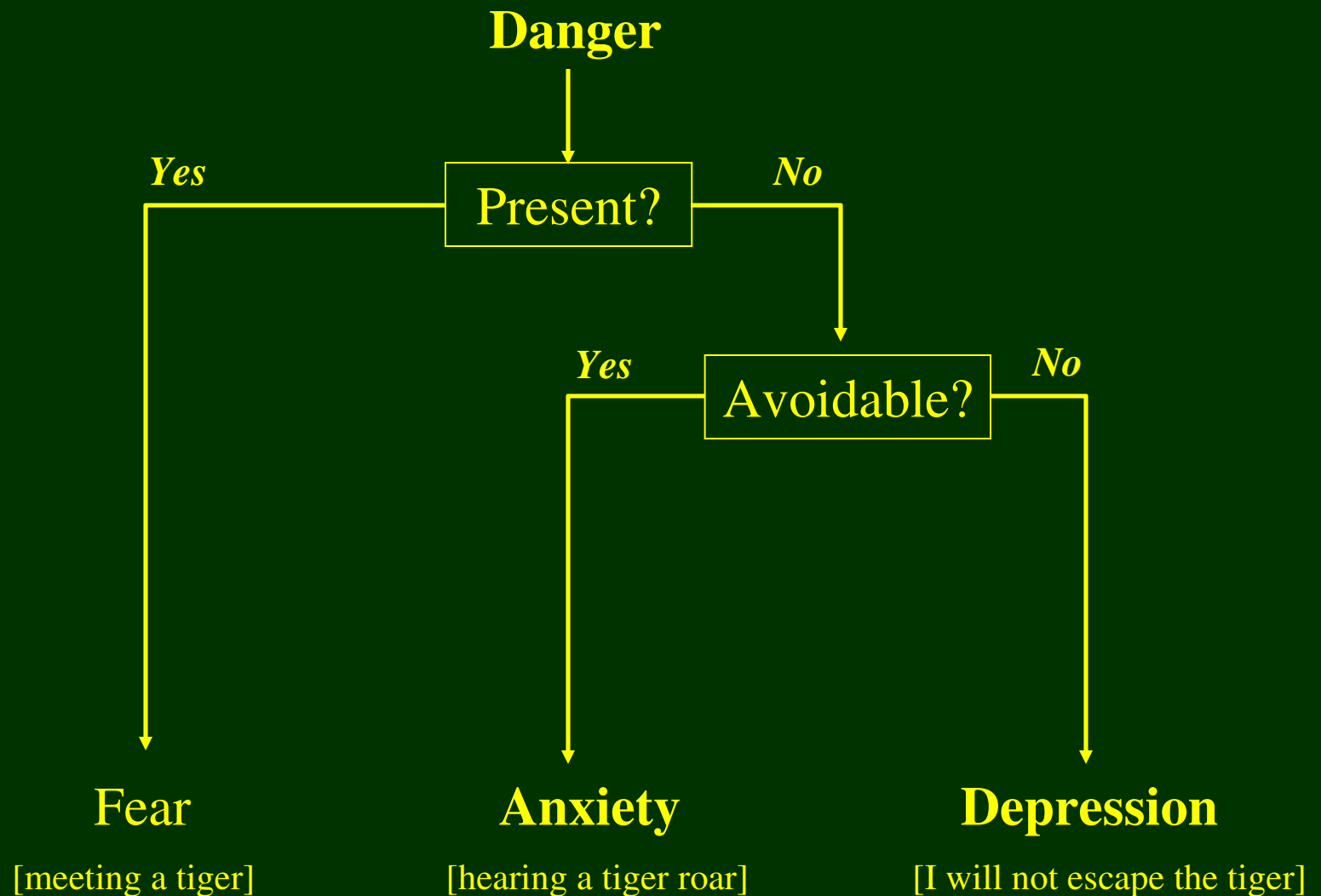


Neurobiology of Anxiety

1st ISBS Summer School
St. Petersburg, Russia
May 9th -15th, 2008

Depression and Anxiety



Brain emotional states

Anxiety



Future

Fear



Present

Depression



PTSD



Past



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

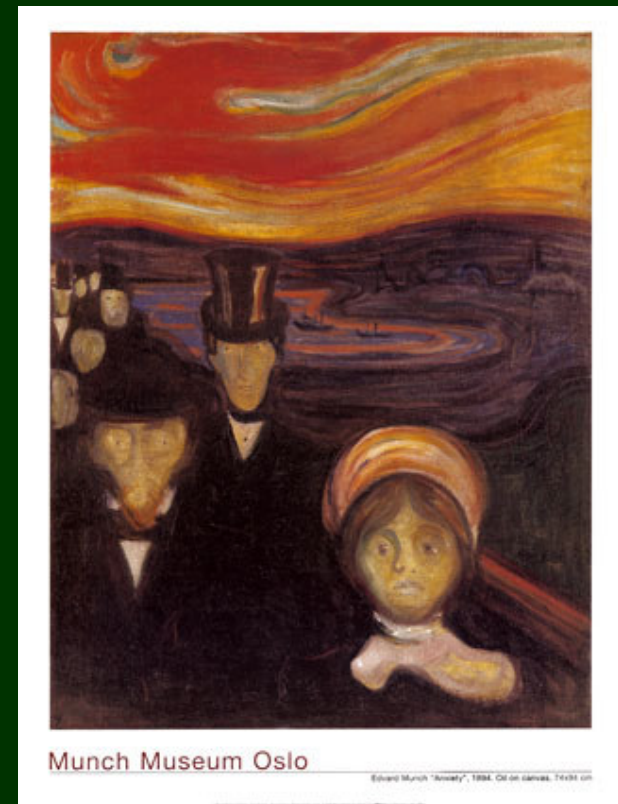
To better differentiate between GAD and other anxiety or depressive disorders, 4 “first rank” and at least 1 “second rank” symptoms are needed

