Joseph

Schizophrenia

- 1% total world population has complex disease. Not strictly degenerative
- 3 types of symptoms
- Negative symptoms (lack of some behaviors)
- Cognitive symptoms (a disorder of information processing)
- Positive symptoms (additional abnormal behaviors)
- Physical traits: Mild facial (larger heads, wide-set eyes, low cars) + finger signatures.
- Late-onset: 20’s
- Symptoms appear gradually within 5 years of onset. Positive symptoms appear last.

Positive symptoms: Dopamine

All positive symptoms may be preceded by short-lived elevation/ euphoria
- Thought disorders: Irrational, disorganized thinking
- Delusions: Non-factual beliefs (persecution, contact with Alien etc.)
- Hallucinations: Sensory perception mal-function auditory.

Chlorpromazine blocks D2 receptors, and eliminate positive symptoms.
- L-Dopa, cocaine, amphetamine: Agonists increase the positive symptoms.

A dysfunction of the mesolimbic dop:anergic system: two much dopamine

VTA> Nucleus Accumbens + Amygdala

Negative symptoms: Brain Damage

Absence of certain behaviors: flat affect. Plat 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

Evidence from anatomy: The loss of brain tissue (cortical gray matter progressive alter onset. More loss in schizophrenic patients

Negative symptoms: Brain Mamas
- Hypofrontality: Evidence from physiology

Decrease of activity in (dorsolateral), frontal cortex

Due to a decrease in dopamine release

Reduced frontal lobe active

Hypofrontality: Evidence from animal studies

Animal models: PCP (angel dust) or Ketamine produce Schizophrenia-like symptoms: Indirect MD A antagonists - Decrease neural activity and do partie modulation in the prefrontal cortex.
- Lack of prefrontal activity/ dopamine

Towards an explanation and an effective treatment for the positive and negative symptoms
- Step 1: hypofrontality
  - Less NMDA and DA release in prefrontal cortex > Less PEC activity
• Negative symptoms
  • Alleviated by indirect NMDA agonists Pretoria
    - Step 2: Too little activity in PFC triggers
      less inhibition of VTA.
  • More DA release in Nuc. Accumbens
• Positive symptoms
  • Alleviated by D2 antagonists
  • Not enough DA in Frontal Cortex, 100 much DA in Nuc.

**Treatment.** Partial competitive DA agonist: Agonist in PFC Antagonist in Nuc. Accumbens
Alleviate all symptoms of Schizophrenia.

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

**Developmental causes**
  - Lack of sociability and psychomotor ski
  - IS In childhood are associated with schizophrenia.
  - Monozygotic twin studies: if twinning occurs before day 4 > separate placenta > decrease likelihood of both twins developing Schizophrenia.

**Genetic cause**
  - Parental schizophrenia increases the risks of children developing Schizophrenia by a factor 10
  - Twins fingerprints correlate With their concordance for schizophrenia.
  - Identical twins from 2 schizophrenic parents: only 45% chance that both develop Schizophrenia (should be >75%)> more than one gene involved or other factors.

**Brain damage**
  - Attention deficits
  - Slow reaction time (Fingers, legs)
  - Deficit in learning and memory
  - Poor planning and problem solving
  - Deficit in abstract thinking

**Depression**
Brain: No clear neural correlates or mechanisms
Bipolar disorder: Cycle between Depression and Mania.
  • Depression: 3x longer than Mania.
  - Mania by itself is rare.
  - Depression (Major Depressive Disorder) by itself is 23 & more likely in Suicide attempts: 15% unipolar, 30% bipolar.
  - Hereditary: one direct parent > 10x increase in risk. No single gents.
  - Seasonality effect: birth in May June/July > high risk for suicide.

**Bipolar treatment.** Lithium
  - Treats bipolar (80%), not unipolar. Fast and effective on Mania
- Side effects include weight gain, increase in Quid intake and excretion, diabetes, fatal overdose.
- Stabilize neuromodulatory pathways. Valproate (increase GABA, effect on Mania)
Problems with the monoamine by polhesis:
  • Lithium does not act on monoamines
  • Increase in monoamine levels is fast, but effects of the drugs are slow.
  • Cocaine inhibits the reuptake of monoamine but is not an antidepressant

**Electro Convulsive Therapy**
Controlled seizures, al Pessthetized, 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 of prefrontal cortex
- Effective in prefrontal cortex
- Need repeated treatments
- Non-invasive

**Deep brain stimulation.**
- Direct stimulation of (subgenual) Anterior Cingulate Cortex
  - Invasive.
  - Fast onset of antidepressant effect.
Accumulating effects (after 6 months: 35% remission, 60% improvements).
- Also: Direct stimulation of nucc. 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.