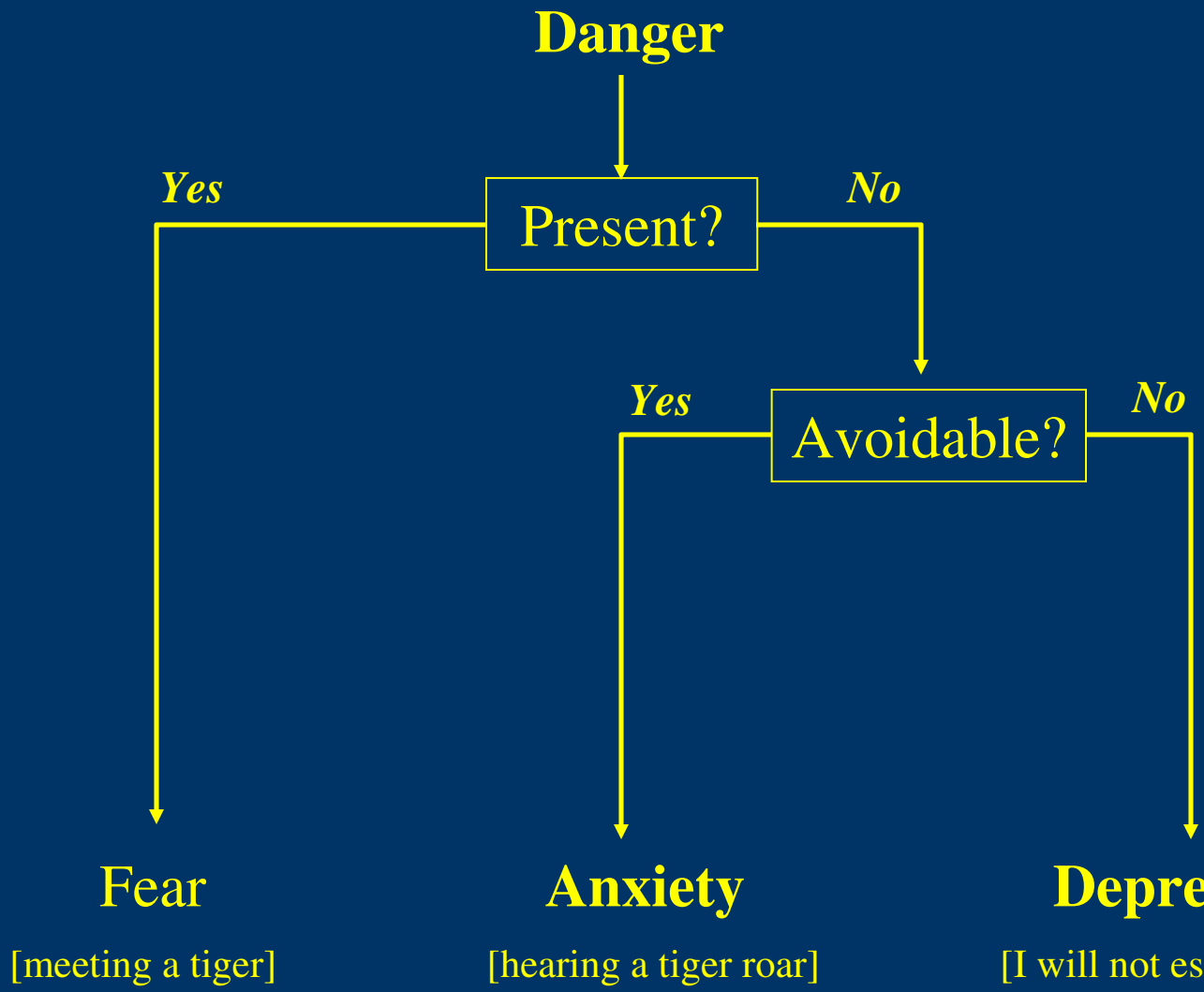
Neurobiology of Affective Disorders: Depression

