Generalized Anxiety Disorder

equipo de uno

Anxiety vs Fear

- *Fear* is an emotional response to real or perceived imminent threat
  - associated with surges of autonomic arousal necessary for fight or flight and thoughts of immediate danger including escape behaviors
- *Anxiety* is anticipation of future threats
  - muscle tension and vigilance in preparation for future danger and cautious or avoidant behaviors
- "Anxiety disorders differ from developmentally normative fear or anxiety by being excessive or persisting beyond developmentally appropriate periods"(1)
  - usually persists >6 mos in duration but this timing is flexible especially in children

DSM-V: Diagnostic Criteria

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

- **Note:** Only one item is required in children.
- Restlessness or feeling keyed up or on edge.
- Being easily fatigued.
- Difficulty concentrating or mind going blank.
- Irritability.
- Muscle tension.
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

DSM-V: Diagnostic Criteria cont…

- The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
- The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Diagnostic Features of GAD

- Intensity, duration, or frequency of the anxiety and worry is out of proportion to the actual likelihood or impact of the anticipated event
- These thoughts are intrusive and difficult to control. Often are everyday, common life occurrences
  - ***Adults***: worry about job responsibilities, finances, health of family members, children, or minor matters
  - ***Children***: worry often worry about school or sports performances
- At least 3 additional symptoms are also present

  (only one additional symptom required for children):

  1. restlessness or feeling keyed up or on edge,
  2. being easily fatigued,
  3. difficulty concentrating or mind going blank,
  4. irritability,
  5. muscle tension, and
  6. disturbed sleep,

Prevalence

- 12-month prevalence of GAD is 0.9% among adolescents and 2.9% among adults in the general US population. Outside US: 0.4% to 3.6%
- Lifetime morbidity risk 0.9%
- Individuals of European descent and living in developed countries often have higher incidence of reporting symptoms of GAD
- F:M= 2:1
- Median age is 30 years old but has a wide span. Often declines with age but true remission rates are very low
  - Usually the earlier the onset, the more debilitating the disease process is to their daily life

Other Factors:

- Risks and Prognostic Factors
  - Temperamental: behavioral inhibition, neuroticism, and harm avoidance are often associated w/ GAD
  - Genetic and physiologic: One-third of the risk of experiencing generalized anxiety disorder is genetic, and these genetic factors overlap with the risk of neuroticism and are shared with other anxiety and mood disorders, particularly major depressive disorder.
- Gender Related Correlates: similar symptoms but differ in comorbidity
  - Females have comorbidities related directly to anxiety or unipolar depression
  - Males have comorbidity related to substance abuse disorder

Differential Diagnosis

- Anxiety Disorder due to Another Medical Condition
- Substance/Medication Induced Anxiety Disorder
- Social Anxiety Disorder
- Obsessive-Compulsive disorder
- Post traumatic stress and adjustment disorders
- Depressive, bipolar, psychotic disorder

referencias

- DSM-V
  - http://dsm.psychiatryonline.org.proxy.library.vanderbilt.edu/content.aspx?bookid=556&sectionid=41101761#103437990
- Kessler RC, Berglund PA, Dewit DJ, et al: Distinguishing generalized anxiety disorder from major depression: prevalence and impairment from current pure and comorbid disorders in the US and Ontario. Int J Methods Psychiatr Res 11(3):99–111, 2002b
- Goldberg DP, Krueger RF, Andrews G, Hobbs MJ: Emotional disorders: cluster 4 of the proposed meta-structure for DSM-V and ICD-11. Psychol Med 39(12):2043–2059, 2009
- Vesga-López O, Schneier FR, Wang S, et al: Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Clin Psychiatry 69(10):1606–1616, 2008

