

Paradigms for Therapeutic Discovery

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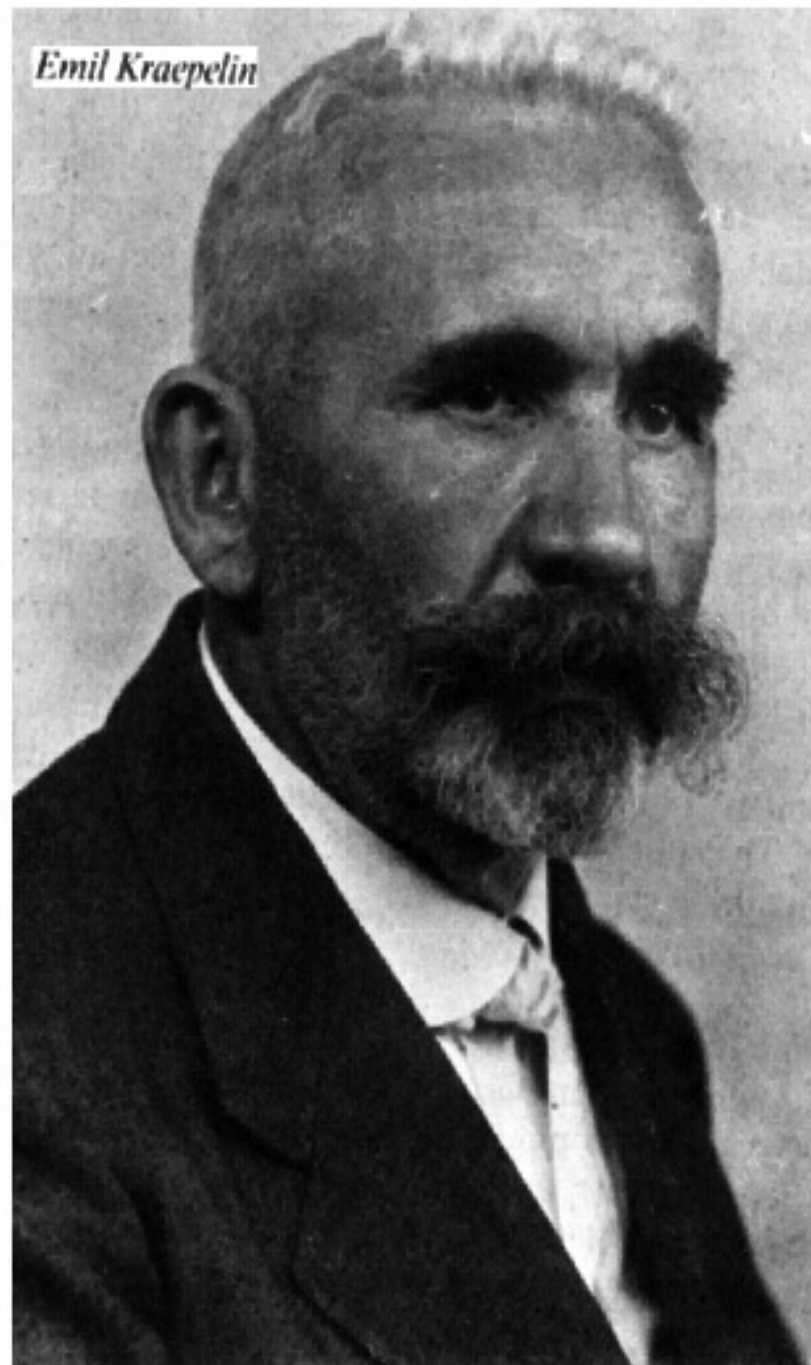
STATEMENT OF INTEREST

Past 12 Months

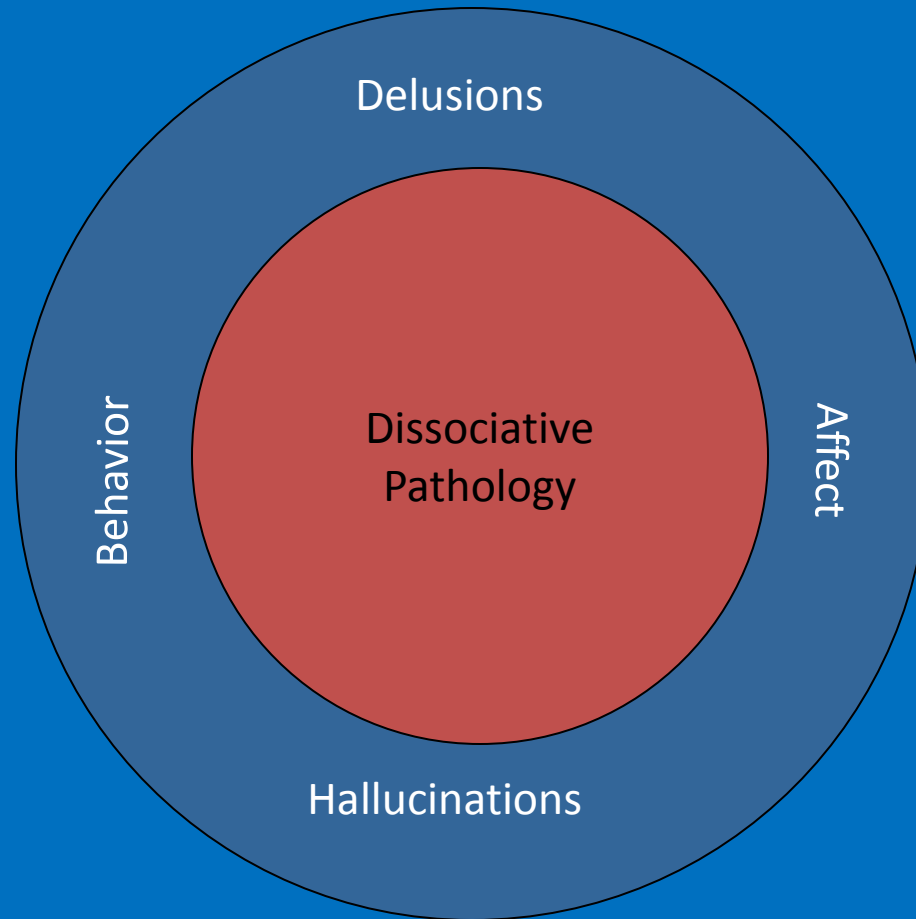
- Speakers Bureau: none
- Stock: none
- Scientific Advisor: **Genentech/Roche**
- Patent: (no personal funds)
- European Regional Patent Number 1487998 (June 6, 2007) “Methods for Diagnosing and Treating Schizophrenia

