Biological Basis of Psychological Disorders

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

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

Characteristics

- Incidence about 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

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 ~20-25%
- Idential twins with same handedness have a 92% concordance rate, that of those with opposite handedness is 25%
- Kids born to nonschizo 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 fraternals). This suggests the unaffected twins still may have “bad gene(s)”.
- BUT: Twins sharing same chorion 60% concordance (vs 11%) & fraternal twins more similar than other siblings. (Both of these support prenatal environmental factors are also 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)
Neurodevelopmental Theory of Schizophrenia

- Proposes schizophrenia & the brain abnormalities associated with it begin prenatally or neonatally
- May relate to adverse prenatal/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

Brain Changes

- Abnormalities in at least 50 different areas have been found
- 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
- Symptoms not apparent until the age where those brain areas mature & normally become fully functional

SCHIZOPHRENIA IN IDENTICAL TWINS

A discordant pair

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 increases DA & 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

Dopamine Theory

Schizophrenia results from or is associated with over-activity or over-response at DA synapses.
“Typical” Antipsychotics/Neuroleptics

- Phenothiazines like chlorpromazine (Thorazine)
- Butyrophenones like haloperidol (Haldol)
- Block DA receptors throughout the brain

Main Side Effects

- Extrapiramidal 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/Neuroleptics

- 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 mimics the negative symptoms of schizophrenia. It induces long-lasting relapses in those with schizophrenia.
- Now working on meds to affect glutamate activity

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/weight w/o dieting
  - Insomnia or hypersomnia
  - More & 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

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
- Risk in adopted kids resembles biological parents
- ~60% 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 none strongly linked

Support for Theory

- Drugs associated with ↑ monoamines elevate mood (cocaine or amphetamine)
- 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.
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 in overdose so were sometimes used in suicide attempts.

Categories of Antidepressants

- Tricyclic antidepressants
- Monoamine oxidase inhibitors (MAOIs)
- Selective serotonin reuptake inhibitors (SSRIs)

Monoamine Oxidase Inhibitors like Nardil (iproniazid; 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 of HR and BP
- Must carefully limit diet while taking MAOIs
- Neglecting restrictions can result in life-threatening hypertensive crisis ("the cheese effect")
- Drugs with stimulating NE-like actions must also be avoided

Tyramine Rich Foods

Meats that are pickled, aged, smoked, processed, fermented, or marinaded; 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, coconuts, 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)
Re-Evaluating The Monoamine Theory
• Antidepressants increase monoamine availability immediately but don’t become clinically effective for weeks
• Why does it take weeks?

Neuroplasticity/Neurogenesis Theory
• 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.

New Drug Research
• One surprising new finding:
  • Low dose intravenous ketamine can produce immediate relief of depressive or serious anxiety symptoms in some individuals. Now in Phase 3 trials – may be available in 2018.
  • Ketamine immediately increases neurogenesis.

Treatment of bipolar disorder
• Lithium
• Anticonvulsants like valproate (Depakote, Depakene) or carbamazepine (Tegretol)

Other Biological Influences on Mood
• Decreased frontal activity, especially on left (happy) side
• Drug or therapy treatment increases activity
• ECT limited to right (sad) hemisphere is often effective
  (individuals with left hem damage often depressed, those with right damage may become manic)
Brain Pathology and Bipolar Affective Disorder

Figure 18.6: Structural MRIs of healthy volunteers with a genetic predisposition to developing depression reveals cell loss in the anterior cingulate and the amygdala.

Cha Brain Stimulation
2008 study found that chronic electrical stimulation near the anterior cingulate gyrus helped relieve depression in treatment-resistant patients.

Brain Pathology and Bipolar Affective Disorder

Hormones & Depression
• Alterations in sex hormones are associated with depression:
  - Post-partum depression
  - Pre-menstrual dysphoria
  - Drug-induced drops in estrogen $\rightarrow$ depression
  - Testosterone decreases $\rightarrow$ depression

Circadian Changes in Depression
• Temp cycle advanced and sleep abnormal: early REM & more REM despite early morning awakening
• 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

Anxiety Disorders
• Twin and adoption studies support an inherited predisposition to suffer anxiety, but not all family members will experience the same variety of anxiety disorder.
• May be some overlap between the genes underlying anxiety and those underlying depression; families experiencing anxiety are also likely to have depressed family members.

Experimental: Deep brain stimulation
Case: http://www.youtube.com/watch?v=x16J4K0AMy8
• Obviously brain surgery is expensive and has risks, so would never be as widely used as other treatments.

Experimental: Brain Pathology and Bipolar Affective Disorder

Observations:
- Structural MRIs of healthy volunteers with a genetic predisposition to developing depression reveal cell loss in the anterior cingulate and the amygdala.

