

Schizophrenia, Schizotypal, and delusional disorders

ICD-10 Classification

F20 Schizophrenia

- F20.0 Paranoid Schizophrenia
- F20.1 Hebephrenic Schizophrenia
- F20.2 Catatonic Schizophrenia
- F20.3 Undifferentiated Schizophrenia
- F20.4 Post-schizophrenic depression
- F20.5 Residual Schizophrenia
- F20.6 Simple Schizophrenia
- F20.8 Other Schizophrenia
- F20.9 Schizophrenia, undifferentiated

A fifth character may be used to classify course:

- .x0 Continuous
- .x1 Episodic with progressive deficit
- .x2 Episodic with stable deficit
- .x3 Episodic remittent
- .x4 Incomplete remission
- .x5 Complete remission
- .x8 Other
- .x9 Course uncertain, period of observation too short

F21 Schizotypal disorder

F22 Persistent delusional disorders

- F22.0 Delusional disorders
- F22.8 Other persistent delusional disorders
- F22.9 Persistent delusional disorder, unspecified

F23 Acute and transient psychotic disorders

- F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia
- F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia
- F23.2 Acute schizophrenia-like psychotic disorder
- F23.3 Other acute predominantly delusional psychotic disorder
- F23.8 Other acute and transient psychotic disorder
- F23.9 Acute and transient psychotic disorder, unspecified

A fifth character may be used to classify the following subtypes:

- .x0 Without associated acute stress
- .x1 With associated acute stress

F24 Induced delusional disorder

F25 Schizoaffective disorders

F25.0 Schizoaffective disorder, manic type

F25.1 Schizoaffective disorder, depressive type

F25.2 Schizoaffective disorder, mixed type

F25.8 Other schizoaffective disorders

F25.9 Schizoaffective disorder, unspecified

A fifth character may be used to classify the following subtypes :

.x0 Concurrent affective and schizophrenic symptoms only

.x1 Concurrent affective and schizophrenic symptoms plus persistence of the schizophrenic symptoms beyond the duration of the affective symptoms

F28 Other non-organic psychotic disorders

F29 Unspecified non-organic psychosis

Psychosis – Epidemiology and basic principles

Incidence

- Varies between 7-60 per 100,000 population per year
- Highest incidence & co-morbidity in inner city areas
- Subgroups:
 - Schizophrenia 40%
 - Schizophreniform disorder 22%
 - Bipolar disorder (manic psychosis) 17%
 - Schizo-affective disorder 12%
 - Psychotic depression 6%
 - Delusional disorder 3%

Racial Differences

		New cases per 100,000 per year
Londoners (Bhugra et al, 1997)	White	35
	African-Caribbean	66
Caribbean	Barbados	32
	Trinidad	22
	Jamaica	21

Psychotic symptoms in general population (van Os et al, 2001)

- Using CIDI in general population:
 - 17.5% report broadly defined psychotic experiences
 - 4.2% report 1st rank symptoms
 - 1.5% meet criteria for caseness

(F20 -) Schizophrenia

Historical concepts

Clinical descriptions

- ‘Démence précoce’ (Morel, 1856)
- ‘Dementia paranoides’ (Kahlbaum, 1860)
- ‘Katatonie’ (Kahlbaum, 1868)
- ‘Hebephrenia’ (Hecker, 1870)

Early concepts

- *Greisinger (1870): ‘unitary psychosis’* – schizophrenia as part of a single psychotic disorder
- *Emil Kraepelin (1893):* divided mental illness into *dementia praecox* (including hebephrenia, catatonia, paranoid schizophrenia and simplex schizophrenia), *manic depressive psychosis* and *paranoia*; ‘dementia praecox’ was presumed organic and seen as a ‘single morbid process’
- *Eugen Bleuler (1911): The Schizophrenias* – collection of psychoses with fundamental symptoms (Four As) representing the splitting (‘Schizo’) of psychic functions:
 1. Ambivalence (coexisting conflicting ideas)
 2. Affective incongruity (the key element for Bleuler)
 3. Loosening of Associations
 4. Autism (withdrawal)
 - Accessory symptoms include hallucinations and delusions
- *Jaspers (1913):* schizophrenia characterized by *non-understandability* of mental functions (‘praecox feeling’)

Sociological concepts

- schizophrenia not an illness but a myth (Szasz, 1961)
- a role forced upon the individual (Goffman, 1961)
- a product of society (Scheff, 1966, Rosenhan, 1976)
- a sane reaction to an insane world (Laing, 1976)

Other concepts / classifications

- *Langfeldt (1939): process schizophrenia* (insidious onset, chronic course) versus *schizophreniform psychosis* (acute onset, affective symptoms, good outcome)
- *Leonhard (1957): systemic schizophrenia* (catatonia, hebephrenia, paraphrenia) versus *non-systemic schizophrenia* (affect-laden paraphrenia, schizophasia, and periodic catatonia)
- *Strömgen (1968): brief reactive psychosis* (‘psychogenic psychosis’)
- *Kurt Schneider (1959) - 1st rank symptoms*
 - 1 in 5 patients have never experienced a 1st rank symptom
 - 1 in 10 non-schizophrenic patients have experienced a 1st rank symptom

- twin studies have shown that Schneider's 1st rank symptoms defined a form of schizophrenia with the least evidence of inheritance
- *Timothy Crow (1980) - Type I and Type II Schizophrenia*
 - Type I is characterized by acute onset, positive symptoms, normal ventricles and good response to medication. Thought to be associated with increased dopaminergic activity
 - Type II presents with insidious onset, negative symptoms, enlarged ventricles, poor response to medication, and deteriorating course

