Biological Basis of Mental Disorders

What can biological research tell us about the causes, influences and effects of different disorders?

Major Depressive Disorder (MDD)
(Prevalence almost 7% in any individual year; almost 17% lifetime prevalence)

- At least 5 of the following almost every day for at least 2 weeks:
- Persistent depressed or irritable mood
- Decreased interest or pleasure
- Significant change in appetite or weight without dieting
- Insomnia or hypersomnia
- May move and talk slowly, or may be restless
- Fatigue, loss of energy, or motivation; apathetic
- Feel worthless; inappropriate guilt
- Can’t make decisions, concentrate
- Suicidal thoughts or actions

http://www.nimh.nih.gov/statistics/1MDD_ADULT.shtml

Genetic Research: Depression shows a moderate degree of heritability

- Depression runs in families; ~10x more risk in those with affected relatives, especially female relatives who had depression early (<30 yrs)
- 25% with major depression and 50% with bipolar disorder have affected parents
- Adopted children resemble biological parents
- ~50% concordance for depression in identical twins; 15-20% in fraternal twins; 80% vs. 40% for bipolar
- Several genes seem to be linked with depression; 2 genes linked to bipolar so far.
- But remember gene-environment interactions……

But Remember Gene-Environment Interaction

- Gene for the SERT reuptake transporter comes in 2 forms (short and long). If you have:
  - 2 short genes – very likely to develop depression if you experience life stresses
  - 2 long genes – very resistant to stress
  - Heterozygous – intermediate in your likelihood to develop depression in response to life stresses
  - (Genes interact with environment)

Possible Viral Cause in Some

- Farm animal Bornavirus is sometimes found in humans
- In a sample of 370 only 12 people tested positive for the virus but all had major depression or bipolar disorder.
- Now 1000’s have been tested & Bornavirus is in:
  - 2% of normal mood individuals
  - 30% of severely depressed
  - 13-14% of those with chronic brain diseases

Brain Changes in Depression

- Decreased frontal activity, especially on left (happy) side
- Drug or therapy treatment increase activity
- ECT limited to right (sad) hemisphere is often effective

(individuals with left hem damage often depressed, those with right damage may become manic)
Hormones & Depression

- Alterations in sex hormones are associated with depression:
  - Postpartum depression
  - Pre-menstrual dysphoria
  - Drug-induced drops in estrogen → depression
  - Testosterone decreases → depression

Circadian Changes in Depression

- Temp cycle advanced and sleep abnormal: early REM & more REM despite early morning awakening
- Circadian rhythms of protein production at the cellular level also abnormal
- Either REM deprivation or total sleep deprivation can relieve depression temporarily
- (Antidepressants decrease REM sleep!)
- Another variety of depression — SAD — tied to changes in day/night cycle & abnormal melatonin secretion. BUT SAD causes a phase-delay in rhythms
  https://www.youtube.com/watch?v=JcMUIw6tXE

Biorhythms

- Peaks ~ 6 hr before bedtime
- Lowest ~ 2 hrs into sleep

Monoamine Theory of Mood

- Normal mood depends on adequate monoamine activity at synapses.
- ↓ levels → depression
- ↑ → euphoria/mania
- Different people may have different monoamine imbalances

Support for Theory

- Drugs associated with ↑ monoamines elevate mood (cocaine or amphetamine use; antidepressant use)
- Drugs or conditions associated with ↓ monoamines trigger depression (e.g., reserpine administration; cocaine or amphetamine withdrawal)
- CSF of suicide victims shows lower levels of 5HT metabolite
- Effective antidepressants increase monoamine activity at synapses in some way.

Categories of Antidepressants

- Tricyclic antidepressants
- Monoamine oxidase inhibitors (MAOIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- “Atypical” antidepressants don’t fit above categories. Example: Wellbutrin (bupropion)
Tricyclic Antidepressants

- 3 best known:
  - amitriptyline (Elavil)
  - desipramine (Norpramin)
  - imipramine (Tofranil)
- Drugs which prevent the reuptake of SHT, NE & DA (transmitters remain available to stimulate receptors for a longer period of time)
- Effective but have annoying anticholinergic side effects
- Also potentially dangerous cardiovascular effects so were sometimes used in suicide attempts.

