Schizophrenia and Other Psychotic Disorders
Shortened productive lives

Source: Mental Health Report of the Surgeon General
Schizophrenia: characteristics

- 1 - 2% of population

- Cross-cultural consistency

- Onset in late adolescence/early adulthood

- More early onset cases for males and late onset cases for females

- More debilitating than any other mental disorder

- Most cases are chronic, with intermittent episodes that occur with less frequency and intensity with advanced age.

- Age of onset
  Males: between 16 and 25
  Females: Late 20’s to late 30’s
Common Misconceptions

SCHIZOPHRENIA IS NOT:

- A "split personality" or “multiple personality”

- Caused by childhood trauma, bad parenting, or poverty

- The result of any action or personal failure by the individual
Schizophrenia and Psychosis: An Overview

• **Psychosis**
  – Hallucinations
  – Delusions

• **Disturbances in:**
  – **Thought**
  – **Emotion**
  – **Behavior**

**Schizophrenia**
**Schizophreniform Disorder**
**Schizoaffective Disorder**
**Delusional Disorder**
**Brief Psychotic Disorder**
**Psychosis NOS**
**Bipolar Disorder with Psychotic Features**
**Dp with Psychotic Features**
Neural Diathesis-Stress Model of Psychotic Disorders

Inherited Constitutional Factors

Acquired Constitutional Factors e.g. Prenatal Events

Stress e.g. Life events/EE

Neuromaturational Processes

Constitutional Vulnerability

Psychotic Outcome
The Prodrome
Predicting Schizophrenia Requires a “Close-in” Approach

Premorbid Phase

Prodromal Phase

Psychosis

Schizophrenia
Positive Symptoms

Perceptual Aberrations

Confusion about what is real and what is imaginary; feeling like your mind is playing tricks on you

Feeling that people are taking special notice of you or singling you out; paranoid thinking

Feeling that your ideas or behaviors are being controlled by outside forces

Unrealistic ideas of special identity or abilities

Preoccupation with the supernatural (telepathy, ghosts, UFOs)
Negative Symptoms

- Feeling like something (emotions, thoughts, behavior) has been taken away or removed
- Wanting to spend more time alone
- Not feeling motivated to do things
- Trouble understanding conversations or written materials
- Difficulty identifying and expressing emotions
- Initially difficult to distinguish from depression
  - Longitudinal perspective is important
Disorganized Symptoms

- Trouble with attention
- Neglect of personal hygiene
- Odd appearance or behavior
- Laughing at odd or inappropriate times
- Problems with communication: vague, confused, muddled, racing or slowed speech, difficulty staying on track or getting to the point
Social/Functional Deterioration

• Social Deterioration is a key aspect of the prodrome
• If there is no social deterioration it is questionable whether the prodrome is present
Social and Role Functioning and Cognitive Changes

IQ in Schizophrenia from Premorbid to First Episode to More Established/Chronic Illness

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Effect Size</th>
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<tbody>
<tr>
<td>Premorbid</td>
<td>PRE -0.54</td>
</tr>
<tr>
<td>First Episode</td>
<td>FE -0.91</td>
</tr>
<tr>
<td>Established/Chronic Illness</td>
<td>CHR -0.96</td>
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</table>

Dysfunctional general behaviour

- Self-care
- Leisure activity
- Speed of coping with daily activities
- Communication/social withdrawal
- Lack of consideration and friction
- Behaviour in emergencies

Dysfunctional behaviour in social / occupational roles

- Participation in family life
- Relationship - emotional
- Relationship - sexual
- Parental role
- Sexual role behaviour
- Work relationships
- Interest in work place
- General responsibility / interest

IQ: 100
IQ: 85
Course of the Prodromal Period

- Roughly 25 - 35% of high-risk individuals convert to psychosis within two-years.

Cumulative survival distribution function modeling time to conversion in 291 high-risk (prodromal) participants and 134 healthy controls.

Cannon., et al., Arch Gen Psychiatry, 2008.
Treatment
Typical Intervention during the Prodrome/First Episode

• Low dose antipsychotics

• School intervention
  – Individualized Education Program (IEP)
  – Non-Public Schools (NPS)

• Psychiatric Consultation/Treatment

• Psychoeducational Multi-Family Group & Skills Groups

• Stress Management and Coping Enhancement.

• Individual Therapy and Individual Family Therapy as Needed
Treatment Benefits with Significant Side Effect Profile

- Low dose antipsychotics
- 60 prodromal cases randomly assigned to Olanzapine (5-15 mg) vs. placebo for 8 weeks
- Olanzapine was associated with significant symptom reduction at 8 weeks
  - But, also with significant weight gain (9.9 lbs).