Schizophrenic thought disorder

- Bleuler (1951) - loosening of associations, condensation
- Cameron (1944) - over-inclusive thinking
- Goldstein (1944) - concrete thinking
- Schneider (1959) - derailment, drivelling, desultory thinking, fusion, omission, substitutions
- *Omission* - a sudden discontinuation of a chain of thought
- *Knight's move thinking* - similar to flight of ideas but the omitted connection bears a more tangential relation to the whole
- *Derailment* - a disruption of the continuity of speech by the insertion of novel and inappropriate material to the chain of thought
- *Fusion* - a merging and 'interweaving' of separate ideas
- *Drivelling* - refers to the muddling of elements within an idea to the extent that the meaning is totally obscured to the listener
- *Desultory thinking* - ideas are expressed correctly in terms of syntax and grammatical construction, but juxtaposed inappropriately – the ideas would be comprehensible if expressed in another context or in isolation
- *Thought blocking* - a sudden cessation of speech mid-sentence with an accompanying sense of subjective distress; patients may complain that their minds have 'gone blank' or that their thoughts have been interfered with
- *Condensations* - common themes from two or more separate ideas are combined to form an incomprehensible concept
- *Schizophasia / Word salad* - incomprehensible speech
- Schneiderian terms:
 - *verschmelzung* – fusion
 - *faseln* – muddling
 - *entgleiten* – snapping off
 - *entgleisen* – derailment

Diagnostic Criteria

- diffuse (overdiagnosable) and unreliable concept of schizophrenia (especially in the USA)
 - phenomenological (Kraepelinian, Schneiderian) concepts in Europe
 - regional differences exposed in International Pilot Study of Schizophrenia (IPSS; WHO, 1973) – psychiatrists in USA and USSR diagnosed schizophrenia twice as often as those in seven other countries
 - pressure to standardize diagnosis led to development of operational and diagnostic criteria:
 - *Research Diagnostic Criteria* (Spitzer *et al.* 1975) – illness duration of at least 2 weeks. Schneiderian concept.
 - *St. Louis criteria* (Feighner *et al.* 1972) – 6 months’ duration, with no prominent affective symptoms. Personal and family history should be taken into account. More restrictive, favour poor prognosis.
 - *CATEGO* – computerized diagnostic algorithms generated from Present State Examination (Wing *et al.* 1974). Updated now to Catego 5 generated from SCAN-PSE-10. Based on the Schneiderian concept of schizophrenia. No account is taken of symptom duration.
 - *DSM Criteria* – favours a more ‘Kraepelinian’ concept of schizophrenia.
- Multiaxial system :
- Axis I major clinical syndrome
 - Axis II developmental or personality disorder
 - Axis III psychosocial stressors (1-7 scale); general medical conditions
 - Axis IV highest level of functioning in the last year (GAF : 10-100 scale)

ICD-10 Criteria

G1. Either at least one of the syndromes, symptoms and signs listed under (1) below or at least two of the symptoms and signs listed under (2) should be present for most of the time during an episode of psychotic illness lasting for at least 1 month (or at some time during most of the days)

(1) At least one of the following must be present:

- a) thought echo, thought insertion or withdrawal, or thought broadcasting;
- b) delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception
- c) hallucinatory voices giving a running commentary on the patient’s behaviour, or discussing the patient between themselves, or other types of hallucinatory voices coming from some part of the body
- d) persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with beings from another world)

- (2) Or at least two of the following :
- a) persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent overvalued ideas
 - b) neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech
 - c) catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor
 - d) 'negative' symptoms, such as marked apathy, paucity of speech and blunting or incongruity of emotional response

Schneider's symptoms of the first rank (FRS) (c. 1959)

1. auditory hallucinations:
 - hearing thoughts spoken aloud
 - third-person hallucinations
 - hallucinations in the form of a commentary
 2. delusions of passivity:
 - thought withdrawal, insertion, thought broadcasting
 - feelings or actions experienced as made or influenced by external agents
 3. somatic passivity
 4. delusional perception
- Limitations:
 - *specificity*: also occur in other 'functional psychoses':
 - 20 % in psychotic depression
 - 40 % in acute mania (Pope & Lipinski, 1977)
 - 15 % in affective disorders
 - 2 % of patients with neurosis in the International Pilot Study of Schizophrenia
 - *sensitivity*: 20 % of chronic schizophrenics never showed FRS
 - of no predictive / prognostic value – they do not distinguish between schizophrenia and cyclothymia, which was Schneider's initial assertion

Second-rank symptoms

- perplexity
- emotional blunting
- other hallucinations and delusions

Most Frequent Symptoms of Acute Schizophrenia

- | | |
|---------------------------|-----|
| • Lack of insight | 97% |
| • Auditory hallucinations | 74% |
| • Ideas of reference | 70% |
| • Suspiciousness | 66% |
| • Flatness of affect | 66% |

- Voices speaking to the patient 65%
- Delusional mood 64%
- Delusions of persecution 64%
- Thoughts spoken aloud 50%

The Prodrome in Schizophrenia

Prodromal symptoms (after Yung & Jackson, 1999)

- Reduced concentration and attention
- Reduced drive, motivation; anergia
- Depressed mood
- Deterioration in role functioning
- Sleep disturbance
- Anxiety
- Social withdrawal
- Suspiciousness
- Irritability

PACE prediction study (McGorry, Phillips & Yung, 1999)

- Followed 65 patients with one or more of the following characteristics:
 1. Family history of psychotic illness
 2. Attenuated symptoms
 3. Brief, Limited, Incidences of Psychosis (BLIPS)

Group	Incidence of Psychosis (one year)
Family history of psychotic illness	37%
Attenuated symptoms	35%
Brief, Limited, Incidences of Psychosis (BLIPS)	25%

- In one year, 40% became psychotic.

