Depression and Anxiety

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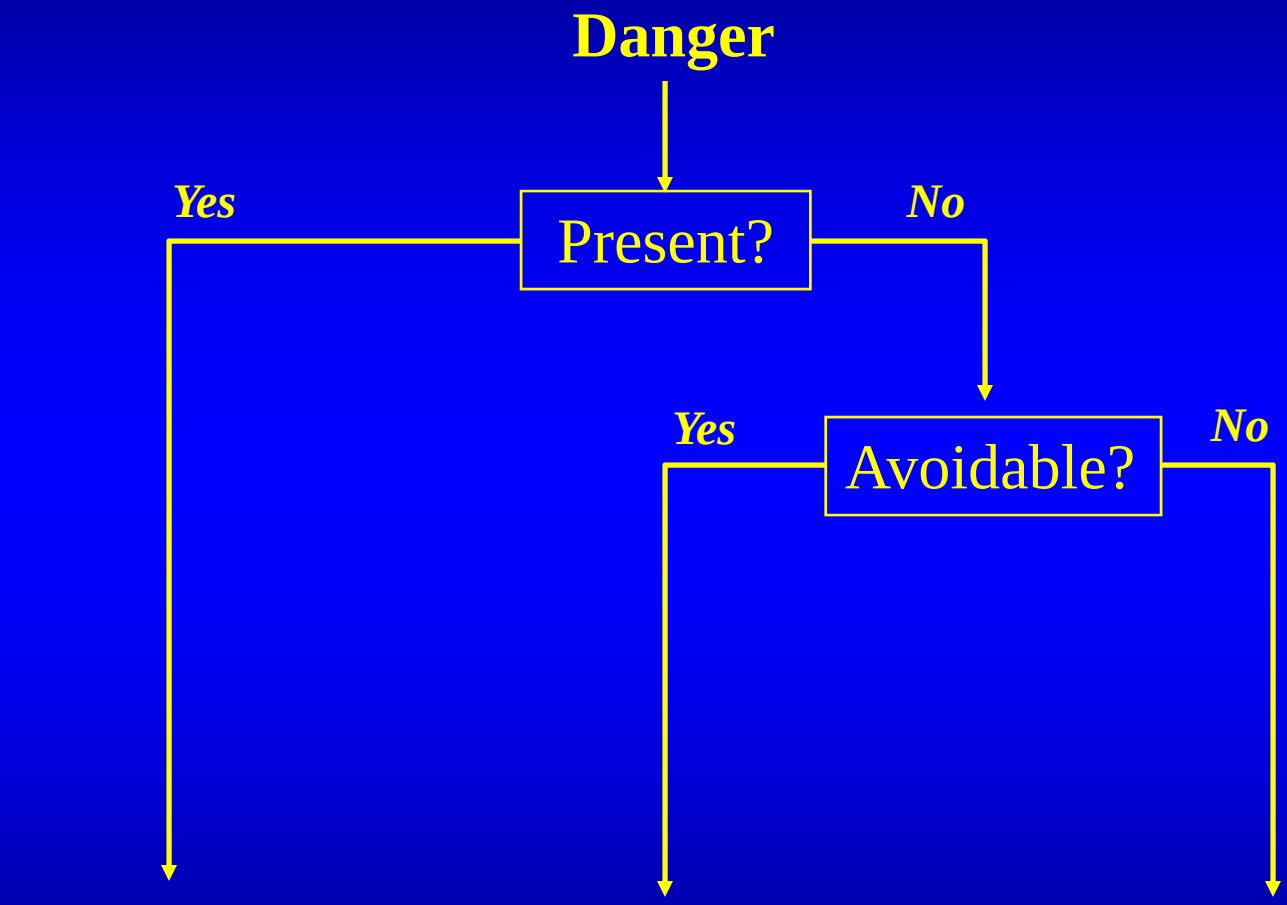
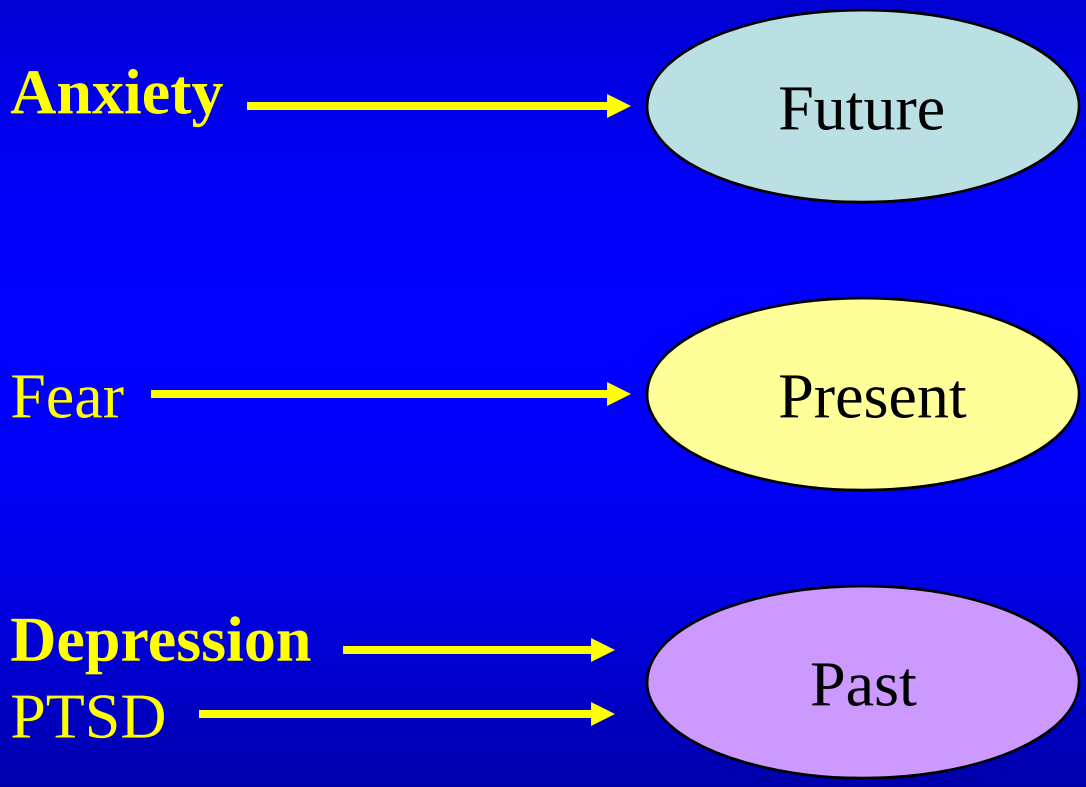
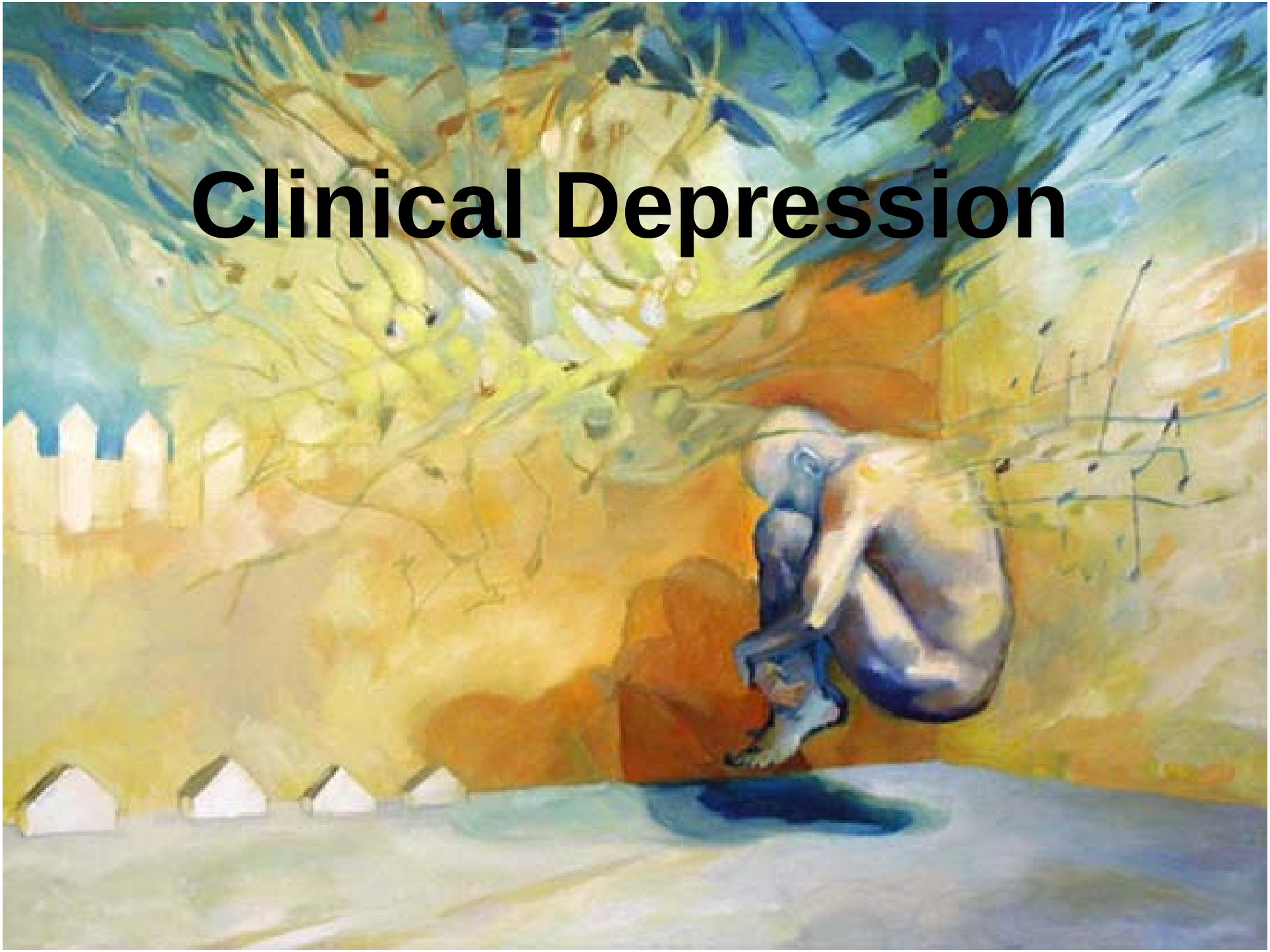
Depression and Anxiety



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, nervousness, helplessness, 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 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

