Psych 181: Dr. Anagnostaras
Lec 7: Schizophrenia and Parkinson's Disease

Incidence about 1 in 100

**RELATIVE PREVALENCE OF SCHIZOPHRENIA**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>1x</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>2x</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>5x</td>
</tr>
<tr>
<td>Insulin-dependent Diabetes</td>
<td>6x</td>
</tr>
<tr>
<td>Muscular Dystrophy</td>
<td>68x</td>
</tr>
</tbody>
</table>

Schizophrenia

*Positive Symptoms*

*Excesses, exaggerations, or distortions (+)*

- Disorganized speech indicating a thought disorder (loose association to word salad)
- Hallucinations sensory experiences without external stimulation commonly auditory
- Delusions beliefs that are contrary to reality commonly persecutory in nature sometimes delusions of grandeur
Schizophrenia
Negative Symptoms

Characterized by behavioral deficits (–)

- **Avolition**
  lack of energy & inability to persist in routine activities

- **Alogia (poverty of speech)**
  reduction in the amount or content of speech

- **Anhedonia**
  inability to experience pleasure

- **Asociality**
  severe impairment in social relationships

- **Flat Affect or Incongruent Affect**
  lack of or inappropriate emotional expression

DSM-IV Criteria

- At least 2 of the following for 1 month:
  - delusions
  - hallucinations
  - disorganized speech
  - disorganized or catatonic behavior

- negative symptoms

- Marked functional impairment

- Continuous signs for 6 months

- Not due to drugs (e.g., amphetamine psychosis)

Type I versus Type II

<table>
<thead>
<tr>
<th>Symptom/Feature</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Impaired social interactions</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Disorganized thought or behavior</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Outcome of illness</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>More than 6 months</td>
<td>Less than 6 months</td>
</tr>
</tbody>
</table>

- Atypical features:
  - Personal & communicative activity
  - Normal level of structure
An Array of Related Psychotic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Key Symptoms</th>
<th>Paranoid</th>
<th>Disorganized</th>
<th>Catatonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Hallucinations, delusions, disorganized speech, thought disorder</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>Mood disorder with psychotic features</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Schizotypal Disorder</td>
<td>Socially disorganized, unusual beliefs, unusual experiences</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Brief Psychotic Disorder</td>
<td>Brief onset of psychotic symptoms</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

Three Subtypes of Schizophrenia (DSM-IV)

**Paranoid Type**
- preoccupation with delusions and hallucinations
- no disorganized speech, catatonia, or flat affect

**Disorganized Type**
- Disorganized speech, behavior, often inappropriate
- does not meet criteria for Catatonic Type

**Catatonic Type**
- Clinical picture with at least two:
  - motoric immobility, catalepsy, stupor (waxy inflexibility)
  - excessive motor activity that is apparently purposeless
  - peculiarities of movement (e.g., voluntary assumption of bizarre postures, stereotypes, odd mannerisms, or grimacing echolalia or echopraxia)

SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 9: 46 year old males

UNAFFECTED

AFFECTED
18.2 PATIENT POPULATIONS in public mental institutions, 1900 to 1975. (After Bausuk and Gerson, 1975.)

Beginning of widespread use of antipsychotic agents.

Patients hospitalized for many years have returned to society.
Increase in DA transmission exacerbates Schizophrenia
Decrease in DA neurotransmission is therapeutic
Neuroleptic or Antipsychotic

- Literally means thins neural transmission
- In practice both terms refer to drugs used to treat schizophrenia only
- Wide variety of off-label applications
- Incorrectly known as "major tranquilizers"

Dopamine

- Schizophrenia is thought to be caused by an overactive dopamine system in the brain.
- Just block the dopamine
- Only helps positive symptoms
- Not the whole picture (i.e. glutamate, 5-HT)
Dopamine Antagonist Drugs

- **chlorpromazine** SmithKlineFrench in 1950
  - Thorazine
  - Derivative of phenothiazine (anti-emetic)
  - Very sedating at first but tolerance builds
  - Some anti cholinergic activity
  - Actively metabolized (Half life of 30hrs)

- Tardive Dyskinesia

Side effects of neuroleptics

- **Parkinsonism**
- **Dystonia** - abnormal face and body movements
- **Akathisia** (restlessness)
- **Tardive dyskinesia** (long term)
  - Exacerbated by drug holiday regime
  - More common in females
  - Worsened in response to reducing drug
  - Irreversible (denervation supersensitivity)
  - Many undesirable side effects (e.g., constipation and metabolic syndromes)
More DA Antagonists

haloperidol (Haldol)
- Long time in the body. Only 60% excreted in the first week.
- Depressent

fluphenazine (Permitil & Prolixin)
- less sedating

Tardive Dyskinesia

Newer Drugs

- Dibenzodiazepine derivatives
- Treat positive and negative symptoms
- Some have less or less severe side effects
- Some have more potential for liver damage
- Expensive
Newer drugs

- **clozapine (Clozaril)**
  - Treats positive and negative symptoms
  - Half Life of 12 hrs
  - Limited to treatment resistant patients
  - Strong risk of seizures
  - Anticholinergic, adrenolytic, antihistaminic and antiserotonergic activity.