Prodrome Treatment Trial (Phillips et al, 2000)

Intervention	Transition Rate to Psychosis
Non-specific intervention (watch and see)	36%
CBT + low dose risperidone	9.7%

- Those fully compliant with Risperidone afforded greatest protection at six months, with only a 5.6% conversion rate to psychosis.

Clinical Syndromes in chronic schizophrenia

Positive and Negative symptoms (Andreasen *et al.* 1983)

- Positive symptoms – hallucinations, delusions, formal thought disorder, bizarre behaviour
- Negative symptoms – affective blunting, alogia (impoverished thinking and speech), avolition/ apathy/ anhedonia/ asociality, disturbance of attention

Positive, Negative, and disorganization syndromes (Liddle, 1987)

- *Reality Distortion Syndrome* (delusions, hallucinations)
- *Psychomotor Poverty Syndrome* (poverty of speech, decreased spontaneous movement, unchanging facial expression, paucity of expressive gesture, lack of affective responsiveness, lack of vocal inflection)
- *Disorganization syndrome* (disorganization: inappropriate affect, incoherent speech, poverty of content of speech)
- syndromes are validated by recent factor-analytic and neuroimaging studies (Liddle *et al.* 1992)

Deficit syndrome (Carpenter *et al.* 1988)

- Primary, enduring negative symptoms reflect a distinct neural substrate
- emphasis on distinguishing primary from secondary negative symptoms (e.g. Parkinsonism, depressed mood)

Continuum of psychosis (Crow, 1990; Greisinger, 1870)

- single psychosis, with schizophrenia most severe, affective disorders least severe, schizoaffective disorders occupy intermediate position

Age Disorientation in Schizophrenia

- occurs in 25 % of long-stay patients
- patients tend to say that they are 5 years younger than their true age
- often say that they are close to the age they were at admission
- duration of stay in hospital is underestimated
- associated with:
 - a younger age of first admission
 - brain CT changes

Neurodevelopmental classification (Murray *et al.* 1992)

Congenital schizophrenia

- abnormality is present at birth

- more likely to involve minor physical abnormalities, abnormal personality, or social impairment in childhood
- more likely to be male and have a poor outcome

Adult-onset schizophrenia

- more likely to exhibit positive and affective symptoms
- may have a genetic predisposition to manifest symptomatology anywhere along a continuum from bipolar disorder, schizoaffective disorder, to schizophrenia

Late-onset schizophrenia

- presents after the age of 60
- good premorbid functioning
- more common in females
- often associated with auditory and visual sensory deprivation
- organic brain dysfunction is often present

Epidemiology

- **incidence:** 15-20 per 100,000 per year (0.2 per 1000)
- **point prevalence** in Europe: 2.5-5 per 1000
- **prevalence:** 0.5-1 %
 - higher in:
 - Sweden
 - Croatia
 - Slovenia
 - Southern/ Western Ireland
 - Catholics in Canada
 - Tamils of Southern India
 - lower in:
 - US Hutterites
 - Anabaptists in USA
- **lifetime risk:** 0.9 %
- in 90 % of patients, **onset** typically occurs between the ages 15 and 45
- annual (direct and indirect) cost of schizophrenia > £ 1.6 billion in the UK, and \$20 billion in the USA (Rupp & Keith, 1993)

Aetiology

Associations

- patients with chronic *temporal lobe epilepsy* have an increased risk of developing schizophrenic symptoms
- patients with *Huntington's chorea* have an increased risk of developing schizophrenic symptoms
- associations exist with brain injury (Achte et al.,1969)

Family Studies

- lifetime risk of schizophrenia, schizoaffective disorder, and schizotypal personality is increased (by over 10 times) in 1st-degree relatives of patients with schizophrenia. Kendler *et al.* (1994)
- risk of both schizophrenia and mood disorder is increased in 1st-degree relatives of patients with schizoaffective disorder
- risk of bipolar illness is not increased in 1st-degree relatives of patients with schizophrenia
- average lifetime risk of 5% among 1st-degree relatives, compared to 0.2-0.6% among 1st-degree relatives of controls
- smooth-pursuit eye-tracking abnormalities in 34 % of parents of schizophrenics (Holzman, 1974) and in schizotypal patients (Siever *et al.* 1993)
- evoked potential abnormalities are found in 'unaffected' 1st degree relatives

Relationship to schizophrenic	% schizophrenic
Parent	6
Sibling	10
Sibling and one parent affected	17
Children of one affected parent	13
Children of two affected parents	46
Uncles, aunts, nephews, etc.	3
Grandchildren	4
General population	0.86

Twin Studies

- MZ:DZ ratios = 48 %: 4% (Gottesman & Shields, 1972; Onstad *et al.* 1991)
- MZ twins discordant for schizophrenia show more brain abnormalities than normal co-twins (Suddarth *et al.* 1990)
- risk of schizophrenia in the offspring of an unaffected twin is the same as that of an affected twin

