Schizophrenia

- History
  - Early Theories of Mental disorders
    - possession by spirits or divine visions
    - punishment by the gods for immoral behavior
    - witches lol
  - Treatments
    - Exposure to certain types of music
    - trephination (while alive)
    - burning at the stake
    - chains, stocks (to "quell the demons")
  - 17th century
    - first psychiatric hospitals in europe
    - new treatments
      - shock methods (cold water)
      - strapping patients to chairs until they lost consciousness (calming them)
  - Schizophrenia as a disease
    - Emile Kraepelin and "dementia raecox" (1887)
      - premature deterioration of the mind
      - not like other dementias (like Alzheimer's)
    - Eugen Bleuler (1911) renamed it Schizophrenia
      - Schizo (greek: split)
      - Phrene (greek: mind)
      - describes the observed "fragmented thinking"
- Demographics
  - Most common psychotic condition (1% of population (2.7 millin in the US))
  - can occur at any age but typically between adolescence and young adulthood
  - sex difference
    - men
      - onset at 15-24
      - paranoid type more common
      - symptoms generally more severe in men
    - women
      - onset at 25-34
      - less severe symptoms
      - more likely to have positive symptoms than negative
- Symptoms
  - Imparement in 5 basic areas
    - thought
      - delusions (strongly held beliefs that appear to have no basis in reality) (T)
      - loose associations (ramble, can't edit)
      - language and speech problems (neologisms, word salad)
      - lack of insight
    - perception
      - hallucinations (perception or sensory experience w/o external stimuli), auditory most common
      - poor performance on perceptual tests (size or time)
      - selective attention deficits (can't filter unimportant stimuli)
    - emotion
      - Flat or blunt affect
      - inappropriate emotional expression
    - movement
      - range from immobility (**catatonia**) to hyperactive
      - **stereotypy**: repeated but aimless movement or behavior (T)
    - social interaction
      - Emotional detachment
      - lack of interest in daily activites
      - little interpersonal interaction
  - Positive vs. Negative Symptoms
    - Positive (things present but normally not)
      - Hallucinations
      - Loose associations
      - Stereotypies
    - negative (things not present but normally are)
      - flat affect
      - social withdrawal
- Genes & Developmental Pathology
  - Is it genetic?
    - Twin studies
      - Risk increases as biological relatedness increases
      - if one MZ twin is schizophrenic, other has a 50% chance of developing disorder
      - if one DZ twin is schizophrenic, other has only a 17% chance of developing disorder
      - Twins are unusual (low birth weights, different developmental progress)
      - Parents treat DZ twins differently than MZ twins (Example of environmental confound)
      - Why dont both twins in an MZ pair have schizophrenia?
        - Genes aren't enough
        - Smyptomatic twin also has
          - lower birth weight
          - stress at birth (long labor)
          - more submissive, tearful, sensitive behaviors (possibly treated differently as a consequence)
          - abnormal eye tracking (see world differently, act differently, treated differently?
    - Adoption studies (control for environment)
      - if you are adopted and schizophrenic, your biological parents are much more likely to also be schizophrenic than adoptive parents
      - this is controlled *only* for the ***postnatal environment***
  - The Neurodevelopmental Hypothesis
    - genetic load *plus*
    - problem during development
      - nutrition
      - smoking, alcohol
      - infections
      - stress
    - Result? neurodevelopmental pathology
  - Developmental Pathology
    - when neurons die in adults, glia proliferate (**gliosis**)
    - in schizophrenia, fewer neurons, but no gliosis
    - so the difference in neuron number is developmental
    - neurotypical neurodevelopment:
      - cells are generated around ventricles
      - cells migrate out to their final location
      - cells differentiate into neurons, glia, stellite vs pyramidal, etc
      - cells form synapses
      - nervous system generates more neurons than it needs, so there is programmed cell death
      - synapses rearrange
- Glutamate Hypothesis
  - Dopamine effects could be due to changes in glutamate release
    - dopamine inhibits glutamate release
    - glutamate inhibits dopamine release
    - glutamate excites neurons that dopamine inhibits
  - PCP (NMDA receptor antagonist) produces some symptoms of schizophrenia
    - social withdrawal, hallucinations
    - thus, the glutamate hypothesis
      - low glutamate activation yields schizophrenia?
