First Episode Psychosis

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Learning Objectives

Understand
- biological and genetic factors associated with risk of schizophrenia
- how comprehensive treatment may impact the course of illness
- conventional and alternative/complimentary treatment approaches
Case: Jim  
October, 2005

- Above average high school student, on tennis team, small group of close friends.
- Did well Freshman year at University
- Early fall Sophomore year Jim’s parents are called by hospital social worker, with “bad news”, Jim has schizophrenia.
- Parents fly out, meet with Jim on the unit. Jim is convinced he has a chip in his head, communicating with aliens, when he meets with his parents he accuses them of being “imposters”.
- The unit social worker meets with parents, informing them that Jim has schizophrenia, that they should be prepared for the fact that he will be disabled by this illness
WHAT WE KNOW ABOUT CAUSE AND COURSE
"You made that diagnosis just to be mean."
Genetics

- Schizophrenia runs in families, but...
- 70% of persons have no close relative with schizophrenia
- Multiple common genetic variants that increase schizophrenia risk by ~5-10%.


Unexpected pathways:
- Immune system
- Glutamate receptors
- Neurodevelopment
Genetics

- Rare “copy number” variants
  - Found in ~ 2.4% of schizophrenia and 0.5% of unaffected persons
  - Associated with elevated paternal age
  - Penetrance:

In utero environmental factors influencing schizophrenia vulnerability

- Maternal infection: ~2–7-fold increase in risk\(^1,^2\)
  - Increased incidence following epidemic (esp. influenza) patterns
  - Maternal cytokine levels associated with subsequent risk
- Maternal stress: ~1.5-fold increase in risk\(^1,^3\)
- Maternal nutrition
  - Maternal starvation: 2-fold increase in risk\(^1,^4\)
  - Micronutrients:\(^1\)
    - Vitamin D deficiency\(^5\) (and the further away from the equator a person lives, the greater the risk)
    - Maternal folate deficiency (elevated homocysteine)
    - Maternal low iron
- Maternal diabetes: ~3-fold increase\(^6\)
- Hypoxic injury at birth: ~2-fold increase\(^1,^7\)

Developmental factors in childhood influencing psychosis risk

• Childhood encephalitis: 1 7–8-fold

• Childhood emotional trauma: 2 2–3-fold

• Status as immigrant: 2.7-fold increase in risk
  – Offspring of first degree relatives: 4.5-fold increase

• Urban environment: 1.9-fold increase in risk; 4-fold risk of hospitalisation for schizophrenia

• Marijuana use (early/heavy): 4-fold increase in risk

Marijuana and Psychosis Risk

- Use in early adolescence or heavy use later in life increases risk of a psychotic illness 4-fold
  
  • ~ 4% of marijuana users develop schizophrenia
  
  • ~ 10–14% of schizophrenia may be related to marijuana use

- “Kind” of schizophrenia related to marijuana use associated with less severe negative symptoms and cognitive impairments

- Continued use once psychosis develops associated with relapse and worse functional outcomes
Environment Impacts Prognosis

Symptomatic and Functional Prognosis at Two Years After a First Episode Schizophrenia

- Continuous or episodic, no complete remissions

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<tr>
<th>Developed Countries* (n=603)</th>
<th>Developing Countries** (n=467)</th>
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<td>60%</td>
<td>30%</td>
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*Czech Republic, Denmark, Ireland, Japan, Russia, UK, USA

**Columbia, India, Nigeria

Jablensky 2000
Environment Impacts Prognosis

Symptomatic and Functional Prognosis at Two Years After a First Episode Schizophrenia

- Remitting, complete remissions

Developed Countries* (n=603)
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*Czech Republic, Denmark, Ireland, Japan, Russia, UK, USA
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Jablensky 2000
Time from Onset of Psychosis to Onset of Treatment

- Treatment Delays Are Common
  - On average, 1 year or more elapses from onset of psychosis to onset of treatment
  - Why the delay?
    - Early stage of psychosis clinically different
      - Patients look more “more normal”
      - Less severe negative symptoms
      - Substance use, school failure, behavioral problems may obscure underlying psychosis
    - Symptoms recognized but misinterpreted
    - Stigma

The Longer the Treatment Delay, the Worse the Prognosis

- Greater the chance of aggression and violence prior to first treatment contact
- Social and role function derailment
- Longer time to recovery
- Less likely to recover from first episode
- Chronic symptoms more severe and worse social and role function
- Greater risk of brain tissue loss

Variable Outcomes in Schizophrenia

• After a first episode, positive symptoms usually remit
• Without maintenance antipsychotic medication, most relapse
Relapse after Treatment of a First Psychosis Episode: Naturalistic Studies

