Schizophrenia: Classification, Phenomenology, Epidemiology, and Genetics

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Introduction: Overview

- broad overview of the schizophrenia’s, in terms of classification, phenomenology, epidemiology, and genetics.
- The psychopharmacology of schizophrenia-spectrum illnesses is covered in the next lecture.
- Up to date to approximately 2011 - 2013, consensus of available information presented.
- References to DSM-4 for historical continuity, brief update on DSM-5 transition.
- We will take one ten minute break during the course of this lecture this morning.
Introduction: Motherhood

- More than any other single illness...
  - the reason there is Psychiatry...
  - is because there is Schizophrenia.
- ~ 1-2 / 100 have it (~240,000 Canadians)
- ~ 20 to 25 persons / 100,000 will get it this year
- A humbling illness: You can know almost everything about it, and sometimes do almost nothing about it
- the cost of treatment is more than all cancers combined...
- ...and schizophrenia remains...
Schizophrenia: The mother of all illnesses

Positive Symptoms
- Delusions
- Hallucinations
- Disorganized speech
- Catatonia

Social/Occupational Dysfunction
- Work
- Interpersonal relationships
- Self-care

Cognitive Deficits
- Attention, Memory
- Executive functions (e.g., abstraction)

Comorbid Substance Abuse

Negative Symptoms
- Affective flattening
- Alogia
- Avolition
- Anhedonia
- Social withdrawal

Metabolic Morbidity

Mood Symptoms
- Depression
- Hopelessness
- Suicidality
- Anxiety
- Agitation
- Hostility
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1. Introduction
2. History of schizophrenia: Concepts and clinical factors
3. Current diagnostic criteria
4. Phenomenology
5. Differential diagnosis, with clinical differentiating factors
6. Epidemiology and course of illness
7. Genetics
History of Schizophrenia:
Concepts and Clinical Factors

Schizophrenia: Mueser, K.T. and McGurk, S.R
The Lancet Vol 363 June 19, 2004 pp.2063-72
Schizophrenia: Early Concepts

- Written descriptions of psychosis dating back to 3rd century BC
Schizophrenia: Early Concepts

- Written descriptions of psychosis dating back to 3rd century BC
- “Modern School” commences circa 1800
- 1801: Pinel introduces the term ‘demence’ to describe the mental deterioration seen in hospitalized psychiatric patients
- Pinel provides first integrated description of what later will be called ‘schizophrenia’
Early Concepts: Kahlbaum

- Classified the ‘degenerative psychoses’
- Catatonic and hebephrenic sub-types
- Emphasized longitudinal course as descriptor
- Degenerative psychoses viewed as diseases of the brain
- Introduces terms cyclothymia, dysthymia, verbigeration, paraphrenia
- First to systematically classify mental disorders based on syndromes
Early Concepts: Morel

- Coined ‘demence precoce’ in 1852 to describe young patients with premature dementia

“His brilliant intellectual faculties underwent in time a very distressing arrest. A kind of torpor akin to hebtude (dullness, lethargy) replaced the earlier activity. In the hospital, the adolescent improved physically, worsened mentally, and eventually was considered a hopeless case.” Etudes Cliniques, 1852
Early Concepts: Hecker

- First precise description of ‘dementia praecox’
- Introduced term ‘hebephrenia’ (Hebe, Greek goddess of youth) to describe young patients manifesting florid psychosis and a deteriorating course
Emil Kraepelin 1856-1926

- Nine editions of textbook, 1883 to 1927
- “Psychic Degenerative Processes” introduced as a distinct class of illness
- “Dementia Praecox” (after Hecker) introduced as sub-type of Psychic Degenerative Processes (1893)
- Emphasized early age of onset and deteriorating course for these disorders
- Deficit symptoms viewed as fundamental to the diagnosis
Kraepelin: Later Contributions

- Established sub classifications of Dementia Praecox, including Hebephrenic (Hecker 1871) Catatonic (Kahlbaum 1874) and Paranoid (Kahlbaum 1873)

- Recognized variability in onset and disease course
Kraepelin: Other Contributions

- Separated major psychotic illnesses into:
  - affective (manic-depressive illness)
  - non-affective (dementia praecox) illness

- Viewed psychotic illnesses as diseases of the brain
Eugen Bleuler 1857-1939

• “The Group of Schizophrenias”
• Divided schizophrenia into:
  – fundamental and
  – accessory symptoms.
• fundamental symptoms comprising the core of the illness
• division anticipated more recent division of positive and negative symptoms in schizophrenia
Bleuler

- Challenged the characterization of schizophrenia as having an early onset and deteriorating course
- Emphasized the heterogeneity of the illness
- Cross sectional diagnostic construct
- “Schizophrenia”
Bleuler: Fundamental and Accessory Symptoms in Schizophrenia

Fundamental
- Affect (-ive flattening)
- Associations (-Looseness of)
- Autism
- Ambivalence
  - Loss of attention
  - Loss of volition

Accessory
- Hallucinations
- Delusions
- Disorganization
- Somatization
Kraepelin vs. Bleuler:

**Kraepelin**
- Deficit symptoms are fundamental
- Multiple subtypes
- Schizophrenia as brain disease
- Longitudinal presentation
- Deteriorating course

**Bleuler**
- Deficit symptoms are fundamental
- Multiple subtypes
- Accessory symptoms as psychodynamic
- Cross sectional presentation
- Heterogeneity of presentation and outcomes
Evolution of “Schizophrenia”: 1800 to 1950

- Tendency to early onset with chronic course
- Heterogeneity in presentation and outcome
- Positive, negative and cognitive symptom clusters
- Separation of affective and non-affective psychotic disorders
- Organic basis is hypothesized
- Importance of genetic and environmental influences is recognized
Evolution of “Schizophrenia”: 1800 to 1950 (contentious)

- Longitudinal versus cross sectional characteristics as primary diagnostic criteria
- Primacy/role of positive, negative and cognitive symptoms
- Role of biological and environmental influences in disease onset and course
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History of Schizophrenia:
Current Diagnostic Criterion
Schizophrenia: 1950 to 1994

- USA: Concept of schizophrenia broadens
- psychodynamic influences (Meyer, Jaspers)
- heavily influenced by Blueler’s 4 A’s, i.e. affect, association, autism and ambivalence
- DSM I, II - Diagnostic criteria psychodynamically influenced
- US-UK Diagnostic Project (Fromm-Reichmann 1959) and International Pilot Study on Schizophrenia IPSS (Cooper et al 1972) demonstrate broad diagnostic tendencies in USA relative to Europe
Kurt Schneider 1887-1967

- Schneider (1959) postulates loss of interpersonal boundaries and loss of sense of personal autonomy as fundamental symptoms in schizophrenia.
- Publishes inventory of “first rank” symptoms
  - **NOT VIEWED AS PATHOGNOMONIC FOR SCHIZOPHRENIA**
  - Designed in part as reliable, well-defined set of diagnostic criteria for schizophrenia, to narrow the circumference of ‘diagnostic net’
• First rank symptoms incorporated into first structured clinical interview for schizophrenia, the Present State Examination (Wing et al 1974), used in the IPSS.

