How To Control Stress – Think That You Can?

• There are stressful situations that are unavoidable (e.g. infections, injuries, etc)
  – These situations will produce similar effects in most organisms

• However, some situations are “perceived” as stressful by some people, but not others
  – To have the perception of control is called a coping response
  – Animals and humans that display coping responses generally have a reduced incidence of some of the negative effects of stress (e.g. cardiovascular problems and gastric ulcers)

Anxiety Disorders

• Anxiety is a fear that disrupts normal functioning and persists in the absence of a direct threat.

• Symptoms can include feelings of fear, worry, and nervousness, and physical perturbations including tachycardia (heart palpitations), hypertension, nausea, sweaty palms, sleep disturbances, and headache.

• Anxiety disorders are the most prevalent of all psychiatric disorders

• Currently affected ~ 19 million in U.S. with only 1/3 receiving treatment
Anxiety Disorders

• Anxiety disorders apparently develop from a complex set of risk factors:
  – genetics (concordance rate is higher for identical twins than for fraternal twins and siblings)
  – brain chemistry
  – personality
  – life events.

There are 4 Major Classes of Anxiety Disorders:

• Phobias - caused by exposure to a specific object or situation
• Generalized – stress response in the absence of an obvious stimulus
• Panic - rapid-onset attacks characterized by extreme fear and stress symptoms (tachycardia, choking)
• Obsessive Compulsive – frequently recurring, uncontrollable anxiety-producing thoughts and compensatory responses
Additional Anxiety Disorders:

- **Posttraumatic Stress Disorder (PTSD)** - can follow an exposure to a traumatic event such as an assault, witnessing a death, the unexpected death of a loved one, or natural disaster.

- **Social Anxiety Disorder**

**Phobias**

- Fear of something (object, situation etc.) that is greatly out of proportion to reality.

- Triggered by specific objects, situations etc.

- **Common object phobias:**
  - Acrophobia = high places
  - Agoraphobia = open places
  - Aquaphobia = water
  - Claustrophobia = confined places
  - Zoophobia = animals

- **Effective treatment:** systematic desensitization
Generalized Anxiety Disorder

- Most common of the anxiety disorders
- DOES NOT require a triggering stimulus
- Persistent, continually present
- Symptoms: inability to relax, jitteriness, sense that something bad will happen, heart palpitations, difficulty in concentrating, fear of losing control or being rejected.

- Treatments:
  - Benzodiazepines (Librium, Valium, Xanax) - increase binding of GABA, to its receptors (side effects can include sleepiness, memory impairment, tremors, nausea and addiction) – NOTE: alcohol has a similar effect – benzodiazepines + alcohol can be lethal
  - SSRI's (Selective serotonin reuptake inhibitors = Prozac, Luvox, Paxil, and Zoloft) – antidepressants that alter serotonergic function are also often effective against anxiety
GABA-A/Benzodiazepine Receptor Complex: An Ionotropic Receptor

Benzodiazepine binding site
GABA binding site
Barbiturate binding site
Cl- ion channel.

Lipid bilayer

Agonists at the benzodiazepine binding site are anxiolytic.

GABA Synapse
Panic Disorders

- Symptoms can include: racing heartbeat, difficulty breathing, terror, dizziness, trembling, choking, chest pains, hot flashes or sudden chills, tingling in fingers or toes, fear that one is going crazy or about to die
- Occurs suddenly, with little or no warning
- Level of fear is way out of proportion to the actual situation – often it’s completely unrelated
- Passes in a few minutes, but repeated attacks can continue to recur for hours
Panic Disorders

• Stressful life events can trigger panic disorders
• Physical sensations, similar to those experienced during an attack, can trigger an attack
• Somewhat more common in females than males
• Twin studies suggest a genetic link
• Treatment can be behavioral, or pharmacological or both

Obsessive-Compulsive Disorder

• Obsession ≠ Compulsion
  • Obsession = a recurrent unwanted anxiety producing thought
  • Compulsion = an impulsive behavior aimed at decreasing the anxiety
Obsessive-Compulsive Disorder

- Recurring (obsessional) thought
- High level of arousal; tendency to overreact to emotionally-provoking stimuli
- Inability to engage in distracting activities or otherwise terminate this thought