First

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

Second

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

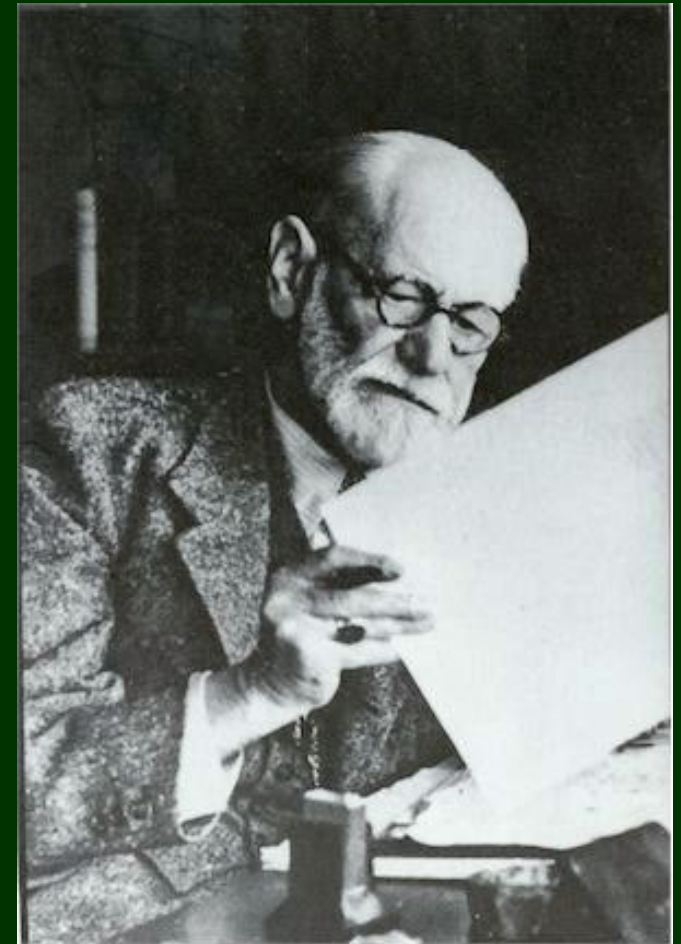


Statistics of anxiety disorders

- 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

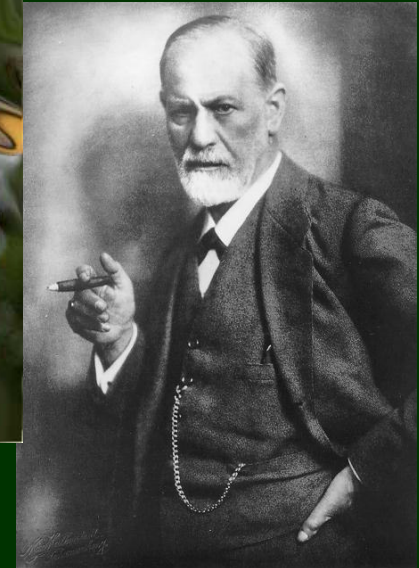
Formulated the State–Trait Anxiety Inventory (STAI) that has been translated and adapted in 66 languages and dialects.

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."

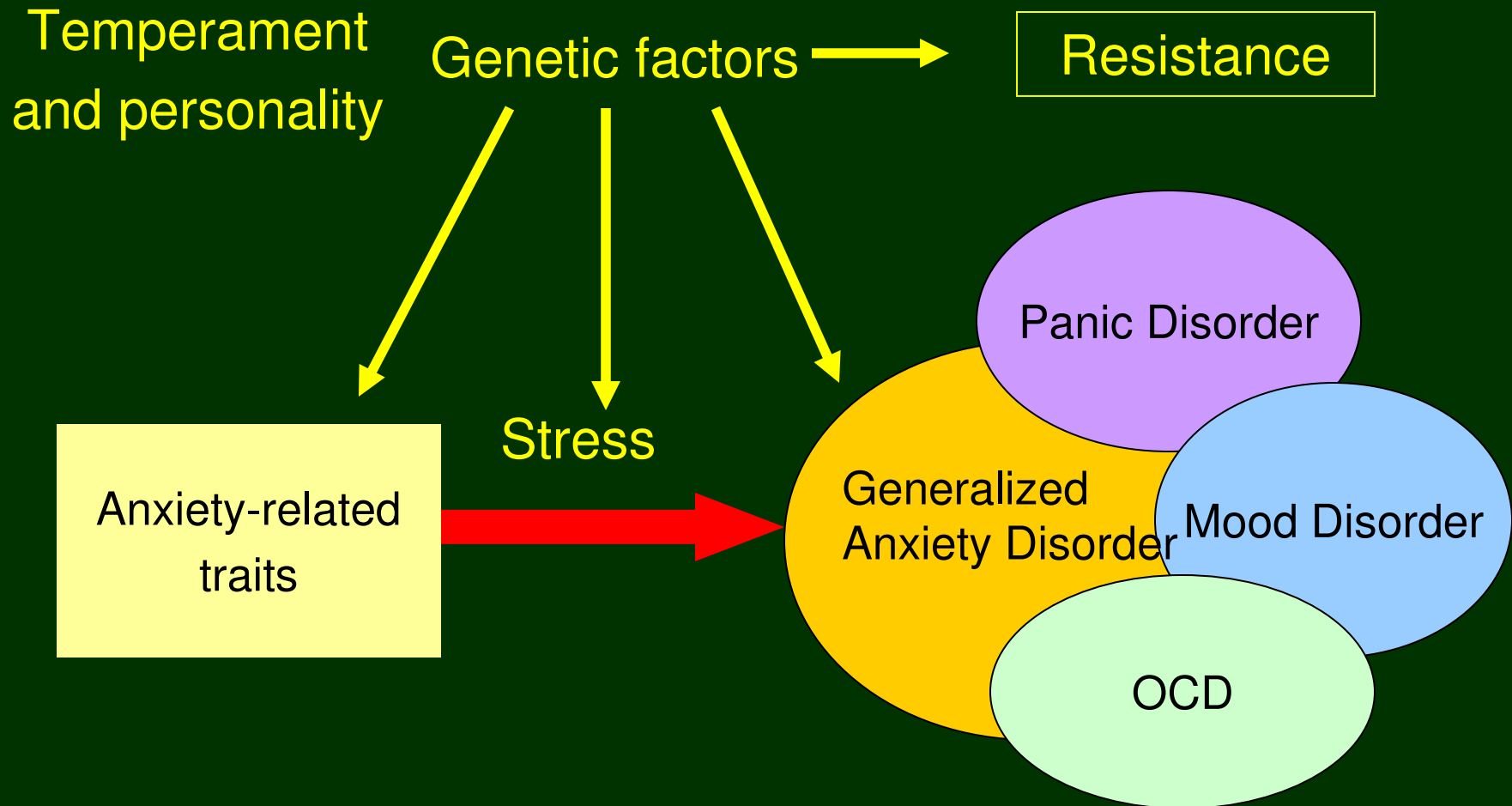
Trait anxiety refers to "relatively stable individual differences in anxiety proneness . . ."