• Also incorporated into the SADS (Endicott and Spitzer 1978), RDC (Spitzer et al 1978), and DSM III (APA 1980)
  – DSM III much narrower concept of schizophrenia
  – Limitation of number of symptoms
  – Requirement for specific duration of symptoms
  – Course criteria
Schneider: First Rank Symptoms

**Auditory hallucinations** consisting of any of the following:

- Voices repeating thoughts out loud
- Two or more voices discussing the patient or arguing about him/her, referring to the patient in the third person.
- Voices commenting on patient’s thoughts, or behavior, often as a running commentary.
Schneider: First Rank Symptoms

- Thought insertion, withdrawal and interruption
- Thought broadcasting
- Passivity phenomena
  - Experience of feelings, impulses, or acts being under external control (ideas or delusions)
  - Experience of being a passive recipient of bodily sensations imposed by some external agency (somatic hallucination)
- Delusional perception
  - Normal perception followed by a delusional and highly personalized interpretation
Schneider: First Rank Symptoms

- A (auditory)
- B (broadcasting and insertion, withdrawal)
- C (control i.e. passivity experiences)
- D (delusional perception)
Prevalence: First Rank Symptoms in Schizophrenia

Prospective Studies

- MELLOR (1970) 72% n=166
- CARPENTER (1973) 51% n=103
- CARPENTER (1974) 57% n=801
First Rank Symptoms: Summary

- Prevalent in schizophrenia; 50%+
- Influenced DSM III to DSM IV-TR, to help narrow diagnostic criteria
- NOT PATHOGNOMONIC FOR SCHIZOPHRENIA, ONLY SUGGESTIVE
- Used today in DSM IV, lost exceptional diagnostic power in DSM-V
DSM IV Criteria for Schizophrenia: Evolution of Concept

- Tendency to early onset with chronic course
  - Presence of illness for six months minimally
  - Substantial functional decline is required
- Heterogeneity in presentation and outcome
  - Multiple symptom combinations are possible
  - Multiple subtypes recognized
  - Multiple course specifiers included
- Positive and negative/cognitive symptom clusters
  - Positive and negative symptoms included, although negative symptoms not required for diagnosis
  - Cognitive symptoms are not included in diagnostic criteria
DSM IV Criteria for Schizophrenia: Evolution of Concepts

- Separation of affective and non-affective psychotic disorders
  - Mood disorders require to be excluded to make diagnosis
- Organic basis is hypothesized
- Importance of genetic and environmental influences is recognized
- DSM IV was a theoretical, descriptive construct
DSM IV: Schizophrenia

- A. Characteristic Symptoms
- B. Social/occupational dysfunction
- C. Duration
- D. Schizoaffective and mood disorder exclusion
- E. Substance/general medical condition exclusion
- F. Relationship to a pervasive developmental disorder
- Classification of longitudinal course
DSM IV: Criterion A (cross sectional)

Two (or more) of the following, each for a significant portion of time during a one month period (or less if successfully treated):

1. Delusions
2. Hallucinations
3. Disorganized Speech
4. Grossly Disorganized or Catatonic Behavior
5. Negative Symptoms (i.e. affective flattening, alogia or avolition)
DSM IV: Criterion A

- NOTE: Only one Criterion A symptom is required if:
  - delusions are bizarre, or
  - hallucinations consist of a voice keeping a running commentary* on the person’s behavior or thoughts, or
  - two or more voices are conversing* with each other.
  - *(after Schneider)
DSM IV: Criterion B
(functional decline)

For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement)
DSM IV: Criterion C (longitudinal)

- Continuous signs of the disturbance for at least 6 months
- 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms)
- During these prodromal or residual periods, the signs of the disturbance may be manifested only by negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)
DSM-IV to DSM V

- Diagnostic “Subtypes” are removed
  - primarily because of loss of diagnostic acumen
  - lack of biomarkers to support diagnostic validity
- elimination of the classic subtypes and special treatment of Schneiderian 'first-rank symptoms’
- addition of unique psychopathological dimensions
- clarification of cross-sectional and longitudinal course specifiers,
- better delineation of schizophrenia from schizoaffective disorder
- and clarification of the relationship of schizophrenia to catatonia.
DSM-5: Criterion A

1. Two Criterion A symptoms are required for any diagnosis of schizophrenia.
2. Elimination of the special attribution of:
   - bizarre delusions and
   - Schneiderian first-rank auditory hallucinations
3. Addition of a requirement in Criterion A that the individual must have at least one “core positive symptom”:
   - delusions
   - hallucinations
   - disorganized speech
Schizophrenia subtypes

- The DSM-IV subtypes of schizophrenia (i.e., paranoid, disorganized, catatonic, undifferentiated, and residual types) are eliminated due to their limited diagnostic stability, low reliability, and poor validity.
- Subtypes also have not been shown to exhibit distinctive patterns of treatment response or longitudinal course.
- Dimensional approach to rating severity for the core symptoms of schizophrenia is included in Section III to capture the important heterogeneity in symptom type and severity expressed across individuals with psychotic disorders.
Schizoaffective Disorder

- Requirement that a major mood episode be present for a majority of the disorder’s total duration after Criterion A has been met.
- Change makes schizoaffective disorder a longitudinal instead of a cross-sectional diagnosis—more comparable to schizophrenia, bipolar disorder, and major depressive disorder.
- These changes were made to:
  - improve the reliability, diagnostic stability, and validity of this disorder,
  - recognize that the characterization of patients with both psychotic and mood symptoms, either concurrently or at different points in their illness, has been a clinical challenge.
Delusional Disorder

• Criterion A - no longer has the requirement that the delusions must be non- bizarre. A specifier for bizarre type delusions provides continuity with DSM-IV.

• Delusional disorder vs psychotic variants of obsessive-compulsive disorder and body dysmorphic disorder is explicitly noted with a new exclusion criterion.

• DSM-5 no longer separates delusional disorder from shared delusional disorder.
Catatonia

- The same criteria are used to diagnose catatonia whether the context is a psychotic, bipolar, depressive, or other medical disorder, or an unidentified medical condition.
- In DSM-5, all diagnostic contexts require three catatonic symptoms (from a total of 12 characteristic symptoms).
- In DSM-5, catatonia may be diagnosed as a specifier for depressive, bipolar, and psychotic disorders; as a separate diagnosis in the context of another medical condition; or as another specified diagnosis.
Catatonia – 3 of 12

- Stupor - no psychomotor activity; not actively relating to environment
- Catalepsy - passive induction of a posture held against gravity
- Waxy Flexibility - slight, even resistance to positioning by examiner
- Mutism - no, or very little, verbal response [exclude if known aphasia]
- Negativism - opposition or no response to instructions or external stimuli
- Posturing - spontaneous and active maintenance of a posture against gravity
- Mannerism - odd, circumstantial caricature of normal actions)
- Stereotypy - repetitive, abnormally frequent, non-goal-directed movements
- agitation, not influenced by external stimuli
- grimacing
- Echolalia - mimicking another's speech
- Echopraxia - mimicking another's movements
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Phenomenology
Measuring Psychopathology

- measuring symptoms is complex because symptoms cover a wide variety of psychopathological domains
- The commonly recognized domains are:
  - positive
  - negative
  - cognitive
  - excitement, and
  - affective domains.
Assessment Rating Scales

• SAPS (scale for the assessment of positive symptoms) and SANS:
  – positive or psychotic cluster [hallucinations, delusions, catatonic symptoms]
  – negative cluster [anhedonia, evolution, poverty of speech, blunted affect]
  – disorganization cluster [disorganized speech inappropriate affect, bizarre behavior].
Assessment Rating Scales

- PANSS (positive and negative symptom scale)
- Five factor model of schizophrenia consisting of:
  1. Positive factor [delusions, hallucinations, grandiosity, unusual thought content, suspiciousness/persecution]
  2. Negative factor [blunted affect, emotional withdrawal, passive apathetic social withdrawal, lack of spontaneity, active social avoidance]
  3. Excitement factor [excitement, hostility, uncooperativeness, poor impulse control]
  4. Cognitive organization factor: [conceptual disorganization, difficulty with abstract thinking, disorientation, poor attention, preoccupation]
  5. Depression and anxiety factor [anxiety, guilt feelings, tension, and depression]
Assessment Rating Scales

- Calgary Depression Scale: a nine item scale designed to estimate the severity of depression in patients who have schizophrenia.
- Superior to the Hamilton Depression rating scale and the Montgomery-Asper Depression rating scale and other depression scales for patients with schizophrenia.
- Excellent psychometric properties of internal consistency, interrater reliability, sensitivity, and specificity.
- Only low to modest overlap with positive and negative symptoms, and no substantial correlation with extrapyramidal symptoms.
Phenomenology
The Prodrome