Cognitive Therapy for Prevention

• Randomized controlled trial:
  – cognitive therapy was provided to 37 prodromal patients
  – monitoring/case management to 23 patients over 6 months.
  – Then diagnostic status was followed for one year.

• 26 sessions over 6 months, based on Beck’s general principals:
  – problem oriented
  – time-limited
  – education
  – using guided discovery and homework task
  – encourage collaborative empiricism

• Results:
  – 6% of the cognitive therapy group converted, whereas 26% of the monitoring group did.
  – The cognitive therapy reduced:
    • the likelihood of making progression to psychosis
    • the likelihood of being prescribed an antipsychotic medication.

• Trouble with attrition (42/58 finished), masking was compromised, number of participants was small, observation period was limited.

Despite an impressive halving of the rate of progression to psychosis in the drug-treated group, the study was inconclusive because of a high dropout rate — nearly half the subjects leaving the study during the year-long treatment phase.

As with the other trial, fatigue and significant weigh gain were major adverse side effects.

The hazard of conversion to psychosis for the placebo-treated patients was 2.5 times that for the olanzapine-treated patients ($p=0.09$).

Maintain a delicate balance between too much and too little stimulation

Normative Tasks of Adolescent Development

Too Little Stress: Boredom, Preoccupation with Symptoms, Stagnation

Too Much Stress: Symptoms, Overwhelmed, Need to Withdraw
In this prospective, longitudinal study, 11 recent-onset schizophrenic outpatients who met criteria for psychotic relapse or significant psychotic exacerbation during a 1-year period of standardized maintenance medication, and 19 patients who did not relapse during this follow-up period, were interviewed monthly regarding life events. As hypothesized, for relapsing patients, a significantly higher number of independent life events (those not the result of symptomatology or personal influence) occurred in the month preceding relapse. This increase was apparent relative to either the analogous month of a “nonrelapse” period in the same patient or the average number of independent events per month during a 1-year standardized medication period for nonrelapsing patients. The methodological advances of this design as well as the consistency of these findings with those of previous retrospective studies supports the hypothesis that life events may sometimes “trigger” schizophrenic episodes.
Stress Management: Enhanced Coping

Observe and Describe Emotions

Reduce Vulnerability to Negative Emotions

Build Positive Experiences

Self Soothe the Five Senses
Adolescent/Young Adult Skills Group

• Every 2 weeks for 90 minutes

• 1st meeting: introductions, self-definition, and goal setting

• 2nd meeting on: skills training - stress identification and management, problem solving, relaxation training, pleasant events scheduling, emotion regulation and distress tolerance, communication skills, etc.
• This **Expressed Emotion (EE)** research and Family Therapy is also relevant to psychosis in adults, but due to time, I will discuss it in the context of the prodrome. Family therapy is a highly effective for Psychosis.

Multifamily Group Meetings

• Every 2 weeks for 90 minutes

• 1st meeting: “Getting to know you”
  – Share personal information and begin to develop a sense of who family members are as people

• 2nd meeting: “Experience with symptoms”
  – Share personal stories re: impact of symptoms
  – Continue to build relationships
Neurotoxicity of Psychosis

Enduring Effects of Untreated Psychosis

- **Short DUP, N=31** (treatment <1 year after psychosis onset)
- **Long DUP, N=22** (treatment ≥1 year after psychosis onset)

~40% Relapse

~80% Relapse

# Months after treatment entry

Summary of Priorities and Challenges for Early Intervention:

• While treatments are showing progress in reducing symptoms, ameliorating the course, and potentially preventing illness onset, there are significant issues relating to side-effects & drop-out, and cost.

• The nature of prodromal populations (e.g., socially anxious, avoidant, paranoid) make treatment adherence costly and difficult.
  – Teenagers and weight gain!

• High-risk individuals have a conversion rate of 35% but we have no idea which of the group fits into this category.
Benefits of Early Identification

- Identifying the subgroup of high-risk participants most likely to convert in the immediate future can help to:
  
  - Focus limited resources and reduce false-positives (significant side-effects).
  
  - Reduce untreated time, improve course, and potentially prevent onset.
  
  - Establish preemptive relationships with treatment providers.
  
  - Utilize individual therapy before cognitive decline and serious symptoms reduce efficiency and effectiveness.
  