THOUGHT & ANXIETY GROW STRONGER

Individual may adopt compulsive actions (rituals) to reduce their growing anxiety

Reported Obsessions and Compulsions of Child and Adolescent Patients - % Reporting Symptom at Initial Interview

Rapoport, J.L. JAMA 1988, 260
Obsessive-Compulsive Disorder

- Affects ~2-3% of the population
- ~1/3 of adults with OCD report symptoms began by age 15
- Most common: germ anxiety and washing / cleaning
- Categories: counting, checking and cleaning
- Treatments
  - Pharmacological: Tricyclic antidepressants (prevent reuptake of serotonin or catecholamines), SSRIs
  - Non-pharmacological: cognitive behavioral therapy

Cognitive Behavioral Therapy

- Combines two kinds of psychotherapy:
  - **Behavior therapy** weakens the *connections* between troublesome situations and the habitual reactions to them (fear, depression or rage, and self-defeating or self-damaging behavior)
  - **Cognitive therapy** teaches how certain *thinking patterns* are causing symptoms — by giving a distorted picture of what's going on, and producing feelings of anxiety, depression or angry for no good reason, or provoking ill-chosen actions.
Posttraumatic Stress Disorder (PTSD)

Relatively common among soldiers, victims of rape, kidnapping, torture and severe accidents, those who have experienced large scale disasters or the sudden death of a loved one

• Three main symptoms associated with PTSD:
  – "reliving" of the traumatic event (such as flashbacks and nightmares)
  – avoidance behaviors (such as avoiding places related to the trauma) and emotional numbing (detachment from others)
  – exaggerated arousal in response to noises and other stimuli, difficulty sleeping, irritability or poor concentration

Posttraumatic Stress Disorder (PTSD)

PTSD does not appear to be just a prolongation of the normal stress response – E.g. people with PTSD show lower than normal cortisol levels, both immediately after the traumatic event and weeks later

• Common Treatments:
  – Cognitive-behavioral therapy (CBT) – learning to change emotions, thoughts and behaviors
  – Medication (particularly antidepressants) can reduce the anxiety, depression and insomnia often experienced with PTSD, and it may help relieve distress and emotional numbness
  – Group therapy – share traumatic material with other survivors
Neural Basis of Anxiety Disorders

- Currently, much attention is focused on the amygdala (plays important role in fear and defensive behaviors)
- Amygdala has large numbers of GABA$_A$ receptors
  - infusions of benzodiazepines into amygdala produce anxiolytic effects in animals
  - Infusions of GABA antagonists do the opposite
- Brain imaging studies have not shown any obvious pathologies in individuals suffering from anxiety disorders

Affective Disorders

- Unipolar
  - Depression
- Bipolar (Manic-Depressive Disorder)
  - Depression
  - Mania
Affective Disorders: Depression and Mania

- Reactive ≠ endogenous depression
  - Reactive = in response to a specific event, loss
  - Endogenous = ongoing, appears independent of obvious external stimulus
- Annually, major depression affects 5% of the population, or 9.8 million Americans
- Likelihood of an episode of major depression in lifetime = about 6%
- Female:male ratio (2-3):1 for depression

Affective Disorders: Depression

- Average duration of a depressive episode = 20 wks
- 80% of patients respond to drugs, psychotherapy or a combination of both
- About 10% of people suffering from an affective disorder will commit suicide
- Genetic link – twin studies of affective disorders suggest a concordance rate of about 60% for identical twins, and 15% for fraternal twins
- Stress can trigger attacks of depression; early exposure to stress may increase likelihood of developing depression in adulthood
Depression

• Symptoms include:
  • Intense feelings of despair
  • Pervasive loss of interest in that which was once pleasurable including appetite, sleep, sex, etc.
  • Sadness, irritability that will not go away
  • Lethargy, fatigue, loss of energy
  • Withdrawal
  • Feelings of worthlessness, hopelessness, helplessness
  • Difficulty in concentrating
  • Sleep disturbances

A Profile of Depression
A Profile of Depression

Complaints Bringing Previously Undiagnosed Depressed Patients to a Physician
Sleep Patterns Are Disrupted In Depression

Treatment of Depression

• Monoamine Oxidase Inhibitors (MAOIs) (Ex. Nardil)

  – Inhibit the enzyme, MAO, that breaks down monoamines (norepinephrine and serotonin), thus increasing levels of monoamines
    • The first antidepressant drug, iproniazid, was developed as a treatment for tuberculosis (TB) – it had no effect on TB, but did make the patients less depressed – first marketed antidepressant (1957).
  
