Role of Dopamine in Different Psychiatric Disorders

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Objectives

Role of Dopamine in:
1. Depression
2. Schizophrenia
3. Bipolar disorders
Introduction

Dopamine is a neurotransmitter released by the brain that plays a number of roles in humans and other animals. Some of its functions are in:
• movement
• memory
• pleasurable reward
• behavior and cognition
• attention
• inhibition of prolactin production
• sleep
• mood
• learning

Dopamine pathways and Functions

<table>
<thead>
<tr>
<th>Dopamine pathways</th>
<th>Functions</th>
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<tbody>
<tr>
<td>A) NIGROSTRIATAL substantia nigra to basal ganglia</td>
<td>part of extrapyramidal nervous system</td>
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<tr>
<td>B) MESOLIMBIC midbrain ventral tegmental area (VTA) to the nucleus accumbens</td>
<td>involved in pleasurable sensations, euphoria of drug abuse, delusions and hallucinations</td>
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<tr>
<td>C) MESOCORTICAL midbrain ventral tegmental area (VTA) to prefrontal cortex</td>
<td>role in mediating cognitive symptoms and affective symptoms of schizophrenia</td>
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<tr>
<td>D) TUBEROINFUNDIBULAR hypothalamus to anterior pituitary gland</td>
<td>controls prolactin secretion</td>
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Dopamine and Pleasure

• Dopamine mediates pleasure in the brain.
• It is released during pleasurable situations and stimulates one to seek out the pleasurable activity.
• This means food, sex, and several drugs of abuse stimulants dopamine release, particularly in the nucleus accumbens and prefrontal cortex.
Dopamine and Depression

Introduction

Depression:

• Affects 100-120 million worldwide at any given time.
• Life time prevalence – 15.3% - 17.9% M.D.D., and 35.4% any depression
• By the year 2020, the World Health Organization (WHO) estimates that depression will be the number two cause of "lost years of healthy life" worldwide.
Depression: Facts

• Depression is **chronic** and **recurrent** illness
• Depression associated with:
  – 2x increased risk of death overall
  – 26x increased risk of suicide
  – 2 - 5x increase in days absent from work
  – Impaired social function

Depression: Facts

• Depression increased vulnerability to **cardiovascular disease**; 4-5 x increased **mortality** post MI
• Depression is a risk factor of cardiovascular disease, stroke, diabetes.
### Diagnostic criteria for major depressive episode

At least 5 of the following criteria (which must include 1 and 2) present for two weeks:

1. **Depressed mood**, most of the day nearly every day
2. Markedly **diminished pleasure or interest**, most of the day nearly every day
3. Significant weight loss or weight gain
4. **Insomnia** or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. **Fatigue** or loss of energy nearly every day
7. Feelings of worthlessness or guilt (may be delusional)
8. **Diminished ability to think** or concentrate
9. Recurrent thought of death or **suicidal ideation**

### Causes of Depression

- The **biopsychosocial model** biological, psychological, and social factors all play a role to varying degrees in causing depression.
- The **diathesis-stress model** depression results when a preexisting vulnerability, or diathesis, is activated by stressful life events.
- The preexisting vulnerability can be either **genetic**, implying an interaction between nature and nurture, or **schematic**, resulting from views of the world learned in childhood.
Biochemical Theories of Depression

**Monoamine hypothesis**

- Depression: functional deficiency of the brain monoaminergic transmitters norepinephrine (NE), 5-HT, and/or dopamine (DA),
- Mania is caused by functional excess of monoamines in the brain.
- Depression or the manic state: altered synthesis, storage, or release of the neurotransmitters, as well as disturbed sensitivity of their receptors or subcellular messenger functions.

**Monoamine Hypothesis of Depression**

- "**Norepinephrine** related to alertness and energy as well as anxiety, attention, and interest in life.
- **Serotonin** related to anxiety, obsessions, and compulsions.
- **Dopamine** to attention, motivation, pleasure, and reward, as well as interest in life."
- This theory recommend the choice of an antidepressant with mechanism of action that impacts the most prominent symptoms.
Dopamine hypothesis in Depression

Mesolimbic Dopamine System, in Depression.
• The nucleus accumbens and its dopaminergic input from the ventral tegmental area (VTA).
• The rewarding effects of food, sex, and drugs of abuse.
• Anhedonia, reduced motivation, and decreased energy level in depression