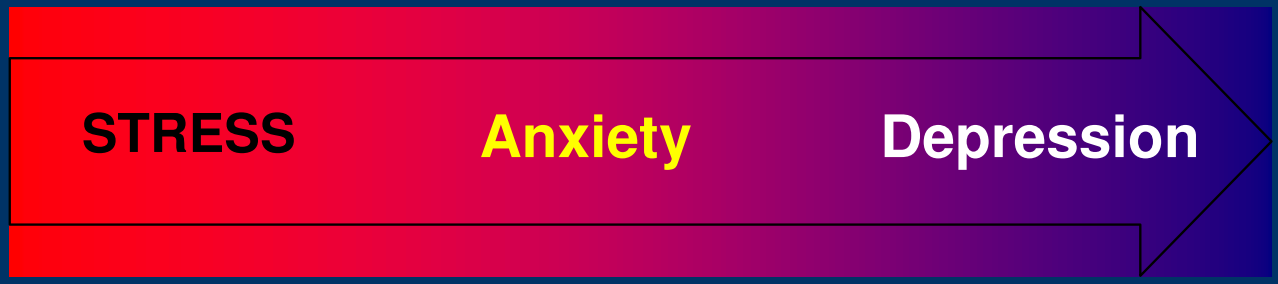
1st ISBS Summer School

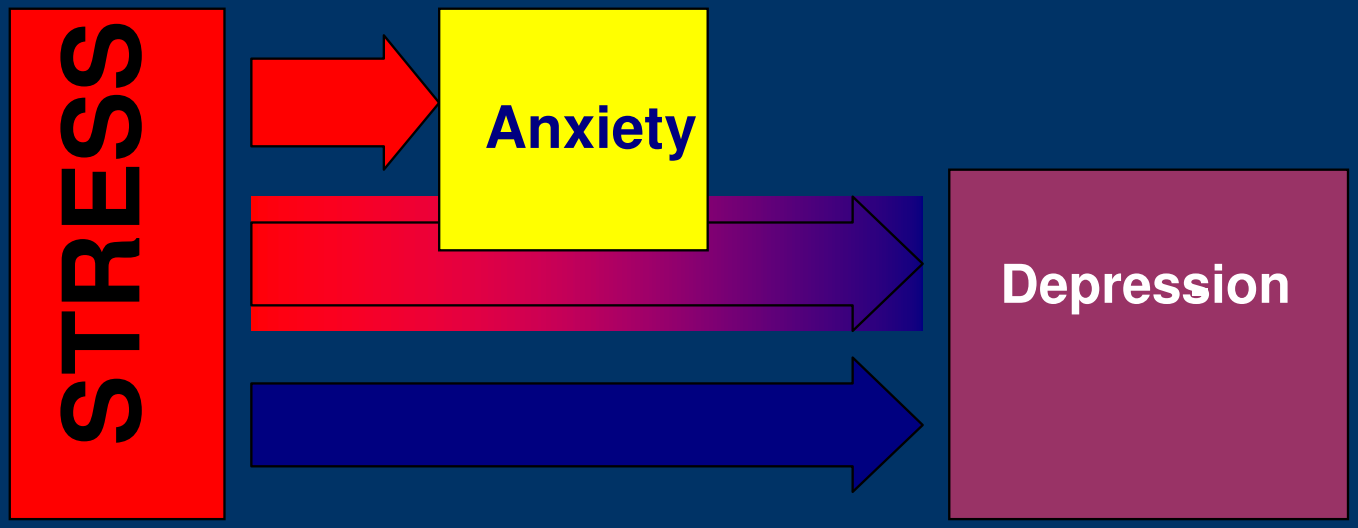
St. Petersburg, Russia

May 9th -15th,2008

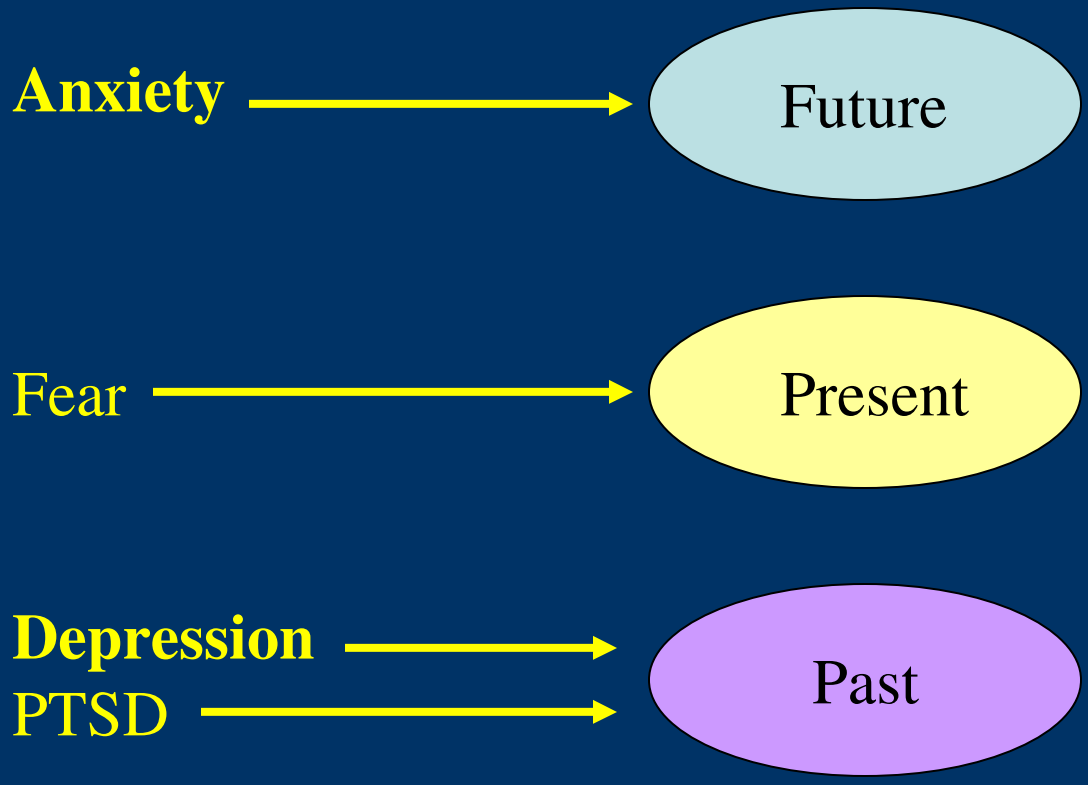
Depression and Anxiety



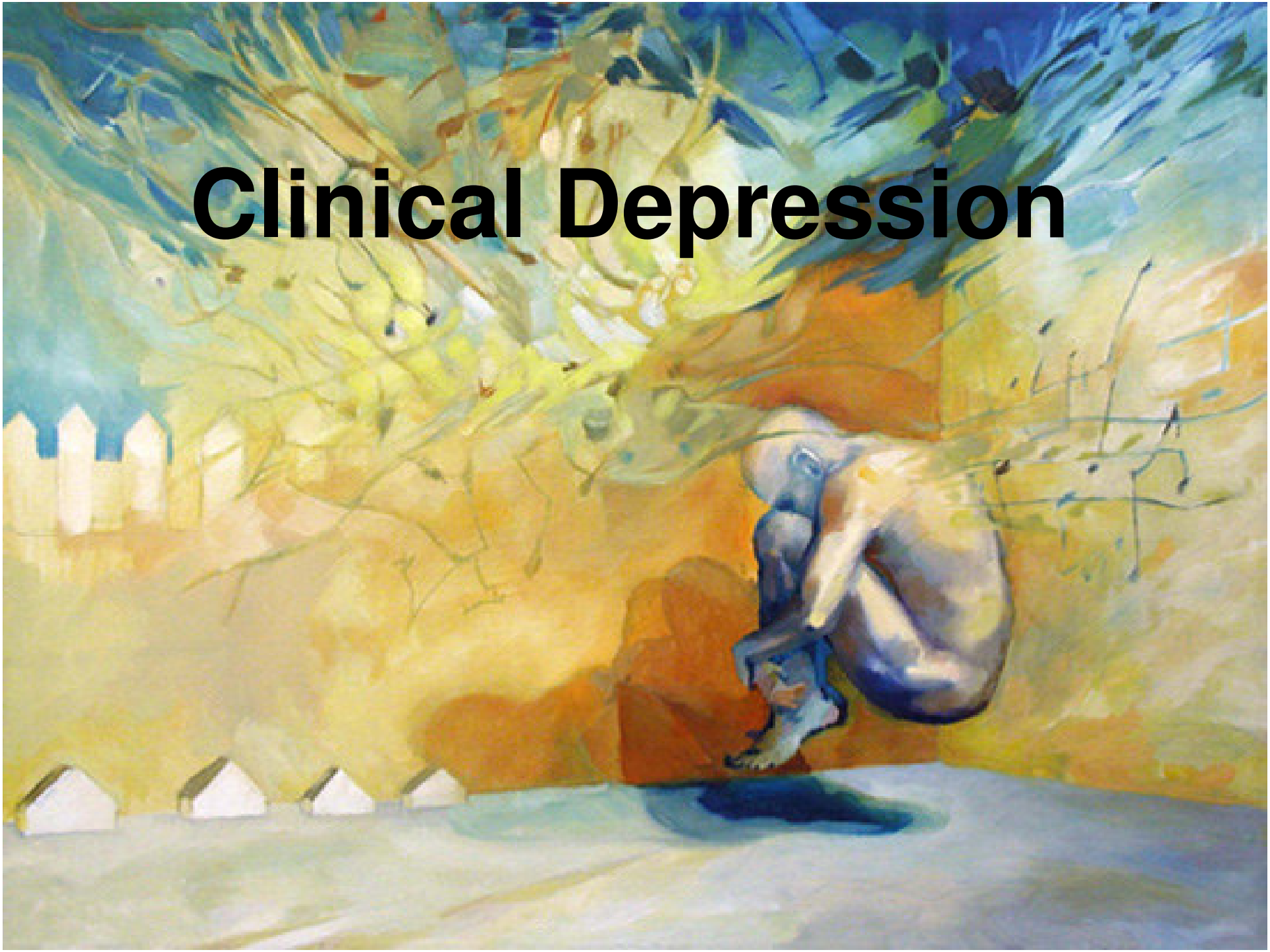

STRESS
Anxiety
Depression


STRESS
Anxiety
Depression

Brain emotional states



Clinical Depression



Definitions

DSM-IV: one of the following must be present for at least two weeks:

- Depressed mood
- Lack of pleasure (anhedonia)

Other symptoms:

- Feelings of overwhelming sadness and/or fear
- Blunt affect/ lack of pleasure
- Weight gain or loss
- Disturbed sleep patterns. Psychomotor agitation nearly every day
- Fatigue, mental or physical
- Intense feelings of guilt, hopelessness, isolation or anxiety
- Cognitive problems: concentrating, keeping focus, poor memory
- Recurrent thoughts of death
- suicide attempt or a specific plan for committing suicide

A total of five symptoms must be present to diagnose a major depressive disorder

Types of depression

- **Major (Unipolar) Depression:** the most severe and frequent type of depression.

