Schizophrenia

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Outline

• History, diagnostic criteria and symptoms
• Possible Causes / Risk Factors
  – Social/Environmental
  – Developmental
  – Genetic
  – Neuroanatomy
  – Neurobiology
    • Dopamine Hypothesis
    • Glutamate Hypothesis
    • Cholinergic Hypothesis
• Current Research
History

• Emil Kraepelin
  – In 1883, separated SZ (which he called dementia praecox) from bipolar disorder (which he called manic-depressive psychosis) largely on the basis of the clinical course of the syndromes.

• Eugene Bleuler
  – In 1911 coined the term SZ, meaning splitting (or more accurately, fracturing) of the mind. Note this is NOT intended to imply “split personalities” but rather a split between thought and emotion.

Sanders A. Don't confuse schizophrenia with multiple personality. Tex Med. 1993 Mar;89(3):8. PMID: 8451749
Onset

- The first signs of schizophrenia often appear as confusing, or even shocking, changes in behavior.

- The sudden onset of severe psychotic symptoms is referred to as an “acute” phase of schizophrenia.

- “Psychosis,” a common condition in schizophrenia, is a state of mental impairment marked by hallucinations and/or delusions.

- Less obvious symptoms, such as social isolation or withdrawal, or unusual speech, thinking, or behavior, may precede, be seen along with, or follow the psychotic symptoms.
What is Schizophrenia?

- **Positive symptoms** include hallucinations, delusions and disorganized speech and behavior.

- **Negative symptoms** include flattened affect, poverty of speech (alogia) or lack of goal directed motivation.

- **Cognitive symptoms** – learning and concentration
Diagnostic Criteria

**Table 14-1 DSM-IV Checklist**

**SCHIZOPHRENIA**

1. At least two of the following symptoms, each present for a significant portion of time during a one-month period:
   a. Delusions.
   b. Hallucinations.
   c. Disorganized speech.
   d. Grossly disorganized or catatonic behavior.
   e. Negative symptoms.
2. Functioning markedly below the level achieved prior to onset.
3. Continuous signs of the disturbance for at least six months, at least one month of which includes symptoms in full and active form (as opposed to attenuated form).

What is Schizophrenia?
What is Schizophrenia?
Schizophrenia

• Approximately 1% of the population develops SZ during their lifetime – more than 2 million Americans suffer from the illness in a given year.

• SZ is found around the world
  • 6 to 12 million people in China
  • 4.3 to 8.7 million people in India
  • 2.2 million people in USA
  • 285,000 people in Australia
  • Over 280,000 people in Canada
  • Over 250,000 diagnosed cases in Britain

Although SZ affects men and women with equal frequency, the disorder often appears earlier in men, usually in the late teens or early twenties, than in women, who are generally affected in the twenties to early thirties.

Prevalence

Relative Prevalence of Schizophrenia

- Schizophrenia
- Alzheimer’s: 2x
- Multiple Sclerosis: 5x
- Insulin-dependent Diabetes: 6x
- Muscular Dystrophy: 60x

Adapted from J.A. Lieberman
Characteristics

• Increased mortality rate from accidents and natural causes:
  – life span is shortened by about a decade
  – some under-diagnosis of medical illness is present
• ~10-15% suicide; ~50% attempt; prominent risks:
  – early in illness and young age
  – depression
  – high premorbid function
  – the latter two often contributing to demoralization
• Illness seems concentrated in urban settings, i.e., it is correlated with population density in larger cities.
• Illness seems concentrated in lower socioeconomic classes.
  – downward drift vs. social causation
Characteristics

• High Co-morbidity with Substance Use
  – ~75% nicotine; ~40% alcohol; ~20% marijuana; ~10% cocaine
  – Substance use comorbidity worsens prognosis.

• ~1/3 or more of homeless population

• Disabling (over 50% unemployed)
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Where are people with schizophrenia?

6% are homeless or live in shelters
6% live in jails or prisons
5% to 6% live in Hospitals
10% live in Nursing homes

25% live with a family member
28% are living independently
20% live in supervised housing (group homes, etc.)
Characteristics
Characteristics

- Costly – for individual and society
Characteristics

• Costly – for individual and society
  – High number years of productive life lost
Characteristics

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  – 50% of all inpatient psychiatry beds
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  - More hospital beds in Canada (8%) are occupied by people with schizophrenia than by sufferers of any other medical condition (Source: BCSS)
Characteristics

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– The overall U.S. 2002 cost of schizophrenia was estimated to be $62.7 billion, with $22.7 billion excess direct health care cost ($7.0 billion outpatient, $5.0 billion drugs, $2.8 billion inpatient, $8.0 billion long-term care). (source: Analysis Group, Inc.)
Causes