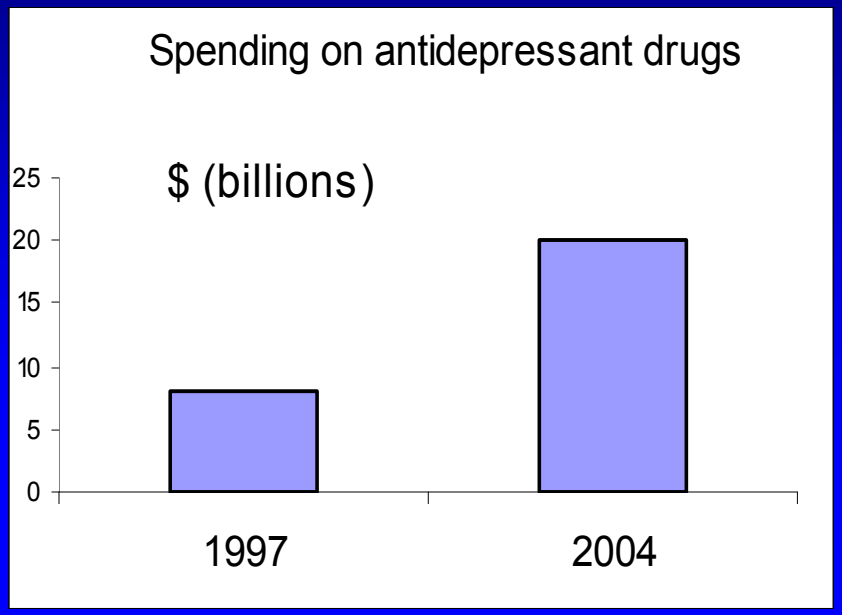
- **Unspecified Depression:**
  people with a serious depression, but not quite severe enough to have a diagnosis of a major depression
  people with chronic, moderate depression, which has not been present long enough for a diagnosis of a Dysthymic disorder

- **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

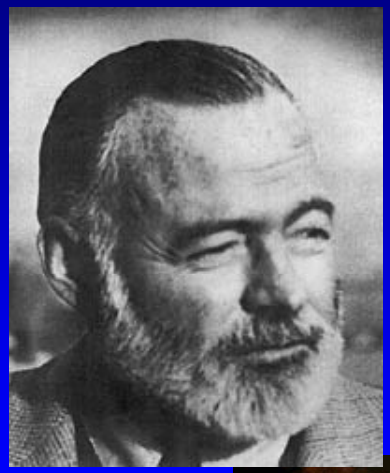
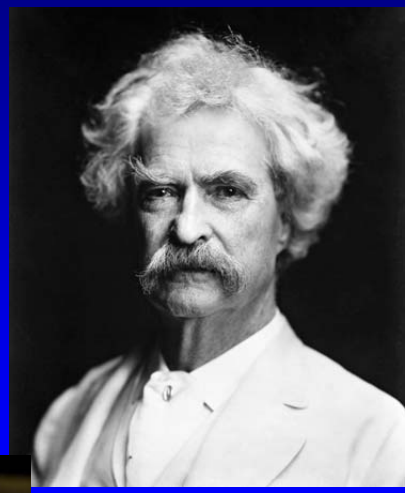
Statistics

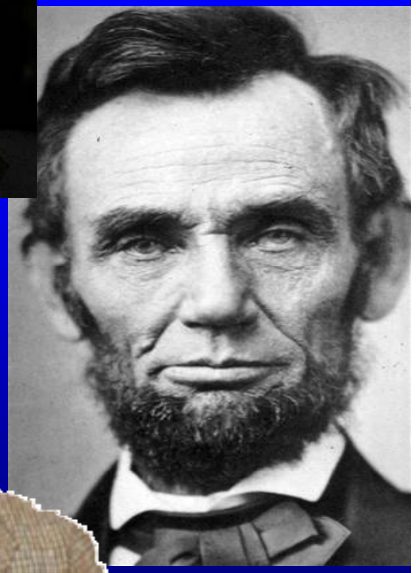
- Spending on antidepressants jumped 150% from 1997 to 2004
- Affect approximately 18.8 million American adults
- 9.5% of the US adult population
- 15% of the population of most developed countries suffers severe depression
- 15% of depressed people will commit suicide
- The World Health Organization forecasts depression will be the second largest killer after heart disease by 2020
- Nearly two-thirds of depressed people do not get proper treatment

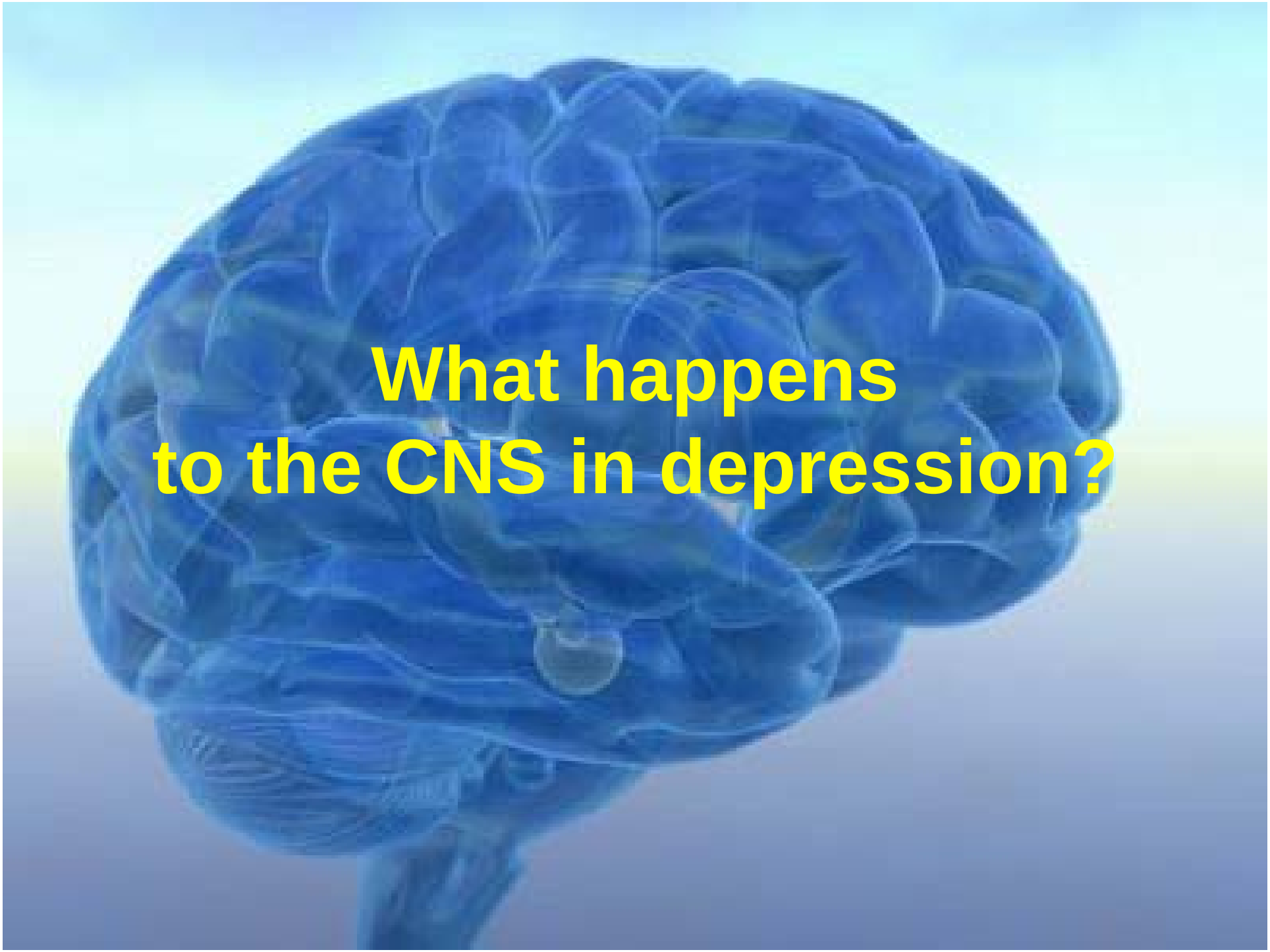


Persons of note with depression

- 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

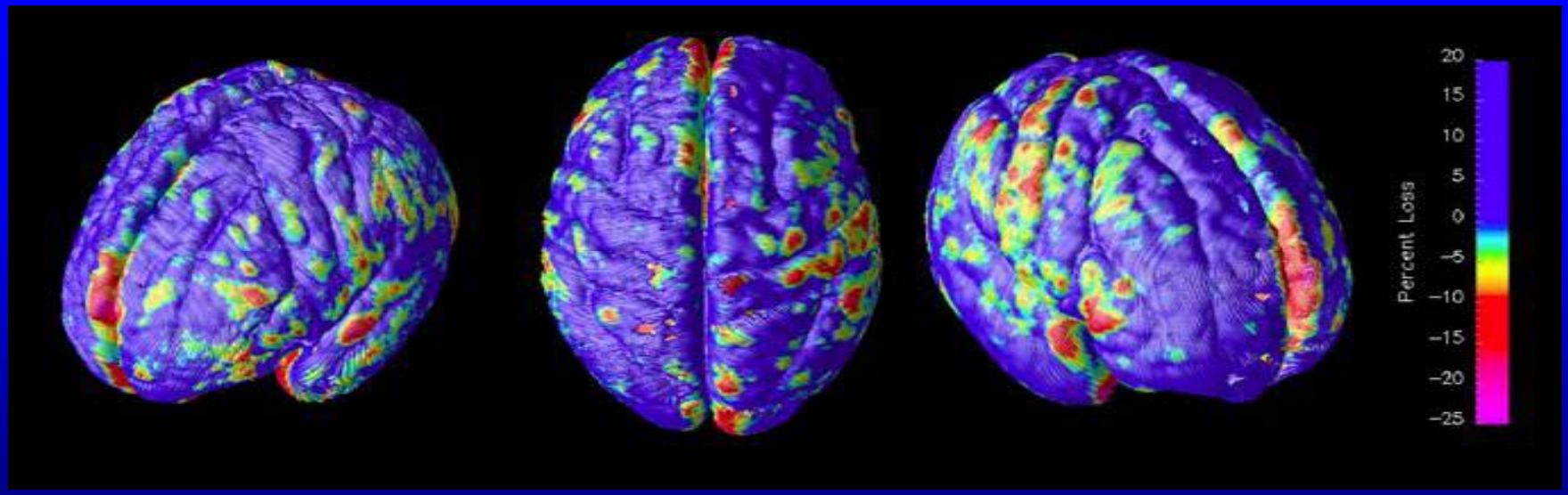
- GABA
- Glutamate

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)