  (!) You do not need to feel suicidal to have a major depression.

  (!) There is no official diagnosis of "moderate depression."

- **Dysthymic Disorder:** a low to moderate level of depression that persists for at least two years. The symptoms are not as severe as a major depression, though are more resistant to treatment

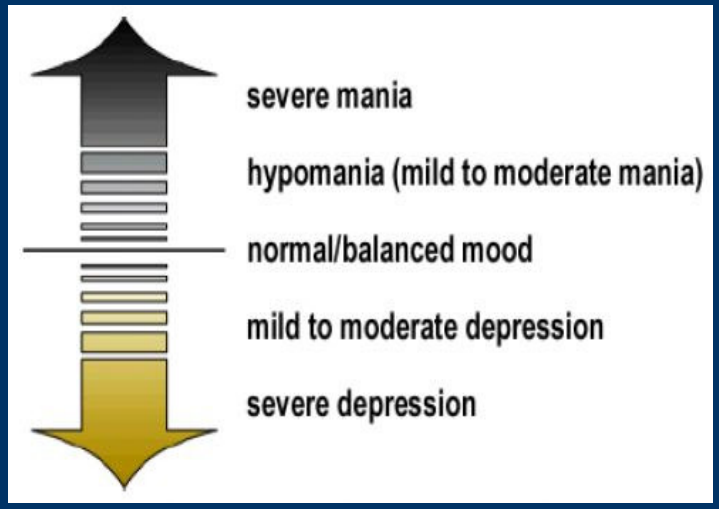
Types of depression

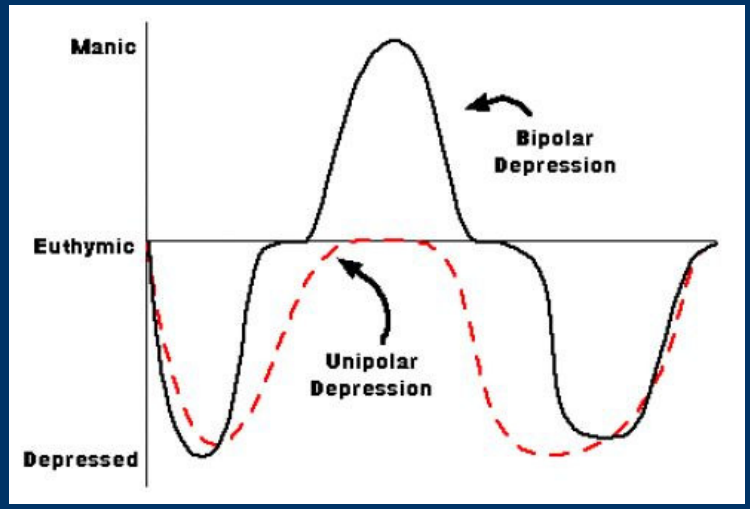
- **Unspecified Depression:**
  people with a serious depression, but not quite severe enough to have a diagnosis of a major depression
  people with chronic, moderate depression, which has not been present long enough for a diagnosis of a Dysthymic disorder

- **Adjustment Disorder with Depression:** This category describes depression that occurs in response to a major life stressor or crisis

- **Bipolar Depression:** This type includes both high and low mood swings, as well as a variety of other significant symptoms not present in other depressions

Bipolar vs. unipolar depression





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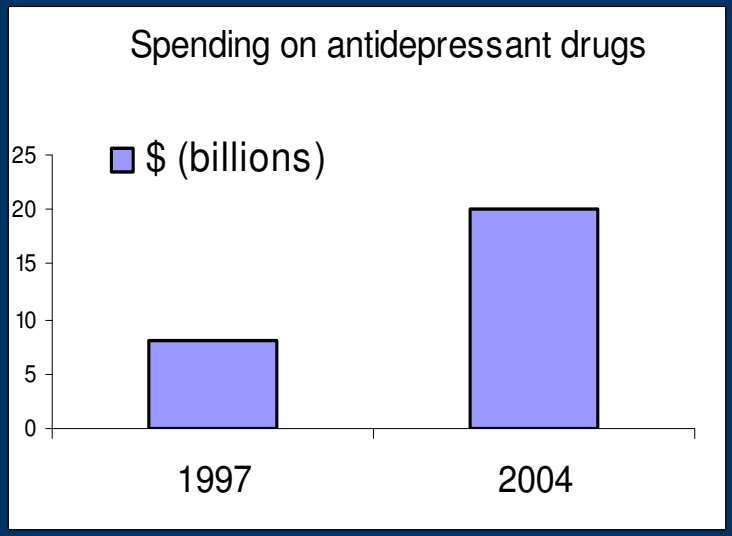
Depressing statistics

- Spending on antidepressants jumped 150% from 1997 to 2004
- Affect approximately 18.8 million American adults
- 9.5% of the US adult population
- 15% of the population of most developed countries suffers severe depression
- 15% of depressed people will commit suicide

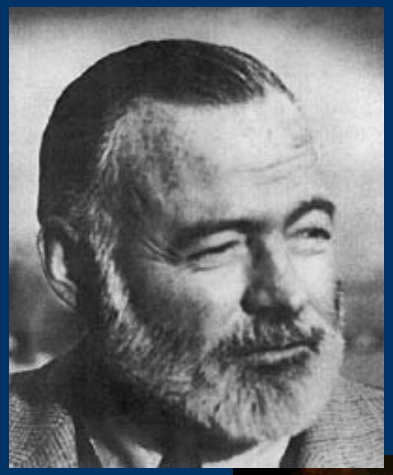
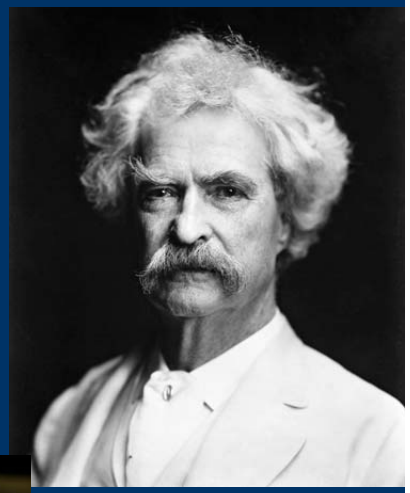
The World Health Organization forecasts depression will be the second largest killer after heart disease by 2020