• No known single cause of schizophrenia

• Likely results from an interplay of genetic, behavioral, and other factors
Social/Environmental Causes

• Social/Environmental Correlates
  – likelihood of SZ highest in low socio-economic groups
    • poor housing, low income, overcrowding or homelessness
    • stressful life events, uncertainty
    • environmental hazards e.g. noise pollution
    • urban versus rural
    • season of birth
    • poor education and/or work opportunities that may provide buffer for stress
Neurodevelopmental Factors

• Obstetrical complications and prenatal infections are two potential non-genetic early influences on neurodevelopment

• Helsinki follow up study of influenza epidemic (Mednick, 1988)
  
  • adults exposed to virus when in 2nd trimester had significantly higher rates of schizophrenia than controls

• Stress

• Nutrition - choline
Figure 15.15 Probabilities of developing schizophrenia

The closer the genetic relationship to someone with schizophrenia, the higher the probability of developing it oneself.

Kalat (2001) p. 442
Genes

- It appears likely that multiple genes are involved in creating a predisposition to develop the disorder.
- Reported links to Chromosomes 3, 5, 6, 8, 10, 11, 13, 15, 18, 22, ...

- de Novo CNVs: 1q21.1, 15q11.2, 15q13.3 (Nature. 2008 Sep 11;455(7210):178-9)
Neuroanatomy

MRI brain images of twins discordant for schizophrenia
35-year-old female identical twins

Well
Affected

28-year-old male identical twins

Well
Affected

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 16.4 © 2004 Sinauer Associates, Inc.
Neuroanatomy

Tregellas et al., 2007
Dopamine Hypothesis

The “dopamine hypothesis” posits that the positive symptoms of schizophrenia result from too much dopamine at the synapse

- Initial observation - chlorpromazine (Thorazine)
  - Henri Laborit – French surgeon looking for antihistamines to treat surgical shock (1949)
  - Noting it seemed to provoke “state of indifference,” theorized it could be useful in psychiatry
- Tried in 24 yr old man with mania
- He lay calm for several hours with his eyes shut (although his facial expression still looked rather maniacal)
- Within three weeks he had largely settled and was even able to play bridge.

- Delay and Deniker (1952) – 1st clinical trial

Decline of hospitalizations following introduction of chlorpromazine
- Chlorpromazine later found to block dopamine receptors (D2 receptors)

- D2 receptor blockade correlates with clinically effective dose of typical antipsychotic medications

- Stimulants such as amphetamine that release DA can produce the positive symptoms of schizophrenia in healthy subjects and relapse in schizophrenics
Chlorpromazine Side Effects

- **Anticholinergic Effects (moisture)**
  - Dry mouth, blurred vision, constipation, dizziness, drowsiness
  - Usually disappear a few weeks after treatment, also meds to reduce

- **Extra-Pyramidal Side Effects (motor)**
  - Meds also block brain areas related to muscle control, get movement disorders, (60% of pts)
  - Muscle spasms, cramps in head and neck (dystonia), fidget or pace restlessly (akathisia), tremors and shuffling feet, facial tics/tongue/lip licking/panting/grimacing (tardive dyskinesia)
Dopamine hypothesis - weaknesses

- Some atypical antipsychotics such as clozapine are not as well correlated with respect to D2 dopamine receptor binding and clinical potency
- DA levels are not always higher in schizophrenic brains
- Does not account for negative symptoms of SZ
- Although dopamine inhibiting medications modify dopamine levels within minutes, the associated improvement is usually not visible for at least several days
- Effective drugs may be ‘effective’ indirectly: Drugs might be acting on other neurochemical systems (in conjunction with the DA system)
Glutamate Hypothesis

- Noncompetitive NMDA receptor antagonists (like PCP and ketamine) induce both positive and negative symptoms.
- Unmedicated schizophrenic patients are more sensitive to the effects of NMDA receptor antagonists.

### Table 1. Differing Psychiatric and Biological Effects of Acute versus Long-Term PCP/Ketamine Exposure in Humans

<table>
<thead>
<tr>
<th></th>
<th>Acute Exposure</th>
<th>Repeated Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>Intense (hours)(^a)^(^b)</td>
<td>Intense (days to weeks)(^c)^(^d)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Visual illusions (hours)(^b)</td>
<td>Auditory and paranoid (days to weeks)(^d)</td>
</tr>
<tr>
<td>Delusions</td>
<td>Yes (hours)(^j)^(^h)</td>
<td>Frequently religious (days to weeks)(^d)</td>
</tr>
<tr>
<td>Thought disorder</td>
<td>Yes (hours)(^j)^(^h)</td>
<td>Yes (days to weeks)(^c)^(^d)</td>
</tr>
<tr>
<td>Affect</td>
<td>Euphoric to catatonic (hours)(^j)^(^h)</td>
<td>Anxious, labile or paranoid (days to weeks)(^d)</td>
</tr>
<tr>
<td>Cognition</td>
<td>Impaired (transiently)(^b)</td>
<td>Impaired (persistently)(^f)</td>
</tr>
<tr>
<td>Frontal blood flow</td>
<td>Increased (transiently)(^f)</td>
<td>Decreased (persistently)(^g)</td>
</tr>
</tbody>
</table>