Adoption studies

- the rate of schizophrenia in adopted-away offspring of schizophrenics was higher than that in the adopted-away offspring of normal parents:
 - 10 % (Heston & Denny, 1968)

- 13 % (Kety *et al.* 1971)
- the rate of schizophrenia in the biological relatives of adoptees who became schizophrenic was much higher than that in the adoptive relatives
- the offspring of normal parents who, by misfortune, were raised by a schizophrenic adoptive parent, did not have an increased risk of the disease

Molecular Genetics

- gene located on chromosome 5 in 7 large pedigree families (Sherrington *et al.* 1988) but unable to replicate
- linkage studies of other chromosomes negative to date
- candidate genes:
 - D4 dopamine receptor gene on chromosome 11
 - serotonin receptor gene on chromosome 5
 - possible linkage reported for chromosome 6 – close to HLA region of C6
- *Pseudoautosomal locus* (Collinge *et al.* 1991) proposed to explain apparent gender-specific pattern of familial transmission

Perinatal factors

- some retrospective studies report more obstetric complications than normal controls
 - pregnancy and birth complications (PBCs) appear to be associated with early onset and possibly male gender
- prematurity, prolonged labour, hypoxia, and foetal distress have all been blamed - perhaps the common pathophysiological mechanism is hypoxic/ ischaemic neuronal injury
 - hypoxic damage to the periventricular vasculature may lead to ventriculomegaly
 - some brain structures, especially the hippocampus, are highly susceptible to hypoxic injury
- schizophrenia is more common (an excess of about 8 %) among people born in the winter than among those born in the summer (between January and April in the Northern Hemisphere, and between July and September in the southern hemisphere) Adams *et al.* 1999
- winter birth may be more common in patients without a family history of schizophrenia
- the colder the temperature around the third month of gestation, the higher the risk of subsequent schizophrenic illness
- reported association of possible exposure during 2nd trimester to 1957 A₂ influenza (O'Callaghan *et al.* 1991)

Childhood development and antecedents

- in a study of children interviewed aged 8-12 for cognitive disturbance, and later aged 26-30 the measures predicting schizophrenia were (Parnas *et al.* 1982) :
 1. poor rapport at interview
 2. social isolation
 3. disciplinary problems mentioned in school reports
 4. reports by the parents that the person had been passive as a baby and had shown a short attention span as a child
 5. fast recovery of galvanic skin responses

- later studies found that those who developed schizophrenia could be distinguished at age 11 by (Doone *et al.* 1994) :
 - a) greater hostility towards adults
 - b) speech and reading difficulties
- Fish *et al.* (1992) propose that *pan-dysmaturation* is associated with the development of schizotypal personality disorder and in some cases schizophrenia

Sex and age of onset

- mean age of onset is about 5 years earlier in men (28 years in men, 32 years in women)
- equal incidence between the sexes
- in women, the incidence is bimodal, with a peak in the 20's and also the 40's (higher incidence around the menopause) - perhaps due to a link with oestrogens down-regulating dopamine
- males:
 - more obstetric complications
 - poorer premorbid adjustment
 - poorer prognosis
 - more structural brain abnormalities
- the key variable determining severity of illness is age of onset
- fertility rates are reduced among schizophrenic patients by about 25 % compared to the general population

Social factors

- schizophrenia is over-represented among people of lower social class (classes IV and V)
 - **social drift hypothesis** (Goldberg & Morrison, 1963) - affected individuals move to lower socioeconomic classes as a consequence of the incompetence associated with schizophrenia; paternal occupations show normal class distribution
 - **social causation hypothesis / Breeder Hypothesis** (Farris & Dunham, 1939) - stresses related to socioeconomic deprivation are risk-increasing or inducing factors for schizophrenia
- increased prevalence in urban versus rural setting, especially for males (Lewis *et al.* 1992)
- patients with schizophrenia are more likely to have been born into socially deprived households (Castle *et al.* 1993)
- high rates of schizophrenia have been reported among migrants
- apparent 10-fold increased incidence among Afro-Caribbean migrants in the UK (Harrison *et al.* 1988)
- schizophrenics often live alone, unmarried, and with few friends, and these patterns began before the illness

Sociodevelopmental Risk Factors (van Os *et al.*, 2002)

- Follow up of 4045 people in Holland for 3 years, looking at odds ratio for developing psychosis

Factor	Odds Ratio (approx.)
Cannabis	13
Childhood Abuse	12
Urban/ Rural	5
Discrimination	3

- More than 50% of the risk could be attributed to pre-existing cannabis use

Dynamic and interpersonal factors

- Freud proposed that the illness developed as patients withdrew libido from external objects tried to restore meaning to a meaningless world by developing abnormal beliefs
- Klein proposed that failure to negotiate the paranoid-schizoid position was the basis of illness
- *schizophrenogenic mother* (Fromm-Reichmann, 1948)
- *Double binds* – Bateson *et al.* (1956):
 - an instruction is given overtly, but is contraindicated by a second more covert instruction
 - leaves the child able to make only ambiguous or meaningless responses, and schizophrenia develops when this process persists
- Wynne *et al.* (1958) identified *amorphous communications* (vague, indefinite, and loose) and *fragmented communications* (easily disrupted, poorly integrated, lacking closure) in parents of schizophrenic patients
- high ‘expressed emotion’ (EE) has proved to be a robust predictor of symptomatic relapse following discharge - those from high EE families relapse more frequently
- Lidz (1957):
 - *family skew* – dominant mother, and submissive father
 - *family schism theory* – parents maintain contrary views so that the child has divided loyalties

