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STATEMENT OF INTEREST

Past 12 Months

Speakers Bureau: none

Stock: none

Scientific Advisor: **Genentech**

Patent: (no personal funds)

European Regional Patent Number 1487998 (June 6, 2007) “Methods for Diagnosing and Treating Schizophrenia”

Mental Disorder

An abnormal psychological or behavioral pattern associated with distress, dysfunction and/or disability.

How a person feels, acts, thinks or perceives.

Disease Entity

- A disease based on etiology/pathophysiology. It is the knowledge of cause and mechanism that distinguishes a disease entity from a disorder or clinical syndrome.

Clinical Syndrome

- A **syndrome** is the association of several features such as symptoms and signs that often occur together in patients.
- E.G., Dementia

Domains of Psychopathology

Symptoms relating to a single construct

- Hallucinations
- Delusions
- Depression
- Aggression

Reliability of Diagnosis

- Do clinicians agree on diagnosis?
- Do clinicians agree on symptoms?

Validity of Diagnostic Class

- Group validity at many levels
 - Symptoms
 - Course
 - Treatment response
 - Neuroimaging
 - Genetics
 - Epidemiologic Risk

Causes of Mental Disorders

Known

- Substance induced
- PTSD
- Syphilitic insanity

Not Known

Causal Pathways for Major Clinical Syndromes

- Genetic risk
- Environmental risk
- Gene/environment interaction

What is Severe and Persistent Mental Disorder ?

- Schizophrenia as paradigm for mental disorders

Schizophrenia: The Big Picture

- Afflicts 1% of the American population
- Accounts for 25% of all hospital bed days
- Accounts for 40% of all long-term care days
- Accounts for 20% of all Social Security benefit days
- Costs the nation up to \$65 Billion per year

Prevalence, Development and Course of Schizophrenia

- Schizophrenia diagnosis usually between 16 and 25 years, later in females.
- Social, cognitive and functional impairments precede psychosis.
- Families undergo severe stress. Schizophrenia is a family crisis.
- Often a societal crisis.

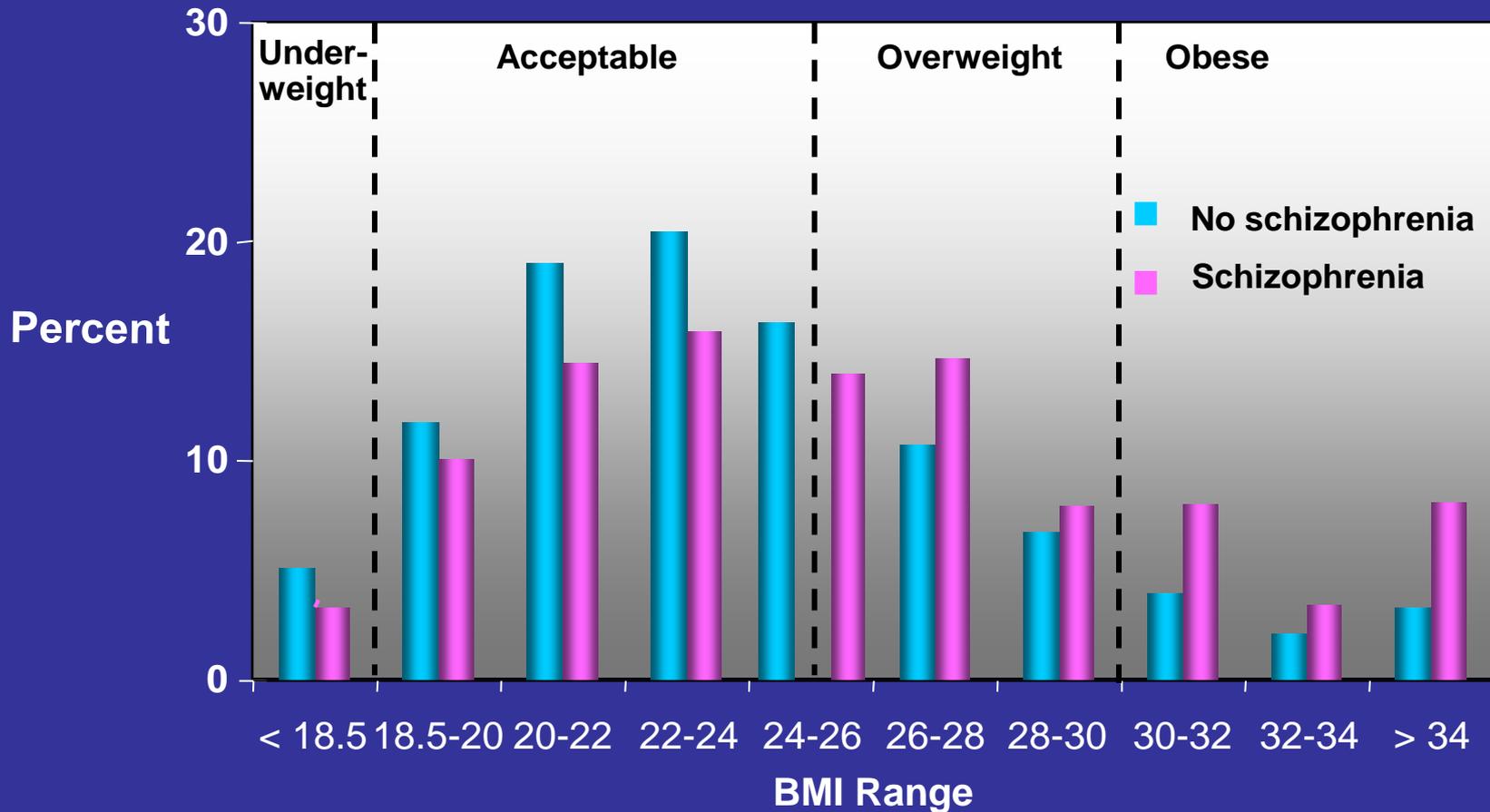
Course of Schizophrenia

- Schizophrenia tends to a lifelong illness.
- Often episodic course with poor function.
- Course tends to stabilize after 5-10 years
- Symptoms gradually improve over the patient's lifetime.
- Remission and Recovery

Adverse Outcomes

- Metabolic
- Suicide
- Hostility/aggression
- Self-image
- Poverty
- Stigma
- Mortality

BMI Distributions for General Population and Those With Schizophrenia (1989)



Where are the People with Schizophrenia?

Approximately:

- 6% are homeless or live in shelters
- 6% live in jails or prisons
- 5% to 6% live in Hospitals
- 10% live in Nursing homes
- 25% live with a family member
- 28% are living independently
- 20% live in Supervised Housing (group homes, etc.)

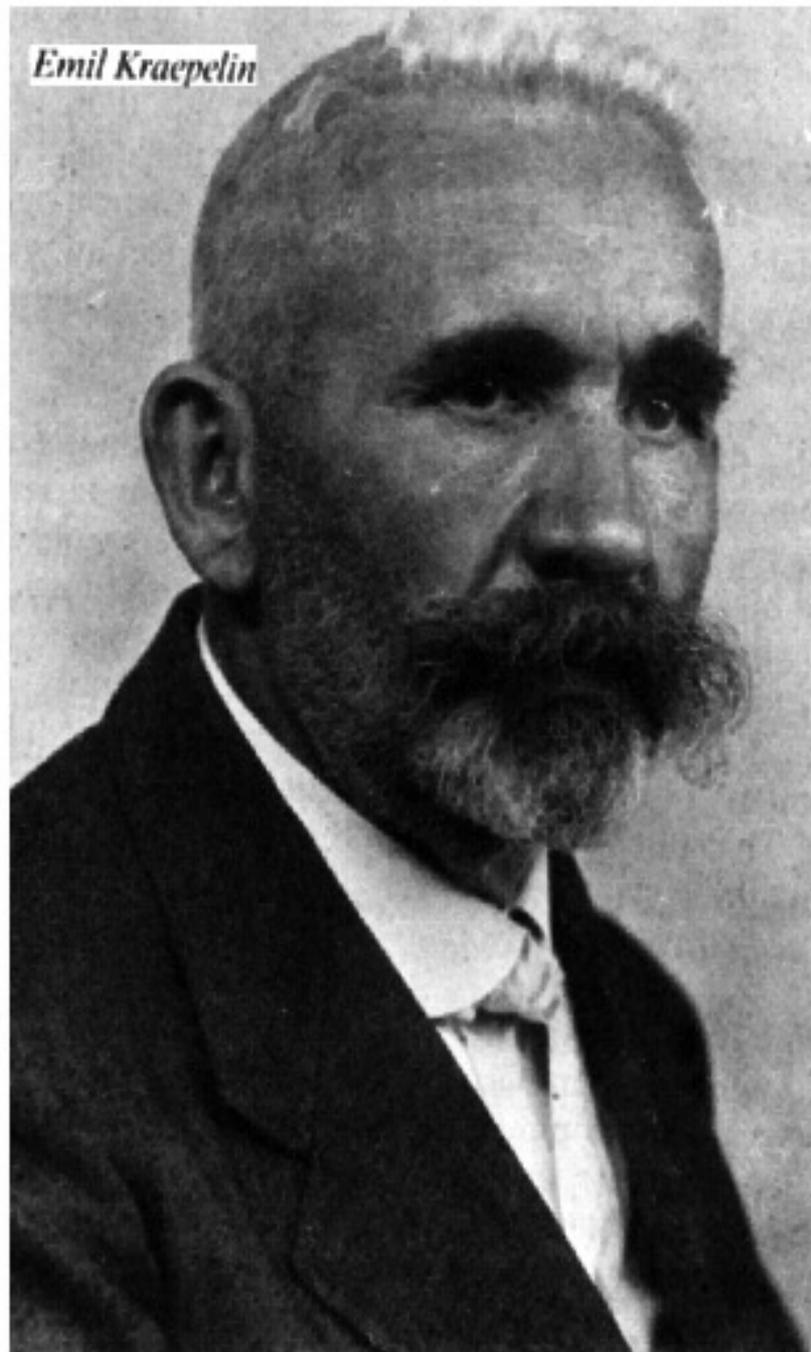
(Source: [Surviving Schizophrenia](#))

Public Perception

- Mentally ill are a threat to society.
- Persons with schizophrenia are at risk for victimization, poverty, unemployment, homelessness, criminalization



Bleuler



Emil Kraepelin

What is Schizophrenia? History

- Manfred Bleuler (1857-1939): Focused more on the nature of symptoms than on the course of the disorder. Saw as the essential feature schiz (split) in the mind (phren). Identified the 4 “A’s”
 - Autism
 - Ambivalence
 - Affect
 - Association

Montevue Asylum Turn of the Century



Ward for 75 Negroes. During the winter, their clothes are hung on overhead wires. Note patients which are shackled. Sanitary and hygienic conditions distressing.

Montevue Asylum Turn of the Century



Montevue Asylum. Negro men sleeping in a cell.

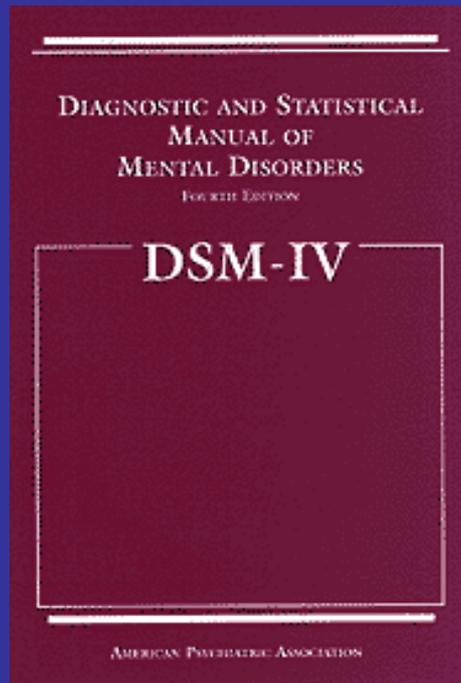
Maryland State Archives

Desperate Therapies of the Past

- Tooth extraction
 - Organ removal
 - Frontal lobotomy
 - Insulin coma
- An amazing exception--ECT

What is Schizophrenia?

