Panic Disorder

DSM-V Criteria

A. **Recurrent unexpected panic attacks**. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time ***four*** (or more) of the following symptoms occur:

NOTE: abrupt surge can occur from a calm or anxious state

DSM-V Criteria - Sx of Panic Attack

- Palpitations, pounding heart, or accelerated HR
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feelings of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- chills or heat sensations
- Paresthesias (numbness or tingling sensations)
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or “going crazy”
- Fear of dying

DSM-V Criteria Continued

B. At least one of the attacks has been followed by ***1 month (or more)*** of one or both of the following:

1. Persistent concern or worry about additional panic attacks or their consequences
2. A significant maladaptive change in behavior related to the attacks

DSM-V Criteria Continued

C. 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, cardiopulmonary disorders).

DSM-V continued

D. The disturbance is **not better explained by another mental disorder** (e.g., the panic attacks do not occur only in the response to feared social situations, as in social anxiety disorder; in response to circumscribed objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

Prevalence and Outcome Predictors of Panic Disorder

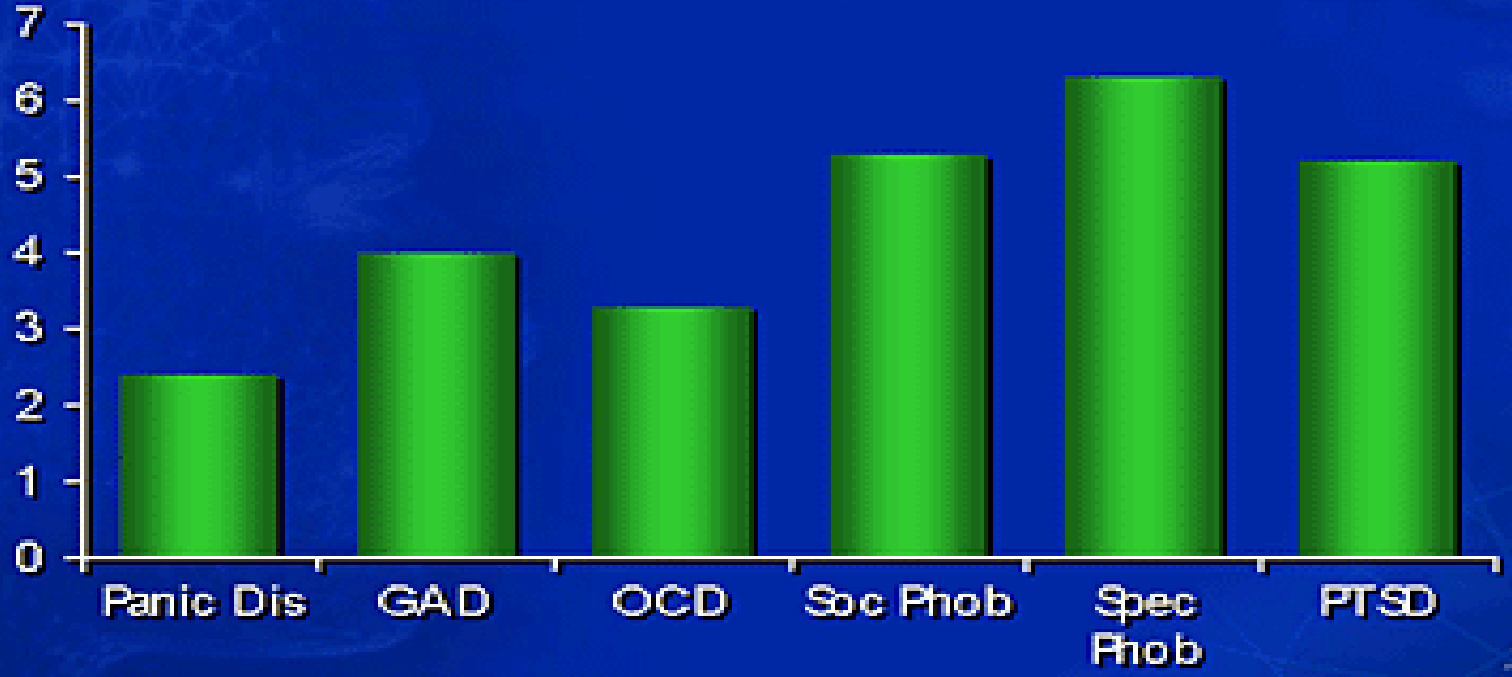
Prevalence of Panic Disorder

- 12-month prevalence: 2.7%*
- Lifetime prevalence: 4.7% *
- European 12-month prevalence: 1.8%
    - Lowest prevalence in Asian, African, and Latin American countries, ranging from 0.1% to 0.8%