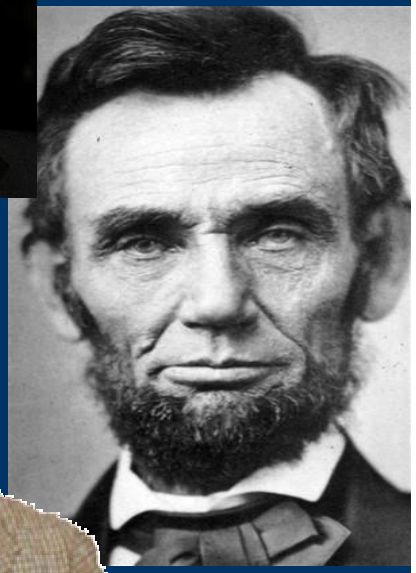
- Nearly two-thirds of depressed people do not get proper treatment



Persons of note with depression

- Woody Allen (film director)
- Ingmar Bergman (film director)
- Albert Camus (writer)
- Jim Carrey (actor)
- Sheryl Crow (musician)
- Fyodor Dostoevsky (writer)
- Vincent Van Gogh (painter)
- Ernest Hemingway (writer)
- Abraham Lincoln (16th President of US)
- Martin Luther (priest and theologian)
- Michelangelo (painter and sculptor)
- Isaac Newton (physicist)
- Friedrich Nietzsche (philosopher)
- Mark Twain (writer)





What happens
to the CNS in depression?

Theories/ hypotheses

- 5HT, NE, and/or DA imbalances
- Supported by the mechanism of action of antidepressants

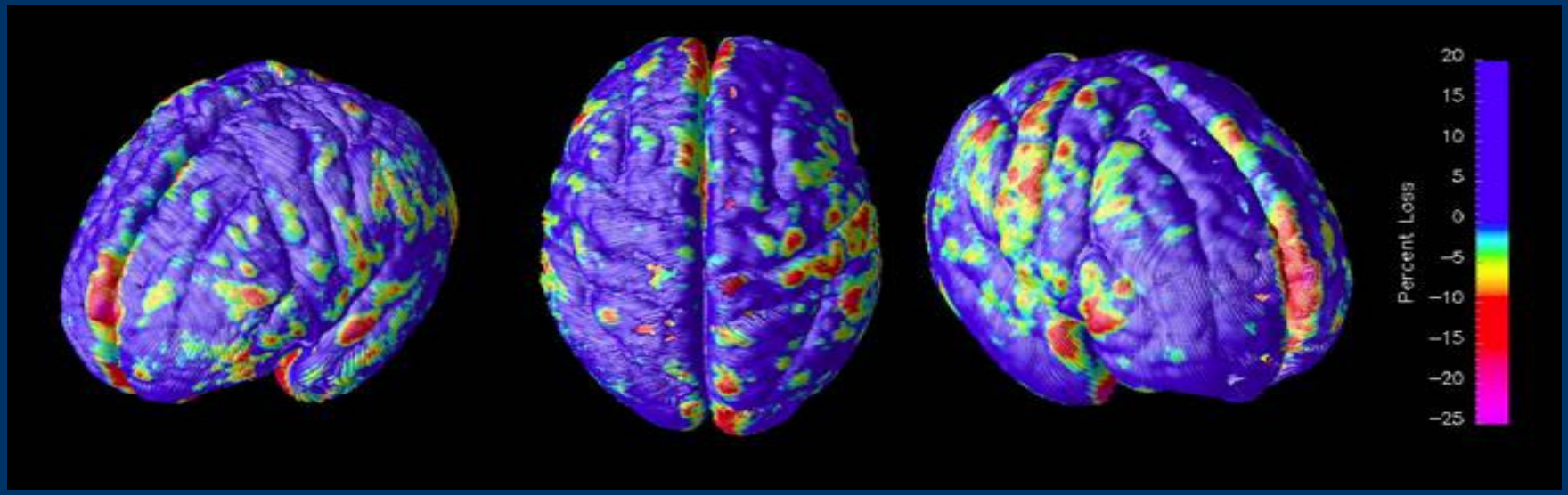
- GABA
- Glutamate

Other theories of depression

- Depression is a consequence of immune activities such as cytokine abnormalities

Morphological alterations

- ↓ hippocampal volume (Neumeister et al, 2005)
- ↓ gray matter volume in frontal cortex, ↓ amygdala (Kugaya et al, 2003)



Genetic Factors

Heritability estimate = 33-42%

Heritability is much higher for women than men (Kendler, 2001)

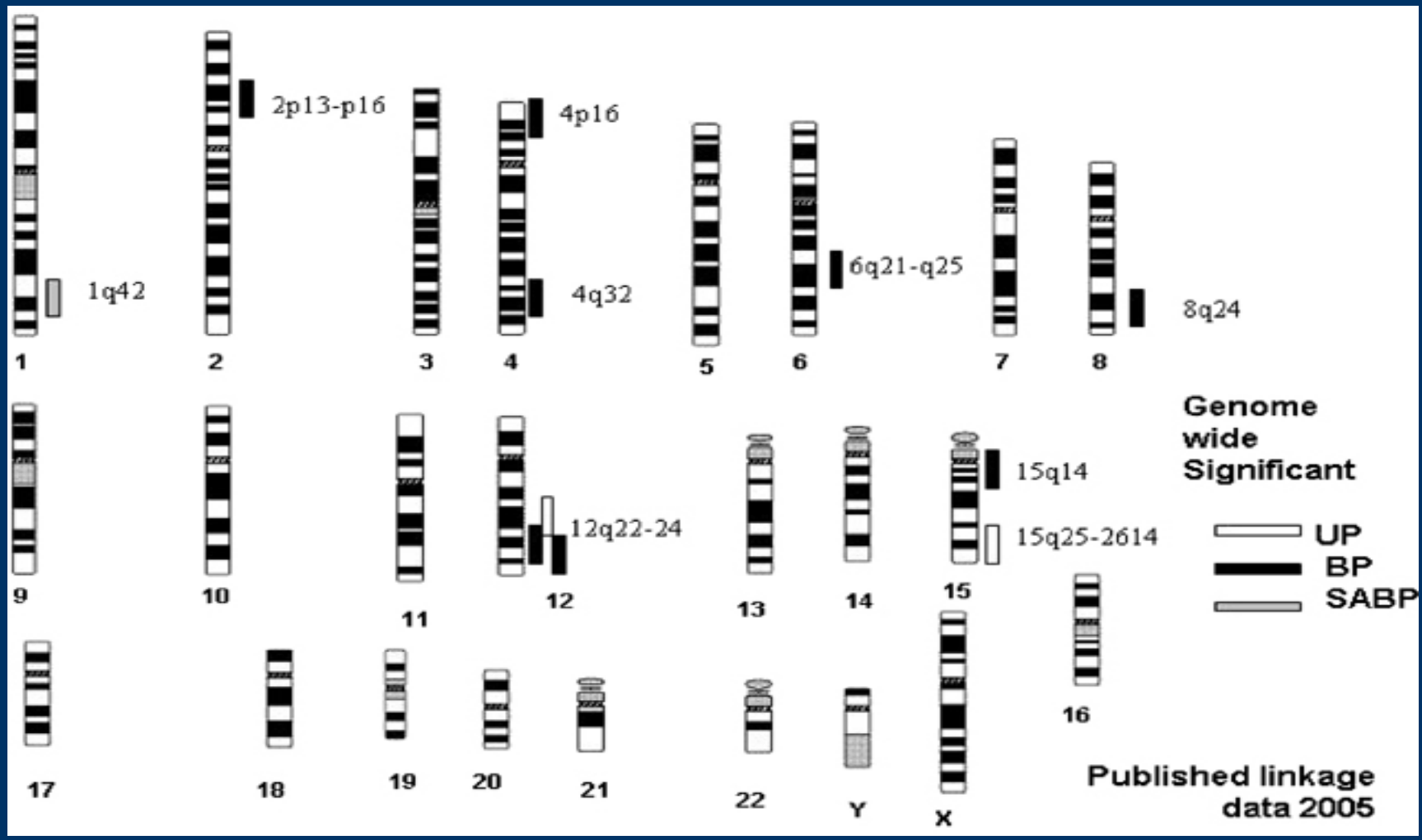
- Serotonergic genes may regulate amygdala's role in depression

