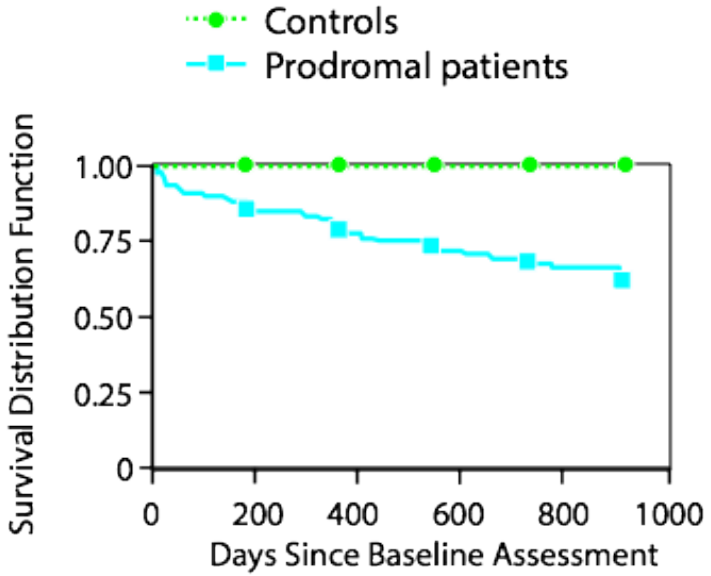


# Prediction of Psychosis in Youth at High Clinical Risk - NAPLS

## Outcomes

- Risk of conversion 35% during f/u period
- 5 features improved prediction: genetic risk for schizophrenia, decline in function, unusual thought content, suspiciousness, social impairment, substance abuse

## Major Results




Cumulative survival distribution function modeling time to conversion to psychosis in 291 clinical high-risk (prodromal) patients and 134 demographically comparable normal control subjects (dashed line).

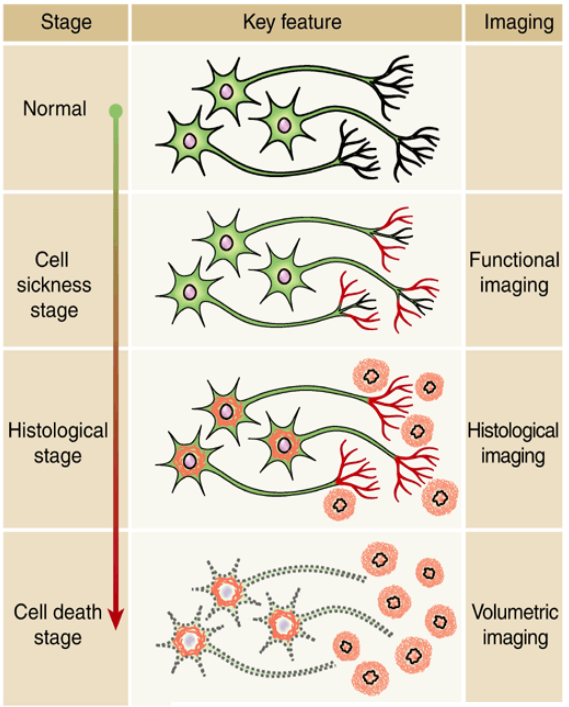
Cannon TD, et al. *Arch Gen Psychiatry*. 2008;65(1):28-37.

# Utility of a Biomarker to Diagnose Disease

| | Diagnosis = Negative | Diagnosis = Positive | |
|---|---|---|---|
| Test Result = Positive | False Positive | True Positive | Positive Predictive Value: TP/(TP+FP) |
| Test Result = Negative | True Negative | False Negative | Negative Predictive Value: TN/(TN+FN) |
| | Specificity: TN/(TN + FP) | Sensitivity: TP/(TP + FN) | |