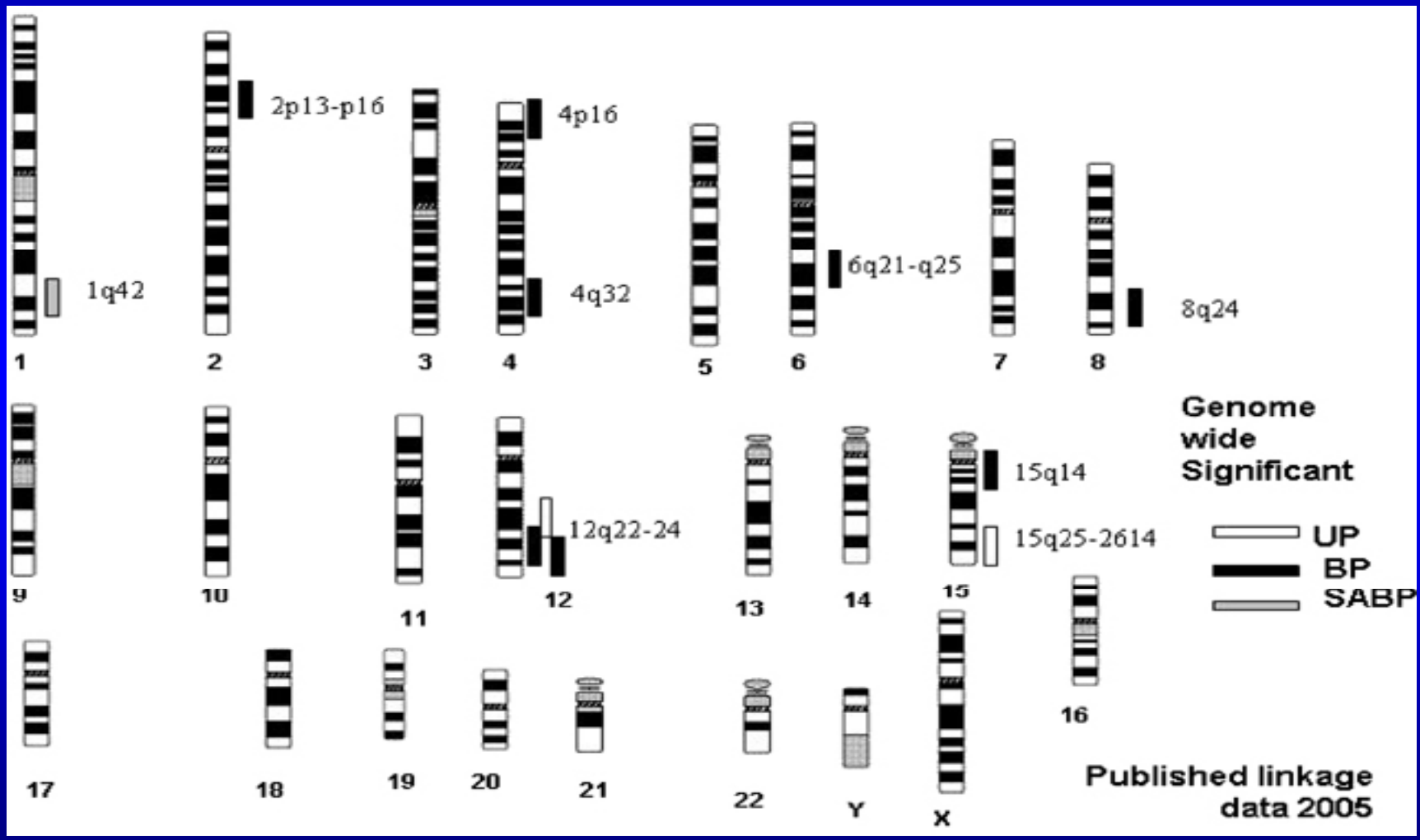
- Serotonergic genes may regulate amygdala's role in depression

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

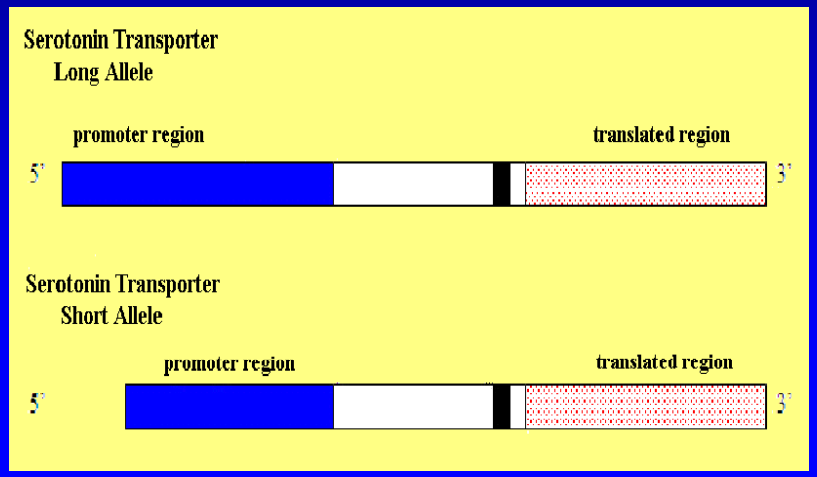
Monoaminergic candidate genes for depression

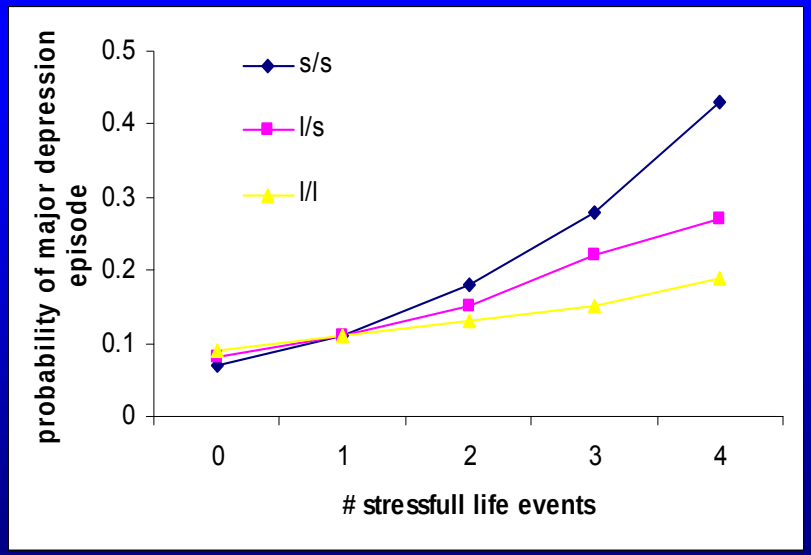
- SERT
- 5HT2A receptor
- Tyrosine hydrolase (limiting enzyme for DA synthesis)
- Tryptophan hydrolase (for 5HT synthesis)
- COMT (for DA catabolism)
- BDNF

Genetic x environmental factors

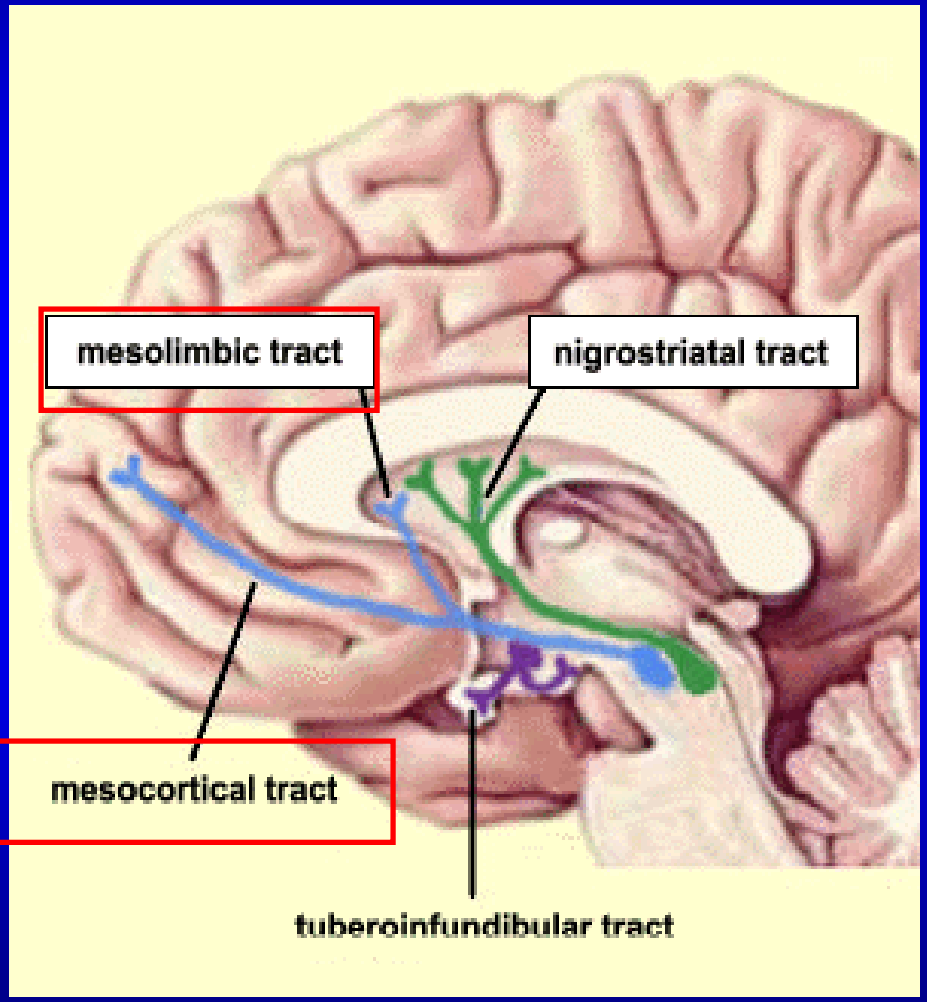
SERT

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)

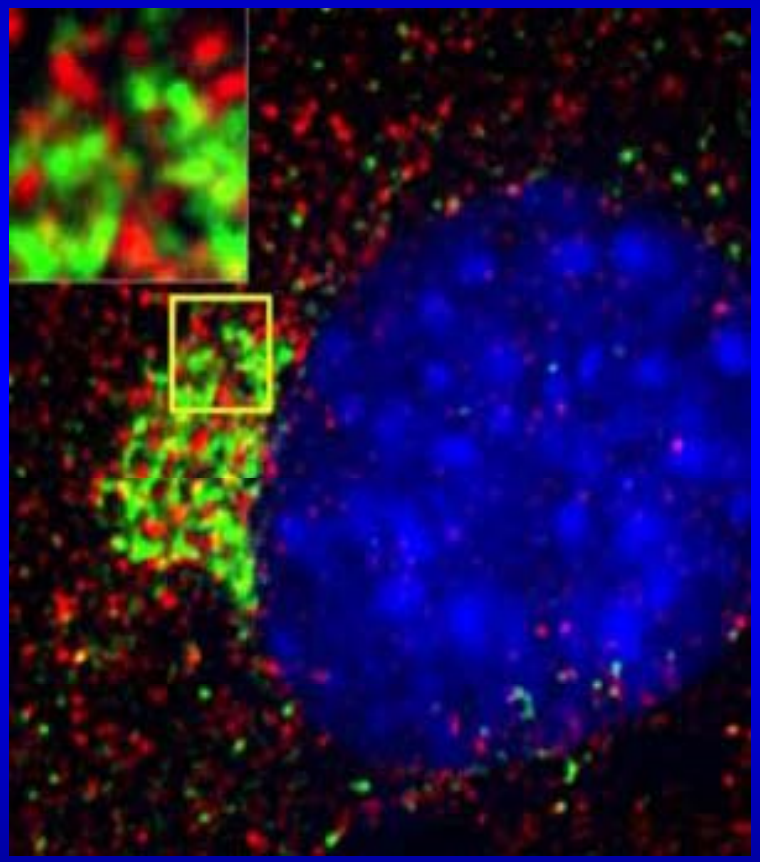




Neural Circuits



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?