  – In combination with foods (ex. cheese, wine, pickles, liver) containing a particular compound (tyramine), they can produce life-threatening surges in blood pressure
Treatment of Depression

• **Tricyclic Antidepressants** (chemical structure includes a 3-ring chain) (Ex. Tofranil)
  - Block the reuptake of both serotonin and norepinephrine
  - Usually more effective than MAOIs, but MAOIs help some patients do not respond to tricyclics
  - Safer than the MAO inhibitors, but can have significant side effects:
    - block histamine receptors (drowsiness), acetylcholine receptors (dry mouth and difficulty urinating) and certain sodium channels (can cause heart irregularities)

• **Selective Monoamine-Reuptake Inhibitors (SSRIs)**
  (Ex. Prozac, Paxil, and Zoloft)
  - Action is similar to tricyclics, but specific to the neurotransmitter serotonin
  - Block reuptake of serotonin
  - Relatively few side-effects, but sometimes produce nervousness, and thus are not recommended for patients with both depression and anxiety
Neural Mechanisms of Depression

• The monoamine theory of depression: depression is associated with under-activity of serotonergic and noradrenergic synapses
• Based on the fact that all clinically effective antidepressants are serotonin and/or norepinephrine agonists
• The theory can’t explain why antidepressant take 3 or more weeks to produce *clinical improvement* when they produce very rapid (minutes - hours) increases in extracellular monoamine levels
• Clinical improvement may require changes in neuronal structure and function produced by neurotrophic factors (e.g. brain-derived neurotrophic factor, BDNF)
Electroconvulsive Therapy (ECT)

- Originated with the observation that people with both epilepsy and schizophrenia sometimes have a decrease in the symptoms of one, when they have an increase in the symptoms of the other.
- ECT not very effective for schizophrenia, but helpful for some depressed patients.
- Used for patients who do not respond to antidepressants.
- Also sometimes recommended for patients with strong suicidal tendencies because it works faster than antidepressant drugs.

Electroconvulsive Therapy (ECT)

- ECT usually applied every other day for about 2 weeks, sometimes longer.
- Most common side effect is memory loss, but this is less common with modern treatments (shock is limited to the right hemisphere).
Depression Is Associated With Decreased Activity Of The Left Hemisphere

- PET scans of the left hemisphere of a depressed person (above) and a person who has recovered from depression (below) – red indicates decreased activity
- If shock is limited to the right hemisphere, antidepressant effects of ECT can be produced with minimal impact on memory
- Theory is that right-hemisphere ECT may either promote a better balance of activity between the two hemispheres, or somehow enhance activity in the left hemisphere

Electroconvulsive Therapy (ECT)

- ECT usually applied every other day for about 2 weeks, sometimes longer
- Most common side effect is memory loss, but this is less common with modern treatments
- About 50% of the people who respond well to ECT relapse into another episode of depression within 6 months – drugs, psychotherapy, or additional ECT treatments are used to try to prevent this
- Mechanism of action is unclear
**St. John’s Wort**

- Because it is marketed as a nutritional supplement instead of a drug, it is not regulated by the US FDA, and purity can vary from one batch to another.
- Apparently, it works the same way as the SSRIs.
- Different studies have yielded mixed results (purity issues?).
- It does have a potentially dangerous side effect:
  - It increases the action of a liver enzyme that breaks down many medications. Therefore, it can decrease the effectiveness of many other drugs (e.g. other antidepressants, cancer drugs, AIDS drugs, birth control pills).

**Affective Disorders: Bipolar Disorder**

- Characterized by cycling between depression and mania.
  - Mania = grandiose ideas, fleeting, elevated expansive mood, increased activity, increased speech, decreased need for sleep, increased distractibility, impulsive behavior. In extreme cases, manic people can be dangerous to themselves and others.
- 1% of population suffers from bipolar disorder.
- Affects 2-3 million in the U.S.
Affective Disorders: Bipolar Disorder

- Average age of onset in the early 20’s
- Men and women equally affected
- Genetic link – twin studies of bipolar disorders suggest a concordance rate of at least 50% for identical twins, and 5-10% for fraternal twins, or children or siblings of bipolar patients

A Profile of Bipolar Disorder
A Profile of Bipolar Disorder

A Profile of Bipolar Disorder
Figure 15.15 Observations of a 3-week manic episode. Source: From Psychiatric Mental Health Nursing by E. Janosik and J. Davies, p. 173. Copyright ©1986 Jones and Bartlett Publishers. Reprinted with permission.

