Mental Illness

Introduction

Neurology encompasses the diagnosis and treatment of nervous system disorders. Psychiatry encompasses the diagnosis and treatment of the "mind." (Brain functions disturbed by mental illness were once thought to be beyond the reach of neuroscience.)

Mental Illness and the Brain

- Behavior is the product of brain activity, and the brain is the product of heredity and the environment; both of which physically change the brain.
- Ignorance about brain function has led to a common distinction between "physical" and "mental" health.

Psychosocial Approaches to Mental Health

Psychoanalysis - Freud (1856-1939)

- Much of mental life is unconscious
- Past experience shapes how a person feels and responds throughout life
- Mental illness occurs when unconscious and conscious elements come into conflict

Behaviorism – Skinner (1904-1990)

- Many behaviors are learned responses to the environment
- The notion of conflicts with the unconscious is rejected
- Mental illness represents maladaptive behaviors that are learned

Biological Approaches to Mental Illness

"Psychosocial" Approaches have a Neurobiological Basis

- The brain is modified through learning and experience
- Modification of the brain will alter behavioral responses

Common "Mental" Disorder caused by Syphilitic Spirochetes

- "General Paresis of the Insane" was originally viewed as caused by weakness of character or constitution
    - Characterized by excitement, euphoria, grandiose delusions; turning to cognitive deterioration, paralysis and death
- Cause traced to infection of the brain by Treponema pallidum
    - Treatable by arsphenamine (the first modern chemotherapeutic agent, 1909) and later by penicillin

Anxiety Disorder

An anxiety disorder is characterized by inappropriate expression of fear.

Description of Anxiety Disorders

- 15% of Americans suffer from an anxiety disorder each year

Panic Disorder

- Sudden feelings of intense terror that occur without warning:
  - Palpitations sweating, trembling, shortness of breath, chest pain, nausea, dizziness, tingling sensations, chills, blushing
  - Usually last fort less than 30 minutes
- About 2% of population suffer from panic disorder; of these
  - About 50% suffer from major depression
  - About 25% will become alcoholic or develop substance abuse

Agoraphobia

- Severe anxiety about being in a situation where escape might be difficult or embarrassing:
  - Leads to avoidance of situation
- About 5% of population suffer from agoraphobia

Obsessive-Compulsive Disorder

- Obsessions: recurrent, intrusive thoughts, images, ideas, or impulses
- Compulsions: repetitive behavior or mental acts that are performed to reduce the anxiety associated with the obsessions
- About 2% of population suffer from obsessive-compulsive disorder

Biological Basis of Anxiety Disorder

- There is a genetic predisposition for many anxiety disorders
- Other anxiety disorders are rooted more in the occurrence of stressful life events
- The hallmark of anxiety disorders is the occurrence of an inappropriate stress response, either when a stressor is not present or when it is not immediately threatening

The Stress Response

A stress response includes:

- Avoidance behavior
- Increased vigilance and arousal
- Activation of the sympathetic nervous system
- Release of cortisol from the adrenal glands
  - Hypothalamus → CRH → Anterior Pituitary → ACTH → Adrenal Cortex → Cortisol

Regulation of the HPA axis by the Amygdala and Hippocampus

- Sensory information → Basolateral Amygdala → Central Nucleus of Amygdala → Bed Nucleus of the Stria Terminalis → Hypothalamus
- Cortisol → Glucocorticoid receptors of Hippocampus → Inhibits CRH neurons of the Hypothalamus
    - Prolonged exposure to cortisol (such as during chronic stress) can cause the hippocampal neurons to die

Treatments of Anxiety Disorder

Psychotherapy

- There is a strong learning component to fear
    - At the neurobiological level, the aim psychotherapy is to alter connections in the brain such that the real or imagined stimuli no longer evoke the stress response

Anxiolytic Medications

- Benzodiazepines
    - Bind to a receptor site of $GABA_A$ receptors (GABA gated Cl^- channels) and make them more responsive to GABA
    - Increases the inhibitory actions of GABA
    - The most well-known benzodiazepine is diazepam (Valium)
- Alcohol also binds to another receptive site of $GABA_A$ receptors
- Serotonin Selective Reuptake Inhibitors (SSRIs)
    - Bind to serotonin transporters and slow the removal of serotonin from synaptic clefts and its reuptake back into synaptic bulbs
        - Serotonin acts primarily on G-protein coupled receptors
    - Prolong the actions of serotonin
    - The most well-known SSRI is fluoxetine (Prozac)
    - The anxiolytic action of SSRIs is slow to develop; taking weeks
        - Effect seems to be due to neural adaptation to chronically elevated brain serotonin
        - The number of glucocorticoid receptors in the hippocampus increases
- Drugs that bind to CRH receptors and drugs that bind to select Glutamate receptors are an emerging target for anxiolytics.

