Neurobiology and Natural History of Schizophrenia:

Jeffrey Lieberman, MD
Department of Psychiatry and New York State Psychiatric Institute
Columbia University College of Physicians and Surgeons
Dementia Praecox

E. Kraepelin 1919
Pathogenesis of Schizophrenia and Related Psychotic Disorders

“Environmental Insults” (e.g. trauma, toxins)

Cellular Programming
Gene and Protein Expression

Cell Development:
Multiple subtle abnormalities in induction, patterning, synaptogenesis

Neural Systems:
Abnormal connectivity in local and macrocircuits

Mental- Behavioral Functions:
Disturbances in perception, cognition, mood regulation.

Genes Polygenic susceptibility alleles and mutations

Adapted from Manji and Weinberger, 2002, Freedman 2003
Natural History of Schizophrenia

Stages of Illness

Premorbid  Prodromal  Onset/Progression  Chronic/Residual

Healthy

Gestation/Birth

Worsening

Severity of

Signs and

Symptoms

First Break

Puberty

Deterioration

Years

0  10  20  30  40  50
Gray matter thickness changes in schizophrenia
Neurodevelopmental vs. Neurodegenerative

Can we change the course or prevent the illness?
Natural History of Schizophrenia
Opportunities for Disease Modification

Stages of Illness

Premorbid

Prodromal

Onset/Progression

Chronic/Residual

PREEMPTIVE

PREVENTIVE

REGENERATIVE

Healthy

Worsening Severity of Signs and Symptoms

Gestation/Birth

10

20

30

40

50

Puberty

Deterioration

Years
Regenerative Drugs that Restore and Enhance Neural Connectivity

BDNF, ERKs, Bcl-2

Downregulation
PKC isozymes

Adapted from H. Manji
# Utility of a Biomarker to Diagnose Disease

<table>
<thead>
<tr>
<th>Test Result = Positive</th>
<th>Diagnosis = Negative</th>
<th>Diagnosis = Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Positive</td>
<td>Positive</td>
<td>Positive Predictive Value: $\frac{TP}{TP + FP}$</td>
</tr>
<tr>
<td>True Negative</td>
<td>True Positive</td>
<td>Negative Predictive Value: $\frac{TN}{TN + FN}$</td>
</tr>
</tbody>
</table>

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

**Specificity:** $\frac{TN}{TN + FP}$

**Sensitivity:** $\frac{TP}{TP + FN}$
Genetic Variation

Mismatch

Single Nucleotide (ATCG) Polymorphism (SNP)

Deletion

Copy Number Variant (CNV)

Repetition or Duplication

Deletion
Understanding Genetic Predisposition
Genes affect synaptic physiology

Disease → Mutation → Molecule → Cell → Circuit → System → Sxs&Behavior → Phenotype → Disease
Glutamate Hypothesis of Schizophrenia Pathogenesis

(a) Inhibitory neurons monitor levels of excitatory activity via NMDA receptor (NMDAR) signaling. Normally, the inhibitory neuron maintains sufficient GABA release to balance inhibition with excitation. (b) In the cortex of individuals with schizophrenia, decreased NMDA receptor signaling disrupts this monitoring function, fooling inhibitory neurons into acting as if there is insufficient excitatory activity. The inhibitory neurons downregulate their output, disinhibiting the excitatory neurons.

