Deconstructing Schizophrenia

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COGS
Consortium on the Genetics of Schizophrenia
Overview of Presentation

- General Background and Description
- Characteristic symptoms of schizophrenia
- Models of schizophrenia
- Prognostic Indicators
- Treatment Recommendations
The Center Cannot Hold

My Journey Through Madness

Elyn R. Saks

“Her descriptions of her descents into psychosis are riveting.”
—Entertainment Weekly
CLINICAL (TRAIT VARIABLES) 

PSYCHIATRIC SYMPTOMS (STATE VARIABLES) 

COGNITION & NEUROPSYCHOLOGICAL FUNCTION 

ATTENTION & INFORMATION PROCESSING 

PSYCHOPHYSIOLOGICAL FUNCTION 
NEUROPHYSIOLOGICAL FUNCTION 

NEUROTRANSMITTER & HORMONAL BALANCE 

NEUROANATOMIC
Impairments in Early Sensory Processing

Braff, Geyer, Light 1990, 1999
Clinical Characteristics

1. Impaired functioning
2. Abnormal content of thought
3. Illogical form of thought
4. Distorted perceptions
5. Changed affect
6. Altered volition
7. Impaired interpersonal functioning
8. Changes in psychomotor behavior
Positive and Negative Symptoms

**Positive Symptoms**
- Hallucinations
- Delusions
- Paranoia
- Disorganized
  - Bizarre Behavior
  - Thought Disorder

**Negative Symptoms**
- Apathy
- Anhedonia
- Poor social function
- Poverty of thought
## Frequency of Specific Psychotic Symptoms in Schizophrenics

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of insight</td>
<td>97%</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>74%</td>
</tr>
<tr>
<td>Verbal hallucinations</td>
<td>70%</td>
</tr>
<tr>
<td>Ideas of reference</td>
<td>70%</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>65%</td>
</tr>
<tr>
<td>Flat affect</td>
<td>65%</td>
</tr>
<tr>
<td>Voices speaking</td>
<td>65%</td>
</tr>
<tr>
<td>Paranoid state</td>
<td>64%</td>
</tr>
<tr>
<td>Thought alienation</td>
<td>52%</td>
</tr>
<tr>
<td>Thought broadcasting</td>
<td>50%</td>
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</tbody>
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World Health Organization, 1974
(Sartorius, 1974)
DSM-IV Diagnostic Criteria

A. Two or more of the following, each present for a significant portion of the time during a 1-month period (or less if successfully treated)
   1) Delusions
   2) Hallucinations
   3) Disorganized speech
   4) Grossly disorganized or catatonic behavior
   5) Negative symptoms

Note: only 1 Criterion A symptom is required if:
   • Bizarre delusions
   • Running commentary
   • 2+ voices conversing
DSM-IV Criteria (continued)

- B. Social/Occupational Dysfunction
- C. Duration > 6 months
- D. Not schizoaffective disorder or mood disorder with psychotic features
  - 1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms
  - 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of active and residual periods
- E. Substance/general Medical condition exclusion
- F. Relationship to a pervasive developmental disorder
What is the Economic Impact of Schizophrenia?
Schizophrenia costs > $100B a year

If the incidence of schizophrenia is only 1%, why is it so costly?
Why is Schizophrenia So Costly?

- Strikes early in life
- Often lasts a long time
- Can be disabling
- Multiple hospitalizations
- Longer lengths of stay when hospitalized
- Some patients require long-term inpatient or structured living environments
- Medications are expensive and have terrible side-effects
### Leading Causes of Disability

**Ages 15-44 in Developed Regions**

<table>
<thead>
<tr>
<th>Both Sexes</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Major Depression</td>
<td>1. Alcohol use</td>
<td>1. Major depression</td>
</tr>
<tr>
<td>5. Self-inflicted injuries</td>
<td>5. Schizophrenia</td>
<td>5. OCD</td>
</tr>
</tbody>
</table>

Murray and Lopez, 1996
NATURAL HISTORY OF SCHIZOPHRENIA

Psychopathology

Premorbid  Progromal  Progression  Stable  Relapsing

Function

Good

Poor

Age (years)

10  20  30  40  50  60
Course of Illness

Course & Outcome
- 25% full recovery
- 50% partial recovery
- 25% long term care
- Chronic and unremitting in 30-50% of patients

Age of Onset
- Men: 90% age of onset < 30 years old
- Women: 60% age of onset < 30 years old

Suicide
- 66% attempt suicide
- 10% successful
  - Male
  - <30 years old
  - Unemployment
  - Chronic course
  - Prior depression
  - Past treatment for depression
  - Recent discharge
Group 1
One episode only—no impairment  22%

Group 2
Several episodes with no or minimal impairment  35%

Group 3
Impairment after the first episode with subsequent exacerbation and no return to normality  8%

Group 4
Impairment increasing with each of several episodes and no return to normality  35%
Quality of Well-Being

Kaplan and Anderson, 1990
Patterson et al, 1996
Good Prognostic Features?

