Course Administration

**Unit 4 Exam:**
Wednesday 12/12; this room; this time

Email: Dr. Davis immediately (if not sooner) if there is a need to make other arrangements

**Review session:**
Monday 12/10: 7-9PM: Room TBA

**Optional Cumulative FINAL EXAM**
Tuesday, December 18TH (this room)
12:30 – 1:45 PM
Psychiatric Disorders

Reading: BCP Chapter 22
Disorders of Psychological Function

Human behavior is the product of brain activity, and the brain is the product of two mutually interacting factors: heredity and environment.

Physical health and illness are two points along a continuum of bodily function, and the same can be said for mental health and mental illness.

Psychiatric disorders are altered processes of thought, mood or behavior that are sufficiently severe as to cause distress or impaired function and require treatment.

Diagnosis is guided by the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association.

Five psychiatric disorders for which neuroscience has provided insight into causes and treatments:
- schizophrenia
- attention deficit hyperactivity disorder
- affective disorders
- anxiety disorders
- Tourette’s syndrome
Schizophrenia

Schizophrenia means “the splitting of psychic functions”, i.e., the breakdown of integration of emotion, thought, and action.

Disease most commonly associated with the concept of madness: affects 1% of the population.

The following are some symptoms of schizophrenia; the recurrence of any two of which for one month is sufficient for diagnosis

- Positive symptoms: delusions, hallucinations, inappropriate affect, incoherent speech/thought, odd behavior
- Negative symptoms: flat affect; alogia, avolition, anhedonia, catatonia

Causal Factors
- genetics (rate in twins: ~50%)
- experience (birth complications, infections, autoimmune reactions, injury, toxins, stress)

Believed to be a neurodevelopmental disorder; diagnosis ~20 years old
Schizophrenia: Genes and Brain Damage

The study of schizophrenia-related genes is in its early stages.

Various related genes have been shown to disrupt neural proliferation, migration and myelination.

Consistent with the developmental effects, patients with schizophrenia have enlarged ventricles (top figure: arrows) and fissures, and have reduced volume (both gray and white matter) in many different brain regions (bottom figure: blue areas = normal volume; red areas = lower volume). Brain damage continues to worsen throughout life.
Much of our understanding of the causes of schizophrenia comes from the drugs that mimic it or are able to treat it.

Cocaine and amphetamines are dopamine agonists (reuptake inhibitors/competitors) and produce psychosis.

Antipsychotic drugs including chlorpromazine and reserpine are dopamine antagonists. The former blocks dopamine receptors (see fig); the latter makes dopamine vesicles “leaky” in the pre-synaptic neuron.

- These data suggest that excess dopamine is a factor in the disorder (in the mesotelencephalic pathway arising from the ventral tegmental area)
In general, the higher affinity a drug has for dopamine receptors, the more effective it is in treating schizophrenia.

This is true for chlorpromazine and other drugs in its same chemical class (the phenothiazines) but it is not true for haloperidol and other potent drugs in its class (the butyrophenones).

The resolution: it was found that dopamine receptors come in 5 subtypes. The phenothiazines bind to D<sub>1</sub> and D<sub>2</sub> receptors, whereas the butyrophenones bind to D<sub>2</sub>.

- The higher affinity a drug has to block D<sub>2</sub> dopamine receptors, the more effective it is in treating the disorder. Side effect: Parkinson-like symptoms.
Non-Dopamine Theories of Schizophrenia

The evidence implicating D₂ dopamine receptors in schizophrenia is strong; however, this theory cannot explain why:

- neuroleptics act quickly at the synapse, but do not alleviate symptoms for weeks;
- neuroleptics are only effective for some people; and
- neuroleptics are mainly effective for reducing positive symptoms.

New research has shown that:

- classical hallucinogens (e.g., LSD) mimic the positive symptoms of schizophrenia by acting as agonists of serotonin receptors
- anesthetics like phencyclidine (PCP) and ketamine mimic the negative symptoms by acting as antagonists of glutamate receptors.
Attention Deficit Hyperactivity Disorder

ADHD is a neurodevelopmental disorder in which there are significant problems with executive functions (e.g., attentional control and inhibitory control) that cause attention deficits, hyperactivity or impulsiveness not appropriate for a person’s age.

To be diagnosed, a person (child) must have symptoms for 6 or more months.
• Inattentive ADHD (previously ADD)
• Hyperactive-impulsive ADHD
• Combined ADHD (most common)

Incidence rate: ~10% (boys>girls); persists into adulthood for 50%

Causal factors:
• genetics (rate for twins: 75%)
• experience (toxins, trauma, disease)
ADHD: Dopamine and Norepinephrine

It is known that prefrontal cortex is not developed fully until adulthood. Studies suggest that this brain area (and that of the posterior parietal cortex) develops more slowly in individuals with ADHD. Full development may explain those that grow out of the disorder.