- Gitlin 2001 (7 years)
- Robinson 1999 (5 years)
- Prudo & Blum 1987 (5 years)
- Robinson 1988;1992 (5 years)
- Kane 1982 (3.5 years)
- Rajkumar & Thara, 1989 (3 years)
- McCreadie 1986 (2 years)
- Zhang 1994 (1.5 years)
- Linszen 1994 (1.5 years)
- Rabiner 1986 (1 year)
- Zhang 1994 (1.5 years)
- Linszen 1994 (1.5 years)
- Crow 1986 (2 years)
Variable Outcomes

- Most patients experience positive symptom remission after a first episode
- Without maintenance antipsychotic medication, most relapse
- Relapse is associated with symptomatic, functional, and brain progression
Normal brain maturation

Gogtay et al. PNAS 2004;101(21):8174–8179
Normal brain maturation
FE Schizophrenia: Change in brain volume over 6 months

axial slice

midsagittal

Sarang Joshi, Matthieu Jomier, Guido Gerig,
Fluid Warping baseline-follow-up after
Intensity Calibration
FE Schizophrenia: Change in brain volume over 6 months

Sarang Joshi, Matthieu Jomier, Guido Gerig,
Fluid Warping baseline-follow-up after
Intensity Calibration
Why Does the Brain “Shrink”?

- Disordered synaptic plasticity
- Loss of glia

Disrupted integrity of white matter

Associated with trauma history and impaired stress reactivity

Do Antipsychotics Contribute to Gray Matter Loss?

All Antipsychotics, size of circle reflects relative sample size in study.

Mean Daily Antipsychotic Dose Administered During Scan Interval
(chlorpromazine equivalents)

P=0.028
Do Antipsychotics Contribute to Gray Matter Loss?

Any treatment with “typical” antipsychotics, size of circle reflects relative sample size in study.

Mean Daily Antipsychotic Dose Administered During Scan Interval
(chlorpromazine equivalents)

P=0.003
Do Antipsychotics Contribute to Gray Matter Loss?

Only treated with “atypical” antipsychotics, size of circle reflects relative sample size in study.

clozapine  olanzapine  quetiapine  risperidone  ziprasidone  multiple-atypicals

P=0.003

Mean Daily Antipsychotic Dose Administered During Scan Interval
(chlorpromazine equivalents)
Variable Outcomes

• Relapse
  – Most patients will relapse if antipsychotics are discontinued
  – Interferes with normal psychosocial development
  – Interferes with educational and vocational achievements
  – Risk of harm to self, others, or property higher during active psychosis
  – Risk of involuntary hospitalization increases
  – Prognosis may be negatively impacted

• Some people have worse schizophrenia than others
  – 10-15% highly treatment resistant
  – 10-15% benign course
Most but not all patients have a recurrent illness

- 207 persons with first episode schizophrenia
- 24 had only a single episode in 7.5 years
- Predictors* of a single episode included shorter duration of untreated psychosis and more rapid time to response to medication
- Single episode patients all stopped taking antipsychotic medication during follow-up period**

*Including only predictors that survived adjustment for multiple testing; **Personal communication Alvarez-Jimenez

What we knew in 2005
Variable Outcomes

• Most patients will have symptomatic recovery from a first episode.
• Most patients elect for a trial off of antipsychotics, most experience multiple relapses
  – Interferes with normal psychosocial development
  – Interferes with educational and vocational achievements
  – Risk of harm to self, others, or property higher during active psychosis
  – Risk of involuntary hospitalization increases
  – Prognosis may be negatively impacted

• Some people have worse schizophrenia than others
  – 10-15% highly treatment resistant
  – 10-15% benign course

• Long-term outcomes: variable, but most show less than 20% have full recovery
  – Almost all VA schizophrenia patients are disabled

• Risk of suicide is high (~5-6%)

Harvey et al. Functional impairment in people with Schizophrenia: Focus on employability and eligibility for disability compensation
University of North Carolina at Chapel Hill Outreach and Support Intervention Services (OASIS)

- In operation since 2005*
- Foster sustained recovery from early psychosis
  - Translate science to practice
  - Translate practice to science
- Increase public understanding of psychotic disorders
- Promote early identification of psychosis

*Funded by the KB Reynolds and Duke Endowment Foundations; *Supported by the citizens of North Carolina
% of OASIS patients with good and excellent functioning as measured by the GAF score
OASIS Patient Outcomes

• 23% on Disability & Medicaid
  – 41% of those on disability are working or in college
  – Over half applied for disability to qualify for Medicaid