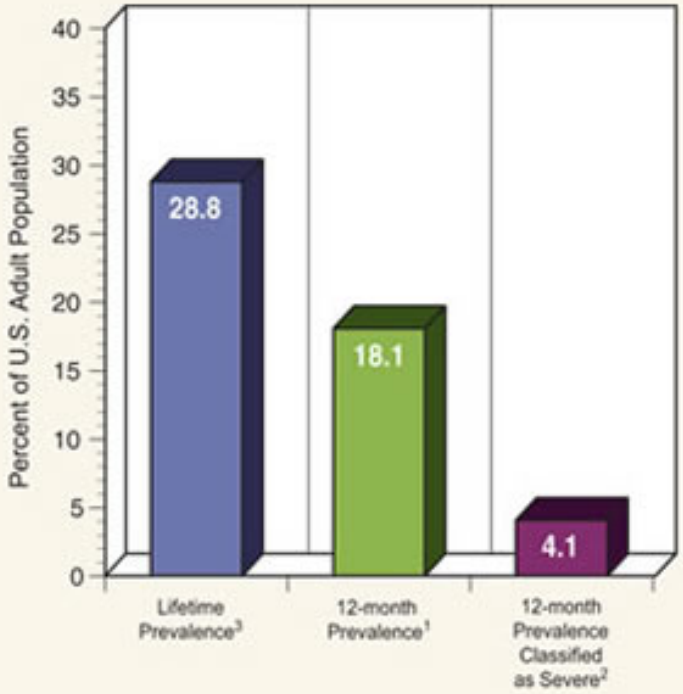
Generalized Anxiety Disorder

Prevalence and Course

All Anxiety Disorders

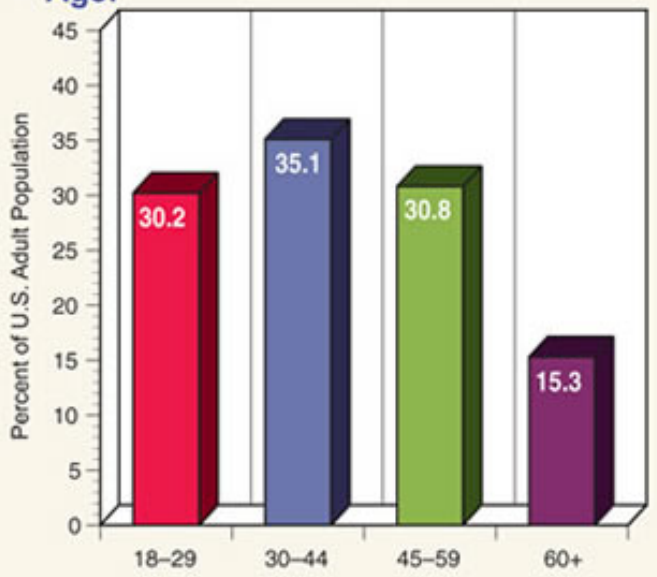
Prevalence

- **12-month Prevalence:** 18.1% of U.S. adult population[1]
- **Severe:** 22.8% of these cases (e.g., 4.1% of U.S. adult population) are classified as "severe"[2]



Demographics (for lifetime prevalence)[5]

- **Sex:** Women are 60% more likely than men to experience an anxiety disorder over their lifetime
- **Race:** Non-Hispanic blacks are 20% less likely, and Hispanics are 30% less likely, than non-Hispanic whites to experience an anxiety disorder during their lifetime
- **Age:**

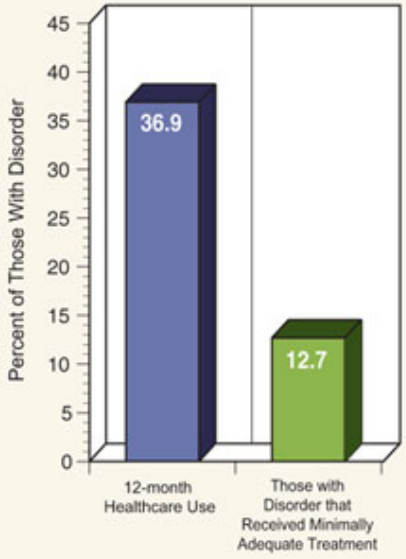


All Anxiety Disorders

Treatment/Services Use[6]

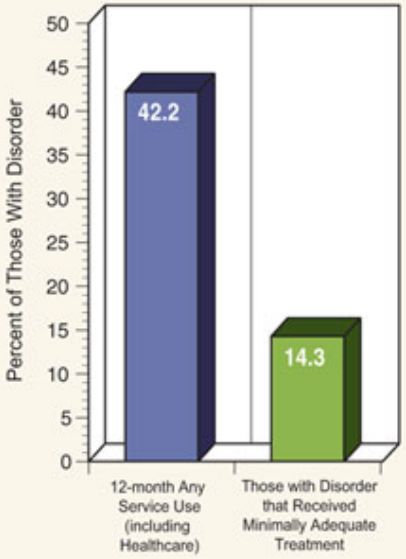
12-month Healthcare Use: 36.9% of those with disorder are receiving treatment

- **Percent Received Minimally Adequate Treatment:** 34.3% of those receiving treatment are receiving minimally adequate treatment (12.7% of those with disorder)



12-month Any Service Use (including Healthcare): 42.2% of those with disorder are receiving treatment

- **Percent Received Minimally Adequate Treatment:** 33.8% of those receiving treatment are receiving minimally adequate treatment (14.3% of those with disorder)



Generalized Anxiety Disorder

- DSM V
  - 12 month prevalence 2.9% in US
  - range of 0.4 to 3.6% for other countries
  - lifetime prevalence close to 9%
- Kessler and Wittchen groups
  - Lifetime prevalence of 5.1 to 11.9% in US
  - Lifetime prevalence of 4.3 to 5.9% in Europe
  - In Nordic countries 4.1-6.0% in men and 3.7-7.1% in females

Generalized Anxiety Disorder

- More common with Europeans and Americans of European decent that those from Asia, Africa, Pacific Islands
- More likely in people from developed countries
- Females approximately twice as likely as males to be diagnosed

Development and Course

- Many individuals with GAD report they have felt nervous and anxious all of their lives
- Median age at onset = 30 years
  - However, spread is very broad
  - Later median onset age than for the other anxiety disorders
- Onset rarely occurs prior to adolescence
- Symptoms of GAD tend to be chronic
  - Wax and wane across the lifespan, fluctuating between syndromal and subsyndromal forms of the disorder
- Rates of full remission are very low

Development and Course

- The clinical expression of GAD is relatively consistent across the lifespan
- Primary difference across age groups is in the content of the individual's worry
  - Children and adolescents → school and sporting performance
  - Older adults → well-being of family or own physical health
- Younger adults experience greater severity of symptoms than do older adults

Course and Development

- The earlier in life individuals have symptoms that meet criteria for GAD, the more comorbidity they tend to have and the more impaired they are likely to be
- GAD may be overdiagnosed in children.
  - Rule out separation anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder

Risk and Prognostic Factors

- Temperamental
  - Behavioral inhibition, negative affectivity (neuroticism), and harm avoidance have been associated with GAD
- Environmental
  - Childhood adversities and parental overprotection have been associated with GAD
- Genetic and physiological
  - 1/3 of the risk of experiencing GAD is genetic
  - These genetic factors overlap with the risk of neuroticism and are shared with other anxiety and mood disorders, particularly major depressive disorder