Monoamine Oxidase Inhibitors like Nardil (phenelzine)

- Drugs which inhibit the action of MAO, an enzyme that normally breaks down SHT, DA and NE
- Transmitters are more available because not inactivated by MAO

MAOI Problems

- MAO normally metabolizes tyramine in foods.
- When MAO is inhibited, tyramine causes sympathetic activation
- Must carefully limit diet while taking MAOIs
- Neglecting restrictions can result in life-threatening hypertensive crisis (“the cheese effect”)
- Tyramine, for some, may aggravate OCD, TS, headaches, flushing and anxiety symps.
- Drugs with stimulating NE-like actions must also be avoided

Tyramine Rich Foods

Meats that are pickled, aged, smoked, processed, fermented, or marinated; chocolate; alcoholic beverages; and fermented foods, such as most cheeses, sour cream, yogurt, soy sauce, tofu, tempeh, miso soup, sauerkraut; green bean pods, Chinese (snow) pea pods, avocados, bananas, pineapple, eggplants, figs, red plums, raspberries, peanuts, Brazil nuts, coconut, yeast

Selective SHT Reuptake Inhibitors (“SSRIs”)

- fluoxetine (Prozac) (also Zoloft, Paxil, Celexa) are selective SHT reuptake inhibitors – keeps SHT active in synapse longer
- Same effectiveness but fewer side effects and risks; patients more willing to take Prozac
  - (But we now know sexual side effects and some withdrawal effects when you stop are possible)

Atypical Antidepressants

- Example: Wellbutrin (bupropion) mostly blocks DA reuptake
- Avoids sexual side effects, but some cannot take this
Re-Evaluating The Monoamine Theory

- Antidepressants increase monoamine availability immediately but don’t become clinically effective for weeks.
- Maybe antidepressants have other critical effects on the nervous system.
- Depression is associated with size of certain brain areas (like hippocampus), production of new neurons, nerve growth factors.
- Hypothesis: improved mood depends on a slower anatomical changes in CNS:
  - Increased neuron production & anatomical “remodeling” due to increased neurotrophins like brain-derived neurotrophic factor (BDNF) follows the rise in neurotransmitter.
  - Preventing neuron production blocks the effectiveness of antidepressants.

Remember Transcranial Magnetic Stimulation?

- Magnetic pulses alter the electrical activity of brain area beneath wand – either increasing or decreasing the activity depending on the settings used.
- Now being used to treat depression (several weeks of daily treatments).

Mania

- Dysregulation of monoamines?
- Excess glutamate?
- Brain inflammation?

Treatment of bipolar disorder

- Lithium
- Anticonvulsants like valproate (Depakote, Depakene) or carbamazepine (Tegretol)
- Are these drugs effective for the same reason?
- 2 actions they share in common:
  - Decrease AMPA glutamate receptors in hippocampus
  - Decrease production of arachidonic acid which is associated with inflammation in CNS.
  - Omega fatty acids (in fish) also do the latter & eating 1 lb fish/week decreases bipolar episodes.
  - But these drugs also have other effects under investigation (affect oxidative stress, gene expression).
Biological Basis of Schizophrenia

Schizophrenia Symptoms

• Hallucinations
• Delusions
• Disorganized speech
• Disorganized behavior
• These are called “positive (+) symptoms”
  • (abnormalities that have been ‘added’ to the person’s behavior and mental processes)

• Normal emotion lost
• Decreased motivation; apathy
• Decreased social interaction
• Decreased speech
• These are called “negative (-) symptoms” – normal behaviors that have decreased

Characteristics

• Incidence a little over 1% of the US population
• Usual symptom onset in early adulthood; on average early 20’s for men, later 20’s for women
• Somewhat more common & more severe in men
• Occurs worldwide but more common in western cultures & in urban environments
• All “schizophrenics” do not show the same behaviors - may be several different types of schizophrenia
• E.g. childhood schizophrenia associated with more severe and different pattern of brain damage

Genetics of Schizophrenia

• Schizo. runs in families - you have increased risk if you have blood relatives with schizo
• Overall concordance in identical twins is ~45-50%, in fraternal twins its ~15-17%
• Identical twins with same handedness have a 92% concordance rate, that of those with opposite handedness is 25%
• Kids born to non-schizo member of identical twin pair have same risk as kids of twin with schizophrenia (17.4% vs 16.8% will develop schizo)(not true of fraternal). This suggests the unaffected twins still have “bad genes”.
• BUT: Twins sharing same chorion 60% concordance (vs 11%) & fraternal twins more similar than other siblings. (Both of these support prenatal environmental factors are important)