TMS-evoked Gamma Band activity in Schizophrenia and Healthy Control subjects

Natural History of Schizophrenia

Stages of Illness

Premorbid  Prodromal/Onset/Deterioration  Chronic/Residual

Healthy  Worsening Severity of Signs and Symptoms

Gestation/Birth  10  Puberty  20  30  40  50  Years

Margin of Prevention

Healthy Person

Person with Schizophrenia

Enlarged Lateral Ventricles
Temporal Cortex Atrophy

Hippocampus Atrophy

Dr. Martha Shenton, Psychiatry Neuroimaging Laboratory, Brigham & Women’s Hospital, Harvard Medical School; N Engl J Med 1992 327(9):604-12. Copyright Massachusetts Medical Society.
# Diagnosing Disease

Adapted from S. Small

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

![Diagram of neuron stages and key features](image)
Diagnosing Psychosis

Presynaptic Neuron

[18F]-DOPA: synthesis and presynaptic storage (activity of AADC)

Postsynaptic Neuron

F-dopa in Prodromal Subjects

No transition to psychosis (N=15)  Transition to psychosis (N=9)

Howes et al., 2011 Am J Psychiatry
Gray matter thickness changes in schizophrenia
Whole Brain Gray Matter Volumes Over 52 Wks on MRI

Whole Brain Gray Matter Volumes Over 52 Wks on MRI

- Healthy volunteers (n=58)
- Patients (n=75)

Diagnosing Psychosis in the Hippocampus

Adapted from Schobel, Small et al
Diagnosing Psychosis in the Hippocampus

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

Hipp

OFC BA11

DLPFC BA46
Progression in Hippocampal Volume vs. CBV

- Schobel et al., *Neuron* 78:81-93, 2013
Therapeutic modulation of NMDA antagonist induced glutamate increases in CA1

Gabapentin (3600 mg/d) - presynaptic release modulator

CA1 Glutamate Change
Ketamine challenge 30mg/kg

Gabapentin vs. placebo
SOPS negative (n=24)

Score

Day of Study

0 21

GABA (p=0.14) Placebo

Δ Psychosis

Δ CA1 CBV

CA1 CBV

CA1 Glutamate Change (μM)
Phenocopies and Genocopies

- Congenital brain anomalies; e.g. congenital hydrocephalus
- Velocardiofacial (DiGeorge) Syndrome; 22q11 microdeletion
- Spongiform encephalopathies
- Chronic substance use; e.g. methamphetamine, PCP
- Neuronal autoimmune syndromes; e.g. limbic encephalitis
Neuronal Autoimmune Syndromes

- The concept that neurons can be the target of an autoimmune attack is not widely known in medical community.

- A large number of patients with neuronal antibodies against extracellular antigens have been described.

- Proposed classification by:
  - **Location of the antigen**: intracellular vs extracellular (within the cell membrane)
  - **Whether associated with cancer**: paraneoplastic vs non-paraneoplastic

- Limbic Encephalitis (LE) – antibodies against limbic structures, present with memory/attention deficits, seizures, psychosis, delirium & autonomic instability.
Antibodies to the GABA<sub>B</sub> receptor in limbic encephalitis with seizures: case series and characterisation of the antigen

Summary
Background Some encephalitis or seizure disorders are aimed to describe the clinical features of one such disease.

Malignancies of the Thymus

Caspr2 Antibodies in Patients with Thymomas

Angela Vincent, FRCPath,* and Sarosh R. Irani, MA*

Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series

Lancet Neurol 2010; 9: 775–85
Published Online June 28, 2010
DOI:10.1016/S1474-4422-

Summary
Background Voltage-gated potassium channels are thought to be the target of antibodies associated with limbic encephalitis. However, antibody testing using cells expressing voltage-gated potassium channels is negative; hence, we aimed to identify the real autoantigen associated with limbic encephalitis.
Treatment of Limbic Encephalitis

Any combination of:

- Intravenous IgG – 400ug/kg x 5 days
- Corticosteroids (prednisone)
- Plasma exchange
- Rituximab (‘resetting B-cell memory’)
- Cyclophosphamide

- Surgical removal of tumor

- Repeated courses of treatment are sometimes necessary
Take Home Points

- Disease modification for SCZ is possible

- Therapeutic strategy must be stage specific
  - Premorbid
  - Progressive
  - Chronic Residual

- Most realistic goal is the progressive phase

- Identify geno and phenocopies
That’s all folks!

Have a good day and good luck!