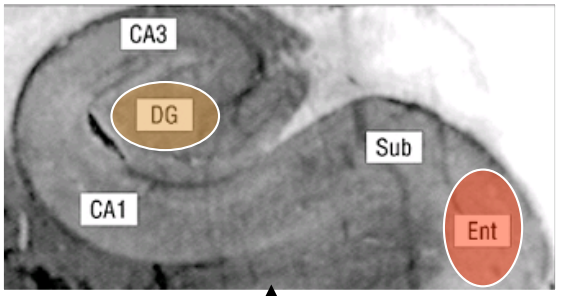
# Neuroimaging Biomarker

### *1. Sensitivity to Function*

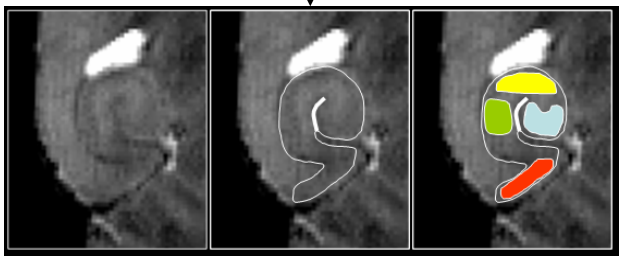



*Small SA, Nature Neuroscience, 2005*

### *2. High Spatial-Resolution*



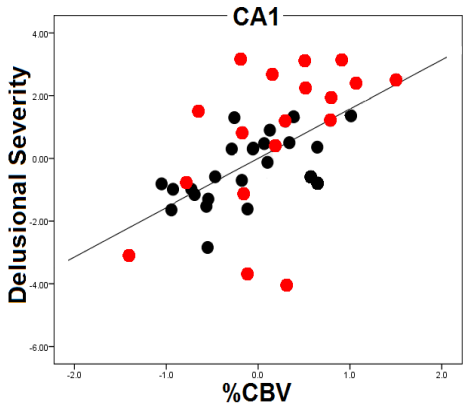

***Translational***

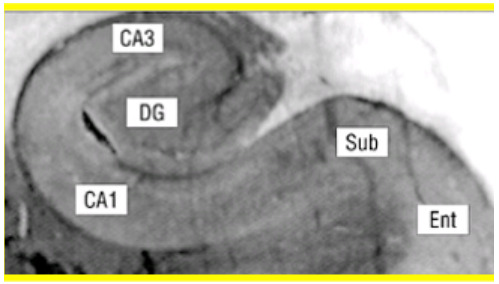


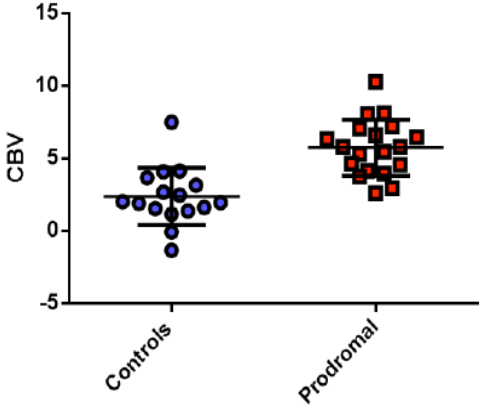
### *3. Cross-Species Capabilities*

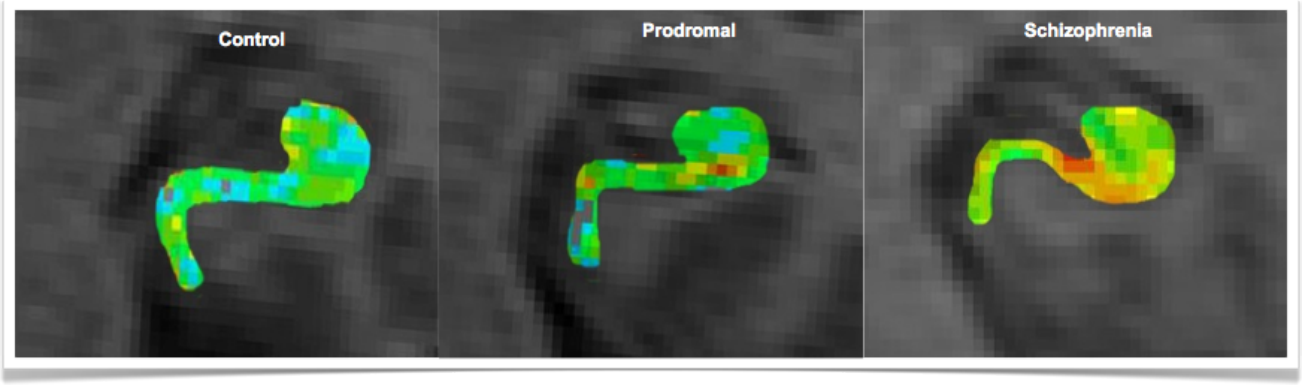
Small SA. *Nat Neurosci.* 2005;8(4):404-405.