\(^a\) Luby et al. (1959).
\(^b\) Krystal et al. (1994).
\(^c\) Rainey and Crowder (1975).
\(^d\) Allen and Young (1978).
\(^e\) Cosgrove and Newell (1991).
\(^f\) Breier et al. (1997a).
\(^g\) Hertzman et al. (1990).

Jentsch and Roth, 1999
The activity of midbrain dopaminergic neurons is regulated, in part, by glutamatergic projections from the PFC acting via glutamatergic N-methyl-D-aspartate (NMDA) receptors.

Dysregulation of DA systems may be secondary to a deficit in the function of the glutamatergic NMDA receptor.
Glutamate Hypothesis

- Chronic PCP leads to behavioral deficits consistent with dorsolateral prefrontal cortex dysfunction

Jentsch et al, Science, 1997
- Chronic PCP reduces cortical dopamine

Jentsch et al, Science, 1997
Glutamate Hypothesis

- behavioral deficits reversed with clozapine

Jentsch et al, Science, 1997
Evidence from human studies

- Alterations in CSF glutamate levels, altered glutamate metabolism and altered NMDA receptor subunit gene expression (Keshavan, 1999)
- Direct evidence is still lacking - lack of adequate radioligands to visualize the GLU system in the living brain

- BUT…
Published online 2 September 2007 | Nature | doi:10.1038/news070827-9

News

**High hopes for new schizophrenia drugs**

**Drug trial hailed as first major breakthrough for 50 years.**

*Alison Abbott ([news/author/Alison-Abbott/index.html](http://news/author/Alison-Abbott/index.html))*

Psychiatrists have welcomed the unveiling by a US drug company of the first new class of schizophrenia drugs since the 1950s.

According to early clinical-trial data, the prototype drug — codenamed LY2140023 and produced by Eli Lilly researchers in Indianapolis, Indiana — seems to be as effective as olanzapine, the best currently available drug. The drug’s developers hope that it will offer psychiatrists a new alternative for treating their patients, and one that may offer greater benefits in relation to the side effects.

According to the World Health Organization, schizophrenia affects around 1% of the population worldwide. Its broad range of debilitating symptoms can include delusions, hallucination, disordered thinking, social withdrawal and emotional ‘flatness’.
LETTERS

Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial

Sandeep T Patil1,13, Lu Zhang1, Ferenc Martenyi2, Stephen L Lowe3, Kimberley A Jackson4, Boris V Andreev5, Alla S Avedisova6, Leonid M Bardenstein7, Issak Y Gurovich8, Margarita A Morozova9, Sergey N Mosolov8, Nikolai G Neznanov10, Alexander M Reznik11, Anatoly B Smulevich9, Vladimir A Tochilov12, Bryan G Johnson1, James A Monn1 & Darryle D Schoeppp1,13
Cholinergic Hypothesis

- Nicotine also modulates response of dopamenergic neurons

- Evidence:
  - Clinical Observations
  - Neurophysiology
  - Post-mortem binding studies
  - Genetics
  - Imaging
Cholinergic Hypothesis

- Smoking incidence in patients with schizophrenia is significantly elevated compared to the general population.
Binding studies suggest fewer $\alpha_7$ nicotinic receptors in schizophrenic subjects

- Also lack of upregulation
Human genetics studies also support involvement of nicotinic receptors in schizophrenia

- Both the P50 auditory gating deficit and SPEM abnormalities are genetically linked in schizophrenic families to a chromosomal locus at 15q14, the locus containing the $\alpha_7$ nicotinic receptor gene.

- Promoter polymorphisms
Evidence for Cholinergic Dysfunction in Schizophrenia

- Nicotine normalizes two common endophenotypes used to study schizophrenia – P50 auditory gating and smooth pursuit eye movement deficits in schizophrenia
The P50 auditory gating paradigm can be extended to animal models (mice), where invasive pharmacological techniques can be used.