Life events

- Paykel (1978) calculated that experiencing a life event doubles the risk of developing schizophrenia in the subsequent six months
- compared to other psychiatric groups, schizophrenic patients do not have more life-events in the weeks or months preceding relapse or admission
- compared to normal controls, schizophrenics may have more life-events particularly clustered in the 3 weeks preceding relapse or admission

Neurodevelopmental versus neurodegenerative hypotheses

- *Neurodevelopment* (Murray *et al.* 1992; Waddington & Buckley, 1995, Weinberger, 1987) – static lesion from CNS disruption *in utero*, typical symptoms emerge later
- Evidence includes:
 - post-mortem and neuroimaging findings, excess of obstetric complications, minor physical anomalies, abnormal dermatoglyphics, season of birth phenomenon, epidemiological association with prenatal exposure to influenza infection

- *Neurodegenerative* (Kraepelin) – progressive degeneration
- Evidence includes :
 - deteriorative course of illness
 - gliosis seen in earlier PM studies, but not found in recent PM studies

The Brain in Schizophrenia

Post mortem studies

The brains of people with schizophrenia are :

- lighter (6 % decrease in brain weight)
- smaller (4 % reduction in anterior-posterior length)
- reduction in neuronal population in the temporal lobes, possibly on the left (Bogerts, 1993)
 - reversed planum temporale asymmetry
 - decreased area of hippocampus amygdala
 - reduced size of parahippocampal gyrus
- increased disorganization of neuronal cells in the hippocampus, parahippocampal gyrus, and entorhinal cortex (pre alpha cell migratory failure during 2nd trimester)

Neuroimaging

CT changes

- associated with:
 - poor premorbid adjustment
 - negative symptoms
 - a negative family history of schizophrenia
 - reduced parahippocampal volume
 - disorientation for age

Diffuse

- enlargement of the lateral and 3rd ventricles (non-progressive)
- cortical sulcal prominence
- enlarged lateral ventricles are correlated with:
 - male sex
 - early age of onset
 - neuropsychological impairment
 - poor response to treatment

Regional

- reduction in the volume of *medial temporal structures* such as the hippocampus and parahippocampal gyrus
 - in first episode patients (n=32), there is a 10% reduction in hippocampal volume compared to controls (Copolov, Velakoulis, Pantelis et al, 2000)
- volume reduction in language associated areas such as the superior gyrus and the planum temporale, and in the hippocampus-amygdala complex and parahippocampal gyrus
- changes more evident on the left side of the brain
- *cytoarchitectural disturbances* in the hippocampus, frontal cortex, cingulate gyrus, and entorhinal cortex

Functional brain imaging

- decrease in blood flow in *frontal and prefrontal cortex* (**hypofrontality**) - demonstrated with tests such as the Wisconsin Card Sorting Test
- the syndrome of ‘reality distortion’ was associated with increased blood flow in the left parahippocampal gyrus

Syndrome	regional Cerebral Blood Flow (rCBF) pattern
Psychomotor poverty	- rCBF in left dorsolateral prefrontal cortex (and left parietal cortex) ↑ rCBF in caudate nuclei
Disorganization	↓ rCBF in the right ventral prefrontal cortex - rCBF in the right anterior cingulate
Reality distortion	↓ rCBF in the posterior cingulate and left lateral temporal lobe - rCBF in the left parahippocampal gyrus (medial temporal lobe)

- auditory hallucinations appear to be associated with increases in the rCBF in language areas in the left frontal and temporal lobes
- patients experiencing auditory hallucinations showed increased blood flow in Broca’s area
- monitoring of ‘inner speech’ by areas in the left medial and superior temporal lobe may be impaired

Neurophysiological changes in schizophrenia

- EEGs show:
 - decreased α activity
 - increased θ activity (more in acute rather than chronic patients)
 - epileptiform activity (increased fast spike activity following stimulation procedures, and increased paroxysmal activity)
 - possibly, more left-sided abnormalities
- reduced amplitude of the *P300 Response* (an evoked potential which occurs 300 ms after a subject identifies a target stimulus embedded in a series of irrelevant stimuli - it is a measure of auditory information processing)
- failure of sensorimotor gating (impaired prepulse inhibition; Braff, 1993)
- abnormal smooth-pursuit eye movements in 50-80 % of patients and their relatives (Levy *et al.* 1993) – may indicate dysfunction in frontal eye fields region
- impaired skin-conductance orienting response to novel stimuli: about 50 % of schizophrenics fail to produce it and in the rest it fails to habituate