- Panic attacks alone (w/o underlying panic disorder) are much more common, occurring in up to 1/3 of all individuals at some point in life

*Age 15 to 54, United States population

Prevalence of Anxiety Disorders (in US Millions)



Source: National Institutes of Mental Health.

Epidemiology of Panic Disorder

Women : men ratio of approx. 2:1

5% lifetime among women vs 2% lifetime among men

Bimodal age distribution

15 to 19 yrs old and again at 35 to 50 yrs old

Median age at onset in U.S. 20 to 24 y/o

Ethnic distribution (In the United States)

Risk/Prognostic Factors

1. Genetic/physiological
2. Temperamental
3. Environmental

Genetic/Physiological Risk Factors

Multiple genes thought to confer vulnerability

Increased risk with positive family history (esp. first-degree relative)

Twin studies: higher concordance between monozygotic twins than dizygotic twins

Respiratory disturbances

e.g. asthma in childhood

Temperamental Risk Factors

Negative affectivity (neuroticism)

Anxiety sensitivity

fear of anxiety symptoms

History of “fearful spells”

limited-symptom attacks

Environmental Risk Factors

Childhood adversity

- –physical or sexual abuse

Smoking

Life stressors

- –an accident, trauma, rape or assault
- –severe illness or death in close friend or

In patients with PD…

Panic disorder is associated with high levels of social / occupational / physical disability

$$$ economic costs and the **highest # of medical visits among the anxiety disorders**

Individuals w panic disorder may miss work, school for doctor/ED visits which can ---> unemployment, dropping out of school

Having a college education and employment are

References

American Psychiatric Association DSM V

Katon, Wayne, MD. "Panic Disorder: Epidemiology, Pathogenesis, Clinical Manifestations, Course, Assessment, and Diagnosis." *UpToDate*. N.p., 28 Aug. 2013. Web. 7 Sept. 2014

Chavira, Denise A., et al. "Predictors of clinical improvement in a randomized effectiveness

Neurobiology of Anxiety

Anxiety and Fear

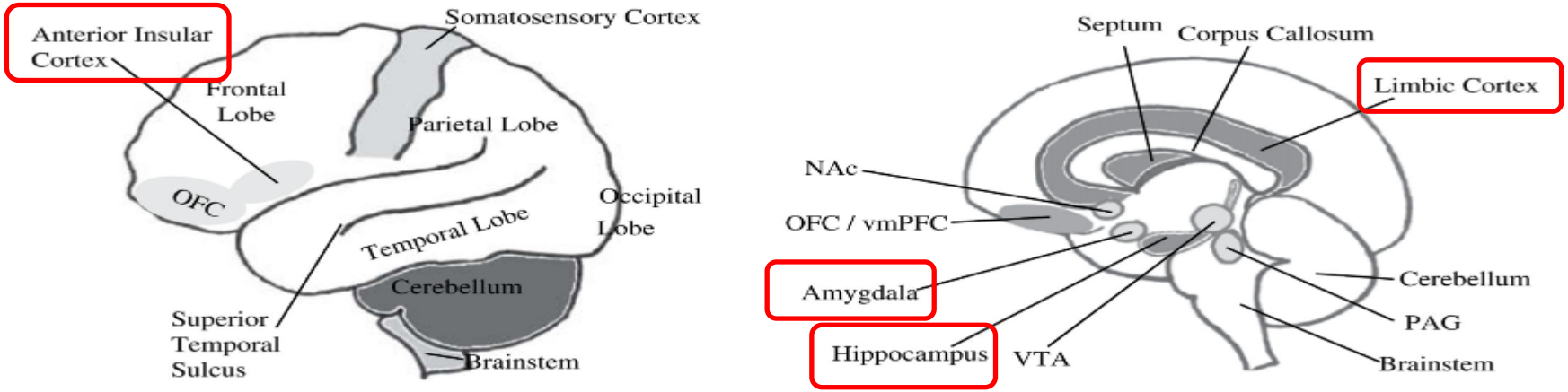
- Anxiety and fear differ in the likelihood, timing, and nature of the future event