Paradigms for Therapeutic Discovery

1. Sz as disease
2. Sz as syndrome comprising disease entities
3. Sz as domains of psychopathology
4. Sz as impaired role and social function
5. Sz endophenotypes
6. Sz behavioral/neural circuit impairment
7. Sz development for primary prevention
8. Sz development for secondary prevention



Schizophrenia





Nuclear Schizophrenia Schneider

First Rank Symptoms

Audible thoughts

Somatic passivity

Thought insertion

Thought withdrawal

Thought broadcast

Made feelings

Made impulses

Made volition

Voices arguing

Voices commenting

Delusional percepts

Drugs for Schizophrenia

1. All approved drugs are antipsychotic
2. All share dopamine blocking mechanism of action
3. All, except clozapine, are similar in efficacy
4. None have efficacy for negative symptoms or cognition
5. The drugs vary in adverse effects
6. 60 years with little advance in drug treatments
7. Discovery becoming based on new paradigms

Paradigm Shift

SZ as Syndrome
Comprising Diseases

Disease #1

Disease #2

Disease #3



Deficit Pathology

Interrelated negative symptoms

1. Blunted affect
2. Diminished emotional range
3. Poverty of speech
4. Diminished interests
5. Diminished sense of purpose
6. Diminished social drive

Paradigm Shift

SZ as a Nosologic Class

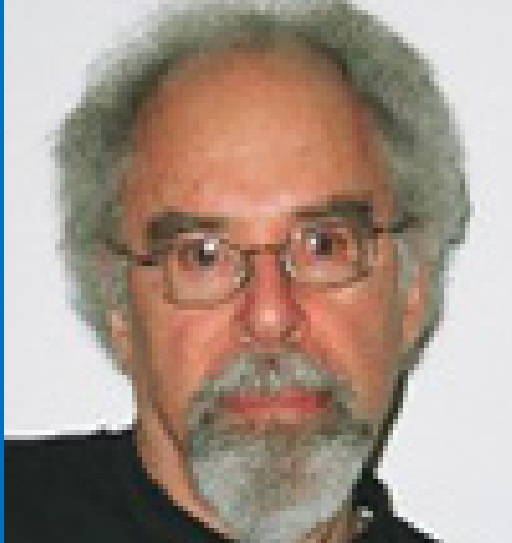
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graph TD; A[SZ as a Nosologic Class] --- B[Domain #1]; A --- C[Domain #2]; A --- D[Domain #3];
```

Domain #1

Domain #2

Domain #3

WHO International Pilot Study of Schizophrenia



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 Domains

(1974)