  - Train families to reduce EE, and provide psychoeducation in enlist member to help track symptoms.
Biomarker Research for Early Intervention

**Inherited Constitutional Factors**
- e.g. Prenatal Events

**Acquired Constitutional Factors**
- e.g. Prenatal Events

**Stress**
- e.g. Life events/EE

**Neuromaturational Processes**

**Constitutional Vulnerability**

**Psychotic Outcome**

- Motor Signs
- Brain Signs
- Prenatal Signs
- Cognitive Signs
30 UHR and Control Participants Returned for an Assessment After One Year

The thalamus acts as a relay between a variety of subcortical areas and the cerebral cortex. Every sensory system (with the exception of the olfactory system) includes a thalamic nucleus that receives sensory signals and sends them to the associated primary cortical area.

Given the role of the thalamus in both FSC and CCTC circuits, this finding is particularly relevant.
Study 4d: Sensory Integration Deficits Predict Cerebellar-Thalamic Tract Development and symptoms in UHR (33) and Healthy Youth (35)
Cool New Treatment Development
Cognitive Remediation

- Developed to “work out” the parts of the brain that are disrupted in schizophrenia

- Patients engage in cognitive tasks (behavioral or computer programs)

- Tasks designed for Traumatic Brain Injury and Learning Disorder cases, not for schizophrenia
Rationale

• Verbal learning and memory disrupted in schizophrenia
  – Abnormalities in fronto-temporal cortical networks during verbal working memory, encoding, and retrieval

• More basic auditory processing also disturbed in schizophrenia, which is crucial for successful verbal learning and memory

• Cognitive training program that targets early auditory processing and verbal working memory

• Exercises continuously adjust the difficult level, so user always responds correctly 85% of the time
Examples:

- Exercise 1: users have to make gradually more difficult distinctions between different auditory frequencies, which are presented at increasing or decreasing time intervals.

- Exercise 2: users have to distinguish between two difficult to distinguish syllables.

\(^{a}\) The learner must perform a time-order judgment task and identify each of two successive frequency modulation sweeps as either “up” (sweep on left) or “down” (sweep on right). Sweep duration and interstimulus interval are modified parametrically as the learner’s performance improves.
Patients showed significant improvements in global cognition, verbal learning and memory, and verbal working memory. No affect on symptoms.
Long Chain Omega 3 Polyunsaturated Fatty Acids
My new study
Medial-Temporal Structures

- If the structures are so important in terms of being susceptible to both endocrine and neuro-reorganizational affects, and serving as an interaction point between susceptibility and environmental stress, then what do we know about them?

- Previous studies are inconsistent:
  
  - Cross-sectional studies have differed about if atrophy occurs before or after the first episode (Phillips et al., 2002; Buehlmann et al., 2010).

  - Prospective studies have also differed: some find when comparing those who do and don’t convert have smaller, larger or no baseline differences. (Lawrie et al., 2002; Pantelis et al., 2003; Wood et al., 2005; Job et al., 2005; Velakoulis et al., 2006; Wood et al., 2010; Bogwardt et al., 2008)
    - Issues with low resolution, varying methods, and wide age-ranges (not adolescence) as well as medications
Prospective view from ongoing study in medication-naïve teens

- A total of **97** (49 UHR, 48 Controls) (mean age = 18.26; SD = 2.33) at baseline and **44** (24 UHR, 20 Control) 12 months later.
  - MRI (3T)
  - Clinical Interviews (SIPS/SCID)
  - Note about attrition

- Significant differences between groups at both time points at baseline, \( t(95) = -2.95, p < .01 \) and follow-up \( t(42) = -3.08, p < .05 \).
- Trend level Integration, \( F(1,42) = 2.13, p = .07 \).
Shape Analysis Reveal’s a Subtle Change that is tied to progression on symptoms

• A total of 80 participants (38 UHR and 42 control) (mean age=18.82, SD=1.70) the. A total of 38 at 1 year visit (19 UHR and 19 Control).

• UHR group showed a significant inward shape transformation from the standard structure when compared with the control group, $t(78) = -3.22$, $p \leq .001$.

• Greater inward transformation was significantly related to more severe positive symptoms $r = -.30$, $p \leq .05$.

• Baseline shape estimates of the left venral posterior hippocampus accounted for 11% of the variance of 12-month positive symptoms, $F(1,16)=4.75$, $p < .01$, $\beta = -.35$, $p \leq .05$, where greater inversion predicted a poorer course of illness.

Left Ventral Posterior Hippocampus:
UHR mean = -.21 (.60)
Control mean = .19 (.50)

Dean et al., under review, Psychological Medicine
• We know there is abnormal development but what can we do about it?

Kim et al., 2002: Photomicrographs of BrdU-positive cells (a marker of DNA replication which is used to highlight neurogenesis) in the hippocampus (SGZ-dentate gyrus). A control group; B exercise group.
Activity Level and Hippocampal Health

- A growing body of evidence suggests that moderate to vigorous activity can affect quality of life, symptoms, memory, and brain structure in patients with schizophrenia (Wolf et al., 2011; Erickson et al., 2011; Farrow et al., 2005; Pajonk et al., 2010).

