Psychopathology (Ch.16) III

- Depression
  - Symptoms, Epidemiological factors
  - Stress-related factors
  - Monoamine Hypothesis
  - Other Brain Abnormalities
  - Treatments
  - Animal models
  - Bipolar disorder/mania

- NOTE: No lectures on anxiety disorders- you will not be tested on this

Depression: What is it?

- Major **unipolar** depression is one of the most common mood disorder, characterized by:
  - Unhappy mood (more an absence of happiness than increased sadness), worthlessness, guilt, desperation
  - Loss of interest, motivation (anergia), and appetite, blunted ability to experience pleasure (anhedonia)- or at least pursue it
  - Difficulty in concentration, restless agitation
- An episode of depression may occur with no apparent cause (endogenous) or can be triggered by external events (reactive)
  - High co-morbidity of depression w/ many other medical conditions
- Major costs to individual and society
  - Dramatically increased risk of suicide (7-15% vs ~1% general population)
  - Impact on relatives/friends of the individual with depression
  - Lost productivity costs

DSM Diagnostic criteria for Major Depressive Disorder

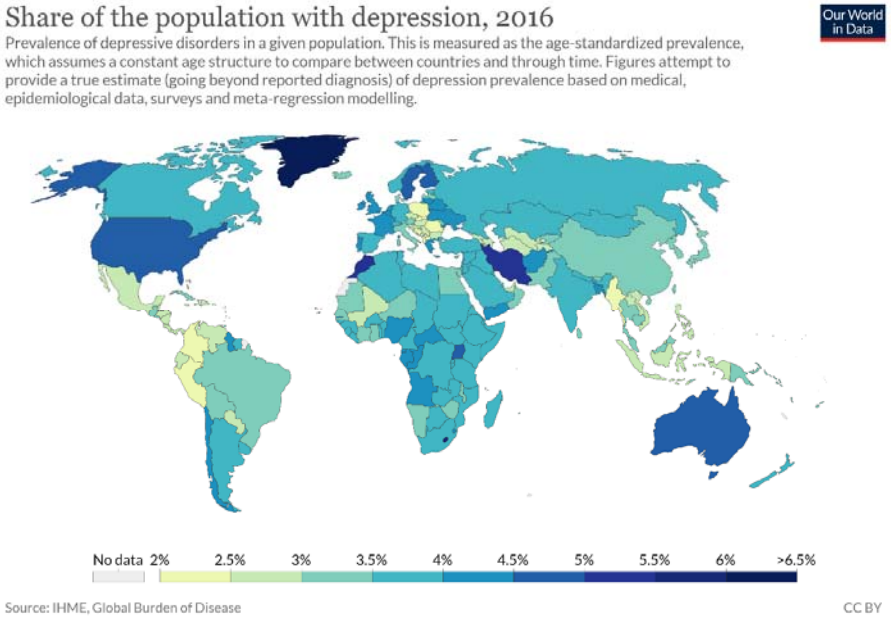
≥5 symptoms during the same two week period that are a change from previous functioning; depressed mood and/or loss of interest/pleasure must be present

Depressed mood	Most of the day, nearly every day; may be subjective (e.g. feels sad, empty, hopeless) or observed by others (e.g. appears tearful); in children and adolescents, can be irritable mood
Loss of interest/pleasure	Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day; may be subjective or observed by others
Weight loss or gain	Significant weight loss (without dieting) or gain (change of >5% body weight in a month), or decrease or increase in appetite nearly every day; in children, may be failure to gain weight as expected
Insomnia or hypersomnia	Nearly every day
Psychomotor agitation or retardation	Nearly every day and observable by others (not merely subjectively restless or slow)
Fatigue	Or loss of energy, nearly every day
Feeling worthless or excessive/inappropriate guilt	Nearly every day; guilt may be delusional; not merely self reproach or guilt about being sick
Decreased concentration	Nearly every day; may be indecisiveness; may be subjective or observed by others
Thoughts of death/suicide	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or suicide attempt, or a specific plan for suicide

- Symptom clusters vary with individuals; there are depression subtypes associated with distinct causes and pathophysiologies.
- Over 200 combination of different symptoms can be diagnosed as “depression”

Epidemiological Factors in Depression

- Unipolar depression typically alternates with normal emotional states, with an episode lasting up to 6-9 months.
  - — Episodes can recur through life, often increasing in frequency and intensity
- **Prevalence**: In North America, > 10% of population may be afflicted at any one time
  - Considerable sex difference: women more likely to be diagnosed
  - In women, incidence often coincides with major hormonal changes (post partum, menopause)



