Biomarkers of Severity and Outcome of Schizophrenia Patients

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Biomarkers for Mental Disorders

- Serve multiple purposes:
  - diagnostic,
  - prognostic,
  - theragnostic;
  - drug development e.g. target engagement, proof of mechanism
- Have an added significance for mental disorders
- Critical to distinguish between measures of pathophysiology and outcome
- Determine state or trait dependency
- Reliability, sensitivity, specificity, confounding factors
  - DA receptors and drug treatment in PET
  - Cardio-respiratory effects on BOLD in fMRI

Biomarkers for Alzheimer's Disease

Association of Dementia Severity and Histopathologic Plaque Count
Blessed, Tomlinson, Roth 1967

Fig 1 *Relationship of dementia score to mean plaque count in 60 aged subjects*
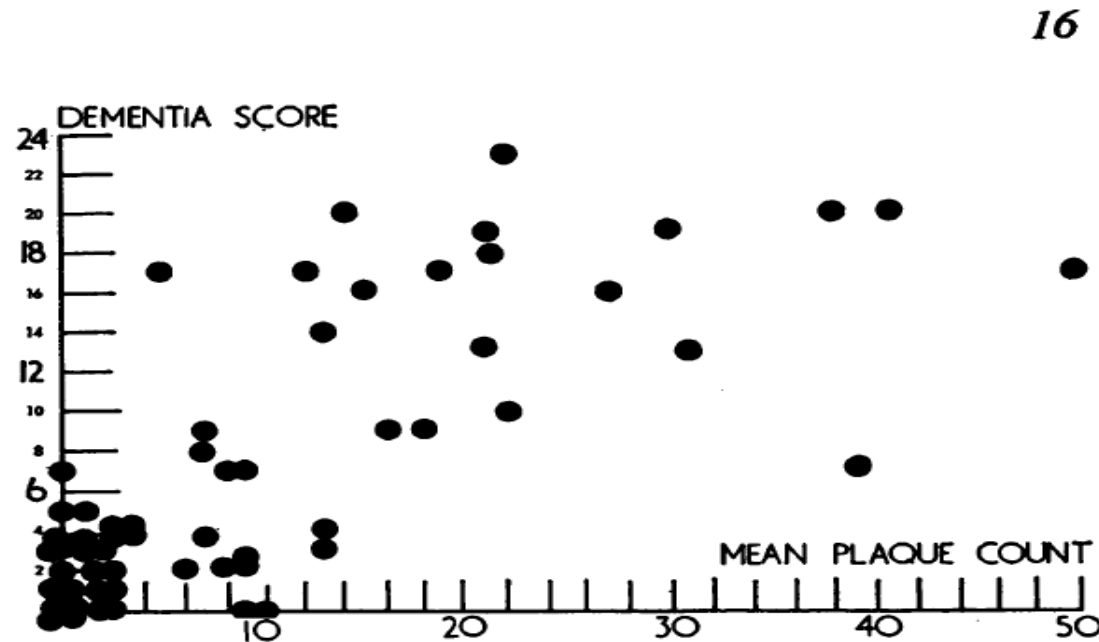
Imaging Biomarkers for Alzheimer's Disease

- PiB Abeta and MK-6240 tau imaging

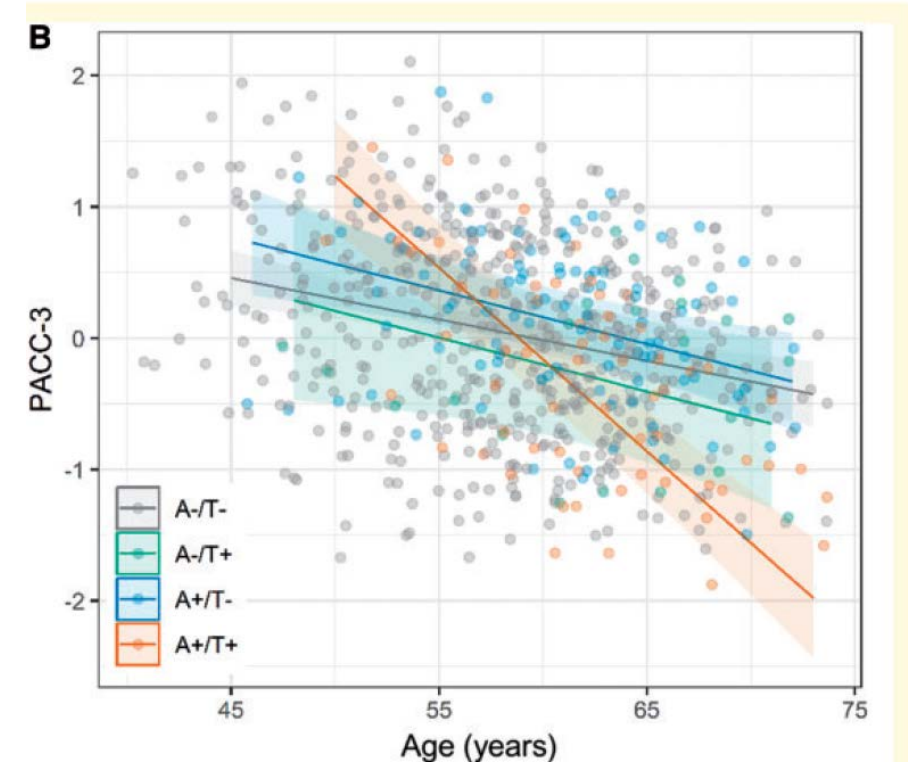- Relationship of biomarker positivity to cognitive decline
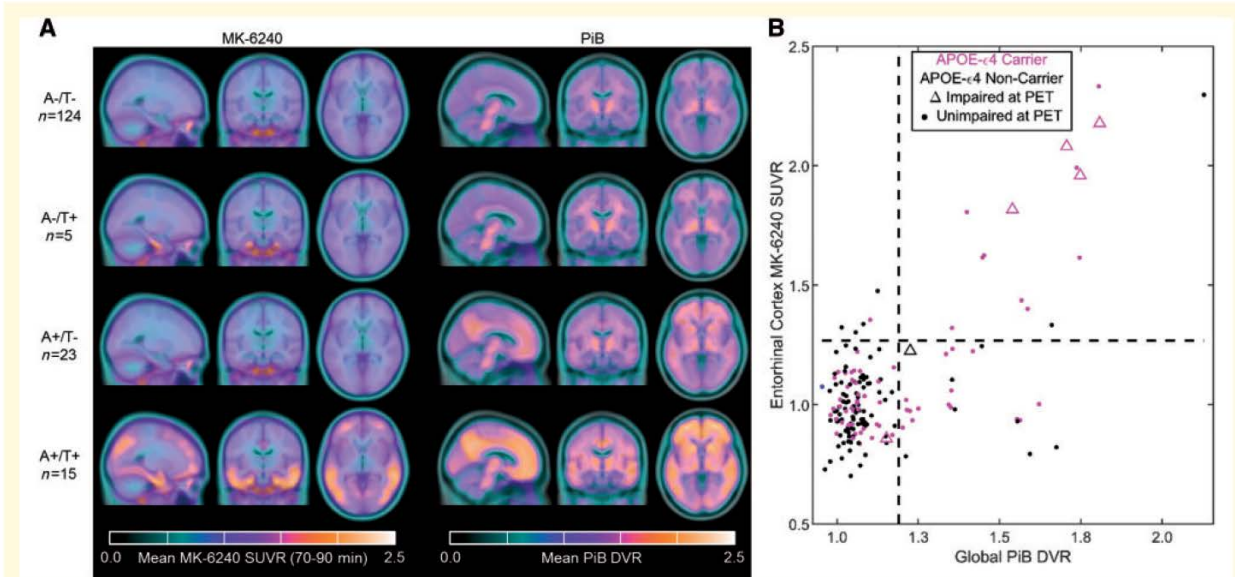
Figure 1 Parametric MK-6240 and PiB images, and biomarker group stratification. Mean parametric MK-6240 SUVR (A, left) and PiB DVR (A, right) images for each biomarker group. Individuals that were A−T+ only had elevated MK-6240 SUVR in the entorhinal cortex, whereas
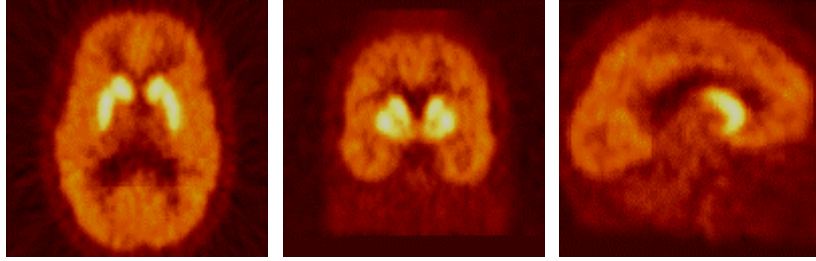
A Hundred Years of Schizophrenia Research
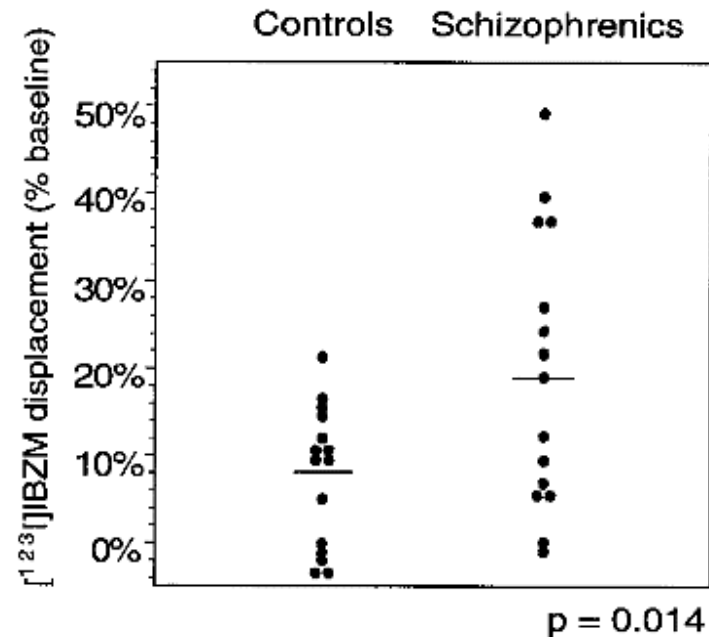
- Runs in Families i.e. Is Genetic