Brain Pathology and Bipolar Affective Disorder

Hormones & Depression
• Alterations in sex hormones are associated with depression:
  - Post-partum depression
  - Pre-menstrual dysphoria
  - Drug-induced drops in estrogen $\rightarrow$ depression
  - Testosterone decreases $\rightarrow$ depression

Circadian Changes in Depression
• Temp cycle advanced and sleep abnormal: early REM & more REM despite early morning awakening
• 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

Anxiety Disorders
• Twin and adoption studies support an inherited predisposition to suffer anxiety, but not all family members will experience the same variety of anxiety disorder.
• May be some overlap between the genes underlying anxiety and those underlying depression; families experiencing anxiety are also likely to have depressed family members.
Brain Differences

- Those with anxiety show evidence of a hyperresponsive amygdala and hyperactive areas of limbic cortex (cingulate, insula).
- Those with PTSD show some signs of stress-related neuron loss in hippocampus & cingulate. Individuals with signs of early stresses are later more susceptible to PTSD.

At the unconscious level, the amygdala triggers

- Fight or flight responses
- Increased vigilance
- Enhanced reflexes
- Stimulates hypothalamic-pituitary-adrenal stress hormone system
- We are evolutionarily primed to response to threatening fear stimuli of our ancient past

fMRI to seeing a fearful face

Amygdala responds even if presentation is too brief to allow conscious recognition

Amygdala Also Responds to Fearful Body Language
Sadly, the built in responses of the amygdala may even contribute to racial biases.

Same-race vs different race stimuli presented below level of conscious awareness. Different race provokes stronger amygdala response.

Urbach-Wiethe Disease: Damage to Amygdala Disrupts Normal Fear/Anxiety Responses

- Rare, hereditary metabolic disorder causing calcification of amygdala, disrupting its normal functions.
- Do not seem to experience or recognize negative emotions (fear, anger, upset, dislike) in faces, body language or vocalizations. Cannot represent (e.g. draw) negative emotions or recall emotional content of a memory. Do not develop classically conditioned fear responses.

The case of SM

Amygdala Reactivity Partly Determined by Genes

- Twin studies suggest genetics play a role in anxiety disorders, shyness
- Had trouble localizing anxiety-related genes until they noticed many (68%) with panic disorder and other anxiety disorders also showed “joint laxity”
- This allowed researchers to track the genes to a region of chromosome 15.
- Those with anxiety more likely to have a genetic “repeat” (multiples of a segment of code where normals only have one)

Pharmacological Treatment of Anxiety Disorders

- Benzodiazepines (Librium, Valium, Xanax) and also alcohol
  - GABA, agonists – bind to receptor and facilitate effects of GABA, enhancing its calming effects
- Serotonin agonists (antidepressants, buspirone) Reduced anxiety without sedation or other depressant risks

GABA Re

Blocks of these sites increase anxiety and decrease the relaxing effects.
RO15-4513 - blocks most effects of alcohol
Obsessive Compulsive Disorder (OCD)

- 63-87% concordance in identical twins, but adverse environmental events also associated with OCD (birth complications, head injury, brain infection, strep infection)
- Abnormalities (e.g. excess activity) in frontal lobe-basal ganglia circuits.
- Decreased 5HT activity in OCD. Treated with 5HT agonists like SSRIs.
- Different mutations of a particular gene (sapap3) are associated with OCD versus compulsive grooming disorders (nail-biting, skin-picking, hair-pulling) and also grooming disorders in mice and dogs.

Tourette Syndrome

- Multiple motor tics - simple tics of eyes, face or limbs and/or more organized complex tics (touching, grimacing, pinching, peaking), adjusting, hitting, jumping, kissing, throwing, gestures) plus:
- Phonic or vocal tics - both simple (throat-clearing, coughing, hiccuping, grunting, yelping) and/or complex tics (actual words, coprolalia, echolalia, assuming different voices, talking to oneself in different voices)
- Like OCD seems to affect frontal lobe-BG connections important for our ability to inhibit actions. Caudate tends to be smaller.

- Some degree of suppressibility, but individual experiences increased tension until tic is released
- Pattern of tics changes & waxes & wanes with changes in stress, anxiety, fatigue.
- Treated with DA blockers (Haldol, Orap).
- Majority experience decreased tics as adults.
- Some kids’ TS symptoms seem to have developed following strep throat infection

Link with Other Disorders

- ~55% concordance in identical twins (vs. 8% in frats)
- ~50-60% also suffer OCD (others estimate that up to 90% experience some involuntary touching compulsions, ritualistic behaviors, intrusive thoughts)
- ~50-90% show evidence of ADHD as well; first signs of Tourette’s are usually impulsive, hyperactive behaviors (before tics appear)
- Initially suspected a single gene with sex-linked, varied forms of expression of disinhibition, but now appears more genetically complicated