Affective Disorders

Affective disorders are also known as mood disorders

Description of Affective Disorders

- Characterized by a feeling that one's emotional state is no longer under one's control
- Can occur suddenly
- About 20% of Americans suffer from an affective disorder during their lifetime

Major Depression

- Lowered mood and decreased interest or pleasure in all activities and present every day for a period of at least two weeks and often include:
    - Loss of appetite, or increased appetite
    - Insomnia or hypersomnia
    - Fatigue
    - Feelings of worthlessness and guilt
    - A diminished ability to concentrate
    - Recurrent thoughts of death
- About 5% of population each year

Bipolar Disorder

- Repeated episodes of mania, or mioxed episodes of mania and depression and often include:
    - Inflated self-esteem and grandiosity
    - A decreased need for sleep
    - Increased talkativeness
    - Flight of ideas
    - Distractibility
    - Increased goal-directed activity
    - Impaired judgment

Biological Basis of Affective Disorders

- There is a genetic predisposition for many mood disorders

Monoamine Hypothesis

- Administration of Reserpine often causes psychotic depression
    - Reserpine depletes central catecholamines and serotonin by interfering with loading into synaptic vesicles
- Administration of MAO inhibitors often causes a marked elevation of mood
    - MAO inhibitors reduce destruction of catecholamines and serotonin
- Administration of Imipramine often reduces depression
    - Imipramine inhibits the reuptake of serotonin and norepinephrine
- These antidepressant actions take several weeks to develop

Diathesis-Stress Hypothesis

- Depressed patients often express hyperactivity of the HPA axis
- Depressed patients exhibit disruption of cortisol feedback inhibition of the HPA axis
- Behavioral signs of depression are seen in animals injected with CRH

Treatments for Affective Disorders

Electroconvulsive Therapy (ECT)

- ECT is one of the most effective treatments for major depression
- Induces seizure activity in the temporal lobes
- Relief can occur quickly
- Adverse effect is memory loss
    - Usually disrupts memories that occurred before ECT, extending back 6 months on average
    - Can temporarily disrupt the storage of new information

Psychotherapy

- The goal of psychotherapy is to overcome negative views of self and future
- The effectiveness of psychotherapy may be through neocortical control of disturbed neural circuits

Antidepressants

- Tricyclic compounds such as Imipramine
    - Block reuptake of both norepinephrine (NE) and serotonin (5HT)
- Serotonin selective reuptake inhibitors (SSRIs) such as Fluoxetime
    - Block reuptake of serotonin (5HT) selectively
- Norepinephrine selective reuptake inhibitors (NESRIs) such as Fluoxetime
    - Block reuptake of norepinephrine (NE) selectively
- Monoamine oxidase (MAO) inhibitors such as phenelzine
    - Reduce enzymatic degradation of serotonin (5HT) and norepinephrine (NE)
- These antidepressant actions take several weeks to develop
- Clinically effective treatment dampens the hyperactivity of the HPA system in humans
    - Long term elevation of serotonin causes increased production of glucocorticoid receptors (these receptors bind cortisol)
- Drugs that bind to CRH receptors and drugs that bind to select Glutamate receptors are an emerging target for antidepressants.

Lithium

- Lithium is highly effective in stabilizing mood of patients with bipolar disorders – preventing mania and the episodes of depression
    - Lithium passes through sodium channels and:
        - Prevents normal turnover of PIP2 and reduces production of IP3 by PLC
        - Interferes with adenylyl cyclase and reduces production of cAMP and glycogen synthase
- The therapeutic effects of lithium require long term use

Schizophrenia

Schizophrenia is commonly associated with distorted thoughts and perceptions.

Description of Schizophrenia

- Characterized by a loss of contact with reality, and a disruption of thought, perception, mood, and movement
- Typically becomes apparent during adolescence or early adulthood
- Symptoms fall into two categories
    - Positive symptoms
        - Delusions
        - Hallucinations
        - Disorganized speech
        - Grossly disorganized or catatonic behavior
    - Negative symptoms
        - Reduced expression of emotion
        - Poverty of speech
        - Difficulty in initiating goal-directed behavior
        - Memory impairment
- Paranoid schizophrenia
    - Preoccupied with delusions
- Disorganized schizophrenia
    - Lack of emotional expression coupled with disorganized behavior and incoherent speech
- Catatonic schizophrenia
    - Peculiarities of voluntary movements

Biological Basis of Schizophrenia

Genes and the Environment

- Likelihood of having the disorder varies directly with the number of genes shared with an affected family member
- Several genes have been identified that increase susceptibility to schizophrenia – all are involved in synaptic transmission, plasticity, or growth of synapses
- Environmental factors are obscure

The Dopamine Hypothesis

- Amphetamine use (over use) can lead to psychotic episodes with positive symptoms that are virtually indistinguishable from those of schizophrenia
    - Amphetamines increase the secretion of catecholamines, including norepinephrine and dopamine
- Chlorpromazine can prevent the positive symptoms of schizophrenia
    - Chlorpromazine block many receptors for neurotransmitter, including dopamine D2 receptors, and some of the acetylcholine, norepinephrine, and serotonin receptors

The Glutamate Hypothesis

- Phencyclidine (PCP) use (over use) can lead to psychotic episodes with hallucinations and paranoia
    - Phencyclidine (PCP) has no effects on dopamine neurotransmission
    - Phencyclidine (PCP) does affect synapses that use glutamate

Treatment of Schizophrenia

- Typical neuroleptics such as chlorpromazine act in part on dopamine receptors and have many side effects, including Parkinson like side effects
    - Reduce many positive symptoms of schizophrenia
- Atypical neuroleptics such as clozapine and risperidone do not act on dopamine receptors and thus do not induce Parkinson like side effects
    - More effective against negative symptoms of schizophrenia