- Involves Chemical Neurotransmission
  - Dopamine
  - Glutamate
  - GABA

- Affects Brain Structure
  - Midbrain
  - Frontal Cortex
  - Hippocampus

Molecular Imaging of Dopamine Activity in Schizophrenia


Amphetamine-induced dopamine release

PNAS, 1996

AMPT-induced dopamine depletion

Increased baseline occupancy of D_2 receptors by dopamine in schizophrenia

Anissa Abi-Dargham[*†‡§], Janine Rodenhiser[*‡], David Printz[*], Yolanda Zea-Ponce[*‡], Roberto Gil[*], Lawrence S. Kegeles[*‡], Richard Weiss[*‡], Thomas B. Cooper[*], J. John Mann[*†‡], Ronald L. Van Heertum[†], Jack M. Gorman[*†], and Marc Laruelle[*†‡]

Departments of [*]Psychiatry and [†]Radiology, Columbia University College of Physicians and Surgeons, New York, NY 10032; and [‡]Division of Brain Imaging, Department of Neuroscience, New York State Psychiatric Institute, New York, NY 10032
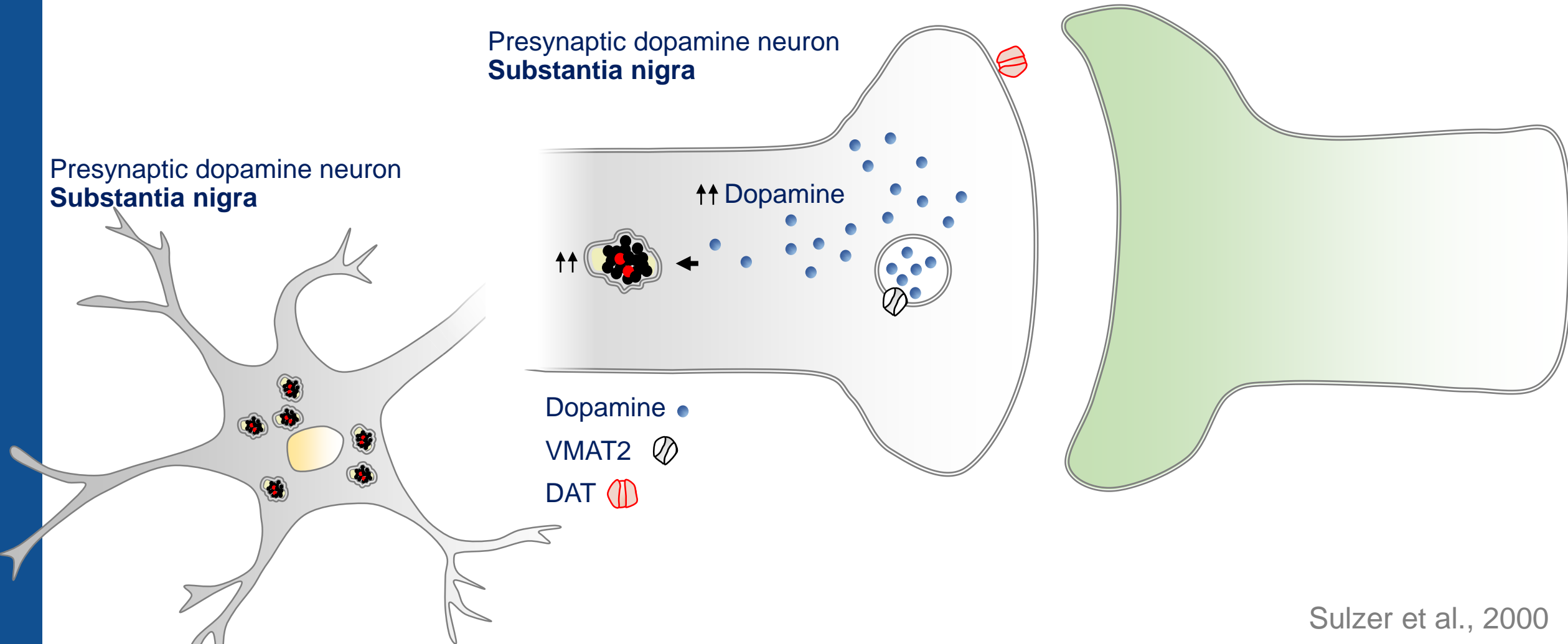
PNAS, 2000
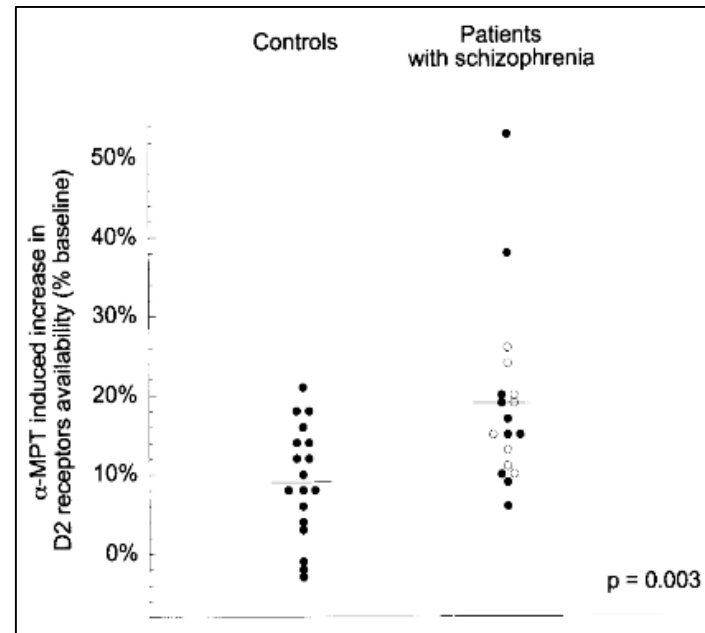
Treatment Response
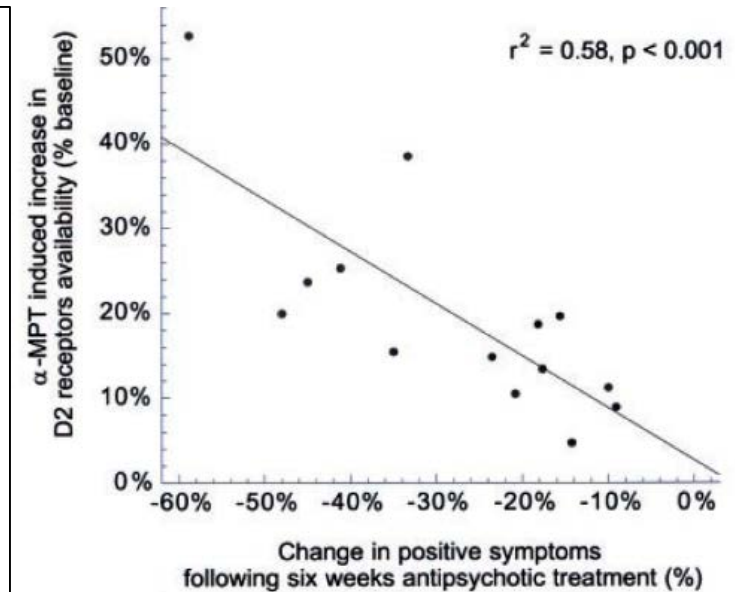
Laruelle, Abi Dargham, Kegeles 2001