Uncertainty requires a difficult balance

EFFICIENCY ←→ EFFECTIVENESS

Primary brain structures implicated include brainstem, limbic

Anxiety and the Limbic System

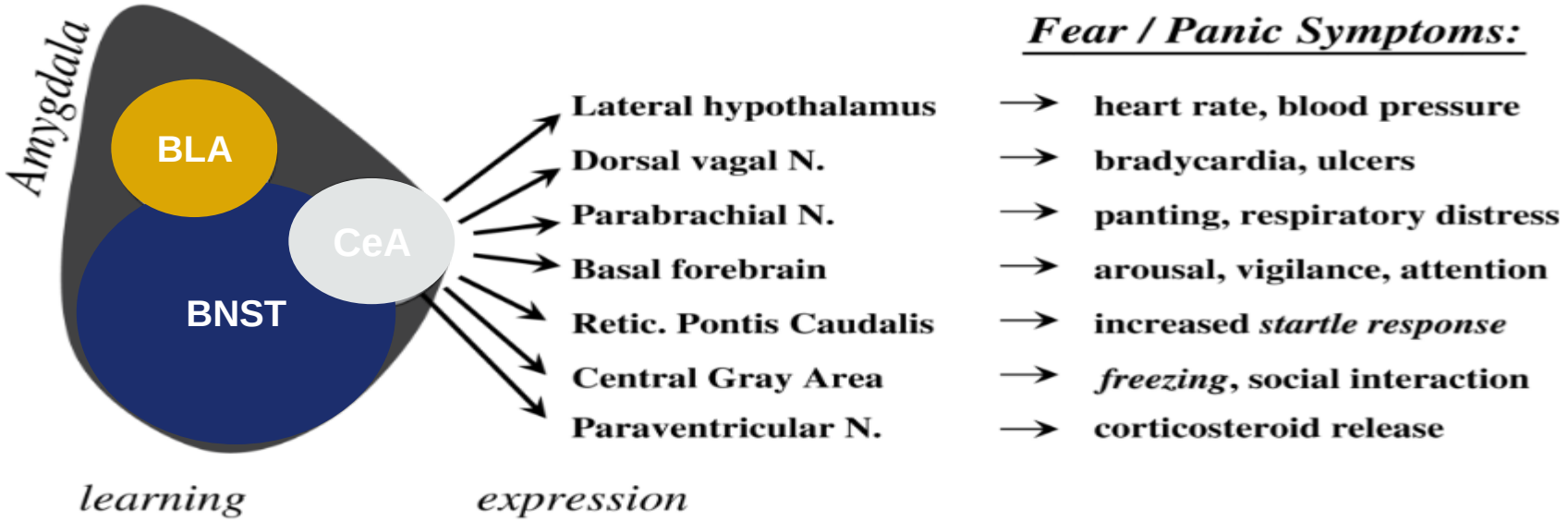


-Disruption of balance in emotional centers of the brain

-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

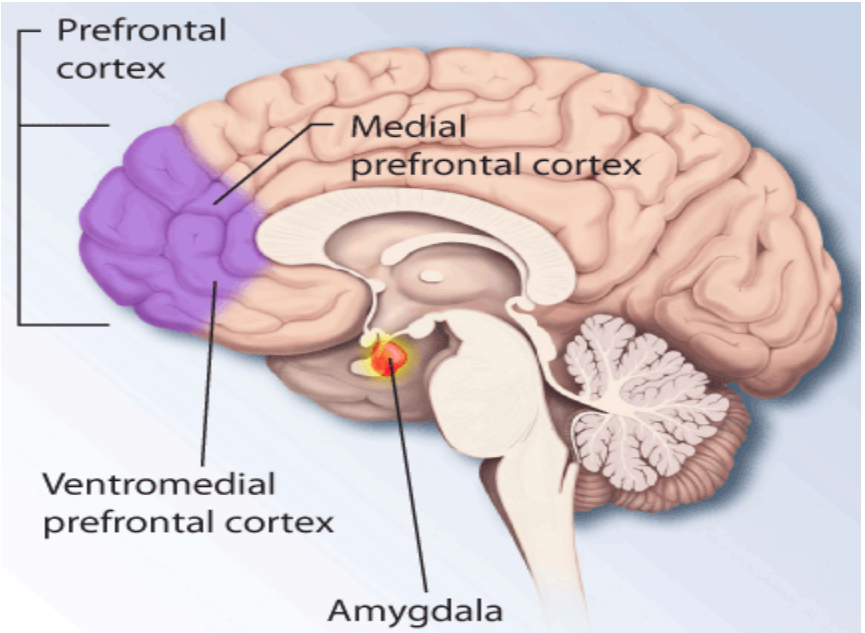


- Hypertrophy of amygdala after stress contributes to anxiety

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

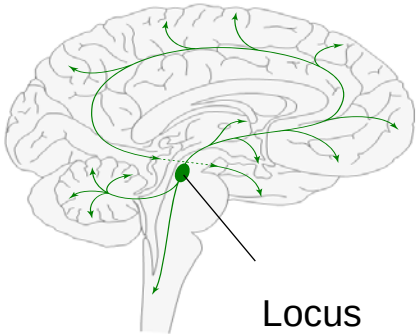
Commonality among anxiety disorders: aberrant and excessive anticipatory response under the condition of threat uncertainty