Culture-Related Diagnostic Issues

- Considerable cultural variation in the expression of GAD
- In some cultures, somatic symptoms predominate in the expression of the disorder, whereas in other cultures, cognitive symptoms tend to predominate
- This difference may be more evident on initial presentation than subsequently, as more symptoms are reported over time
- No information as to whether the propensity for excessive worrying is related to culture, although the topic being worried about can be culture specific
- It is important to consider the social and cultural context when evaluating whether worries about certain situations are excessive

Gender-Related Diagnostic Issues

- In clinical settings, GAD is diagnosed somewhat more frequently in females than in males (about 55-60% of those presenting with the disorder are female)
- Patients of both genders who experience GAD appear to have similar symptoms but demonstrate different patterns of comorbidity
- In females, comorbidity is largely confined to the anxiety disorders and unipolar depression
- In males, comorbidity is more likely to extend to the substance use disorders as well

Functional Consequences of Generalized Anxiety Disorder

- GAD is associated with significant disability and distress that is independent of comorbid disorders
- Most non-institutionalized adults with the disorder are moderately to seriously disabled

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- Wittchen HU, Zhao S, Kessler RC, et al: DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 51:355-364, 1994
- American Psychiatric Association DSM V
- National Institutes of Mental Health

Neurobiology of Anxiety

Anxiety and Fear

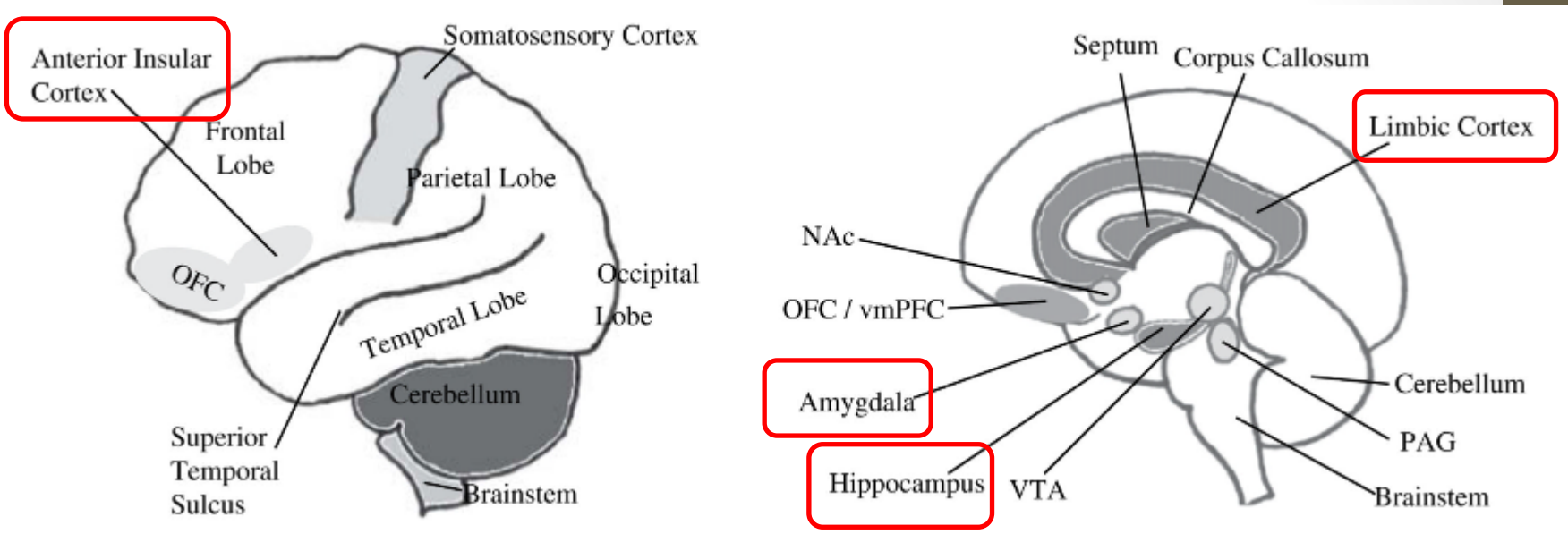
- Anxiety and fear differ in the likelihood, timing, and nature of the future event

- Uncertainty requires a difficult balance

EFFICIENCY ←→ EFFECTIVENESS

- Primary brain structures implicated include brainstem, limbic system, and prefrontal cortex