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)



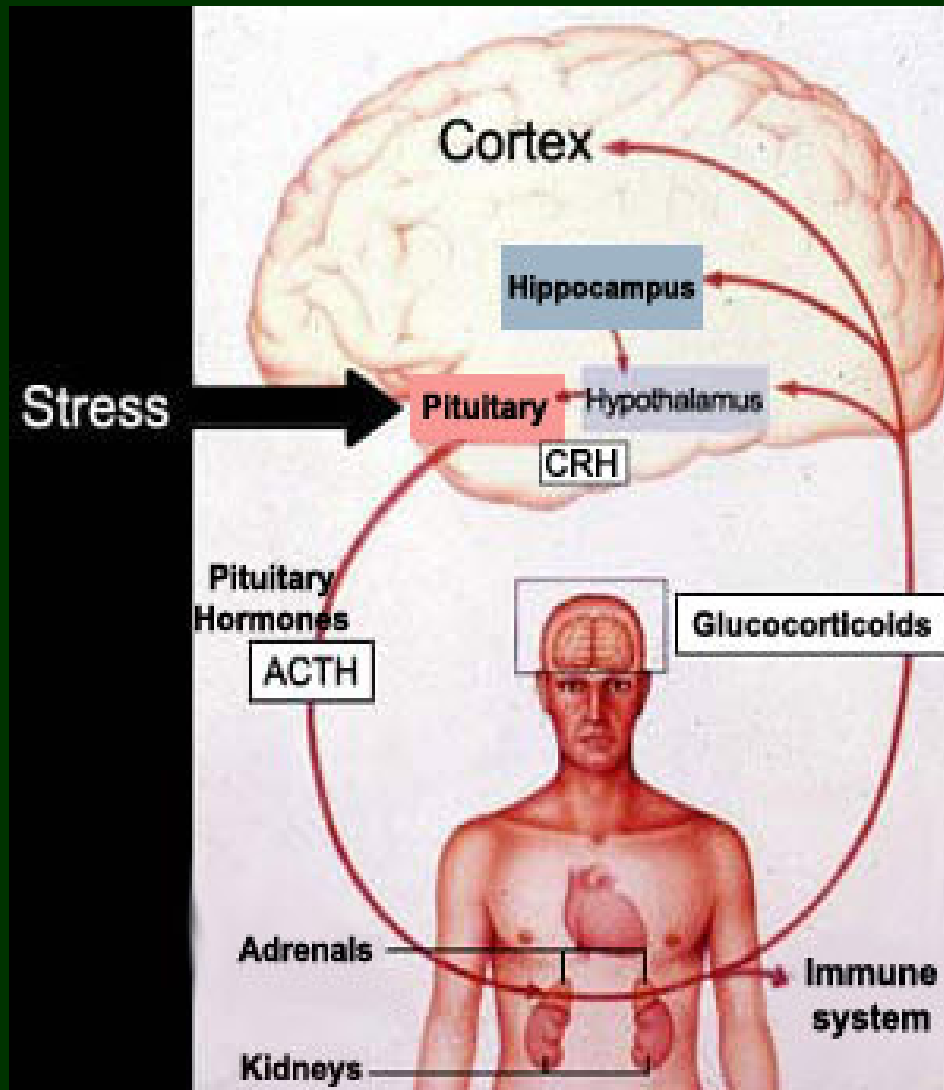
Genetics of anxiety



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

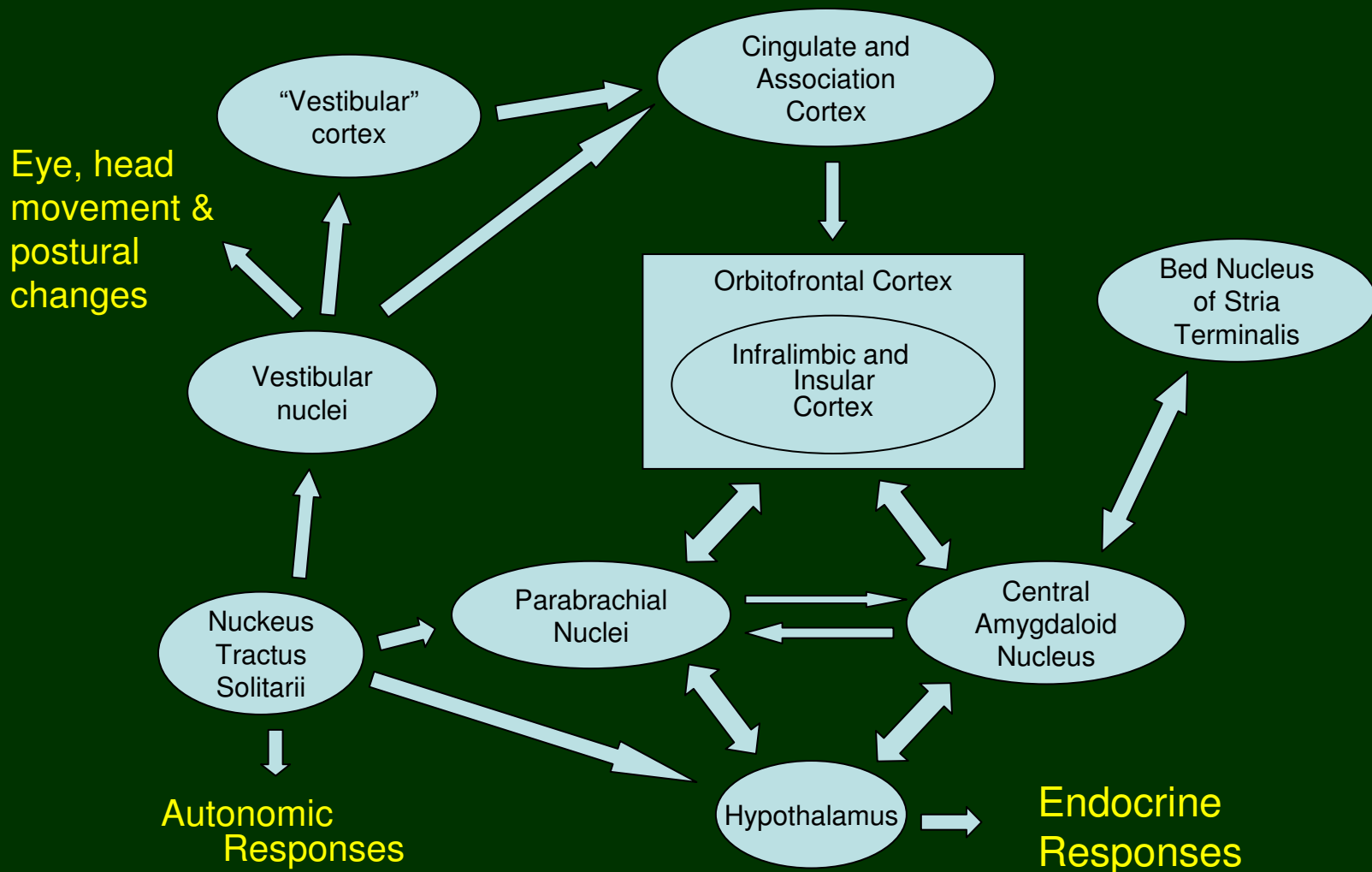


- **Anxiety = stress + center + periphery**
- **Limbic system** overactivity can increase arousal and awareness of the environment, leading to symptoms of anxiety (Gray, 1983).
- **Hypothalamic-pituitary-adrenal (HPA) axis:** amygdala and BNST mediate anxiogenic behavior and HPA activation (Green et 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)