# Hippocampal Biomarker for Psychosis



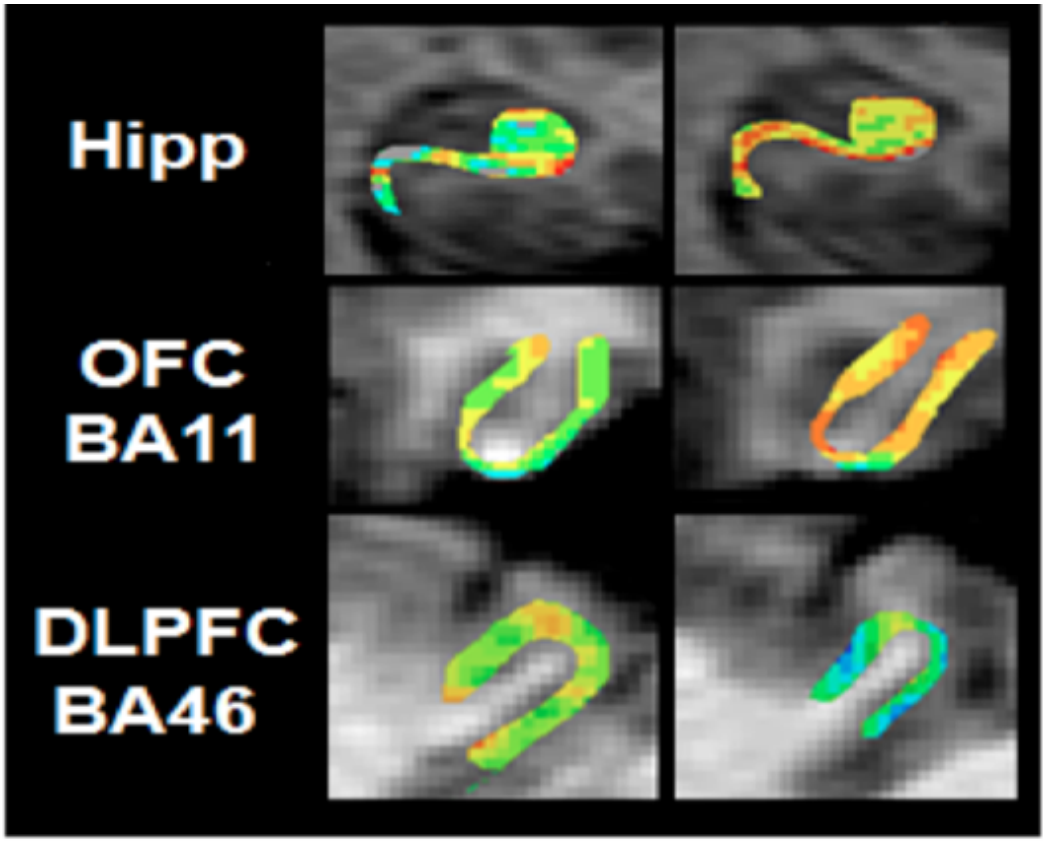



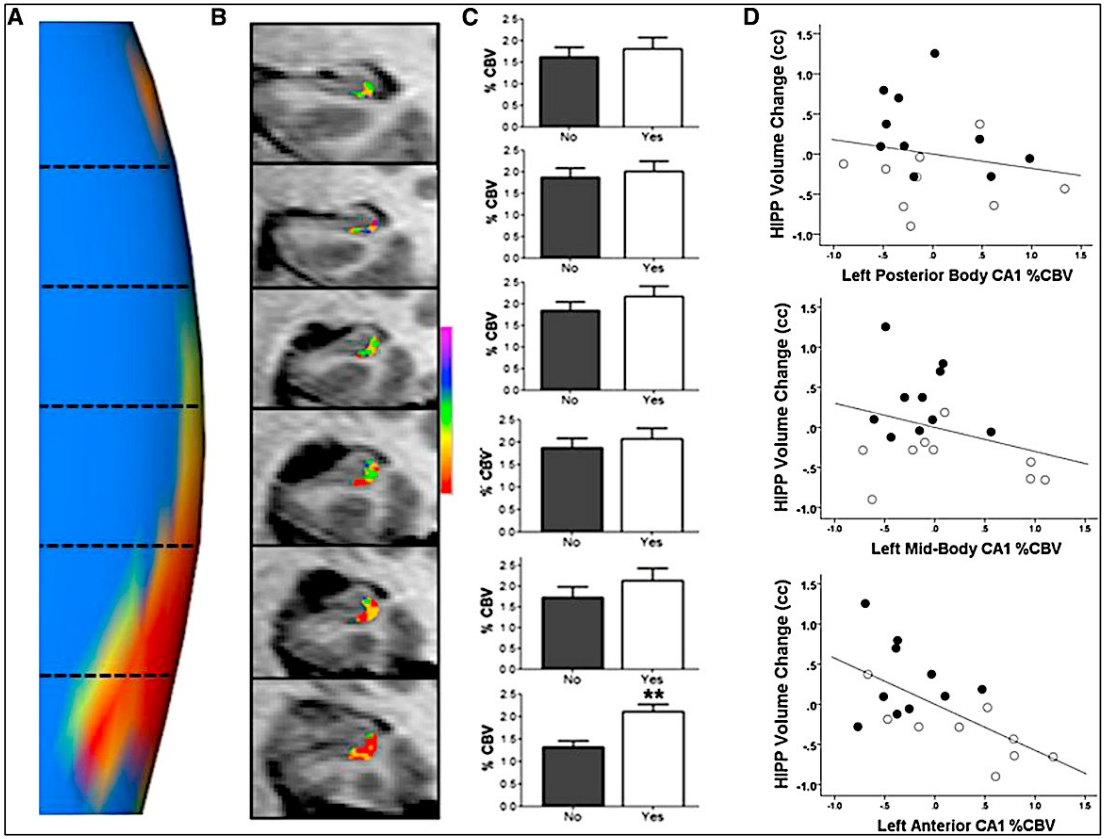

Adapted from Gaisler-Salomon I, Schobel SA, Small SA, et al. *Schizophr Bull*. 2009;35(6):1037-1044

# High Risk → First Episode




Gaisler-Salomon I, Schobel SA, Small SA, et al. *Schizophr Bull*. 2009;35(6):1037-1044.

# Correlation Between CBV and Atrophy
# The Importance of High Resolution



# Limbic Cortical Hyperactivity in Schizophrenia

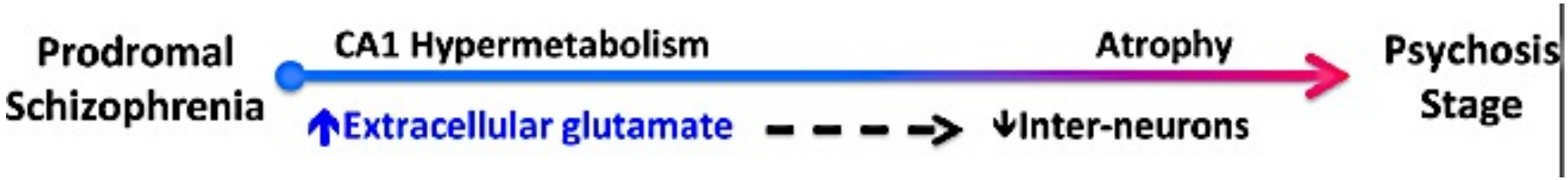
Basal-state cerebral blood volume (a measure of metabolic activity) in the hippocampus is a focal, proximal biomarker that