Figure 15.16 PET scans of a bipolar patient. Horizontal planes through three levels of the brain are shown for each day. On May 17 and May 27, when the patient was depressed, brain metabolic rates were low. On May 18, when the patient was in a cheerful, hypomanic mood, the brain metabolic rate was high. Red indicates the highest metabolic rate, followed by yellow, green, and blue.
Treatment of Bipolar Disorder

• Lithium
  – Therapeutic effects thought to be mediated by its agonistic effects on serotonin function
    • Commonly used to treat bipolar disorder (particularly in cases characterized by strong manic phases) – stabilizes mood, preventing a relapsing into either mania and depression
    • Some anticonvulsants have mood stabilizing effects and can be used to treat bipolar episodes that don’t respond to lithium

Seasonal Affective Disorder

• Depression that occurs during a particular season (usually winter)
• Most common near the poles, where winter nights are very long
• Responds very well to treatment with bright lights (particularly effective in the morning).
Tourette’s Syndrome

- Characterized by tics, or involuntary, repetitive movements
- Usually begins in childhood; symptom often become more complex and more severe with time
  - Common motor tics include lewd gestures, hitting, touching, squatting, hopping and twirling
  - Common vocal tics include barking, grunting, uttering obscenities, and repeating themselves
- 3X more common in males than females
- There is a genetic component – concordance rate is 55% for identical twins and 8% for fraternal twins
- Often accompanied by obsessive-compulsive disorder
- Neuropathology believed to arise from abnormalities in the neural circuits between the basal ganglia and the cortex
- Often treated with drugs that block dopaminergic function

Schizophrenia (“split mind”)

- About 1% of the population is schizophrenic; incidence the same all over the world
- Disorder usually becomes apparent between the ages of 15 and 25
  - Some patients fully recover following treatment (about 15% return to normal life after a single episode)
  - Most continue to have moderate or severe symptoms, particularly in response to stress (60% will have intermittent episodes throughout their lives; another 25% will not recover their ability to live as independent adults
Schizophrenia

- Characterized by complex and diverse symptoms that often overlap with other forms of mental illness, and may change with time:
  - Negative symptoms (tend to be stable over time and difficult to treat)
    - Weak social interactions, emotional expression, speech, and working memory
  - Bizarre delusions, hallucinations, inappropriate affect, incoherent thought, or odd behavior (e.g. catatonia)
  - Positive symptoms (more sporadic)
    - *Delusions* – unfounded beliefs, such as the conviction that is being persecuted or that aliens from outer space are trying to control one’s behavior
    - *Hallucinations* – abnormal sensory experiences, such as hearing voices when no one is speaking

A Portraits of Schizophrenia
PET scans have determined that hallucinations occur during periods of increased activity in the thalamus, hippocampus, and parts of the cortex (including many of the areas activated by actual hearing).

Enlargement Of The Ventricles Is Sometimes Associated With Schizophrenia
Brain Scans Of Some Schizophrenics Show Some Brain Structures Are Reduced Size

Some Schizophrenics Also Show Brain Abnormalities At The Cellular Level
Relatives Of Schizophrenics Have An Increased Probability Of Developing Schizophrenia

- The closer the genetic relationship, the greater the probability of developing the disorder
- The concordance rate of schizophrenia in identical twins is about 45%; in fraternal twins or sibs is about 10%

Causal Factors in Schizophrenia

- Father’s age (the older the father, the greater the chance of schizophrenia in the offspring)
- Regions of several different chromosomes have been implicated in the vulnerability to schizophrenia
  - When apparent linkages are found, they are generally small effects (e.g. having a particular gene increases the risk of developing schizophrenia by 0.5%)
  - Why such small effects?
    - Misdiagnosis?
    - Schizophrenia depends on a combination of genes?
      - The more of those genes, the greater the risk
    - Maybe people develop schizophrenia for different reasons?
      - E.g. genetics, environment, or combination of both
Causal Factors in Schizophrenia

