Theories of Schizophrenia

Dr Bharat Shah
History

- Benedict Morel (1809-1873) a French psychiatrist, used the term *demence precoce* to describe deteriorated patients whose illness began in adolescence.
- Emil Kraepelin (1856-1926) translated Morel’s *demence precoce* into *dementia precox*. Patients with dementia precox were described as having a long-term deteriorating course and the clinical symptoms of hallucinations and delusions. Kraepelin distinguished these patients from manic-depressive psychosis and paranoia, which was characterized by persistent persecutory delusions and lacked the deteriorating course of dementia precox.
History

• A. Alzheimer (1864–1915) made detailed observations of the cerebral pathology of psychotic patients. Consequently, he found that patients with psychotic symptoms exhibited no gliosis.

• As an expression describing this prolonged era, it was said that “schizophrenia is a graveyard for neuropathologists.” At the 1st International Congress of Neuropathology in 1952 (in Rome), the conclusion that “there is no neuropathology of schizophrenia”
Bleuler’s theory

• Eugene Bleuler (1857-1939) coined the term schizophrenia, which replaced dementia precox. He chose the term to express the presence of schisms between thought, emotion, and behavior in patients with the disorder.

• Fundamental (or primary) symptoms of schizophrenia: Asociational disturbances of thought, especially looseness, Affective disturbances, Autism, and Ambivalence. Accessory (secondary) symptoms: hallucinations and delusions.

• “They have encased themselves with their desires and wishes, have cut themselves off as much as possible from any contact with the external world. This detachment from reality with the relative and absolute predominance of the inner life is autism”
Psychoanalytical theory

- Schizophrenia is a regression to the oral stage when the ego has not emerged from the id. As there is no distinct ego, by regressing to the primary narcissistic stage, schizophrenics lose contact with the world.

- There is heightening of id impulses specially of sexual nature during adolescence. Lack of interpersonal relations and libidinal attachment are attributed to pt’s heightened sensitivity to criticism. By trying to adapt with the demands of the id impulses and to have contact with some stimulus, symptoms of delusions, hallucination and thought disorders are found.
Psychoanalytical theory

• Freud named the illness as narcissistic neuroses. In his view, positive symptoms such as hallucinations and delusions were restitutinal. His famous quote is - A delusion is like a patch applied over the tear between the ego and external world
Psychosocial theory

• Harry Sullivan viewed SCZ as disturbance in interpersonal relatedness. Severe anxiety that threatens sense of self and unrelatedness is rescued by distortions which lead to paranoia.
Family Systems

• An early, but since discredited theory, focused on the role of the *schizophrenogenic* mother.

• In what some feminists view as historic psychiatric sexism, the *schizophrenogenic* mother was described as cold, aloof, overprotective, and domineering.

• She was characterized as stripping her children of self-esteem, stifling their independence, and forcing them into dependency on her.

• Children reared by such mothers were believed to be at special risk for developing schizophrenia if their fathers were passive and failed to counteract the mother’s pathogenic influences.
Family Systems Theory

• Origins in:
  – The psychoanalytical tradition (the influence of the family on abnormal behaviour)
  – Systems thinking (idea that things are best understood by looking at the relationships between a set of entities)
A family can be seen as a set of entities, each interacting with all the others.

The behaviour of each entity can only be understood by looking at its relationships with the others.
If one person starts to behave abnormally the problem might not lie within that person. Their behaviour may be a manifestation of a problem occurring within the wider family system.
Double Bind Theory

• In a double bind situation a person is given mutually contradictory signals by another person
  – This places them in an impossible situation, causing internal conflict
  – Schizophrenic symptoms represent an attempt to escape from the double bind
  – The patient is a ‘symptom’ of a family-wide problem
  – They become ‘ill’ to protect the stability of the family system
Family System-EE

• Some evidence that family processes play a role in relapse of schizophrenia patients following stabilisation
  – Relapse more likely (58% vs. 10%) where family is high in ‘expressed emotion’
  – Families high in
    ✓ criticism,
    ✓ hostility
    ✓ over-involvement
LEARNING THEORY

Punishment

Withdrawal

Labelled as odd

Reinforced by attention

Conforming to label
Neuropathology

• Subsequently, in the 1980s, with progress in brain imaging technology such as CT, morphological abnormalities of schizophrenia were reported, and moreover, with MRI, PET, SPECT, and the like, detailed brain images including the functions of schizophrenia cases were examined.