Biochemical abnormalities in schizophrenia

The dopamine hypothesis

- dopamine overactivity in mesolimbic pathways
- recent theories include:
 - deficit in corticofugal / corticothalamic DA inhibitory output (Carlsson, 1995)
 - DA receptor supersensitivity occurs with neuroleptic treatment (Grace, 1992), and can occur with one dose
 - interaction of DA with other neurotransmitters
- For:
 - AMPHETAMINE (releases dopamine at central synapses), LEVODOPA (dopamine precursor), DISULFIRAM (dopamine metabolism inhibitor) administration leads to exacerbation of schizophrenic symptoms, and also induces a disorder indistinguishable from acute schizophrenia in some normal people (Connell, 1958)
 - clinical potency of most antipsychotic drugs correlates with their binding affinity to D₂ receptors (Seeman *et al.* 1976)
 - increased levels of Homovanillic acid (metabolite of dopamine) in the body fluids of schizophrenic patients
 - CIS-FLUPENTHIXOL (DA blocker) clinically effective, but TRANS-FLUPENTHIXOL (no DA blockade) ineffective (Johnstone *et al.* 1978)
 - some reports indicate increased dopamine receptor density in the caudate nucleus, putamen, and nucleus accumbens, of increased dopamine concentrations in the amygdala of the left hemisphere, and of increases in the peptides cholecystokinin, somatostatin, and vasoactive polypeptide in the limbic regions
 - increased growth hormone response to APOMORPHINE (dopamine agonist)
- Against:
 - delayed clinical response to antipsychotic medication while the effect of neuroleptics on dopaminergic transmission is fully developed within hours of administration
 - 15-30% of schizophrenics fail to respond to dopamine antagonists
 - dopamine antagonists are effective in the treatment of all psychoses, not just schizophrenia
 - antipsychotics have a better effect on positive than on negative symptoms
 - increase in D₂ receptor density is more likely to be a result of treatment

Amino acids (Glutamate)

- glutamate is the major excitatory neurotransmitter in the cortex and has extensive interactions with dopamine pathways
- 3 groups of receptors:
 1. kainate
 2. quisqualate
 3. N-methyl-D-aspartic acid (NMDA)
- activation of glutamate receptors located on dopamine nerve terminals inhibits dopamine release

- a reduction in these receptors can lead to increased dopamine release
- hypothesis of decreased glutaminergic inhibition of subcortical and mesiotemporal DA neurones
- post-mortem studies have revealed abnormalities in glutamatergic neurotransmission (reduced GABA receptors in hippocampus)
- For:
 - Phencyclidine (PCP) which is a NMDA agonist can induce a syndrome that mimics both the positive and negative symptoms of schizophrenia
 - [³H]-D-aspartate (a marker for glutamate terminals) is *decreased* in the cortex of the temporal lobe and *increased* in the orbitofrontal cortex
 - loss of kainate and NMDA receptors in the hippocampus and entorhinal cortex, but excess in the frontal cortex
- Against:
 - experimental pharmacological agents acting on the glutamate system have not shown any antipsychotic effect
 - most of the above studies have not been replicated
 - loss of glutaminergic receptor sites may be due to neuronal loss

GABA

- loss of GABA-ergic neurones in the hippocampus

5-HT

- similarity of the molecular structure of LSD and 5-HT
- LSD (5-HT agonist) induces psychosis; M-CHLOROPHENYL-PIPERAZINE (MCPPE; 5-HT agonist) worsens psychosis
- 5-HT receptor antagonists such as CLOZAPINE have antipsychotic effect

Hormones

- reduced FSH and LH
- abnormal cortisol regulation, which can be detected with a dexamethasone suppression test

Neuropeptides and phospholipids

- possible abnormalities of cholecystokinin (CCK) and neurotensin
- abnormalities of essential phospholipid metabolism (brain membrane components)

Immunological theories

- stem from geographical variations in prevalence, season of birth phenomenon
- direct viral CNS toxicity ?
- immunological response ?
- epiphenomenon (e.g. temperature) ?
- inconclusive immunological findings (Kirch, 1993) of :
 - increased B lymphocytes
 - decreased T lymphocytes
 - increased CSF antibodies to some viruses

- negative association with rheumatoid arthritis

Neuropsychological abnormalities in schizophrenia

- patients with schizophrenia have defects in:
 - *verbal learning and memory*
 - *attention*
 - *memory tasks* (may correlate with negative symptoms)
 - *frontal lobe function* (e.g. Wisconsin Card Sorting test)
- when performance is controlled for, schizophrenics activate their frontal lobes to the same extent as normal volunteers, but the pattern of activation remains abnormal
- suggests a defect of the *supervisory attentional system* whose role is to allocate attentional resources to specific cognitive tasks
- impairments in executive and memory functions may relate to structural abnormalities in frontal and temporal regions (Weinberger *et al.* 1992)
- reduction in *prepulse inhibition*
- increased scores on *semantic priming*

Memory impairment in Schizophrenia

- short term memory normal
- LTM (episodic and semantic) impaired
- ?post-encoding or encoding deficit
- impairment of :
 - verbal memory and learning (suggests left temporal-hippocampal involvement)
 - serial learning
 - executive functioning (frontal lobe)
 - verbal fluency
 - delayed recall
- unrelated to poor motivation, lack of attention
- disproportionate to the intellectual impairment

Clinical Neurological Aspects of Schizophrenia

- most common abnormalities are in *stereognosis, graphaesthesia, balance, and proprioception*
- **movement disorders** occur in those who have never had antipsychotic drug treatment

Course and Prognosis

- in most cases, schizophrenia seems to follow one of four broad patterns :
 1. one episode only - no impairment (22 %)
 2. several episodes with no or minimal impairment (35 %)
 3. impairment after the first episode with subsequent exacerbation and no return to normality (8 %)

4. impairment increasing with each of several episodes and no return to normality (35 %)

- illness course may plateau after the first 5 years (M. Bleuler, 1950; Carpenter and Strauss, 1991)
- IPSS study (1973, 1992) indicates a more benign course in developing countries
- schizophrenics have a higher mortality than the general population (increased cardiovascular and respiratory deaths)
- Lifetime risk of suicide (Krausz et al, 1995) = 13.2% (21.5% males)
 - suicide risk is increased in:

Demographic factors	Young Male Unemployed Socially isolated
Clinical features	High or low premorbid functioning Numerous relapses Poor global functioning Hopelessness Akathisia Persistent delusions and hallucinations
Periods of greatest risk	Early in illness Immediately after discharge (especially first admission) On leave from hospital

- Patients with adolescent onset schizophrenia (Lay et al, 2000) – 10 year follow-up (n=96)
 - 83% rehospitalised with 10 years (55% > 3 times)
 - 15% in hospital at 10 years follow up
 - 74% still receiving some kind of psychiatric treatment
 - 57% rated as having moderate vocational impairment
 - 66% serious social disability
 - 75% financially dependent

Good Prognosis	Poor Prognosis
Sociodemographic :	
Married	Single, separated, widowed, divorced
Female	Male
	Greater genetic loading
Premorbid adjustment :	
No previous Ψ H _x	Previous Ψ H _x
<i>Good previous personality</i>	<i>Abnormal previous personality</i>
Good work record	Poor work record

Good social relationships	Social isolation
Good psychosexual adjustment	Poor psychosexual adjustment
Clinical :	
<i>Acute onset</i>	<i>Insidious onset</i>
<i>Onset precipitated by stressful event or situation</i>	
Older age of onset	Younger age of onset
Short episode	Long duration of untreated psychosis
Florid psychotic presentation	
<i>Prominent affective symptoms</i>	<i>Negative symptoms</i>
Good response to medication	Poor response
Good compliance	Poor compliance
Absence of ventricular enlargement	Enlarged lateral ventricles
Good neuropsychological testing	poor neuropsychological testing
Other:	
<i>Family History of depressive illness</i>	Co-morbidity
<i>Confusion/ Perplexity</i>	
<i>No family history of schizophrenia</i>	

Italicized factors indicate good prognostic indicators according to a study by Vaillant (1964)

Management

Neuroleptics

- No evidence that any conventional neuroleptic is better than any other – choice guided by previous response, side-effect profile, compliance issues (Johnstone, 1993)
- Minimum 6-week therapeutic trial warranted; $\geq 50\%$ of patients relapse by second year
- *Low dose maintenance* (approx. 5mg HALOPERIDOL) – regime less effective than moderate dosage treatment when used for stable outpatients: more prodromal symptoms and relapses
- *Intermittent treatment strategy* (attempt to ‘target’ prodromal symptoms to avoid frank relapse) – not yet useful alternative for most patients (Jolley *et al.* 1990)
- *Treatment resistance* (Meltzer, 1992):
 - $\geq 25\%$ of patients treatment resistant
 - 14 % of ‘first episode’ patients are non-responders by 12 months (Lieberman *et al.* 1993)
 - augmentation strategies of limited benefit
 - CLOZAPINE is the drug of choice

ECT

- may be helpful in catatonic states, occasionally in secondary depression

Psychosocial treatments

- components include:
 - cognitive retraining
 - crisis management
 - education
 - vocational rehabilitation
 - family therapy
 - group therapy
 - social skills training

High expressed emotion

- Family intervention strategies (Falloon; Hogarty; Leff) based upon *High Expressed Emotion* of relatives (HEE: critical comments, hostility, emotional overinvolvement; rated from Camberwell family interview)
- **Camberwell Family Interview (CFI):**
 - critical comments
 - hostility
 - emotional involvement
 - warmth
 - positive remarks
- predictive of relapse (Vaughn & Leff, 1976):

	Relapse rate in 9 months after discharge
Patient on neuroleptics, low EE family	12 %
Patient on neuroleptics, HEE family, less than 35 hours contact weekly	42 %
No neuroleptics, HEE family, more than 35 hours contact	92 %

- intervention strategies aim to reduce HEE and relapse (Kavanagh, 1992) :

	<i>Relapse 0-9 months</i>	<i>Relapse 0-24 months</i>
Family intervention	10 %	33 %
Routine treatment	48 %	71 %

It is likely that the better prognosis in less developed countries (e.g. India) is to do with the reduced amount of expressed emotion.

(F25) Schizoaffective disorder

Classification

- *Kasanin (1933)* – described patients with illness of both affective and schizophrenic symptoms, sudden onset after stressor, good premorbid adjustment
- subsequent definitions and application of different diagnostic criteria led to confusion and poor reliability of schizoaffective (SA) disorder
- SA unlikely to be either:
 1. Co-occurrence of schizophrenia and affective disorder in the same patient
 2. Separate disease entity
- SA more likely to be:
 1. a subtype of schizophrenia
 2. a subtype of affective disorder
 3. heterogeneous disorder, intermediate between schizophrenia and affective disorder (i.e. continuum model)
- available data from family and twin studies suggest continuum model
- schizodepressive subtype more related to schizophrenia, schizomanic subtype more related to affective disorder

Diagnostic criteria

F25.0 Schizoaffective disorder, manic type

F25.1 Schizoaffective disorder, depressive type

F25.2 Schizoaffective disorder, mixed type

F25.8 Other schizoaffective disorders

F25.9 Schizoaffective disorder, unspecified

A fifth character may be used to classify the following subtypes :

- .x0 Concurrent affective and schizophrenic symptoms only
- .x1 Concurrent affective and schizophrenic symptoms plus persistence of the schizophrenic symptoms beyond the duration of the affective symptoms

ICD-10 Criteria

- G1. The disorder meets the criteria for one of the affective disorders (F30.-, F31.-, F32.-) of moderate or severe degree, as specified for each category
- F2. Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks (these groups are almost the same as for schizophrenia)
 - (1) thought echo, thought insertion or withdrawal, thought broadcasting
 - (2) delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations

- (3) hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient between themselves, or other types of hallucinatory voices coming from some part of the body
- (4) persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory
- (5) grossly irrelevant or incoherent speech, or frequent use of neologisms
- (6) intermittent but frequent appearance of some forms of catatonic behaviour, such as posturing, waxy flexibility and negativism

- G3. Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode
- G4. Exclusion criteria.