2 or more of the following:

1. Rapid onset of prominent psychotic symptoms relative to first noticeable change in behavior or functioning
2. Confusion or perplexity at height of psychotic episode
3. Good premorbid social and occupational functioning
4. Absence of blunted or flat affect
Common Contributors to Symptom Relapse

- **Antipsychotic medication nonadherence**
  - Adherence can reduce risk of relapse to < 30%/year
  - Without maintenance treatment, 60-70% will relapse within 1 year. 90% within 2 years
  - 80% of patients in remission will have reoccurrence of symptoms in 5 years following remission

- **Substance use**
  - Male gender, single, < education, earlier onset, frequent & longer hospitalizations, > positive symptoms, grey matter volume deficits, poor treatment adherence, depressive symptoms, suicide, violence, legal problems, incarceration, financial problems, family burden, housing instability, > risk HIV, Hep.

- **Stressful life events**
Homelessness

- 25% of homeless have a severe and persistent mental illness
- 130,000 seriously mentally ill individuals who are homeless
- 120,000 seriously mentally ill in jails & prisons
  - LA County jail is, de facto, the largest mental institution in the nation
- 4-16% of homeless have schizophrenia
- Only half of homeless with schizophrenia receiving treatment
Unsupported Theories About Schizophrenia:

- Demonic possession
- Caused by physical/sexual abuse
- Cold, uncaring, domineering mothers use their children to fill their own needs and ignore those of child
- “Schizophrenogenic Mother”
- Behavioral: Operant Conditioning (also not much evidence)
- Patients are lazy
- Can “cure” themselves if they really wanted to
Other Theories of Schizophrenia

- Genetic
- Environmental
- Stress-Vulnerability
- Neurodevelopmental
Genetic Model

MUTANT GENE

ALTED
GENE FUNCTION
OF MUTANT GENE

SCHIZOPHRENIA

Bayer et al, 1999
"Two Hit Model"

- Mutant Gene
- Modulated Gene Function of Mutant Gene
- Schizophrenia

Bayer et al, 1999
Lifetime Risk of Schizophrenia: Genes Contribute, Not Determine

Gottesman et al, 1991
Mendel’s Garden at the monastery at Brno, Austria

-Haines, Pericak-Vance: Approaches to Gene Mapping in Complex Human Diseases
The Human Genomics Project
Human Genome

- 3,000,000,000 base pairs, of which 1-2% are expressed into proteins
- 30,000 genes are expressed
- 16,000 genes are expressed in the brain
- 6,000+ are expressed only in the brain
- No "cures"
Genetic Architecture of Complex Disorders

A complex disorder for which a "genetic solution" is unlikely

Diabetes?

Schizophrenia?
(may need contributions from 2 or 3 “major” genes and 1-5 “minor” genes)

Huntington’s Disease
(one major gene)

Hypertension?

A complex disorder for which a “genetic solution” is unlikely

Probability of Finding a "Genetic Solution"

Number of Genes
Neurodevelopmental Hypotheses of Schizophrenia

- Both genetic and environmental influences contribute to abnormal brain development
- Pathogenic processes in schizophrenia are active for many years during the vulnerable period when the brain is still developing
- Subtle alterations of specific neurons and circuits lead to vulnerability that does not fully present for 1 to 3 decades
Figure 5.1  One of the earliest images of a brain from a schizophrenic patient. We can see that the sulci are unusually large, especially in the frontal and parietal (upper rear) regions. The American Journal of Psychiatry 92(1), pages 43–67, 1935. Copyright 1935, the American Psychiatric Association. Reprinted by permission.

SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 2: 44 year old males

UNAFFECTED

AFFECTED
Offspring of Mothers Exposed to Influenza Virus by Trimester

Mednick et al, 1988
Alter the course and preventing progression

- Antipsychotic medication *may* ameliorate the pathophysiologic process, especially early in course of illness
- Duration of untreated psychosis is associated with worsened outcome
- Antipsychotics prophylactic in preventing relapse
Treatment Recommendations

1. Treat psychotic symptoms aggressively with medication
2. Engage patient in empathetic relationship
3. Psychoeducation
4. Help the patient find a daily routine to improve socialization and reduce boredom
5. Psychosocial and vocational groups/interventions
6. Integrate care with other providers
7. Family interventions & support
How do you Assess Functioning?
“Respek!”