• Neuropathological techniques such as image analysis with a computer, and immunohistological special staining and post 1990, genetic research added to the view of brain damage
Neuropathology in SCZ,

<table>
<thead>
<tr>
<th>Macroscopic findings</th>
<th>Strength of evidence</th>
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<tbody>
<tr>
<td>Enlarged lateral and third ventricles</td>
<td>shown by meta-analysis</td>
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<tr>
<td>Decreased cortical volume</td>
<td>shown by meta-analysis</td>
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<tr>
<td>The above changes present in first-episode patients</td>
<td>strong</td>
</tr>
<tr>
<td>Disproportionate volume loss from temporal lobe (incl. hippocampus)</td>
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<tr>
<td>Decreased thalamic volume</td>
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<tr>
<td>Cortical volume loss affects grey rather than white matter</td>
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<tr>
<td>Enlarged basal ganglia secondary to antipsychotic medication</td>
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<table>
<thead>
<tr>
<th>Histological findings</th>
<th></th>
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<tbody>
<tr>
<td>Absence of gliosis as an intrinsic feature</td>
<td>good</td>
</tr>
<tr>
<td>Smaller cortical and hippocampal neurons</td>
<td>good</td>
</tr>
<tr>
<td>Fewer neurons in dorsal thalamus</td>
<td>good</td>
</tr>
<tr>
<td>Reduced synaptic and dendritic markers in hippocampus</td>
<td>good</td>
</tr>
<tr>
<td>Maldistribution of white matter neurons</td>
<td>moderate</td>
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</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th></th>
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<tbody>
<tr>
<td>Alzheimer’s disease is not more common in schizophrenia</td>
<td>Shown by meta-analysis</td>
</tr>
</tbody>
</table>
Brain volume loss in SCZ

Pathology in schizophrenia:
1. Smaller cell bodies
2. Decrease neurite
3. Shortening dendrite
4. Decrease in presynaptic terminals

Decrease in presynaptic terminals
Two hit theory

First hit (embryonic/perinatal)
(infection/nutrition/birth trauma, etc.)

Second hit (adolescence/young adult)
(stress events)

Further (third) hit
(inappropriate support)

Troubles in neurodevelopment

Onset

Positive symptoms
(psychosis/Schneiderian first-rank symptoms)

Recurrence

Ingravescence/Negative symptoms
Neuro developmental dysfunction hypothesis
Environmental risk factors in schizophrenia

The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene.

Caspi et al, 2005.
13% of individuals carrying the Val/Val genotype and using cannabis had schizophreniform disorder.

Good idea to genotype yourself before you fly to Amsterdam.
13% of individuals carrying the Val/Val genotype and using cannabis had schizophreniaiform disorder.

Good idea to genotype yourself before you fly to Amsterdam.

Immunological theories in SCZ
The familial risk of schizophrenia

A graph to show the genetic risk of developing schizophrenia.
Genetics

• Generally speaking, the more closely one is related to people who have developed schizophrenia, the greater the risk of developing schizophrenia for oneself.

• **Monozygotic (MZ)** twins, whose genetic heritages are identical, are much more likely than **dizygotic (DZ)** twins, whose genes overlap by 50%, to be concordant for schizophrenia.
Genetics: The Copenhagen High-Risk Study

• Kety and colleagues (1962) identified 207 offspring of mothers diagnosed with schizophrenia (high risk) along with a matched control of 104 children with ‘healthy’ mothers (low risk).

• Children aged between 10-18 years at start of study and matched on age, gender, parental socio-economic status and urban/rural residence.
• Follow-up studies conducted in 1974 and 1989

Results:
• Schizophrenia diagnosed in 16.2% of high risk group compared to 1.9% in low risk group
• Schizotypal personality disorder diagnosed in 18.8% of high risk group vs 5% of low risk group
Genetics: Twin Studies

- Compare concordance rates for identical (MZ) and dizygotic (DZ) twins
- Both share the same environment but only MZ twins have identical genetics
- Many studies conducted – all show much higher concordance rate in MZ than DZ twins
- To separate environment from genetic influences, researchers have sought out MZ twins reared apart where at least 1 has been diagnosed with schizophrenia
Gottesman & Shields (1982) used the Maudsley twin register and found 58% (7/12 MZ) twins reared apart were concordant for schizophrenia.