Neuromelanin Is a Biomarker of Dopamine Pathophysiolgy in Schizophrenia

Presynaptic dopamine neuron
Substantia nigra

Presynaptic dopamine neuron
Substantia nigra

↑↑ Dopamine

↑↑

Dopamine ●

VMAT2

DAT

Sulzer et al., 2000

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Neuromelanin Is a Biomarker of Dopamine Pathophysiology in Schizophrenia

Presynaptic dopamine neuron
Substantia nigra

Dopamine
VMAT2
DAT

Coronal View of Midbrain

Substantia nigra

a

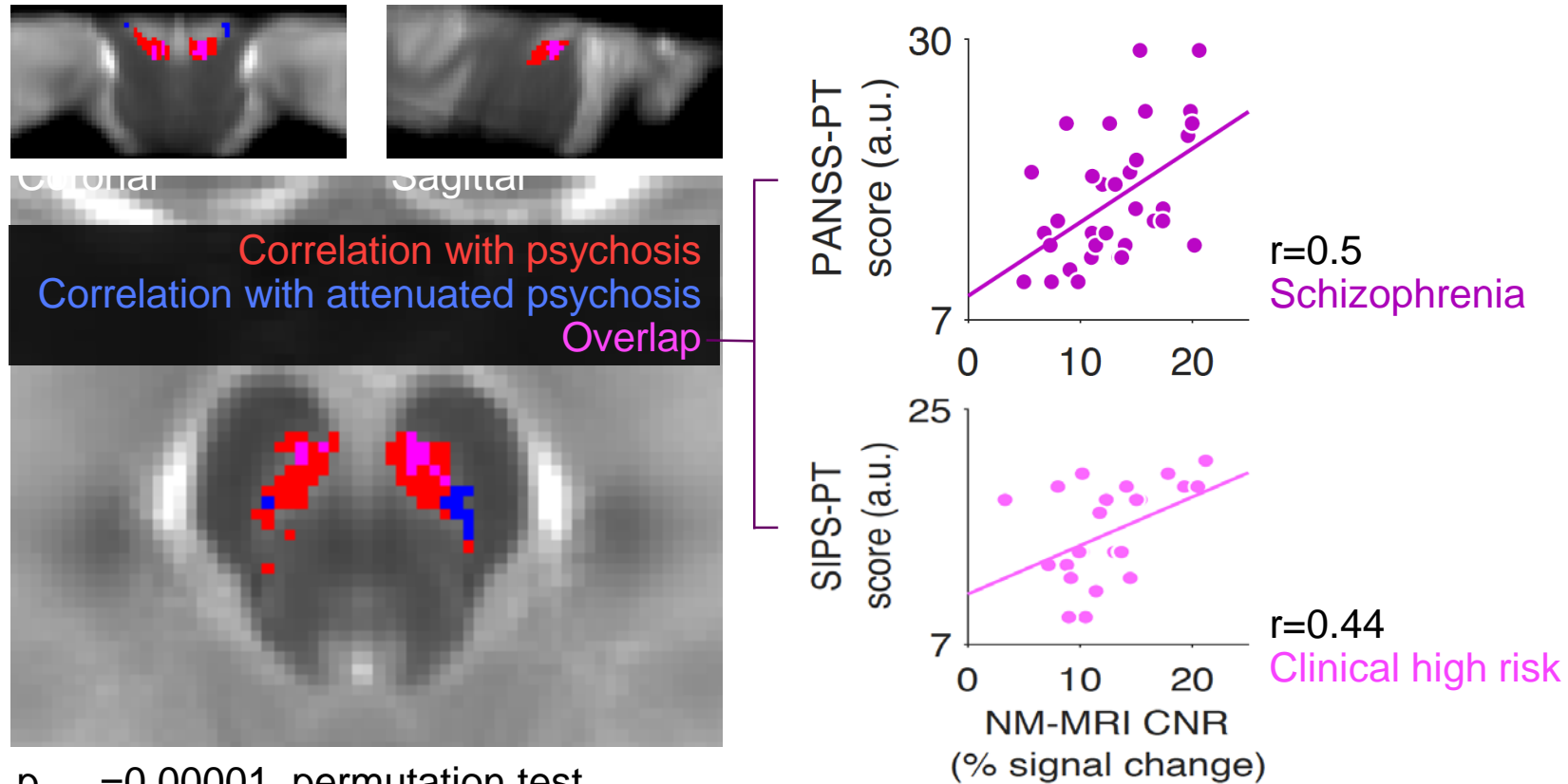**Coronal View of Midbrain**

Substantia nigra

b
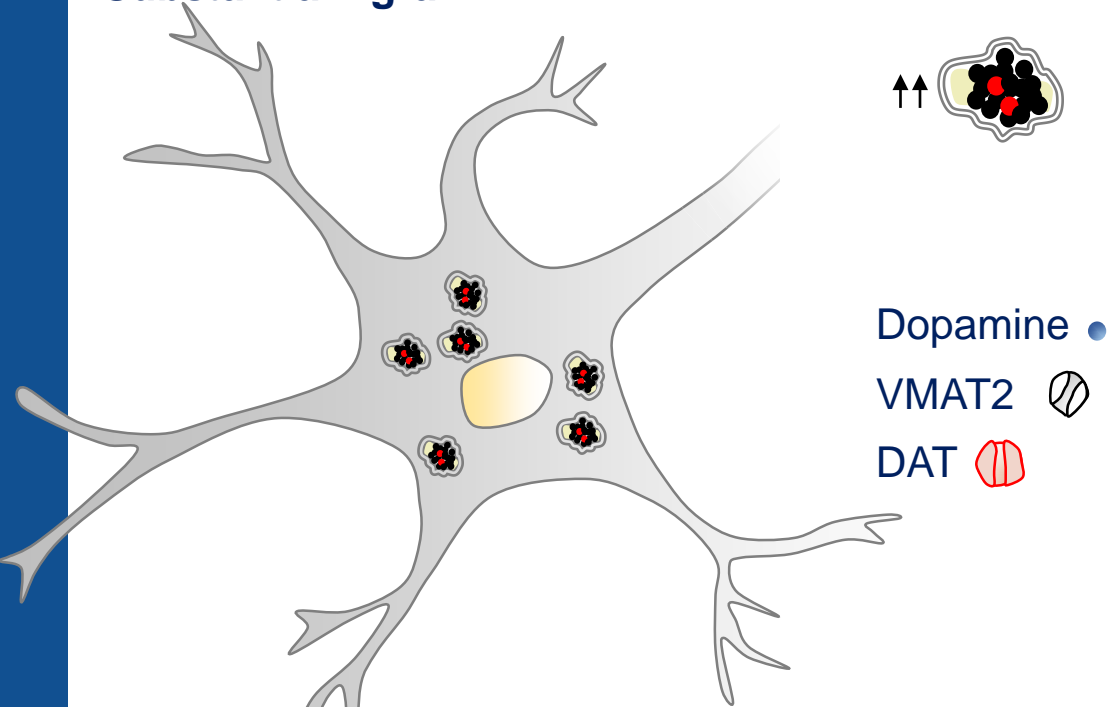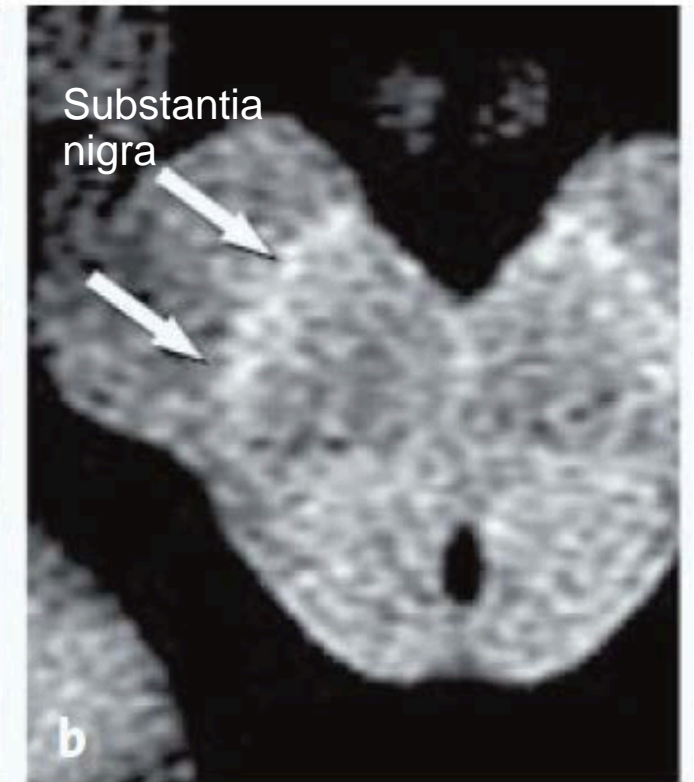
Neuromelanin-sensitive (NM) MRI T1 contrast and magnetization transfer contrast

