Early Course and Intervention in Youth At-Risk for Psychosis: Results from Longitudinal Studies

Raquel E. Gur, M.D. Ph.D.
Schizophrenia: A Neurodevelopmental Disorder

Grey-matter volume changes during normal development

G Matthew Hrut and Brian Keshavan

From Insel
Paradigm Shift: Clinical Risk Strategy

Pre-Illness  Prodromal  Psychosis  Remission  Relapse

First symptoms  Onset of First Episode  Onset of relapse

Adapted from Knowles, 2004

Courtesy Monica Calkins
Traditional Strategy for Studying and Treating Psychotic Disorders

From Insel
Clinical Risk Strategy

From Insel
The paradigm shift mandates:

- Bridging pediatrics and adult divide establishing developmental trajectories
- Dissecting complex phenotypes applying multi-dimensional levels of analysis
- Convergence large samples, establishing common measures
- Integration with genomics
Why Identify Early?

Enhance understanding of underlying neurobiology of psychosis

Early identification $\rightarrow$ timely treatment of psychosis

- The first episode of schizophrenia often goes untreated for an average of one year
- Longer duration of untreated psychosis is correlated with greater disability
- Early treatment can reduce relapse and deterioration
- Early response may prevent treatment resistance
Psychosis Symptoms

Positive
- Delusions
- Hallucinations

Negative
- Affective flattening
- Anhedonia
- Avolition
- Alogia

Disorganized
- Speech
- Behavior
Subthreshold Psychosis Symptoms

- **Attenuated Positive**
  - Unusual thought content or referential thinking
  - Suspiciousness or persecutory ideas
  - Grandiose ideas
  - Perceptual abnormalities

- **Attenuated Negative**
  - Reduced emotional expression
  - Decreased social interest
  - Low motivation
  - Trouble thinking abstractly
  - Trouble with occupational/school functioning

- **Attenuated Disorganized**
  - Odd speech
  - Odd or unusual behavior or appearance
  - Trouble with focus and attention
  - Impairment in personal hygiene
**Figure 2.** Meta-analyses of transition risks from clinical high risk to full psychosis at different time points of follow up.
Psychosis as a Continuum in the General Population

Fig. 4. Psychosis: variation along a continuum.

J. van Os et al.
Psychosis: Complementary Lines of Research

At-Risk, help-seeking

At-Risk, population-based

Genetically informative – 22q11.2 Deletion Syndrome
The Philadelphia Neurodevelopmental Cohort

- Community based study of 9,500 children age 8-21.
- Goal of establishing national resource for investigation of relationships among genes, brain, and behavior in young people.
- Participants initially genotyped by the Center for Applied Genomics (CAG) and re-contacted.
Clinical Assessment: GOASSESS

Computerized Neurocognitive Battery (CNB)

Neuroimaging: sMRI, DTI, fMRI, ASL

PHENOTYPING

CAG

EMR

Center for Applied Genomics
Psychopathology Prevalence

- Behavior disorders most frequent, followed by ADHD, mood and anxiety
- Males: greater rates of ADHD and behavior disorders
- Females: greater rates of anxiety and mood disorders

Adapted from Merikangas et al.
A

Overall Psychopathology

GOASSESS Interview
112 Items

35 Items
Anxious-Misery

27 Items
Psychosis

25 Items
Behavioral

25 Items
Fear

B

Orthogonal dimensions of psychopathology

Kaczkurkin et al.,
Molecular Psychiatry, in press
• ~4% of youths reported psychotic symptoms
• 12.3% reported significant sub-psychotic symptoms
• Psychosis spectrum symptoms associated with
  • Reduced global functioning
  • Increased odds of depression, anxiety, behavioral disorders, substance use and suicidal ideation
PNC CNB Battery

Duration is ~1 hour
14 tests administered, measuring 5 domains
  – Executive (Abstraction & Mental Flexibility, Attention, Working Memory)
  – Episodic Memory (Verbal, Facial, Spatial)
  – Complex Cognition (Language, Non-Verbal, Spatial)
  – Social Cognition (Emotion Identification, Emotion Intensity Differentiation, Age Differentiation)
  – Sensorimotor Speed (Praxis, Finger Tapping)

99% validity of CNB data within the PNC participants
CNB assessors blind to participant clinical data or diagnosis
The Computerized Battery: Illustration of Test Stimuli and Domains

**Working Memory**
- 0-BACK: Press the spacebar when you see the letter X.
- 1-BACK: Press the spacebar when the letter you see is the same as the previous letter.
- 2-BACK: Press the spacebar when the letter you see is the same as the one before the previous letter.