- **risperdone (Risperdal)**
  - Blocks DA and 5-HT receptors.
  - Dose related mild parkinsonian side effects
  - Some cases of cardiac hypotension

- **olanzapine (Zyprexa)**
  - Binds to lots of DA and 5-HT receptors
  - Lower Tardative Diskinesia risk
  - Lower seizure risk

![Diagram of medication receptors](image)
Pre-pulse inhibition of startle

**Figure 1**

Endogenous 5-HT antagonism and inhibition of startle. The endogenous 5-HT antagonists are: (1) haloperidol (3 mg/kg), (2) chlorpromazine (10 mg/kg), and (3) promethazine (10 mg/kg). The horizontal line represents the startle response latency at each time point. The startle response latency is defined as the time from the onset of the sound stimulus to the startle response. The startle response latency is expressed in seconds. The startle response latency is measured from the onset of the sound stimulus to the peak of the startle response. The startle response latency is measured in seconds. The startle response latency is measured in seconds.
DA Model of Schizophrenic Dysfunction

What do these people have in common?

20.2 CLASSIC SYMPTOMS OF LATE-STAGE PARKINSON’S DISEASE, including a stooped and rigid posture, shuffling gait, tremor, a masklike facial appearance, and “pill rolling” (unreal. After Murray, 1996.)
James Parkinson, 1917
"...involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and the intellects uninjured."

- rhythmic tremor at rest
- rigidity with “cog-wheel characteristic”
- akinesia

Pathology of Parkinson’s

- Death of Dopamine neurons in the Substantia Nigra
- Loss of Dopamine in the Caudate
- Loss of Inhibition in the Caudate
- Overactive output (globus pallidus) to the thalamus
- Thalamus overinhibits the motor cortex
- Complex basal ganglia-cortical loops

EPIDEMIOLOGY

- fifth or sixth decade of life
- 85% idiopathic
- prevalence: 3 per 1000
- cumulative life-time risk: 1 in 40
- approximately 1 million patients
- no cure
ETIOLOGY

Genetic Factors
- 1999 - examined 17,000 twins
  - > 50 years old: no genetic effect
  - < 50 years old: 10% genetic defect

Diet
- ↓ vitamins, antioxidants ⇒ ↑ incidence

Smoking
- → ↓ incidence

Environment
- ↑ Incidence in rural areas
dopamine neuron toxins

![Chemical structures of MPP+ and Rotenone](image)

20.14 PARKINSONIAN BEHAVIOUR OF A MPTP-TREATED MONKEY AND REGRESSION BY VARIOUS TREATMENTS. The effect of MPTP (20 mg/kg) injected intraperitoneally, with a dose of 40 mg/kg/day given to monkeys over a 10-day period, is a state of rigidity followed by a progressive loss of motor control, akin to Parkinsonian disease. In the monkey pictured on the left, the progression of the disease is accompanied by weight loss and an inability to move. After 14 days, the animal showed no signs of rigidity and touched, face with self. The animal on the right, after the intervention, shows an improved posture and reduced rigidity. (From Tane et al., 1981.)
Mona Thiruchelvam, Eric K. Richfield, Raymond B. Baggs, Arnold W. Tank, and Deborah A. Cory-Slechta


Paraquat + Maneb impairs movement.
Paraquat + Maneb depletes Dopamine

Pathophysiology of Parkinson’s Disease

STAGES OF PARKINSON'S DISEASE
Levodopa therapy

- Main treatment is with L-DOPA
  Precursor for dopamine
- Sinemet is L-DOPA + carbidopa
  carbidopa is a peripheral decarboxylase inhibitor
  - prevents L-DOPA catabolism
- Main problems:
  - on/off fluctuations
  - dyskinesias
  - eventually doesn’t work
  - peripheral side effects (NE and E)
- Anticholinergics help as well
- On-off fluctuations too great with DA agonists
18

Drugs used to treat Parkinson's Disease

Parkinson's: Outlook

- Chronic dopamine treatment can also result in Schizophrenic symptoms
- Several surgical treatments for Parkinson's
  - used after therapeutic window closes
  - stem cell transplantation
  - pallidotomy and thalamotomy