• Two persons committed suicide
Treatment Philosophy

• “Psychosis” and Schizophrenia-spectrum disorders are heterogeneous
  – Symptom characteristics
  – Etiology
  – Course

• People who develop “psychosis” and schizophrenia-spectrum disorders are heterogeneous
  – Experience (especially with the illness)
  – Personality
  – Culture
  – Resources
Treatment Philosophy

• Treatment interventions must be individualized
  – Stage of illness
  – Stage of person

• Treatment interventions must be multimodal
  – Address symptoms
  – Address function
  – Address meaning
Interventions

• Multidisciplinary Team Approach
  – Medication Management
    • Collaborative model
    • Adherence/insight addressed with motivational interviewing
    • Long-acting injectable first choice
    • Clozapine option after 2-3 medication failures
    • Treat-to-Target
    • Alternative/complimentary treatments
Redox and Free Radicals

• Includes reactive oxidative species and nitric oxide free radicals$^{1,2}$
• Highly reactive molecules generated during normal metabolic processes$^3$
• Generated during metabolism of neurotransmitters$^3$
  – Dopamine
  – Glutamate
• Neutralized in the body by a host of antioxidants$^{4,5}$
  – Endogenous (eg, glutathione)
    • Dietary supplements that increase glutathione levels: n-acetylcysteine, S-adenosylmethionine, alpha lipoic acid, vitamin D)
  – Exogenous (eg, vitamins E and C, flavonoids, niacin, lipoic acid, carotenoids)

Oxidative Stress

Normal happy molecule

Loss of an electron

Leaves behind a hole, it needs to be filled! The free radical goes crazy trying to "feel whole" again.

Free radical accepts the new electron

Antioxidant has an electron to donate

Complete again, the free radical is neutralized!
By-product normal metabolism

Smoking/Pollution

Poor nutrition

Stress

Sun/Radiation

Other diseases

Schizophrenia

Aging

Diabetes

Heart Disease

Diabetes
Antioxidants And Oxidative Stress

• Oxidants are neutralized in the body by a host of antioxidants\(^4,5\)
  – Produced by our body (eg, glutathione, uric acid, melatonin, etc.)
  – From food and supplements (eg, vitamins E and C, flavonoids, niacin, lipoic acid, carotenoids)

High Oxidative Stress in Schizophrenia

• Levels of endogenous antioxidants, especially glutathione, are low\(^1\)

• Levels of free radicals are high\(^1\)

• Mitochondrial function is impaired\(^1\)

• High dopamine levels lower endogenous antioxidants\(^1\)

• Animal models suggest oxidative stress can cause many of the abnormalities found in schizophrenia\(^2\)

• Glutathione depletion results in NMDA receptor hypofunction\(^2\)

NMDA Tunes Dopamine Tone in Brain

- Overactivation
- Normal
- Hypoactivation

NMDA Tunes Dopamine Tone in Brain

- Overactivation
- Normal
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Glutathione tunes the NMDA receptor “up”

Glutathione tunes the NMDA receptor “up”
N-Acetyl Cysteine: Clinical Trial

- **Rationale**
  - N-acetyl cysteine is a glutathione precursor, oral administration increases glutathione levels

- **Subjects**: 140 subjects with schizophrenia

- **Design**: 24-week, randomized, double-blind, placebo-controlled augmentation on current antipsychotic

- **Treatment**: 1000 mg BID N-acetyl cysteine

- **Outcomes**: N-acetyl cysteine augmentation is associated with reduced total ($P = .009$), negative ($P = .028$), and general psychopathology

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N-Acetyl Cysteine: Clinical Trial

- **Rationale**
  - N-acetyl cysteine is a glutathione precursor, oral administration increases glutathione levels

- **Subjects**: 42 subjects with schizophrenia, acutely psychotic

- **Design**: 8-week, randomized, double-blind, placebo-controlled augmentation on current antipsychotic

- **Treatment**: 1000 mg BID N-acetyl cysteine

- **Outcomes**: N-acetyl cysteine augmentation is associated with reduced total ($P = .006$), negative ($P = .001$), and general psychopathology ($P = .005$), not for positive symptoms ($p = .42$)
  - No adverse effects were reported

Interventions

- Multidisciplinary Team Approach
  - Medication Management
    - Collaborative model
    - Adherence/insight addressed with motivational interviewing
    - Long-acting injectable first choice
    - Clozapine option after 2-3 medication failures
    - Treat-to-Target
    - Alternative/complimentary treatments discussed
  - Individual therapy
    - Engagement in treatment
    - Disease management/education
    - Address meaning of psychosis to individual
    - Substance use
    - Stress reactivity
STRESS REACTIVITY, RESILIENCE, AND PSYCHOSIS
Mobilizing Our Bodies for a Challenge

