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Schizophrenia: General Findings and Current Status

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Schizophrenia : General Findings and Current status

Amresh Shrivastava
Mumbai
# Genetic Risk Of Schizophrenia

<table>
<thead>
<tr>
<th>Relative</th>
<th>Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1%</td>
</tr>
<tr>
<td>Second degree Relative</td>
<td>2.5%</td>
</tr>
<tr>
<td>Parents</td>
<td>3.8%</td>
</tr>
<tr>
<td>Sibling</td>
<td>8.7%</td>
</tr>
<tr>
<td>Child, 1 parent</td>
<td>12%</td>
</tr>
<tr>
<td>Child, 2 parents</td>
<td>30-40%</td>
</tr>
<tr>
<td>Twin Monozygotic</td>
<td>40-50%</td>
</tr>
</tbody>
</table>
Risk factors for schizophrenia

Genetics
Pre-or-perinatal events
Factors during childhood and adolescence
Psychological and electrophysiological characteristics of schizophrenia

Cognitive dysfunction

Neurophysiologic dysfunction
1% Schizophrenia
5% Schizophrenia-related Personality Disorders
Brain Structure and Function in schizophrenia

Brain Structure
Brain Function
Theories of schizophrenia

Dopamine
Neuronal System
Neurodevelopmental factors
Limbic structures
Postmortem studies in schizophrenia

Established by systematic reviews:
- Enlargement of lateral and third ventricles (+25%-40%)
- Smaller brain volume (-3%)
- Smaller Grey matter volume (-6%)
- Relatively smaller medial temporal lobe volume (-5%)
- Relatively smaller thalamic volume (-4%)
- Larger basal ganglia (especially globus pallidus)
Characteristics of Structural imaging findings in schizophrenia

- Differences are readily apparent in discordant monozygotic twins
- Differences are present in first-episode, untreated patients, and high-risk and unmedicated individuals.
- No convincing evidence of heterogeneity (e.g., Subtypes or gender differences), although this remains controversial.
- The alterations are not seen in Bipolar Disorder to the same extent.
## Histological findings in schizophrenia.

0 no good evidence, +/- equivocal data, 
+ to ++++ increasing amount of supportive data

<table>
<thead>
<tr>
<th>finding</th>
<th>Weight of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of neurodegenerative lesion (e.g., Alzheimer Changes)</td>
<td>++++</td>
</tr>
<tr>
<td>Lack of Gliosis</td>
<td>++++</td>
</tr>
<tr>
<td>Smaller cortical and hippocampal pyramidal Neurons</td>
<td>+++</td>
</tr>
<tr>
<td>Decreased Cortical and Hippocampal Synaptic markers</td>
<td>++</td>
</tr>
<tr>
<td>Decreased Dendritic Spine Density</td>
<td>++</td>
</tr>
<tr>
<td>Loss of Neurons from Dorsal thalmus</td>
<td>++</td>
</tr>
<tr>
<td>Abnormalities of white matter neurons</td>
<td>+</td>
</tr>
<tr>
<td>Entorhinal Cortex Dysplasia</td>
<td>+</td>
</tr>
<tr>
<td>Disarray of hippocampal neuron orientation</td>
<td>+/-</td>
</tr>
<tr>
<td>Loss of hippocampal or cortical neurons</td>
<td>0</td>
</tr>
</tbody>
</table>
Histological and Molecular pathology in Schizophrenia

- Gliosis & Neurodegeneration
- Neuronal Cytoarchitecture
- Synapse & dendrites.
- Location and extent of pathology
Neurochemistry of schizophrenia

- Dopamine
- Serotonin
- Glutamate
- Gama-aminobutyric acid (GABA)
# Dopamine

<table>
<thead>
<tr>
<th>Main postmortem Findings</th>
<th>Other supportive evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Density of D2 receptors</td>
<td>DA – releasing agent produce psychosis</td>
</tr>
<tr>
<td>Decreased Cortical DA innervation</td>
<td>All antipsychotics are D2 Receptor antagonists</td>
</tr>
<tr>
<td>Increased D4 –like receptor binding</td>
<td>Increased striatal DA release in vivo</td>
</tr>
<tr>
<td>Alteration in D3 receptor splicing</td>
<td></td>
</tr>
</tbody>
</table>
## Glutamate

