Class 26- Schizophrenia, Affective (and anxiety) Disorders

Schizophrenia

- Effects 1% of world population, complex disease, not strictly degenerative
- 3 types of symptoms
  - Negative symptoms (lack of some behaviors)
  - Cognitive symptoms (disorder of information processing)
  - Positive Symptoms (additional abnormal behaviors)
- Physical traits: Mild facial (larger heads, wide-set eyes, low ears) + finger signature (length, fingerprint, in males)
- Late onset: rarely happens or is diagnosed before the 20’s
- Symptoms appear gradually within 5 years of onset. Positive symptoms appear last, negative first

Positive Symptoms: Dopamine

- All positive symptoms may be preceded by short-lived ‘elation’/’euphoria’
- Thought disorders: Irrational, disorganized thinking
- Delusions: Non-factual beliefs (persecution, contact with aliens, grandeur)
- Hallucinations: Sensory perception mal-function (auditory hallucinations)

Why?

- Chlorpromazine blocks D2 receptors, and eliminate positive symptoms
- L-Dopa, cocaine, amphetamine: agonists increase the positive symptoms
- A dysfunction of the meso-limbic dopaminergic system: ‘too much dopamine’
- VTA→ Nucleus Accumbens + Amygdala
- The more D2 receptors which are blocked in a schizophrenic patient, the larger the anti-schizophrenia effects seen in that patient.

Negative Symptoms: Brain Damage
• Absence of certain behaviors: flat affect, flat motivation, unusual facial expressions, social inhibition, anhedonia, poor eye pursuit, deficit in eye-blink reflexes…
• Enlarged ventricles
  ○ Large lateral (and third) ventricles → Less gray matter (temporal and frontal lobes)

![Graph showing relative ventricular size in chronic schizophrenics and controls.](image)


• Evidence from anatomy: In normal individuals, the loss of brain tissue (cortical gray matter) is progressive after onset. However, there is more loss in schizophrenic patients, sooner.
• Hypofrontality: evidence from physiology → Reduced frontal lobe activity
  ○ Decrease of activity in dorso-lateral frontal cortex
  ○ Due to decrease in dopamine release
• Animal Models: PCP (angel dust) or Ketamine produces Schizophrenic-like symptoms: Indirect NMDA antagonists → decrease neural activity and dopamine modulation in prefrontal cortex
• Lack of prefrontal activity/dopamine results in perseverating behaviors (behaviors which require perseverance)
• Clozapine increases dopamine in the prefrontal cortex and alleviates symptoms.

Towards an Explanation and Effective Treatment for Positive and Negative Symptoms:
• Step 1: Hypofrontality
  ○ Less NMDA and DA release in prefrontal cortex → Less PFC activity
○ Negative symptoms
○ Alleviated by indirect NMDA agonists

● Step 2: Too little activity in PFC triggers less inhibition of VTA
○ More DA release in Nucleus Accumbens
○ Positive Symptoms
○ Alleviated by D2 antagonists

● **Conclusions**: Not enough DA in Frontal Cortex, too much DA in Nucleus Accumbens

**Treatment**

● Partial competitive DA agonist: high affinity, but less efficient than DA. Atypical antipsychotic (e.g. clozapine, Aripiprazole)
  ○ Agonist in Prefrontal Cortex
  ○ Antagonist in Nucleus Accumbens
  ○ Alleviates **all symptoms** of Schizophrenia

**Multiple Causes (Risk Factors) of Schizophrenia**

● Viral Causes:
  ○ Epidemiology: Study of disease at the population level
  ○ Latitude Effect: increase risk if birth occurs far from equator.
  ○ Seasonality effect: late- Winter/ early-Spring births
  ○ Births after a flu epidemic on 2nd trimester of pregnancy are at risk
● Births in cities: 3x more schizophrenia. Easy transmission of viruses.

● Other Risk Factors:
  ○ Vitamin D deficiency (lack of sunlight or milk)
  ○ Smoking and Alcohol consumption during pregnancy

● Developmental Causes
  ○ Lack of sociability and psychomotor skills in childhood are associated with Schizophrenia
  ○ Monozygotic twin studies: if twinning occurs before day 4 → separate placenta → decreased likelihood of both twins developing Schizophrenia

![Placenta](image)

**Figure 3** Monozygotic Twins. (a) Monochorionic twins, sharing a single placenta. (b) Dichorionic twins, each with its own placenta.