**Abstraction & Mental Flexibility (PCET)**
- FOIL: Click on the object that does not belong.
- NUMBER TARGET: Remember – only press the SPACEBAR when you see the letter "X" in the upper half of the screen.

**Attention (CPT)**
- LETTER TARGET: Click on the green box.

**Emotion Recognition (ER40)**
- Happy
- Sad
- Anger
- Fear
- No Emotion

**Word Memory (CPW)**
- Reaction
- Definitely Yes
- Probably Yes
- Probably No
- Definitely No

**Face Memory (CPF)**
- Spatial Memory (SVOLT)
- Attention / Inhibition (GNG150)

**Spatial Ability (PLOT)**
- Language Reasoning (PVRT)
- Motor Speed (MOT)
- Sensorimotor Speed (SM)

**Emotion Discrimination (MEDF)**
- Which face is more happy?

**Age Differentiation (ADT)**
- Which face is older?

**Nonverbal Reasoning (PMAT)**

Gur et al., J Neuroscience Methods, 2010
Gur et al., Neuropsychology, 2012
Factorial Structure of the CNB

Note. Results are standardized such that the variance of the latent variables is 1.00. All coefficient estimates are significant with standard errors of 0.01.

Moore et al., Neuropsychology, 2014
Brain Mapping with fMRI

In-Scanner CNB

Roalf et al., Neuropsychology, 2013
THE PHILADELPHIA NEURODEVELOPMENTAL COHORT: Sex differences in neurocognitive profile across age groups

Gur et al., JAMA Psychiatry, 2014
Neurocognitive Profile of Psychosis Spectrum (PS, n=1171) Compared to No Psychosis (NP, n=3684) Age 11-21
Adolescents with Psychosis-Spectrum Symptoms have Reduced GM Volume

Satterthwaite et al., JAMA Psychiatry, 2016
Wolf et al., JAMA Psychiatry, 2015
A

Typically Developing

Psychosis Spectrum

B

Within Network Connectivity

Salience

Default Mode

C

Connectivity with Frontal Pole

Salience

Default Mode

Typically Developing

Psychosis Spectrum

Satterthwaite et al., Molecular Psychiatry, 2015
Auditory hallucination

Clinical Dimension Score

Brain Connectivity Score

\( r = 0.71 \)

\( p < 0.001 \)
The role of environment

<table>
<thead>
<tr>
<th>NEIGHBORHOOD</th>
<th>Females</th>
<th>Males</th>
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<tbody>
<tr>
<td>Poor/Uneducated</td>
<td>-0.3</td>
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<tr>
<td>Average</td>
<td>-0.25</td>
<td></td>
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<tr>
<td>Wealthy/Educated</td>
<td>-0.2</td>
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<tr>
<td></td>
<td>-0.15</td>
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<tr>
<td></td>
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</table>

PSYCHOSIS RISK SCORE
Symptom persistence predicted by baseline

- higher severity of subclinical psychosis
- lower global functioning
- prior psychiatric medication

Youths classified as resilient nonetheless exhibited comparatively higher symptom levels and lower functioning at both baseline and follow-up than TD.
Fig. 1. Convergence of two research traditions—treatment and high risk—on the schizophrenia prodrome. Source: Cornblatt et al. [2002].

From Cornblatt et al., 2002 Am J Med Gen (Neuropsychiatric Genetics), 114: 956-966
Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

John M. Kane, M.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Kim T. Mueser, Ph.D., David L. Penn, Ph.D.,
AJP in Advance (doi: 10.1176/appi.ajp.2015.15050632)

FIGURE 2. Model-Based Estimates of Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score

A. QLS total score

B. PANSS total score

(a) PANSS=Positive and Negative Syndrome Scale.
(b) Treatment by square root of time interaction, p=0.015.
(c) Treatment by square root of time interaction, p=0.016.
Early psychosis: A unique opportunity for intervention

Decreasing duration of untreated psychosis is high priority

Prevention of chronic illness and disability

Specialized phase specific intervention services
• may improve symptoms and clinical course
• increase retention in treatment program
• improve outcome
• reduce cost of treatment
Christian Kohler, M.D.