Perhaps counterintuitively, stimulants are the most common treatment for ADHD. Stimulants include dextro-amphetamine (Adderall) and methyl-phenidate (Ritalin). Both are potent agonists (reuptake inhibitors) of dopamine and norepinephrine.
Affective Disorders

Affective disorders are characterized by disturbances of mood or emotion (specifically, sadness and happiness). Mood disorders include:

- depression: a state of low mood that persists for more than 2 weeks.
- mania: overconfidence, impulsivity, distractibility, and high energy

Types of Depression

- unipolar or bipolar (with mania)
- reactive vs. endogenous (no cause)

Affective disorders are very common (10% chance during a lifetime)

Causal factors:

- genetics (rate for twins: 60%)
- experience (stress, trauma, zeitgebers-SAD, birth-postpartum depression)
Numerous MRI studies of the brains of bipolar patients have been published.

Reductions in overall brain size and in the size of several brain structures have been reported.

Although the pattern of damage differs from patient to patient, four structures have been found to be abnormal in many studies:

- amygdala;
- ventral anterior cingulate
- ventromedial prefrontal cortex
- hippocampus
Four classes of drugs have been used in the treatment of affective disorders. Three are antidepressants; the fourth is mood stabilizers.

Antidepressants are agonists of the monoamines serotonin/norepinephrine:
- monoamine oxidase inhibitors (MAOIs) which prevent breakdown and
- tricyclic antidepressants and
- selective reuptake inhibitors (e.g., Prozac) which prevent reuptake

Antidepressant drugs may trigger bouts of mania. Thus, the search for mood stabilizers (e.g., lithium; mechanism of effect is unknown).

- These data suggest that depression and mania are on a continuum from low to high levels of monoamines.
The evidence implicating monoamine receptors in affective disorders is strong; however, this theory cannot explain why:

- antidepressants act quickly at the synapse, yet take weeks for effect; and
- antidepressants are only effective for some people.

The neuroplasticity theory suggests that depression results from a reduction in the synthesis of neurotrophins in cortical areas (e.g., brain-derived neurotrophic factor, BDNF), and a decrease in adult neurogenesis in the hippocampus.

In support of this theory, antidepressant drugs, and electrical or magnetic stimulation promote such neuroplastic mechanisms.
Anxiety disorders are characterized by an inappropriate expression of fear that persists in the absence of any direct threat. These disorders are usually accompanied by physiological symptoms including tachycardia, hypertension, sleep disturbances, and nausea.

Anxiety disorders are the most prevalent of all psychiatric disorders (17% chance during a lifetime)

Causal factors:
- genetics (rate for twins: >40%)
- experience (in particular, stress)

The five major anxiety disorders are:
- Generalized anxiety disorders: stress and anxiety in the absence of a stimulus
- Phobic anxiety disorders: stress and anxiety triggered by a particular stimulus
- Panic disorders: sudden attacks of extreme fear and stress
- Obsessive-compulsive disorders (OCDs): frequently recurring, anxiety-producing thoughts and impulsive acts
- Posttraumatic stress disorder: pattern of distress following extreme stress
Fear is usually evoked by a threatening stimulus. The amygdala assesses its emotional significance and activates the appropriate response circuits.

One such circuit is the hypothalamic-anterior pituitary-adrenal cortex (HPA) axis to release cortisol that enables the body to maintain prolonged alertness, fight infections and heal wounds.

The HPA axis is excited by the amygdala and inhibited by the hippocampus (activated by cortisol). Both the amygdala and hippocampus receive inputs from the ventromedial prefrontal cortex.
Treatments for Anxiety Disorders

Two categories of drugs are commonly prescribed for the treatment of anxiety disorders.

Benzodiazepines (Librium, Valium) are GABA (inhibitory transmitter) agonists. These drugs reduce the activity of neurons in the ventro-medial prefrontal cortex – humans with anxiety disorders (right) show fewer benzodiazepine binding sites and elevated activity with respect to healthy brains.

Serotonin agonists (including buspirone and antidepressants) function by increasing the number of cortisol receptors in the hippocampus, thereby enhancing feedback inhibition of the HPA axis. (Anxiety and depression are often comorbid – serotonin agonists can relieve both.)
Tourette Syndrome

Tourette syndrome is a disorder of tics (involuntary movements, often including the face) or vocalizations.

It typically begins early in childhood (develops in <1% of the population), peaks and then gradually subsides. There is a major genetic component (concordance rate in twins = 55%).

Patients tend to have smaller caudate nuclei; and there is evidence for the thinning of the sensorimotor cortex (face, mouth, larynx).

It is usually treated with neuroleptics. The effectiveness of $D_2$ blockers suggests abnormality in the basal ganglia-thalamus-cortex feedback circuit.
Despite progress in treating psychiatric disorders, knowledge as to how the current treatments work is incomplete.

In addition, most treatments were discovered virtually by chance, and target whole neurotransmitter systems rather than specific circuits. As a result, the treatments tend to show:

- delayed effects (suggesting adaptive changes)
- side effects (multiple systems targeted)

An exciting new way to understand brain malfunction has been unleashed by knowledge of the human genome. The approach (illustrated to the right) of using genetic information to develop a treatment is referred to as molecular medicine.

Enormous promise, unique challenges

- numerous small mutations in many different genes
- one mutation in one of many different genes