● Genetic Causes
  ○ Parental schizophrenia increase the risks of children developing Schizophrenia by a factor of 10
  ○ Twins fingerprints correlates with their concordance for schizophrenia
  ○ Identical twins form 2 schizophrenic parents: only 45% chance that both develop Schizophrenia (should be >75%) → more than one gene involved, or other factors
  ○ Multiple Genes involved

**Cognitive Symptoms: Brain Damage**

● Attention deficits
● Slow reaction time (fingers, legs)
● Deficit in learning and memory
● Poor planning and problem solving
• Deficit in abstract thinking
• Brain: No clear neural correlates or mechanisms yet

**Affective Disorders: Mania and Depression**

• Bipolar disorder: Cycle between Depression and Mania
• Depression: 3x longer than Mania
• Mania by itself is rare
• Depression (Major Depressive Disorder) by itself is 2-3x more likely in women (7%) than men (3%).
• MDD (Major Depressive Disorder): unworthiness, guilt, low energy, difficulty to fall asleep
• Suicide attempts: 15% unipolar, 30% bipolar.
• Accompanied by sleep disorder: Less SWS, more stage 1, earlier REM onset
• Hereditary: one direct parent → 10x increase in risk. No single genes
• Seasonality effect: birth in May/June/July → higher risk for suicide

**Unipolar Treatments of Depression**

• The monoamine hypothesis: depression is due to a lack of monoaminergic activity

Following list goes in order from earliest treatments to latest treatments

• MAO inhibitors (increase levels of NE, DA, 5HT). 65% success
• Reserpine (monoamine antagonist) induce depression
• Tricyclic Antidepressants (inhibits reuptake of NE and 5HT)
• Levels of 5HT in blood lower in suicidal depressive patients
• Tryptophan depletion induces depression
• Selective Serotonin Reuptake Inhibitors (SSRIs like prozac, celexa, paxil): high treatment success
• Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs): high treatment success as well

**Bipolar Treatment: Lithium**

• Treats bipolar (80%), not unipolar. Fast and effective on Mania
• Side effects: weight gain, increase in fluid intake and excretion, diabetes, and fatal overdose
● Stabilizes neuromodulatory pathways. Valproate (increase GABA, effect on Mania)

● Problems with the monoamine hypothesis:
  ○ Lithium does not act on monoamines
  ○ Increase in monoamine levels is fast, but effects of the drugs are slow
  ○ Cocaine inhibits reuptake of monoamine, but is not an antidepressant

Affective Disorders: Other Treatments

● ElectroConvulsive Therapy
  ○ Controlled seizures, anesthetized, under curare (muscle paralysis)
  ○ For bipolar patients, when everything else fails.
  ○ Fast, 50% success in responding
  ○ Side effects: memory loss, risk of focal seizures
  ○ Acts by increasing Gaba and Neuromodulators

● New Technique: Transcranial magnetic Stimulation (TMS) of prefrontal cortex
  ○ Effective in prefrontal cortex
  ○ Need repeated treatments
  ○ Non-Invasive

● Deep brain stimulation
  ○ Direct stimulation of subgenual anterior cingulate cortex (ACC)
  ○ Invasive
  ○ Fast onset of antidepressant effect
  ○ Accumulating effects (after 6 months: 35% remission, or 60% improvement
  ○ Also: direct stimulation of nucleus accumbens

● Vagus Nerve Stimulation
  ○ Indirect form of deep brain stimulation by stimulating the periphery
  ○ Indirect stimulation of the brain stem
  ○ Exact mechanisms unknown, but related to seizure prevention

Bipolar Disorders: Treatments

● Sleep therapy
- Delaying or preventing REM sleep. Slow, but effective. A common side effect of antidepressants.
- Slow wave sleep deprivation: Effective faster (1-2 nights)
- **Total Sleep deprivation**
  - Depressogenic hypothesis: a depression-inducing substance is secreted at night and is cleared during the awake state.
  - Fast effects, but not for everyone, works best for depressed patients with fluctuating daily moods
  - Not long lasting
- Partial/Intermittent sleep deprivation helps the effect of antidepressants

**Bipolar Disorders: Mania**

- Due to hyperactivity in the Anterior Cingulate Cortex (ACC)
- ACC normally regulates emotions (inhibition)
- Mostly involved in the manic phase
- Most Effective treatments of depressions result in decrease in activity in ACC

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**Figure 10** Decreased Activation of the Subgenual ACC After a Variety of Successful Treatments for Depression. The figure shows a standard drawing of an anterior midsagittal view of the human brain with tracings of regions of increased (red) or decreased (blue) activation seen in functional imaging studies of brain responses to successful treatment for the symptoms of depression. Treatment with (a) DBS, (b) TMS, (c) VNS, (d) SSRIs, (e) SNRIs, (f) placebo.

**Seasonal Affective Disorders (SAD): Hypothalamus?**
Depression that is thought to be caused by the processing of daylight in the brain.

- Unipolar depression
- Short days, long nights (winters) → depression
- Summer depression is rare
- Genetic basis (melanopsin gene)
- Treatments: phototherapy, light therapy, and exercise.