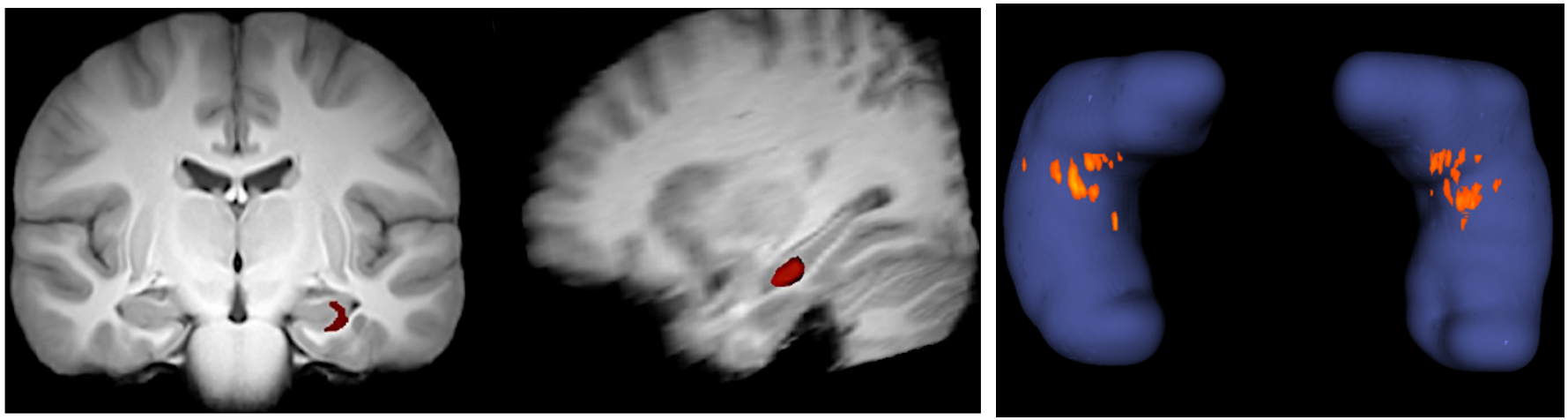
- Predicts progression to psychosis
- Correlates with psychotic symptom severity
- Predicts hippocampal structural change

*As psychosis emerges, abnormal metabolic activity "propagates"*

What is the pathophysiological basis of limbic hyperactivity?