Limbic System:
Threat Appraisal
Mobilizing Our Bodies for a Challenge

Sympathetics: Signal threat

Parasympathetics: Signal that “all is well”
Mobilizing Our Bodies for a Challenge

• Threat/Stress
  – Essential body functions prioritized
  – Energy systems mobilized
  – Immune system prepared for injury and infection
  – Brain on “auto-pilot”

• All is well
  – Repair/restoration prioritized
  – Immune system in surveillance mode
  – Brain on social engagement, thinking things through

• Chronic threat/stress
  – Repair/restoration neglected
  – Immune system: In a pro-inflammatory state
  – Metabolism dysregulated
  – Brain dysregulated
Chronic stress is bad for the brain!

• Cognitive function is impaired (foggy brain)
• Brain “shrinks”
• Aging accelerated!
• Related to:
  – Hormonal imbalance (like cortisol)
  – Chronic inflammation
  – Oxidative stress
  – Impaired vagal tone
Well-Regulated Immune System Required for Normal Brain Function

• Bidirectional regulation:
  – Brain regulates immune and hormonal systems
    • Hypothalamus Hormones
    • Vagus Immune Reflex
  – Body regulates brain;
    • Immune cell signals (cytokines)
    • Vagus nerve transmits signals from organs
  – Influence behavior (e.g. sickness syndrome)
  – Regulate the brain’s immune cells, microglia, level of activation, that influence brain plasticity

Well-Regulated Immune System Required for Normal Brain Function

• Immune-deficient mice:
  – cognitive impairments that are improved with immune cell transplantation
  – impaired resilience to stress that is improved with immune cell transplantation
  – Impaired neurogenesis that is improved with immune cell transplantation

• Offspring of mothers that were immune-activated during pregnancy:
  – altered immune cell populations
  – behavioral abnormalities
  – brain plasticity impairments
  – brain structure changes
  – **Behavior, brain and immune alterations reversed with bone marrow transplantation from normal mice**

Well-Regulated Immune System Required for Normal Brain Function

• Better neurocognitive test performance in healthy seniors associated with a well-regulated immune system
• Healthy humans exposed to endotoxin had transient impairments in social cognition (ToM)
  – Impairments were not associated with magnitude of cytokines response

Sierre-Miranda 2015 Neurology: Neuroimmunology & Neuroinflammation in press,
Hodes et al. 2014 PNAS111:18799-16141,de Vellejo et al 2013 The Journal of Immunology 190:
Immune Cell Populations Altered in Schizophrenia

- Schizophrenia associated with peripheral “pro-inflammatory” state
  - Elevated inflammatory cytokines
  - Immune cell populations shifted towards inflammation

Miller et al. 2013 Biological Psychiatry 73:993-999
Dalmau et al. 2008 Lancet Neurol 7:1091-1098
Stress Response Dysregulated in Persons with Schizophrenia

- Impaired stress response found in persons recovered from a first episode of schizophrenia
  - Resting stress level is high
  - Poor ability to mount a robust stress response to acute stress
  - Difficulty engaging relaxation response
Interventions

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    - Address meaning of psychosis to individual
    - Substance use
    - Stress reactivity
  - Family therapy
    - Multifamily group
    - Individual family therapy
  - Group interventions
    - Social skills/social cognition
    - Monthly recreation activity
    - Quarterly workshops
  - Health and Wellness
Health and Wellness

- Patients with schizophrenia die early from cardiovascular disease, lung and breast cancers, and respiratory diseases
- Emphasis on monitoring and prevention
- 100% of patients receive health and wellness counseling
  - Daily exercise
  - Healthy diet
  - Smoking cessation
- Weight gain prevention
  - Monitor closely (weekly intervals)
  - Pharmacological interventions: e.g. metformin

Cardiometabolic Risk Factors

NC data from [http://www.eatsmartmovemorenc.com/ObesityInNC/ObesityInNC.html](http://www.eatsmartmovemorenc.com/ObesityInNC/ObesityInNC.html);
Correll et al., JAMA Psychiatry, in press
OASIS data “snapshot” as of 6 November 2014
Cardiometabolic Risk Factors

![Graph showing the prevalence of various risk factors in North Carolina (N.C.), OASIS, RAISE, and CATIE.](http://www.eatsmartmovemorenc.com/ObesityInNC/ObesityInNC.html)

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