- The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)



What are the Symptoms of Schizophrenia?

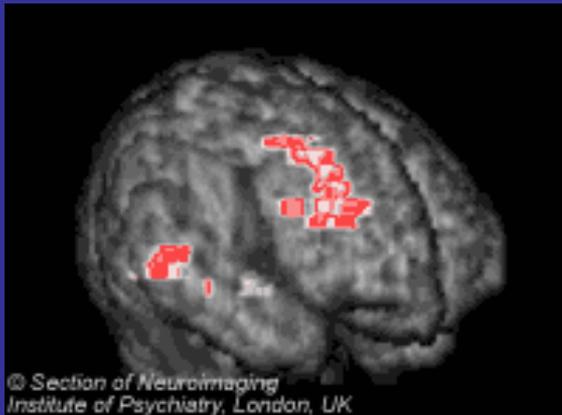
“Positive Symptoms”

- Delusions are false, fixed ideas
 - Persecutory, reference, control, grandiose, somatic, guilt, thought broadcasting
 - Bizarre (implausible and not understandable and not deriving from ordinary life experiences).

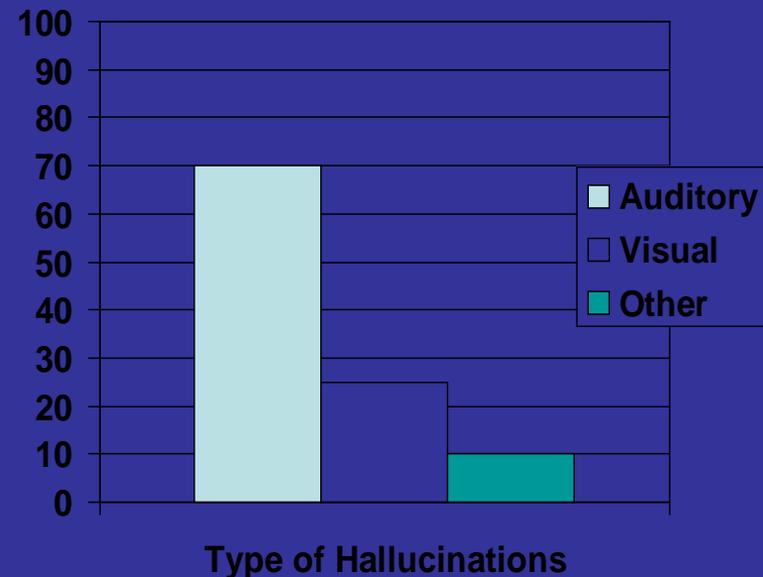
What are the Symptoms of Schizophrenia?

“Positive Symptoms”

- Hallucinations are false perceptions. Can be auditory, visual, gustatory, tactile, or olfactory.



fMRI activation during auditory hallucinations in schizophrenia



What are the Symptoms of Schizophrenia?

“Positive Symptoms”

- Disorganization
 - Disorganized Speech (tangentiality, incoherence, looseness of association, word salad)
 - Inappropriate affect (laughing oddly at sad situations)
 - Grossly disorganized behavior

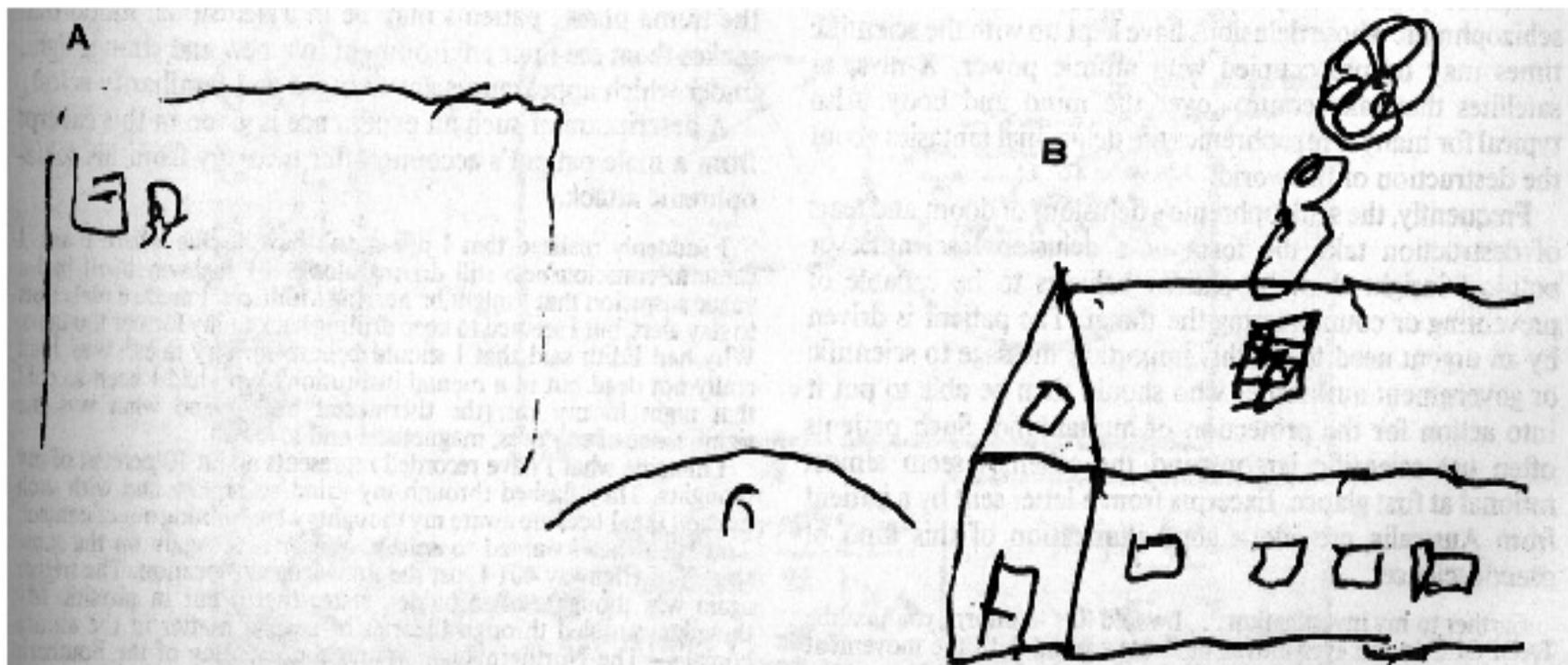


FIGURE 15.4-3. Drawings of a house made by a young man during an acute schizophrenic illness. Figure A was drawn on admission to the hospital; Figure B was drawn after 1 week of phenothiazine treatment. The percept house in the first drawing is fragmented: The windows are displaced, and the roof is lying on the ground, beside the walls. In the second drawing, the structure and the perspective of the house are restored. (Courtesy of Heinz E. Lehmann.)

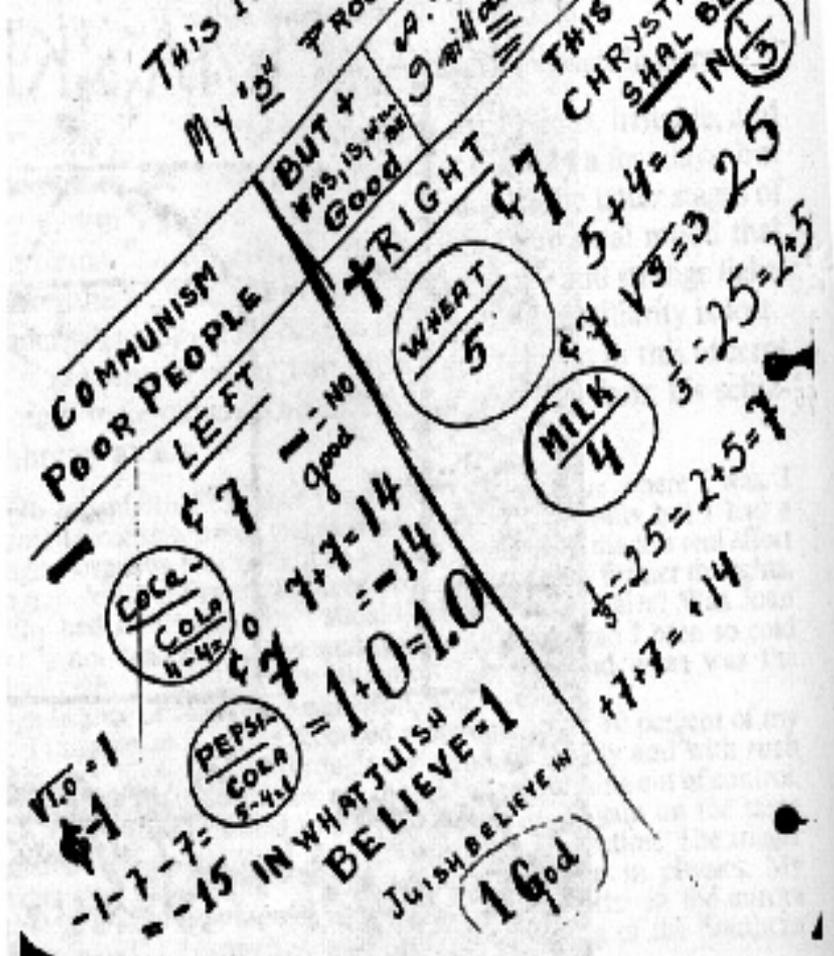


FIGURE 15.4-5. Schizophrenic patient's schema. It illustrates his fragmented, abstract, and overly inclusive thinking and preoccupation with religious ideologies and mathematical proofs. (Courtesy of Heinz E Lehmann.)