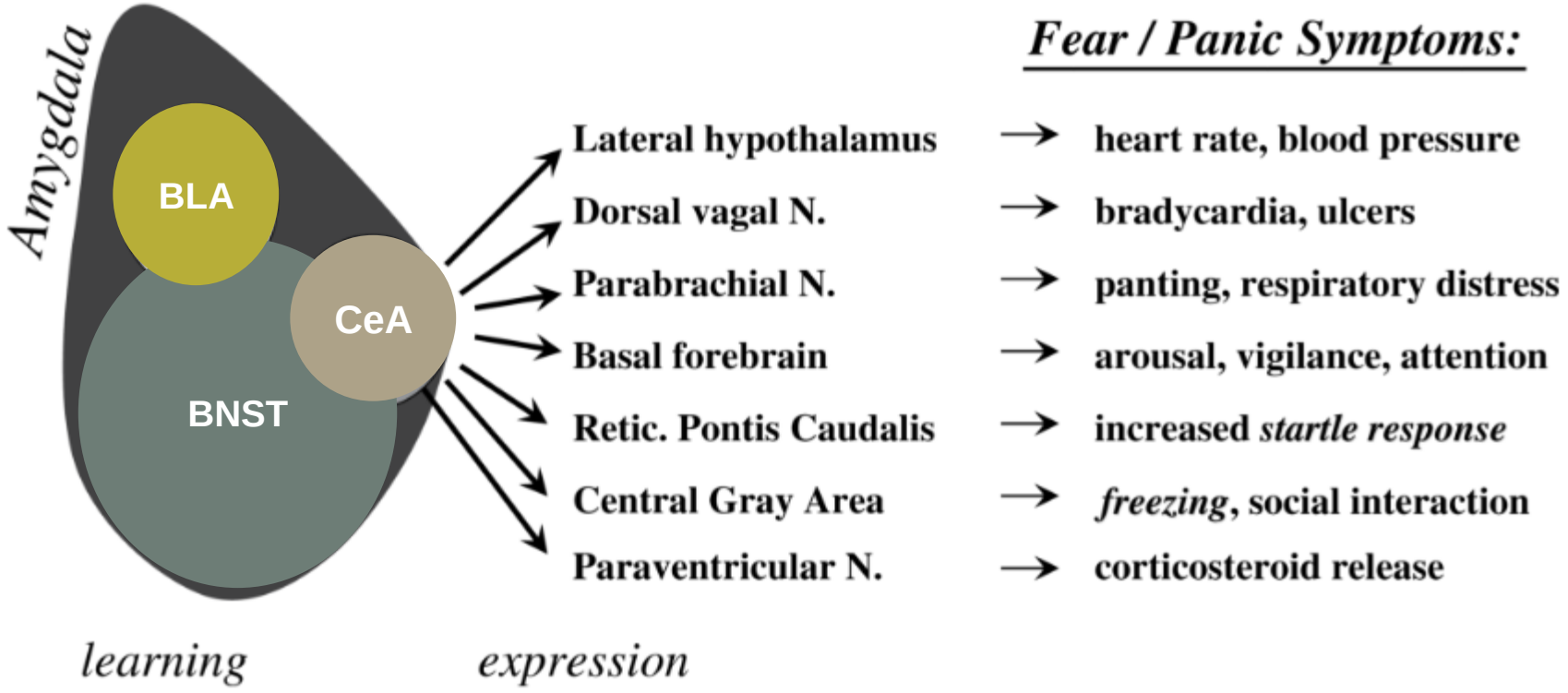
Anxiety and the Limbic System



- Disruption of balance in emotional centers of the brain
- Functions to integrate sensitive, affective, cognitive components of pain; processes information regarding the internal bodily state

Martin et al, *Psych Clin Nor Am* 2009

Amygdala and Fear

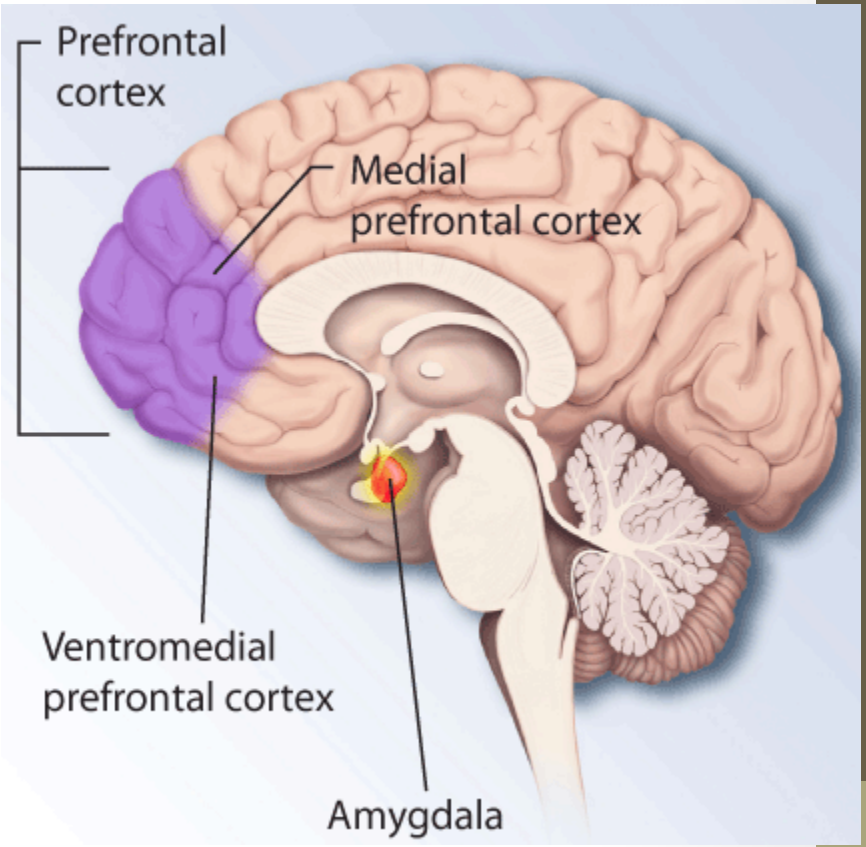


- Hypertrophy of amygdala after stress contributes to anxiety

Martin et al, *Psych Clin Nor Am* 2009
Radke, *J Ner*

Prefrontal Cortex and Anxiety

- Implicated neural circuitry involved in value calculations
- Dorsomedial prefrontal cortex- probability assessment
- Orbitofrontal cortex- anticipated cost of future events