Other theories of depression
1. Structural changes in brain in depression (e.g., smaller hippocampal volumes, anterior cingulate cortex, the dentate gyrus of the hippocampus).
2. Glutamate hypothesis and depression. Glial cell abnormalities (glial cells play a primary role in synaptic glutamate removal). (Antiglutamatergic agents, such as lamotrigine, have potential antidepressant efficacy).
3. The neurotrophic hypothesis of depression. (Antidepressants induce upregulation of BDNF and help repair some stress induced damage to hippocampus and resolution of depression).
Structural Changes in Brain in Depression

Medial prefrontal cortex
Atrophy

HIPPOCAMPUS
Atrophy

AMYGDALA
Hypertrophy and Later atrophy

Anterior cingulate cortex
Treatment

• 20 FDA approved antidepressants as well as several scientifically tested psychotherapies.
• No one treatment is universally effective for everyone: many depressed patients do not experience a satisfactory clinical benefit from the initial treatment they receive.
• Some may require the combination of two or more treatments.
Treatment goals

- Unfortunately, about 60% to 65% of patients do not achieve remission following initial antidepressant treatment.
- **Treatment response** is a 50% reduction in symptoms from baseline
- **Remission** is a symptom-free state.
- Treating patients to remission lowers the risk of relapse and improves physical and social functioning.

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Aims of Treatment

- Minimize relapse/recurrence risk
- Reduce/remove signs, symptoms
- Restore role function
Antidepressant Target Symptoms

- Pharmacotherapy directed at a single neurotransmitter system results in suboptimal response as well as reduced likelihood to induce remission and minimize residual symptoms.
- The majority of antidepressant drugs lack direct pharmacologic effects on dopamine neurotransmission.

<table>
<thead>
<tr>
<th>Single action</th>
<th>Dual action</th>
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<tbody>
<tr>
<td>Mostly NE</td>
<td>Both NE &amp; 5-HT</td>
</tr>
<tr>
<td>– Desipramine</td>
<td>– Clomipramine</td>
</tr>
<tr>
<td>– Bupropion</td>
<td>– Other TCAs</td>
</tr>
<tr>
<td>– Reboxetine</td>
<td>– Mirtazapine</td>
</tr>
<tr>
<td>Mostly 5-HT</td>
<td>– MAOIs</td>
</tr>
<tr>
<td>– SSRI’s</td>
<td>– Venlafaxine</td>
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Choice of an antidepressant

- Anxious and irritable patients should be treated with SSRIs or norepinephrine reuptake inhibitors, and those experiencing a loss of energy and enjoyment of life with norepinephrine- and dopamine-enhancing drugs.

Antidepressants with Direct Dopaminergic Effects

- For example, MAOIs increase brain concentrations of—norepinephrine, serotonin, and dopamine.
- Efficacy across a spectrum of depressive and anxiety disorders.
- MAOIs relative disuse due to drug-drug interactions and tyramine-associated hypertensive episodes.
Antidepressants with Direct Dopaminergic Effects

- The dual SNRI venlafaxine, modestly inhibits dopamine reuptake.
- At high doses, the SSRI sertraline can also inhibit dopamine reuptake.
- Bupropion, a dual-acting DNRI, targets specific MDD symptoms, may offer therapeutic advantage over other antidepressants (eg, loss of pleasure).

Agomelatine and the treatment of anhedonia

- Agomelatine represents a new approach to depression with an innovative mechanism of action.
- It is an agonist of melatonergic receptors MT1 and MT2 and a selective antagonist of 5-HT2c receptors.
- It increases noradrenaline and dopamine release specifically in the frontal cortex.
Role of Dopamine in Schizophrenia

Psychosis

• Psychosis is a mental state where there is a grossly impaired appreciation of reality as evidenced by the presence of delusions, hallucinations and bizarre behaviour.
• Many disorders cause psychosis, including organic states, schizophrenia, mania, psychotic depression and paranoid syndromes.
**Schizophrenia, Epidemiology**

- Schizophrenia occurs equally in males and females, although typically appears earlier in males.
- Onset in childhood is much rarer, as is onset in middle- or old age.
- The lifetime prevalence of schizophrenia—is 1%.

