

Schizophrenia: New Concepts for Therapeutic Discovery

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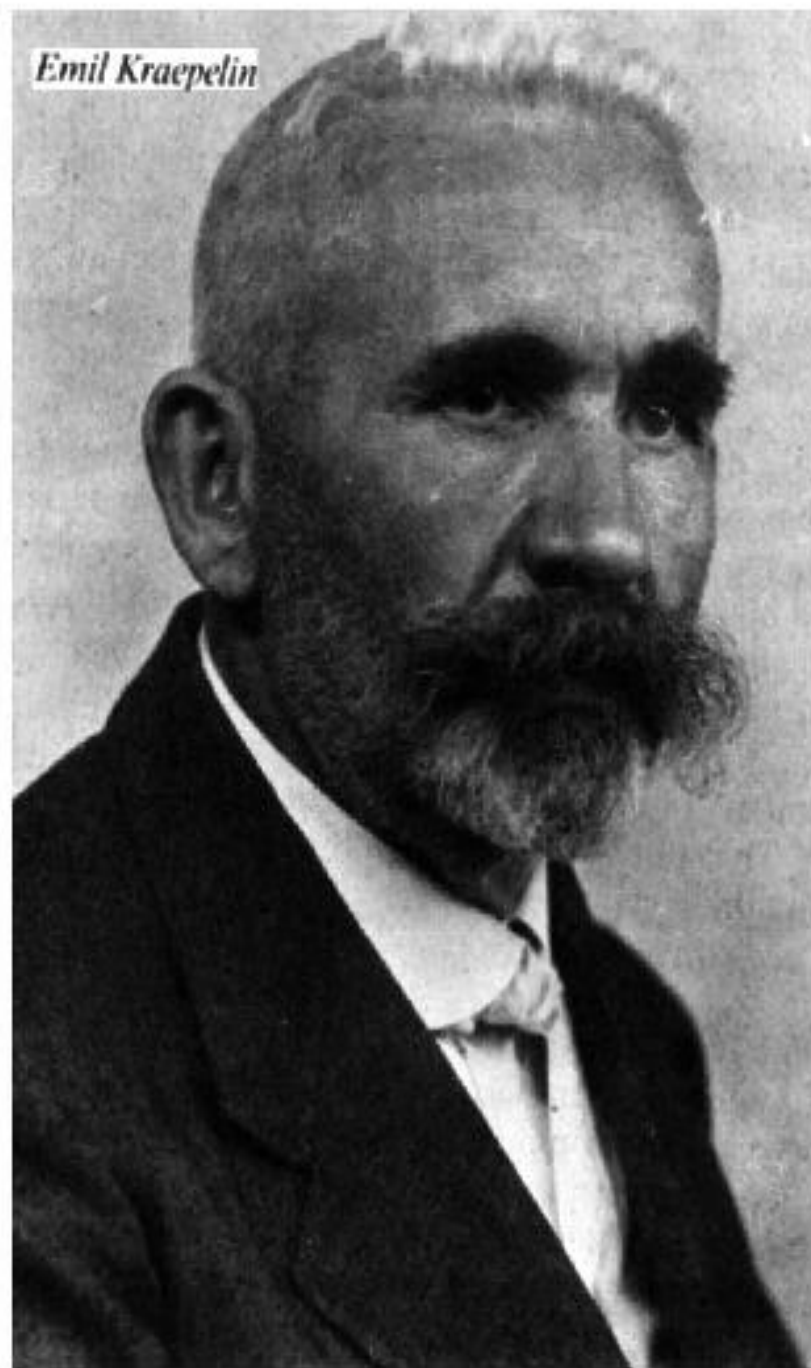
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Concepts

- Schizophrenia
- Deconstruction
- Prognosis and Course
- Therapeutic Targets
- Across Diagnostic Boundaries
- First Episode Therapeutics
- Clinical High Risk
- Prevention





Nuclear Schizophrenia

Schneider

First Rank Symptoms

Audible thoughts
Somatic passivity
Thought insertion
Thought withdrawal
Thought broadcast
Thought broadcast
Made feelings

Made impulses
Made volition
Voices arguing
Voices commenting
Delusional percepts

Domains of Pathology: Strauss, Carpenter and Bartko

- 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

Schizophrenia Bulletin, 1974

Psychopathological Dimensions: What and How Many?