If the genetic hypothesis is correct, then the offspring of a non-affected discordant MZ twin should still be high-risk.

A study found that 9.4% of such offspring developed schizophrenia, which is a much higher incidence than in the general population (1%)
Genetics: Adoption Studies

• More effective in separating effects of genetic and environmental factors

• Look at adopted children who later develop schizophrenia and compare to biological parents
• **The Finish Adoption Study** (1969) identified adopted offspring of biological mothers with schizophrenia (112 cases)
• Matched control group (135 adopted offspring of non-schizophrenic biological mothers)
• Adoptees ranged from 5-7 yrs at the start of the study, and separated from mothers before 4
• Study checked children again in 1987
• Reported 7% of high risk group developed schizophrenia compared to 1.5% of controls.

• **The Danish Adoption Study (1994)** took a national sample across Denmark
• Found high rates of diagnosis for chronic schizophrenia in adoptees whose biological parents had the same diagnosis, despite living with ‘healthy’ parents
Genetics

• Strategies to find specific genes that cause SCZ:

✓ Linkage studies
✓ Association studies
✓ Single nucleotide polymorphism (SNP) genotyping
✓ Copy number variants
My Lord, they have discovered the human genome!

Damn hackers, I will have to change the password now.
# Candidate genes in schizophrenia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Cytogenetic Band</th>
<th>Genome Scan Meta-Analysis</th>
<th>Linkage Evidence</th>
<th>Association Study Support</th>
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<tbody>
<tr>
<td>AKT1</td>
<td>V-AKT murine thymoma viral oncogene homolog 1</td>
<td>14q32.33</td>
<td>No</td>
<td>No</td>
<td>2+ &amp; 1– studies</td>
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<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
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<td>DISC1</td>
<td>Disrupted in schizophrenia 1</td>
<td>1q42.2</td>
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<td>Yes</td>
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<td>DRD3</td>
<td>Dopamine receptor D3</td>
<td>3q13.31</td>
<td>Yes</td>
<td>Yes</td>
<td>Inconsistent Meta-analysis +</td>
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<td>DTNB1</td>
<td>Dystrobrevin binding protein 1</td>
<td>6p22.3</td>
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<td>G30/G72</td>
<td>Putative proteins LG30 &amp; G72</td>
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<td>HTR2A</td>
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<td>PRODH</td>
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<td>RGS4</td>
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<td>SLC6A4</td>
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<td>ZDHHC8</td>
<td>Zinc finger/DHHC domain protein 8</td>
<td>22q11.21</td>
<td>Yes</td>
<td>Yes</td>
<td>2+ &amp; 1– studies</td>
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</table>
Multiple Susceptibility
Genes Converge on NMDA Synapses in Schizophrenia

- ErbB4
- dysbindin
- neuregulin
- DISC1
- DAQA
- D2R
- MAO-A
- MTHFR
- D3R
- RGS4
- AKT
- NUR77
- TOH
- calcyon
- spinophylin
- 5HTT
- 5HT
- MAO-A
- RGS4

GABA

NMDA receptor

dysconnectivity

NMDA-R hypofunction

abnormal competitive elimination of synapses

abnormal LTP

abnormal synaptic plasticity and connectivity

inadequate synaptic strength

dysregulation of AMPA-R
Neurophysiological Evidence
: Auditory P300 Abnormalities

One of the most consistently replicated neurophysiological abnormalities observed in schizophrenia.

- Auditory P300 amplitude is reduced, often delayed
  Observed in chronic patients, first episode patients, schizophrenia spectrum patients, and first degree relatives of schizophrenic patients. Good Endophenotype (A possible marker of genetic vulnerability and/or neurodevelopmental insult)

Another abnormality is N100.

Interpretation is Pts are highly sensitive to incoming stimuli and compensate by blunting the processing at a higher cortical level.
PPI and MMN

• Inability to filter irrelevant sensory information is cognitive defect.
• A neuro physiological correlate of this deficit is evaluated by a pre-attentive paradigm called paired pulse inhibition (PPI). Subjects are presented a startling (test) stimulus with or without a preceding non-startling (conditioning) stimulus.
• In control subjects, the response to the test stimulus is suppressed by the conditioned stimulus, but this suppression is reduced in SCZ subjects.