Schizophrenia

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graph TD; A[Schizophrenia] --- B[Psychosis]; A --- C[Negative]; A --- D[Interpersonal]
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Psychosis

Negative

Interpersonal

Psychopathological Domains

(1980)

Schizophrenia

Reality distortion

Disorganization

Negative

Andreasen NC and Olsen S. Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry. 39(7):789-794, 1982.



Psychopathological Dimensions: What and How Many?

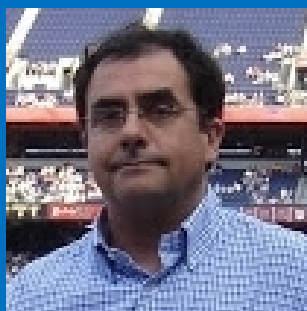
Peralta and Cuesta

Schizophrenia Research, 2001

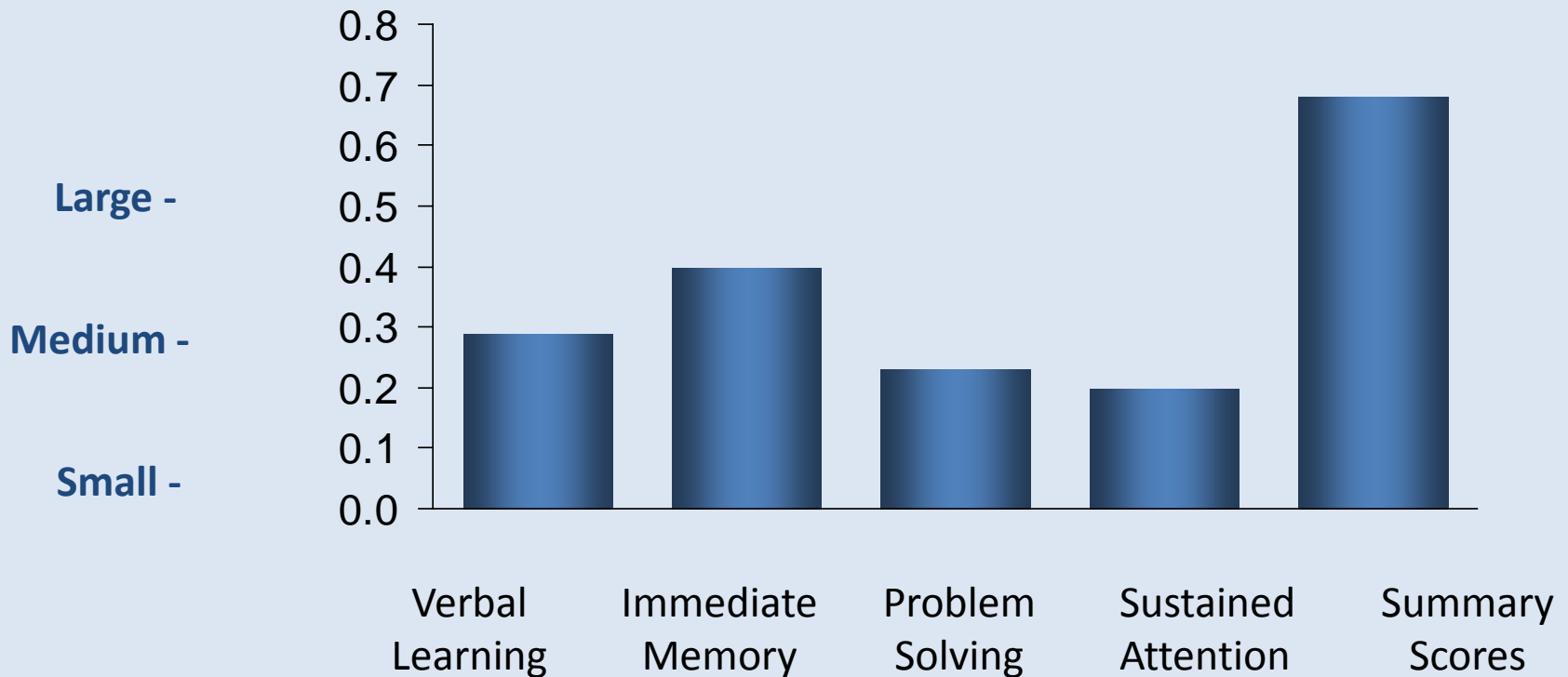


Eight Major Dimensions

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



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

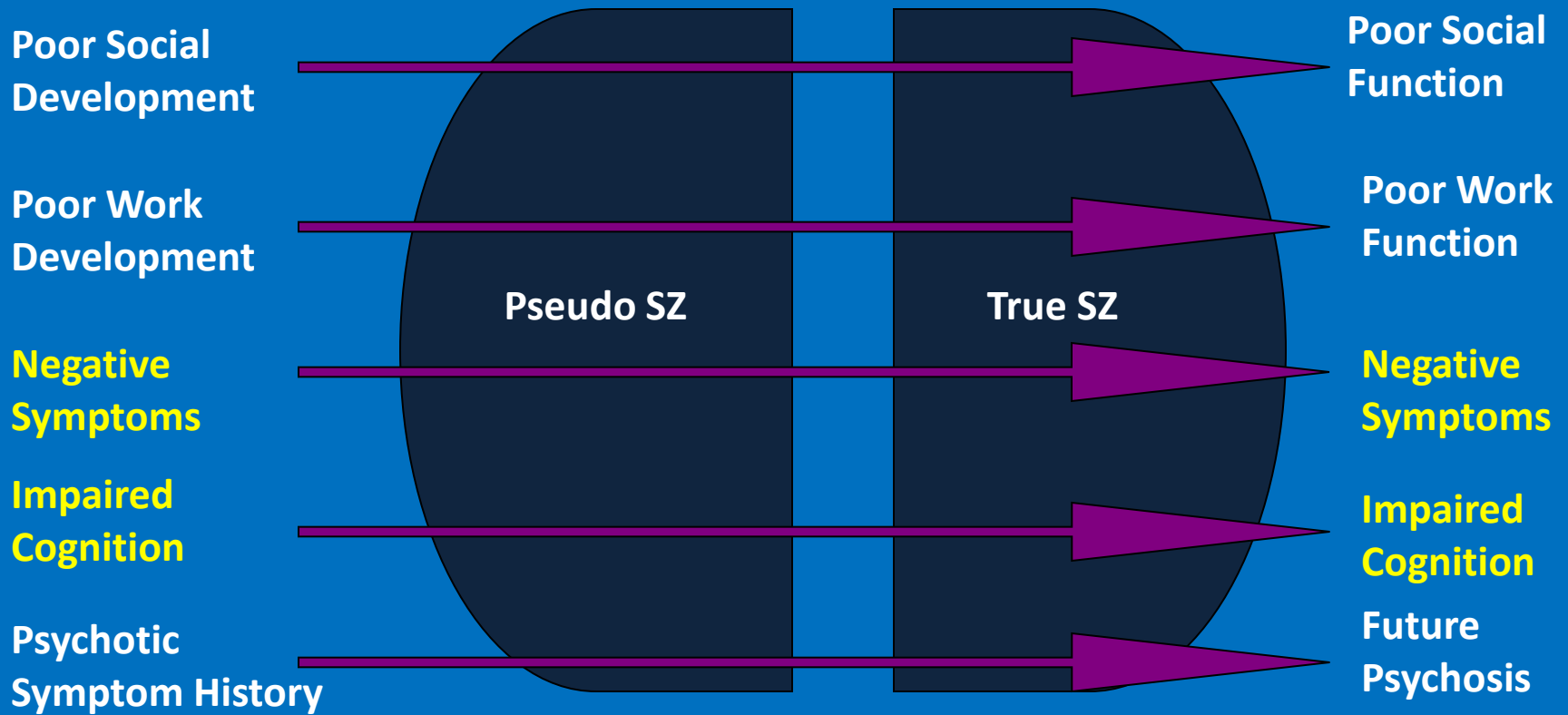


