Prevention of Schizophrenia
An idea whose time has come

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“Advances in health care are due to the application of existing knowledge as much as the discovery of new knowledge”

Carlton Gadjusek
World Bank Study of the Global Burden of Disease: Disease Burden by Age

World Bank Study
World Bank Study of the Global Burden of Disease

Direct Costs of Mental Illness in U.S.: $99 billion
Mental Health Care of the Past

E. Kraepelin
1919
Longitudinal Course of Schizophrenia

Stages of Illness

Premorbid  Prodromal  Onset/Progression

Healthy

Worsening Severity of Signs and Symptoms

Puberty

First Break

Deterioration

Chronic/Residual

Gestation/Birth 10 20 30 40 50

Years
Gray matter volume changes in the course of schizophrenia

Courtesy of Jay Giedd and Paul Thompson et al
Pathophysiology and Neuropathology of Schizophrenia

adapted from Glantz and Lewis
Neurodevelopmental Versus Neurodegenerative

Can we change the course or prevent the illness?
Antipsychotic Drugs:
What they can and can’t do

- Suppress psychotic symptoms
- Prevent psychotic relapse
- Refractory psychotic symptoms
- Negative symptoms
- Cognitive symptoms

Prevent progression
Natural History of Schizophrenia
Rationale for Early Detection and Intervention

Stages of Illness

- Premorbid Prodromal Onset/Progression
- Chronic/Residual End-Stage

Healthy

Worsening Severity of Signs and Symptoms

Gestation/Birth 10 20 30 40 50 Years

Abnormal Brain Development
   - No Sxs

Puberty
   - Neurochemical Dysregulation
   - Psychotic Sxs

Years
   - 30
   - 40
   - 50

Neurodegeneration
   - Psychotic Sxs
   - Negative Sxs
   - Cognitive Sxs

Margin of Prevention

Elyn R. Saks

Nathaniel Ayers
Dr. Elyn R. Saks from “Charlie Rose: The Brain Series” (June 22, 2010)
Limitations of Existing Interventions

• Long Duration of Untreated Illness

• Inadequate Implementation

• High Attrition Rates
Can any treatment put Humpty Dumpty back together again?
Regenerative Drugs that Restore and Enhance Neural Connectivity

BDNF, ERKs, Bcl-2

Downregulation PKC isozymes

Adapted from H. Manji
An Ounce of Prevention is Worth a Pound of Cure

- Ben Franklin
Dwight D. Eisenhower
## Diagnosis and Rx of Coronary Artery Disease

### Stage 1: Presymptomatic
- Family hx
- Genes
- Stress EKG
- Plasma biomarkers
- Diet
- Exercise
- Statin
- ASA

### Stage 2: Early symptoms
- Stress thallium
- Stress EKG
- ECHO

### Stage 3: Late symptoms
- EKG
- Enzymes
- Angiogram
- Medications
- Angioplasty
- Surgery
- Rehab

Adapted from T. Insel
# Diagnosis and Rx of Schizophrenia

## Stage 1: Presymptomatic
- Family hx
- Cognitive deficits?
- Biomarkers?

## Stage 2: Early Sxs
- Odd thoughts
- Drug abuse
- Social impairment

## Stage 3: Late Sxs
- Psychosis
- Cognitive deficits
- Functional deficits

### Rx
- Antipsychotics
- Psychotherapy
- Rehab

Adapted from T. Insel
Can Treatment Prevent the Onset of Mental Illness?

**Stages of Illness**

- Premorbid
- Prodromal
- Onset/Progression
- First Break
- Deterioration
- Chronic/Residual

**Healthy**

**Worsening Severity of Signs and Symptoms**

- Gestation/Birth
- Puberty

<table>
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<th>Years</th>
<th>10</th>
<th>20</th>
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Prediction of Psychosis in Youth at High Clinical Risk - NAPLS

• OUTCOMES

- Risk of conversion 35% during f/u period
- 5 features improved prediction: genetic risk for schizophrenia, decline in function, unusual thought content, suspiciousness, social impairment, substance abuse

MAJOR RESULTS


Cumulative survival distribution function modeling time to conversion to psychosis in 291 clinical high-risk (prodromal) patients and 134 demographically comparable normal control subjects (dashed line).
RCTs of Interventions to Prevent Psychosis

- Randomized, unblinded comparison of risperidone+therapy vs TAU (McGorry et al 2003)
- Randomized unblinded comparison of cognitive behavioral therapy (Morrison et al 2004)
- Randomized, double blind comparison of olanzapine vs PBO (McGlashan et al 2006)
- Randomized double blind comparison of omega-3 fatty acid vs PBO (Amminger et al 2010)
Time to Conversion to Psychosis

Kaplan-Meier estimates of the risk transition from the at-risk states to psychotic disorder in patients assigned to $\omega$-3 fatty acids or placebo ($P<0.007$).

Amminger GP, et al., *Arch Gen Psych* 2010; 67(2):146-154
“We want to know how to split clearly between the people who are having troubles in living and those who are at grave risk of psychosis”

- Harry Stack Sullivan (1938)
“What do you mean ‘Your guess is as good as mine’? My guess is a hell of a lot better than your guess!”
# Utility of a Biomarker to Diagnose Disease

<table>
<thead>
<tr>
<th>Diagnosis = Negative</th>
<th>Diagnosis = Positive</th>
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<tbody>
<tr>
<td>Test Result = Positive</td>
<td>False Positive</td>
<td>True Positive</td>
</tr>
<tr>
<td>Test Result = Negative</td>
<td>True Negative</td>
<td>False Negative</td>
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</tbody>
</table>

- **Specificity:** $\frac{TN}{TN + FP}$
- **Sensitivity:** $\frac{TP}{TP + FN}$
Gray matter volume changes in the course of schizophrenia

Courtesy of Jay Giedd and Paul Thompson et al
Diagnosing Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Key feature</th>
<th>Imaging</th>
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<td>Normal</td>
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<td>Cell sickness stage</td>
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<td>Functional imaging</td>
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<tr>
<td>Neuropil structural change</td>
<td><img src="image" alt="Neuron" /></td>
<td>Volumetric Imaging</td>
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Adapted from S. Small

COLUMBIA PSYCHIATRY
Diagnosing Disease in the Hippocampus

Adapted from Schobel, Small et al.
Diagnosing Disease in the Hippocampus

Adapted from Schobel, Small et al.
High Risk → First Episode

Hipp

OFC
BA11

DLPFC
BA46
Human CBV phenotype replicated in rodent model

Adapted from Schobel, Moore, Small et al.
Modulation of NMDA antagonist increases in extracellular glutamate in CA1

CA1 Glutamate Change
Ketamine challenge 30/kg ↓

Adapted from Schobel, Moore, Small et al
Take Home Messages

• Schizophrenia derives from a genetically mediated neurodevelopmental diathesis and are progressive

• Symptoms are expressed due to dysregulation of dopamine and glutamate

• The clinical deterioration and residual morbidity are due to structural pathology in frontal and temporal regions

• Medications target psychosis and can prevent progression

• Early detection and intervention is effective in preventing or limiting illness but requires better diagnostic methods, interventions and models of service delivery
Obstacles to Progress in Mental Illness Research

- Funding
- Funding
- Funding
Obstacles to Progress in Mental Illness

• STIGMA
Obstacles to Progress in Mental Illness Research Anti-Psychiatry Coined in 1967 by David Cooper
Thank You for your attention