<table>
<thead>
<tr>
<th>Main Postmortem findings</th>
<th>Other supportive evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased presynaptic markers</strong></td>
<td>NMDA receptor antagonists produce schizophrenia-like psychosis</td>
</tr>
<tr>
<td><strong>Decreased HC AMPA and kinetic receptor expression</strong></td>
<td>Roles of NMDA in development and neurotoxicity</td>
</tr>
<tr>
<td><strong>Minor changes in FC NMDA receptor subunits</strong></td>
<td>Partial NMDA agonists have some therapeutic benefits</td>
</tr>
<tr>
<td><strong>Altered Glutamate fibers in cingulate cortex</strong></td>
<td></td>
</tr>
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- Decreased presynaptic markers
- NMDA receptor antagonists produce schizophrenia-like psychosis
- Roles of NMDA in development and neurotoxicity
- Partial NMDA agonists have some therapeutic benefits
- Altered Glutamate fibers in cingulate cortex
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<tr>
<th>Main Postmortem findings</th>
<th>Other supportive evidence</th>
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<tr>
<td>Decreased FC 5-HT 2A receptor expression</td>
<td>5-HT 2 agonists e.g. LSD are psychotomimetic</td>
</tr>
<tr>
<td>Increased FC 5-HT 1A receptors</td>
<td>5-HT 2 receptor polymorphism associated with schizophrenia and clozapine response</td>
</tr>
<tr>
<td>Increased 5-HT transporter affinity</td>
<td>Atypical antipsychotics have high affinity for several 5-HT receptors</td>
</tr>
<tr>
<td>Developmental and trophic role of 5-HT</td>
<td></td>
</tr>
<tr>
<td>Main Postmortem findings</td>
<td>Other supportive evidence</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Decreased base density of FC GABAergic terminals</td>
<td>Role of GABA in stress and Neurotoxicity</td>
</tr>
<tr>
<td>Increased GABA, A receptor subunits</td>
<td></td>
</tr>
<tr>
<td>Increased GABA, A, receptor binding in limbic areas</td>
<td></td>
</tr>
<tr>
<td>Decreased FC expression of glutamic acid decarboxylase</td>
<td></td>
</tr>
<tr>
<td>Altered density of cingulate GABAergic cells</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Which of the cytoarchitectural and synaptic alterations are robust?</td>
<td></td>
</tr>
<tr>
<td>Is there a single pathology or several?</td>
<td></td>
</tr>
<tr>
<td>How are the structural and neurochemical findings related?</td>
<td></td>
</tr>
<tr>
<td>Does the neuropathology underlie the aberrant functional connectivity?</td>
<td></td>
</tr>
<tr>
<td>Does the neuropathology relate to psychotic symptoms or cognitive deficits?</td>
<td></td>
</tr>
<tr>
<td>Are the changes diagnostically specific?</td>
<td></td>
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</tbody>
</table>
Dopamine in schizophrenic brain

- Brain Imaging as a tool for measuring DA synaptic activity.
- Imaging amphetamine-induced DA release in Schizophrenia.
- Imaging baseline DA activity in schizophrenia.
- Cortical Regulation of subcortical DA transmission
- Schizophrenia and endogenous sensitization.
- DA hyperactivity, neuroplasticity, and positive symptoms.
- Implications for treatment
Gene → Neurodevelopmental abnormality → Deficient cortical control of subcortical DA activity

Stress → Increased subcortical DA release (stress-related)

Endogenous sensitization

Sustained subcortical DA release (non stress-related)

Altered information flow in corticostriatothalamocortical loops (DA-dependent)

Long term plasticity

Psychotic episode (treatment-responsive)

Treatment

No Treatment

Chronic Psychotic State (treatment-unresponsive)
Q1. Whether the disease would develop or NOT?
Q2. If so, when?
Q3. Whether it would be treatment responsive or resistant?
Q4. If treatment responsive, will it Relapse or NOT?
Only partly answered

- Genetic loading
- Developmental Insult
- Genetic Expression: time, speed, specificity, partial/complete expression.
- Stress factors
- Biochemical dysregulation
- Neuronal plasticity
Violence in schizophrenia

Where is the evidence?
Predicting violence
Clinical implications
Predictors of violence common to patients with clinically stable schizophrenia and the General population

- Sociodemographic factors (age, gender, economic status and unemployment)
- Drug abuse
- Antisocial personality
- Family history of violence
- Previous violence
Clinical predictors of violence in schizophrenic patients with exacerbation of psychotic symptoms