Negative Symptoms

- a. Restricted affect
- b. Diminished emotional range
- c. Poverty of speech
- d. Curbing of interests
- e. Diminished sense of purpose
- f. Diminished social drive

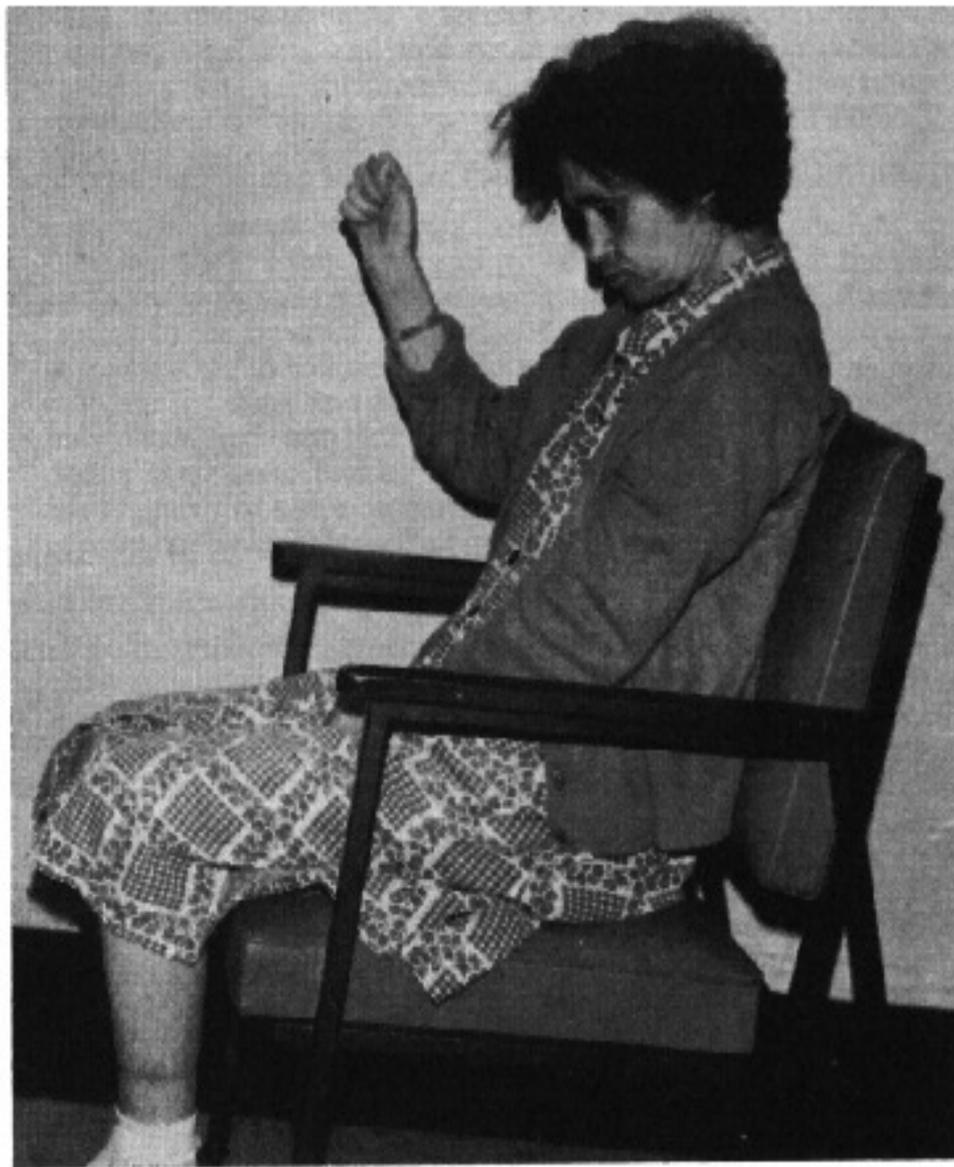


FIGURE 15.4-11. *Chronic catatonic patient. This patient is immobile, demonstrating waxy flexibility. Her arm is in an uncomfortable position, elevated without support, and her stony facial expression has a Schnauzkrampf or frozen pout. (Courtesy of Heinz E Lehmann.)*

What are the Symptoms of Schizophrenia?

Relational Problems

Social Interactions

Intimacy

Self Concept

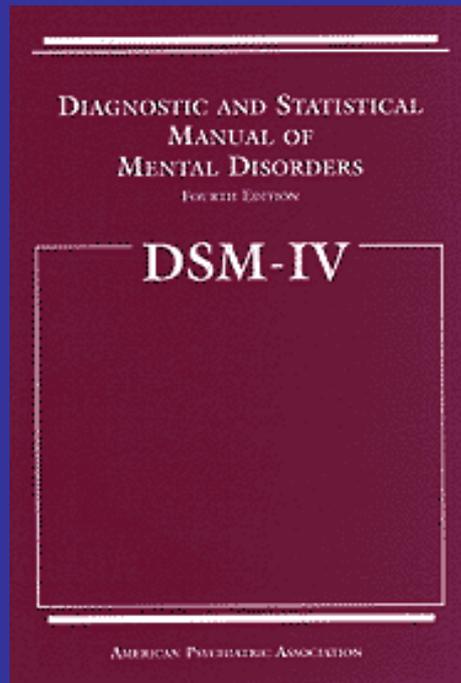
Self-other

Autonomy

Sense of agency

What is Schizophrenia?

- The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)



DSM-IV Criteria

- Delusions*
- Hallucinations
- Disorganized speech
- Disorganized or catatonic behavior
- Negative symptoms

What is Schizophrenia (DSM-IV)

- B. Social or Occupational Dysfunction:

What is Schizophrenia (DSM-IV)

- Duration: Continuous signs of the disturbance persist for at least 6 months.

Schizophrenia Subtypes

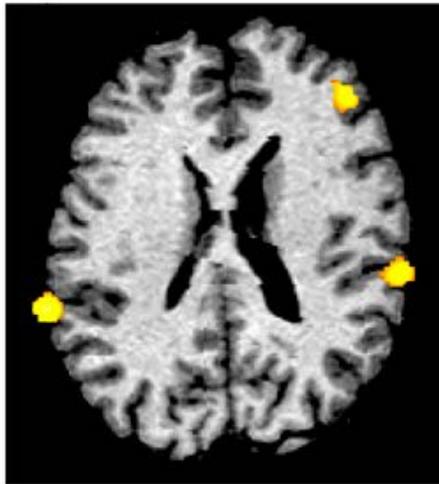
- Paranoid
- Catatonic
- Undifferentiated
- Residual
- Disorganized

Deficit Syndrome of Schizophrenia: Diagnostic Criteria

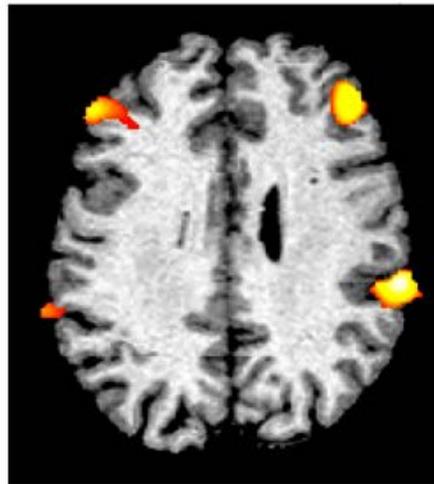
- a. Restricted affect**
- b. Diminished emotional range**
- c. Poverty of speech**
- d. Curbing of interests**
- e. Diminished sense of purpose**
- f. Diminished social drive**

SPM Derived from ^{15}O labeled PET Scans: Significant Deficit/Non-Deficit Differences [N=10/10]

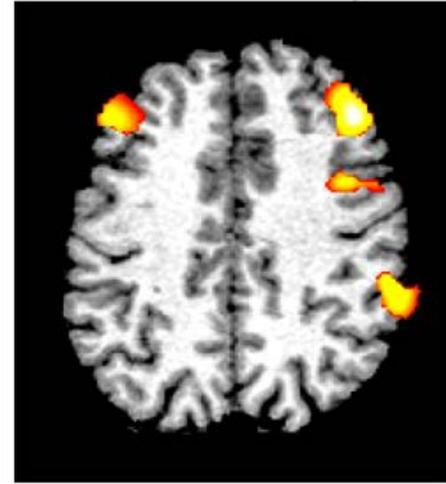
z = 20mm



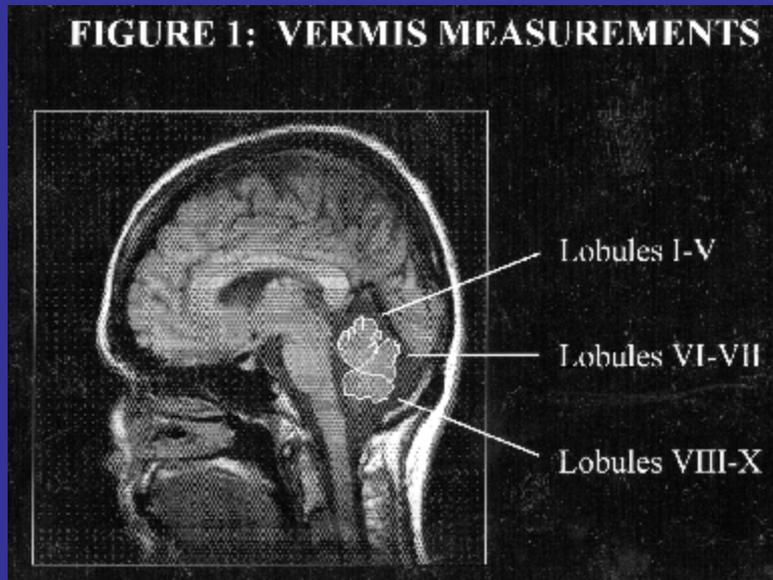
z = 26mm



z = 34mm



Cerebellar Vermis VIII-X



Deficit (N=9)	$299.4 \pm 77.5 \text{ mm}^2$	P<0.05
Non-Deficit (N=23)	$241.7 \pm 69.1 \text{ mm}^2$	
Reverse Correlation with Wisconsin Card Sort (Perseverative Errors) and Verbal Fluency		

Schizoaffective Disorder

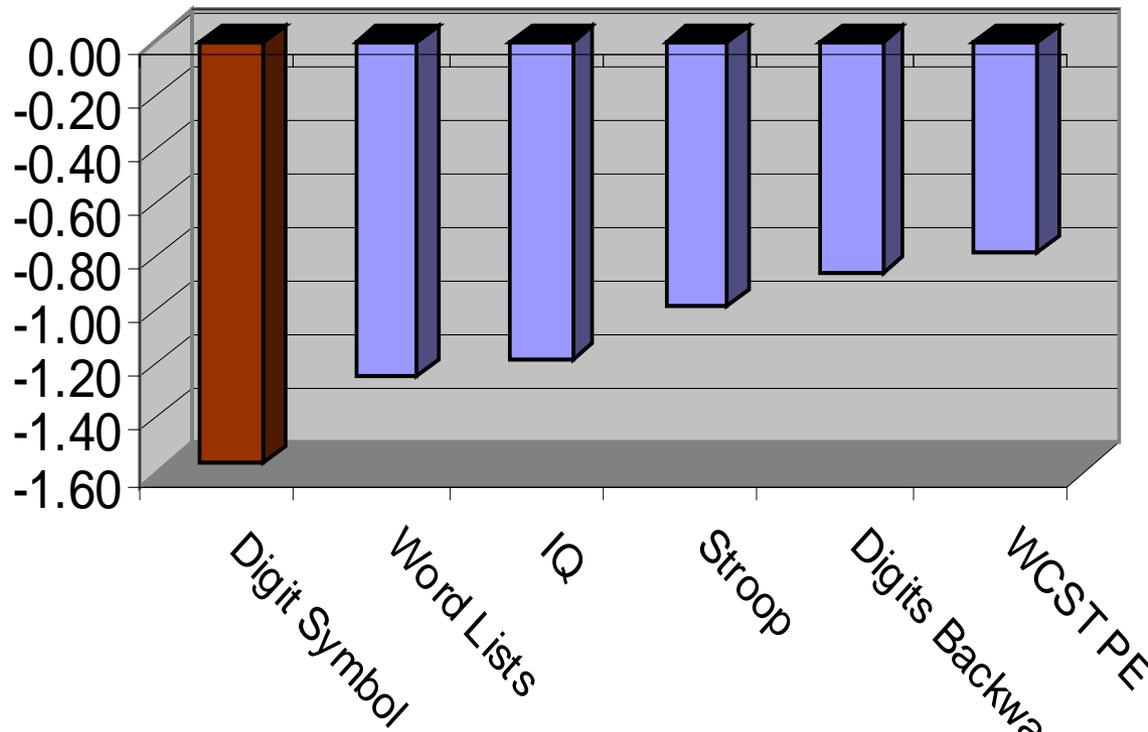
- “Between” schizophrenia and mood disorders
- Periods of psychosis in the absence of mood symptoms. This rules out mood disorders.
- Periods of mood disturbance that are NOT brief relative to the duration of the entire disorder. This rules out schizophrenia

What are the Cognitive Symptoms of Schizophrenia?