Grupe et al, *Nat Neurosci* 2013

UAMA: Uncertainty and Anticipation Model of Anxiety

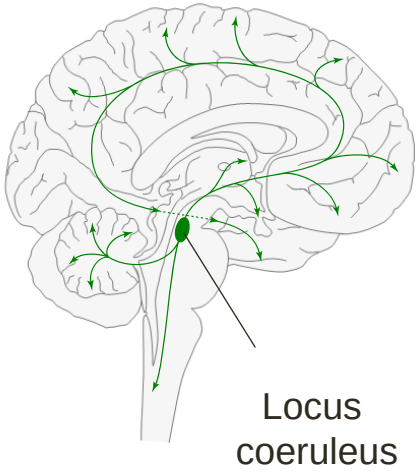
- Commonality among anxiety disorders: aberrant and excessive anticipatory response under the condition of threat uncertainty

Implicated Brain Structures	Maladaptive Stress Responses
dorsal medial prefrontal cortex	Inflated estimates of threat cost and probability
Amygdala → basal forebrain	Increased threat attention and hypervigilance
Ventral prefrontal cortex→ amygdala	Deficient safety learning
Orbitofrontal cortex Dorsalateral prefrontal cortex striatum	Behavioral and cognitive avoidance
BNST, amygdala Hypothalamus, pons, periaquductal grey	Heightened reactivity to threat uncertainty

Grupe et al, *Nat Neurosci* 2013

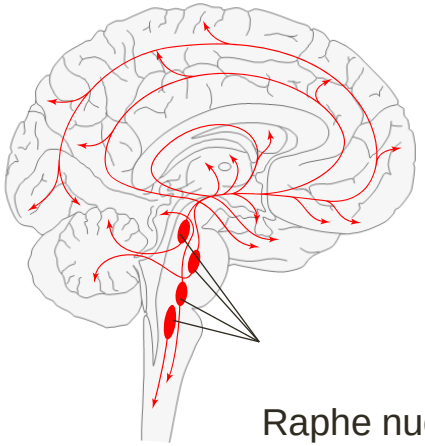
Neurotransmitters and Anxiety

Norepinephrine
excitatory



excessive
excitatory
effect

Serotonin
modulatory



dysregulated

GABA
inhibitory

hypofunction
lack of inhibitory
effect

Jacobowski, Amison, Blackford

Neuropeptides and Anxiety

Neuropeptide	Role in Stress Neurobiology	Role in Psychopathology
CCK	Weak ACTH secretagogue	↑ anxiety Pts with anxiety disorders are hypersensitive to CCK
Galanin	Increased by physiological and psychological stress/pain	↑ depression Antagonists being developed as antidepressants
NPY	Increased during stress Endogenous “alarm system” Stress-induced feeding increase Behavioral moderator	Antidepressant, anxiolytic Depressed pts have ↓ NPY; normalized by antidepressants
Oxytocin	Weak ACTH secretagogue	↓ oxytocin in CSF of depressed women
Vasopressin	Increased by stress Moderate ACTH secretagogue	↑ depression
Corticothropin-releasing factor	Increased by stress Primary ACTH secretagogue	↑ in MDD, PD, PTSD; HPA axis hyperactivity in MDD HPA axis hypoactivity in PTSD

Disruption of Balance

"Stepping on the Gas Pedal"

Overactive amygdala

"Releasing the Brakes"