Natural History of Schizophrenia

- Good
- Function
- Psychopathology
- Poor

Adapted from J.A. Lieberman

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The Prodrome:

- prodromal symptoms are “often present” prior to the active phase
- these may be subthreshold forms of the positive symptoms
  - e.g. unusual or odd beliefs not of delusional intensity, unusual perceptual experiences, digressive or vague speech, peculiar behavior
- negative symptoms “particularly common in the prodrome phase”
  - e.g. social withdrawal, anhedonia, alogia
The Prodrome:

“The onset may be abrupt or insidious, but the majority of individuals display some type of prodromal phase manifested by the slow and gradual development of a variety of signs and symptoms (e.g., social withdrawal, loss of interest in school or work, deterioration in hygiene and grooming, unusual behavior, outbursts of anger).”
The Prodrome

- extends from a stable or premorbid phase until the time of onset of frank psychotic features (Keith 1991, Loebel et al., 1992, Beiser et al., 1993)
- on average, can last between 1 and 5 years (Loebel et al., 1992, Beiser et al., 1993, Hafner et al., 1993)
- often associated with substantial levels of psychosocial impairment and disability (Jones et al., 1993, Yung et al., 1996)
The Prodrome

- cognitive deficits seen in prodromal phase

- gray matter deficits present in prodromal patients
## Symptoms: Prodromal Phase
(Yung and McGorry 1996)

<table>
<thead>
<tr>
<th>positive (attenuated)</th>
<th>negative</th>
<th>cognitive</th>
<th>general</th>
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<tbody>
<tr>
<td>unusual perceptions</td>
<td>Affect: blunted or inappropriate</td>
<td>reduced concentration, attention</td>
<td>depressed mood, irritability, anxiety, poor hygiene, deterioration in role functioning, poor sleep</td>
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<tr>
<td>odd beliefs, magical thinking, suspiciousness</td>
<td>Amotivation, Anergia, social withdrawal</td>
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<tr>
<td>vague, elaborate speech, circumstantiality</td>
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Symptoms: Prodromal Phase

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So what’s the point???

- Largely non-specific
- Essentially most average teenagers
- Retrospective validity
- How do we determine when an actual prodrome exists?
- Can we predict for progression?
Predictors of Progression to Psychosis in the Prodrome

<table>
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<tr>
<th>attenuated positive</th>
<th>negative</th>
<th>cognitive</th>
<th>general</th>
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Diagnosis in the Prodrome

- No specific lab or other biological markers. Diagnosis is clinical.
- Consider list of prodromal symptoms, especially attenuated positive symptoms: Look for these in conjunction with *psychosocial deterioration and genetic risk*
- Consider use of existing prodrome scales/inventories.....
Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al., 2001)

4 part interview
1. Scale of Prodromal Symptoms (SOPS)
   - Positive symptoms
   - Negative symptoms
   - Disorganization
   - General symptoms
2. Global Assessment of Functioning (GAF)
3. Schizotypal Personality Disorder criteria
4. Family history of psychotic illness
SIPS conversion rates

- 35% within 2.5 years
- If 2 or 3 factors present, then rates of conversion are 68% and 80% respectively
5 Features *most* predictive of progression:
SIPS $n = 291$ (Cannon et al. 2008)

- Genetic risk with recent deterioration in function
- Higher levels of unusual thought content (attenuated positive symptoms)
- Higher levels of suspicion/paranoia (attenuated positive symptoms)
- Greater social impairment
- History of substance abuse
Comprehensive Assessment of At Risk Mental States (CAARMS)

3 part interview
1. Presence of at least one attenuated psychotic symptom
2. Evidence of at least one episode of brief limited psychotic symptoms (BLIPS)
3. Functional decline in past year and genetic risk (one relative with Schizotypal PD or a psychotic illness)

- N = 104, 35% conversion rate

Yung 1996
Prodrome Treatment

- Antipsychotic meds are still in research phase for the prodrome and are NOT indicated at present
- Some early evidence for Omega 3 fish oil (Amminger, P. et al ArchGenPsych 2010)
- Active follow up
- Supportive and family therapy
- Education
- Monitoring of safety issues
- Treat co-morbid conditions if present

(McGorry et al 2005)
Elements of the schizophrenia prodrome include...
(all of these, from most specific to the least specific)

- Attenuated positive symptoms
- Negative symptoms
- Cognitive symptoms
- BLIPS
- Prolonged global deterioration in functioning
- Presence of general psychiatric symptoms
  - Depression, Anxiety, Role deterioration
What factors would predict for progression in the prodrome?

(all of these, from most important to the least)

- Attenuated positive symptoms
- BLIPS
- Family history of schizophrenia spectrum illness
- Pre-existing schizotypal personality disorder
- Prolonged global deterioration in functioning
- Presence of negative symptoms
- Presence of general psychiatric symptoms
  - Depression, Anxiety, Role deterioration
Phenomenology: Positive Symptoms
Positive Symptoms: Disturbance of Thought Content

- Delusions: False beliefs about which a person is firmly convinced and is impervious outside contradictory evidence

- Must be distinguished from religious or cultural beliefs
Positive Symptoms:
Disturbance of Thought Content

- Persecutory Delusions
  - Among the most common symptoms of schizophrenia but not pathognomonic
  - Can be present in delusional disorder, major mood disorders and organic delusional syndromes
  - Mood incongruent or idiosyncratic content is suggestive of schizophrenia
  - Can be vague, unstable, few in number, or systematized and numerous
Positive Symptoms: Disturbance of Thought Content

- Other Delusions
  - Control (outside force or agency controlling thoughts, feeling or body parts, also called delusions of passivity)
  - Reference (personal meaning attached to random events)
  - Grandiose (belief in extraordinary power, wealth, fame or talents)
  - Religious (extraordinary preoccupations of a religious nature)
  - Somatic (preoccupations that a body part is diseased or malfunctioning)
  - Nihilistic (Guilt, sin, apocalyptic)
Positive Symptoms: Disturbance of Thought Content

- Delusions of Thought
  - Thought insertion (some thoughts have been implanted by an outside agency)
  - Thought Withdrawal (thoughts taken out of the mind)
  - Thought Broadcasting (thoughts are passively transmitted to others, often through electronic or telepathic means)
Positive Symptoms: Disturbance of Thought Content

- Capgras Syndrome
  - Named for French psychiatrist Jean Marie Joseph Capgras (1873-1950)
  - Content consists of the belief that people in one’s life have been replaced by exact doubles
  - 35% of such cases are organic in etiology
  - Can be seen in schizophrenia and mood disorders
Positive Symptoms: Disturbance of Thought Content

- Cotard’s Syndrome
  - Named after French neurologist Jules Cotard (1840-1889)
  - *Le delire de negation*
  - Content consists of the belief that one is dead, or it is after the end of the world
  - Seen in organic conditions as well as schizophrenia and mood disorders
Positive Symptoms: Disturbance of Perception

- Hallucinations: Sensory perceptions in the absence of any externally generated stimulus or perception.
- Must be distinguished from “prehallucinatory experiences” such as hypersensitivity to light and sound, misperceptions of movement and changes in the perception of faces or bodies.
- Self-talk or internal monologueing
Postive Symptoms: Disturbance of Perception

- Hallucinations
  - Auditory
    - The most common type of hallucination seen in schizophrenia *but not pathognomonic*
    - are reported in 50% - 70% of patients with schizophrenia (Andreasen and Flaum 1991, Hoffman et al, 2001)
    - Can range from sounds to voices, from muffled to clear
    - May be heard from inside or outside the head
Positive Symptoms: Disturbance of Perception