Dannlowski et al, 2006

- Measured amygdala's response to happy or sad faces
- Found genetic susceptibility to Depressio based on dysfunctions in emotional processing

Significant linkages for mood spectrum disorders

UP, Unipolar Depression; BP, Bipolar; SABP, Schizoaffective disorder, bipolar type



Craffock and Forty, 2006

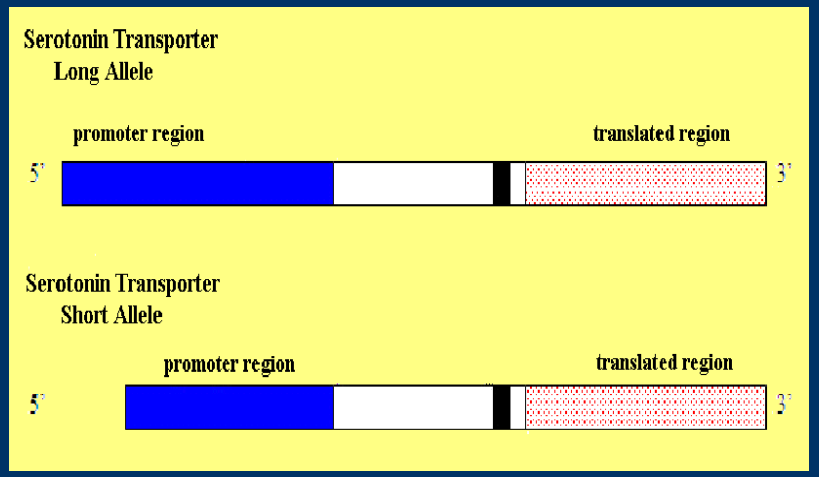
Monoaminergic candidate genes for depression

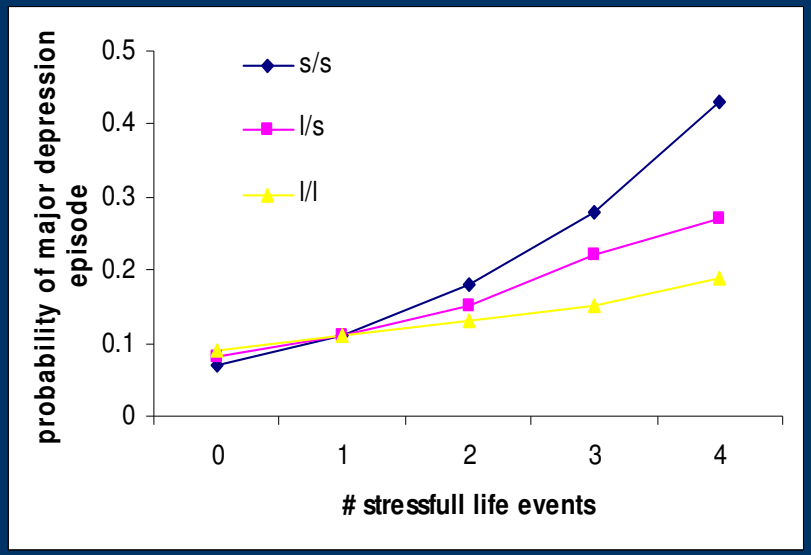
- SERT
- 5HT2A receptor
- Tyrosine hydrolase (limiting enzyme for DA synthesis)
- Tryptophan hydrolase (for 5HT synthesis)
- COMT (for DA catabolism)
- BDNF