Anxiety-vestibular system



Mediators and hormones

Adrenaline

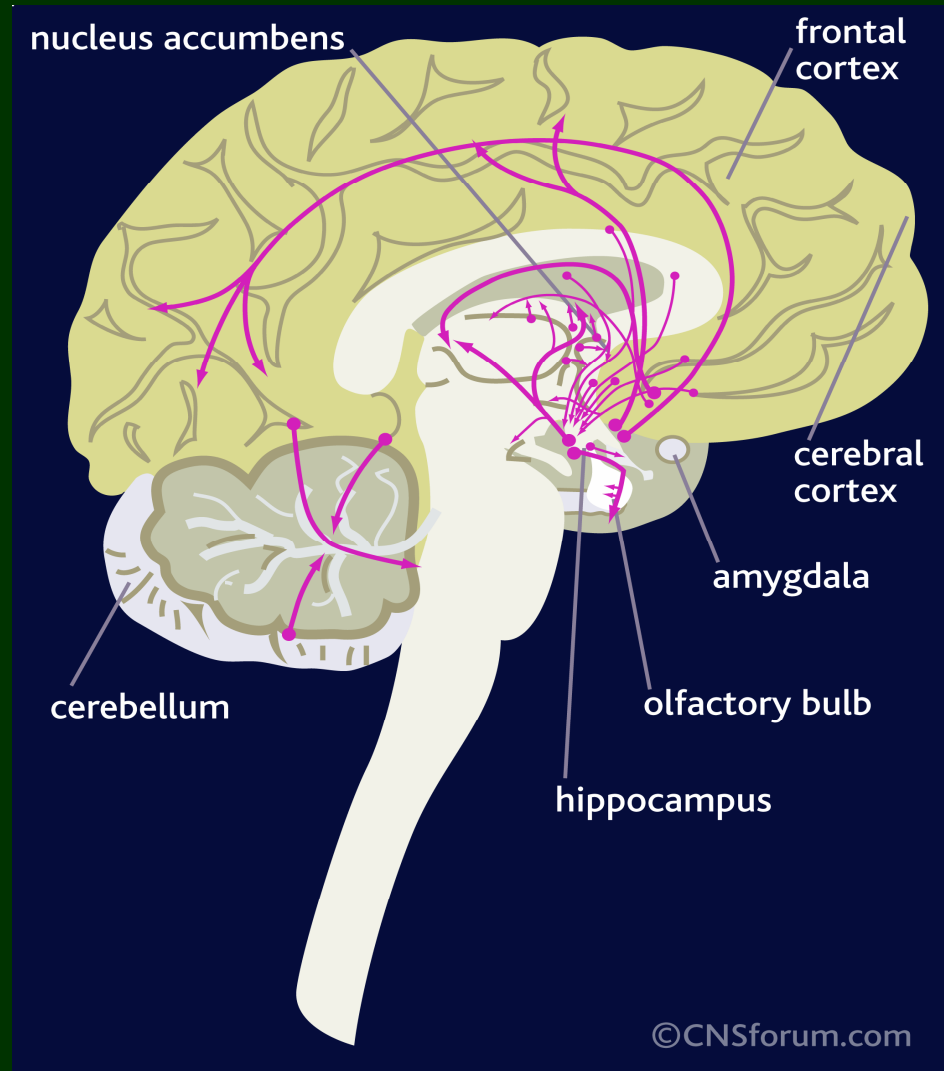
- Exaggerated responsiveness of presynaptic α_2 autoreceptors (Koob, 1999)

Serotonin

- Both excesses and deficiencies in serotonin can create anxiety

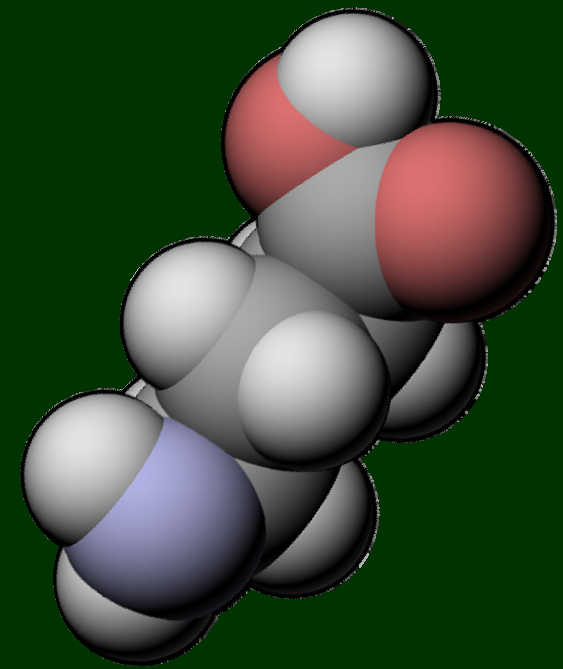
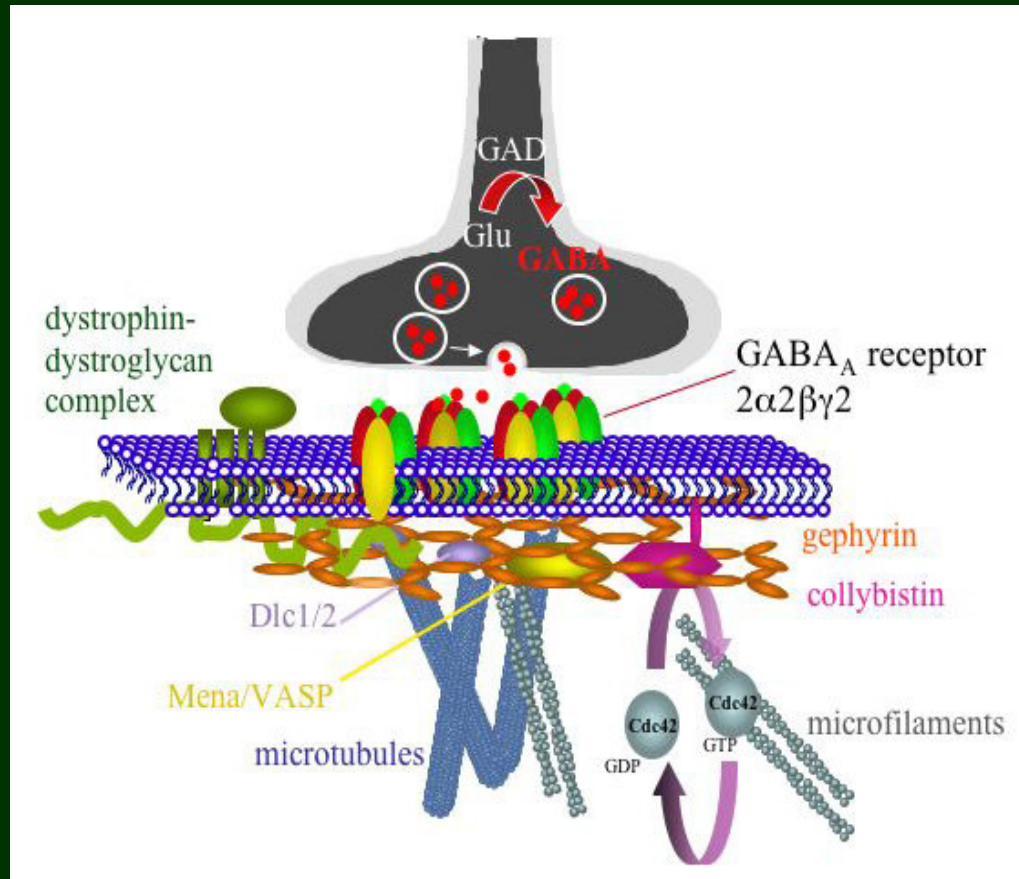
Corticosteroids

