• 12-1: Schizophrenia Affective (and Anxiety) Disorders
  ○ Schizophrenia:
    ■ 1% total world population.
    ■ Complex disease
    ■ Not strictly degenerative
    ■ 3 types of symptoms:
      ● Negative symptoms (lack of some behaviors)
        ○ 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, frontal lobes…)
        ■ Hypofrontality: Evidence from Physiology
          ● Decrease of activity in (dorso-lateral) frontal
            cortex
          ● Due to decrease in dopamine release
          ● Reduced frontal lobe activity
        ■ Hypofrontality: evidence from animal studies
          ● Animal models: PCP (angel dust) or
            Ketamine produce schizophrenia-like symptoms: indirect
            NMDA antagonists -> decrease neural
            activity and dopamine modulation in
            prefrontal cortex
          ● Lack of prefrontal activity/dopamine results
            in preserving behaviors
            ○ Perseverance: inability to change
              strategy
          ● Clozapine increases dopamine in prefrontal
            cortex and alleviate symptoms
        ○ Towards and Explanation and an effective treatment for the
          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 triggered less
            inhibition of VTA
            ● More DA release in Nuc. Accumbens
            ● Positive symptoms
- Alleviated by D2 antagonists

**Conclusion:**
- Not enough DA in frontal cortex, too much DA in Nuc. Accumbens

- Cognitive Symptoms (disorder of information processing)
  - Cognitive symptoms: brain damage
    - Attention deficits
    - Slow reaction times (fingers, legs)
    - Deficit in learning and memory
    - Poor planning and problem solving
    - Deficit in abstract thinking
    - Brain: no clear neural correlates or mechanisms yet

- Positive symptoms (additional abnormal behaviors)
  - Positive symptoms: Dopamine
    - All positive symptoms may be preceded by short-lived ‘elation’/’euphoria’.
    - Thought disorder: irrational, disorganized thinking
    - Delusions: non-factual beliefs (persecution, contact with aliens, grandeur)
    - Hallucinations: sensory perception mal-function (auditory…)
  - Chlorpromazine blocks D2 receptors, and eliminate positive symptoms
  - L-dopa, cocaine, amphetamine: agonist increase the positive symptoms
  - A dysfunction of the meso-limbic dopaminergic system: ‘too much dopamine’
    - VTA-> Nucleus Accumbens + Amygdala
  - D2 binding and potency
    - The more D2 receptors are blocked, the larger the anti schizophrenia effect

- Physical traits: mild facial (larger heads, wide-set eyes, low ears) + finger signatures (length, fingerprint, in males)
- Late onset: 20s
- Symptoms appear gradually within 5 years of onset.
- Positive symptoms appear last, negative symptoms first
- Evidence from anatomy: In normals, the loss of brain tissue (cortical gray matter) is progressive after onset. More loss in schizophrenia patients

**Treatment:**
- Partial competitive DA agonist: high affinity, but less efficient than DA (Aka Atypical antipsychotic (ex. clozapine, aripiprazole))
  - Agonist in PFC
  - Antagonist in Nuc. Accumbens
  - Alleviate all symptoms of Schizophrenia
Schizophrenia: Multiple Causes

Viral Cause
- Epidemiology: study of disease at the population level
- Latitude effect: increased risk if birth occurs far from the equator
- Seasonality effect: late-winter / early-spring births
- Birth after a flu epidemic on 2nd trimester of pregnancy are at risk
- Birth 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 -> decrease likelihood of both twins developing schizophrenia

Genetic Causes:
- Parental schizophrenia increases the risk of children developing schizophrenia by a factor of 10.
- Twins fingerprints correlates with their concordance for schizophrenia
- Identical twins from two schizophrenic parents: only 45% chance that both develop schizophrenia (should be 75%) - more than one gene involved, or other factors
- Multiple genes involved

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 2-3 times more likely in women (7%) than men (3%). MDD: 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 -> high risk for suicide

Unipolar (Depression) Treatments:
- The monoamine hypothesis:
  - Depression is due to a lack of monoaminergic activity
- Serotonin Specificity:
  - MAO inhibits (increase levels of NE, DA, 5HT). 65% success
- Reserpine (monoamine antagonist) induce depression
- Tricyclic antidepressants (inhibits reuptake of NE and 5ht)
- Levels of 5-HT in blood lower in suicidal depressive patients
- Tryptophan depletion induces depression
- Selective/Specific Serotonin Reuptake Inhibitors (SSRI) (prozac, celica, paxil..) highly effective ~90%
- Serotonin and norepinephrine Reuptake Inhibitors (SNRI)

■ Bipolar treatment: Lithium
  - Treats bipolar (80%), not unipolar. Fast and effective of mania
  - Side effects include weight gain, increase in fluid intake and excretion, diabetes, fatal overdose
  - Stabilize neuromodulatory pathways. Valproate (increase GABA, effect on Mania)

■ Problems with 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 Disorder: 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: TMS (transcranial magnetic stimulation) of prefrontal cortex
    - Effective in prefrontal cortex
    - Need repeated treatment
    - Non-invasive
  ■ Deep brain stimulation:
    - Direct stimulation of (subgenual) Anterior Cingulate Cortex (ACC)
    - Invasive
    - Fast onset of antidepressive 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

- **Bipolar Disorders: Mania**
  - Due to hyperactivity in the ACC
  - ACC normally regulates emotions (inhibition)
  - Mostly involved in the manic phase
  - Most effective treatments of depressions result in decrease in activity in ACC
  - Fragmentation of sleep:
    - Other Treatments of Bipolar disorders:
      - Fact: Major depression -> less stages 3 and 4, more sleep fragmentation, REM occurs earlier and is more intense
    - 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 effect, 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

- **Other affective disorders:**
  - Seasonal affective disorders (SAD): hypothalamus
    - Unipolar depression
    - Short days, long nights (winter) -> depression
    - Summer depression is rare
    - Genetic basis (melanopsin gene)
    - Treatments: Phototherapy, light therapy and exercise