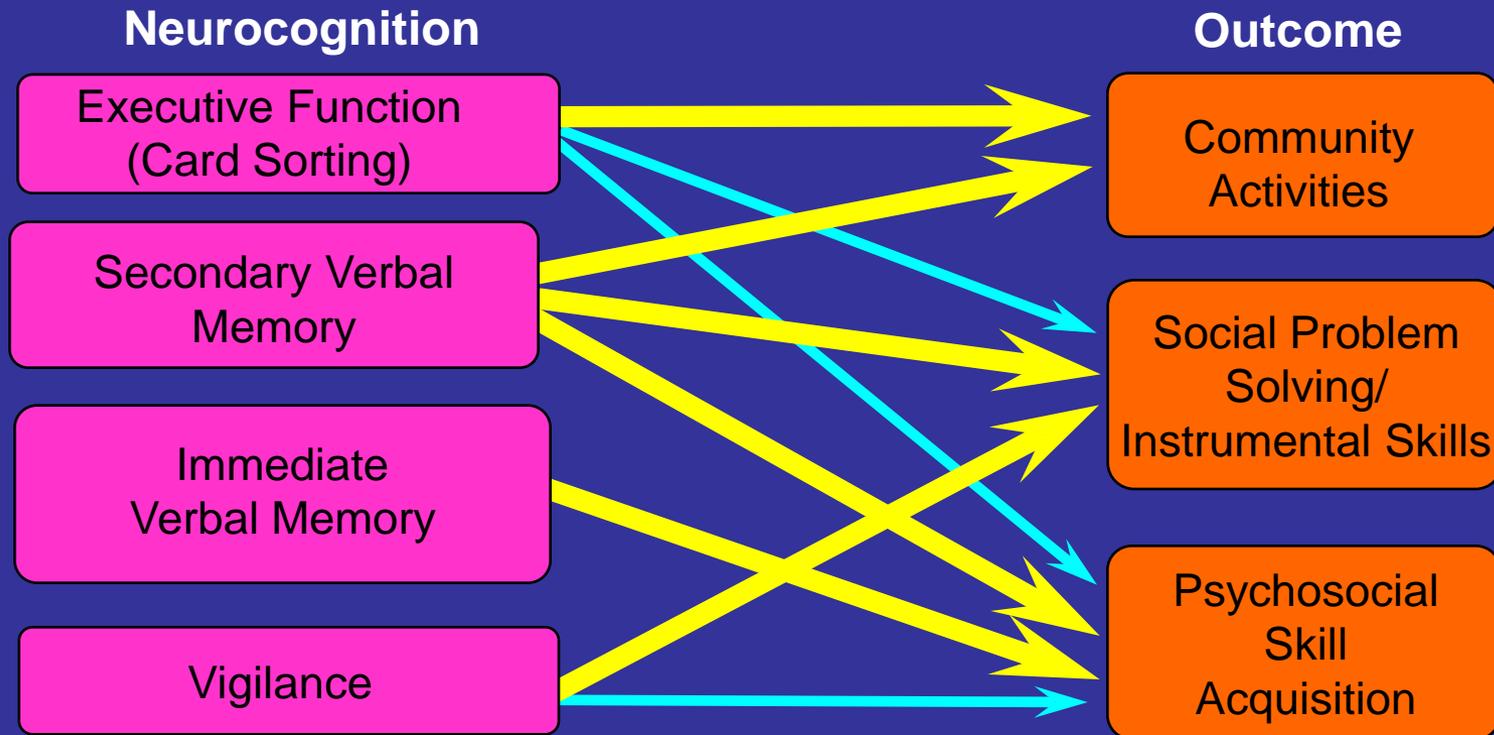
- Attention/Vigilance
- Processing Speed
- Reasoning and Problem Solving
- Verbal Learning and Memory
- Visual Learning and Memory
- Working Memory
- Social Cognition

Meta-analysis of cognitive deficits in schizophrenia

Digit Symbol and the Schizophrenia 'All-Stars'
(Deficit z-scores relative to controls)



Cognition: a more reliable relationship to functional status than symptomatology . . .



Cognitive Impairments in Schizophrenia

- Core feature of the illness
- Onset in childhood/early adolescence
- Orthogonal to hallucinations and delusions

How Do You Make a Diagnosis?

- History (patient, family, friends, teachers, other professionals)
- Physical Exam (rule out other causes of symptoms)
- Mental Status Exam
- Medical Records
- Laboratory Tests (urine toxicology exam)

How do you make a diagnosis of schizophrenia?

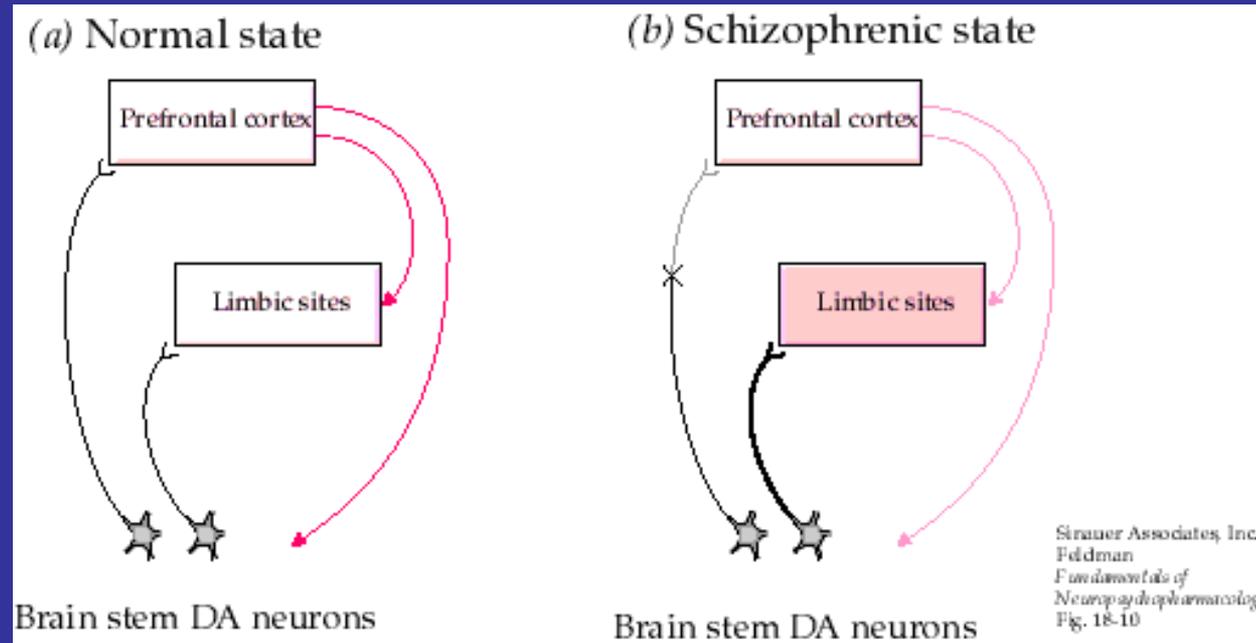
- Prototype
- Meets A, B criteria
- R/o medical, substance
- R/o mood
- Duration six months

What (all) causes
schizophrenia?

Neurodevelopmental Theory

- Postulates schizophrenia is caused by a subtle defect in cerebral development that disrupts late-maturing, highly evolved neocortical functions, and fully manifests itself years later in adult life.

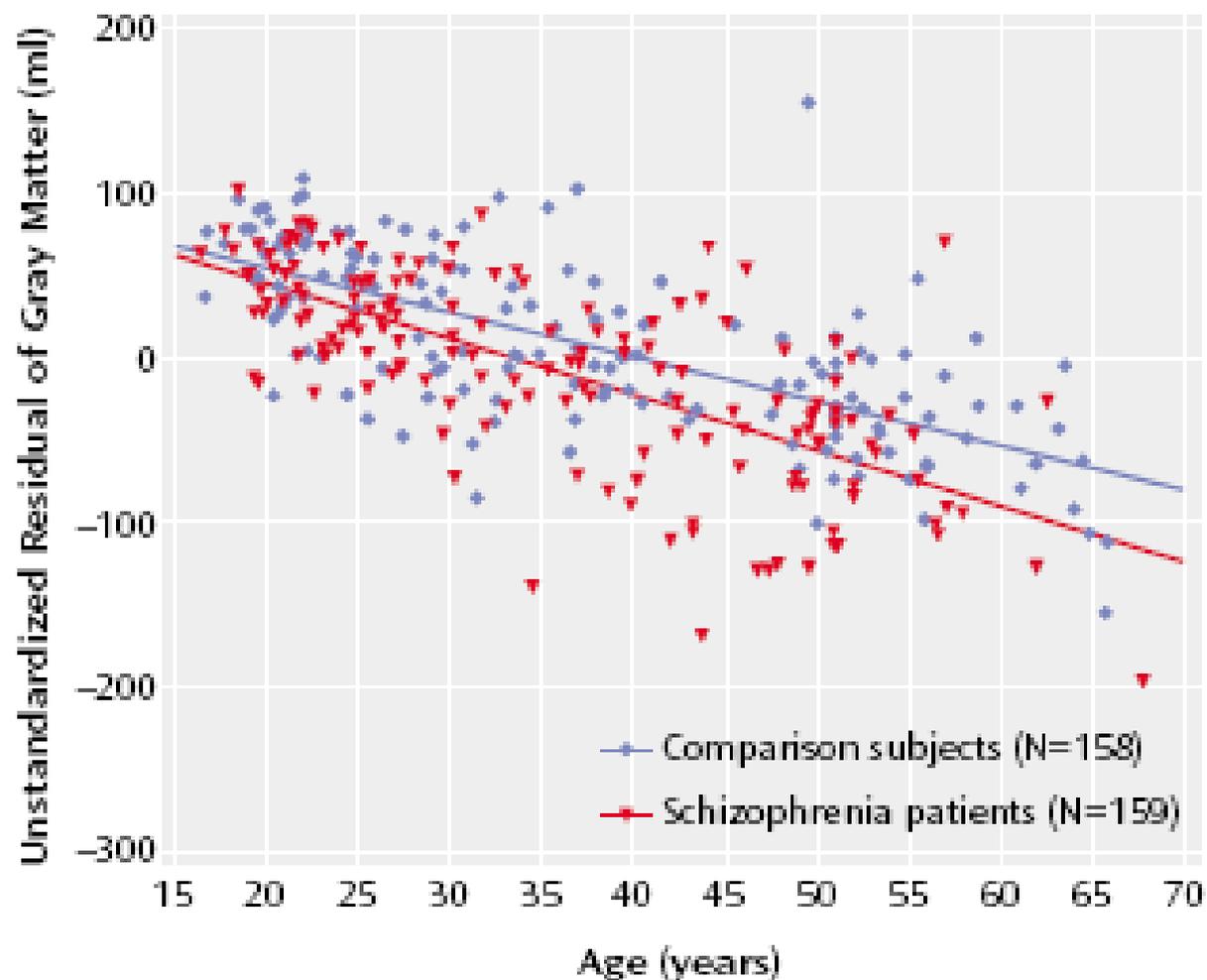
Neurodevelopmental Model



Neurodegenerative Models

- Data also suggest that schizophrenia may be caused by neurodegenerative processes.
- It is difficult to unravel the effects of medication treatment, other potential toxicities (e.g., diabetes, nicotine use) from the primary illness.

FIGURE 1. Relation of Cerebral Gray Matter Volume to Age for Schizophrenia Patients and Healthy Comparison Subjects^a



There was a more pronounced decrease in gray matter volume in the older patients with SZ. Moreover, irrespective of age grey matter volume was smaller and ventricles larger in SZ.