Sulzer et al., 2000

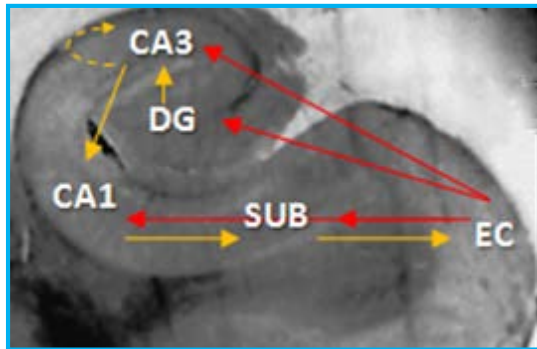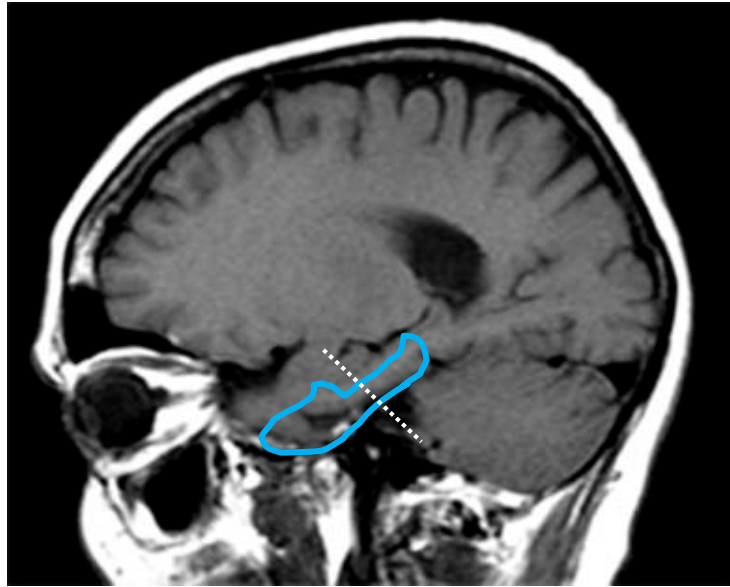# NM on MRI Correlated with Psychotic Symptoms in Schizophrenia

- Antipsychotic-free patients with schizophrenia (n=33)
- Individuals at clinical high-risk for psychosis (n=25)
- (Attenuated) positive symptom severity: PANSS-PT and SIPS-PT

Correlation with psychosis
Correlation with attenuated psychosis
Overlap

Coronal   Sagittal

r=0.5
Schizophrenia

r=0.44
Clinical high risk

PANSS-PT score (a.u.)

SIPS-PT score (a.u.)

NM-MRI CNR (% signal change)

$p_{FWE}=0.00001$, permutation test

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Hippocampal Biomarkers in Schizophrenia

Archives of Neurology, 2001

Neuron
Article

Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner

Dorothy P. Schafer,[1] Emily K. Lehrman,[1,5] Amanda G. Kautzman,[1,5] Ryuta Koyama,[1] Alan R. Mardinly,[3] Ryo Yamasaki,[4] Richard M. Ransohoff,[4] Michael E. Greenberg,[3] Ben A. Barres,[2] and Beth Stevens[1,*]

[1]Department of Neurology, F.M. Kirby Neurobiology Center, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA
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[3]Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA
[4]Neuroinflammation Research Center, Department of Neurosciences, Lerner Research Institute, and Mellen Center for MS Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[5]These authors contributed equally to this work
*Correspondence: beth.stevens@childrens.harvard.edu
DOI 10.1016/j.neuron.2012.03.026
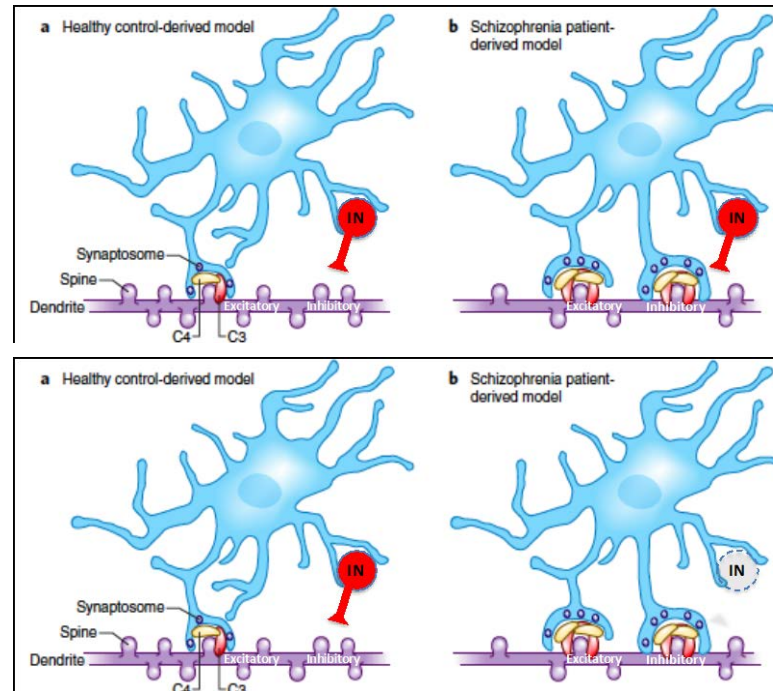
NMDA Hypofunction
C4 Microglia Activation