- Corticosteroids are unbalanced due to chronic stress



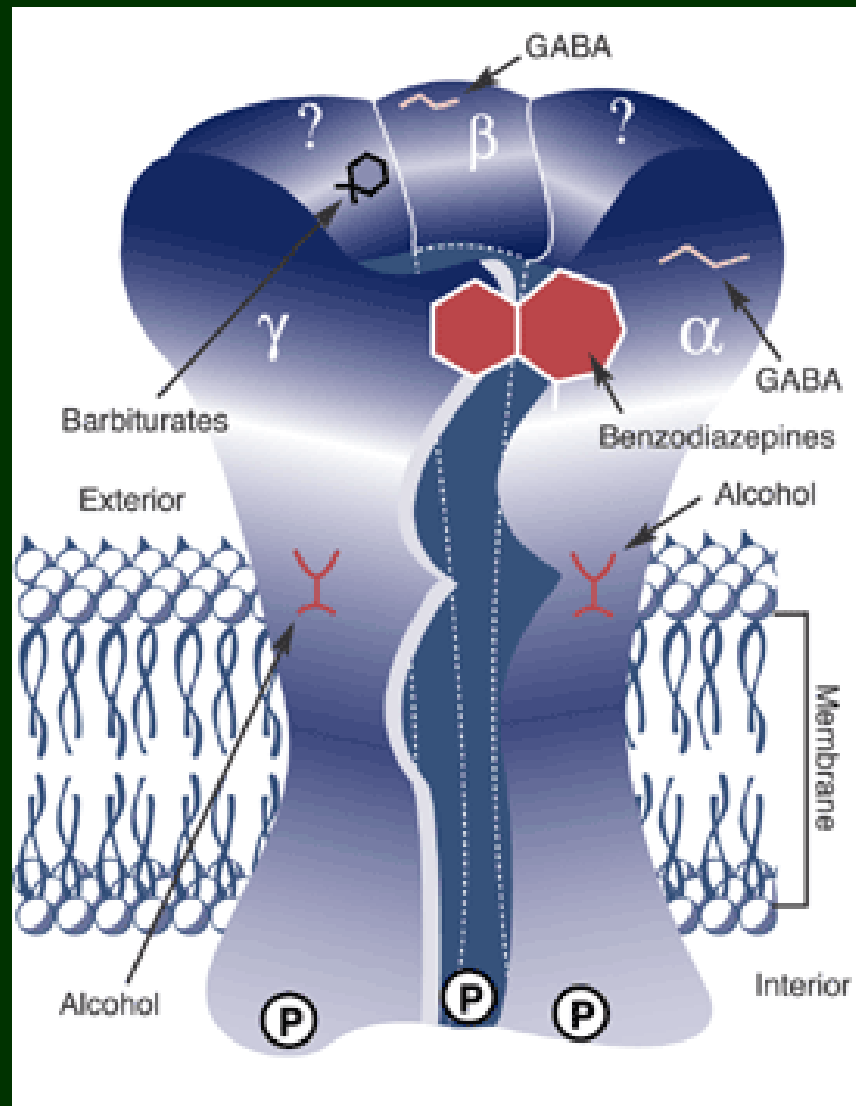
GABA pathways in normal brain

GABAergic system



GABA

GABA_A receptor

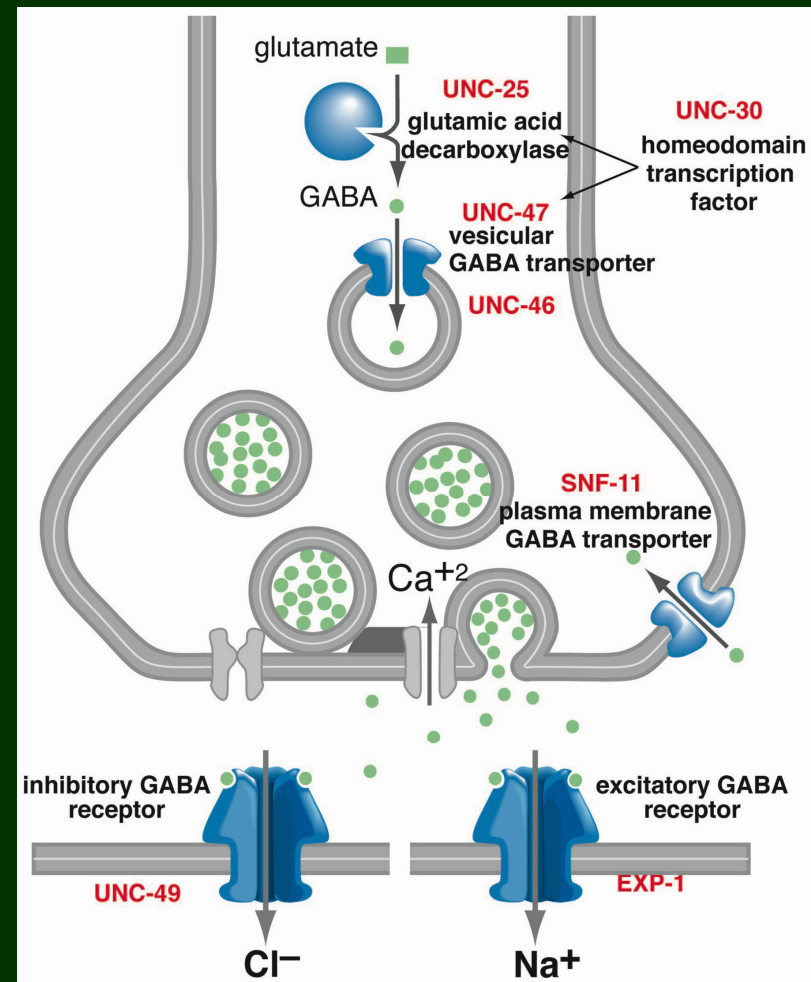


The role of GABA

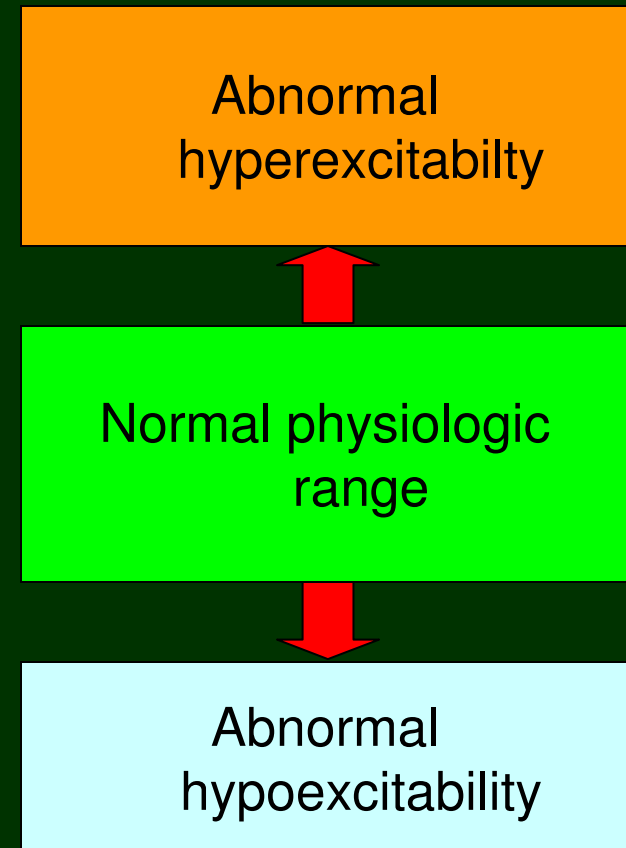
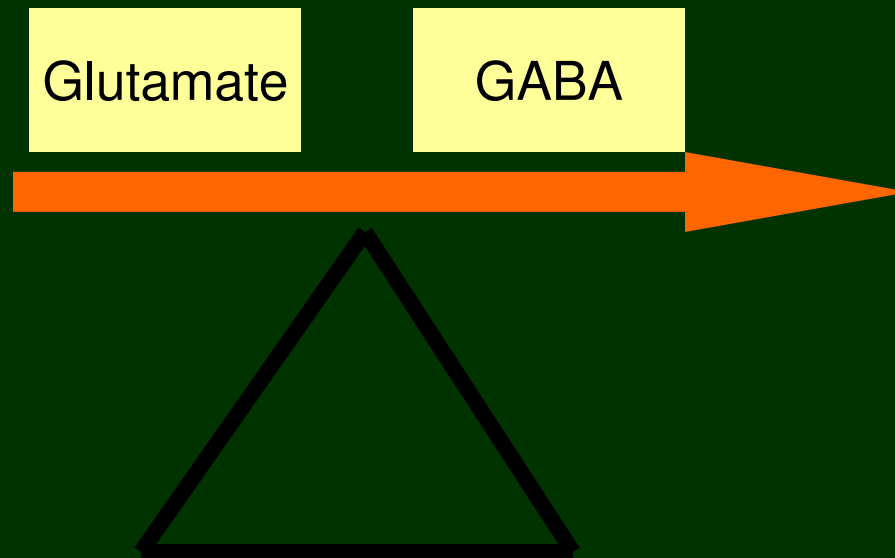
GABAergic system: works with

Glutamate to modulate neuronal excitability and CNS arousal