  - schizophrenics have reduced glutamate release, especially in prefrontal cortex and hippocampus
  - schizophrenics have reduced gene expression for glutamate receptors, especially in frontal cortex and hippocampus
- Dopamine Hypothesis
  - The Hypothesis
    - Schizophrenics have more dopamine receptors
    - Dopamine agonists produce "positive" symptoms
      - paranoia
      - delusions
      - hallucinations
    - Antipsychotic drugs block dopamine receptors
      - amphetamine (T)
        - big release, no re-uptake of dopamine and norepinephrine
      - cocaine
        - no re-uptake
      - haloperidol
        - blocks receptors
      - dopamine agonists (specifically D2 receptors) produce symptoms of schizophrenia (amphetamine-induced psychosis)
  - The Evidence
    - Against
      - some schizophrenics have decreased levels of dopamine metabolites (like homovanillic acid [HVA])
      - classical antipsychotics don't work for everyone
      - classical antipsychotics don't treat negative symptoms well
    - For
      - put stuff from hypothesis like dopamine stuff
  - The Current Hypothesis
    - three major dopamine pathways
      - nigrostriatal
        - substantia nigra to basal ganglia
        - D2 receptors on targets are inhibitory
      - mesolimbic
        - ventral tegmental area (VTA) to amygdala, basal ganglia
        - D2 receptors on targets are inhibitory
      - mesocortical
        - VTA to prefrontal cortex
        - D1 receptors in cortex are excitatory
    - Nigrostriatal and mesolimbic pathways are hyperactive
      - basal ganglia targets involved in selective attention and sensory gating
        - sensory gating
          - selective attn - attending to behaviorally relevant stimuli and filtering irrelevant
          - links stimulus w/ appropriate motor response
      - too much dopamine activation (increased D2 receptors) means too much inhibition of basal ganglia
      - result? not enough selective attention and sensory gating
        - can't filter irrelevant stimuli
        - motor disturbances (stereotypy)
    - evidence for new hypothesis of dopamine hyperactivity in basal ganglia
      - drugs that increase DA transmission produce positive symptoms
      - classical antipsychotics block D2 receptors
      - increased D2 receptors in caudate nucleus in schizophrenics
      - increased dopamine metabolite HVA (homovanillic acid) in bloodstream in some schizophrenics
      - larger basal ganglia in schizophrenics
        - more pronounced in patients with positive symptoms
        - possibly from larger cells
      - mesocortical pathway
        - prefrontal cortex involved in emotion, motivation
        - hypoactive in schizophrenia (decreased D1 receptors)
          - decreased activity in prefrontal cortex
          - negative symptoms similar to frontal damage
            - social withdrawal
            - flat affect
      - hypoactivity of DA in frontal cortex
        - reduced HVA in some patients
          - low hva levels are associated with poor performance on the wisconson card sort
        - decreased activity of frontal cortex
          - decrease correlates with negative symptoms
        - atrophy of frontal cortex
          - atrophy correlates with negative symptoms
        - frontal activity increases with DA agonists
- Neuropathology
  - Enlarged Ventricles (generally lateral ventricles)
    - less brain
  - Smaller amygdala, hippocampus, and temporal cortex
  - cellular disorganization
    - fewer, smaller neurons
    - dendritic disorientation
  - prefrontal cortex
    - atrophy
      - fewer, smaller neurons
      - fewer dendritic spines
      - abnormal neuron migration
    - decreased activity ("hypofrontality")
      - at rest
      - during tests of FR functioning
      - correlations with negative symptoms
  - cerebellum - smaller vermis (middle part)
  - thalamus - smaller, especially the dorsomedial nucleus (which projects to the frontal cortex)
  - basal ganglia
    - larger
    - more D2 receptors (in the caudate, nucleus accumbens)