Peralta and Cuesta

Schizophrenia Research, 2001



Eight Major Dimensions

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



Paradigm Shift

Psychosis Dx	Delusions
	Hallucinations
	Disorganized Thought
	Psychomotor
	Negative symptoms
	Depression
Cognitive Pathology	Mania

Domain Specific Therapy

- Suicide
- Aggression
- Stress
- Anxiety
- Sleep disturbance
- Obsessive/compulsive

Functional Targets

- Social interactions
- Social withdrawal
- Major role performance
- Sexual dysfunction

Prognosis/Course

1. Heterogeneous course and outcome
2. Within domain prediction
3. Developmental pathology

Therapeutic Issues

- Biopsychosocial medical model
- Integrative therapeutics
- Personalized medicine/individualized Rx

Issues in Treatment

- Unmet needs
- Pseudospecificity
- Novel mechanism

Mechanisms

- Pathophysiology
- Common final pathways
- Compensatory
- Resiliency
- Motor

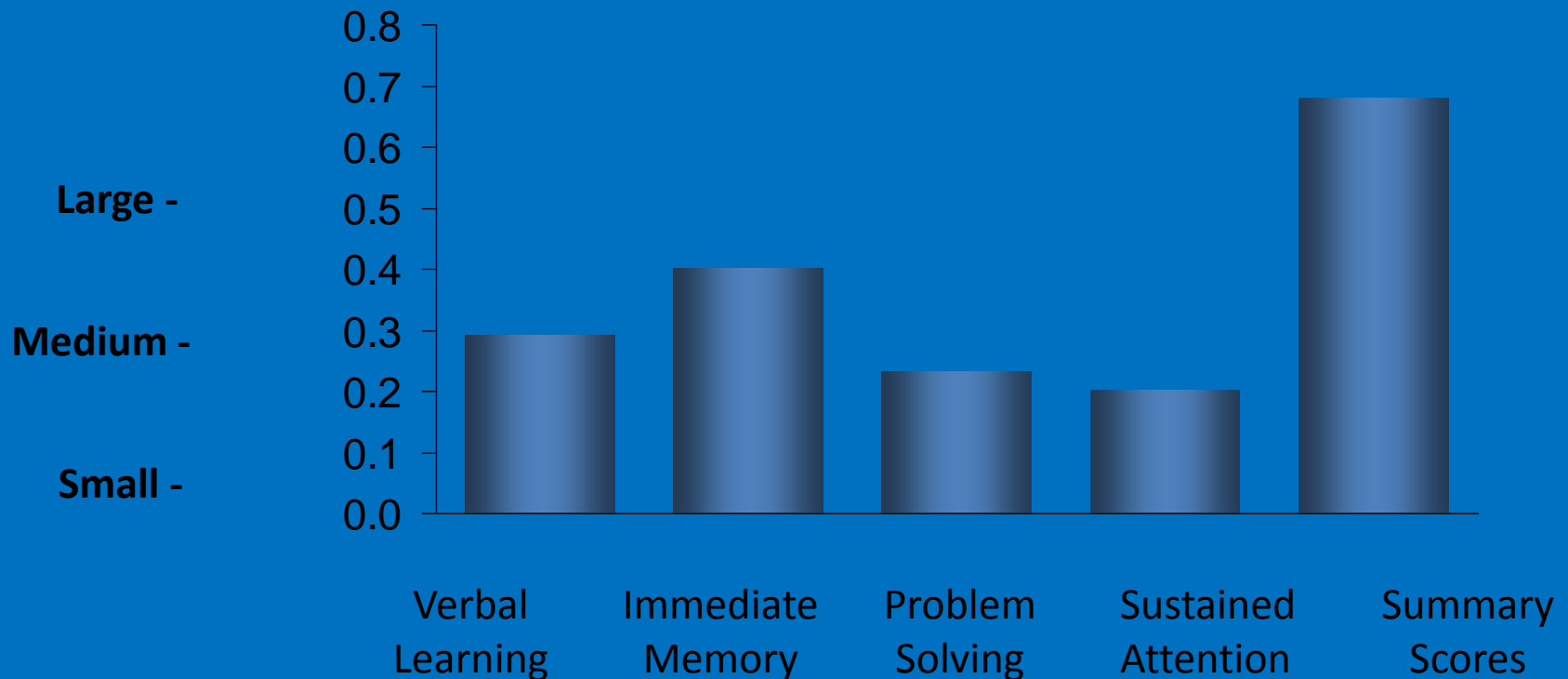
Unmet Therapeutic Needs

- Negative symptoms
- Impaired cognition

Negative Symptom Construct: Five Domains

- Five domains, two factors
 - Diminished expression
Diminished verbal output
 - Anhedonia
Diminished interest
Diminished social drive

Cognition and Functional Outcome in Schizophrenia: Strengths of Relationships^a



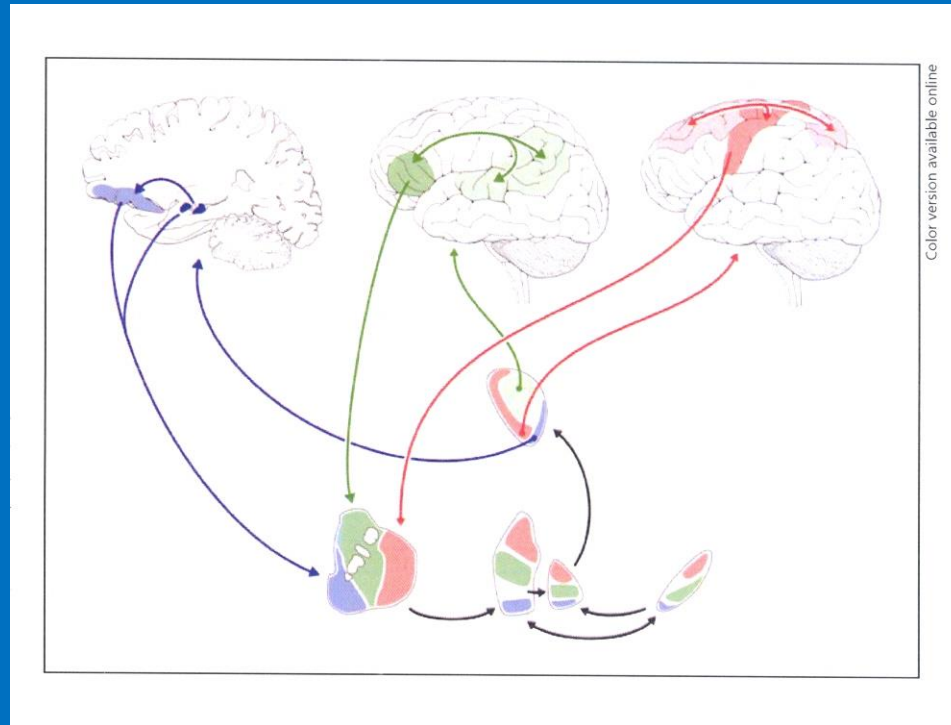
^aEffect size based on Cohen's r.

Green MF et al. *Schizophr Bull.* 2000;26(1):119-136.

Other Psychopathology Concepts

- HiTOP
- Extended Psychosis Phenotype
- Bern: Language, emotion, motor

SyNoPsis

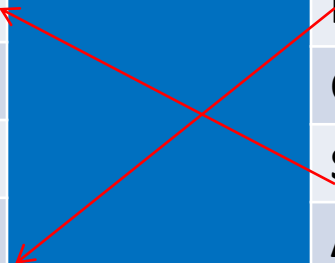


Mapping RDoC to DSM-V

How to map DSM-V onto RDoC?