- Hallucinations
  - Auditory
    - Single or multiple voices may be heard, recognized or unrecognized
    - May be constant or intermittent
    - Often comment on the person’s behavior
    - May be threatening
    - May command to mundane or lethal actions
    - Beware of “pseudo-hallucinations”
Positive Symptoms: Disturbance of Perception

- Hallucinations
  - Auditory
    - Often occur together with delusions or may have delusional interpretations
    - If auditory hallucinations exist in isolation then consider other etiologies such as mood disorder or organic disorder
Postive Symptoms: Disturbance of Perception

- Hallucinations
  - Visual
    - Patients may observe people, shapes, colors and/or objects that are not actually present
    - Seen more frequently in delirium
    - Delirium is suggested by more elementary subjects such as animals and may be accompanied by tactile hallucinations
    - Acute cognitive impairment also suggests organic pathology
- Charles Bonnet Syndrome
Positive Symptoms:
Disturbance of Perception

- Hallucinations
  - Somatic and Tactile
    - Physical sensation, *in the absence of any actual stimuli*
    - May include the experience of being a *passive recipient* of bodily sensations imposed by some external agency
    - May include Haptic/Kinesthetic hallucinations, which consist of *physically impossible sensations* such as heat, cold or electric shocks, usually coming from *inside the body*
Positive Symptoms: Disturbance of Organization

- Thought disorders:
  - related directly to disordered language functioning
  - a reflection of poor neurocognitive functioning
Positive Symptoms: Disturbance of Organization

- Tangentiality (deviating readily and gradually from the topic under discussion, but connections are still recognizable to the listener)
- Circumstantiality (unwarranted detail, which is frequently tangential, elaborate and irrelevant, but returns to the original topic)
- Derailment (loss of logical connection between words or sentences)
- Incoherence (complete loss of logical connections between words or sentences)
- Illogicality (responses to questions are not logically connected)
Positive Symptoms: Disturbance of Organization

Thought Blocking (cessation or complete interruption in the flow of the stream of thought)

Clanging (using words that sound similar to those being used in a discussion, but have unrelated meanings)

Echolalia (repeating words, phrases or sounds presented in conversation)

Neologism (nonsensical words condensed or combined from two or three different words)
Postive Symptoms: Disturbance of Organization

Disorganized behavior
- Aggression, agitation
- Inappropriate social or sexual behavior
- Bizarre appearance, manner of dress
- Mannerisms, (repetitive or exaggerated expressions or gestures)
- Echopraxia (repetition or imitation of observed gestures or physical expressions)
- Stereotypies (repetitive, meaningless actions)
- Regression
Phenomenology
Negative Symptoms
Negative Symptoms

- Affective flattening
  - Absence or diminution of emotional reaction to stimuli
  - Does not imply loss of feeling emotions
  - Associated clinical signs may be decreased spontaneous movements, lack of gestures, poor eye contact and lack or vocal inflection
Negative Symptoms

- Alogia
  - Deficient fluency or productivity of speech or thought
  - Main issue in poverty of speech, a restriction in the amount of spontaneous speech, or poverty of content, in which fluent speech conveys little information
  - “Response latency” consists of the affected individual taking long periods to respond to questions
Negative Symptoms

- Avolition and Apathy
  - Loss of energy, drive or interest
  - Loss of motivation to complete tasks or achieve goals
  - Grooming and hygiene may be affected
Negative Symptoms

- Passive/Apathetic Social Withdrawal
  - Loss of social connections secondary to apathy, loss of interest
  - Affected individuals typically do not miss or desire social connectedness
Negative Symptoms

Negative symptoms may be secondary to...

- Medication effects (typical antipsychotics)
- Depression
- Reaction to positive symptoms (isolation)
- Pre-existing personality disorder (cluster A)
- Understimulation (reduction in motivation, socialization)
- Substance abuse (cannabis, sedative hypnotics, opiates, amphetamines in toxic or withdrawal states)
Phenomenology
Cognitive Symptoms
Cognitive Deficits in Chronic Schizophrenia

• Heinrichs & Zakzanis (Neuropsychology, 12, 426-445, 1998)
  – Conducted a series of 22 meta analyses, examining the nature and severity of cognitive deficits in schizophrenia, and the role of potential moderator variables
  – Examined studies published between 1980 and mid-1997
    • 204 studies
    • 7,420 schizophrenic patients and 5,865 control participants
Cognitive Domains Assessed

- **Memory**
  - Global Verbal (e.g., Index scores)
  - Selective Verbal (e.g., intrusion rates)
  - Nonverbal

- **Motor**
  - Unilateral Skill
  - Bilateral Skill

- **Attention**
  - Digit Span
  - Trail Making Test – Part A
  - Trail Making Test – Part B
  - Continuous Performance Test
  - Stroop

- **General Intelligence**
  - WAIS-R IQ
  - Non-WAIS-R IQ
  - Performance IQ
  - Verbal IQ

- **Spatial Ability**
  - Block Design
  - Line Orientation
  - Facial Recognition

- **Executive Function**
  - Wisconsin Card Sorting Test (categories, number of perseverative errors and responses, percent perseverative errors)

- **Language Function**
  - Word Fluency
  - Token Test
  - Vocabulary

- **Tactile Transfer**
  (contralateral finger localization, tactile recognition)
# Mean Neurocognitive Effect Sizes Ordered by Magnitude and Corrected for Sample Size

<table>
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<tr>
<th>Test/Construct</th>
<th>Mean d (SD)</th>
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<tbody>
<tr>
<td>Global Verbal Mem.</td>
<td>1.41 (0.59)</td>
</tr>
<tr>
<td>Bilateral Motor Skill</td>
<td>1.30 (0.38)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>1.26 (1.00)</td>
</tr>
<tr>
<td>CPT</td>
<td>1.16 (0.49)</td>
</tr>
<tr>
<td>Word Fluency</td>
<td>1.15 (1.00)</td>
</tr>
<tr>
<td>Stroop Test</td>
<td>1.11 (0.49)</td>
</tr>
<tr>
<td>WAIS-R IQ</td>
<td>1.10 (0.72)</td>
</tr>
<tr>
<td>Token Test</td>
<td>0.98 (0.49)</td>
</tr>
<tr>
<td>Tactile-Transfer</td>
<td>0.98 (1.71)</td>
</tr>
<tr>
<td>Select Verbal Mem.</td>
<td>0.90 (0.62)</td>
</tr>
<tr>
<td>Wisconsin Card Sort</td>
<td>0.88 (0.41)</td>
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<tr>
<td>Verbal IQ</td>
<td>0.88 (0.66)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test/Construct</th>
<th>Mean d (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral Motor Skill</td>
<td>0.86 (0.39)</td>
</tr>
<tr>
<td>Trail Making – Part B</td>
<td>0.80 (0.50)</td>
</tr>
<tr>
<td>Non-Verbal Memory</td>
<td>0.74 (1.98)</td>
</tr>
<tr>
<td>Trail Making – Part A</td>
<td>0.70 (0.36)</td>
</tr>
<tr>
<td>Facial Recognition</td>
<td>0.61 (0.36)</td>
</tr>
<tr>
<td>Digit Span</td>
<td>0.61 (0.43)</td>
</tr>
<tr>
<td>Line Orientation</td>
<td>0.59 (0.63)</td>
</tr>
<tr>
<td>Non-WAIS-R IQ</td>
<td>0.59 (0.51)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.53 (0.21)</td>
</tr>
<tr>
<td>Block Design</td>
<td>0.46 (0.39)</td>
</tr>
</tbody>
</table>
Conclusions in Chronic Population

- Neurocognitive dysfunction is a reliable finding in schizophrenia (estimated in 61%-78% of cases, depending on cognitive domain under consideration)
- No single cognitive domain or test is able to completely separate schizophrenia and control distributions
- Largest mean effect size (supported by an adequate number of studies):
  - Global verbal memory
  - Performance IQ
  - Full Scale IQ
  - Continuous Performance Test
  - Word fluency
What About First Episode Patients?
Bilder et al.  