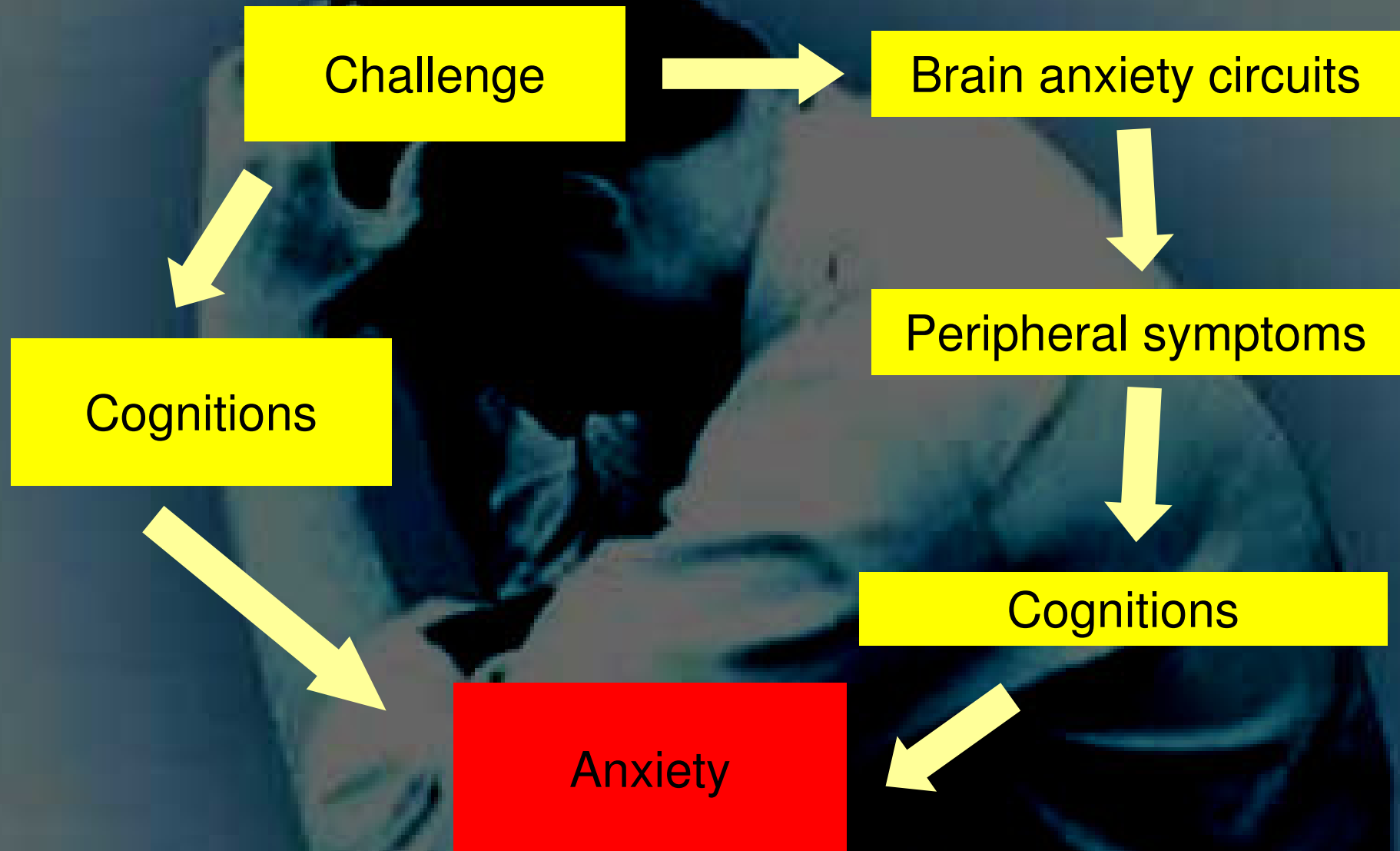
- Imaging studies on patients with panic disorder revealed reduced benzodiazepine binding (Kaschka et al., 1995)
- Anxious patients have downregulated GABA system in frontal cortex (Goddard et al., 2001)
- Negative correlations found between baseline cerebrospinal fluid GABA and anxiety and panic attack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