↓

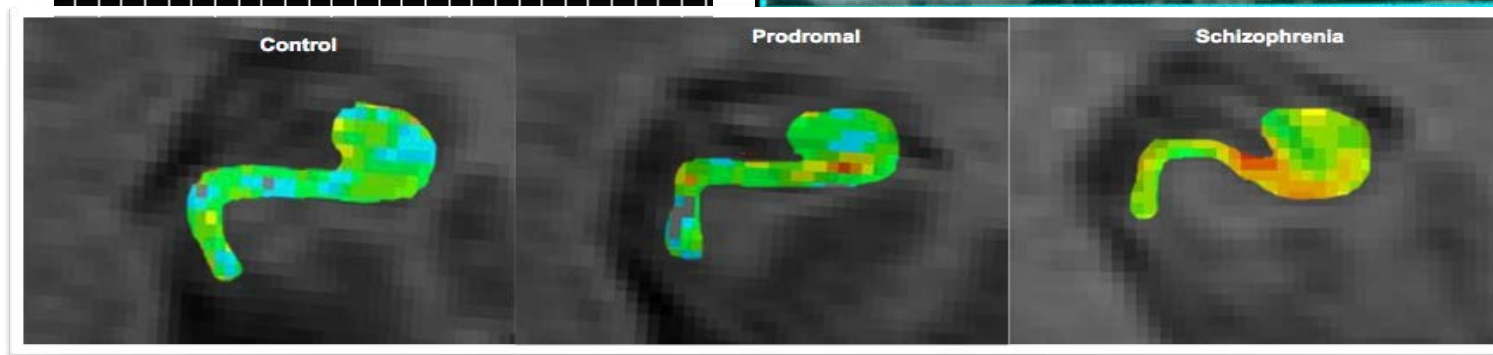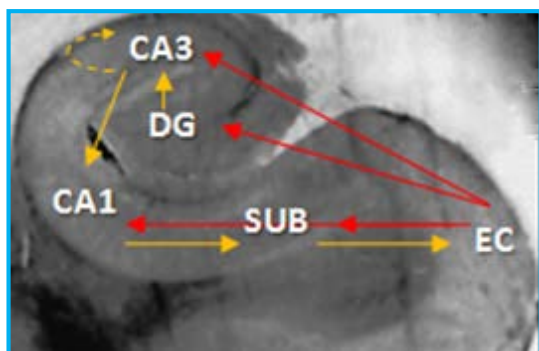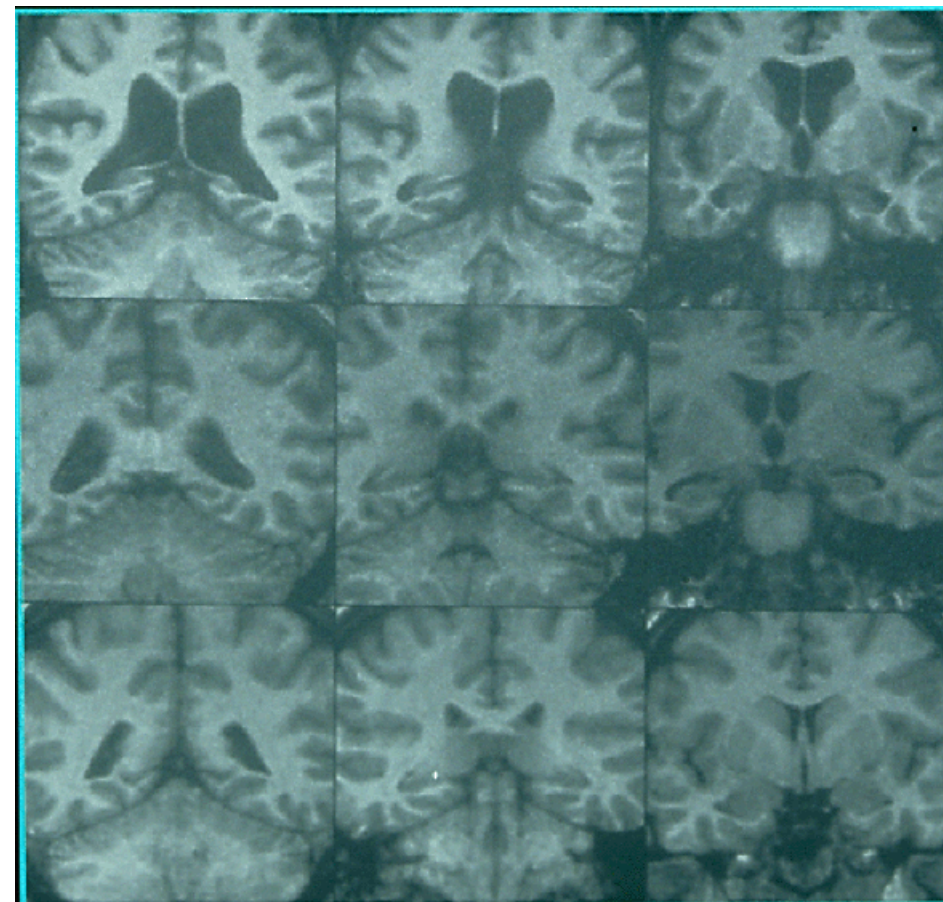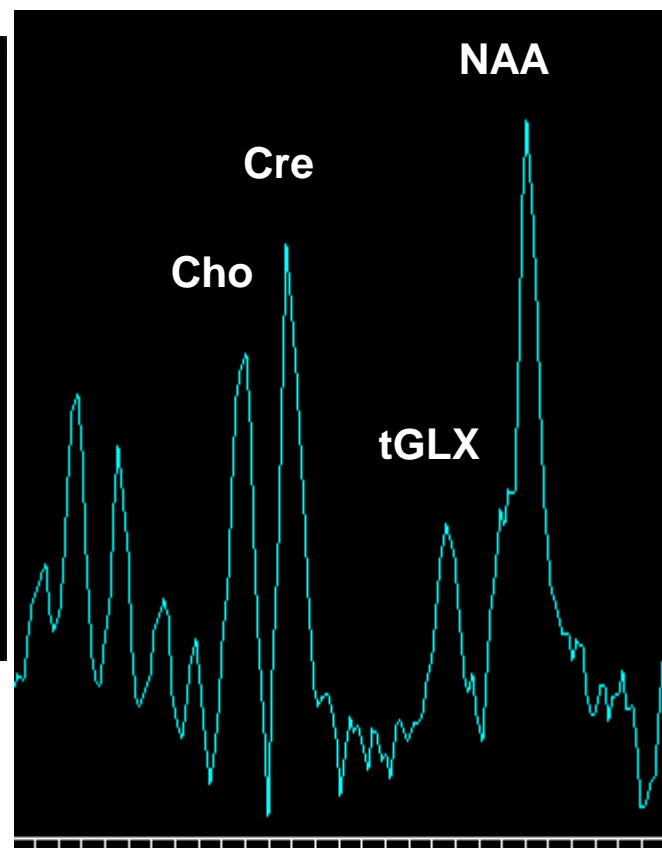**Excess Glutamate**

↓

Hyperactivity

↓

Activity-Dependent Pruning

↓

Excess GABA

↓

Volume Loss Atrophy

↓

GABA Reduction?

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Hippocampal Biomarkers in Schizophrenia
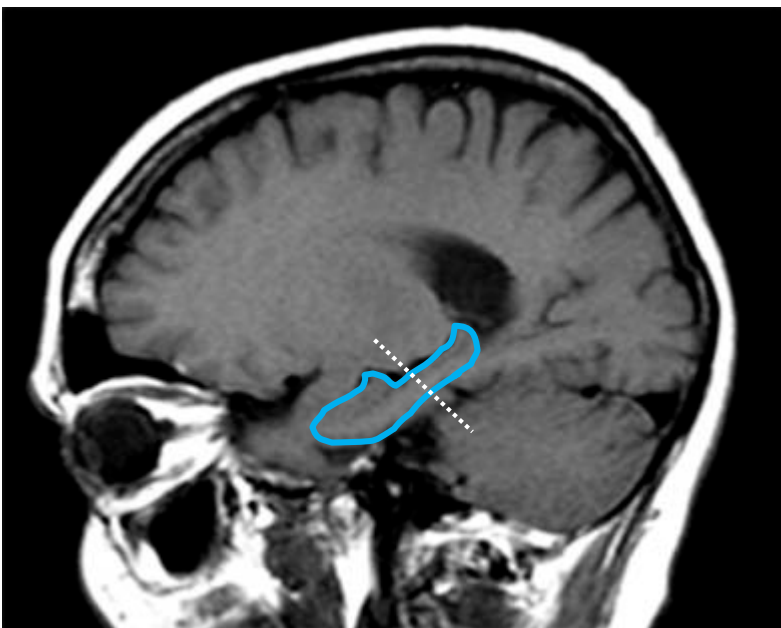
Glutamate and Gaba
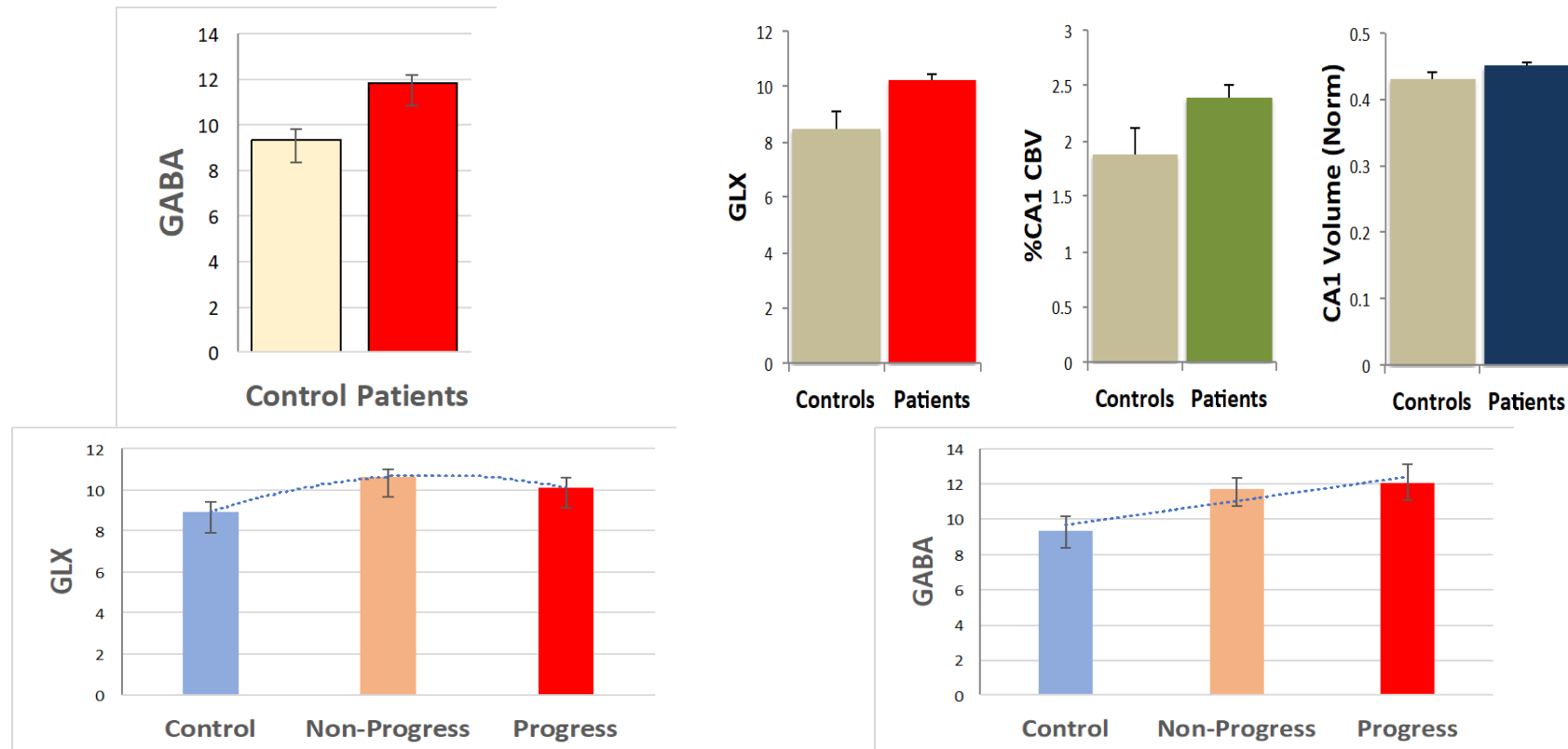
Correlations		Glx_1	GABA_1	P1	P2	P3	P4	P5
Glx_1	Pearson Correlation	1	.112	.109	.085	.112	.255	.207
	Sig. (2–tailed)		.433	.421	.530	.406	.056	.123
	N	59	51	57	57	57	57	57
GABA_1	Pearson Correlation	.112	1	.432**	.386**	.187	.444**	.287*
	Sig. (2–tailed)	.433		.001	.005	.184	.001	.039
	N	51	54	52	52	52	52	52