**DSM-IV-TR**

**Three diagnostic criteria must be met:**

1. **Characteristic symptoms:** Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
   - Delusions
   - Hallucinations
   - Disorganized speech, which is a manifestation of formal thought disorder
   - Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
   - Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

   If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient’s actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.
**DSM-IV-TR**

2. **Social/occupational dysfunction**: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

3. **Duration**: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

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**Causes of schizophrenia**

- Genetic and environmental factors can act in combination to result in schizophrenia.
- The inherent vulnerability (or diathesis) in some people, can be unmasked by biological, psychological or environmental stressors, is known as the stress-diathesis model.
- The idea that biological, psychological and social factors are all important is known as the "biopsychosocial" model.
Causes of Schizophrenia

• Early neurodevelopmental risk factors of schizophrenia.
  1. People born in winter or spring
  2. prenatal exposure to infections

• Social risk factor for schizophrenia
• Drug abuse
• Structural and functional differences in brain activity

Neurotransmitter Hypothesis of Schizophrenia

• While the etiology and pathology of schizophrenia remains unclear.
• Alteration in several neurotransmitter systems
• Among these, dopamine, glutamate and serotonergic systems.
• Other systems such as GABAergic, cholinergic, neuropeptides, adrenoreceptors and second messengers have also been implicated.
Dopamine hypothesis of schizophrenia

- Dopamine in the **mesolimbic pathway**
  1. Drug which blocks dopamine, as the *phenothiazines*, could reduce psychotic symptoms.
  2. *Amphetamines*, which release dopamine may exacerbate the psychotic symptoms in schizophrenia
- Excess activation of $D_2$ receptors cause of the positive symptoms of schizophrenia.

Modified Dopamine Hypothesis of Schizophrenia:

- **MESOLIMBIC DOPAMINE HYPOTHESIS**
  Diseases or drugs that increase dopamine in mesolimbic area enhance or produce positive symptoms.
- **MESOCORTICAL DOPAMINE HYPOSTHESIS**
  Cognitive and some negative symptoms of schizophrenia are due to deficit of dopaminergic activity in mesocortical projections to dorsolateral prefrontal cortex.
Dopamine Theory of Schizophrenia

- Brain injury to prefrontal cortex
- Dopamine neuron underactive in prefrontal cortex
- Release of mesolimbic dopamine neurons from inhibitory control
- Negative symptoms of schizophrenia
- Positive symptoms of schizophrenia

Schizophrenia - symptoms

**Positive Symptoms**
- Hallucinations
- Delusions (bizarre, persecutory)
- Disorganized Thought
- Perception disturbances
- Inappropriate emotions

**Negative Symptoms**
- Blunted emotions
- Anhedonia
- Lack of feeling

**Cognition**
- New Learning
- Memory

**Mood Symptoms**
- Loss of motivation
- Social withdrawal
- Insight
- Demoralization
- Suicide
Evidence against Dopamine Theory of Schizophrenia

- Antipsychotics are only partially effective in most (70%) and ineffective for some patients.
- Phencyclidine, an NMDA receptor antagonist, produces more schizophrenia-like symptoms in non-schizophrenic subjects than DA agonists.
- Atypical antipsychotics have low affinity for D2 receptors.

Glutamate hypothesis

- Reduced function of the NMDA glutamate receptor in schizophrenia.
- Low levels of glutamate receptors in postmortem brains of people with schizophrenia
- Glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition.
Serotonin hypothesis of schizophrenia

• The “serotonin hypothesis of schizophrenia” is informed by several observations:
  1. Psychotomimetic properties of hallucinogens [e.g., lysergic acid diethylamide (LSD)] may be caused by **5-HT2 receptor agonists**.

  2. Alterations in the concentration of 5-HT and its metabolite (5-HIAA) and the density of 5-HT1A or 5-HT2A receptors in postmortem brain specimens; abnormalities of 5-HT and its metabolites in blood or CSF.

  3. Alteration of serotonin transporters.

Serotonin Receptors

• 5HT2A antagonism reduces negative symptoms:
• In mesocortical pathway, 5HT2A antagonism increases DA release and reduction in negative symptoms.

Antipsychotic medications
Typical antipsychotics

- Antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia).
- Also used for the treatment of acute mania, agitation, and other conditions.
- The first typical antipsychotics to enter clinical use were the phenothiazines.