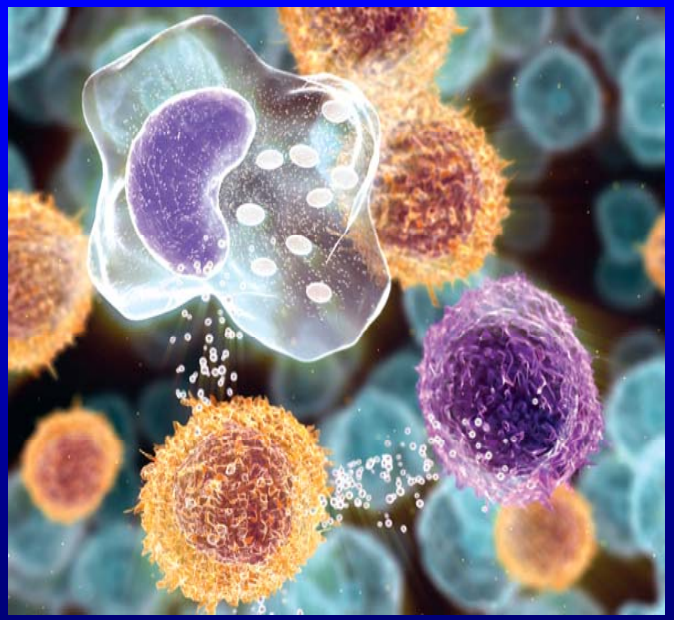
Role of cytokines in depression

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

Treatments

"Snap out of it."

Drugs

Selective serotonin reuptake inhibitors (SSRIs)

- citalopram (*Celexa, Cipramil, Emocal, Sepram, Seropram*)
- escitalopram oxalate (*Lexapro, Cipralex, Esertia*)
- fluoxetine (*Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR)*)
- fluvoxamine maleate (*Luvox, Faverin*)
- paroxetine (*Paxil, Seroxat, Aropax, Deroxat, Rexetin, Xetanor, Paroxat*)
- sertraline (*Zoloft, Lustral, Serlain*)
- Dapoxetine

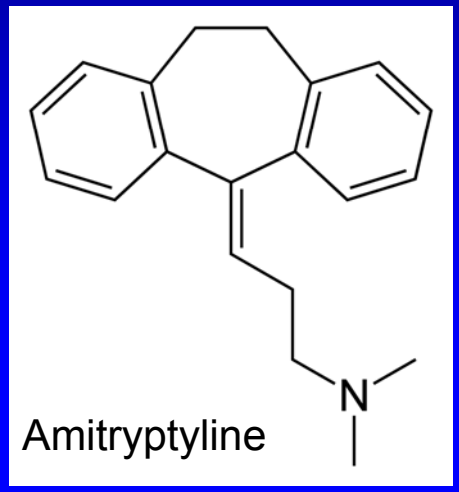
Monoamine Oxidase Inhibitors (MAOI's)

- Isocarboxazid *(Marplan)*
- Moclobemide *(Aurorix, Manerix, Moclodura®)*
- Phenelzine *(Nardil)*
- Rasagiline *(Azilect)*
- Nialamide
- Iproclozide
- Toloxatone
- Tranylcypromine

Drugs

Tricyclics

- Amitriptyline *(Elavil, Endep, Tryptanol, Trepiline)*
- Amoxapine *(Asendin, Asendis, Demolox, Moxadil)*
- Clomipramine *(Anafranil)*
- Desipramine *(Norpramin, Pertofrane)*
- dothiepin hydrochloride *(Prothiaden, Thaden)*
- lofepramine (Gamanil)
- Nortriptyline (Pamelor)
- Opipramol (Opipramol-neuraxpharm, Insidon)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)



Amitryptyline

Herbs and nutrients

- St John's Wart
- Phenylalanine
- tyrosine
- tryptophan
- 5-Hydroxytryptophan
- choline


St John's Wart

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

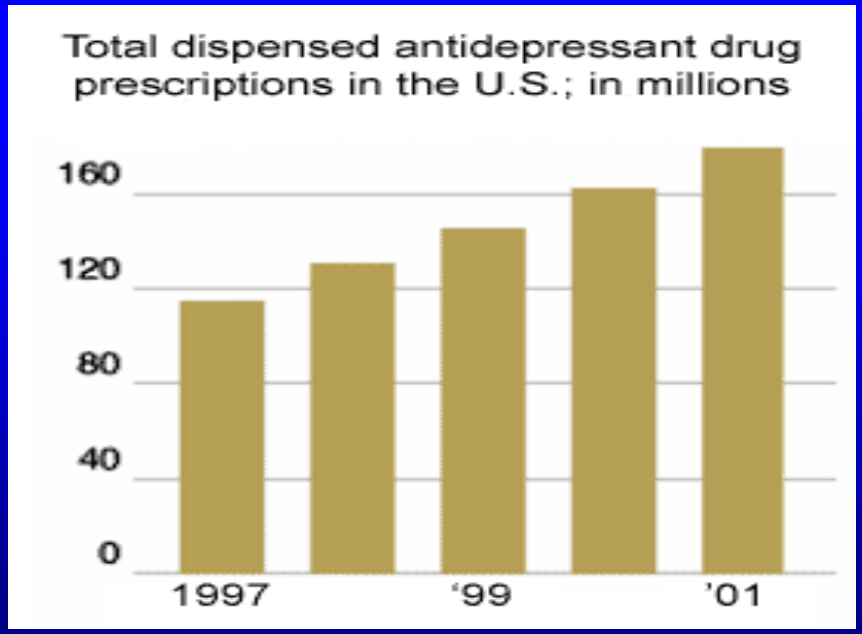
Exercise

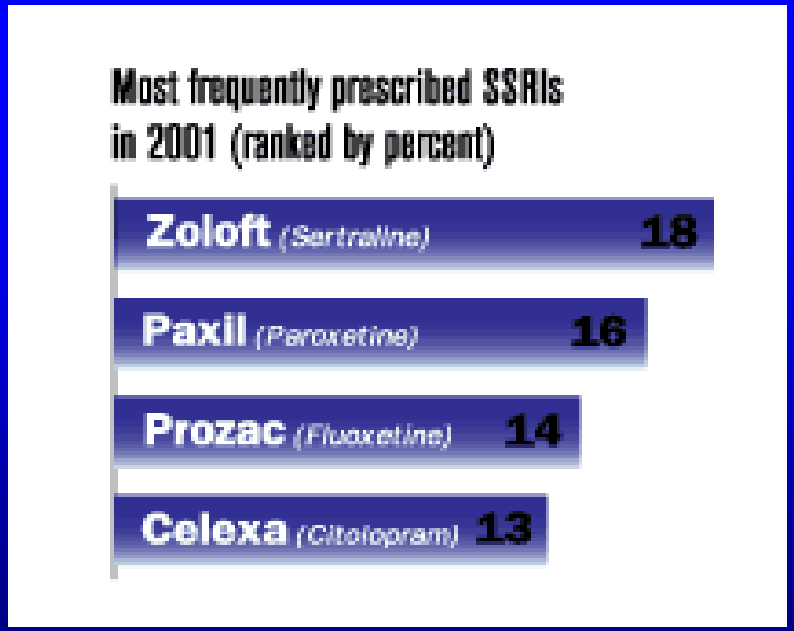
Exercising groups show lower depression scores than non-exercising groups (Legrand and Heuze , 2007)

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

Antidepressant use on the rise

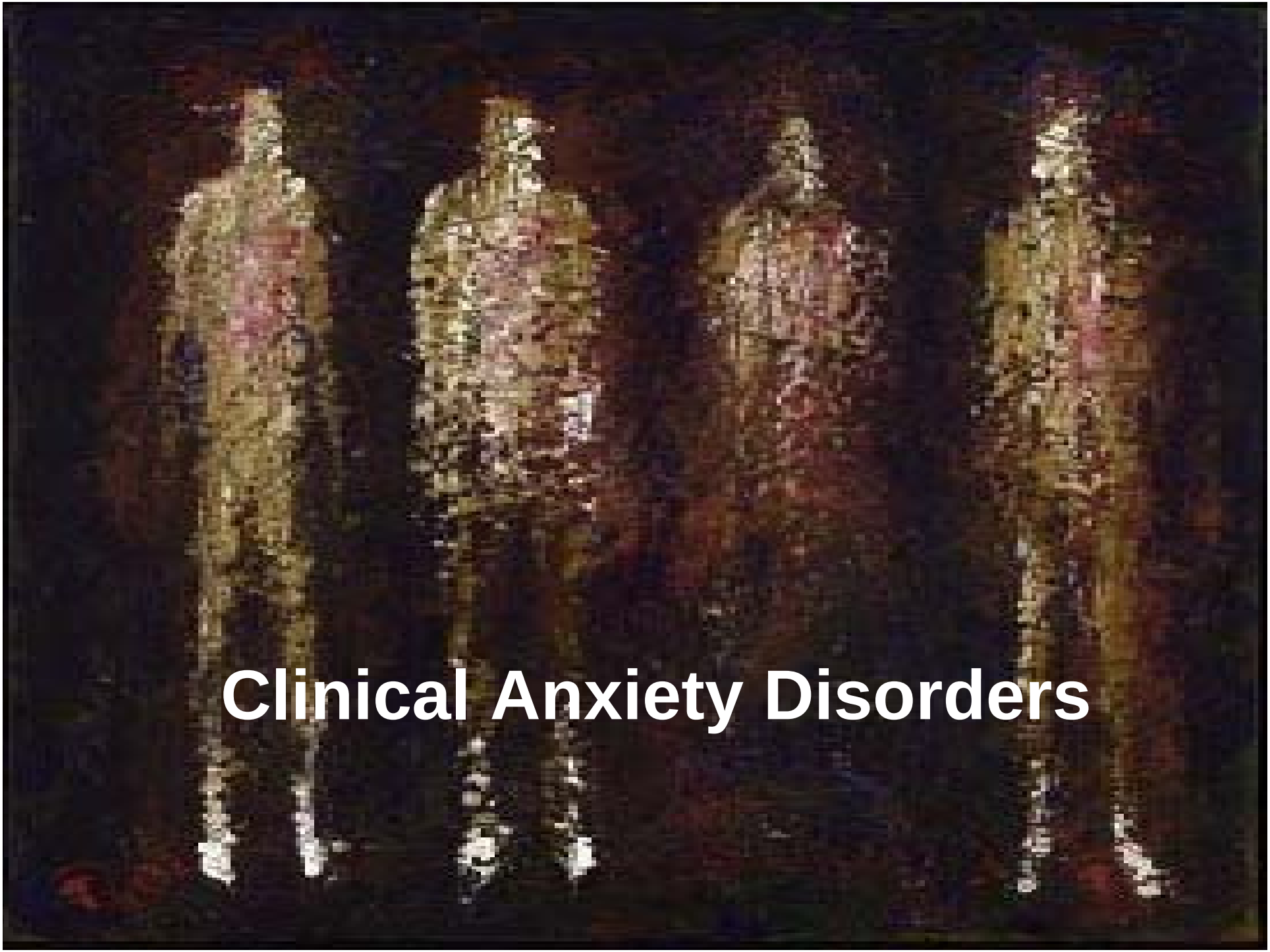
- Adult use of antidepressants tripled between the periods 1988-1994 and 1999-2000
- Of the 2.4 billion drugs prescribed in 2005, 118 million were for antidepressants





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


Clinical Anxiety Disorders

Subtypes of anxiety

- **Panic disorders** with or without agoraphobia
- **Phobias**, including specific phobias and social phobia
- **OCD:** unwanted, intrusive, persistent thoughts or repetitive behaviors. Affects between 2-3% of the population
- **Stress disorders:** post-traumatic stress disorder (PTSD) and acute stress disorder
- **Generalized anxiety disorder (GAD).** The most commonly diagnosed anxiety disorder, occurs most frequently in young adults
- **Anxiety disorders due to known physical causes** (medical conditions or substance abuse)
- **Anxiety disorder not otherwise specified:** ???