- Compelling findings with exercise trials and neurogenesis in animal models, other clinical populations, and one study of schizophrenia patients (Pajonk et al., 2010).

- The prodrome may represent a viable period for early intervention.
<table>
<thead>
<tr>
<th></th>
<th>Healthy Control</th>
<th>Ultra High-Risk</th>
<th>Grand Total</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>12(44%)</td>
<td>18(62%)</td>
<td>30(54%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Females</td>
<td>15(56%)</td>
<td>11(38%)</td>
<td>26(46%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>29</td>
<td>56</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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</tr>
<tr>
<td>Mean Years (SD)</td>
<td>17.63(2.70)</td>
<td>18.52(1.90)</td>
<td>18.09(2.34)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Parent Education</strong></td>
<td></td>
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<tr>
<td>Mean Years (SD)</td>
<td>15.26(2.93)</td>
<td>14.07(4.86)</td>
<td>14.65(4.04)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
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<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>.93(.54)</td>
<td>11.72(4.86)</td>
<td>6.52(6.54)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>.81(1.39)</td>
<td>11.82(7.49)</td>
<td>6.52(7.77)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td>Avolition</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>.15(.60)</td>
<td>2.41(1.59)</td>
<td>1.32(1.66)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td>Occupational Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>.26(.59)</td>
<td>2.38(1.81)</td>
<td>1.36(1.73)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td><strong>Total Activity Counts</strong></td>
<td>458.17(222.76)</td>
<td>364.30(177.31)</td>
<td>409.10(203.51)</td>
<td>$p = 0.06$</td>
</tr>
<tr>
<td><strong>Hippocampus</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Right Mean % ICV (SD)</td>
<td>.28(.02)</td>
<td>.26(.02)</td>
<td>.27(.02)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td>Left Mean % ICV (SD)</td>
<td>.28(.03)</td>
<td>.26(.03)</td>
<td>.27(.03)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td><strong>Parahippocampal Gyrus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Right Mean % ICV (SD)</td>
<td>.14(.02)</td>
<td>.13(.01)</td>
<td>.13(.02)</td>
<td>$p \leq 0.01$</td>
</tr>
<tr>
<td>Left Mean % ICV (SD)</td>
<td>.15(.02)</td>
<td>.14(.02)</td>
<td>.14(.02)</td>
<td>$p = 0.13$</td>
</tr>
</tbody>
</table>

Note: not significant (N.S.); Positive and negative symptoms as well as Avolition and Occupational Functioning scales reflect total sums from domains from the Structured Interview for Prodromal Syndromes (SIPS); Global Role Functioning reflects scores on the Global Functioning Scale- Role (GFS-R); Brain volumes represent the respective structure divided by total intracranial volume. Brain volumes represent the respective structure divided by total intracranial volume.
FIGURE 1. Group Differences in Activity Between Ultra High-Risk Youth and Matched Controls

Note: Activity represents the proportion of time awake spent in four levels of activity based on actigraph counts per minute. * Indicates a statistically significant group difference, $p \leq .05$; † Indicates a trend level difference $p \leq .15$; Error bars represent...
Furthermore, activity was associated with performance in verbal fluency ($r = .35, p \leq .01$), trail making ($r = .28, p \leq .05$), and verbal learning ($r = .25, p \leq .05$).
Translation: an exercise intervention
Phase I-
• 1) Which of two conditions of exercise intensity and frequency
  – Moderate: 65% intensity of VO2max /2 sessions a week
  – Vigorous: 85% intensity of VO2max /3 sessions a week
provides the optimal intervention to improve cardiovascular fitness in UHR adolescents. (n=18)
• 2) If changes in aerobic fitness are associated with medial temporal cell growth (i.e., volume and shape), improvements in cognitive function (e.g., episodic memory), and symptoms/functioning.

Phase II-
• RCT with exercise-UHR, wait-listed UHR and active Healthy Controls (n=75)

Exploratory Aim
• A) If the intervention has an influence on course of illness and conversion rates.

V02 Max is calculated before and after the trial as well as at long-term follow-ups (to determine if gains are maintained)
Conclusion

- Data collection is ongoing (-2020) and findings from phase 1 and phase 2 will be presented as they become available (2017/2019).

- If the trial proves to be feasible, and the results suggest improvement on any of the key domains, the next stage will be an multisite investigation.

- Thus far, the UHR participants are showing good adherence and both conditions are associated with good tolerability.

Participants exercise 2-3x weekly at moderate to moderate-vigorous activity.