• Another ERP is MisMatch Negativity (MMN). An evoked potential generated in the supra-granular layer of primary auditory cortex called mismatch negativity is reduced in schizophrenia.
Dopaminergic theory: History

- How did chlorpromazine work?
- Role of dopamine.
- The relation between the clinical effectiveness of antipsychotic drugs and their affinity for dopamine receptors.
Dopamine Pathways and Key Brain Regions

Schizophrenia: Too Much Dopamine?

High

Hyperactive!

Mesolimbic pathway

Positive symptoms

Schizophrenia: Too Little Dopamine?

Mesocortical pathway

Low Hypoactive

DLPFC VMPFC

Cognitive symptoms

Negative symptoms

Affective symptoms

“Revised” dopamine hypothesis of schizophrenia: Prefrontal deficit and subcortical hyperdopaminergia

- Mesocortical DA projections to the prefrontal cortex might be hypoactive -> hypostimulation of D1 receptors -> negative symptoms and cognitive impairment

Subcortical mesolimbic DA projections might be hyperactive -> hyperstimulation of D2 receptors -> productive symptoms

Frontal cortex hypoactivity

Limbic system hyperactivity

Negative symptoms

Positive symptoms

Dopamine in schizophrenia

- Patients with schizophrenia have elevated synthesis and storage of dopamine in presynaptic dopaminergic nerve terminals in striatum. This is the most consistent finding. The increased levels are linked with increase in psychosis.

- Increased dopamine release at synapses and baseline increased occupancy of D2 receptors by dopamine.

- There is some evidence of D1 receptor levels in PFC and that reflects chronic low dopamine levels in PFC and relates with negative and cognitive defects.


Aberrant Salience

“Salience” refers to the motivational properties of a stimulus, which can cause it to attract attention and drive behavior.

Aberrant salience refers to the tendency for irrelevant stimuli to be attributed motivational salience and thus to attract attention and influence behavior inappropriately.

Aberrant Salience

- Increasing evidence of dopamine’s role in motivational incentive salience.

- Abnormal firing of dopamine neurons and the abnormal release of dopamine leads to an aberrant assignment of salience to innocuous stimuli.

- Over time the individual’s own explanation of the experience of aberrant salience leads to formation of delusions and hallucinations.

Environmental factors and Dopamine

- Late environmental markers of adversity such as migration, unemployment, urban upbringing, lack of close friends, and childhood abuse are all associated with a well-established increased risk for schizophrenia.

- Animal Studies of social isolations and subordination find that these factors lead to dopaminergic overactivity.
Dopamine model of psychosis

Oliver D. Howes and Shitij Kapur
Glutamate hypothesis

- Phencyclidine (PCP): dissociative anesthetic: Noncompetitive NMDA antagonist (blocks Ca\(^{2+}\) channel)
- 2 weeks PCP in monkeys $\rightarrow$ schizophrenia-like symptoms
  - Including poor performance on frontal lobe-sensitive task
- Ketamine (NMDA antag) $\rightarrow$ similar effects

- In Schizophrenia is there a pathology that is causing NMDA hypofunction?
Glutamate system and schizophrenia

(1) **NMDA Receptors Hypofunction Hypothesis of Schizophrenia**
   • (The Glutamate theory vs the Dopamine theory in schizophrenia)

(2) **The Glutamate Excitotoxicity as part of the Neurodevelopmental Theory of Schizophrenia**
   • The excessive pruning theory
Gluamate

- Glu is an aminoacid involved in building proteins, and in energy metabolism. It is also a NT.
- Glu is the workhorse transmitter for excitatory signaling in the nervous system.
- > 60% receptors in brain.
- Involved in many behavioral and physiological functions, but perhaps the most important is synaptic plasticity:
  - Changes in the strength of connections
  - Learning and memory
Glutamate receptors may be divided into 2 broad categories: ionotropic (cation channels) and metabotropic receptors (G-protein coupled receptors). Three classes of ionotropic glutamate receptors have been identified, which were named on the basis of agonist selectivity: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate (KA). To date, 8 metabotropic glutamate receptors (mGluRs) have been identified; they are generally categorized into 3 groups (groups I, II, III) based on related effects on messenger cascades and homology.
NMDA receptors

• NMDA receptors require two different neurotransmitters to open the channel
  – 1) Glutamate
  – 2) Glycine or D-serine

• Glycine (or D-serine) has its own binding site.
  – Thus glycine (or D-serine) is considered to be a co-agonist.