Neuroanatomical Findings

- The most widely replicated pathological anatomical finding in both postmortem and neuroimaging studies of schizophrenia is the increased volume of the lateral and third ventricles when compared to controls

This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

SCHIZOPHRENIA IN IDENTICAL TWINS

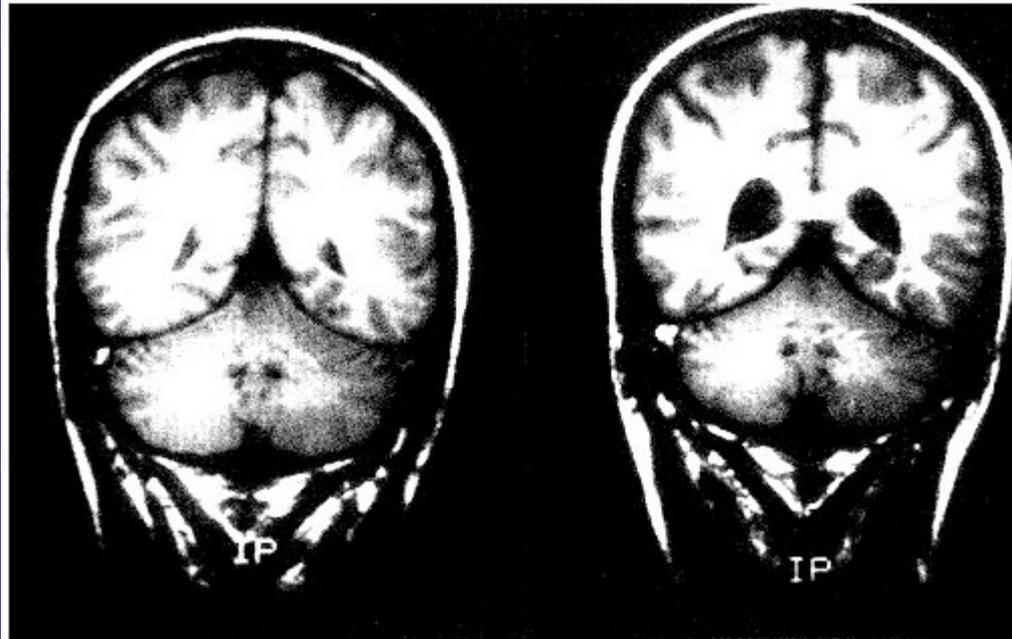


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

Pathophysiology

- Focus on neurotransmitter systems
- Focus on neuroanatomical areas
- Focus on neurocircuitry—[eg, faces]

Pathophysiology: Neurotransmitters

- Dopamine Hypothesis: There is a hyperactivity of dopaminergic systems in schizophrenia
- All effective antipsychotics bind to dopamine receptors
- Amphetamine and levodopa exacerbate some symptoms (and this is correlated with increased dopamine release as measured by PET imaging studies)

Problems with Dopamine Hypothesis

- Effectiveness of DA antagonists not limited to persons with schizophrenia
- Antipsychotics primarily improve positive, not negative symptoms or cognition

Glutamate

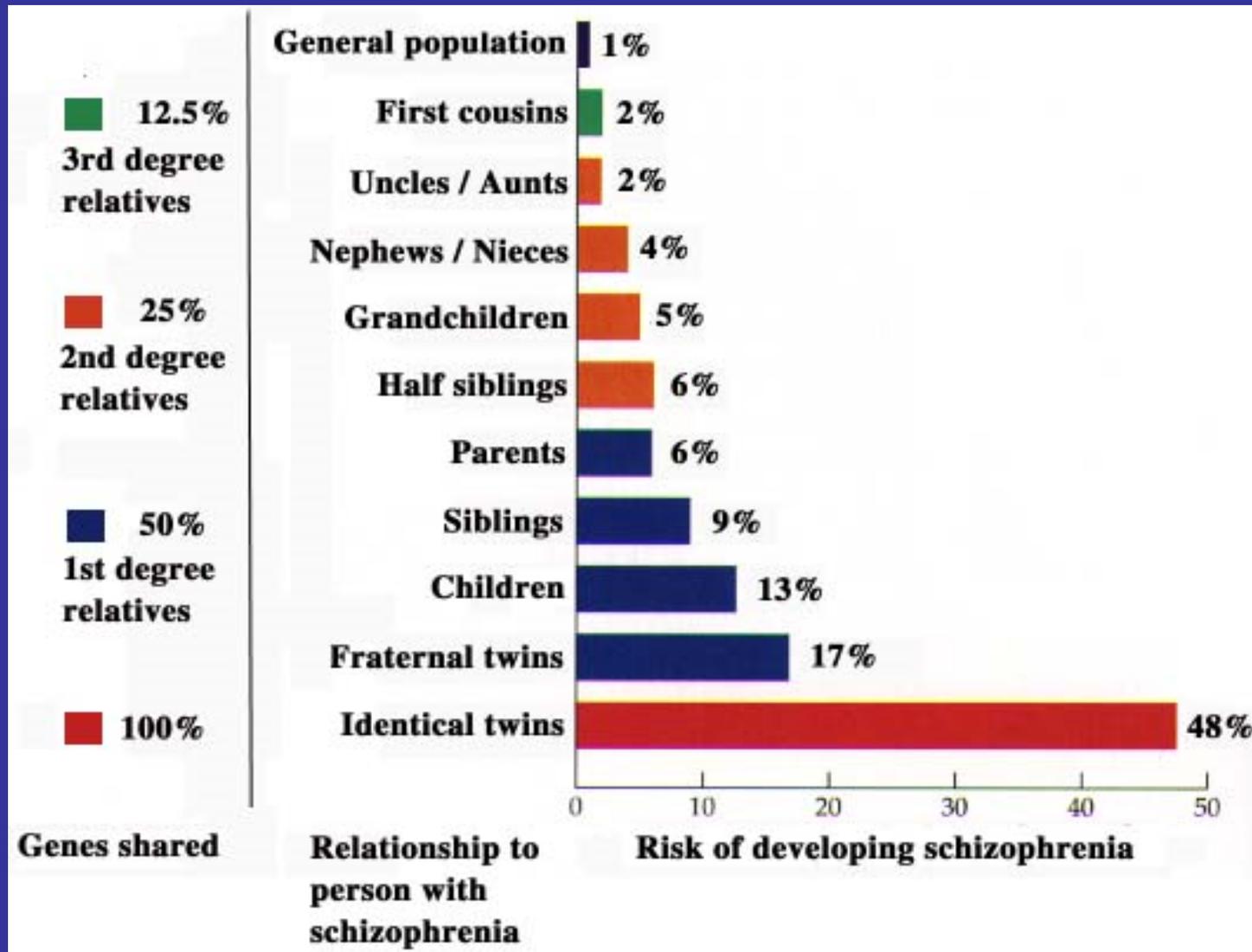
- NMDA is a subtype of glutamate receptor
- Hypofunction of NMDA receptors induced by PCP precipitates a transient psychotic state in healthy subjects
- Animals exhibit disorganized behavior on PCP
- Animals exhibit working memory loss on PCP
- Depressed levels of glutamate have been hypothesized to be involved in schizophrenia

NEUROBIOLOGY

The *WHERE* and the *HOW* but not the *WHY*

- Current data shows *WHERE*
- Current data shows *HOW*
- But not the *WHY*

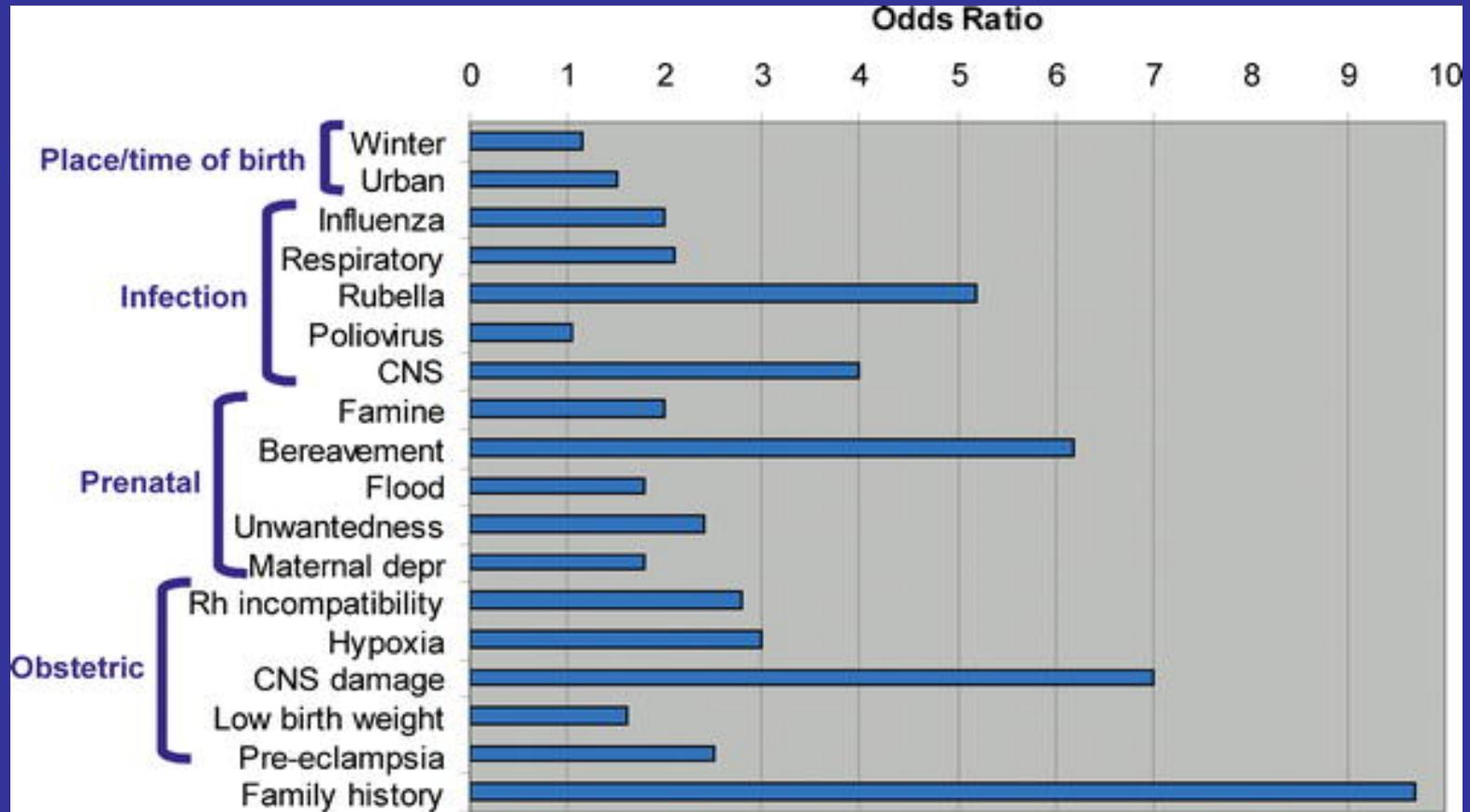
The Genetics of Schizophrenia



Candidate Genes

Gene		What's Known About It
NR1	8p	Affects neurodevelopment as well as glutamatergic system (regulates NMDA receptor); mutant mice show hyperactivity and PPI deficit.
Dysbindin	6p	Presynaptic reduction of DTNBP1 in hippocampus in SA. May affect presynaptic proteins (e.g., SNAP 25), and glutamate release
RGS4	1q	Evidence from both postmortem and linkage studies. Increased gray matter in DLPFC.
G72	13q	D-amino-acid oxidase activator, interacts with DAO, regulates NMDA

Odds Ratios Different Potential Contributors to SZ



<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020212>

Post-Natal Risk Factors

- Abuse
- Cannabis
- Family disruption
- Migration

Gene/Environment Interaction

- Genetic vulnerability
- Stress-Environmental insult

The Russians, the flu and the Germans

- What do they have in common?