^aEffect size based on Cohen's r.
Green MF et al. *Schizophr Bull.*
2000;26(1):119-136.

Paradigm Shift

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

Nuclear Schizophrenia Onset and Course

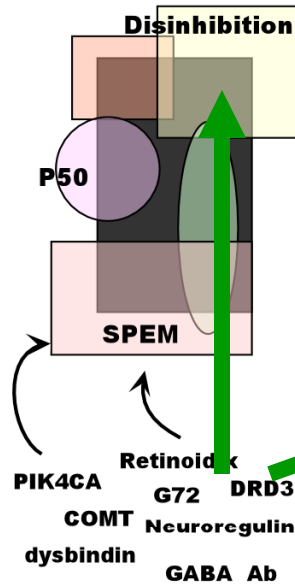


Clinical Dx of Schizophrenia

encompasses

Multiple phenotypes

Proof of Concept drug study



Drug A

Drug B

Drug C

Molecular Target 1

Molecular Target 2

Molecular Target 3

Molecular Target 4

Gene/Phene Project

PIK4CA
Retinoid X
G72 DRD3
COMT Neuroregulin
dysbindin GABA Ab



Brain Tissue

Hot spots based on linkage studies

??

Background

- Five RDoC domains have been proposed that are thought to cut across current DSM diagnostic categories:

RDoC Dimensions

Negative Valence

Positive Valence

Cognitive Systems

Systems for Social Processes

Arousal/Regulatory Systems