- Type and characteristic of delusions.
  - delusions causing fear and anguish.
    - persecutory delusions
    - active seeking of information to confirm or refute the delusional belief.
  - systematization and conviction of the delusion
  - quality of hallucination
- Previous violence
- Less insight into symptoms
- Higher PANSS general psychopathology score
Approach to reducing noncompliance

- Use of depot medications
- Patient recognition of need of treatment
- Close monitoring to adherence.
- Use of drugs with better side-effect profiles.
- Subjective experience.
Future actions

- Treatment programme that are effective in prevention of violence.
- Investigation of the variables associated with violence that are amenable to therapeutic approaches.
- Strategies to increase compliance with treatment, which may translate into a reduction in number of violent episodes and fewer psychotic relapses.
- Treatment reducing poor impulse control.
- Competent well developed community support and comprehensive mental health follow up to identify and successfully deal with early signs of violent behaviour.
- Development of validated instruments for assessment of future violence.
Conventional Antipsychotics

Not effective in 50% & in NS; SE, EPS, TD, PRL, NMS

SE contributes to treatment nonadherence

Relapse

Rehospitalization

To minimize SE
- Lowering the Dose
- Decreases SE
  decreases Efficacy & Relapse

CAPD do not reduce all symptoms and disability in Schizophrenia.

At least 50% patients live with persistent, residual Symptoms;
at least 20% relapse Despite adequate doses.
substantial % continue as severely disabled, frequently relapse,
Conventional antipsychotics

Despite substantial data from controlled trials that support the efficacy of CAPD for the positive symptoms, the effectiveness of these agents in everyday clinical practice is substantially less than their efficacy as determined by controlled trials.

Although many factors may be involved, we do not know all the causes of this Efficacy-effectiveness gap.
Antipsychotics: Second generation

- Action of CAPD involves D2 blockade in limbic system and striatum.
- Receptor blockade in limbic system is basis for antipsychotic action.
- Reduction of activity in striatum is related to EPS & TD.
- D2 blockade of HPA-axis leads to hyperprolactaemia.
Antipsychotics: Second generation

- Newer drugs have lesser affinity to D2; and greater affinity to other receptors like 5 HT, NA [alpha 1 & 2],
- Ability to modulate glutamate receptor-mediated functions and behavior.
Antipsychotics: Second generation

- Typical characteristic of atypicals is a ‘low D2 & 5-HT Ratio’.
- There is some degree of regional anatomical specificity. [very little effect on corpus striatum].
- Various claims have lead to a debate.
- Question of well-being of millions suffering from schizophrenia and a billion dollars of costs.
- If the additional cost of atypical is justified by potential benefit? To influence clinicians and policy makers.
Claim of superior efficacy and safety have been made but ‘the evidence’ is variable and often ‘inadequate’.
There is now strong evidence that AAPD are efficacious and have less SE [low risk of EPS] than CAPD.

The advantage of EPS and TD might be offset by disadvantage of other SE e.g. weight gain, DM, glucose metabolism, hyperlipidaemia.
Existing studies have found that atypical antipsychotics cause fewer EPSs side effects than their conventional counterparts, especially when the conventional comparator is haloperidol.

In spite of marketing claims, studies of effect on cognitive functions are wholly inconclusive, as are effect on mood symptoms.
The effects of AAPD on

- Long-term outcome
- Relapse prevention
- Social and vocational functioning
- Suicide prevention
- Quality of life
- Family and caregivers burden

Have just begun to be explored
Risperidone, olanzapine and Quetiapine account for > 50% of the prescriptions of New Antipsychotics in North America.

The rate of usage in other countries varies from 5% to 40%.
Patients who had *inadequate response* to conventional antipsychotics or who suffered *problematic side effects* are the first to be switched to atypical APD.

Now, however, many newly diagnosed or first-episode patients are initially prescribed these newer agents with the hope (not yet backed by evidence) of giving them very early advantage.[Lieberman JA, JCP, 1996]
Atypical agents are several time more expansive, average being $5000 or more per patient per year.

Even if atypical antipsychotic drugs do not decrease the overall cost of care, their usage may be warranted if their benefits are judged to be substantial enough to justify the increased expenditure.

Currently the cost-effective justification, in scarce resources of public health, does not hold valid.
The clinical and public policy decision to supplant conventional with atypical APD requires empirical evidence.

This is important because the spending of large sum of money on treatments that are less cost-effective than available alternatives may result in needless waste of scarce resources and deprive some patients of clinical benefits to which they would otherwise have access.
Existing evidence does not adequately address the long-term effectiveness and cost issue.