Normal Environment and Risk

- Family disruption
- Family interaction

Treatment

- Pharmacotherapies
- Psychosocial therapies
- Social therapies

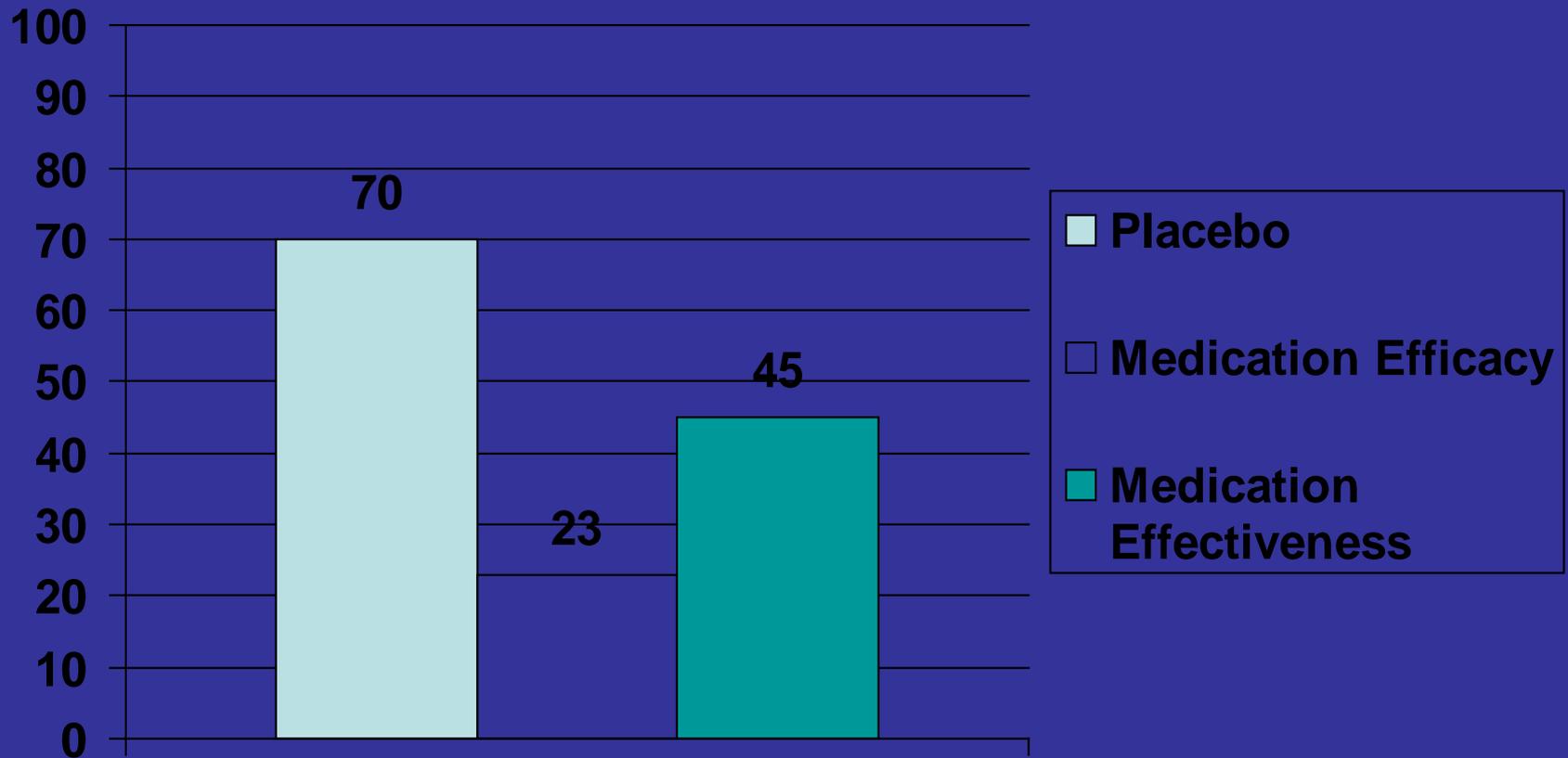
Sixty Years since Thorazine

- Dopamine antagonist
- Anti-psychotic, not anti-schizophrenia
- First generation drugs
- Clozapine [Clozaril]
- Second generation drugs

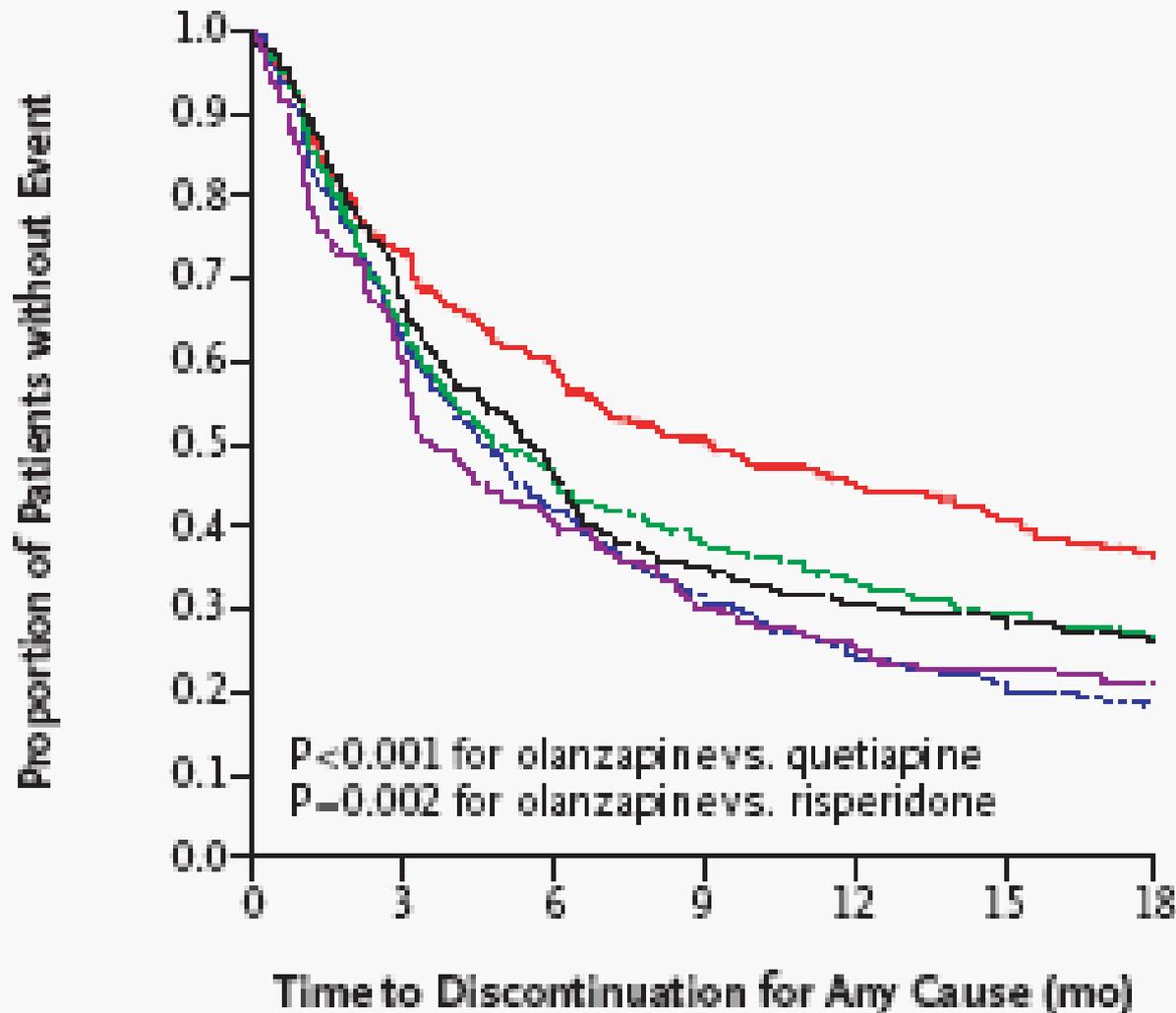
Medication Effects

- Reduce hallucinations, delusions, and disorganized thought and behavior
- Behavioral management
- Relapse prevention
- Adverse effects

Efficacy and Effectiveness of Antipsychotic Medications: Annual Relapse Rates



A



Most patients discontinued medications

— Olanzapine (N=330) - - - Risperidone (N=333) - - - Ziprasidone (N=183)
— Perphenazine (N=257) - - - Quetiapine (N=329)

Are New Drugs Better?

CATIE

CUTLASS

Molidone

Meta-analysis

Treatment Recommendations 2009:

- Clozapine should be offered to people with schizophrenia who continue to experience persistent and clinically significant positive symptoms after two adequate trials of other antipsychotic agents. A trial of clozapine should last at least 8 weeks at a dosage from 300-800mg/day.

Clozapine

- Persistent symptoms of hostility and/or persistent violent behaviors.
- Marked and persistent suicidal thoughts or behaviors.

Treatment Recommendations 2009 (Draft):

- Low frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS), over the left temporoparietal cortex, is a recommended treatment option for the acute treatment of refractory auditory hallucinations.

Treatment for Catatonia

- Benzodiazepines
- ECT

Psychological Therapies

Interpersonal

Skills training

Cognitive behavioral

Cognitive remediation

Psychoeducation

Family to family

Combined Psychosocial and Psychopharmacological Treatments

- All evidence-based psychosocial treatments for persons with schizophrenia are recommended within the context of appropriate pharmacotherapy
- Combined treatment (pharmacotherapy plus psychosocial interventions are generally more effective than pharmacotherapy alone)
- Many treatments and services are *effective*
- There is a *gap* between what science tells us to do and what we do in actual practice

Social Therapies

- Crisis intervention
- Supported employment

Anticipated Advances in Therapeutic Discovery

- Psychopathology domains crossing diagnostic boundaries
- Behavioral constructs with neural circuits
- Treatment discovery for new targets