Aetiology

Family studies

- 1st degree relatives have an increased risk for both mood disorders and schizophrenia

Management

- lithium – most beneficial for mainly affective SA patients; schizophrenic symptoms show less response
- neuroleptics – used in combination with lithium or antidepressant, more effective than neuroleptic monotherapy
- ECT – useful in patients with mainly affective symptoms, perplexity, family history of SA

Outcome

- generally better outcome than for schizophrenia
- worse outcome than for mood disorder
 - schizomanics have a more episodic course and better outcome
 - schizophrenic symptoms associated with poor outcome
- early onset associated with schizophrenic symptoms and poor outcome
- Cologne follow-up study (Marneros *et al.* 1989):

	<i>SA</i>	<i>Schizophrenia</i>
<i>Very poor outcome</i>	6 %	52 %
<i>Very good outcome</i>	51 %	12 %

Delusional disorders

Classification issues

- distinct mental disorder ('paranoia'; Kahlbaum, 1863; Kraepelin, 1919)
- milder form of schizophrenia (Kolle, 1931; Roth, 1955)
- 'late paraphrenia' (Fish, 1965)

Epidemiology

- point prevalence: 0.03%
- lifetime risk: 0.05-0.1%
- mean age of onset: 35 years for males, 45 years for females
- equal sex ratio

Aetiology

- genetic and outcome studies support the present classification under rubric of schizophrenia/ related psychotic disorders

Features

- more common in:
 - immigrants
 - the hearing impaired
 - older than 40 years
- often unmarried, high marital breakdown, low fecundity
- increased family history of psychiatric disorder, but not of delusional disorder or schizophrenia
- onset gradual in 62%
- course unremitting, severity may fluctuate
- 16% have evidence of minimal brain dysfunction

ICD-10 Criteria

- A. A delusion or a set of related delusions, other than those listed as typically schizophrenic (i.e. other than completely impossible or culturally inappropriate), must be present. The commonest examples are persecutory, grandiose, hypochondriacal, jealous (zealotypic), or erotic delusions
- B. The delusion(s) in criterion A must be present for at least 3 months
- C. The general criteria for schizophrenia are not fulfilled
- D. There must be no persistent hallucinations in any modality (but there may be transitory or occasional hallucinations that are not in the 3rd person or giving a running commentary)
- E. Depressive symptoms (or even a depressive episode) may be present intermittently, provided that the delusions persist at times when there is no disturbance of mood

Outcome

- poor prognosis in:
 - insidious onset
 - late age of presentation

- lack of precipitating factors

Delusional jealousy

Aetiology

- associations with :
 - paranoid schizophrenia (17-44 %)
 - depressive disorder (3-16 %)
 - neurosis and personality disorder (38-57 %)
 - alcoholism (5-7 %)
 - organic disorders (6-20 %)
- personality :
 - pervasive sense of own inadequacy
 - low self esteem
 - discrepancy between ambitions and attainments
- no link with erectile dysfunction in men

Risk of violence

- no direct statistical evidence
- in one study (Mullen and Maack, 1985) :
 - 25 % had threatened to kill or injure their partner
 - 56 % of men, and 43 % of women had been violent to, or threatened the supposed rival
- there may be an increased risk of suicide

Other psychotic disorders

Schizophreniform psychoses

- applied by Langfeldt (1961) to good prognosis cases
- main features are:
 - presence of a precipitating factor
 - acute onset
 - clouding of consciousness
 - depressive and hysterical features

Cycloid psychoses

- Leonhard (1957), Perris (1974)
- distinguished by:
 - prominent symptoms
 - good prognosis
 - no chronic defect state
 - tend to be 'bipolar' in nature
- according to Perris, at least two of the following have to be present:
 1. perplexity or confusion

2. delusions of reference, influence or persecution and/ or hallucinations not syntonetic with mood
 3. hypo- or hyperkinesia
 4. episodes of ecstasy
 5. overwhelming fear of some catastrophe (pananxiety)
- **Anxiety elation psychosis**
 - prominent symptom is mood change
 - at one 'pole' anxiety is associated with ideas of reference and sometimes with hallucinations
 - at the other pole, the mood is elated, often with an ecstatic quality
 - **Confusion psychosis**
 - thought disorder is the prominent symptom
 - the picture varies between excitement and a state of underactivity with poverty of speech
 - **Motility psychosis**
 - the changes are in psychomotor activity

Monosymptomatic hypochondriacal psychosis

- Munro, 1980
- Is a form of delusional disorder

Bouffee delirante

- Literally, a 'puff of madness'
- term coined by Magnan
- characterised by dramatic suddenness, usually not in response to any obvious stress
- central feature is a polymorphous delusional state
- mood is constantly changing
- hallucinations may also be present
- the illness lasts from a few days to a few weeks, and full recovery is the commonest outcome
- the illness is probably a schizophreniform psychosis