- Compared:
  
  • 94 patients with first episode psychosis \textit{after initial stabilization of psychosis} (70 schizophrenia and 24 schizoaffective disorder) to normal controls
  
  - patients admitted to hospital inpatient service with first episode of psychosis and less than 12 prior weeks of cumulative lifetime neuroleptic treatment.

  • no co-morbid diagnoses
FIGURE 1. Deficits in Scores for Neuropsychological and Premorbid Abilities of 94 Patients With First-Episode Schizophrenia
Conclusions in First Episode

- Neuropsychological profiles are generally consistent with studies of samples of patients with chronic schizophrenia.

- Substantial compromise in a wide range of domains, 0.5 to 2.0 SD below controls.

- Cognitive functioning had little relation to psychiatric symptoms at study entry, but was correlated with negative symptoms once patients were clinically stabilized (possible persistent, trait deficits).
Conclusions Regarding Cognitive Deficits

- At Diagnosis, significant cognitive impairment is typically present (prior to initiation of antipsychotic treatment, or hospitalization).
- Overall, individuals presenting with a first episode of psychosis tend to exhibit generalized cognitive impairment with evidence of relatively selective impairment in:
  - Memory (immediate and delayed verbal and visual memory).
  - Attention and information processing speed.
  - Executive functioning e.g. (mental flexibility, conceptual reasoning, abstraction, sequencing).

Bilder at al., 2000; Fitzgerald et al., 2004; Hoff et al., 1992; Mohamed et al., 1999; Saykin et al., 1994
Cognitive Deficits in Schizophrenia: Summary

- “schizophrenia involves a broad compromise of cognitive function…” (Gold 2004)
  - *triad*: memory, attention and exec. functioning
- Ability scores are 1.0 to 2.0 standard deviations below normal means
- Deficits affect 70% to 80% of patients (Palmer et al 1997, Wilk et al 2004)
- Are present at onset (Bilder et al. 2000, Hill et al 2004) and prior to onset (Jahshan et al. 2010, Harvey P.D., 2009, Hawkins et al. 2008)
- Remain stable over time (Hoff 1999, Gold 1999)
Affective/Mood Symptoms in Schizophrenia:

- Depressive, anxiety and/or manic symptoms may be present in the acute phase of schizophrenia.
- Thought by many to be an inherent domaine of the syndrome of schizophrenia.
- Often respond to treatment with antipsychotics alone.
- Do not treat with thymoleptics unless:
  - Full mood syndrome is present, and is present....
    - For a significant length of time, or
    - Predates the onset of psychotic symptoms, or
    - Is present after psychotic symptoms are controlled, or
    - There has been a full mood syndrome present historically.
Catatonia

- a marked psychomotor disturbance that may involve stupor and rigidity, (these are most important)
- also mutism, negativism, purposeless excitement, echolalia, echopraxia, and inappropriate or bizarre posturing
- is associated with various medical and psychiatric conditions, but no longer a subtype specific to schizophrenia
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1. Introduction
2. History of schizophrenia: Concepts and clinical factors
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6. Epidemiology and course of illness
7. Genetics
Differential Diagnosis in Schizophrenia
## Differential Diagnosis in Schizophrenia

<table>
<thead>
<tr>
<th>Differential Syndrome/Illness</th>
<th>Differentiating Factor(s) from Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief psychosis</td>
<td>Onset of psychosis is usually acute&lt;br&gt;Can be associated with stressors&lt;br&gt;Duration of psychosis less than one month with good resolution</td>
</tr>
<tr>
<td>Schizophreniform Disorder</td>
<td>Onset is usually acute&lt;br&gt;Duration of disturbance, (prodrome, active and residual), lasts more than one but less than six months with good resolution</td>
</tr>
<tr>
<td>Delusional Disorder</td>
<td>Symptoms uniquely involve delusions, which are crystalized, few, and non-bizarre&lt;br&gt;Functioning is not greatly impaired</td>
</tr>
<tr>
<td>Differential Syndrome/Illness</td>
<td>Differentiating Factor(s) for Prodrome Patients</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>Mood symptoms, whether unipolar, bipolar or mixed, are <em>prominent and co-occur</em> with Criterion A symptoms of psychosis</td>
</tr>
<tr>
<td></td>
<td>Mood symptoms are “present for a substantial portion of the total duration of the active and residual phases of the illness”</td>
</tr>
<tr>
<td>Mood disorders with psychosis</td>
<td>Psychotic symptoms <em>only</em> occur during diagnosable periods of mood disturbance</td>
</tr>
<tr>
<td></td>
<td>Psychotic symptoms are not bizarre and are mood congruent</td>
</tr>
<tr>
<td></td>
<td>Family history of mood disorder</td>
</tr>
<tr>
<td></td>
<td>Inter-episodic recovery with no negative or cognitive symptoms</td>
</tr>
</tbody>
</table>
# Differential Diagnosis in Schizophrenia

<table>
<thead>
<tr>
<th>Differential Syndrome/Illness</th>
<th>Differentiating Factor(s) from Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCD</td>
<td>Insight into obsessive thoughts is preserved. Obsessive thoughts are ego-dystonic No symptoms of psychosis are present</td>
</tr>
<tr>
<td>Pervasive Developmental Disorders</td>
<td>Usually recognized before age 3 Hallucinations and delusions are not present</td>
</tr>
<tr>
<td>Cluster A Personality Disorders</td>
<td>Symptoms of psychosis are not present Gross deterioration in role functioning often not seen</td>
</tr>
<tr>
<td>Paranoid, Schizoid, Schizotypal</td>
<td></td>
</tr>
</tbody>
</table>
# Differential Diagnosis in Schizophrenia

<table>
<thead>
<tr>
<th>Differential Syndrome/Illness</th>
<th>Differentiating Factor(s) from Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis Secondary to a General Medical Condition</td>
<td>Presence of related symptoms and signs of the underlying disorder are manifest in history and physical exam</td>
</tr>
<tr>
<td></td>
<td>Lab data/physical markers are often available, while none are available or diagnostic in schizophrenia</td>
</tr>
<tr>
<td>Substance-induced psychotic disorders</td>
<td>Psychosis must arise uniquely within the context of intoxication or withdrawal, as manifest in history (clear temporal relationship)</td>
</tr>
<tr>
<td></td>
<td>Lab markers are often available</td>
</tr>
<tr>
<td></td>
<td>Psychosis is often limited</td>
</tr>
</tbody>
</table>
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Epidemiology and Clinical Course
Schizophrenia: Incidence and Prevalence

- Point Prevalence ~5 per 1000 population,
- Range is 2.7 to 8.3 per 1000
- Lifetime prevalence rates similar
- Incidence ~0.20 per 1000 per year, or 20 per 100,000 per year
- Range is 0.04 to 0.58 per 1000 per year (Beiser et al 1993, Rajkumar 1993)
Risk Factors: Summary

- Genetics
- Winter birth
- Maternal infections and birth complications
- Advanced paternal age
- Substance abuse (MJ, early, heroic)
- Ethnicity and immigration
- Autoimmune processes
- Urbanicity
Risk Factors: Family Aggregation

- General Population 0.5 - 1%
- First degree relatives 6%(3-7%)
  - Parent 6%
  - Sibling 10%
- Two affected parents 46%
- Monozygotic twin 40-60%
The figure illustrates the risk of developing schizophrenia based on the degree of genetic relationship to a person with schizophrenia. The risk is highest among identical twins, with a risk of 48%. Among first-degree relatives (parents, siblings, children), the risk ranges from 6% to 13%. Second-degree relatives (uncles/aunts, nephews/nieces, half siblings) have a lower risk, with 5% to 6%. The risk is even lower for third-degree relatives (first cousins) at 2%. The general population has the lowest risk at 1%.