Genetic x environmental factors

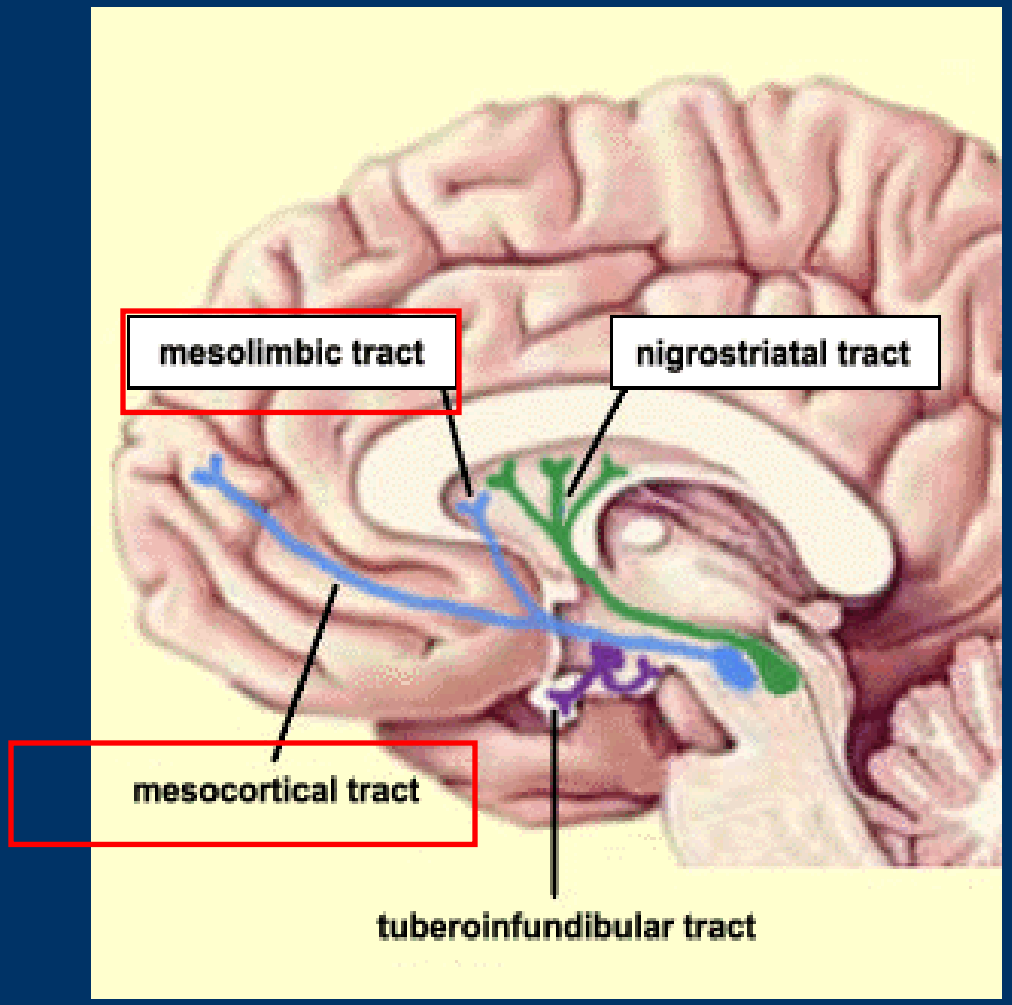
SERT

Stressful life events and the number of short 5-HTTLPR alleles (l/l, l/s, or s/s) predicts occurrence of depression (Caspi et al, 2003)

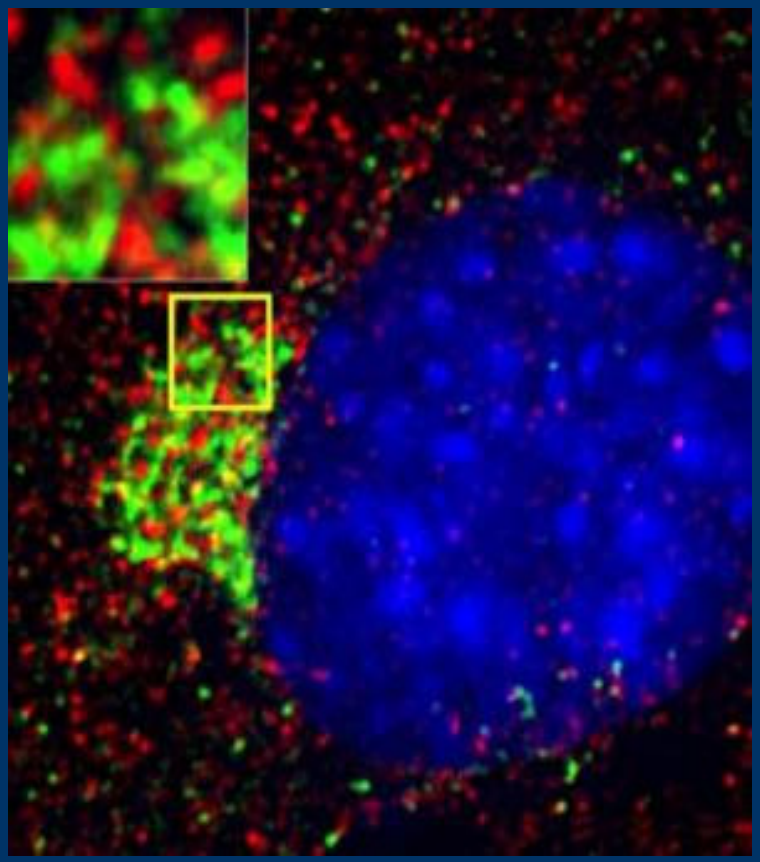




Neural Circuits



Neurotrophic factors



- Antidepressants return BDNF to normal levels
- ↓ BDNF in depressed patients
- Growth factors may modulate depression through regulation of neuronal plasticity (Castren et al, 2007) => memory?

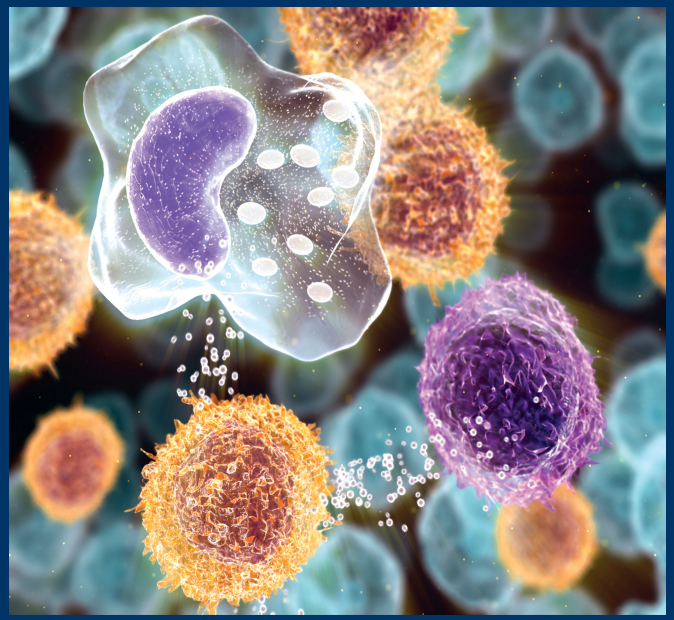
Role of cytokines in depression

Sickness behavior

- Behavioral changes that develop in sick individuals during/after infection
- motivational state that reorganizes the organism priorities to cope with infections

Statistics

- Depressed persons: general population = 3-5%.
- In population with chronic inflamation = 12-30%



Link between sickness behavior and depression

Chronic immune activation associated with depression

1) Immunotherapy
2) Somatic disorders with inflammatory component
3) Aging

The macrophage theory of depression (Maes et al, 1993)

Hormones

Steroid hormones (e.g. Corticoids)

- depressed patients had significantly greater cortisol, 11-deoxycortisol, androstenedione and 17 a-hydroxyprogesterone responses (Gehris et al., 1991)

Adrenocorticotropic hormone (ACTH)

- important player in the hypothalamic-pituitary-adrenal axis

Estradiol

- The higher rates of depression in women disappear after menopause, suggesting important of interactions among estrogens, serotonin, and mood

Drugs

Selective serotonin reuptake inhibitors (SSRIs)

Monoamine Oxidase Inhibitors (MAOI's)

Tricyclics

Herbs and nutrients (e.g., bananas, pasta)

Agatha Cristi's method

Other potential remedies

Electroconvulsive Therapy (ECT)

A modern ECT unit

- **ECT alleviates symptoms through changes in blood flow and GABAergic neurotransmission**
- ↑ blood perfusion in cortex
- ↑ benzodiazepine receptor uptake in cortex