DSM-V Dimensions
Hallucinations
Delusions
Disorganized Speech
Abnormal Psychomotor Behavior
Negative Symptoms (diminished emotional expressivity; avolition)
Cognitive Impairment
Depression
Mania

RDoC Dimensions
Negative Valence
Positive Valence
Cognitive Systems
Systems for Social Processes
Arousal/Regulatory Systems



New Directions in Therapeutic Discovery

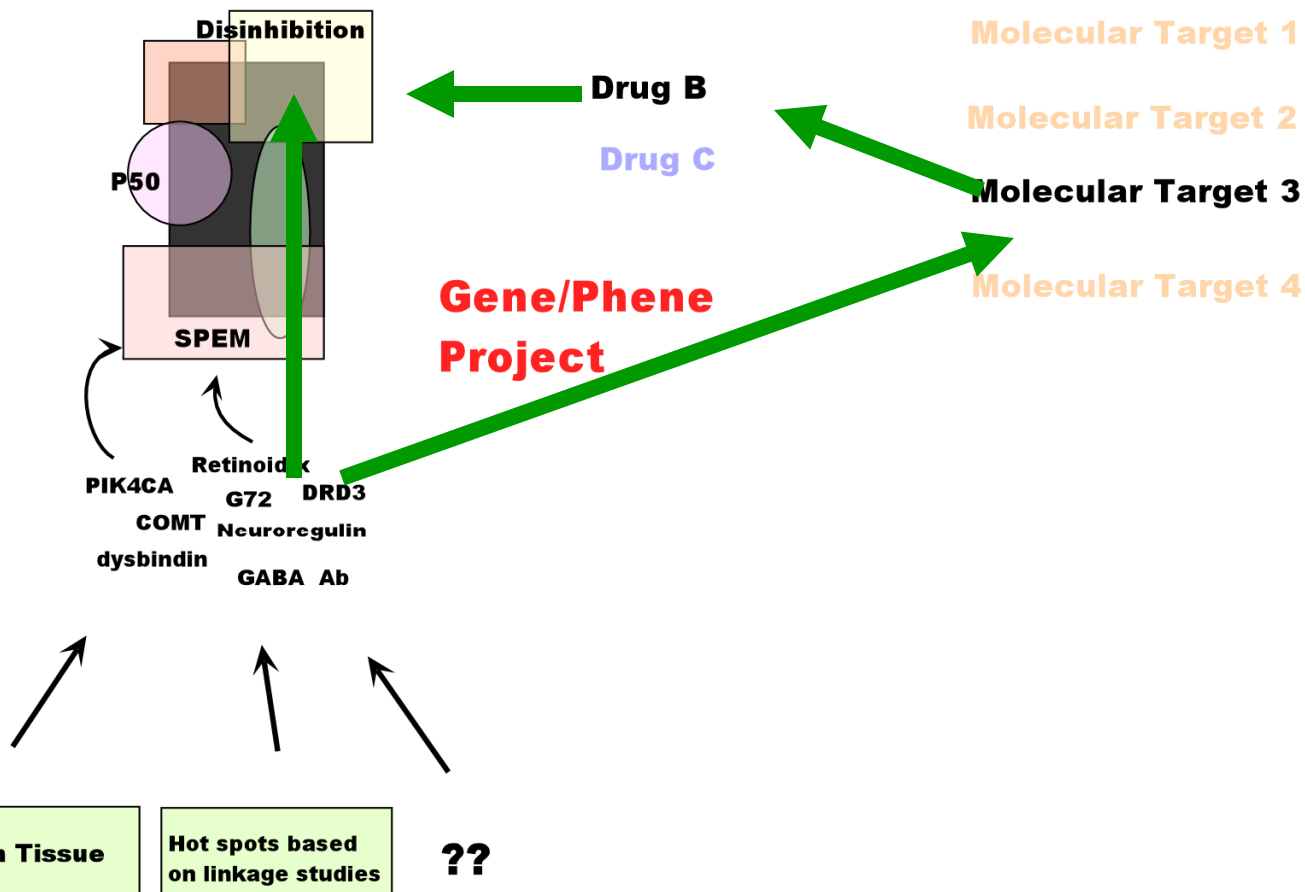
- Genetics: molecular targets
- Brain Imaging: network targets
- Focus: unmet needs
- New paradigms: RDoC, SyNoPsis, HiTOP