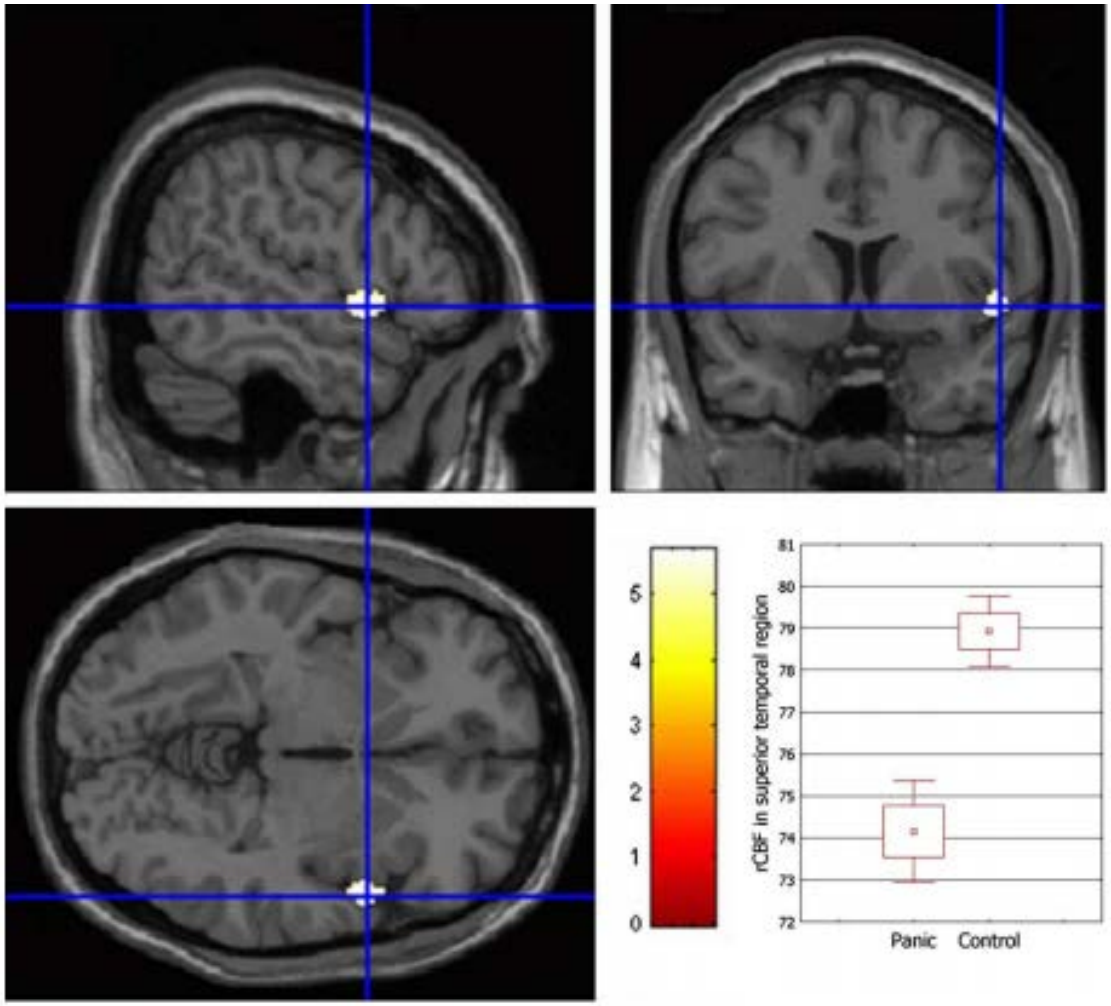
Underactive prefrontal cortex

Neuroimaging Modalities for Studying Anatomic Panic

- CT
  - Bad modality for neuroimaging; low resolution
- MRI
  - found alteration in the right temporal lobes of panic pts; diminished temporal lobe volume
  - Also found reduced l/r amygdala, left hippocampus
- Functional PET Imaging
  - Cerebral blood flow evaluate cerebral blood flow- lower in left inferior parietal lobe, posterior temporal lobe, cerebellar cortex
  - 5FDG-PET scanning: Cerebral glucose metabolism increased/higher levels of glucose update in the bilateral amygdala, hippocampus, thalamus, midbrain, caudal pons, medulla, cerebellum…restored to normal levels upon antidepressant treatment