Findings include:

- Administration of $\alpha$-bungarotoxin, a low affinity $\alpha_7$ nicotinic receptor antagonist, produced a loss of the gating response.
- Administration of mecamylamine, a high affinity nicotinic receptor antagonist, did not effect the gating response.
- DBA/2 inbred mice, which show low levels of $\alpha$-bungarotoxin binding, exhibit an inhibitory deficit in auditory gating similar to that seen in schizophrenia.
- This deficit is normalized by nicotine and by DMXB-A, a selective $\alpha_7$ nicotinic receptor agonist.
Sensory Gating Deficits in Schizophrenia
Sensory Gating Deficits in Schizophrenia
Studying Sensory Gating with EEG

- Conditioning-testing paradigm -- P50 auditory evoked potentials are measured from repeated pairs of clicks, separated by 500 ms.
Evidence for Cholinergic Dysfunction in Schizophrenia

- Nicotine also normalizes both P50 auditory gating and smooth pursuit eye movement deficits in schizophrenia.
Greater activation of the hippocampus, thalamus and DLPFC in schizophrenia (N=12,12)
Correlations between P50 sensory gating ratios and hemodynamic response during fMRI sensory gating task.
Response to Urban White Noise Stimulus

SUPERIOR TEMPORAL GYRUS

MEDIAL GENICULATE

INFERIOR COLLICULUS
Urban White Noise Task
Schizophrenia > Controls
Nicotine normalizes smooth pursuit abnormalities
Movement of eyes and optic nerve during SPEM task

Time series of 80 sequential epi images
Alternating 30s blocks of task/no task, 4 min total
Movement of eyes and optic nerve during SPEM task

Time series of 80 sequential epi images
Alternating 30s blocks of task/no task, 4 min total
Detecting task performance in the scanner by evaluating eye movements in EPI data
SPERM Response in Healthy Subjects

FEF - Frontal eye fields
IPS - Intraparietal sulcus
OCC - Occipital region
SEF - Supplementary eye field
Results:

schizophrenia > control

Also:
schizophrenia > control -- fusiform gyrus
Decreased hippocampal activity following nicotine during SPEM
Less task-related activity in the right hippocampus in patients with schizophrenia treated with 150 mg DMXB-A compared with placebo.
Inverse correlation between 150 mg DMXB-A plasma levels and task-related hippocampal activity.

Tregellas et al., 2010
DMXB-A Clinical Trials

Phase 1 study: safe, improvement in cognition (RBANS), improved sensory gating (Olincy et al., 2006)

Phase 2 study: Improvement in negative symptoms

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**TABLE 2. Scores for Negative Symptoms and Overall Symptoms for 31 Patients With Schizophrenia During Crossover Treatment With Placebo and Two Doses of DMXB-A**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean</th>
<th>Baseline SD</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>DMXB-A, 75 mg b.i.d. Mean</th>
<th>DMXB-A, 75 mg b.i.d. SD</th>
<th>DMXB-A, 150 mg b.i.d. Mean</th>
<th>DMXB-A, 150 mg b.i.d. SD</th>
<th>150-mg DMXB-A Dose Versus Placebo (p)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totalb</td>
<td>22.0</td>
<td>18.3</td>
<td>22.3</td>
<td>18.8</td>
<td>20.4</td>
<td>18.2</td>
<td>20.6</td>
<td>18.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>6.9</td>
<td>6.8</td>
<td>6.7</td>
<td>7.4</td>
<td>5.7</td>
<td>6.8</td>
<td>6.4</td>
<td>6.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alogiac</td>
<td>2.0</td>
<td>3.0</td>
<td>2.1</td>
<td>3.3</td>
<td>1.7</td>
<td>3.0</td>
<td>1.3</td>
<td>2.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Anhedoniad</td>
<td>6.9</td>
<td>7.1</td>
<td>7.4</td>
<td>6.5</td>
<td>6.8</td>
<td>6.5</td>
<td>6.7</td>
<td>6.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Apathy</td>
<td>5.9</td>
<td>5.6</td>
<td>6.1</td>
<td>4.9</td>
<td>6.1</td>
<td>5.5</td>
<td>6.3</td>
<td>5.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale</td>
<td>30.0</td>
<td>8.8</td>
<td>28.7</td>
<td>8.9</td>
<td>28.0</td>
<td>7.7</td>
<td>27.4</td>
<td>7.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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Initial Phase 2 Trial of a Nicotinic Agonist in Schizophrenia

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Thursday, April 1, 2010
Summary

- Schizophrenia is a heterogeneous illness with no currently known pathology

- Dopamine hypothesis not entire story

- Other mechanisms, involving Glutamatergic or Cholinergic systems, offer new insights and hope.

- Imaging studies suggest:
  - Hyper-responsivity in specific brain regions – hippocampus, thalamus
    - may be therapeutic target
Collaborators

Robert Freedman, M.D.
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Jamey Ellis, B.S.
Deb Singel, R.T.
Everyone else in the SRC!