Cognitive-behavioral therapy

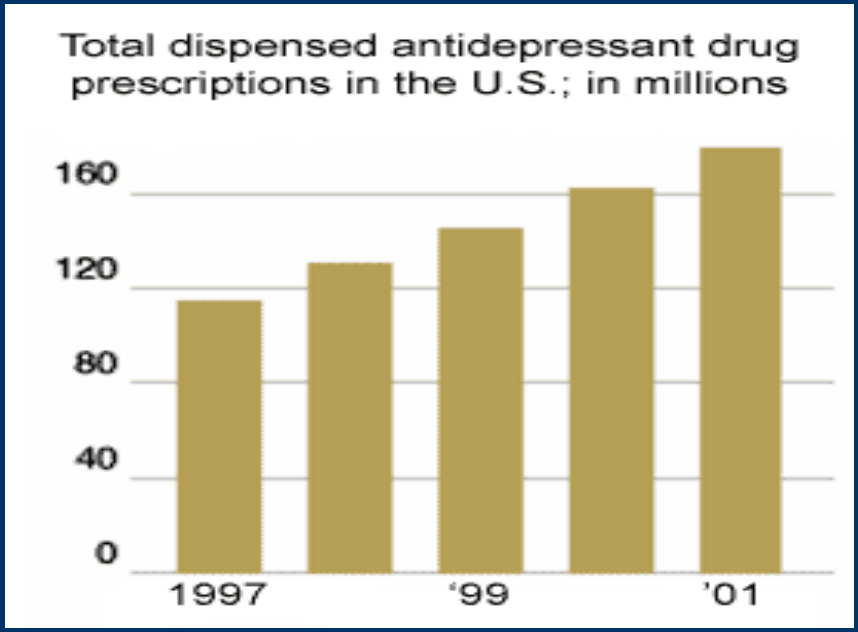
Exercise

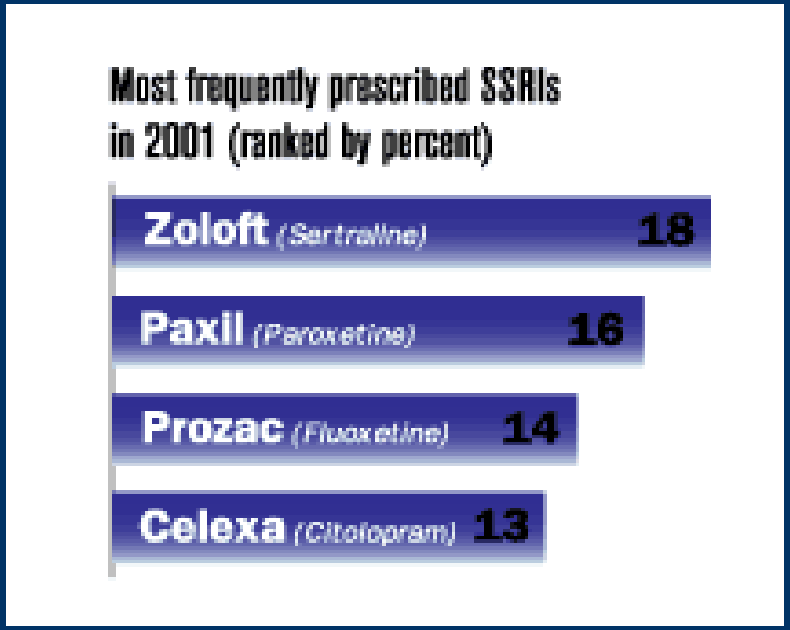
Exercising groups show lower depression scores than non-exercising groups (Legrand and Heuze , 2007)

Exercise may be roughly as effective as antidepressant treatments (Blumenthal et al, 2007)

Antidepressant use on the rise

- Adult use of antidepressants tripled between the periods 1988-1994 and 1999-2000
- Of the 2.4 billion drugs prescribed in 2005, 118 million were for antidepressants





Side effects of antidepressants

- Dry mouth
- Urinary retention
- Blurred vision
- Constipation
- Sedation
- Sleep disruption
- Weight gain
  Headache
- Anxiety
- Nausea
- Gastrointestinal disturbance/diarrhea
- Abdominal pain
- Sexual dysfunction
- Agitation
- Suicides
- Serotonin toxicity

Sex differences in anxiety and depression

•Adolescent females are significantly more likely to experience low to moderate levels of depression and anxiety than adolescent males.

•Some factors stem from reproductive differences, such as post-partum depression or menopausal alterations in mood/hormones.

•Women are 2-3 times more likely to develop PTSD after a traumatic episode than men

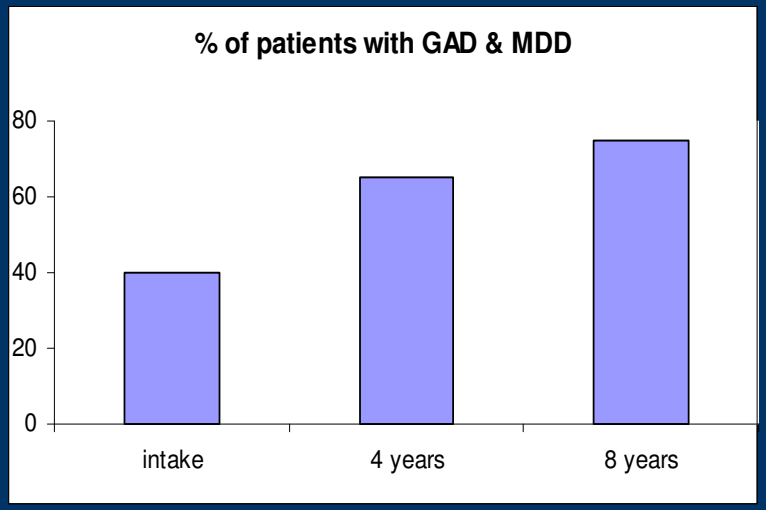
•Women are twice more likely to be diagnosed with depression

•Generalized Anxiety Disorder (GAD) and PTSD occur twice as frequently in women as in men

(Afifi, 2000; Halbreich and Kahn, 2007)

Comorbidity: anxiety and depression

- Comorbidity of anxiety and depression: up to 60-70%
- Anxiety and depression have common genetic origins (Kendler et al., 1992, 1996)
- Patients with both disorders show more impairment than those with only one
- Comorbidity lowers chances of remission from either depression or anxiety (Sherbourne and Wells, 1997).