- **Identical twins**: 48% risk
- **Fraternal twins**: 17% risk
- **Children**: 13% risk
- **Siblings**: 9% risk
- **Parents**: 6% risk
- **Half siblings**: 6% risk
- **Nephews/Nieces**: 4% risk
- **Uncles/Aunts**: 2% risk
- **First cousins**: 2% risk
- **General population**: 1% risk

Colors represent the percentages, with green for 12.5%, orange for 25%, blue for 50%, and red for 100%.
Winter Births and Birth Complications

- Season of Birth: winter births, small relative risk on the order of 10% increase, possible relation to maternal influenza in second trimester pregnancy.
- Birth Complications: relative odds of about two for those with one or another sort of birth complication.
- Recent meta-lab analysis: (1) complications of pregnancy [bleeding, diabetes, rhesus, preeclampsia], (2) abnormal fetal growth and development, (3) complications of delivery, (variable support for malnutrition, extreme prematurity and hypoxia or ischemia as possible causes).
- Studies tend to be small in number, Effect Size is small, but findings consistently emerge.
Maternal Infections

- Infections and the Immune System: second trimester of pregnancy during an influenza epidemic are at a higher risk of developing schizophrenia is consistent with the neurodevelopmental various schizophrenia.
- Evidence that having antibodies to toxoplasmosis gondii have higher prevalence for schizophrenia (Fuller-Torrey).
- Relative risk of 5.2 for individuals with documented infection by the rubella virus during fetal development (one study).
- High risk of psychosis and individuals whose mothers had higher levels of antibodies to herpes simplex virus.
Advanced Paternal Age

- Slightly elevated parental ages occasionally noted, recently evidence provided stronger evidence for the role of parental age and schizophrenia. I.e. maximum relative risk of 2.96 [95% confidence interval and bracket in the group aged 55 years or older comparison with a paternal age of 20 to 24 years.

- Current population-based cohort research suggests that the increased risk of schizophrenia related to advancing paternal age seem significant only among those without a family history of schizophrenia indicating the possibility that mutations accumulate in sperm.
Cannabis Use and Abuse

- Numerous case-control studies show the persons who have schizophrenia are more likely to have taken or be using cannabis (Hall and Degenhardt 2000).
- Risk for developing schizophrenia is 2 to 25 times higher in persons who have used cannabis (Arsenault et al 2002, van Os et al 2002, Weiser et al 2003, Zammit et al 2002).
- Individuals in the premorbid phase of schizophrenia might be responding to initial, mild symptoms of schizophrenia by using drugs.
- Could be that cannabis precipitates or even causes the episode of schizophrenia (especially early and heroic).
Ethnicity and Immigration

- United Kingdom, immigrants from Africa or the Caribbean and their second-generation offspring have rates of schizophrenia up to 10 times higher than those in the general population.
- Immigrant groups who do not have black skin do not have higher rates and because second-generation is affected, the stresses of immigration are unlikely to be causative.
Autoimmune Diseases/Processes

- Small but consistent literature suggests persons have schizophrenia may have resistance to autoimmune disorders
- Studies have consistently shown individuals who have schizophrenia are less likely to have rheumatoid arthritis.
- Other autoimmune disorders that have been linked to schizophrenia include thyroid disorders, type I diabetes, celiac disease.
- Ongoing clinical trials of anti-inflammatory and antibiotic agents for schizophrenia
Urban Residence

- Faris and Dunham (1930’s), showed addresses of first admissions for manic-depressive illness were contributed more or less randomly throughout Chicago,
- admissions for schizophrenia tended to come from the center of the city with rates decreasing as one moves outwards into zones of transition portion class and family neighborhoods.
- The relative risk of developing schizophrenia is about 2 to 4 times higher for those born in urban areas.
NATURAL HISTORY OF SCHIZOPHRENIA

Adapted from J.A. Lieberman
Course of Illness: Premorbid Childhood Developmental Abnormalities

- Early studies: offspring of schizophrenic patients were more likely to have lower IQ, poor attention skills, thought disorder like symptoms, poor social adjustment, and psychiatric symptoms.
- Recent studies: individuals who have schizophrenia differ from their peers even in early childhood in a variety of developmental markers such as age of attaining developmental milestones, level of cognitive functioning, educational achievement, neurological and motor development, social competence, and psychological disturbances.
- Association with low IQ is specific to schizophrenia because it was not found in bipolar disorder.
Course of Illness: Premorbid Childhood Developmental Abnormalities

- No causal paths linking developmental markers for schizophrenia.
- Individuals may have experienced childhood or general pan developmental impairment early in their childhood.
- 1972 – 1973 New Zealand birth cohort study showed that schizophrenic subjects may have suffered significant deficits in motor, language, and cognitive development in the first decade of their lives.
- Linking between childhood developmental abnormalities and schizophrenia echoes the hypothesis that schizophrenia is a neurodevelopmental disorder for which causes may be traced to defect in the early brain development.
Course of Illness: Prodrome

- Cognitive deterioration begins before onset of psychosis
- 25-50% have poor premorbid adjustment
- Negative symptoms tend to occur approximately five years before the initial psychotic episode
- Positive symptoms onset much closer to the first hospitalization
Course of Illness: Onset

- Approximately 50% have acute onset,
- 50% have a long prodrome
- The age of onset varies to men and women with males tending to have a younger onset
- Peak in incidence for males and females is in the decade between the ages of 15 and 24 years
- The peak for young adults is more marked for males and women have a second peak in the years between the ages of 55 and 64 years.
Course of Illness: Onset

- morbidity for schizophrenia peaks in young adulthood
- Average age of onset:
  - women is 29,
  - men is 25 (Hafner et al 1998, Jablensky and Cole 1997)
- Males have an approximately 30 to 40% higher lifetime risk for schizophrenia
Course of Illness: Post First Episode Psychosis

- 35% Multiple Episodes - No Symptoms
- 31% Multiple Episodes - Symptoms
- 16% Single Episode Only
- 7% Single Episode - No Recovery

Long-term (> 6 years) follow-up study of clinical outcome in 436 patients with a first episode of schizophrenia*

* Additional data: Died during first episode = 1%, Pattern of illness cannot be determined = 9%

Course of Illness: Progression

- 9% to 38% of individuals with schizophrenia will achieve a sustained symptomatic and functional recovery after one or more episode of psychosis (Svedberg et al 2001, Harrison et al 2001)
- 5% to 22% of first episode patients recover without a subsequent recurrence of symptoms (Lee et al 1998, Shepherd et al 1989, Wiersma et al 1998)
Course of Illness: Progression

- 1/3: chronic unremitting with poor outcome
- 1/2: undulating course with partial or full remissions followed by recurrences in an unpredictable pattern
- Small minority steady recovery (~ 1/10)

Ciompi, Schiz Bull, 1980
Course of Illness: Stabilizing/Relapsing

- The clinical progression occurs in the first decade followed by relative stability or improvement (Hafner et al 1997, Harrison et al 2001)
- Duration of untreated illness, as well as number of relapses predict poorer outcome
- Studies that are not strictly prospective can be deceptive because there’s a tendency to focus on a residue of chronic cases making the disorder see more chronic than it actually is
- More recently, 55% moderately good outcomes, 45% poor outcomes in 25-40 year follow up studies
Course of Illness: Stabilizing/Relapsing

- 10% of patients will die by suicide
- Long term mortality is 5x general population for men and 2x for women with schizophrenia
- Suicide accounts for half of these differences.
- Highest rate of completed suicide during the early recovery phase of illness (Kua et al 2003)
- Also increased lifetime risk for cardiovascular disease, diabetes, lungs disease and accidents (Brown et al 2000)
Course of Illness: Outcome

- Predictors of outcome remain elusive
- 13 prospective studies on course of illness in first onset cohorts:
  - negative symptoms predicted poor outcome
  - gradual onset predicted poor outcome
- Influenced by social variables, including socioeconomic position and marital status
- Scandinavian research suggest that parents of persons or have schizophrenia are likely to come from a higher, not lower social position
Course of Illness: Outcome

- Competitive employment < 20%
- Supported employment;
  - Lasts approx several months,
  - as many as 50% of patients who attain work having unsatisfactory job terminations.
- Achieve lower educational levels and will be expected by socioeconomic status
- Deficits in iADL’s (i.e. public transportation, cooking, finding/caring for living quarters, money management, and medication adherence).
Approximate two thirds with schizophrenia unable to fulfill basic social roles even when symptoms are in remission.