Converters to Psychosis vs. non-Converters
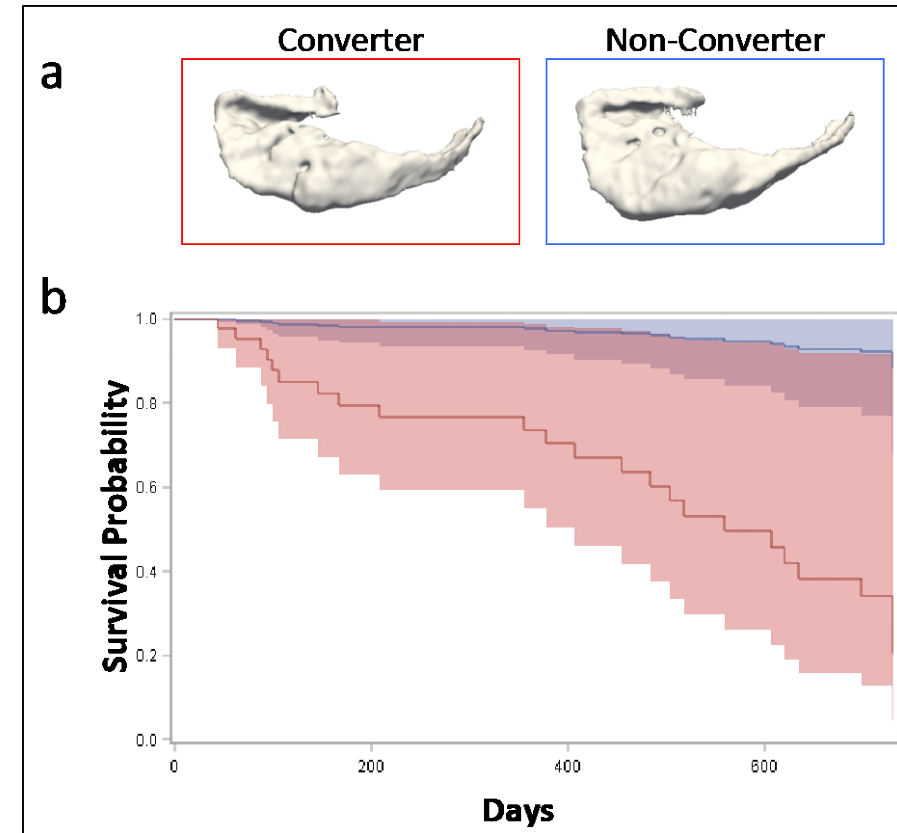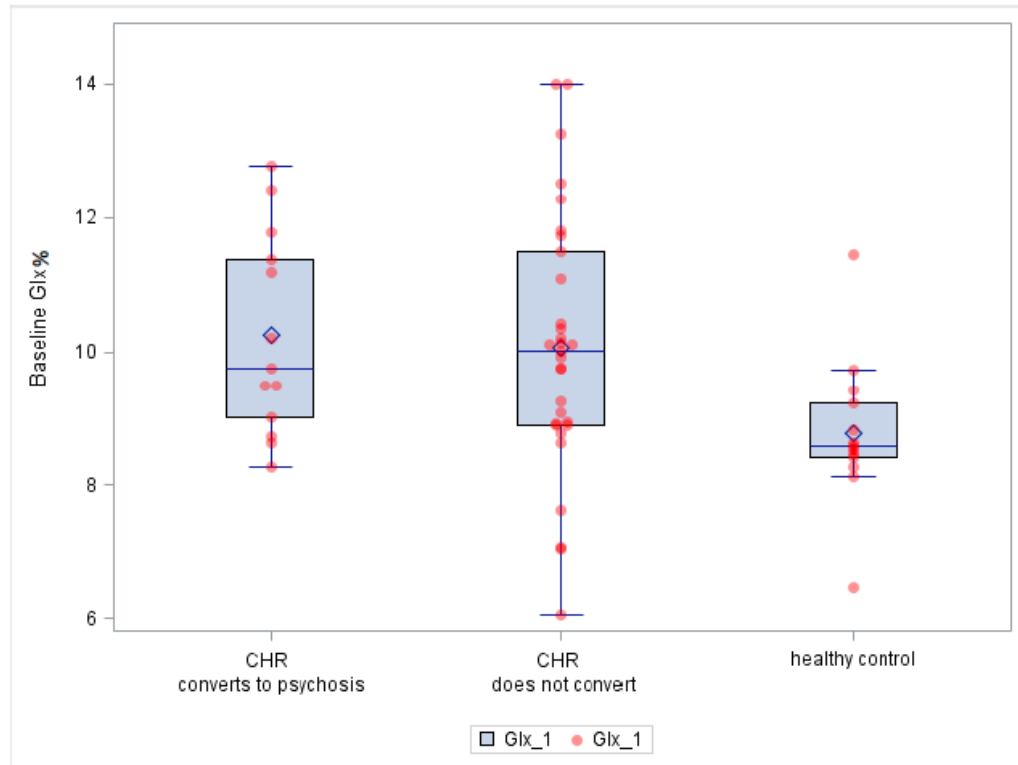
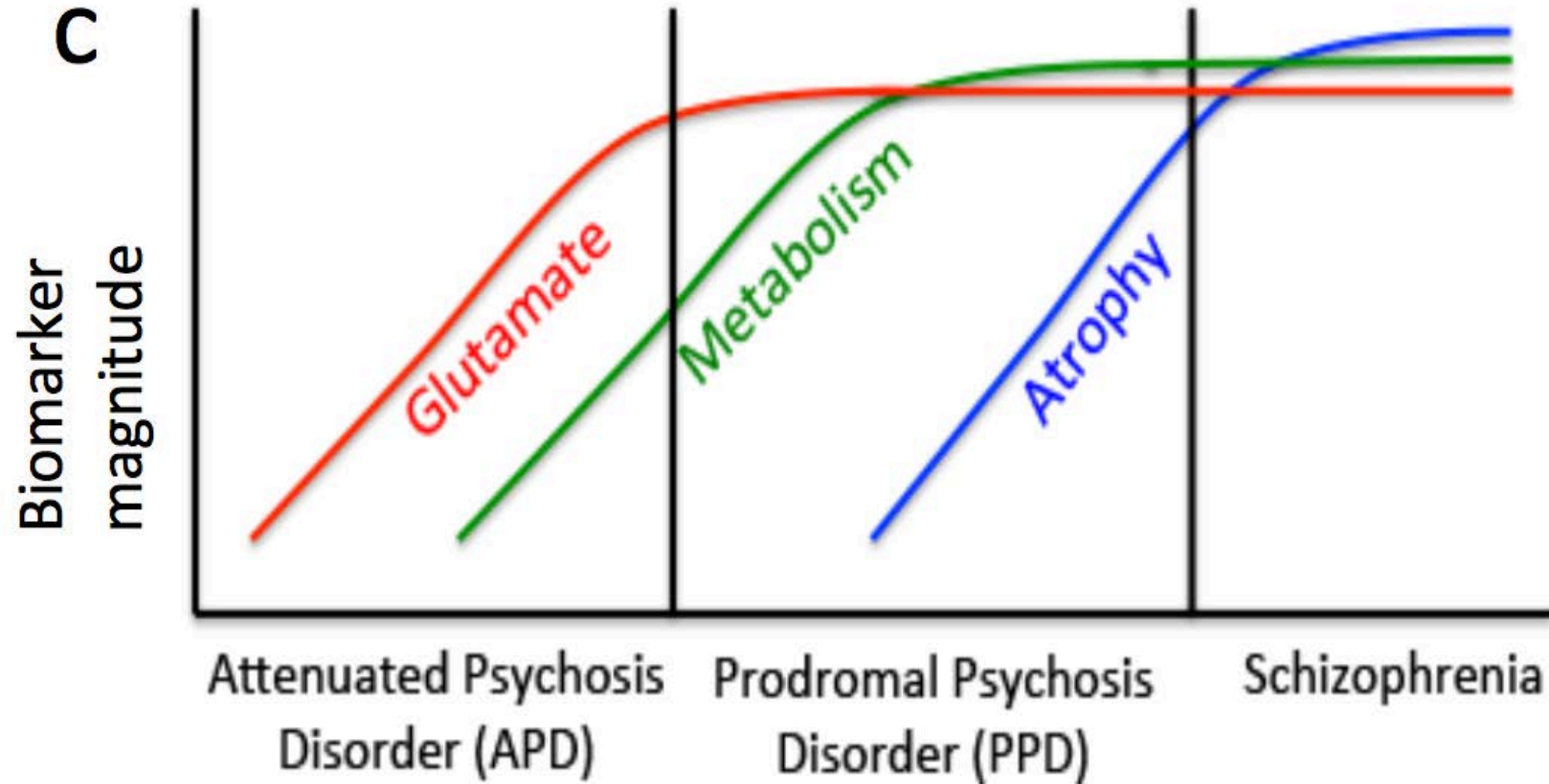# Volume Loss Required for Clinical Progression
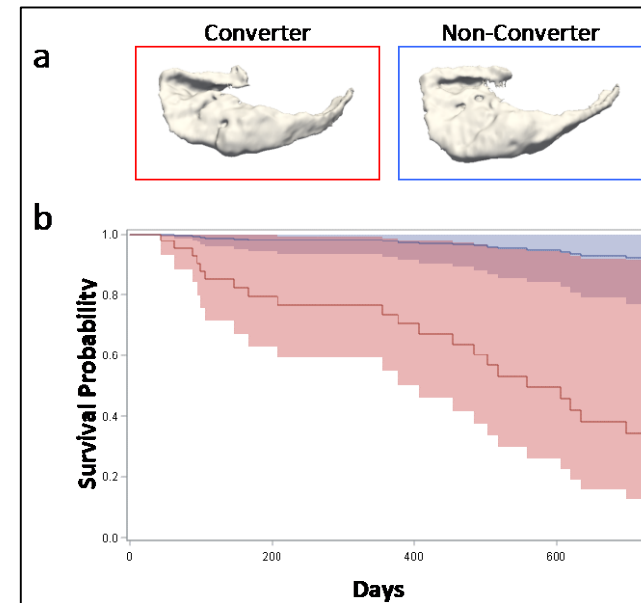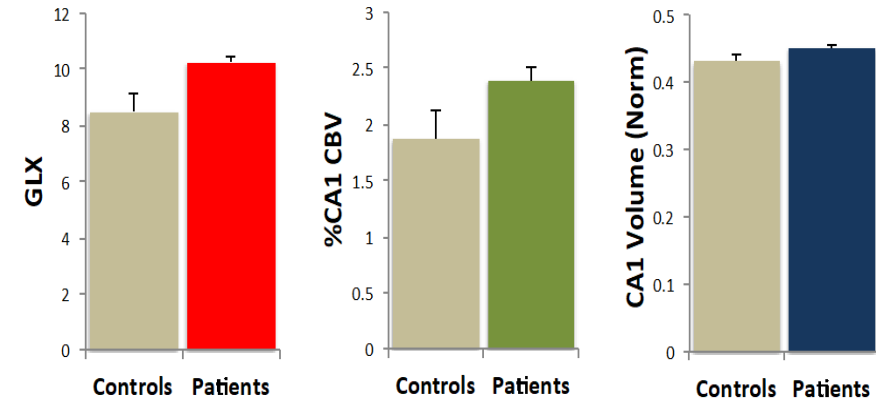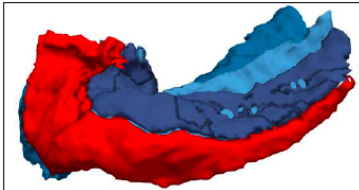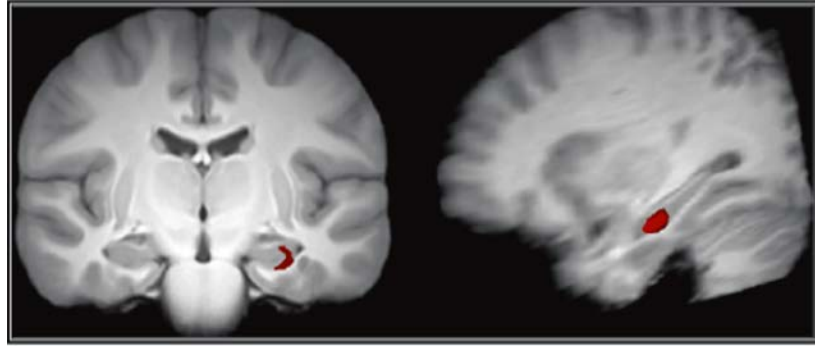
Model of Pathogenesis in Schizophrenia