- Incidence of depression has increased over the last 50 years, and age of onset has decreased (currently ~ 27 years old)
- **Genetic influences:** Some types of depression may have a genetic influence, whereas others less so

Stress and Depression (I)

•Depression is viewed as a stress-related disorder

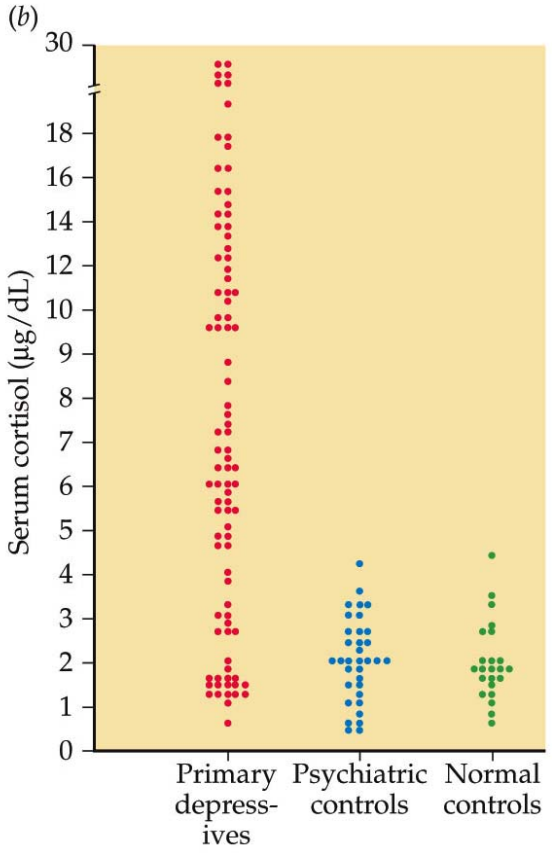
– Can emerge during stressful life periods

•At least some forms of depression may be linked to alterations in HPA-axis and higher cortisol (CORT) levels

•People with **Cushing's syndrome** have high levels of glucocorticoids and are prone to depression.

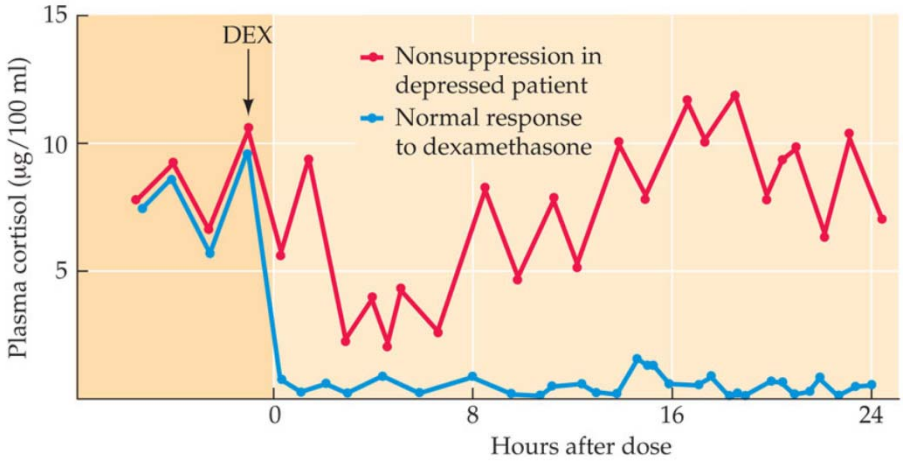
•Circulating CORT levels tend to be higher in depressed subjects vs other disorders or controls.

➢ A popular theory of depression is the **diathesis-stress model** (ie: an individual has some sort of predisposition for depression, and stress can trigger the syndrome)



Stress and Depression (II)