Premorbid social competency is among the best predictors of long-term outcome.

Minimal progress has been made in treating major role impairments associated with schizophrenia.
Course of Illness: Outcome

- Risk of being single, compared with those never diagnosed as having schizophrenia, peak at the time of admission to hospital remained high for decades afterward
- More likely be unmarried than other members of age cohort
- Effect is greater for males possibly because their earlier onset occurs during the years of primary social maturation.
- More likely to be unemployed many years earlier
Course of Illness: Outcome (Developing Countries Paradox)

- Better prognosis seems to occur in so-called "developing" countries, risk of sample bias
- Schizophrenic persons in developing countries are less likely than those in developed countries to have been chronically psychotic over the period of follow-up and are more likely to have no residual symptoms after five years
- A possible interpretation is that the environment of recovery in the developed world is more pernicious, involving harsher economic competition, a greater degree of stigma, and smaller family networks to share the burden of care for persons and have schizophrenia
Prognosticating Factors

- Clinical syndrome
- Diagnostic
- Environmental
- Treatment
- Genetic
Prognosticating Factors: Clinical

  - Poor premorbid social and school function
  - Insidious onset
  - Early onset
  - Prominent and severe negative symptoms
  - Prominent and severe cognitive symptoms
  - Male sex
Prognosticating Factors: Clinical

- Clinical features of good prognosis
  - Acute onset of illness with identifiable stressor (van Os et al 1994)
  - Paucity of negative or cognitive symptoms
  - Female sex
- Women typically have a milder form of illness, with less severe pathology, better recovery, shorter and fewer hospitalizations (Lee et al 1998, Leung and Chue 2000)
Prognosticating Factors: Diagnostic

- Longer duration of illness i.e. greater than 6 months, is associated with worse prognosis
- Lack of prominent mood symptoms is associated with worse prognosis
- Brief psychosis, schizophreniform and schizoaffective diagnoses have better outcomes (Svedberg et al 2001)
Prognosticating Factors: Environmental

- Predictors for poor prognosis include
  - Perinatal obstetrical complications
  - CNS viral infections in youth
  - Substance abuse including cannabis
  - Living in developed first world countries
Prognosticating Factors: Treatment

- General improvement in outcomes is seen after introduction in antipsychotic medications in mid 20th century
- Antipsychotic use is associated with reduced likelihood of relapse after recovery from a first episode of psychosis (Crow et al 1986, Kane et al 1982)
Prognosticating Factors: Treatment

- Recurrent episodes early in the course of illness associated with development of chronic residual symptoms (Rabiner et al 1986)
- Strongest predictor of long term outcome is the amount of time patients are psychotic in the first two years after illness onset (Harrison et al 2001)
- Conclusion: Relapse prevention through early treatment and maintenance therapy may improve long term outcomes
Prognosticating Factors: Genetic

- Some gene abnormalities may be associated with more severe illness
- Associations are speculative at present
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Genetics of Schizophrenia
Linking Schizophrenia Risk Genes to Abnormal Behavior?

- The functions of the proteins concerned?
- The cells in which they are expressed?
- The time during which they are functional?
- The circuits in which they function?
- How mutations lead to circuit dysfunction?
- How circuit dysfunction leads altered behavior and psychopathology?
Gene Discovery

- Identify chromosomal loci or genes containing risk variants, which then can be investigated using fine mapping association analysis in families or case-control samples for positional cloning of the gene.
- Many studies reported, but results are surprising given that genes subsequently identified at several of these loci have modest effect sizes, involve multiple risk variance at each gene, and may contribute to susceptibility in certain populations but not in others.
- Suggestion is that multiple risk variants or more than one susceptibility gene may be involved at each loci.
Genetics of Schizophrenia: Types of Analyses

- Association Studies
- Linkage Analysis
- Cytogenetic abnormalities
Familial Aggregation in Schizophrenia: Early Studies

- Early studies show greater risk of schizophrenia in first degree relatives of schizophrenic probands, but...
  - no matched controls
  - researchers not blinded to diagnosis/presence of illness in family
  - interviews and diagnostic criteria not standardized
  - 40 studies summarized by Gottesman et al.
Familial Aggregation in Schizophrenia: Later Studies

- well-controlled studies, n=11 in past 20 years, with DSM III, or RDC criteria, and matched controls, confirm.....
  - first degree relatives of schizophrenic probands have a significantly increased risk for the disorder compared to relatives of non-affected controls, although at levels of risk less than those found in early studies
  - first degree relatives = parents, full siblings, offspring
Familial Aggregation in Schizophrenia: Later Studies

- Risk of having schizophrenia in first degree relatives of schizophrenia probands is always higher than relatives of controls, an average of 11 times higher.
- Risk to relatives of controls is same risk in general population studies.
- Risk for schizophrenia in first degree relatives of affected probands varies widely, from 1.4% to 16.2%, (vs. 0.0 to 1.9%): possible result of sample size OR population differences OR diagnostic criteria.
- Average risk for first degree relatives is 6.4%, ranging from 3% to 7%.
Familial Aggregation in Schizophrenia: Specific Risks

- General Population: 0.5 - 1%
- First degree relatives: 6% (3-7%)
  - Parent: 6%
  - Sibling: 10%
- Two affected parents: 46%
- Monozygotic twin: 40-60%
Familial Aggregation in Schizophrenia

- Is increased incidence of schizophrenia in first degree relatives a function of genetic or environmental factors?

- Evidence is derived from twin and adoption studies.
Familial Aggregation in Schizophrenia: Twin Studies

- All studies demonstrate that the risk for schizophrenia in co-twins of schizophrenia proband twins is much higher in MZ twins than in DZ twins
- Range of concordance for MZ pairs is 31% to 76% (median is 50%)
- Range of concordance for DZ pairs is 6% to 28% (median is 15%)

Gottesman and Shields, Tienari, Kendler and Robinette, Cannon, Onstad
The major twin studies agree that the heritability of liability to schizophrenia is between 0.6 and 0.9, (i.e. the proportion of the liability to schizophrenia due to genes vs. environment)

This is twice the heritability of liability to schizophrenia of first degree relatives of schizophrenia probands.
Familial Aggregation in Schizophrenia: Twin Studies

- Conclusion: Genetic factors play a major role in the familial transmission of schizophrenia.