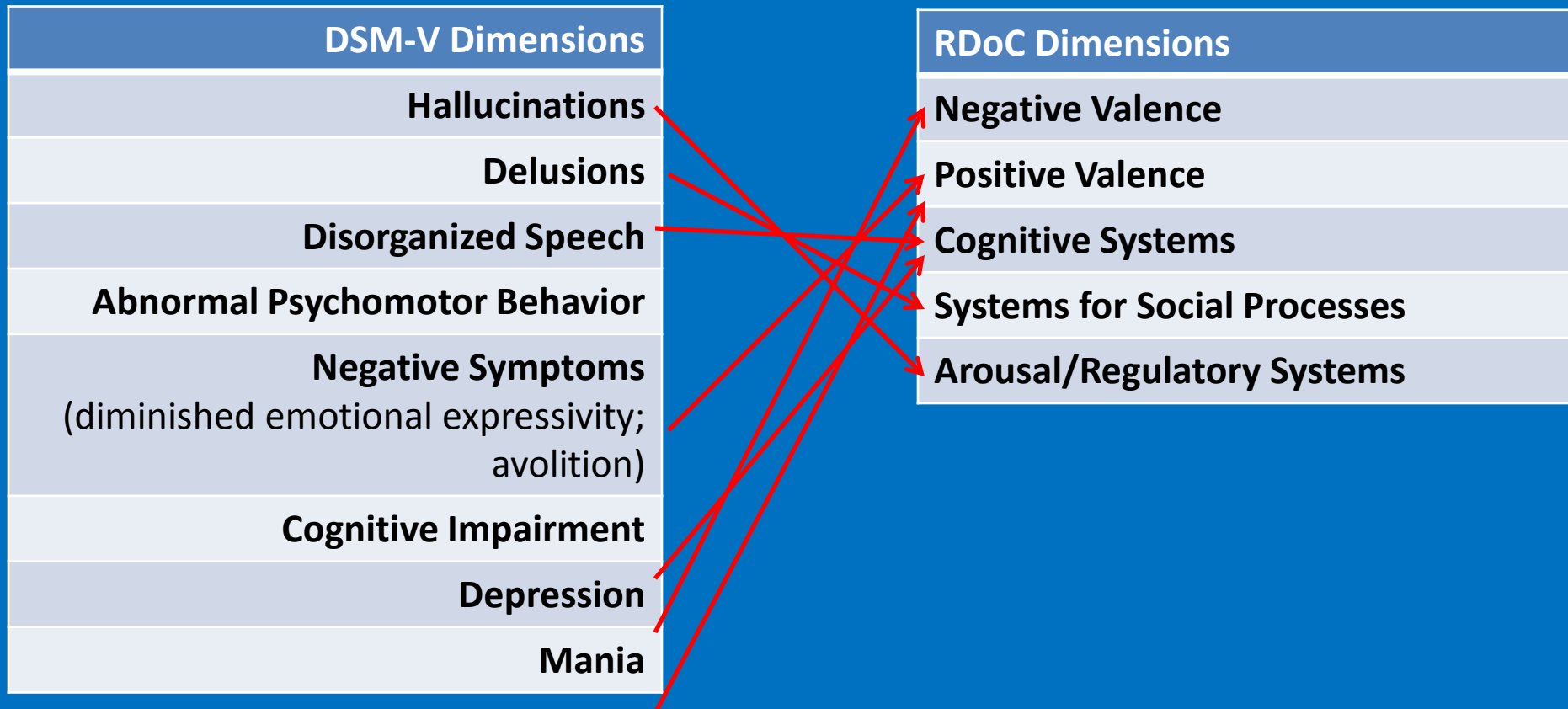
RDoC: Candidate Domains/Constructs and Units of Analysis (v. 2.1)

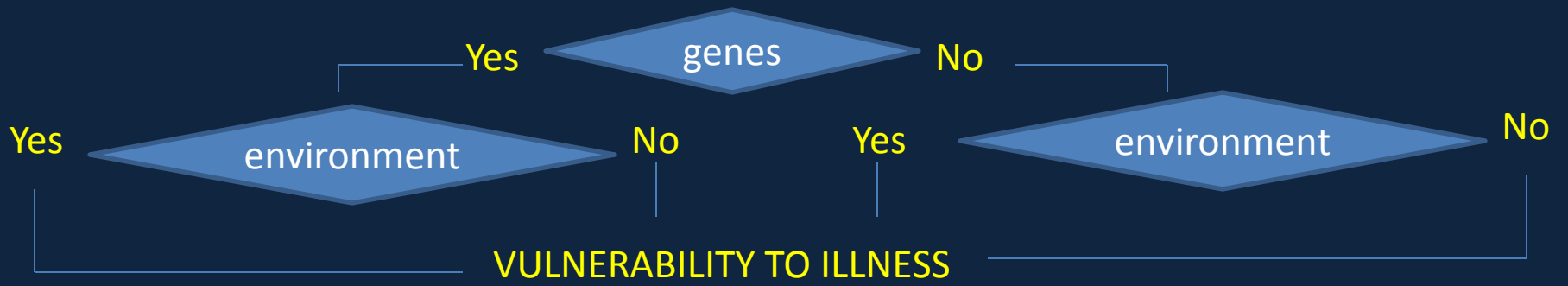
v. 3.1, 6/30/2011	DRAFT RESEARCH DOMAIN CRITERIA MATRIX							
	----- UNITS OF ANALYSIS -----							
DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/Regulatory Systems								
Arousal & regulation (multiple)								
Resting state activity								

Two criteria for a Construct: Empirical support for (1) a functional dimension of behavior and (2) an implementing brain circuit).

Mapping RDoC to DSM-V

How to map DSM-V onto RDoC?





VULNERABILITY TO SCHIZOPHRENIA



SCHIZOPHRENIA



Primary Prevention

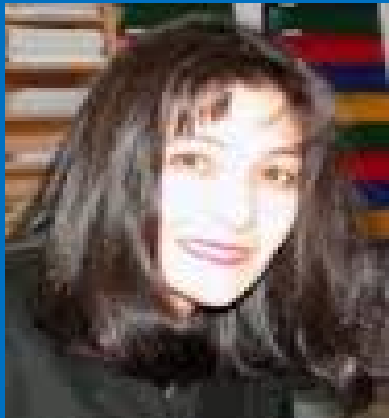
Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*, 170(3):290-8, 2013.

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.