**Clinical Dx of
Schizophrenia**

encompasses

**Multiple
phenotypes**

**Proof of Concept
drug study**



Treatment Summary

- Modest advances in Drug and Psychosocial Rx
- Emphasis on integration of Rx, multiple clinical targets, and individualized
- Early recognition and Rx of first episode psychosis
- Across diagnostic boundaries
- New paradigms for discovery

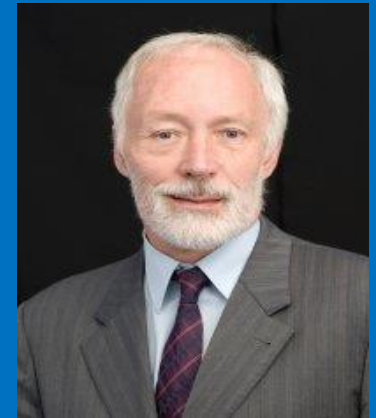
Treatment: First Episode Psychosis

- Duration of Untreated Psychosis
- Pharmacotherapy
- Education/Social Support
- Resilience/Compensatory
- Domain Specific Therapeutics
- Integrative treatment

At Risk Mental State



- Basic Symptom
- Schizophrenia prodrome
- BLIPS-Brief limited intermittent psychosis
- UHR-Ultrahigh risk
- CHR-Clinical high risk
- APS-Attenuated psychosis syndrome





Criteria for the Attenuated Psychotic Symptom Syndrome

- A. At least one of the following symptoms are present in attenuated form, with relatively intact reality testing, and are of sufficient severity or frequency to warrant clinical attention:
 - 1. Delusions
 - 2. Hallucinations
 - 3. Disorganized speech
- B. Symptom(s) must have been present at least once per week for the past month.
- C. Symptom(s) must have begun or worsened in the past year.