Genetics of Schizophrenia

• Adoptees with schizo are more likely to have schizo biological parents/relatives than schizo adoptive parents/relatives.
• A child of a schizo parent raised by a normal couple is more likely to develop schizophrenia than a child of normal parents raised by a schizo adopted parent.
• Have identified >12 genes more common in schizos, but these can vary with population sample.
• Schizos show 3X as many mutations or “SNPs” in genomes.
• Also, the older the father, the higher the risk of schizophrenia in his kids (sperm more likely to show mutations in genetic codes)
Brain Changes

- enlarged ventricles
- Decreased brain volume
- smaller thalamus, prefrontal & temporal cortex, & hippocampus, especially on left side
- language areas abnormal
- less lateralization or reversed lateralization
- loss of cells, smaller or disorganized cells in these regions
- damage not very progressive in most (Childhood Onset Schizo. is exception)
- Symptoms not apparent until the age where those brain areas mature & normally become fully functional

Functional Differences

- less brain activity in these regions
- problems with frontal lobe memory tasks
- signs of less sharing across corpus callosum, less lateralization
- some of these changes also present in nonschizophrenic family members

PET Scans

![PET Scan Image]

Neurodevelopmental Hypothesis of Schizophrenia

- Brain abnormalities associated with schizo begin **prenatally or neonatally**
- May relate to adverse perinatal/neonatal conditions as well as genetics
- Birth records of schizos show more "nonoptimal" signs during preg/labor (nutritional deficiencies, Rh incompatibility, prematurity, delivery complications, low birth weight, illness during pregnancy, etc.) — all things that affect early development of CNS.
- Early childhood head injury also linked with schizo.
- Second or later sons with Rh incompatibility with their mom are about twice as likely to develop schizophrenia (mom’s immune system may affect neurodevelopment)

Season-of-Birth Effect (may help explain schizo in those w/o family history)

- 5-8% increase in risk of schizo in those born in winter, especially in winter-weather climates.
- Higher rate of schizophrenia in those born in winters of years with bad fall viral epidemics
- If an epidemic occurs in other seasons, there’s more schizophrenia among those born 3 months later
- Probably not the virus but the fever it causes that affects CNS development (variety of viruses associated with increased risk)
- Schizo. more likely in those whose mom’s had rubella, herpes, or had a cat during pregnancy or right after
Dopamine Hypothesis

Schizophrenia results from or is associated with over-activity or over-response at DA synapses.

Support for DA theory:
DA Drug-Induced Psychosis
- amphetamine or cocaine use increases DA activity & can trigger a drug-induced paranoid psychoses
- excess l-dopa can cause symptoms of schizophrenia in Parkinson's patients
- amphetamine or l-dopa given to schizophrenics worsens their symptoms
- About twice as many DA receptors in schizos – the more receptors/the more symptoms
- DA BLOCKERS treat schizophrenia

“Typical” Antipsychotics
- phenothiazines like chlorpromazine (Thorazine)
- butyrophenones like haloperidol (Haldol)
- Block DA receptors throughout the brain

Main Side Effects
- Extrapyramidal Motor Disorders
  - Parkinson's disease-like symptoms
  - A variety of other motor abnormalities
- Tardive dyskinesia
  - Involuntary movements, particularly of the face and mouth
Newer Atypical Antipsychotics

- Prototype: Clozaril (clozapine)
- Block selected DA and 5HT2 receptors
- Fewer extrapyramidal side effects
- Helped previously unresponsive patients
- Improve “negative” symptoms and disorganization; decrease suicides
- BUT can cause agranulocytosis in 1-2% so requires blood monitoring

Newer Atypical Antipsychotics

- risperidone (Risperdal)
- olanzapine (Zyprexa)
- These show less agranulocytosis, but increase risk of serious weight gain and diabetes.

Problems With DA Theory

- Antipsychotics block DA immediately but therapeutic effect builds over weeks
- Blocking DA is only partially effective
- Differences noted in other transmitters

Glutamate Hypothesis

- Underlying problem in schizophrenia is underactivity of glutamate (↓release, ↓receptors) especially in frontal lobe & limbic areas.
- This does not necessarily conflict with the DA hypothesis because these neurotransmitter systems interact & have opposite effects
- PCP (phencyclidine) acts by blocking glutamate receptors & it produces both positive and negative symptoms of schizophrenia. It induces long-lasting relapses in those with schizophrenia.
- Now working on meds to affect glutamate activity
- Atypical antipsy. Meds may stimulate glu release