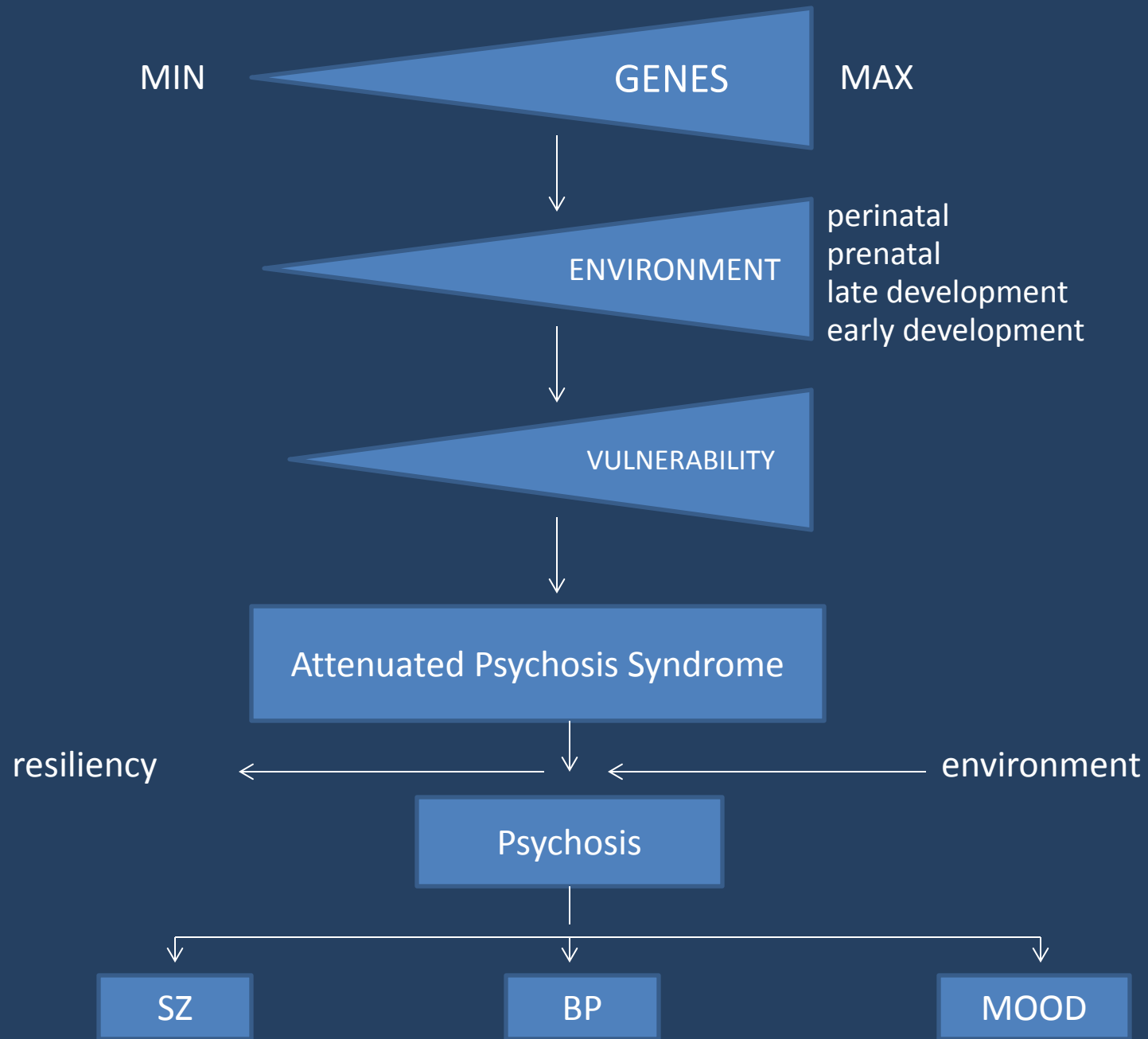
Comment in: Rapoport JL. Prevention of schizophrenia: an impossible dream? *Am J Psychiatry* 170(3):245-7, 2013.

At Risk Mental State



- Ultra High Risk
- Basic Symptom
- Attenuated Psychosis Syndrome
- Schizophrenia prodrome
- BLIPS-Brief limited intermittent psychosis
- UHR-Ultrahigh risk
- CRH-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)

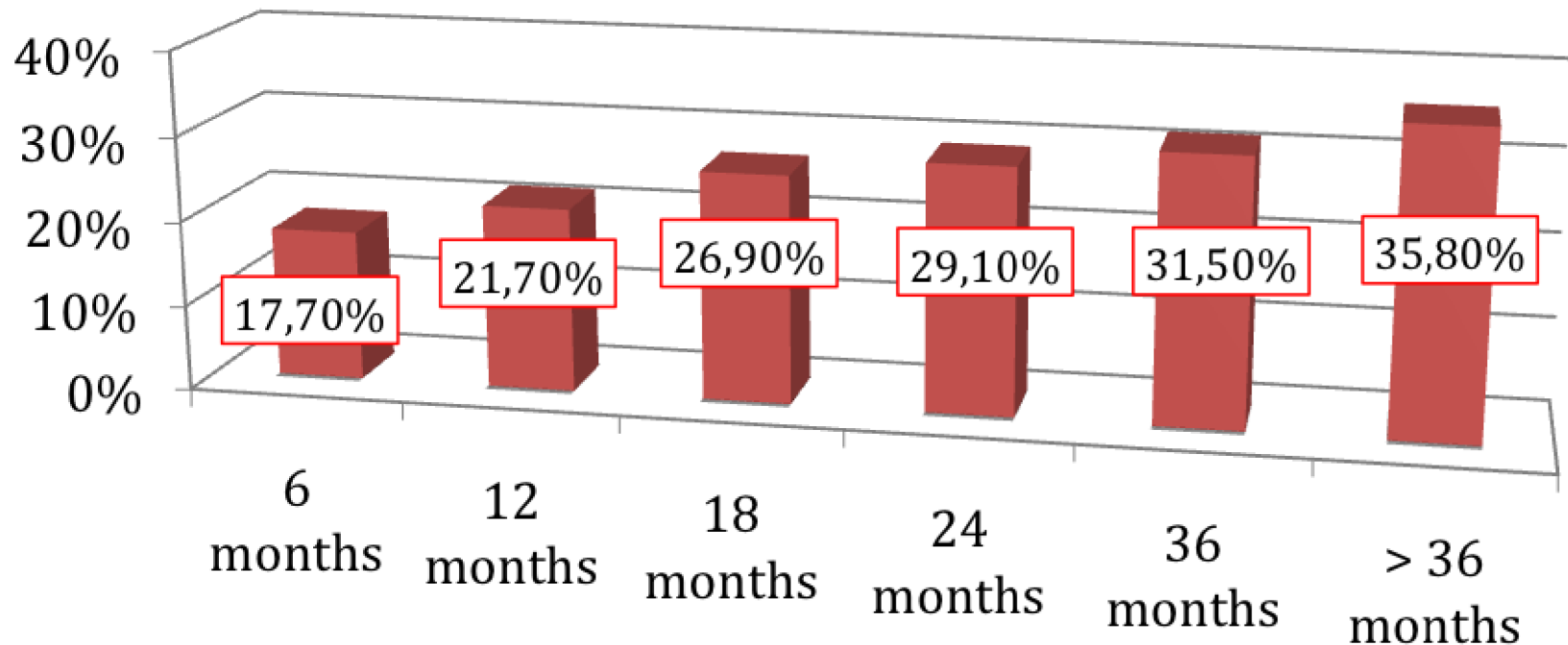
- D. Symptom(s) are sufficiently distressing and disabling to the individual to warrant clinical attention.
- E. Symptom(s) are not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and are not attributable to the physiological effects of 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. Cognition impairment
6. Negative symptoms
7. Transition to psychosis