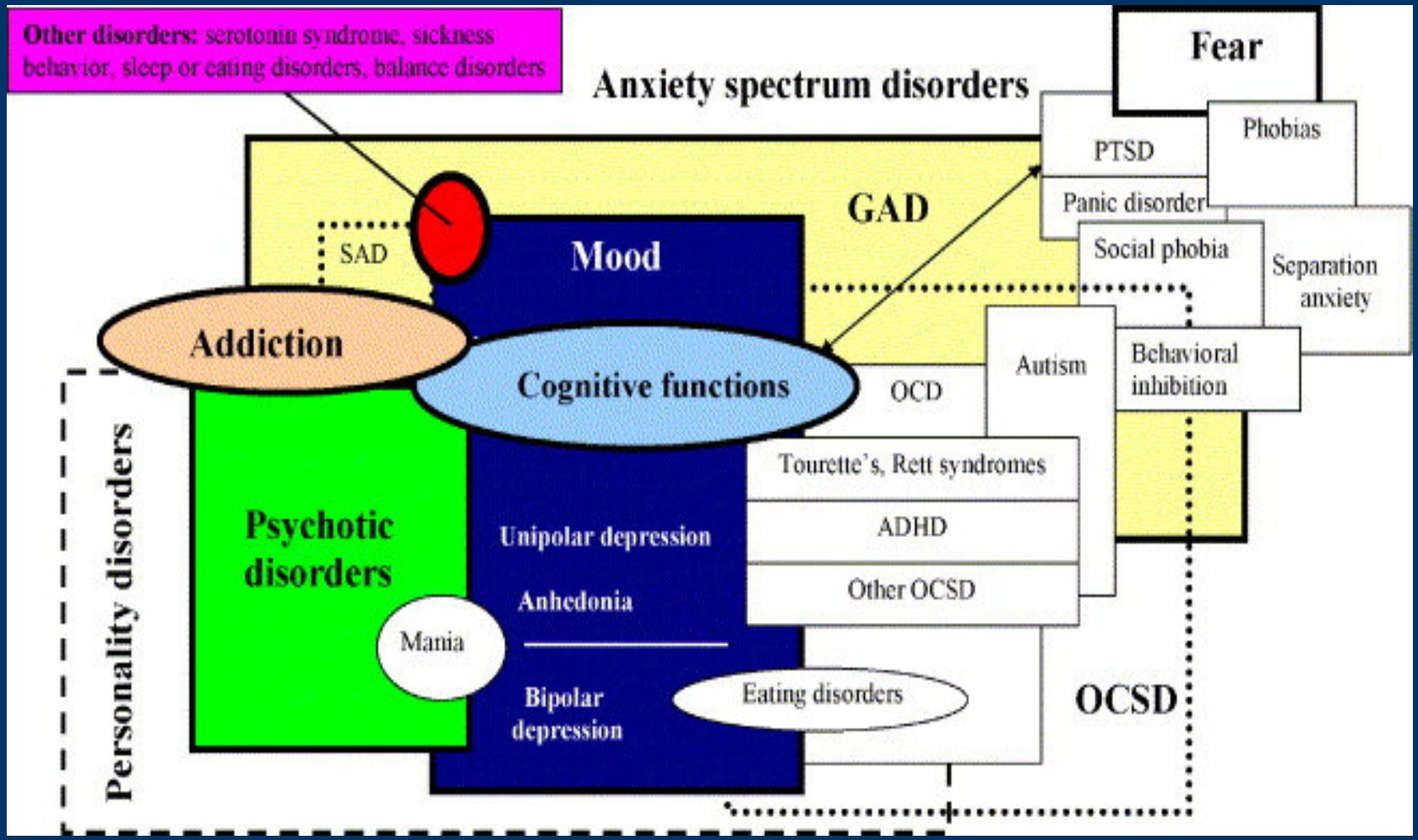


Bruce et al., 2001

Comorbidity with other disorders

- Eating disorders
- Irritable bowel syndrome
- Substance abuse
- Asthma (with comorbid anxiety and depressive disorders)
- Tourette's syndrome
- Compulsive behaviors
- Schizophrenia
- Autism
- Epilepsy
- Cognitive/memory deficits
- Neurodegenerative disorders

Comorbidity with other disorders



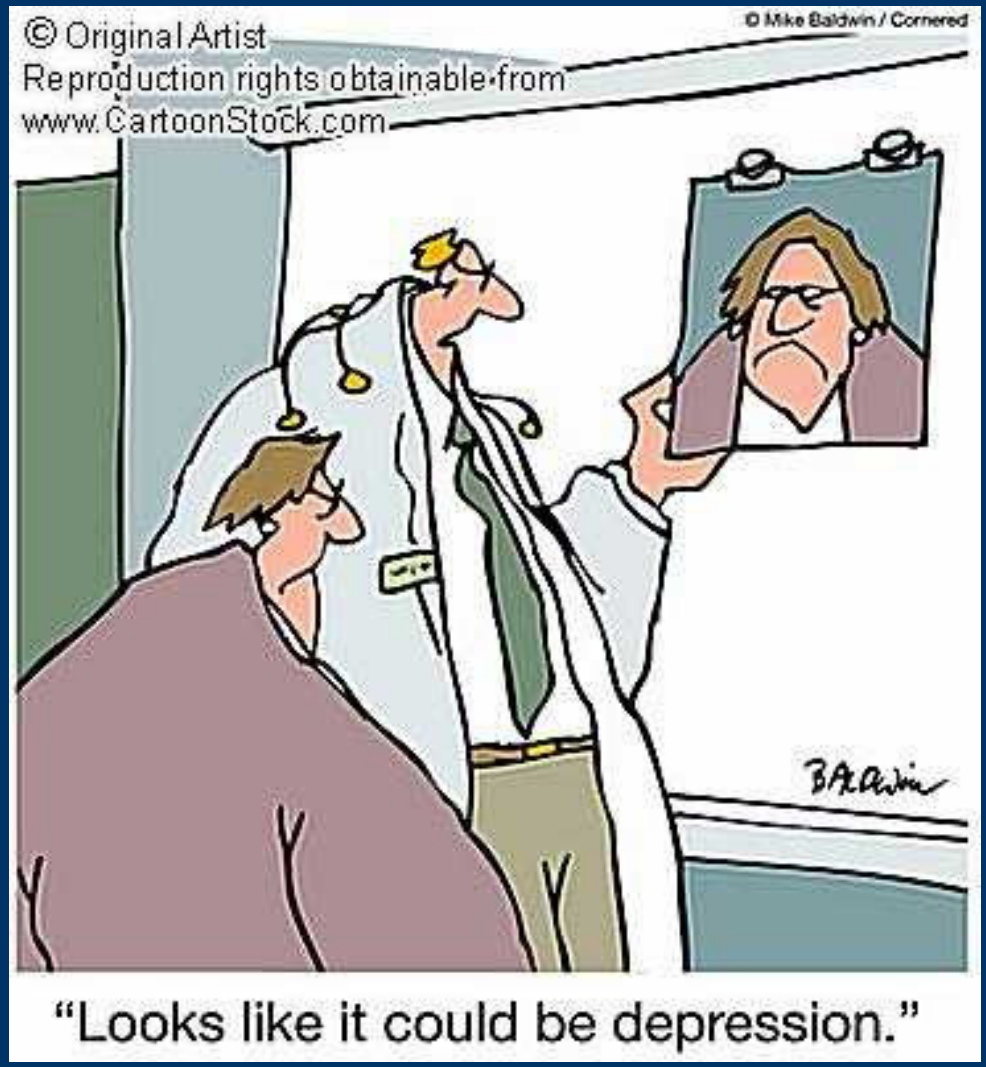
Kalueff et al., 2007

Depression and Art:
Sergey Rakhmaninov (1873-1943)

First Symphony (1895):
Overcoming personal blues

Summary

- Affective Disorders (AD), such as depression, are perhaps the most serious brain disorders
- Precipitated by stress
- AD represent a complex spectrum of overlapping brain disorders, particularly with anxiety
- Substantial commonality of brain genetic, molecular and behavioral mechanisms
- Not fully clear causes
- Can be modeled in animals
- Creativity helps!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BAldwin
"Looks like it could be depression."