Diagnosis

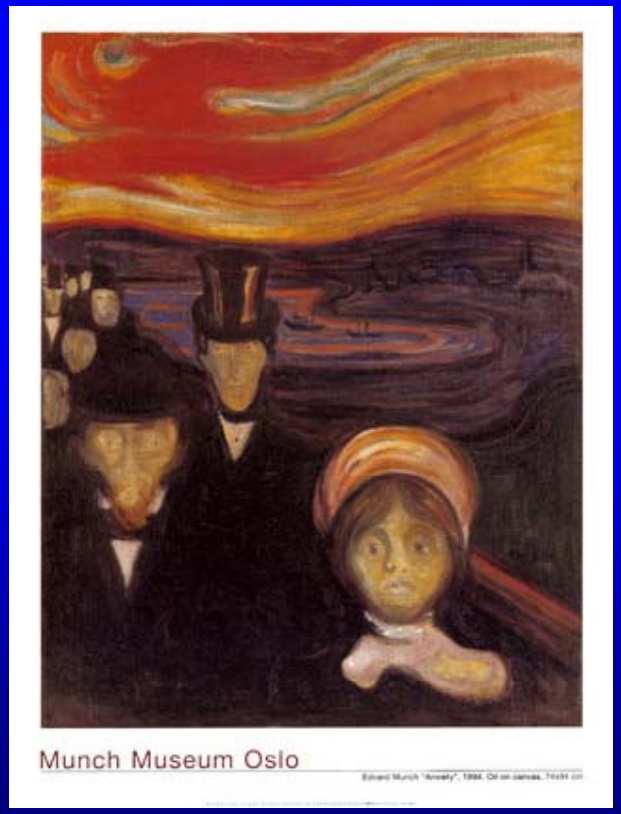
To better differentiate between GAD and other anxiety or depressive disorders, 4 “first rank” and at least 1 “second rank” symptoms are needed

<u>First</u>

- Inability to relax, restlessness
- Fatigueability
- Exaggerated startle response
- Muscle tension
- Sleep disturbances
- Difficulty in concentrating
- Irritability

<u>Second</u>

- Nausea or abdominal complaints
- Dry mouth
- Tachycardia
- Tremor



Statistics of anxiety disorders

- The most common mental illness in the US
- 40 million (18%) of the adult US population affected
- Cost $ 42 billion a year
- People with anxiety are 6 times more likely to be hospitalized for psychiatric disorders than non-sufferers
- Commonly co-occur with other mental or physical illnesses, including alcohol or substance abuse
- The lifetime prevalence of Anxiety Disorders is 25%

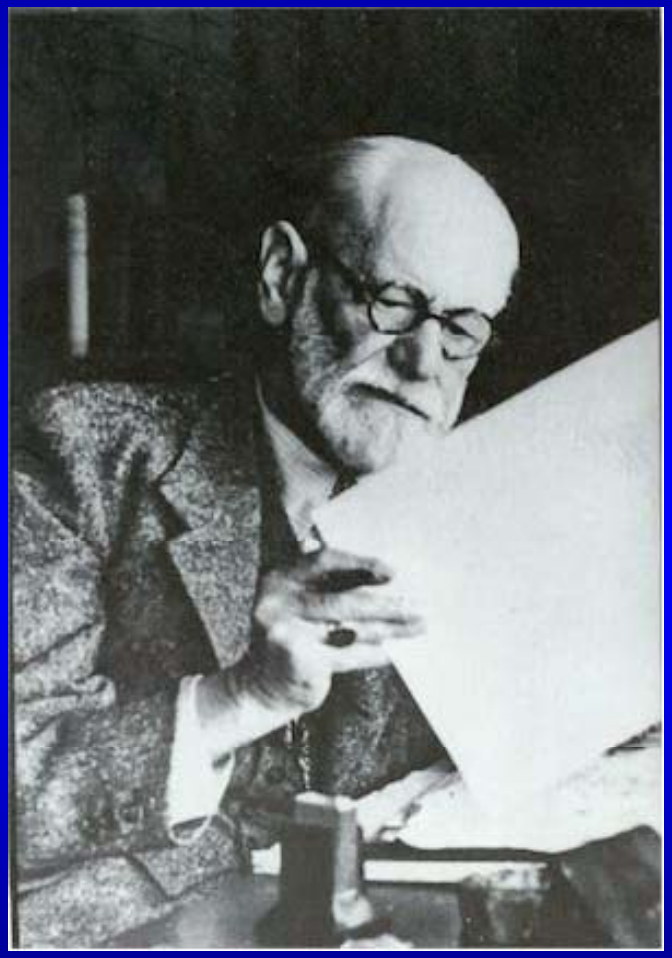
Sigmund Freud

- thought anxiety was a product of unresolved psychosexual tension that had not been released

- Later distinguished two types of anxiety:

1) Traumatic – arising from the person being overwhelmed by stressors

2) Neurotic – anticipation of negative consequences that activates defensive processes



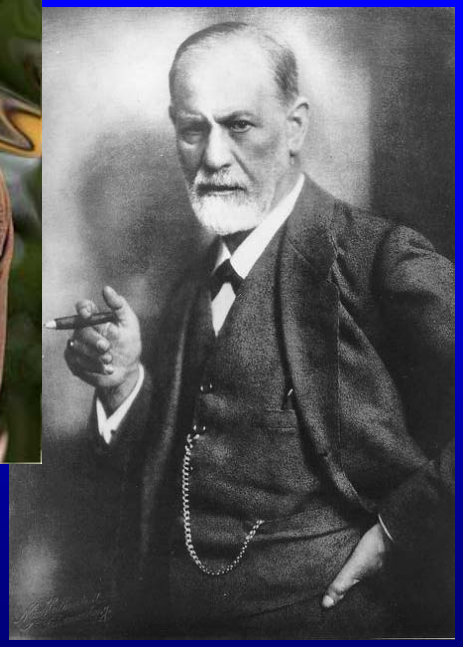
Anxiety: state vs. trait

Charles D. Spielberger

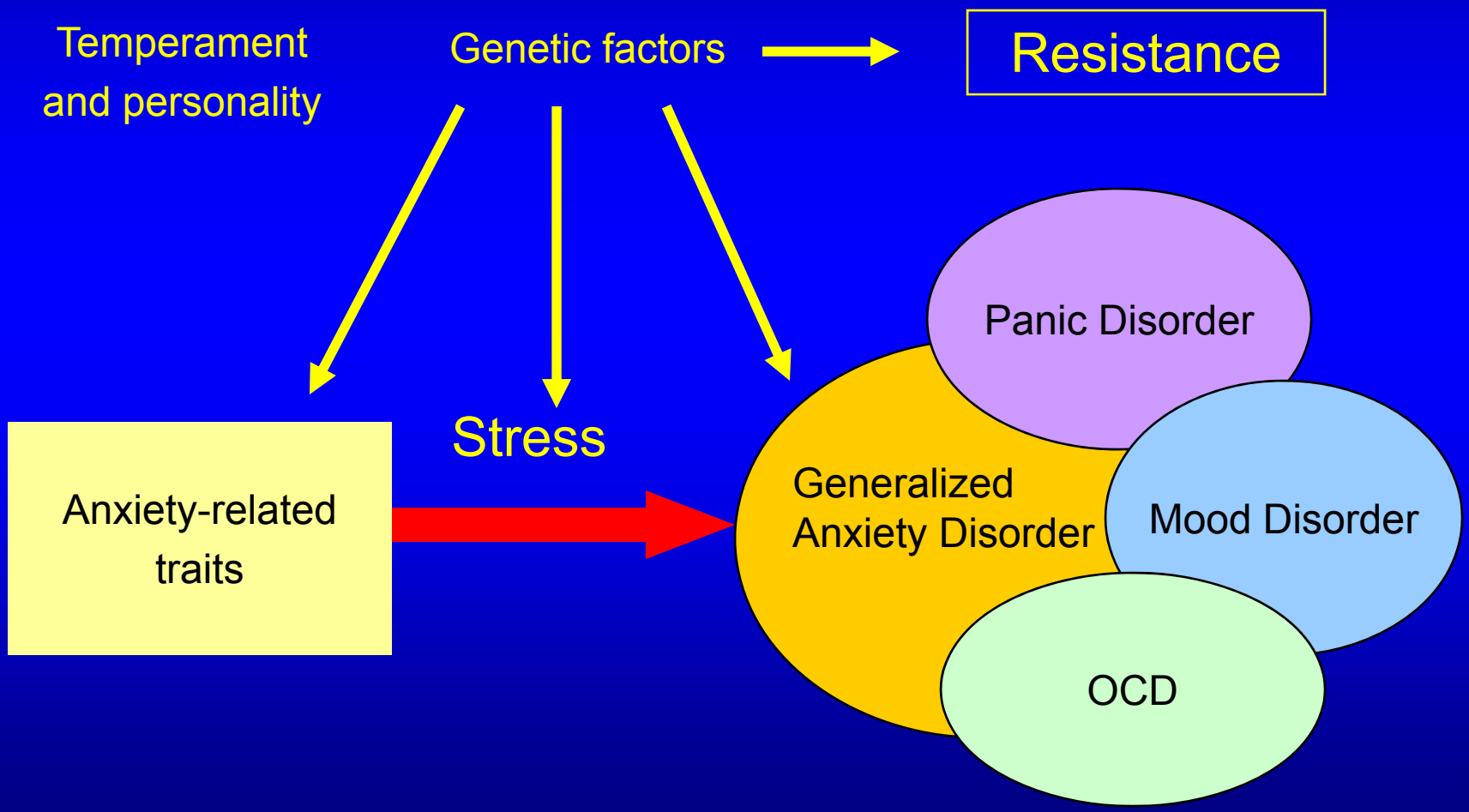
- Formulated the State–Trait Anxiety Inventory (STAI) that has been translated and adapted in 66 languages and dialects.
- state anxiety reflects a "transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity."
- trait anxiety refers to "relatively stable individual differences in anxiety proneness . . ."