Monica Calkins, Ph.D.

Paul Moberg, Ph.D.

Raquel Gur, M.D. Ph.D.

Anup Sharma, M.D.

Lyndsay Schmidt, M.A.

Kelly Peters, M.A.

Bridgette Patton, B.A.
Eligibility

- **Key Inclusion Criteria**
  - Early warning signs of psychosis or onset of psychosis within the past 3 years
  - Males and females between the ages of 14-34

- **Key Exclusion Criteria**
  - Severe medical illness
  - Diagnosis of intellectual disability
  - Onset of psychotic disorder greater than 3 years
  - Severe substance use disorder interfering with ability to complete study procedures, based upon clinician's review
Program Overview

– Community Outreach
– Assessment
– Recovery Planning
– Cognitive Behavioral Therapy (CBT)/Case Management
– Psychopharmacology
– Cognitive Remediation
– Multi-family Group Psychoeducation
– Occupational Intervention
Patients Enrolled: 125

Age Range yrs 14-34 (Mean = 21.7)

- Male: 84%
- Female: 16%

- Caucasian: 52%
- African American: 30%
- Asian: 7%
- Hispanic/Latino: 7%
- Other: 4%
Symptom Improvement

Beck Depression Inventory

Baseline: 18
Follow-up: 4

Baseline: 18
Follow-up: 4

Sleep Disturbance

Baseline: 5.9
Follow-up: 5.1
Functional Improvement

**Daily Activities**

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<thead>
<tr>
<th>Daily Activities</th>
<th>Baseline</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Work</td>
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<tr>
<td>School</td>
<td></td>
<td></td>
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<tr>
<td>Structured Activity</td>
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<td></td>
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<tr>
<td>Unstructured Activity</td>
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</table>

**Independent Living Skills Survey (Collateral)**

<table>
<thead>
<tr>
<th>Specific Levels of Functioning (Collateral)</th>
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<tbody>
<tr>
<td>Baseline</td>
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<tr>
<td>2.7</td>
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</table>

**Specific Levels of Functioning (Clinician)**

<table>
<thead>
<tr>
<th>Specific Levels of Functioning (Clinician)</th>
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<tbody>
<tr>
<td>Baseline</td>
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<tr>
<td>183</td>
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</table>
Social Cognition in Psychosis Risk

- Evidence for impairment in this domain
- Associated with negative symptoms and poorer functional outcome
### CBT-informed social enactment training curricula for CHR youth