Typical antipsychotics

- All antipsychotic drugs block D<sub>2</sub> receptors in the dopamine pathways and reduce positive symptoms of schizophrenia.
- They also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway and produce side effects.
Atypical antipsychotic

• Some atypical antipsychotics are FDA approved for use in the treatment of schizophrenia.
• Some carry FDA approved indications for acute mania, bipolar depression, psychotic agitation, bipolar maintenance, and other indications.
Atypical antipsychotic

- All antipsychotics work on the dopamine system but all vary in regards to the affinity to the dopamine receptors.

The "fast-off" theory
- AAP have low affinities for the D2 receptor.
- The AAP transiently bind and rapidly dissociate from the D2 receptor to allow normal dopamine transmission.
- This keeps prolactin levels normal, spares cognition and no EPS.

Atypical antipsychotic

- Atypical antipsychotic drugs like clozapine, olanzapine, quetiapine, risperidone and asenapine are relatively potent antagonists of 5-HT$_{2A}$ receptors.
- serotonin antagonist is not sufficient to produce an antipsychotic effect but serotonergic activity in combination with D2 receptor blockade may be responsible.
Second Generation Antipsychotics

- In mesolimbic pathway, the action of D₄ receptor blockade and antipsychotics are more robust than 5HT₂A antagonism. This may help reducing positive symptoms.

- In mesocortical pathway, dopamine deficiency causes negative and cognitive symptoms. In mesocortical pathway, there is more 5HT₂A receptors than D₂ receptors. Thus 5HT antagonistic property is more profound that D₂ receptor blocking property. This may help improving negative symptoms.
3rd Generation Antipsychotics

• Is a partial dopamine agonist with additional antidepressant properties
• Used in the treatment of schizophrenia, bipolar disorder, and clinical depression.
• E.g., Aripiprazole’s mechanism of action is different from those of the other FDA-approved atypical antipsychotics

3rd Generation Antipsychotics

• It acts as a D₂ partial agonist.
• It acts as 5-HT₁A receptor partial agonist
• like the other atypical antipsychotics displays an antagonist profile at the 5-HT₂A receptor.
3\textsuperscript{rd} Generation Antipsychotics

- **Antagonist** in areas of high levels of dopamine, such as the mesolimbic pathway.
- **Agonist** ($D_2$ partial agonist) in regions of low dopamine concentration, such as mesocortical pathway.
- $D_2$ partial agonist reduce the positive symptoms of schizophrenia without producing movement disorders or elevated prolactin levels.

Role of Dopamine in Bipolar Disorder
Bipolar disorder
(Manic-depressive illness)

- Chronic mental disorder
- Recurrent episodes, characterized by alternating manic and depressive episodes.
- Lifetime prevalence of 0.5 to 1.5%.
- Average onset of the disease: 21 years with similar rates in males and females
- 15% of patients eventually die by suicide.

Causes of BP disorders

- The cause is unclear, although genetics, brain chemistry and environment may contribute to the disorder.
Dopamine Hypothesis of Bipolar Disorder

• Similar to schizophrenia, alterations in the different DA tracts may be hypothesized for bipolar disorder.
• Dopamine is at the center of an apparent link between bipolar and schizophrenia.

Dopamine Hypothesis of Bipolar disorder

• Mania in bipolar disorder is associated with increased dopamine activity.
• Depression in bipolar disorder is linked to decreased dopamine activity.
Dopamine Hypothesis of Bipolar disorder

• The dopamine transporter (DAT) has been implicated as a candidate gene in several disorders, including bipolar disorder and attention-deficit hyperactivity disorder.

Evidence of Dopamine Hypothesis

Particularly in mania.

• Cocaine and amphetamine increase synaptic dopamine concentrations by acting at DAT to inhibit dopamine reuptake.
• Cocaine and amphetamine:
  1. The acute effects resemble mania
  2. The chronic administration provoke a manic episode in bipolar patients and trigger psychosis in nonbipolar patients.
Evidence of Dopamine Hypothesis

• In Parkinson’s disease, administration of high-dose dopamine precursors can produce a ‘maniform’ picture, which switches into a depressive on withdrawal.

Evidence of Dopamine hypothesis of bipolar disorder.

• Antipsychotic drugs, which block dopamine receptors, are an effective treatment for mania
• Finally, the antidepressant bupropion acts at DAT and has been reported to be of particular efficacy in bipolar depression
Dopamine in Schizophrenia and BP Disorders

- Elevations in dopamine receptor values may occur in psychiatric states with psychotic symptoms rather than being specific to schizophrenia.

Thank You