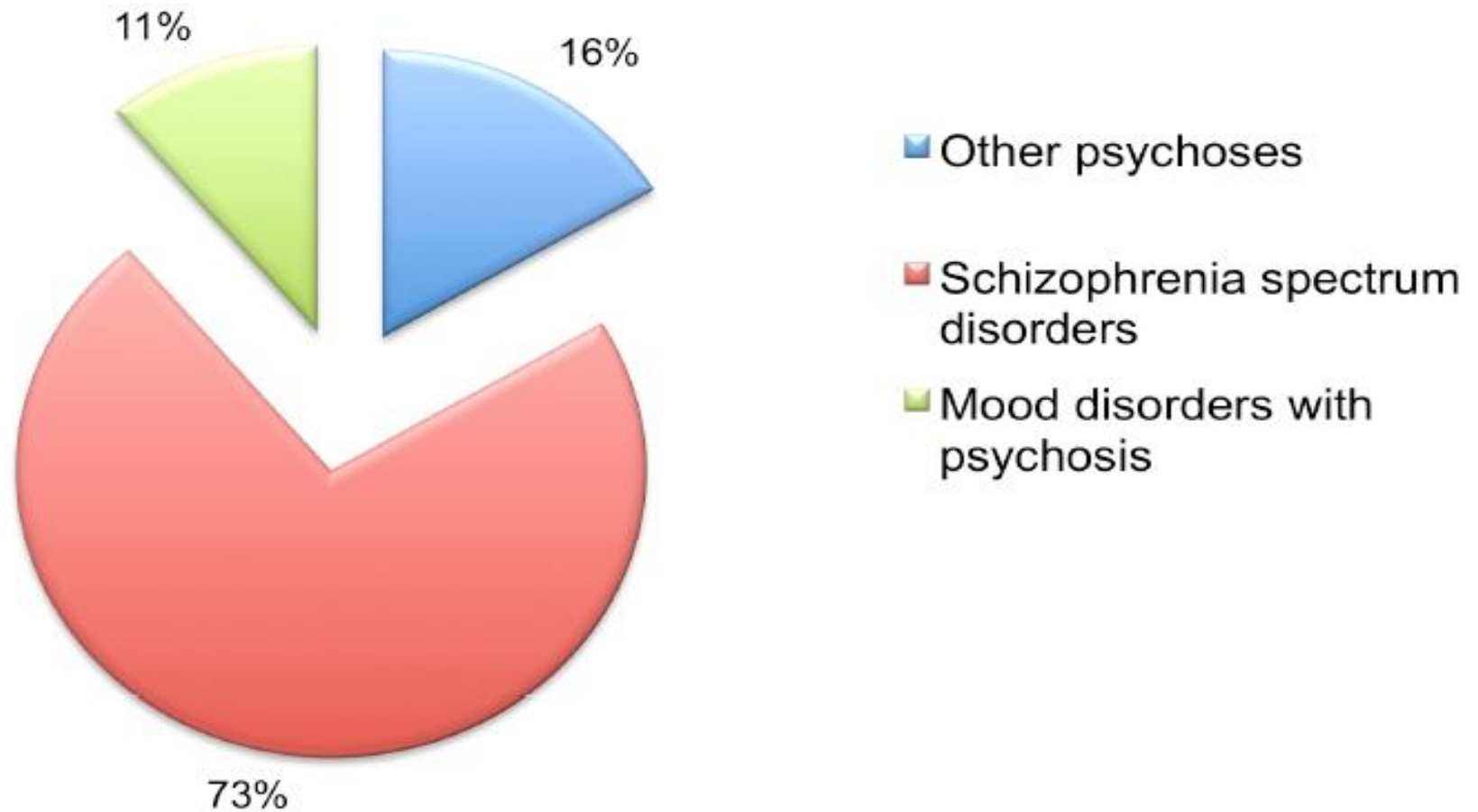
Criteria for the Attenuated Psychotic Symptom Syndrome (continued)

- D. Symptom(s) are sufficiently distressing and disabling to the individual to warrant clinical attention.
- E. Symptom(s) are not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and are not attributable to the physiological effects of a substance or another medical condition.
- F. Criteria for any psychotic disorder have never been met

APS: a Validated Disorder

1. Distress
2. Dysfunction
3. Gray matter reduction
4. White matter reduction
5. Electrophysiology
6. Cognition impairment
7. Negative symptoms
8. Transition to psychosis
9. Schizophrenia spectrum

ICD/DSM diagnostic outcomes in transitions (n=560)



RCT: Stafford et al, BMJ; Jan. 2013

- 1246 participants
- Approximate one year transition: 7% versus 20%
- 11 trials
- All control groups received treatment

Non-pathological Targets

- Compensatory
- Resilience
- Positive psychiatry



Primary Prevention

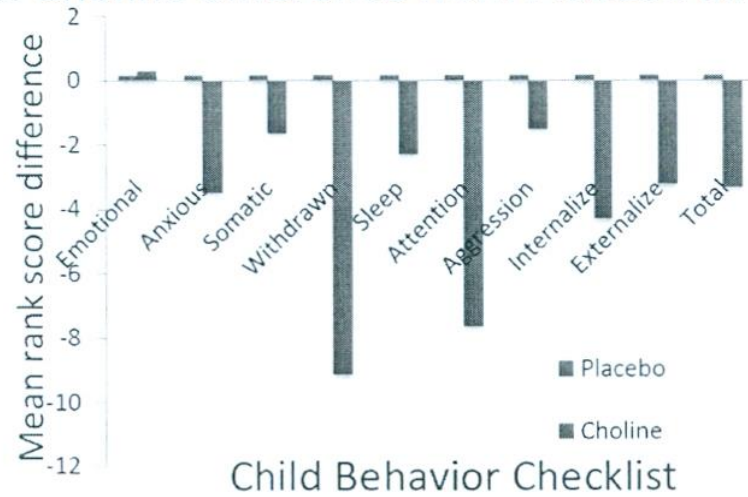
Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*, 170(3):290-8, 2013.