Dementia Praecox: Extreme Phenotypes of Schizophrenia

New York State Precision Neuropsychiatry Pilot Study

Severe, Extremely-Treatment-Resistant Schizophrenia (SETRS):
Patients with > 5 years of continuous hospitalization in NYS OMH inpatient facilities

"Schizophrenia"

Identify Extreme Presentations (ETRS)

Whole Genome Sequencing
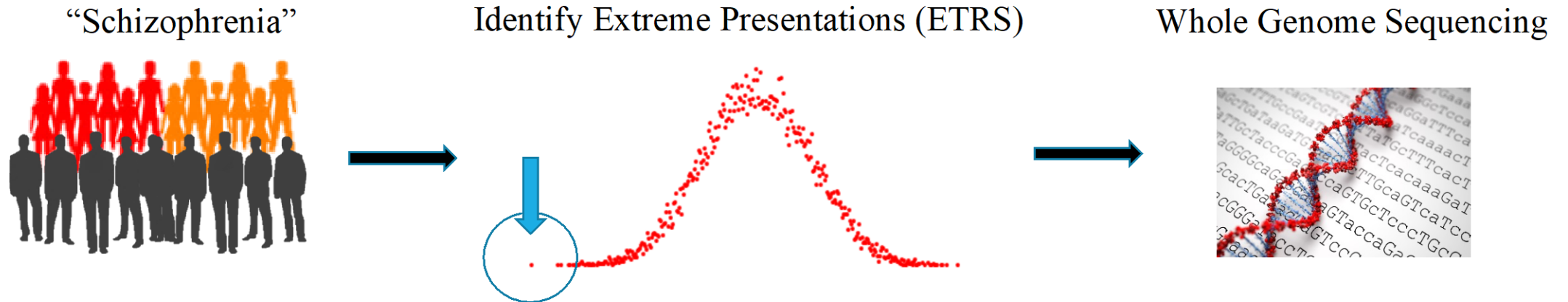
Demographic and Clinical Characteristics of 90 SETRS Individuals

Demographic Characteristics	
Mean Age in Years (±SD)	61.9 (8.1)
Sex (%)	
Male	55 (61.1)
Female	45 (38.9)
Had Children (%)	
Male	3 (5.5)
Female	12 (26.6)
Clinical Characteristics	
Age of Onset of Psychosis: Mean in Years (±SD)	
Male	18.6 (3.4)
Female	18.3 (3.5)
Average Years of State Hospitalization (±SD)	27.2 (12.3)

Genetic Results

- **50%** of ETRS patients have a rare, damaging mutation in the intolerant gene set

- ETRS patients **7 times** more likely than typical schizophrenia patients to have a rare damaging mutation in genes previously associated with schizophrenia

Disease	Missense Mutations	Loss-of-Function Mutations
SETRS	**OR 2.62***	**OR 1.95****
Typical SCZ	OR 1.08	OR 1.25
Autism	OR 1.2	OR 1.8
Epilepsy	OR 1.1	OR 1.3