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

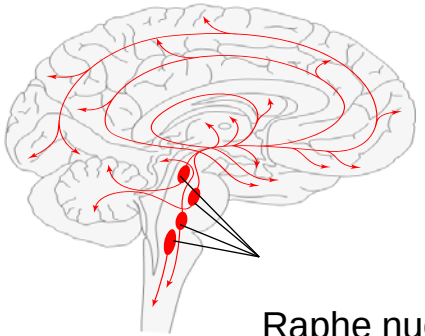
Norepinephrine
excitatory



Locus coeruleus

excessive excitatory effect

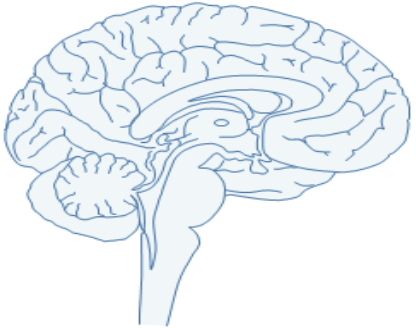
Serotonin
modulatory



Raphe nuclei

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

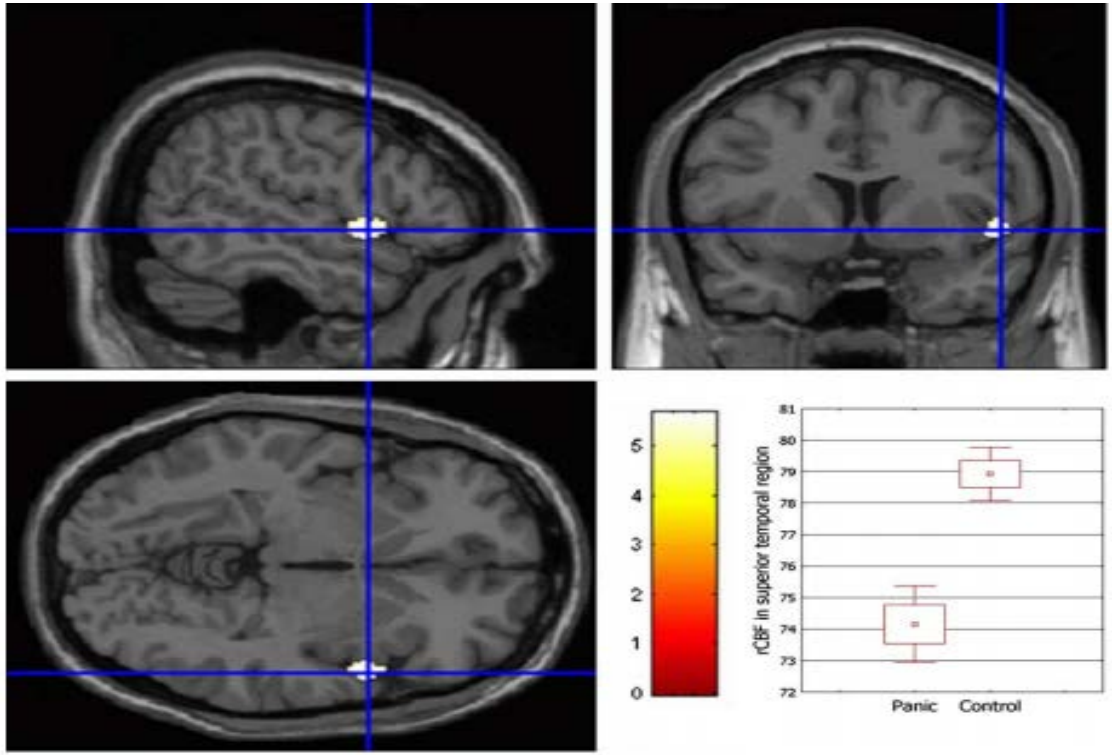
Functional PET Imaging

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

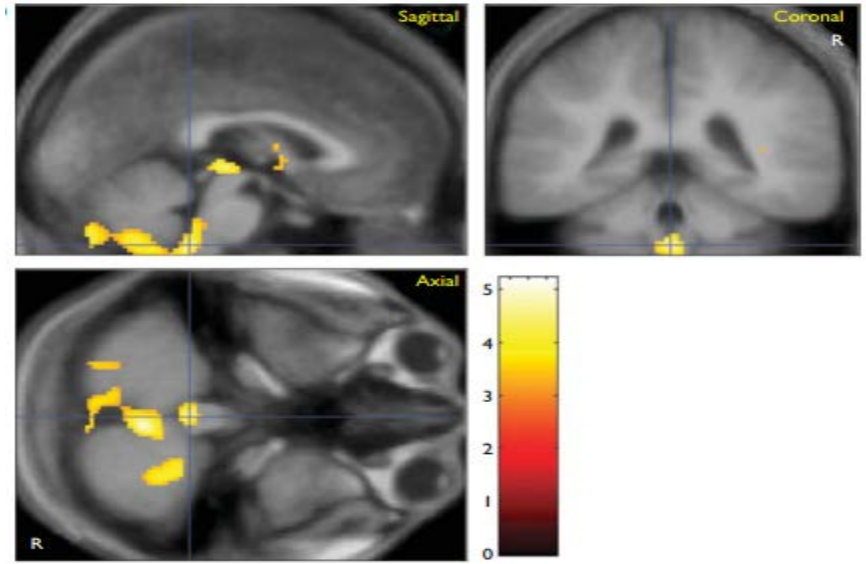
Decreased CBF in R Temporal Lobe



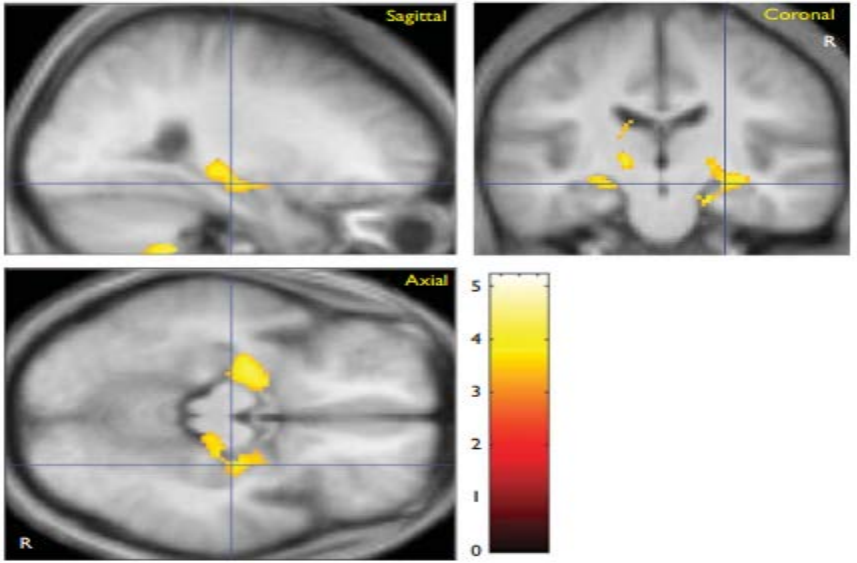
Lee et al, *Journ Psych Res* 2006

Increased Metabolic Activity in Panic Disorder

Brainstem, Cerebellum



Hippocampus, Thalamus

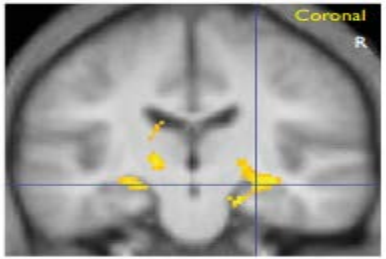


Sakai et al, *Neurorep* 2005

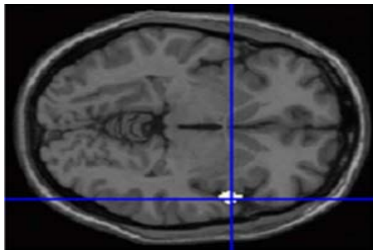
Take-Home Point

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

Overactive limbic system



Underactive prefrontal cortex



Treatment of Panic Disorder

Team 5

Psychotherapy - CBT

- Recreation of feared symptoms and modification of patient’s responses
- Teaches coping skills for somatic symptoms
  - Education
  - Self-monitoring
  - Breathing Retraining
  - Progressive Muscle Relaxation (PMR)
  - Cognitive Restructuring
  - Exposure
  - Relapse Prevention

CBT

- Most effective for highly motivated individuals