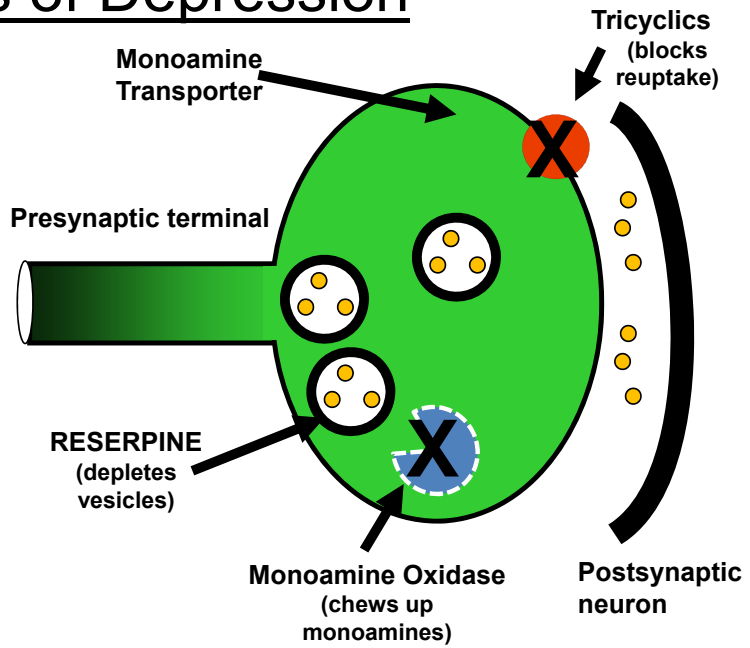
- The **dexamethasone suppression test** can show excessive CORT release
- Dexamethasone, a synthetic glucocorticoid, can suppress CORT release in normal people, but not in depressed patients.



- Dexamethasone can "fool" the HPA axis into believing there are higher levels of CORT than normal – through negative feedback, levels drop in healthy controls
- In many depressed patients, negative feedback mechanisms are disrupted.

The Monoamine Hypothesis of Depression

- Three major monoamine neurotransmitters are **5-HT**, **noradrenaline** and **dopamine**
- **1950-60s: Reserpine** (drug that reduces monoamine levels) induces depression
- First **monoamine oxidase inhibitors** (which block metabolism of monoamines and increase brain levels) alleviated depression
- First tricyclic antidepressant (***Imipramine***, which blocks monoamine reuptake) also found effective



- **1980s: Fluoxetine (aka-**Prozac™) a -selective serotonin reuptake inhibitor (SSRI) found to be effective at treating depression
- All of these findings support the **monoamine *hypothesis:***

➢ **Depression is the result of abnormal reductions in brain monoamine (mostly 5-HT and noradrenaline) levels**

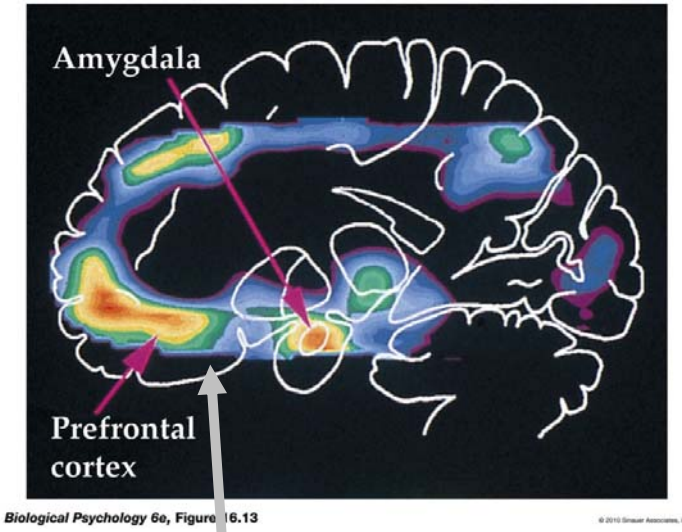
Treatment Issues and Limitations of the Monoamine Hypothesis

- **1) Antidepressants increase monoamine levels quickly, yet there is a lag in the reduction of symptoms** (chronic treatment is required)
- **2) Not all depressed patients respond to drugs that increase monoamine levels**
  - There is a large placebo effect – antidepressants tend to improve symptoms vs placebo in the most severely depressed patients
  - SSRIs are not more effective than classic tricyclics that effect noradrenaline release as well (but have fewer side effects)
- **3) SSRIs associated with increased risk of suicide in children and adolescents** (but causal relationship unclear).
- **4) In animal models, depletion of 5-HT does not cause a depressive-phenotype**
  - Suggest that there is more to the disorder than merely a overall decrease in 5-HT levels in the brain

Brain Changes With Depression

Functional imaging studies have revealed:

- Increased blood flow to amygdala and ventral parts of medial prefrontal cortex
  - Some aspects of depression may be caused by disrupted regulation of amygdala emotional processing by certain parts of PFC
- Alterations in brain activation can be ***normalized with antidepressant treatment***
- Reduced hippocampal volumes also observed



Higher activity in ventromedial PFC

- Dysfunction of prefrontal cortex may be one of the underlying mechanisms that leads to aberrant negative appraisals of life events (everything seems a lot worse than it is, persistent rumination on negative events)