• Usually the co-agonist binding site is occupied though, so the presence or absence of glutamate determines channel opening
GABA receptors
GABA interneurons

• Most Gabaergic cortical interneurons can be divided into three distinct subgroups based on several neurochemical markers: parvalbumin- (PV+), somatostatin- (Sst+), or calretinin-expressing (CR+) interneurons.

• PV+ are fast-spiking (FS) and comprise two major subtypes: basket and chandelier cells.
Evidence: Neuropathology in GABA cells

- There is decreased expression of GABA synthesizing enzyme—Glutamic acid decarboxylase (GAD) esp its isoform GAD67 in parvalbumin containing GABAergic chandelier and basket cells in DLPC, hippocampus.

- These cells innervate Glutamatergic Pyramidal cells and inhibit them.
GABA and Epigenetics

- GAD67 levels are tightly controlled by neural activity via transcriptional regulation of \textit{GAD1}, the gene encoding GAD67. Different levels of \textit{GAD1 transcription may be linked to genetic variability}, and polymorphisms in the 5’ region of \textit{GAD1 have been associated with schizophrenia and decreased GAD67 transcription}.

- In the cortex of a subset of schizophrenia patients, methylation of histones (the core proteins of chromatin) near the promoter region of \textit{GAD1 shows a shift from transcription-open to transcription repressive chromatin structure}, which is accompanied by a reduction in GAD67 mRNA in the same individuals.
GABA and cortical oscillations

• GABA-mediated inhibition may play roles in addition to oscillatory synchronization of neuronal activity.
• GABA mediated inhibition are important to maintain and terminate persistent activity. Persistent activity is viewed as the cellular basis of working memory, a form of memory that is altered in schizophrenia and is essential for cognitive function.
GABA and cortical oscillations

• Mice were genetically engineered to express light-sensitive ion channels exclusively in pyramidal cells or PV neurons in order to selectively drive cell activity by means of light flashes. Selective activation of PV cells in these mice produced γ band oscillations, whereas inhibiting PV neurons suppressed them.

• Moreover, nonrhythmic stimulation of pyramidal neurons drives PV cells to produce feedback inhibition generated a γ rhythm. These and other elegant optogenetics experiments show that PV cell activity, possibly driven by pyramidal cells via AMPARs, generates γ oscillations.
NMDA Receptor Hypofunction in Cortico-Brainstem Projections: Hyperactivity of Mesolimbic Dopamine Pathway

Normal state
Glutamate acts as a brake on DA

Hypoactive state
Glutamate brake is off

DA neuron
GABA neuron

glu neuron

Overactivation
Normal
Baseline
Hypoactivation

Positive Symptoms

NMDA Receptor Regulation of Mesocortical Dopamine Pathways: Tonic Excitation

Normal state
Cortical glutamate provides tonic excitation of mesocortical DA

glu neuron

Overactivation
Normal
Baseline
Hypoactivation

NMDA Receptor Hypofunction in Cortico-Brainstem Projections: Hypoactivity of Mesocortical Dopamine Pathways

- Hypoactive state
  - Excitation is lost

- Overactivation
- Normal
- Baseline
- Hypoactivation

- Negative symptoms
- Cognitive symptoms
- Affective symptoms

Ketamine & Sigma receptor

- Ketamine has mild sigma R blocking action.
- The sigma receptor is a nonopioid receptor found in the endoplasmic reticulum. The sigma-1 receptor is involved in mitochondrial Ca2+ signaling, neuroprotection, neuroplasticity, and neurite outgrowth, thus leading to the hypothesis that it is also necessary for optimal cognition and cerebral metabolism.
- Sigma receptor ligands can protect dopaminergic cells from the excitotoxic effects of NMDA.
- Mice that are repeatedly administered PCP show frontocortical reductions of the sigma-1 receptor.
Ketamine & Kappa opioid receptor

- Ketamine to be an agonist of the kappa opioid receptor. Salvinorin A is a kappa receptor agonist and the most potent naturally occurring hallucinogen. Many studies report a positive correlation between levels of dynorphins, endogenous kappa receptor ligands, in the cerebrospinal fluid of schizophrenia patients and psychotic symptoms.
- An abnormal laminar distribution of kappa receptors in the hippocampus has also been reported for schizophrenia patients.
- Finally, kappa receptor agonists administered to rats have varied effects on prepulse inhibition, which is reduced in schizophrenia.
THANK YOU