Persons of note with anxiety

- Anthony Hopkins (actor)
- Barbra Streisand (singer)
- Abraham Lincoln (president)
- David Bowie (singer)
- Edvard Munch (artist)
- Eric Clapton (musician)
- Johnny Depp (actor)
- Nicholas Cage (actor)
- Nicole Kidman (actress)
- Oprah Winfrey (host)
- Sigmund Freud (psychiatrist)
- Sir Isaac Newton (scientist)



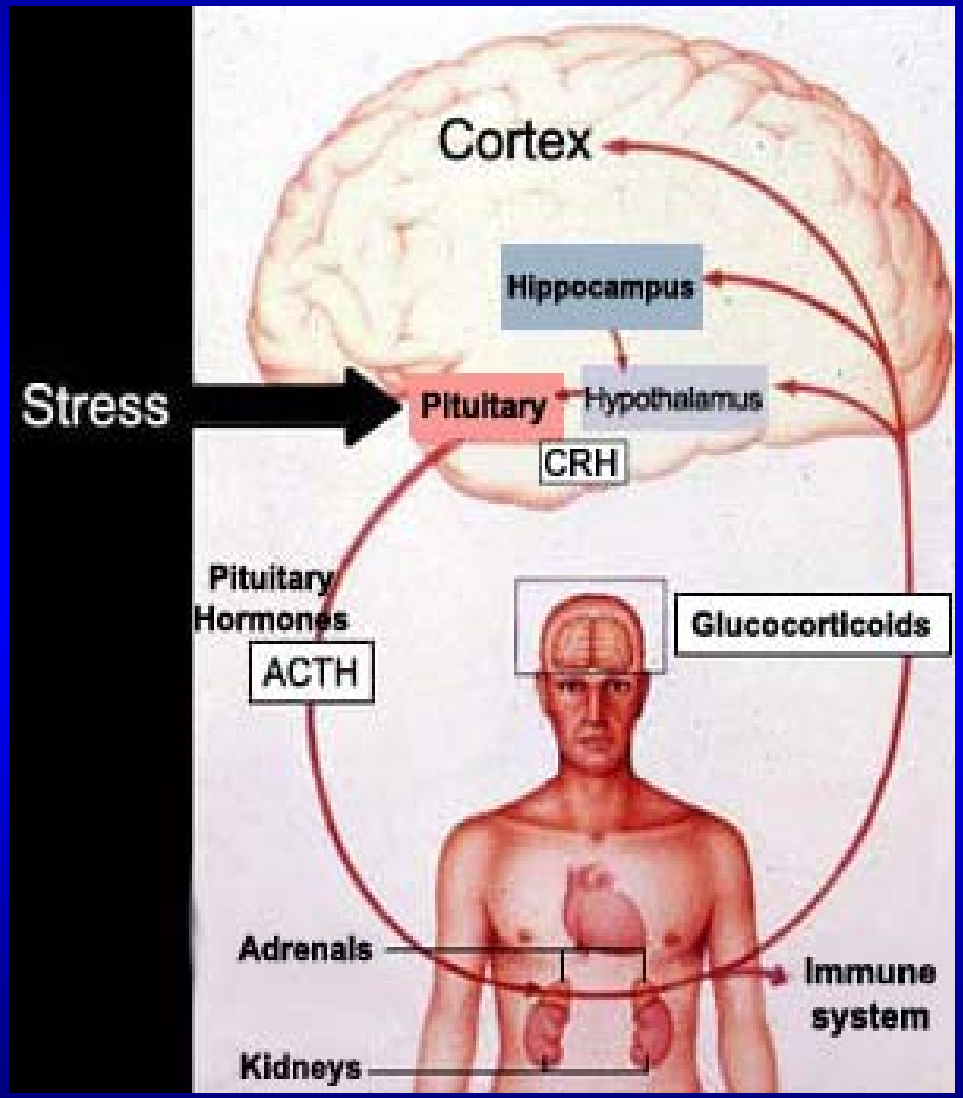
Genetics of anxiety



Anxiety is genetically determined

- Twin studies: 40-60% of variance in anxiety levels is due to genetic factors
- Twin and adopted sibling studies: both genetic and environmental factors play a role in susceptibility to anxiety
- Hints from evolutionary psychology: Possible adaptive significance of anxiety in some populations to prevent becoming socially isolated from the larger group

Circuits



- **Anxiety = stress + center + periphery**
- **Limbic system** overactivity can increase arousal and awareness of the environment, leading to symptoms of anxiety (Gray, 1983).
- **Hypothalamic-pituitary-adrenal (HPA) axis:** amygdala and BNST mediate anxiogenic behavior and HPA activation (Green et al., 2003)
- **The serotonergic system:** serotonergic drugs increase mouse anxiety in one tests and reduce in another tests: “stress trigger”? (Graeff et al., 1997).

Pathophysiology: Cytokines

- Exposure to stress (e.g., surgery) up-regulates pro-inflammatory cytokines, which are also involved in mood and memory disturbances (Shapira-Lichter et al., 2007)
- Preoperative anxiety, during the waiting weeks before cardiac surgery increase plasma levels of IL-6 (Ai et al, 2005)

Mediators and hormones

Serotonin

- Exaggerated responsiveness of presynaptic alpha$_2$ autoreceptors (Koob, 1999)

Serotonin

- Both excesses and deficiencies in serotonin can create anxiety

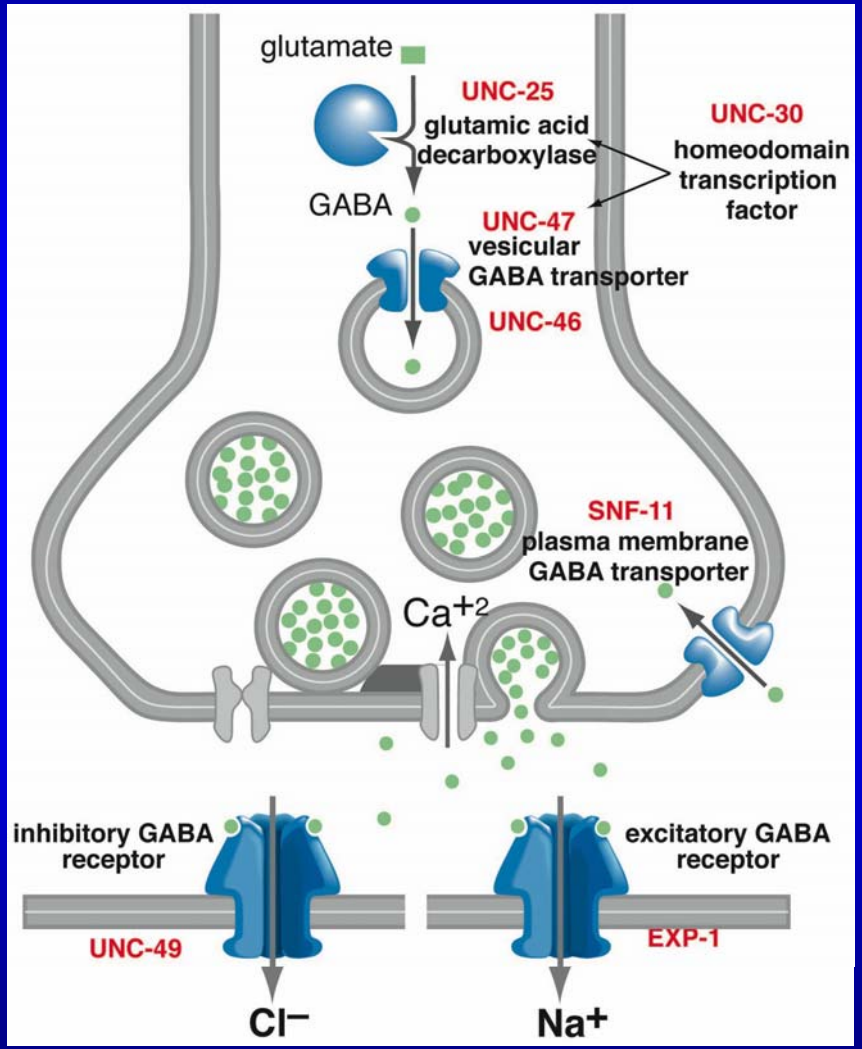
Corticosteroids

- Corticosteroids are unbalanced due to chronic stress

The role of GABA

GABAergic system: works with Glutamate to modulate neuronal excitability and CNS arousal

- Imaging studies on patients with panic disorder revealed reduced benzodazepine binding (Kaschka et al., 1995)
- Anxious patients have downregulated GABA system in frontal cortex (Goddard et al., 2001)
- Negative correlations found between baseline cerebrospinal fluid GABA and anxiety and panic attack frequency (Goddard et al., 1996)