Studies designed to obtain FDA permission [6-8 weeks trials] do not definitively demonstrate “the real World” effect of AAPD.

Eversince the disease was described by Kraepeline, 100 years back, treatments have been in progress. Major advances are noticed That:

- Treatment of schizophrenia and other mental disorders have become more Humane and now aligned more closely to other medical disorders.
- Antipsychotics have become the first line of defence, and have improved the lives of most patients.
- A greater understanding of the genetic basis of schizophrenia underlies much of the recent progress, in part through its focus on reliable diagnosis.
One consequence of Genetic studies is the recognition that schizophrenia illness is broader than the DSM or ICD diagnosis of schizophrenia, and exists as a "Spectrum" of conditions.

While some spectrum disorders are as severe as schizophrenia like schizo-affective disorder, others are milder and do not involve psychosis eg. Schizotypal personality disorder [SPD].
The spectrum concept has numerous implications for treatment.

- Therapeutic efforts vary across schizophrenia spectrum disorders as function of both severity and type of symptoms.
- These differences are of great importance in understanding the core features of schizophrenia.
- Fact that ‘psychosis is not a major feature of spectrum disorder’ suggests that other more subtle symptoms might better reflect underlying etiology.
If such deficits are identifiable, they may provide foundation for treatment strategies.

Moreover, if they are identifiable early, they may even prevent psychosis.

Discussion on spectrum disorder should focus on reflections of genetic predisposition.

There is a need to redefine and reformulate Meehl’s notion of ‘schizotaxia’.

Scizotaxia is perhaps the core liability for Schizophrenia and spectrum disorder.
Schizophrenic patient

Family studies

The relatives

Relatives with schizophrenia

Relatives with Schizotypal personality disorder

Relatives with other Psychotic illness

Relatives with Schizophrenia

Relatives with schizotypal personality disorder

Relatives with other Psychotic illness

Relatives with Psychotic affective disorder

Relatives with Alcoholism Comorbid schizophrenia

Normal – asymptomatic

Relatives with Nonpsychotic illness

Relatives with Mood Disorder

Relatives with other Psychiatric illness

Relatives with alcoholism
Lessons from family studies of nonpsychotic relatives of schizophrenic illness

- Progress in identification of neuropsychological and structural brain abnormalities in the relatives. [mainly first-degree]. Data show:
  - (i) relatively specific N-Psy. deficits in both, patients and their relatives.
  - (ii) the stability of these deficits over time.
  - (iii) the structural and functional brain abnormalities in patients and relatives.
  - (iv) the effect of genetic loading on N-Psych. Functions and neuroanatomical structures.

These findings form the foundation of current efforts to define, validate and treat ‘schizotaxia’.
Neuropsychological functions among adult relatives: functions studied

1. Abstraction / executive memory
2. Verbal ability
3. Spatial ability
4. Verbal memory
5. Visual memory
6. Verbal memory
7. Learning
8. Perceptual-motor speed
9. Mental control/encoding
10. Motor functions
11. Auditory attention
Findings in controlled studies

- The relatives performed more poorly and had greater variability on three predicted functions:
  1. Abstract/Executive function
  2. Verbal memory
  3. Auditory attention/vigilance
- Lower scores on mental control and verbal ability.
- Showed more variability on learning and motor ability.
- Two groups did not differ on visual ability, visual memory, or perceptual motor function.
- The deficits observed did not account for by psychopathology in relatives, by level of education or parental social class.
Findings in controlled studies

- Neuropsychological measures might be useful in detecting putative carriers of the schizophrenia genotype, who cannot be detected with psychiatric assessment.
- These are at best the 'risk indicators for underlying vulnerability to schizophrenia.
- It could be hypothesised that, if the expression of neuropsychological risk indicators in the relatives was due to an underlying genotype, then the neuropsychological indicators of schizophrenia genotype would intercorrelate to a greater degree within the relative's group.
- Men with schizophrenia have greater degree of neuropsychological deficits than women.
Stability of neuropsychological deficits
Schizophrenia and spectrum Disorder: Genetic phenomenology

Decreasing Genetic Risk for schizophrenia in Relatives

Increasing Genetic Risk for affective Disorders and alcoholism in Relatives

Schizophrenia

1%

1%

1%

1%

Affective schizophrenia

Core/ deficit Schizophrenia

Schizotypal Personality Disorder