- 12-16 sessions over 3-4 months
- 60-120 minutes per session
- Initial response in 4-8 weeks, full response in 8-12 weeks
- Predictors of poor response:
  - Many medical comorbidities
  - Attrition from CBT program (often due to low education and SES)

Neural Basis of CBT

- MPFC/ACC - amygdala interactions implicated in fear extinction
- In patients with panic disorder with agoraphobia, non-responders to CBT showed increased activity in pregenual ACC, amygdala, and hippocampus during safety signal processing
- CBT treatment response predicted by pre-treatment strength of MPFC/ACC - amygdala inhibitory circuit
  - Patients with stronger circuits show more benefit from CBT

Pharmacotherapy

- First Line:
  - SSRI
- Second line:
  - SNRI or second trial of SSRI
- Alternative:
  - Benzos
  - TCA
  - MAOI

Drugs - First Line

- No SSRI proven to be more effective than the others
- Chosen based on drug interactions and SE profile
- SSRI:
  - Fluoxetine/Prozac – medication interaction
  - Paroxetine/Paxil – short $T_{1/2}$, sedating
  - Citalopram/Celexa – limited SE and interactions
  - Escitalopram/Lexipro – limited SE and interactions
  - Sertraline/Zoloft – diarrhea, limited interactions
  - Fluvoxamine/Luvox – short $T_{1/2}$, uncommonly used

Drugs - Second Line