#### Theater Improvisation Training to Promote Social Cognition (TIPS)

<table>
<thead>
<tr>
<th>Week</th>
<th>Introduction</th>
<th>Character &amp; Body (Week 2)</th>
<th>Character, Body &amp; Body Language (Week 3)</th>
<th>Character, Intention &amp; Tension (Week 7)</th>
<th>Character Status, Conflict &amp; Story (Week 8)</th>
<th>Story Building (Week 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
<td>1st 4 sessions</td>
</tr>
<tr>
<td>1</td>
<td>Introduction</td>
<td>Class ritual</td>
<td>Class ritual</td>
<td>Class ritual</td>
<td>Class ritual</td>
<td>Class ritual</td>
</tr>
<tr>
<td>2</td>
<td>Character &amp; Body</td>
<td>Improve games designed to open people up and banish embarrassment</td>
<td>Improve games designed to open people up and banish embarrassment</td>
<td>Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want</td>
<td>Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want</td>
<td>Class ritual</td>
</tr>
<tr>
<td>3</td>
<td>Character, Body &amp; Body Language</td>
<td>Improve exercise dealing with character development</td>
<td>Improve exercise dealing with character development</td>
<td>Improve exercise that is completely physical</td>
<td>Improve exercise that is completely physical</td>
<td>Use improv skills for improvisors to generate new story</td>
</tr>
<tr>
<td>4</td>
<td>Character &amp; Intention</td>
<td>Begin working on body, and how we use our bodies to reveal our character</td>
<td>Begin working on body, and how we use our bodies to reveal our character</td>
<td>Continue working on physicalization, in particular how we can use our bodies to communicate without speaking</td>
<td>Continue working on physicalization, in particular how we can use our bodies to communicate without speaking</td>
<td>Warmup</td>
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<tr>
<td>5</td>
<td>Character &amp; Intention</td>
<td>Class ritual</td>
<td>Class ritual</td>
<td>Character's status, conflict and story</td>
<td>Character's status, conflict and story</td>
<td>Personal</td>
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<tr>
<td>6</td>
<td>Character, Intention &amp; Tension</td>
<td>Share character sketches</td>
<td>Share character sketches</td>
<td>Assignment: Write a character sketch</td>
<td>Assignment: Write a character sketch</td>
<td>Personal</td>
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<td>7</td>
<td>Character, Status, Conflict &amp; Story</td>
<td>Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want</td>
<td>Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want</td>
<td>Assignment: Write a sketch on your own</td>
<td>Assignment: Write a sketch on your own</td>
<td>%time</td>
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<tr>
<td>8</td>
<td>Story Building</td>
<td>Assignment: Go to a place where there are a lot of people. Listen to how they talk and discover if how they sound reveals anything about who they are and what they want</td>
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<td>Story Building</td>
<td>Assignment: Go to a place where there are a lot of people. Listen to how they talk and discover if how they sound reveals anything about who they are and what they want</td>
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<td>%time</td>
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<td>10</td>
<td>Mask Work &amp; Script Sharing</td>
<td>Assignment: Write a character's status, conflict and story</td>
<td>Assignment: Write a character's status, conflict and story</td>
<td>Assignment: Write a character's status, conflict and story</td>
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<td>Mask Work &amp; Script Sharing</td>
<td>Assignment: Write a character's status, conflict and story</td>
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<td>Mask Work &amp; Script Sharing</td>
<td>Assignment: Write a character's status, conflict and story</td>
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<td>Assignment: Write a character's status, conflict and story</td>
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<td>13</td>
<td>Rehearsal</td>
<td>Assignment: Do a full run-through of the play</td>
<td>Assignment: Do a full run-through of the play</td>
<td>Assignment: Do a full run-through of the play</td>
<td>Assignment: Do a full run-through of the play</td>
<td>%time</td>
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<td>14</td>
<td>Rehearsal</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
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<td>Rehearsal</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
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<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
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<td>Rehearsal</td>
<td>Assignment: Work your part</td>
<td>Assignment: Work your part</td>
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<td>%time</td>
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<td>18</td>
<td>Sharing</td>
<td>Assignment: Write your part</td>
<td>Assignment: Write your part</td>
<td>Assignment: Write your part</td>
<td>Assignment: Write your part</td>
<td>%time</td>
</tr>
</tbody>
</table>
Symptom severity change following intervention

CHANGE TIME2-TIME1

GAF  POS  NEG  DIS  GEN
Symptom severity change following intervention

- Grandiosity
- Experience of Emotions and Self
- Ideational Richness
- Odd Behavior or Appearance
- Sleep Disturbance

Symptom severity change following intervention.
Neurocognitive performance change following intervention
Strategies for Early Detection and Intervention

- Screening, education
- Establishing programs nationwide
- Complementary concomitant approaches
  - Cognitive remediation
  - Social cognition
  - Psychotherapy – CBT
  - Parents and family support
  - Medications
- Collaborative evidence-based studies
COLLABORATORS

Ruben C. Gur, PhD
Monica Calkins, PhD
Tyler Moore, PhD
Christian Kohler, MD
Irene Hurford, MD
Theodore Satterthwaite, MD
Daniel Wolf, MD PhD
David Roalf, PhD
Bruce Turetsky, MD
Warren Bilker, PhD
Christos Davatzikos, PhD
Mark Elliott, PhD
Ragini Verma, PhD
Sunny Tang, MD
J. Eric Schmitt, MD PhD

Danielle Bassett, PhD
Russell T. Shinohara, PhD
Hakon Hakonarson, MD PhD
Beverly Emanuel, PhD
Donna McDonald-McGinn, MS CGC
Elaine H. Zackai, MD

INDIVIDUALS AND FAMILIES
THE RESEARCH TEAM
SUPPORTED BY NIMH