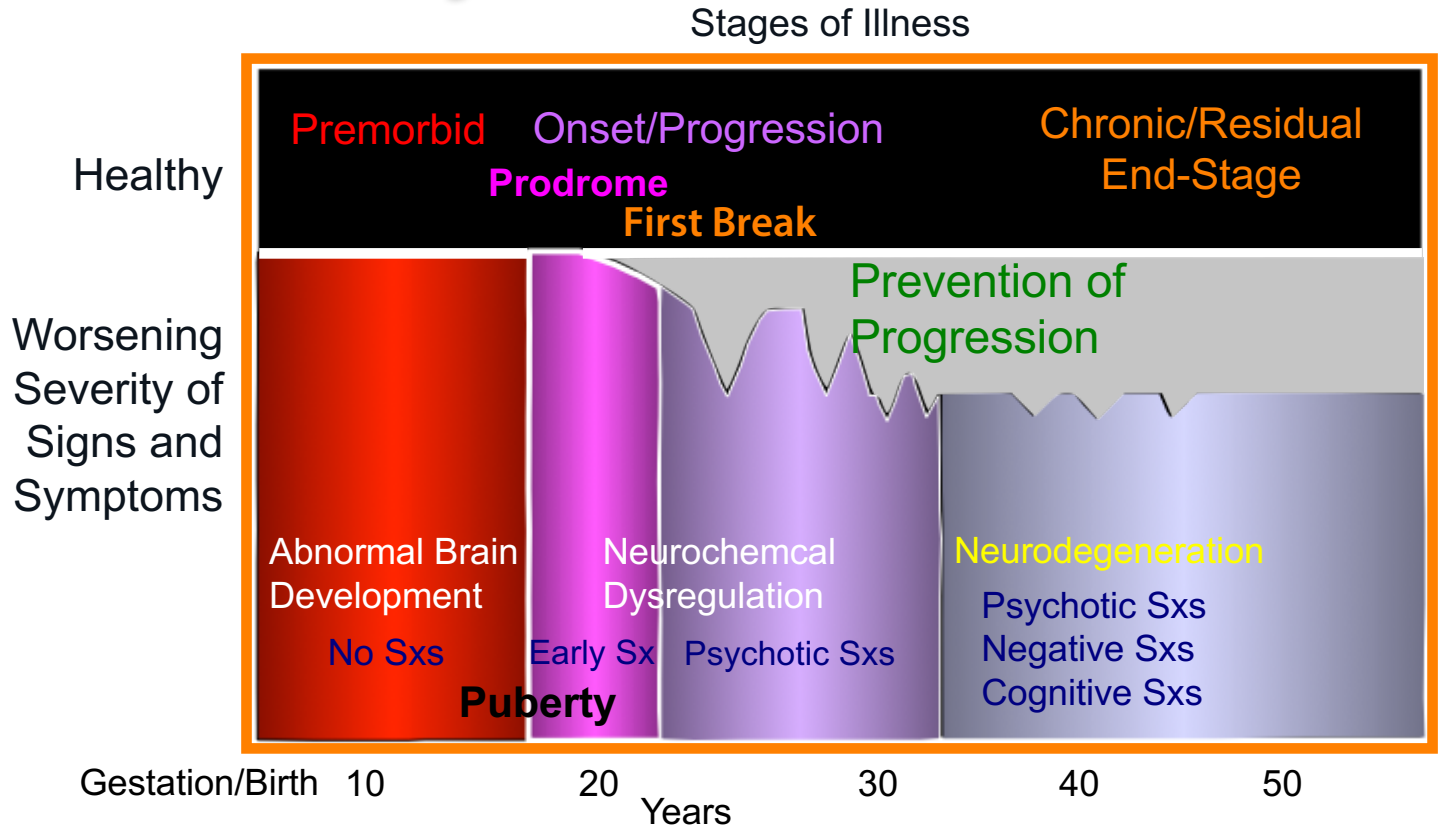
# Pathogenesis of Psychosis in Schizophrenia



Small SA. *Neuron*. 2014;84(1):32-39.

# Natural History of Schizophrenia
# Rationale for Early Detection and Intervention




Lieberman JA, et al. *Biol Psychiatry*. 2001;50(11):884-897.

# End Stage of Schizophrenia (Dementia Praecox)

E. Kraepelin 1919

# Thank You

Diana Perkins (UNC)
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Cecil Charles (Duke)
Martin Syner (UNC)
Guido Gerig (UNC)
Del Robinson (NS-LIJ)
Antony Loebel (NS-LIJ)
John Kane (NS-LIJ)
Paul Thompson (USC)