- SNRI proven to be just as effective as SSRI in treatment of Panic Disorder
- SSRI still preferred because of greater SNRI SE
  - Increased BP at higher doses
- SNRI:
  - Venlafaxine/Effexor
  - Duloxetine/Cymbalta

Drugs - Alternatives

- TCA shown to be effective – imipramine, clomipramine
  - Usually avoided because of greater side effect profile
  - SE may increase anxiety (somatic awareness)
- MAOI rarely used due to SE and dietary restrictions
- Benzos should be used with caution – alprazolam and clonazepam
  - potential for abuse
  - Used only when pt not responsive to first and second line therapies
- Combination Therapy
  - SSRI takes 2-4 weeks, up to 12 weeks to manifest response
  - Benzos show effect within 1 week
  - Benzos can be used to “bridge the gap” in therapeutic effect

Efficacy

- Either CBT alone or medications alone are more effective than placebo
- CBT and medications are equally effective
- Effects of CBT are more enduring
- CBT + medications is superior to either alone

Summary

- Psychotherapy in combination with Pharmacotherapy is most effective
- Psychotherapy:
  1. CBT
- Pharmacotherapy:
  1. SSRI
  2. SNRI
  3. Alternatives or combination therapy

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1. Katon, WJ. Panic Disorder. NEJM (2006).
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