GABAergic-glutamatergic balance



Potential routes to anxiety



Treatments

Pharmaceuticals

- SSRIs
- Benzodiazepines



Kava plant

Herbal

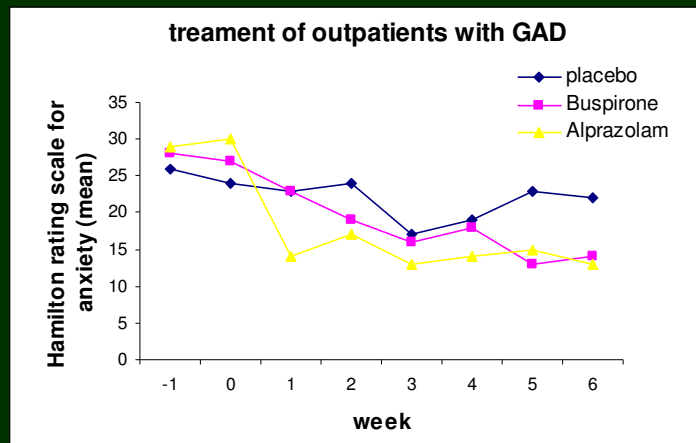
- Relaxant made from the root of Kava plant

Other therapies

Cognitive behavioral therapy

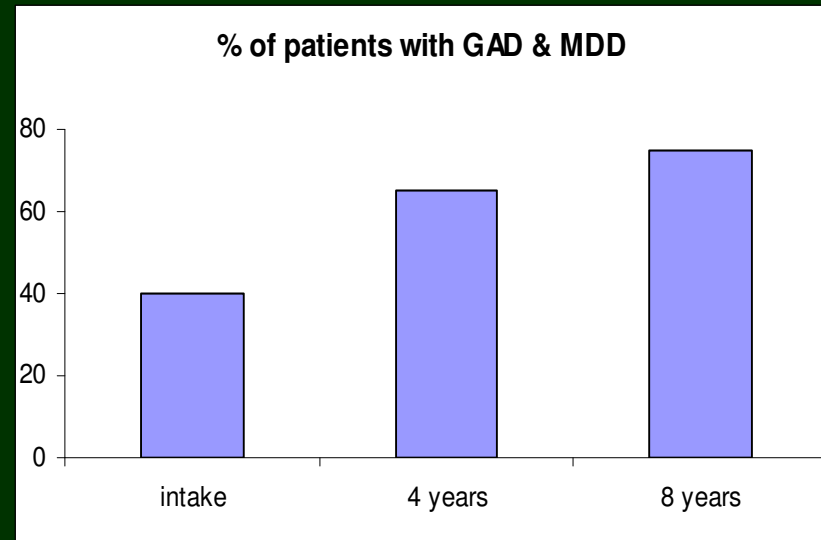
- Relaxation training to alleviate somatic symptoms
- Re-shaping cognitive skills and positive psychology
- Exposure and response prevention to worry behaviors
- Imagery and habituation to feared situations
- Self monitoring and early problem-detection
- is significantly more effective than no treatment
- 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)

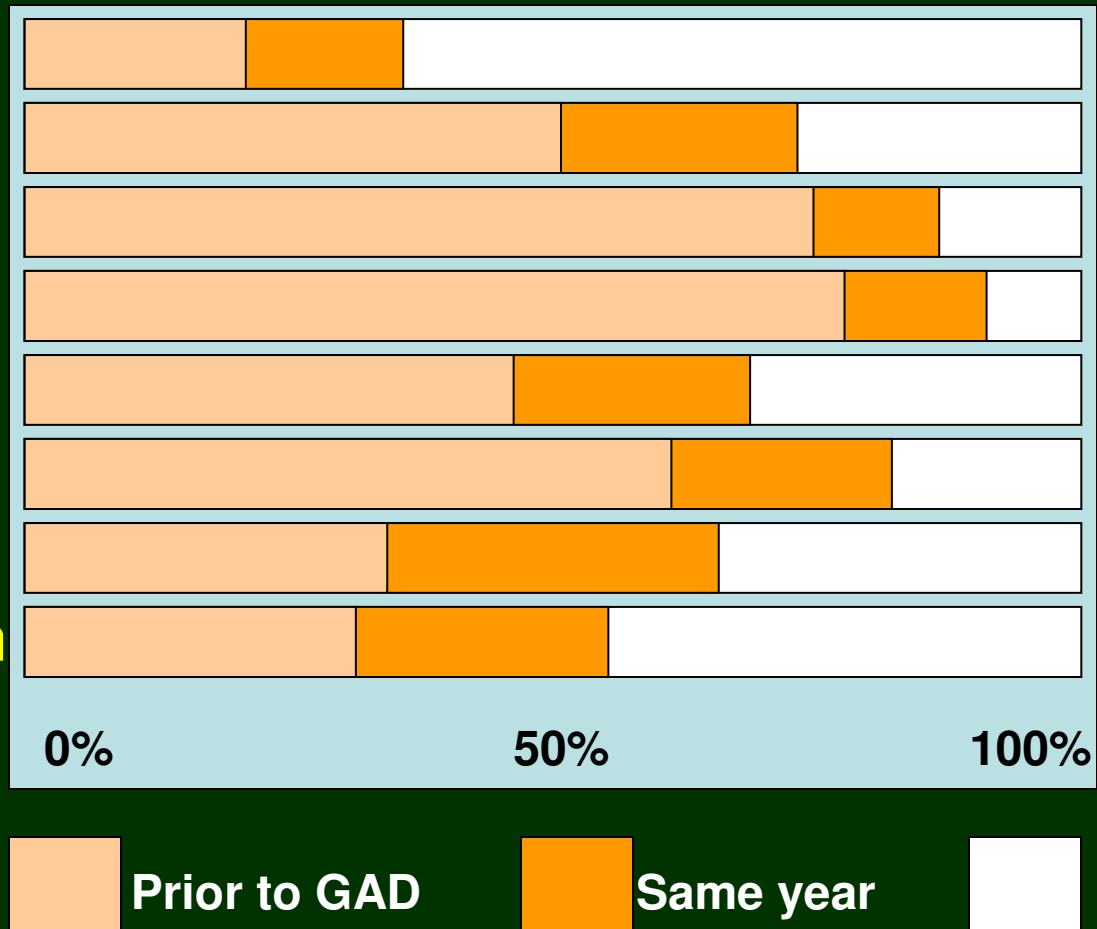


Bruce et al., 2001

- 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).