Experimental Overview

E14-21

Restraint Stress

Overnight Fast

Swim Stress



Cold Stress

Social Stress



Cognitive Assessment

PND 35 & PND 56

Molecular Analyses

PPI

AMPH LMA

N40

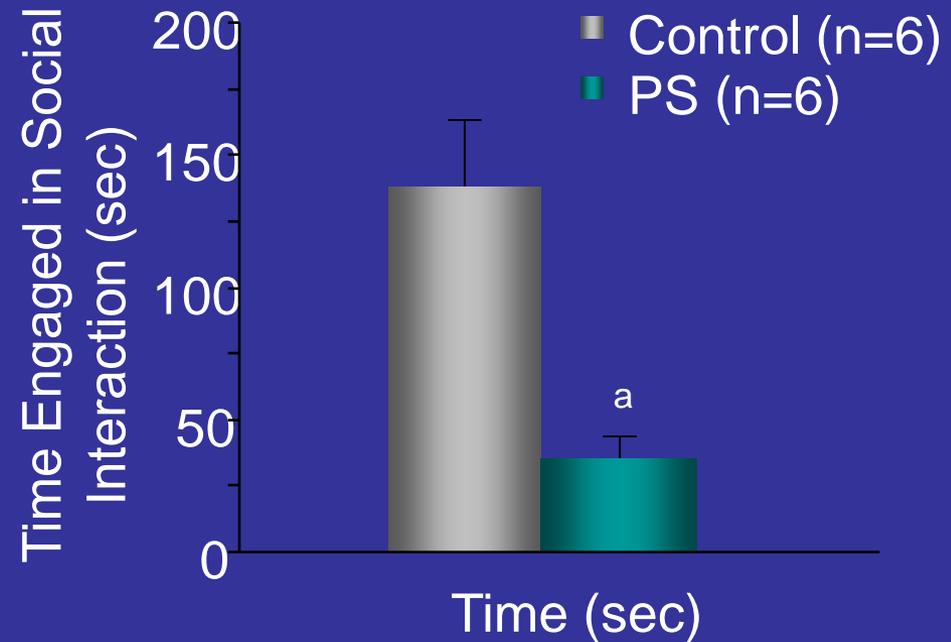
HPA Responses

Social Behavior

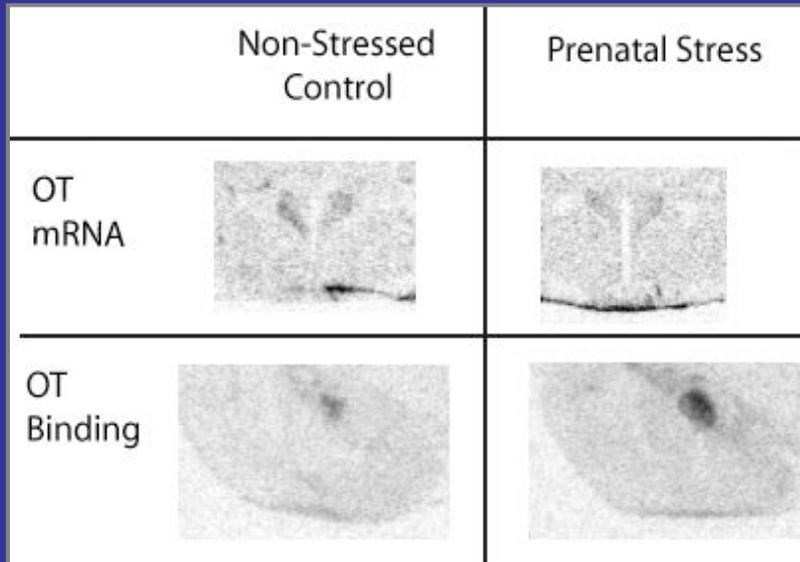
Prenatal Stress and Social Interaction on Day 56 in Male Rats



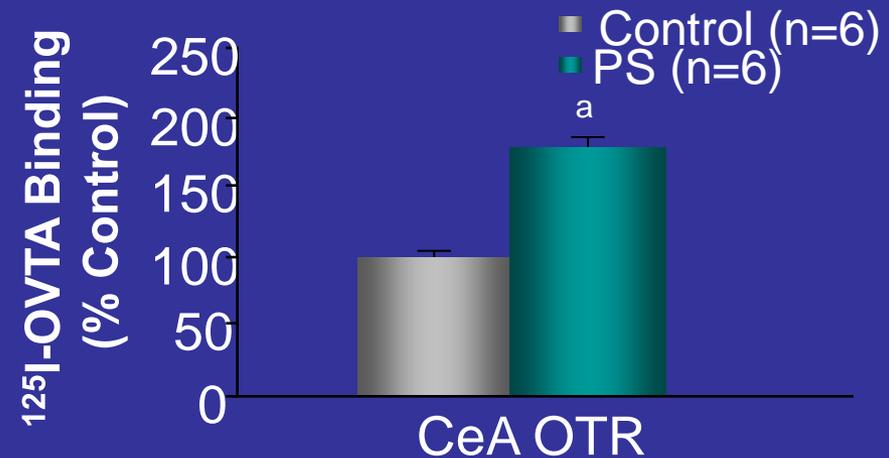
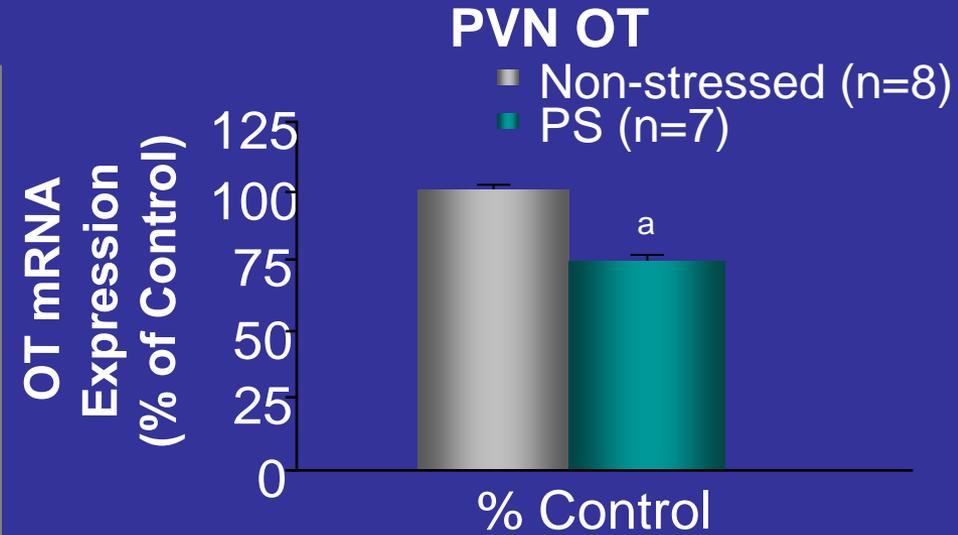
Normal Interaction