- In addition to a genetic predisposition, susceptibility factors may include:
  - Prenatal trauma (a developmental disorder?)
    - No obvious signs of ongoing degeneration in brains of schizophrenics
    - Brain pathology associated with schizophrenia seems to be largely developed when the disorder is first diagnosed
  - Infection
    - People born in winter have a slightly (5-8%) higher probability of developing schizophrenia – this occurs only where the weather changes by season, and is particularly pronounced in large cities
  - Stress

- Current view is that people inherit a predisposition for schizophrenia which may or may not be activated by experience

Schizophrenia Is Thought To Reflect Changes In The Brain, Possibly Caused By Disease Or Injury At The Time Of Birth

- The prefrontal cortex (the area that shows the most consistent abnormalities) matures very slowly (reaches full function in late teens)
- The effects of the damage would be presumably be less apparent when the damaged region isn’t doing much; as the region begins to assume more functions, the damage would become more apparent
The First Anti-schizophrenic Drugs

- Chlorpromazine (Thorazine) was initially developed as a new antihistamine
  - When it was used to prevent swelling associated with surgery (early 1950s), it was found to calm patients down
  - Seemed to calm agitated schizophrenia patients, and to activate catatonic ones – effect specifically anti-schizophrenic, not just sedative (sleep inducing)
  - Frequently relieves positive symptoms of schizophrenia
  - Sometimes halts the progress of the disease if treatment begins early

- Snake root plant
  - Used in India for centuries to treat psychiatric disturbances
  - Active ingredient, reserpine, proved an effective anti-schizophrenic, but it is no longer used for treatment of schizophrenia because it can dangerously lower blood pressure
Most of the drugs that are most effective against schizophrenia are also most effective at blocking dopamine receptors

- Drugs that block dopamine receptors in the mesolimbic system also block dopamine receptors in other locations, including those in the basal ganglia
- The result is tardive dyskinesia (characterized by tremors and other involuntary movements) – can develop over periods ranging from a few days to over 20 years
- Tardive dyskinesia can last for years even after drug is stopped

![Diagram of brain pathways](image)

**Figure 15.26 Two major dopamine pathways**
The mesolimbocortical system is apparently responsible for the symptoms of schizophrenia; the path to the basal ganglia is probably responsible for tardive dyskinesia, a movement disorder. Source: Adapted from Holzel, 1980

---

**Anti-Schizophrenic Drugs**

- Atypical anti-psychotics (Clozapine) act somewhat differently from other anti-psychotics
  - Help with both positive and negative symptoms
  - Seldom produce movement problems
  - Differ from other anti-psychotics in their effects on dopamine and serotonin receptors
  - Also increase the release glutamate
- Used to treat patients not helped by conventional medications (approximately 30%)
  - Can induce a potentially fatal blood disorder in about 1% of patients
  - May increase the risk of diabetes
  - May impair immune function
  - Requires frequent blood tests, makes use very costly
Drugs That Can Produce Schizophrenic Symptoms

- Large, repeated doses of certain drugs can produce substance-induced psychosis (hallucinations and delusions)
- Drugs that commonly produce these symptoms include amphetamine, methamphetamine, cocaine, and LSD (best known for effects on serotonin synapses) - all increase activity at dopamine synapses
  - Individuals who stop taking the drug are likely, though not certain, to recover from these symptoms
  - Substance abuse often results in visual hallucinations (less common in schizophrenia)
- Phencyclidine (PCP) (“angel dust”) inhibits glutamate (NMDA) receptors
  - At low doses effects look somewhat like the effects of alcohol
  - At high doses produces both positive and negative symptoms
Schizophrenia Due To Altered Neurotransmitter Activity?

- **Dopamine Hypothesis**
  - Excess dopamine activity
    - Drugs that block activity at dopamine synapses reduce positive symptoms, drugs that increase dopamine activity can induce positive symptoms

- **Glutamate Hypothesis**
  - Deficient glutamate activity
    - PCP, which blocks NMDA receptors, produces both positive and negative symptoms of schizophrenia, especially in people predisposed to schizophrenia