Comorbidity

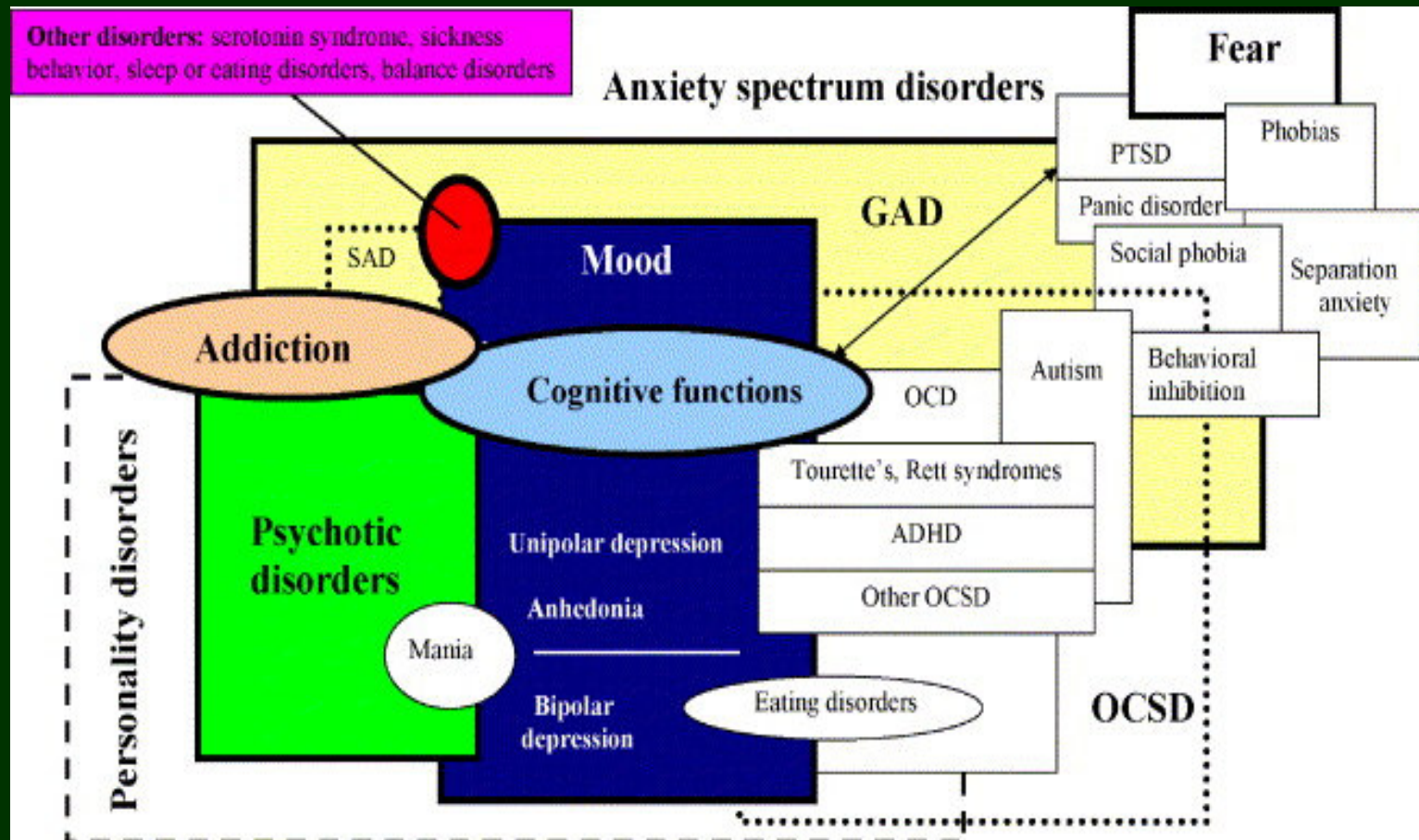
Drug disorder
Alcohol disorder
Social phobia
Simple phobia
Agoraphobia
Panic disorder
Dysthymia
Major depression



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



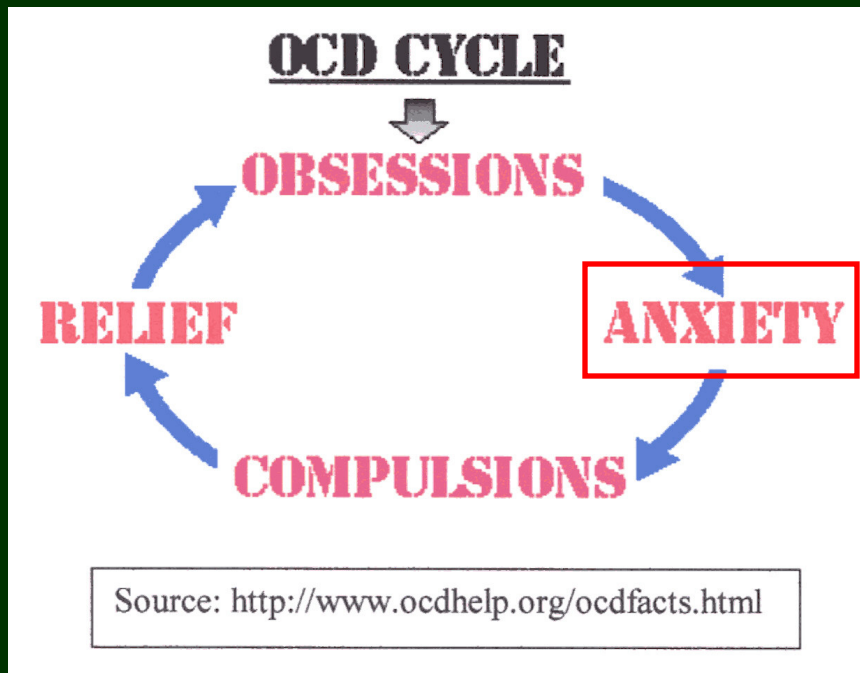
Kalueff et al., 2007

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

Obsessive-compulsive disorders

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



Famous people with OCD:

Howard Hughes
Martin Scorsese
Stanley Kubrick
Harrison Ford
Paul Gascoigne
Nikola Tesla
Donald Trump
Ludwig van Beethoven
Albert Einstein
Leonardo DiCaprio
Michael Jackson



OCD

Compulsions

- Contamination
- Pathological doubt
- Somatic
- Need for symmetry
- Aggressive impulse
- Sexual impulse
- Other
- Multiple obsessions

Obsessions

- Checking
- Washing
- Counting
- Need to ask or confess
- Symmetry/precision
- Hoarding
- Multiple compulsions

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"And that one's for the relief of anxiety
caused by the high cost of medication."