GABAergic-glutamatergic balance

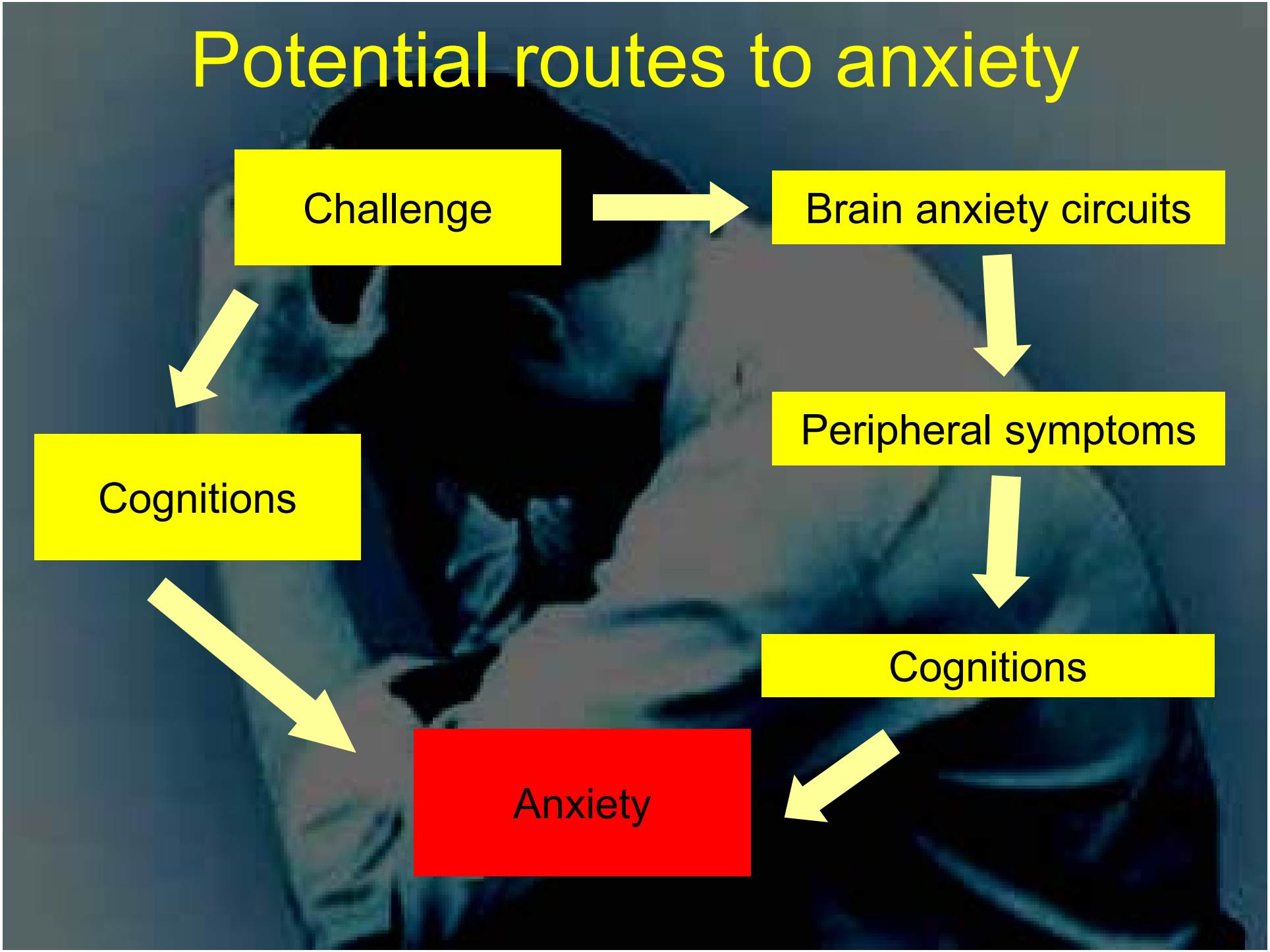
Glutamate

GABA

Abnormal hyperexcitabilty

Normal physiologic range

Abnormal hypoexcitability

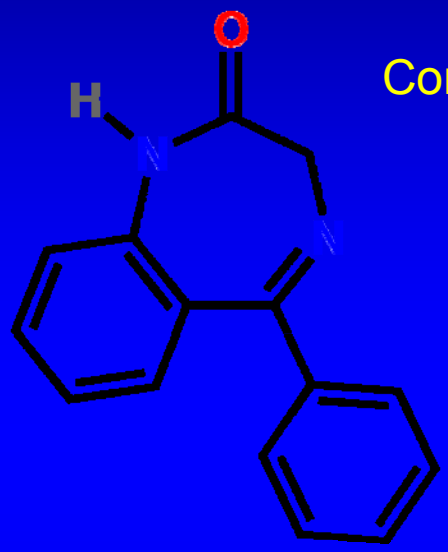

Potential routes to anxiety
Challenge
Brain anxiety circuits
Peripheral symptoms
Cognitions
Cognitions
Anxiety

Treatments

Pharmaceuticals

SSRIs

- fluoxetine (*Prozac*)
- paroxetine (*Paxil*)
- escitalopram (*Lexapro*)



Core chemical structure of benzodiazepines

Benzodiazepines

- alprazolam (*Xanax*)
- chlordiazepoxide (*Librium*)
- clonazepam (*Klonopin*)
- diazepam (*Valium*)
- lorazepam (*Ativan*)

Kava plant

Herbal

- Kava (relaxant made from the root of Kava plant)

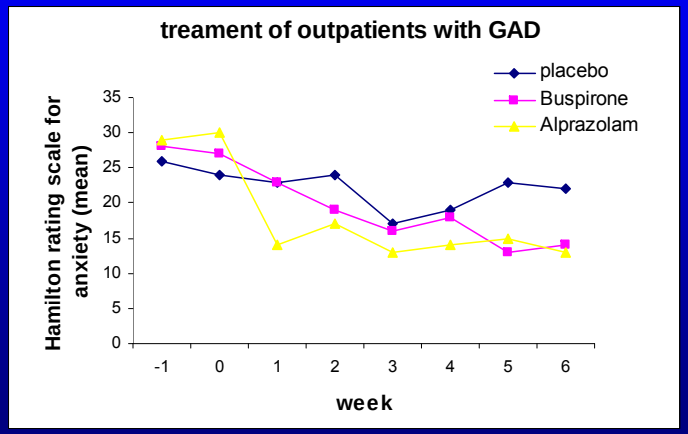
Other therapies

Cognitive behavioral therapy

- Relaxation training to alleviate somatic symptoms
- Re-shaping cognitive skills
- Positive psychology
- Exposure and response prevention to worry behaviors
- Imagery and habituation to feared situations
- Self monitoring and early problem-detection

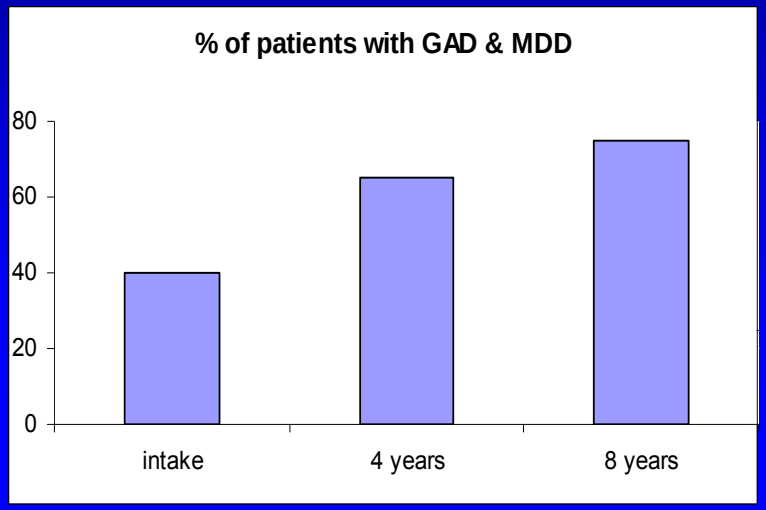
- is significantly more effective than no treatment
- Shows 40-60% improvement rates (Durham et al., 1999)

Placebo



Comorbidity: anxiety and depression

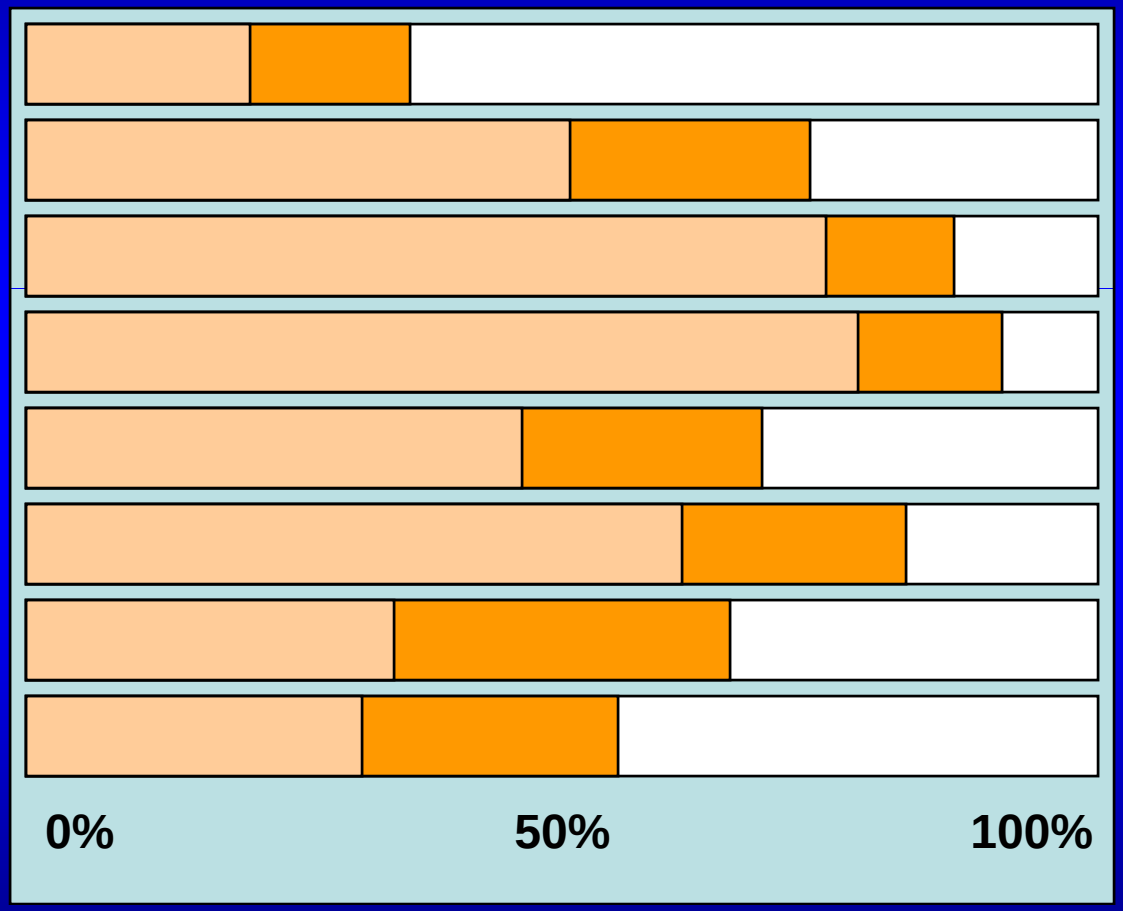
- Comorbidity of anxiety and depression: up to 60-70%
- Anxiety and depression have common genetic origins (Kendler et al., 1992, 1996)
- Patients with both disorders show more impairment than those with only one
- Comorbidity lowers chances of remission from either depression or anxiety (Sherbourne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



Bruce et al., 2001

Comorbidity

Drug disorder
Alcohol disorder
Social phobia
Simple phobia
Agoraphobia
Panic disorder
Dysthymia
Major depression