Comparison to Typical Schizophrenia
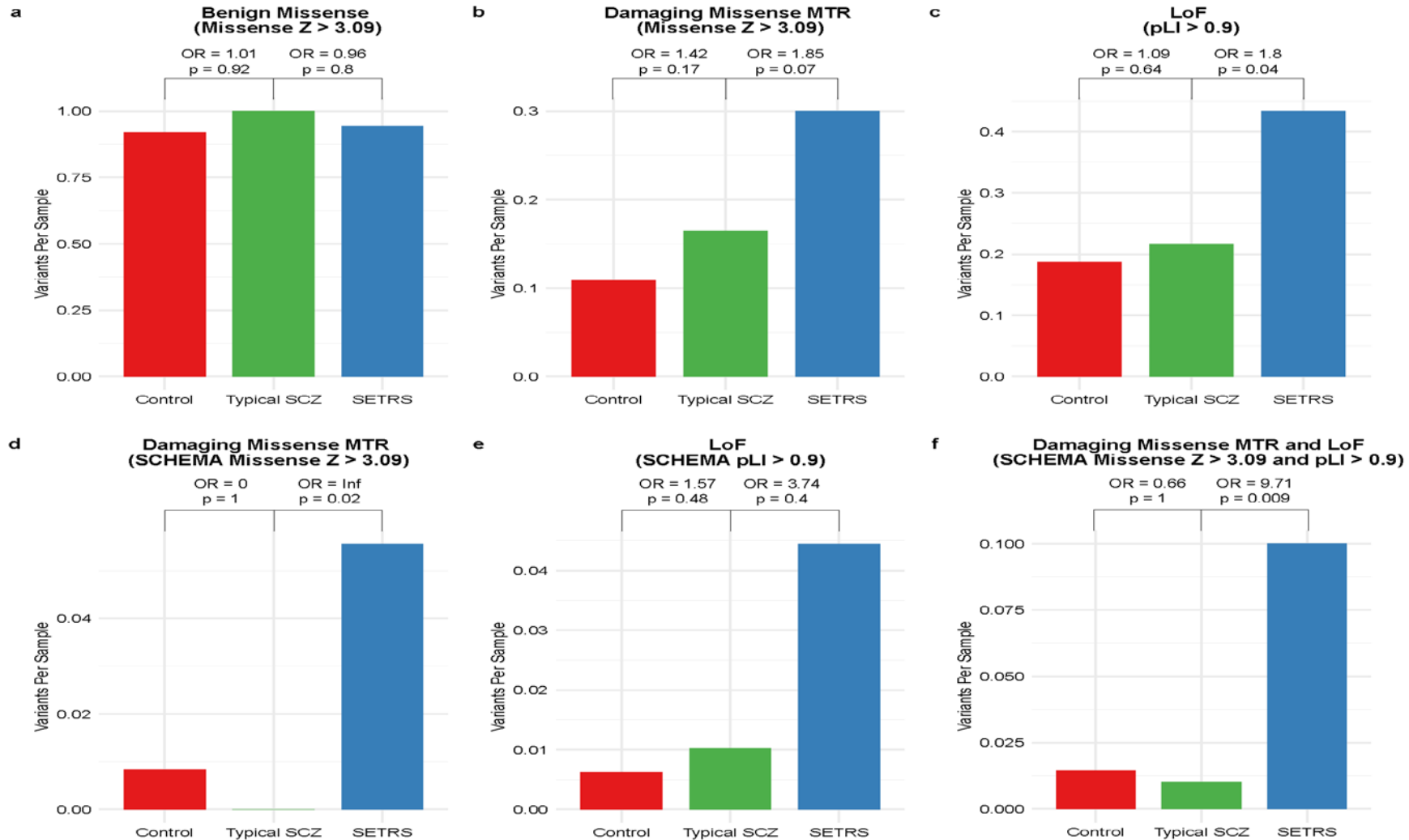
Biological Pathways with Mutations in SETRS

Autoimmune Encephalitis and Psychiatric Presentations

Figure 3   Immunologic triggers in anti-NMDA receptor (NMDAR) encephalitis
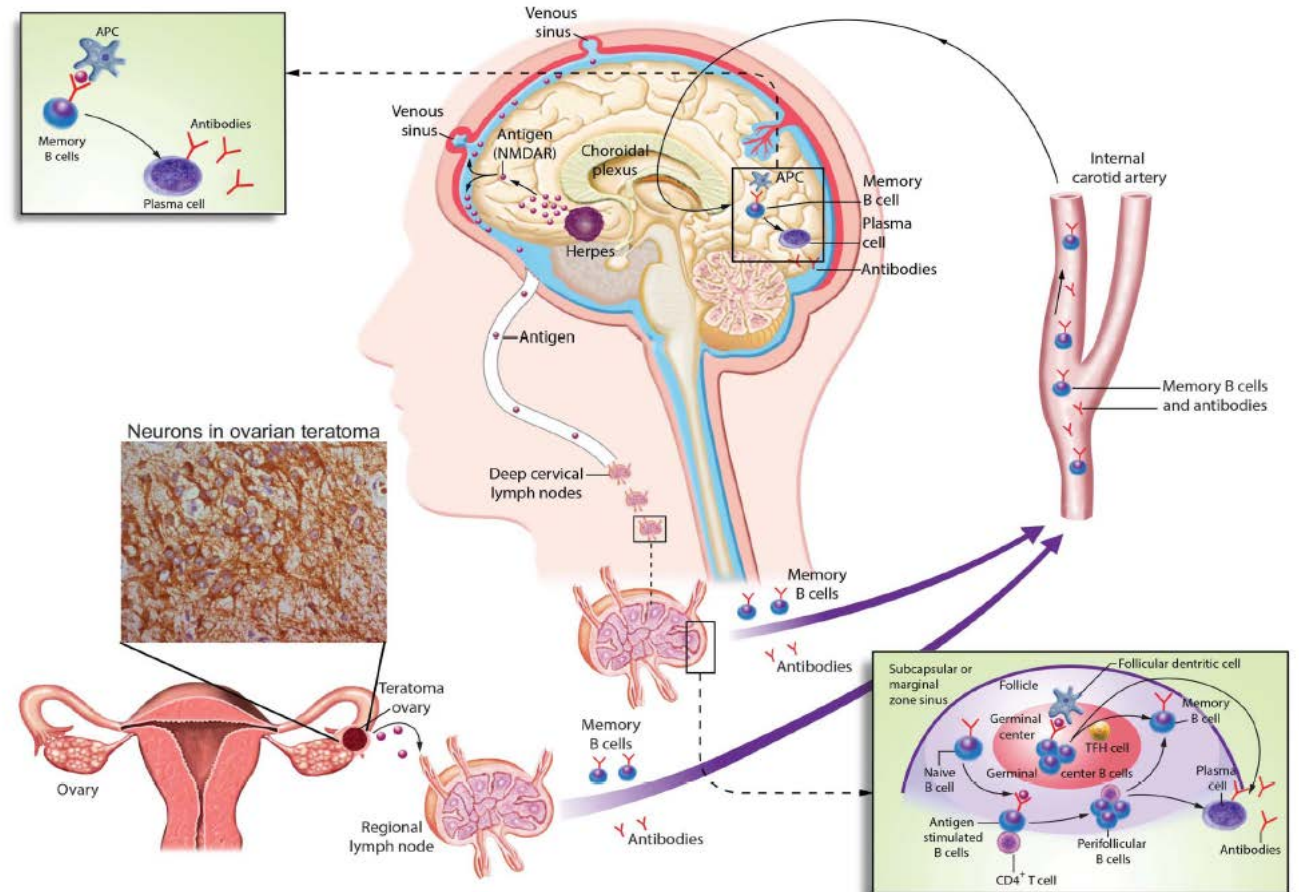
Ms. B

- Ms. B is a 44 year-old African American woman who was the valedictorian of her high school class and on the Dean's list every semester at college. She developed florid psychosis at age 21 and has been hospitalized continuously at Pilgrim since 2000 with a marked deterioration in her functioning.

- She is constantly responding to internal stimuli was disoriented thinking that she was in her kitchen, unaware of the year, president, or other basic factual information and incontinent of stool and urine daily. She has tried multiple antipsychotics, mood stabilizers, and ECT with no change in her symptoms. It was noted that she had elevated anti-TPO antibodies in 2008 to 1000 and on repeat testing she had elevated anti-TPO antibodies to 240. She was transferred to Columbia for further diagnostic workup and treatment.

Clock Draw Task Pre-Treatment

- Her initial MOCA, performed by Terry Goldberg showed a clock that was not consistent with someone of her prior level of functioning and she scored an 12 out of 30 (severely demented range)