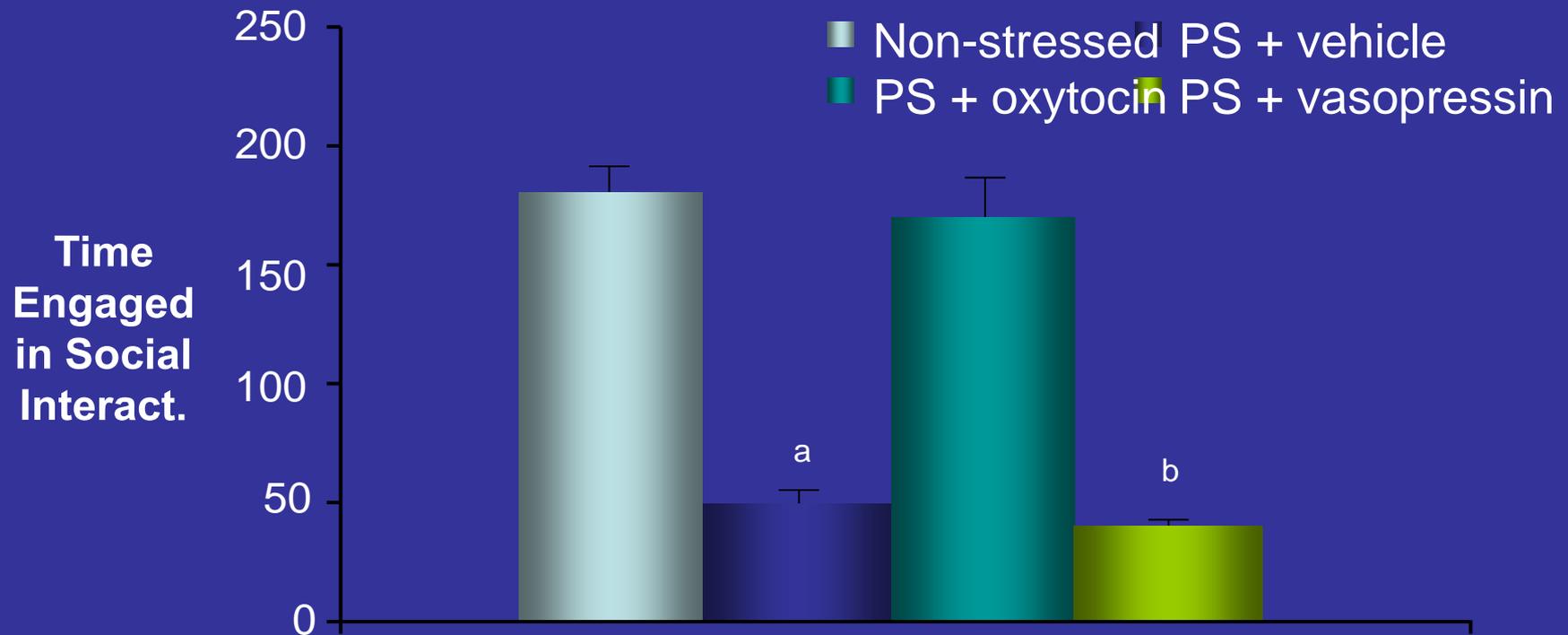
Oxytocin Parameters in PSup Male Rats



CeA OT Binding



Prenatal Stress and Reversal of SI Deficit by CeA Peptide Infusion



Novel Object Recognition Test

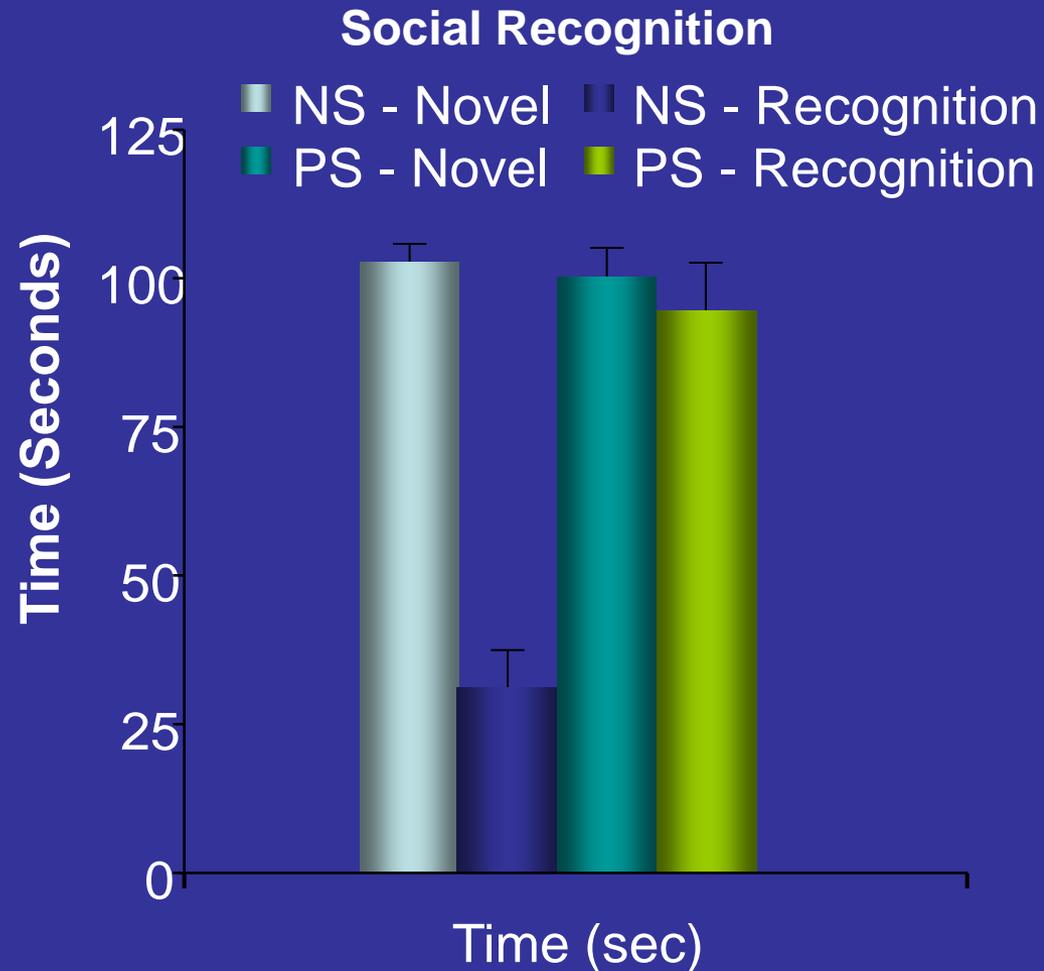
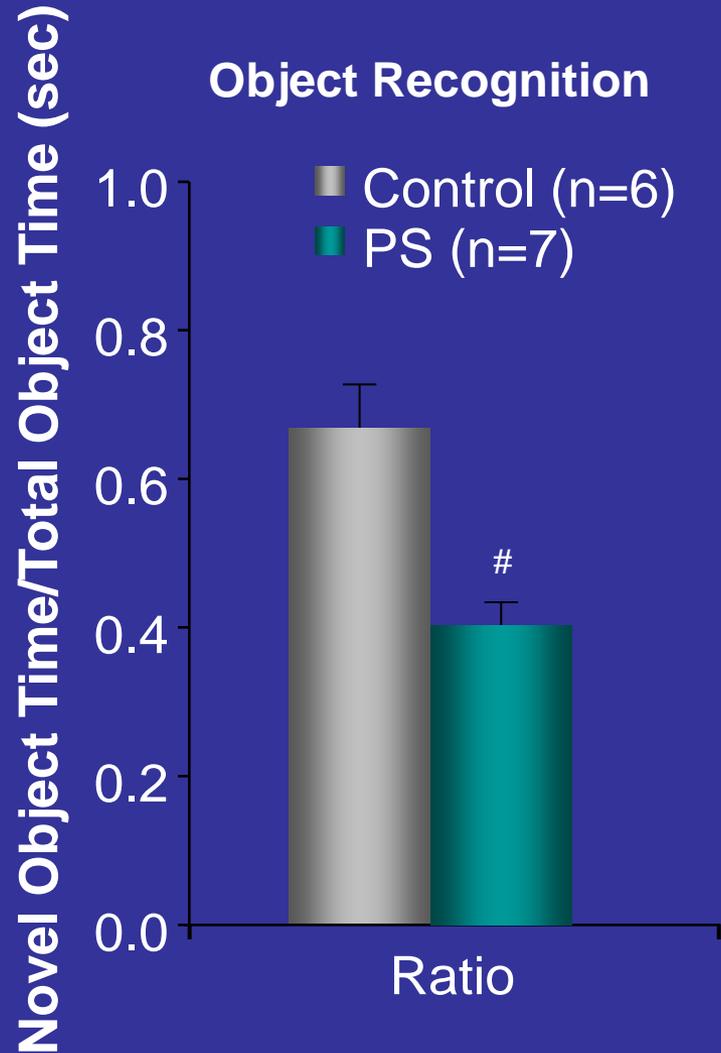


Novel Object Recognition Test

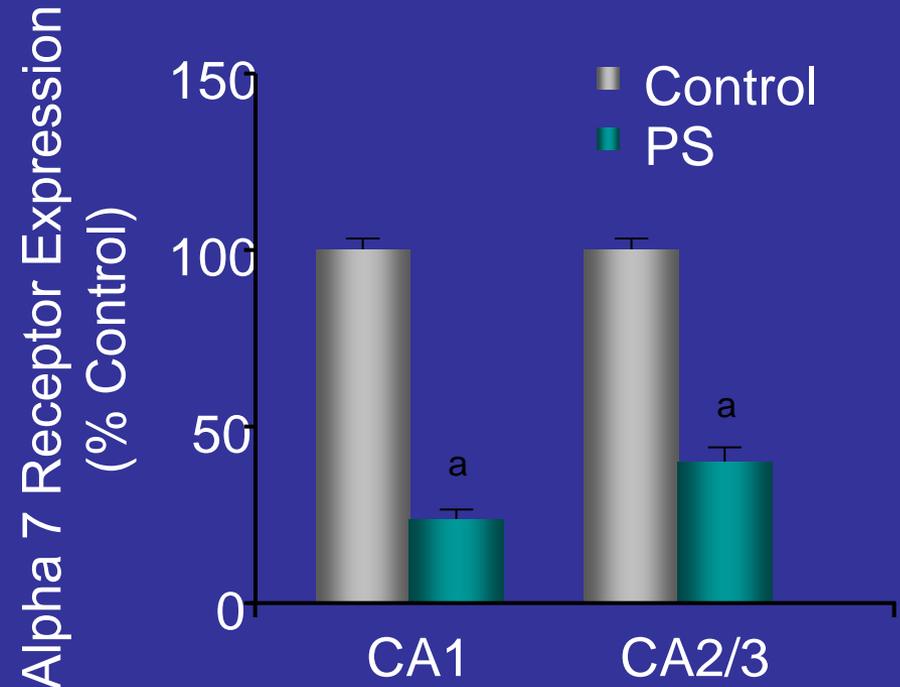
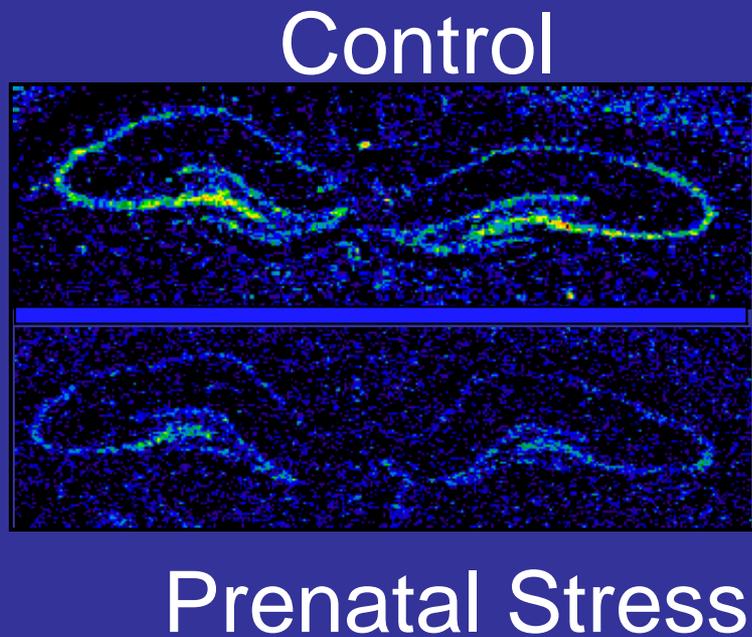


Memory = Novel/Total Investigation Time
A value of >0.5 implies memory for familiar object

Prenatal Stress and Cognitive Function Recognition Tests on Day 56 in Male Rats



Prenatal Receptor mRNA Quantification at Stress and HPC Alpha-7 in 56-Day-Old Rats



Therapeutics and DSM-5

- Categories
- Dimensions

Domains of Pathology within the Schizophrenia Syndrome

Strauss, Carpenter and Bartko

Schizophrenia Bulletin, Winter 1974

- Disorders of content of thought and perception
- Disorders of affect
- Disorders of personal relationships
- Disorder of form of speech and thought
- Disordered motor behaviors
- Lack of insight

Psychopathological Dimensions: What and How Many?

Peralta and Cuesta

Schizophrenia Research, 2001

Eight Major Dimensions

1. Psychosis
2. Disorganization
3. Negative
4. Mania
5. Depression
6. Excitement
7. Catatonia
8. Lack of insight

Paradigm Shift

Psychosis Dx	Delusions
	Hallucinations
	Disorganized Thought
	Avolition
	Restricted Emotion
	Depression
Cognitive Pathology	Mania

Recovery

- Course and Outcome
- Remission
- Recovery [medical]
- Recovery [process]

Elements of Recovery (SAMHSA, 2005)

- Self-direction
- Individualized and person-centered
- Empowerment
- Holistic
- Non-linear
- Strengths-based
- Peer Support
- Respect
- Responsibility
- Hope

Other Axis I Disorders

- Depression
- Bipolar
- Anxiety
- PTSD
- TBI
- OCD

Prevention of Mental Disorders

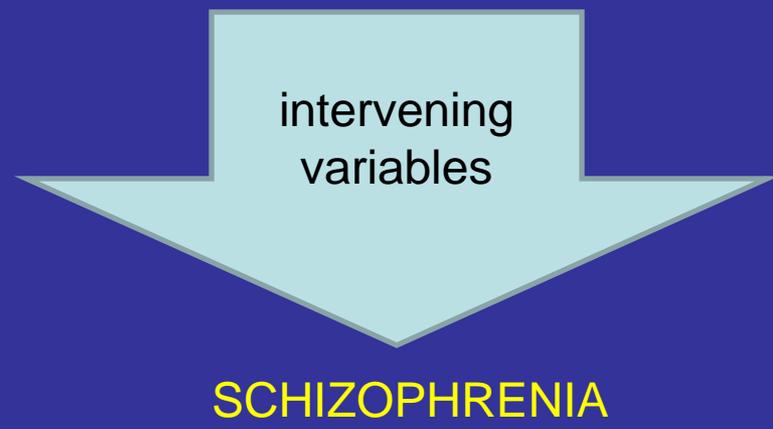
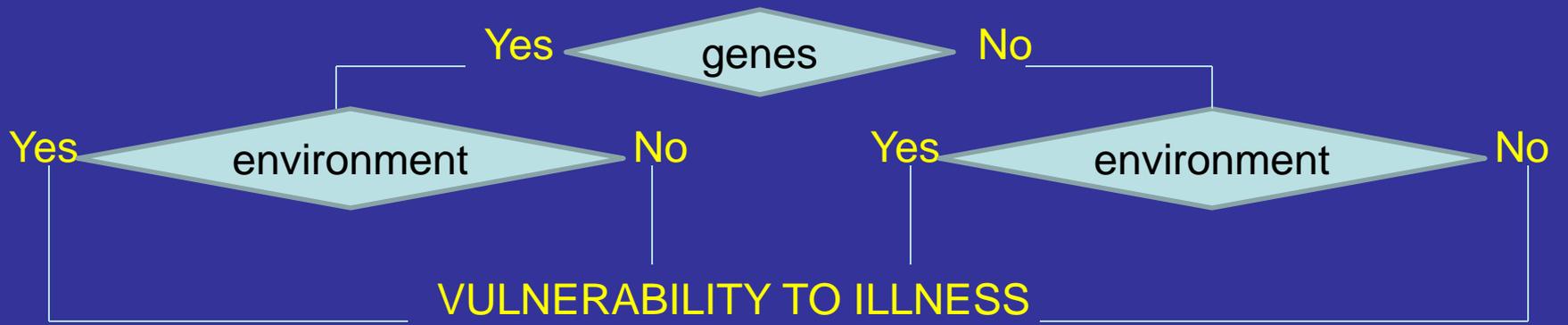
- Primary prevention--risk factors at the population level
- Secondary prevention--early detection and intervention
- Tertiary prevention--recovery process, independent living, quality of life

Attenuated Psychosis Symptom Syndrome

delusions/delusional ideas

hallucinations/perceptual abnormalities

disorganized speech/communication



A Closing Note

- On violence, stigma, and societal support for the care and treatment of mentally ill persons

Acknowledgments

- Lisa Dixon, M.D.
- Jim Koenig, Ph.D.
- NIMH
- Brain and Behavior Foundation [NARSAD]