CONCLUSIONS:

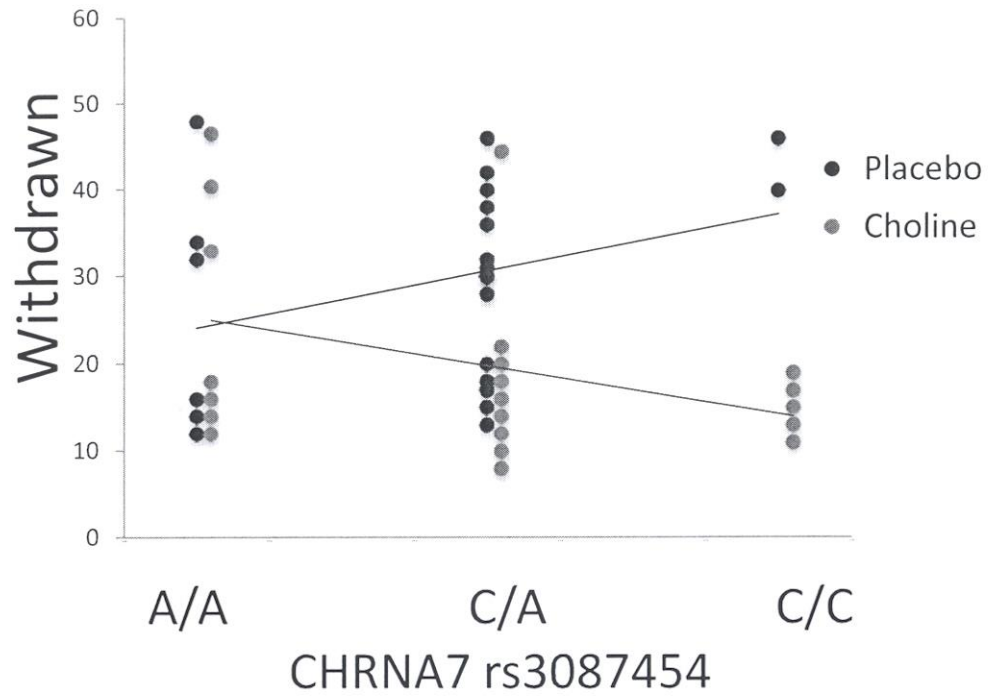
Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

Comment in: Rapoport JL. Prevention of schizophrenia: an impossible dream? *Am J Psychiatry* 170(3):245-7, 2013.

C. Choline difference from Placebo at 40 months



The American Journal of Psychiatry



Current

- Primary Prevention of vulnerability
- Treat disorder at vulnerability stage
- Secondary Prevention of psychosis
- Tertiary Prevention of functional decline
- Reduce time of untreated pathology

Drug Discovery

- FDA adopts new concepts
- Behavioral constructs provide clinical targets
- Neurobiology identifies mechanisms
- Enhanced validity of pre-clinical models

Near Future

- Animal models that predict human Rx efficacy
- Biobehavioral types that predict Rx efficacy
- Establish early detection/intervention
- Primary prevention of vulnerability
- Broaden Rx discovery to Wellness discovery

Near Future

- Transcranial stimulation
- Mobile devices
- Novel compounds for negative symptoms
- Special subgroups [e.g., gliadin AB positive]
- Exercise
- Function oriented therapies
- Integrative treatment