- HOWEVER: Studies with MZ twins ALSO demonstrate a role for environmental factors, in addition to genetic factors, in the expression of the disorder.
Familial Aggregation in Schizophrenia: Adoption Studies

- Adopted-away persons with schizophrenia and schizophrenia spectrum illnesses
  - significantly greater prevalence of schizophrenia in biological relatives (13%)
  - **not** in adoptive relatives, as compared to adopted away controls (3%).
Familial Aggregation in Schizophrenia: Adoption Studies

- The majority of adoption studies find limited evidence for non-genetic, i.e. familial/environmental factors for schizophrenia.
Familial Aggregation in Schizophrenia-Spectrum Disorders

- Risk for non-schizophrenia psychotic disorders (especially schizoaffective and psychotic disorder NOS) is increased in relatives of schizophrenia probands; 9% average (Gottesman)

- Schizotypal personality disorder is more common in relatives of schizophrenic probands. Absolute rates vary widely across studies, from 4.2 to 26.8% (Baron, Kendler, Siever)
Familial Aggregation in Schizophrenia-Spectrum Disorders

- Neuropsychological deficits seen in schizophrenia such as impairments in eye tracking and attention, aggregate in relatives of those diagnosed with schizotypal personality disorder (Cornblatt, Levy)
- Evidence for relationship between schizoid and paranoid personality disorders and schizophrenia is limited and inconclusive
Genetics of Schizophrenia: Linkage Studies

- Objective is to identify regions of the genome that are co-transmitted with the disease in families
- DNA fragments each containing many genes are examined and compared
- Whole genome can be screened efficiently
- Limited power to detect individual genes: i.e. limited resolution
Genetics of Schizophrenia: Linkage Studies

- DNA strands (from the entire genome) cleaved at specific sites by restriction endonucleases
- Fragment sizes from every chromosome will tend to be similar within family groups
- Looking for association between unique lengths of DNA fragments and the presence of schizophrenia within family groups
- THEN specific candidate genes within affected DNA fragments can be examined and compared
Chromosomal Regions Implicated in Schizophrenia

- 1q22
- 1q23
- 1q42.1
- 5q33
- 5q34
- 6p22
- 6q23
- 8p12
- 8p21
- 13q34
- 22q11

Gogos and Gerber 2006
Chromosomal Regions Implicated in Schizophrenia 
(with associated candidate genes)

- 1q22    CAPON
- 1q23    RGS4
- 1q42.1  DISC1
- 5q33    EPN4
- 5q34    GABA(A) receptors
- 6p22    DTNBP1
- 6q23    TAAR6
- 8p12    NRG1
- 8p21    PPP3CC
- 13q34   G72
- 22q11   PRODH, ZDHHC8, COMT

Gogos and Gerber 2006
Chromosomal Regions and Specific Genes Implicated in Schizophrenia (strongest evidence for association)

- 1q42.1 DISC1, DISC2
- 6p22 DTNBP1
- 8p12 NRG1
- 13q34 G72
- 22q11 PRODH
- 22q11 COMT

Gogos and Gerber 2006
DISC-1: Disrupted In SChizophrenia

- Balanced translocation involving chromosomes 1 and 11
- evidence for co-segregation of a chromosomal translocation with clinical phenotype similarities Scottish pedigree
- high degree of linkage was strong evidence that the translocation was responsible for the mental illness at least in this particular family
- Strongly linked to schizophrenia, depression and mania
- DISC I is multifactorial with possible involvement in:
  - cytoskeletal centromere function and
  - cell membrane receptor localization and
  - signal transduction
DTNBP1: Dysbindin

- Dystobrevin-binding protein I, 6p22
- Reduction in this protein results in a reduction of presynaptic glutamate release, may increase proportion of D2 receptors
- May influence exocytotic glutamate release
- Normally wide distribution in the brain including pyramidal neurons, hippocampus and the dorsolateralprefrontal cortex
- Has found to be reduced in both hippocampus and DLPFC in schizophrenia
Neuregulin 1

- A family of growth and differentiation factors that interact with transmembrane receptors inducing growth and differentiation of epithelial, neuronal, glial, and other cell types.
- Implicated in neuronal differentiation and myelination and in the development and functioning of glutaminergic NMDA receptor systems.
- Stimulation suppresses NMDA receptor activation in the prefrontal cortex and this suppression may be more pronounced in schizophrenia.
22q11: COMT
Catechol-O-Methyltransferase

- small interstitial deletions, 1:4000 live births
- at least a 20 fold increase in risk for psychosis
- also presents with craniofacial morphology, renal problems, and congenital heart disease
- Linkage with Proline dehydrogenase (PRODH).
- COMT has a role in dopamine catabolism. A functional polymorphism that substitutes a valine for methionine reduces the activity of the enzyme. Having more copies of the methionine allele would result in higher dopamine levels and thus might be expected to increase the risk of schizophrenia
22q11: PRODH: Proline Dehydrogenase

- 22q11 microdeletion associated with velocranial facial syndrome
- Risk of schizophrenia for a patient with 22q11 microdeletion is 25 to 30 times the general population,
- Rate of this microdeletion in schizophrenia is 12 to 80 times higher than general population
- Family-based samples demonstrate the presence of several PRODH variants
- PRODH encodes for an enzyme that could indirectly influence glutamate-mediated transmission
Functional Genomics and Schizophrenia

- Schizophrenia is a complex genetic disorder
- Schizophrenia is likely both:
  - a continuum of an illness phenomenon, and
  - a collection of multiple illnesses with overlapping phenotypes
- Expression likely involves:
  - the interplay of multiple susceptibility genes,
  - epigenetic factors,
  - environmental influences.
- Heritability is substantial, and etiology is poorly understood
- Currently, overwhelming number of implicated genes
Schizophrenia Working Group of the Psychiatric Genomics Consortium

- multi-stage schizophrenia genome-wide association study
- up to 36,989 cases and 113,075 controls.
- identified 128 independent associations
- over 108 conservatively defined loci that meet genome-wide significance,
- 83 of which have not been previously reported.
SWG-PGC

- Associations enriched among genes expressed in brain, providing biological plausibility
- Suggest:
  - Schizophrenia is a highly heritable disorder
  - Genetic risk is conferred by a large number of alleles
- Potential to provide new insights into aetiology
- Associations with immunity genes providing support for the speculated link between the immune system and schizophrenia.
Genetic Associations to Biological Mechanisms

- associations at each locus have not yet been firmly linked to specific genes.
- schizophrenia-associated loci contain multiple genes involved in synaptic function and plasticity, particularly genes involved in:
  - glutamatergic neurotransmission (GRM3, GRIN2A, GRIA1, and SLC38A7) and
  - neuronal calcium signaling (CACNA1C, CACNB2, CAMKK2, CACNA1I, NRGN, and RIMS1).
- DRD2, which a priori is possibly the strongest of all conceivable candidate genes for schizophrenia based on function, is also associated with the disorder.
Pleiotropy

- when one gene/genetic variant contributes to multiple phenotypes
- characteristic of identified genetic risk factors for neuropsychiatric disorders.
- common genetic risk variants between:
  - schizophrenia
  - bipolar disorder
  - major depressive disorder
  - Autism Spectrum Disorder
  - Intellectual disabilities
  - attention deficit hyperactivity disorder (less consistent than that for other phenotypes).
Preliminary work suggests the first GWAS-identified schizophrenia risk gene associated with cognition, clinical subdimensions, and brain phenotypes. Small samples limit the robustness of the conclusions that have emerged so far from this sort of research.
Are New Genetically-based Treatments Inevitable?

- undiscovered treatments for schizophrenia are possible
- unlikely that the only effective treatment has already been discovered
- opportunities for better understanding of pathogenesis that flow from the genetic data have potential to accelerate new drug discovery.
Genetics of Schizophrenia:
Summary Points

- Schizophrenia is a genetic illness
- Single schizophrenia gene has not been discovered
- Illness is likely polygenetic
- Interaction of genetic misinformation and the environment likely results in phenotypic expression(s) of the illness
- “Similar to many common complex disorders, schizophrenia is a multifactorial disorder that is characterized by the contribution of multiple susceptibility genes that could act in conjunction with epigenetic processes and environmental factors.”

Gogos and Gerber 2006
So, What Causes Psychosis?

- **Genes**
  - Number or combination of target genes normally dispersed through genome

- **Neurobiology**
  - Expression of gene products

- **Environmental Insults**
  - Advanced paternal age (Malaspina et al 2001)
  - Urban living, ethnic minorities (Johns et al 2004, Eaton and Harrison 2000)
  - Social isolation and interruption (Pedersen 2001)
  - Obstetrical Insults (Susser 1992)

- **Behavior**
  - Substance abuse (Arsenault et al 2002)