Concepts

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

First Rank Symptoms

<table>
<thead>
<tr>
<th>Audible thoughts</th>
<th>Made impulses</th>
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<tbody>
<tr>
<td>Somatic passivity</td>
<td>Made volition</td>
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<tr>
<td>Thought insertion</td>
<td>Voices arguing</td>
</tr>
<tr>
<td>Thought withdrawal</td>
<td>Voices commenting</td>
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<tr>
<td>Thought broadcast</td>
<td>Delusional percepts</td>
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<tr>
<td>Made feelings</td>
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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
Eight Major Dimensions

1. Psychosis
2. Disorganization
3. Negative
4. Mania
5. Depression
6. Excitement
7. Catatonia
8. Lack of insight
<table>
<thead>
<tr>
<th>Cognitive Pathology</th>
<th>Delusions</th>
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<tr>
<td></td>
<td>Hallucinations</td>
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<tr>
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<td>Disorganized Thought</td>
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<td>Psychomotor</td>
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<td>Negative symptoms</td>
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<td>Depression</td>
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<td>Mania</td>
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**Psychosis Dx**
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

- Large -
- Medium -
- Small -
- Verbal Learning
- Immediate Memory
- Problem Solving
- Sustained Attention
- Summary Scores

\(^a\)Effect size based on Cohen’s r.
Other Psychopathology Concepts

- HiTOP
- Extended Psychosis Phenotype
- Bern: Language, emotion, motor
SyNoPsis
## Mapping RDoC to DSM-V

How to map DSM-V onto RDoC?

<table>
<thead>
<tr>
<th>DSM-V Dimensions</th>
<th>RDoC Dimensions</th>
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<tbody>
<tr>
<td>Hallucinations</td>
<td>Negative Valence</td>
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<tr>
<td>Delusions</td>
<td>Positive Valence</td>
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<tr>
<td>Disorganized Speech</td>
<td>Cognitive Systems</td>
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<tr>
<td>Abnormal Psychomotor Behavior</td>
<td>Systems for Social Processes</td>
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<tr>
<td>Negative Symptoms (diminished emotional</td>
<td>Arousal/Regulatory Systems</td>
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<td>expressivity; avolition)</td>
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<td>Cognitive Impairment</td>
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<td>Depression</td>
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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. The diagram illustrates a Gene/Phene Project with hot spots based on linkage studies in brain tissue. Proof of Concept drug study involves drugs A, B, and C targeting molecular targets 1 to 4.
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)

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

- Compensatory
- Resilience
- Positive psychiatry
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.

C. Choline difference from Placebo at 40 months

Child Behavior Checklist
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