8. Schizophrenia spectrum

30% TRANSITION RISK AT 2 YRS

Meta-analysis of transition outcomes in 2500 HR subjects



RCT: Stafford et al, BMJ; Jan. 2013

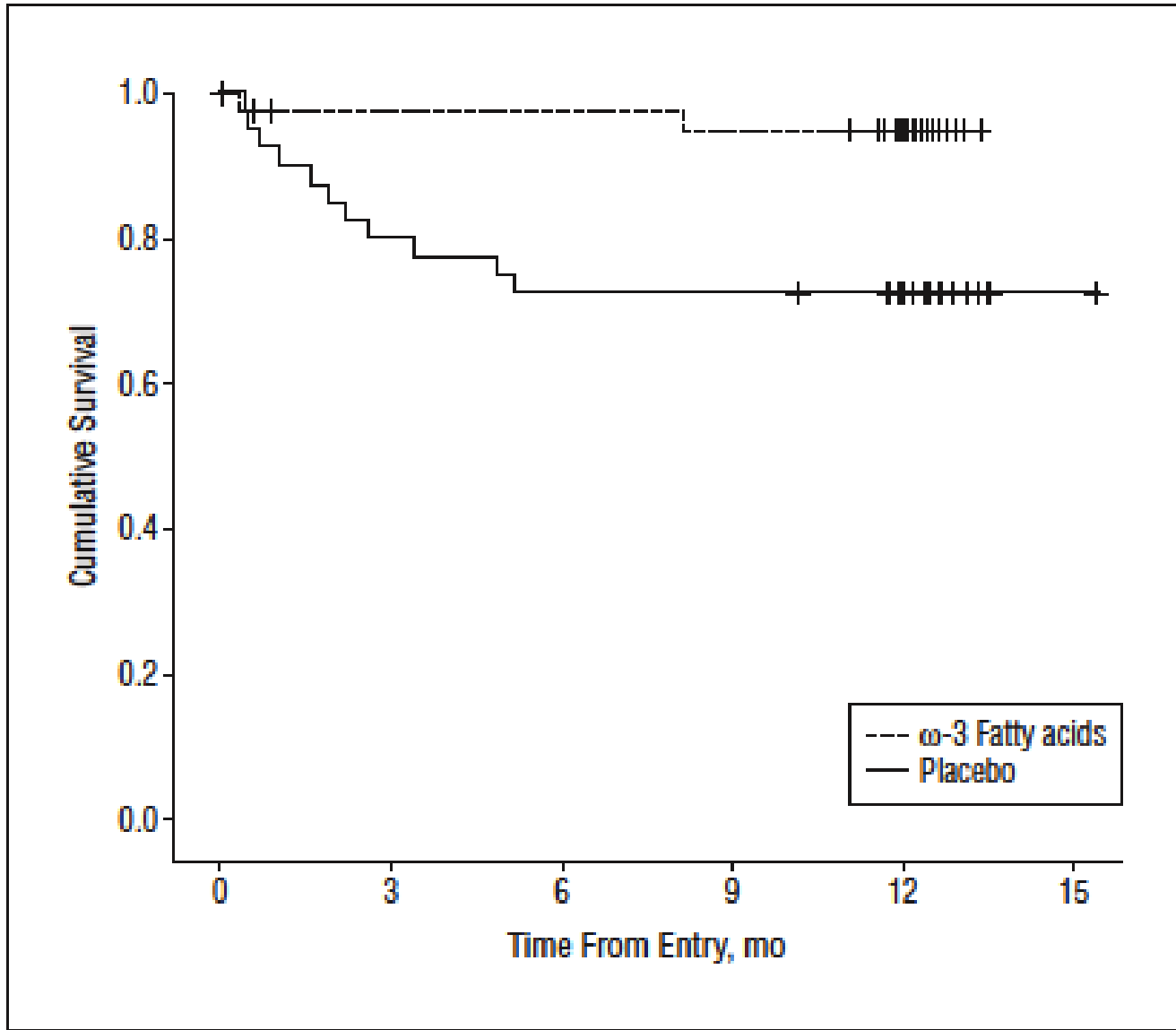
- 1246 participants
- Approximate one year transition: 7% versus 20%
- 11 trials
- All control groups received treatment

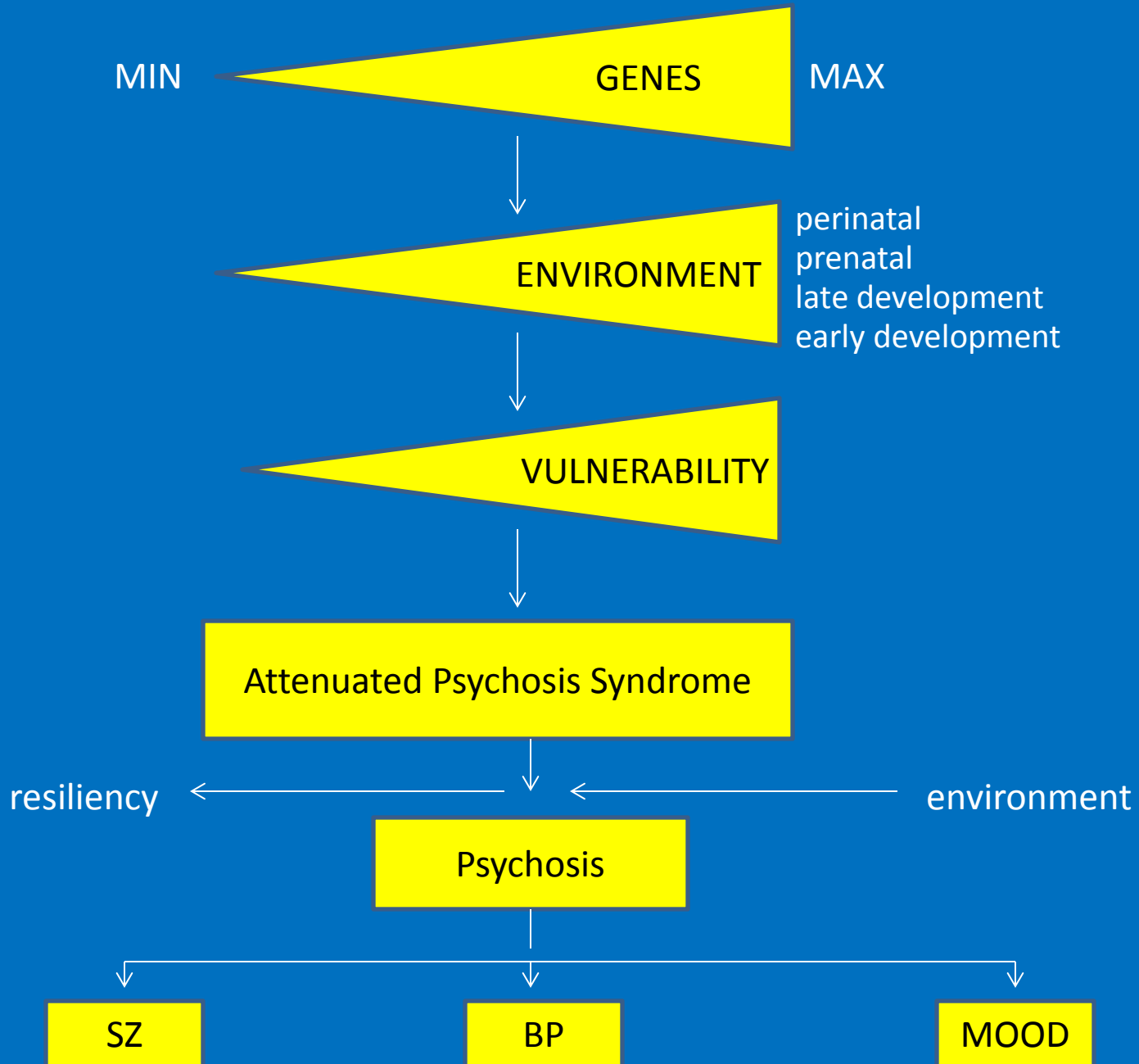
Long-C of Psyc

A Randomi

*G. Paul Amming
Claudia M. Klier
Patrick D. McGe*

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SUMMARY

- Primary Prevention of vulnerability
- Treat disorder at vulnerability stage
- Secondary Prevention of psychosis
- Tertiary Prevention of functional decline
- Reduce period of untreated psychopathology
- Novel therapeutic discovery with paradigms that address heterogeneity of clinical syndromes and across Dx pathologies