**Scott Small (CU)**

**Jeffrey Lieberman (CU/PI)**

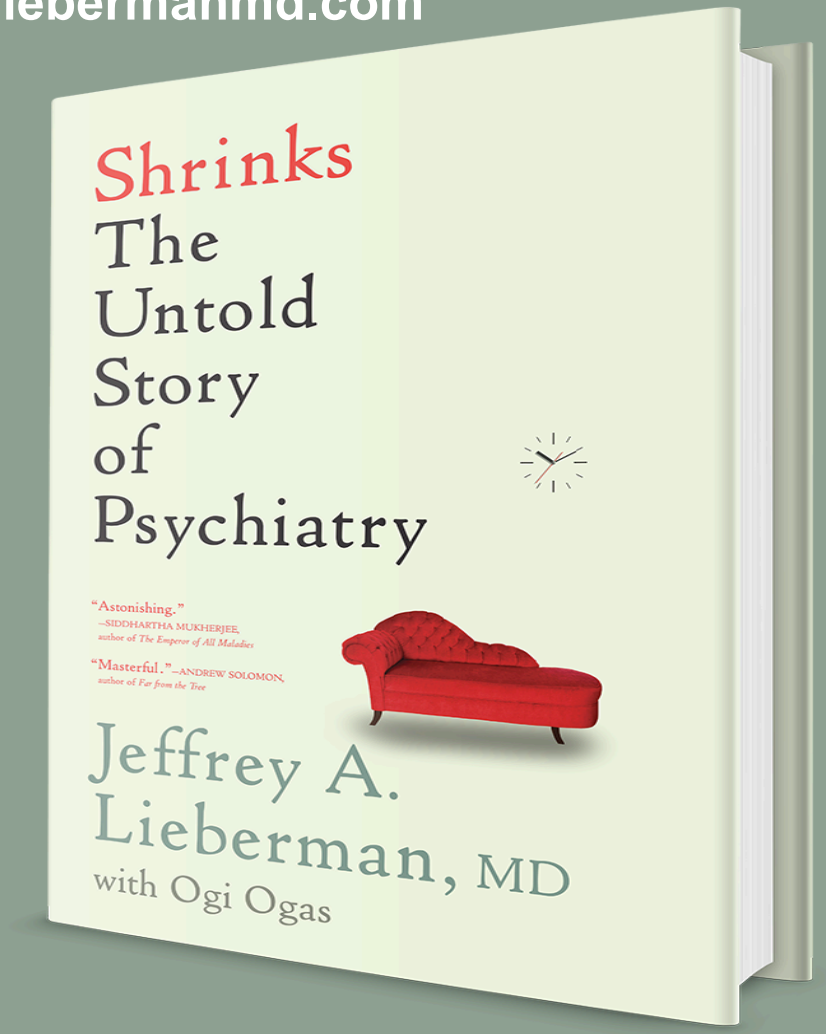
**Lisa Dixon (CU/PI)**

Frank Provenzano (CU/PI)
Steve Rayport (CU/PI)
Andrew Dwork (CU/PI)
Gary Brucato (CU/PI)
Cheryl Corcoran (CU/PI)
Dolores Malaspina (NYU)
Susan Essock CU/PI)
Ilana Nossel (CU/PI)
Josh Kantrowitz (CU/PI)
Doug Rothman (yale)
Graeme Maason
Dan Javitt (CU/PI)
Anissa Abi Dargham (CU/PI)
BME Post-docs
**Ragy Girgis (CU/PI)**