Engel et al, *J Neural Transm* 2009

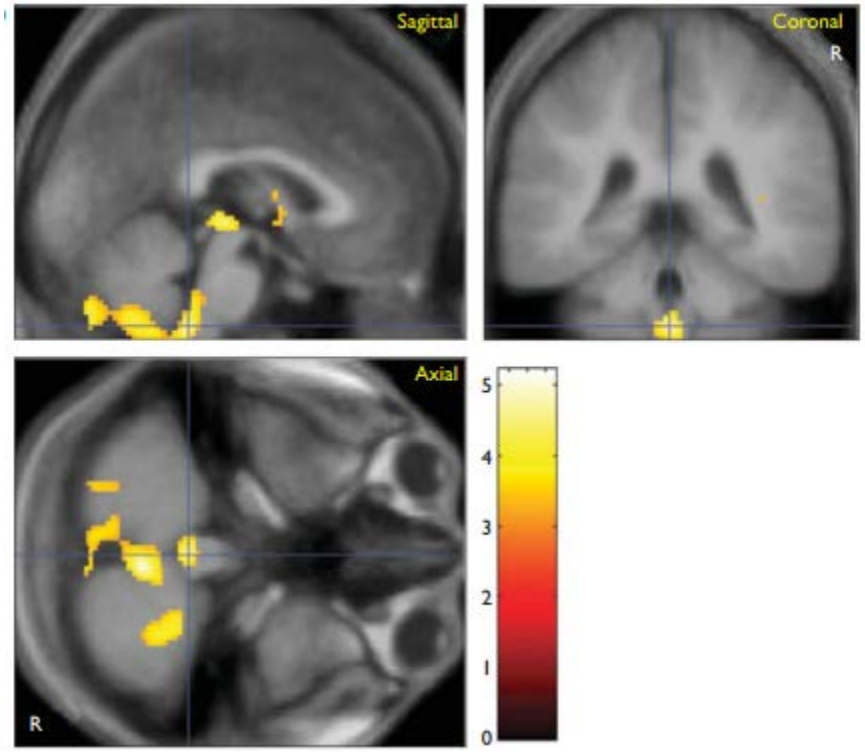
Decreased CBF in R Temporal Lobe



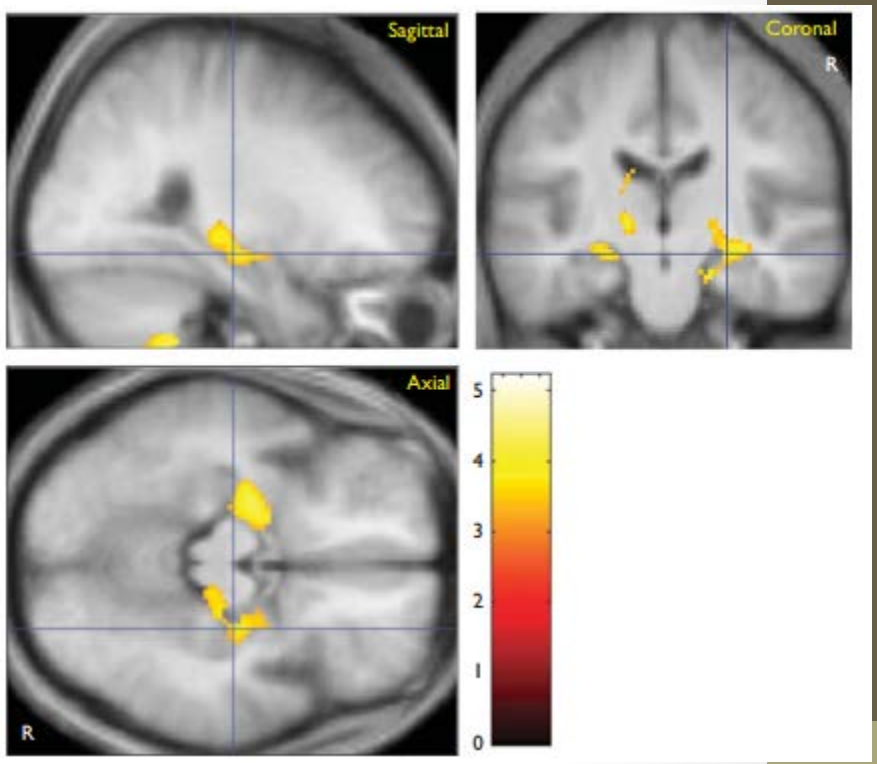
Lee et al, *Journ Psych Res* 2006

Increased Metabolic Activity in Panic Disorder

Brainstem, Cerebellum



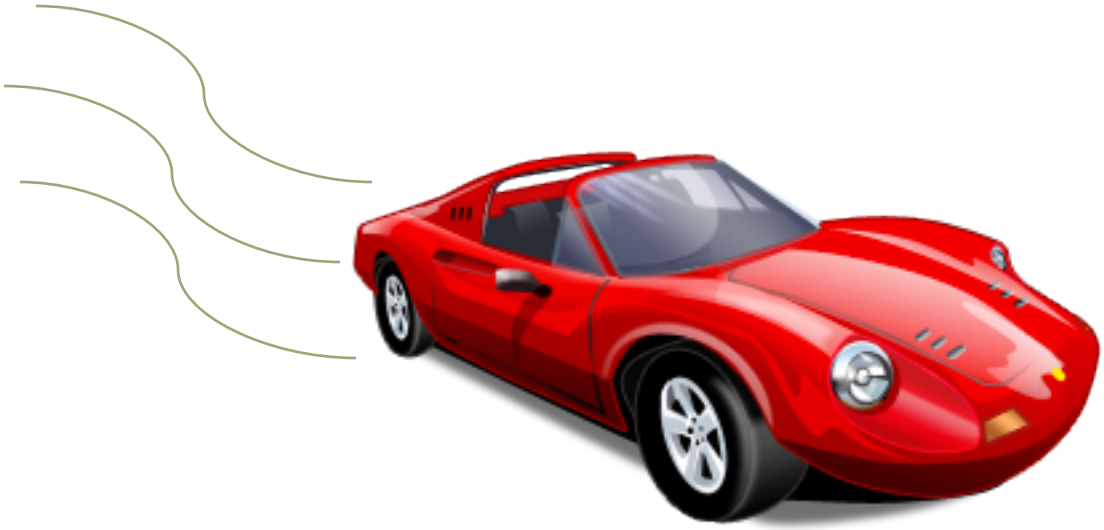
Hippocampus, Thalamus



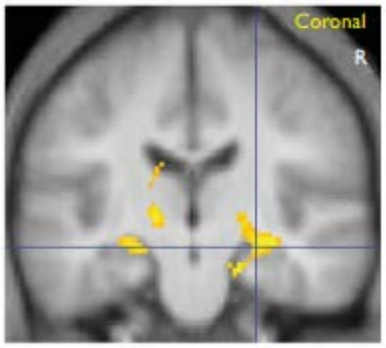
Sakai et al, *Neurorep* 2005

Take-Home Point

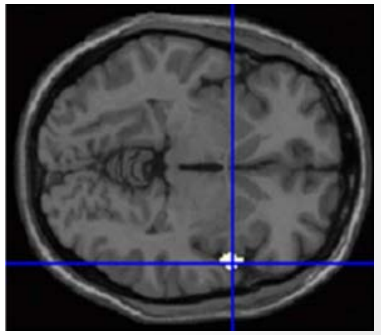
- Anxiety disorders involve the limbic system, brainstem, and prefrontal cortex



Overactive limbic system



Underactive prefrontal cortex



Treatment of Generalized Anxiety Disorder

Pharmacotherapy

First-line medications

- SSRIs
- SSNIs

- SSRIs generally preferred; but consider:
  - Side-effect profile
  - Drug interactions
  - Pt history/preference

First-line

SSRIs

- paroxetine
- sertraline
- citalopram
- escitalopram

- Also: fluoxetine, fluvoxamine

- NNT: 5

SNRIs

- venlafaxine ER
  - More effective than placebo at 75 and 150mg qday
  - Not more effective than placebo at 37.5mg qday
  - L/T trials have show efficacy for >6months
- duloxetine

SSRIs

- Paroxetine at 20mg qday and 40mg qday vs. placebo:
  - After 8 weeks:
  - both doses →greater reduction of anxiety sx than placebo (62% and 68 % vs. 46%)
  - Rates of remission: 30% and 36% vs. 20%

Second-line medications

- TCAs:
  - imipramine has been found to be effective
- BZDs:
  - Can lead w/in minutes to reduction in emotional and somatic sx
  - But: risk of dependence, tolerance
  - Consider using for acute mgmt. of sx during period before SSRI/SNRI takes effect