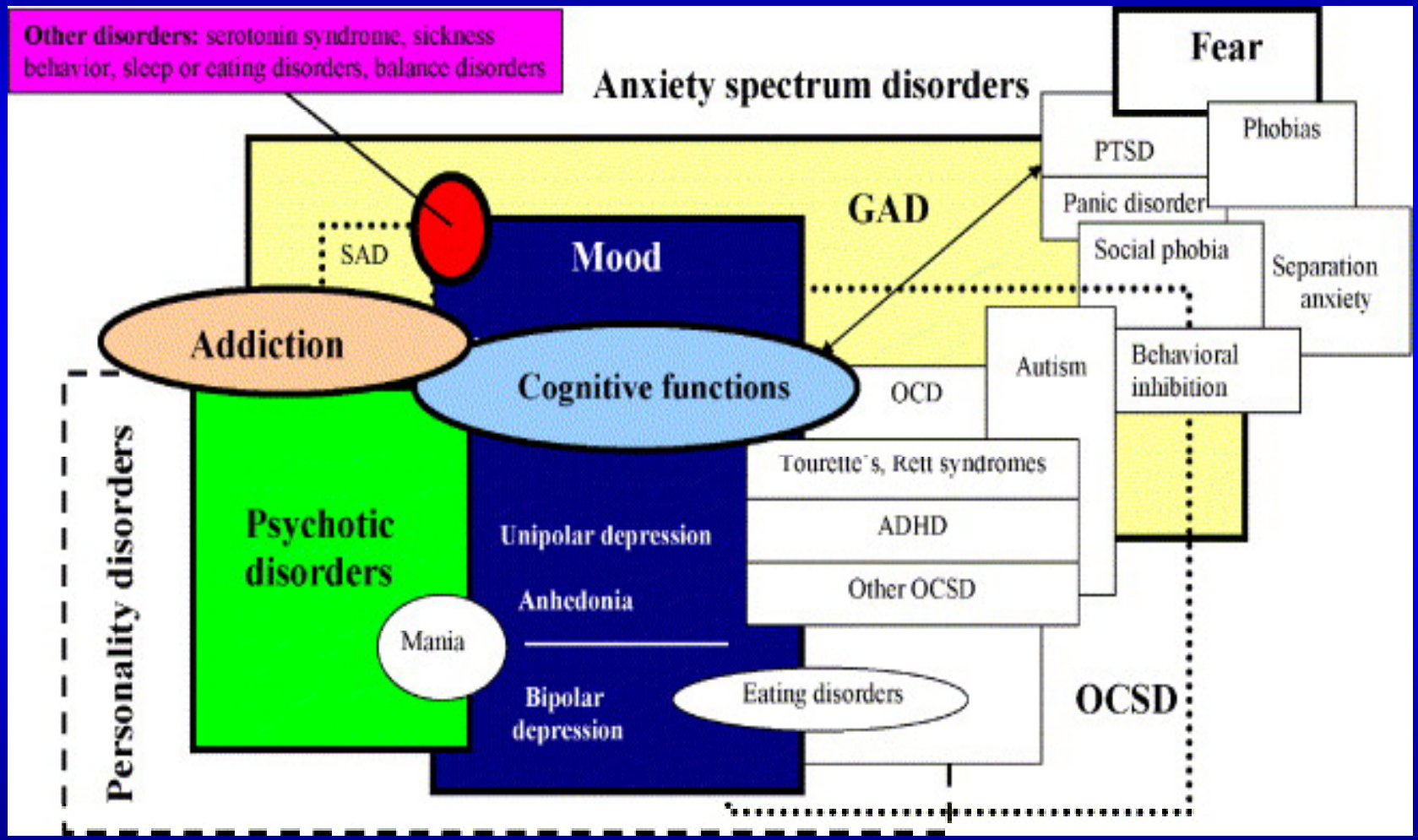
Prior to GAD

Same year

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

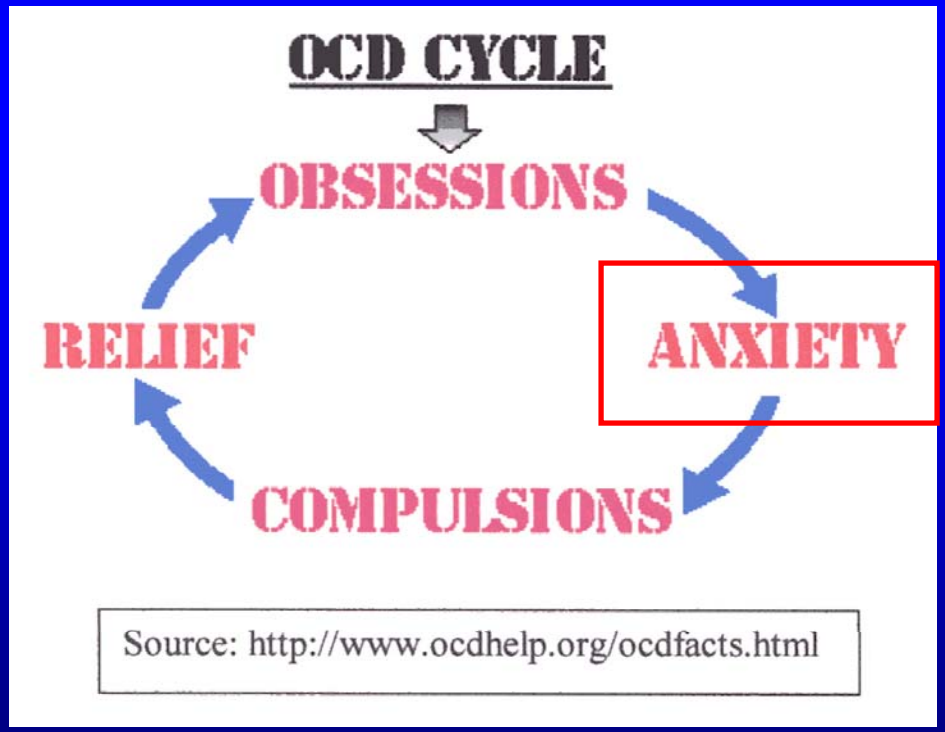
Comorbidity with other disorders



Kalueff et al., 2007

Obsessive-compulsive disorders

- A common, debilitating brain disorder
- Currently under “Anxiety spectrum disorders”
- Has many specific pecularities (a separate nosological entity?)



Famous people with OCD

Howard Hughes
Martin Scorsese
Stanley Kubrick
Harrison Ford
PenΓ©lope Cruz
Paul Gascoigne
Nikola Tesla
Donald Trump
Cameron Diaz
Ludwig van Beethoven
Albert Einstein
Leonardo DiCaprio
Michael Jackson

OCD

Compulsions	**Obsessions**
• Contamination	• Checking
• Pathological doubt	• Washing
• Somatic	• Counting
• Need for symmetry	• Need to ask or confess
• Aggressive impulse	• Symmetry/precision
• Sexual impulse	• Hoarding
• Other	• Multiple compulsions
• Multiple obsessions	

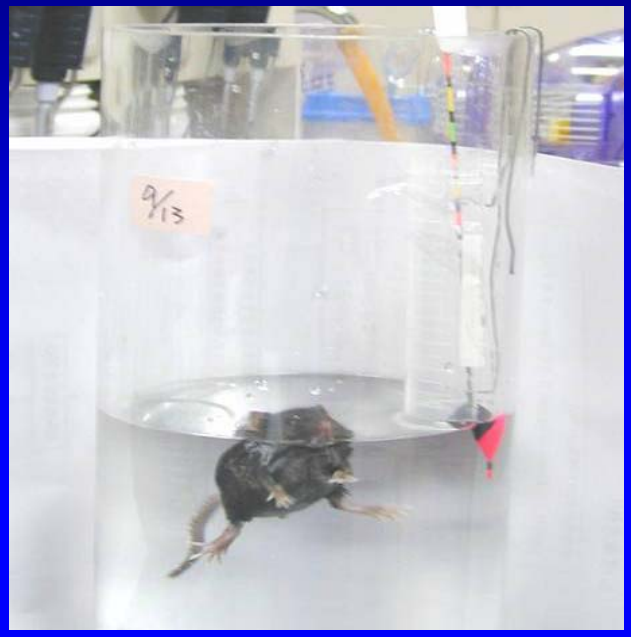
Animal models of depression

Porsolt test (Forced Swim test)

•Based on a rationale of “learned helplessness”

•Quantifies the number and duration of immobility episodes

•More immobility generally indicates more depression



Tail-suspension test

- “dry version” of the forced swim test

Animal models of anxiety

Open field test

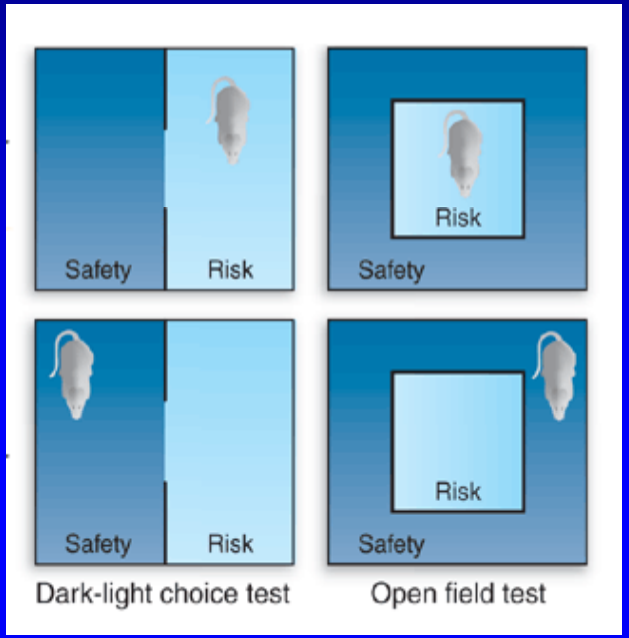
- Measures the distance moved, and time spent in the center (instinctually aversive) vs the periphery.

Light/dark box

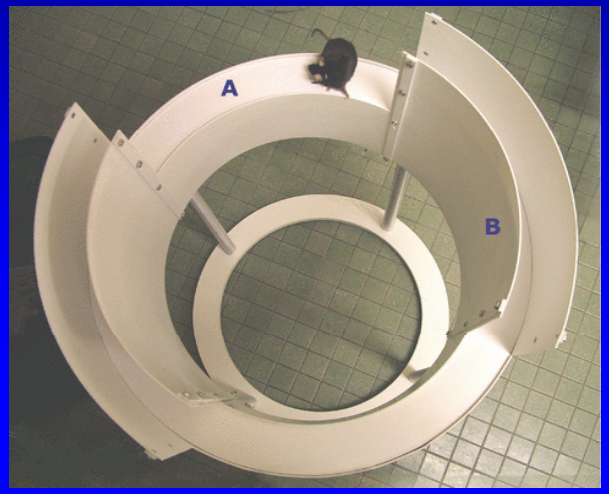
- Quantifies the number of entries and time spent in the in the lighted area (the aversive side). Exploratory behaviors vs. anxious behaviors

Suok test

- Combines elements of the open field test, such as novelty exploration, and adds heights as another anxiety-inducing stimuli.
- Relevance for modeling anxiety-vestibular deficits because of balance domain.



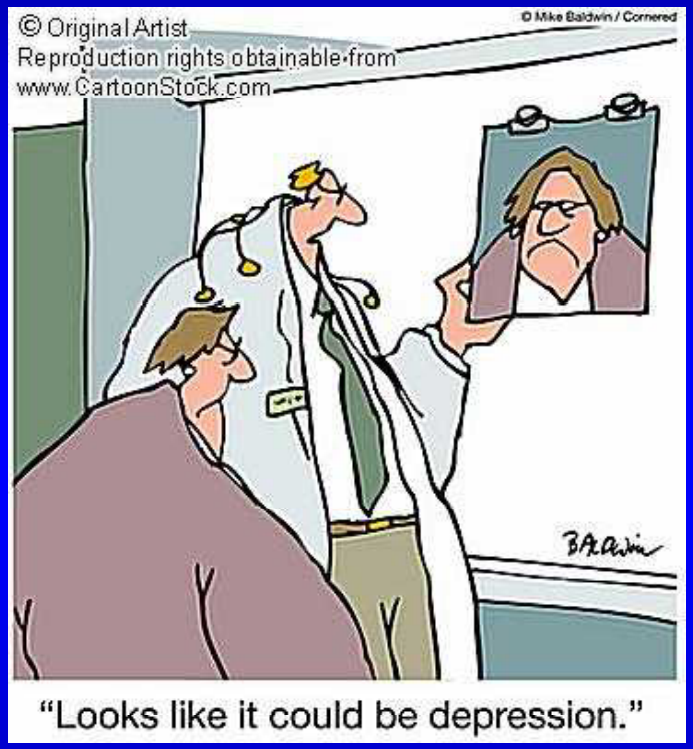
Elevated plus and zero mazes



Social interaction test

Rat exposure

Summary



- A and D are perhaps the most serious brain disorders
- Precipitated by stress
- A and D represent a complex spectrum of overlapping brain disorders
- Substantial commonality of brain genetic, molecular and behavioral mechanisms
- Not fully clear causes
- Can be modeled in animals