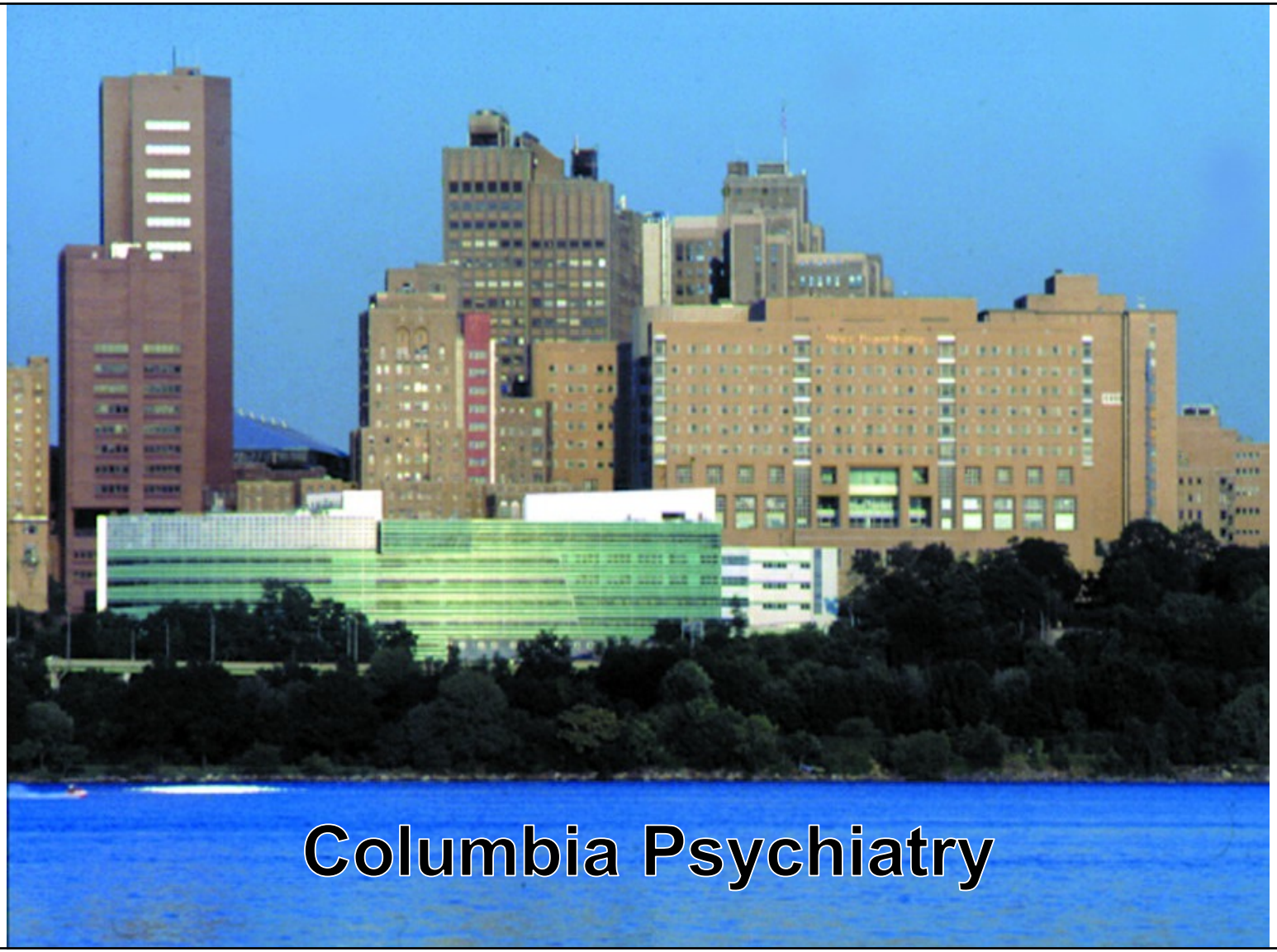
**Scott Schobel (Roche)**

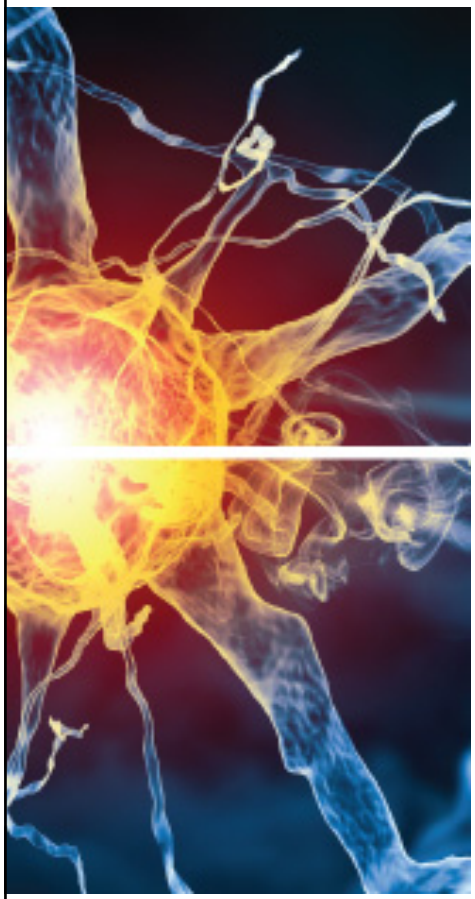
**Holly Moore (CU/PI)**

www.jeffreyliebermanmd.com




Jeffrey Lieberman MD Shrinks


Columbia Psychiatry



# Questions & Answers