Other medications

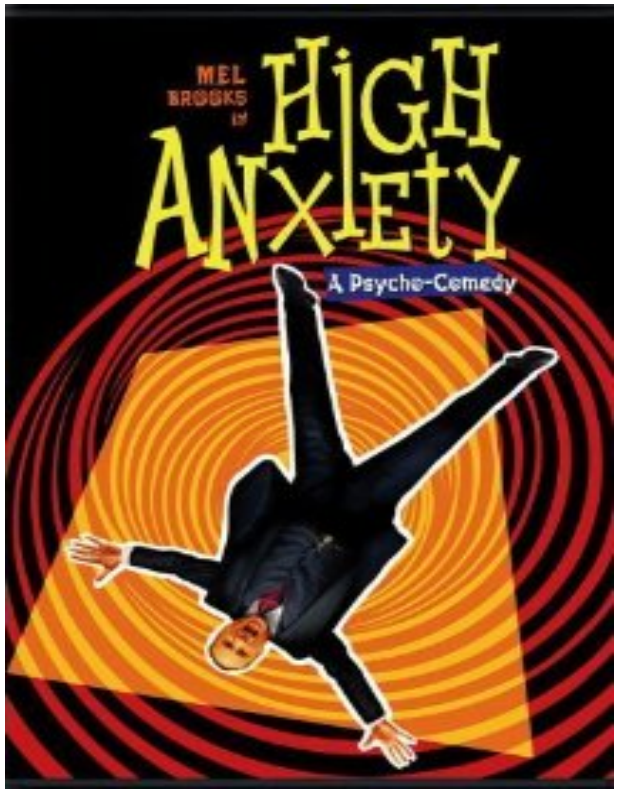
- buspirone
  - FDA approved for anxiety disorders
  - generally considered to apply to dx of GAD
  - mechanism:
    - blockade of 5HT1A autoreceptors

Other medications

- mirtazipine
- quetiapine

- -as single agent or as augmentation
- -not FDA-approved for GAD
- -consider side effects

Psychotherapy



CBT

- Found in clinical trials to be effective
  - vs. controls and other psychotherapies
- Addresses cognitive, behavioral and physiological features of GAD

CBT

- encourages evidence-based thinking
- works on problem-solving
- addresses behavioral skills
- exposure therapy

Exposure

- Repeated exposure to anxiety-provoking situations:
  - leads to decrease in emotional response and autonomic arousal
  - reduces drive to worry excessively about avoiding such situations/images

Progressive muscle relaxation

- brief, deliberate tension, then progressive relaxation of all muscle groups in a systematic manner
- reduces muscle tension and vigilance to threat, poor sleep, poor concentration
- can incorporate cue-control relaxation and/or breathing exercises

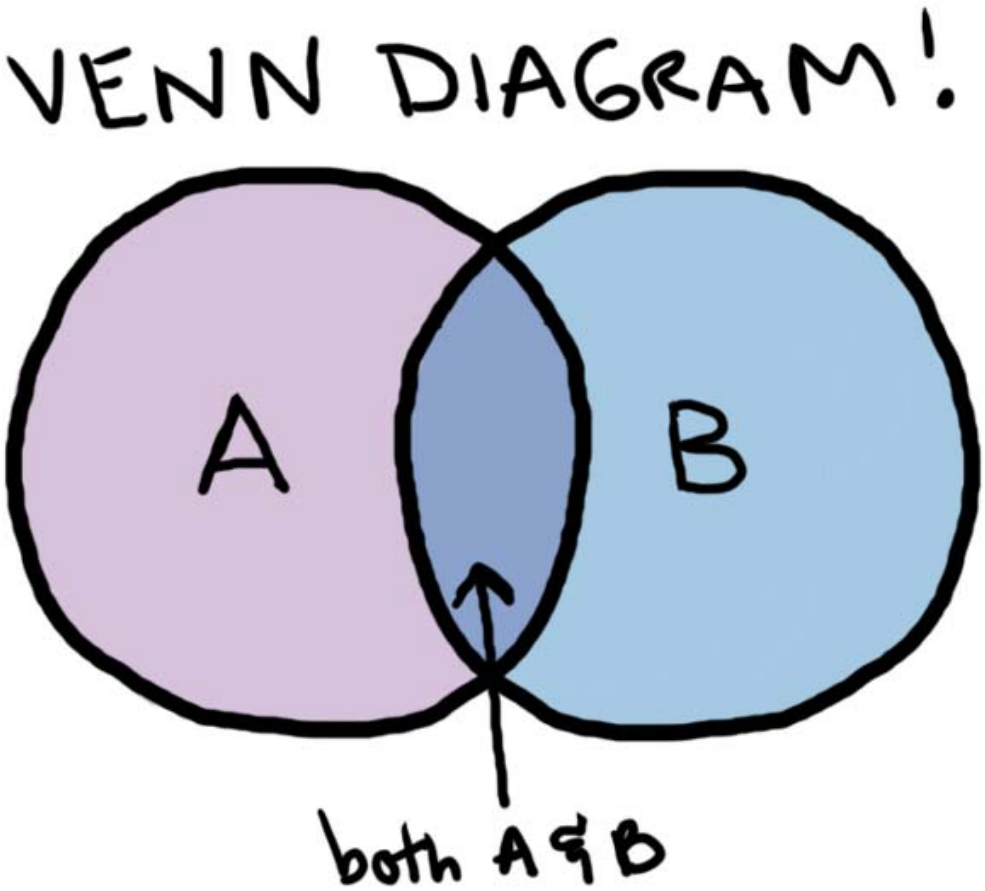
Efficacy of CBT

- a 2005 meta-analysis of 65 RCTs and NRCTs found CBT to be effective for GAD
  - superior to “no treatment”
- Treatment effects have been found to persist for 6-12 months
  - Avg. response rate: 56% (44-71%) at end of tx and 57% (39-76%) at 6 month f/u

Other psychotherapies

- Psychodynamic therapy
- Emotional regulation therapy
- Acceptance and commitment therapy

Combination of meds + CBT



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