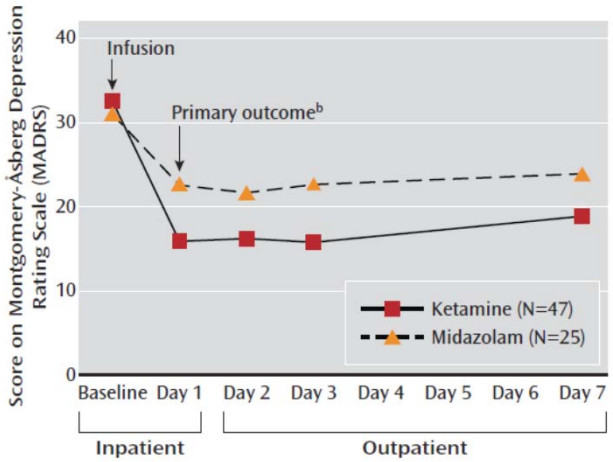
Other Treatments for Depression

- ***Electroconvulsive shock therapy*** **(ECT):** one of the original treatments for depression
  - Method of action poorly understood, still used today in extreme cases.
- ***Transcranial magnetic stimulation*** **(TMS)** also alters cortical electrical activity.
- ***Deep Brain Stimulation*** **(DBS) –** electrode is surgically implanted in brain, very high frequency stimulation given continuously.
  - Thought to inactivate targeted brain region – DBS in ventromedial PFC or other subcortical areas has been shown to be effective at alleviating depression in **treatment resistant** patients
  - No controlled experiments have been done

Other Treatments for Depression

- **Ketamine** (non-competitive NMDA antagonist): Sub-anesthetic doses induce rapid reduction in symptoms for ~70% of treatment-resistant patients (after psychosis dissipates).
  - — Effects last 1-3 weeks
  - — Nasal formulation recently approved for use
- Method of action not fully understood, but may be linked to increased cortical activity

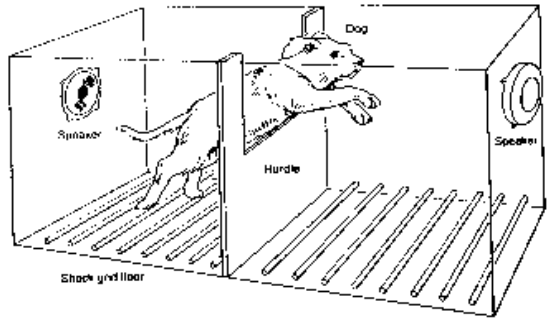
FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]



- ***Cognitive/Behavioural Therapy*** – takes a longer time, but ***just as effective*** as antidepressant drugs – when used in combination with other treatments, even more effective.

Animal Models of Depression

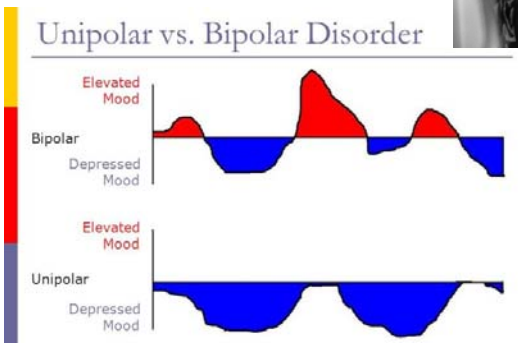
- ***Models*: certain experimental manipulations may cause some sort of "depressed" condition in laboratory animals**
  - Learned helplessness animal is exposed to a repetitive, inescapable stressful stimulus. After repeated exposure, **some more sensitive** animals will not escape when given opportunity.



  - Those that do not escape tend to have cellular/neurochemical alterations in the brain, (eg: decrease in 5-HT function).
  - Acute antidepressant treatment can reduce behavioral despair

Bipolar Disorder (Mania/Depression)

- **Bipolar disorder** is characterized by periods of depression alternating with expansive mood, or mania.
- The rate of cycling varies; rapid cycling consists of four or more cycles in one year.
  - Some may cycle several times in one day.
- Neural basis not fully understood but appears to involve abnormalities in the hippocampus, amygdala



- **Lithium** is a mood-stabilizing drug used to treat bipolar disorder that has widespread actions in the brain.
- Modulates 5-HT AND dopamine transmission
- Interacts with the circadian clock
- Lithium may enhances Brain Derived Neurotrophic Factor (BDNF) activity that may reduce cell death associated with bipolar disorder.