Neurobiology of Fear and the Pathology of Anxiety

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"I'm free-range, but I still feel caged in by my doubts and fears."
A review of DSM 5

Anxiety Disorders,

Obsessive-Compulsive and Related Disorders,

Trauma and Stressor-Related Disorders,

and the underlying neurobiology and neurocircuitry of the brain modulating fear and anxiety
What we will review

• Brain neurocircuits and Neurochemistry
• Epidemiology of Anxiety Disorders
• Epidemiology of OCD and Related Disorders
• Epidemiology of Trauma and Stressor Related Disorders
• Comorbid psychiatric diagnoses
• Diagnostic criteria for these disorders
• Brain study findings of these disorders
Limbic System and Related Structures
Focused Neuroanatomy Review

- Amygdala: involved with processing of emotionally salient stimuli
- Medial prefrontal cortex (includes the anterior cingulate cortex, the subcallosal cortex and the medial frontal gyrus): involved in modulation of affect
- Hippocampus: involved in memory encoding and retrieval
Amygdala

• The amygdala is a well-known epicenter for the emotional "understanding" of stimuli.

• In other words, the amygdala helps the brain to remember the averseness of otherwise neutral stimuli.

• Therefore, the amygdala is an integral part of the circuitry maintaining memories for aversive events.

• Clinical studies based on animal data consistently point to amygdala hyperactivity in anxiety disorders.
Amygdala- Numerous Connections and Fear Pathways
Amygdala

Fear / Panic Symptoms:

- heart rate, blood pressure
- bradycardia, ulcers
- panting, respiratory distress
- arousal, vigilance, attention
- increased startle response
- freezing, social interaction
- corticosteroid release

HPA Axis

Hippocampus

Hypothalamus

Pituitary

Adrenal Cortex

LA

CeA

Basolateral

Lateral hypothalamus
Dorsal vagal N.
Parabrachial N.
Basal forebrain
Retic. Pontis Caudalis
Central Gray Area
Paraventricular N.

learning

expression
Locus Coeruleus

- Principal site for brain synthesis of Norepinephrine
- Projects into the spinal cord, brain stem, amygdala, Hypothalamus and cortex
- Component of the Reticular Activating System
- Likely involved in depression, panic disorder, memory, arousal, Parkinson’s and Alzheimer’s disease
### Differential Activation of Brain Structures

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Neurotransmitters and Neuropeptides Dysregulation

- Dopamine
- Serotonin
- Norepinephrine
- Vasopressin
- Oxytocin
- Cholecystokinin
- Galanin
- Neuropeptide Y
- Corticotropin–releasing factor
- Multiple genes also regulate expression
- Epigenetic factors influence expression
Normal versus Pathologic Anxiety

• Normal anxiety is adaptive. It is an inborn response to threat or to the absence of people or objects that signify safety can result in cognitive (worry) and somatic (racing heart, sweating, shaking, freezing, etc.) symptoms.

• Pathologic anxiety is anxiety that is excessive, impairs function.

• Anxiety may be due to one of the primary anxiety disorders OR secondary to substance abuse (Substance-Induced Anxiety Disorder), a medical condition (Anxiety Disorder Due to a General Medical Condition), another psychiatric condition, or psychosocial stressors (Adjustment Disorder with Anxiety)
General considerations for anxiety disorders

- Often have an early onset- teens or early twenties
- Show 2:1 female predominance
- Have a waxing and waning course over lifetime
- Similar to major depression and chronic diseases such as diabetes in functional impairment and decreased quality of life
DSM 5 Anxiety disorders

- Specific phobia
- Social anxiety disorder (SAD)
- Panic disorder (PD)
- Agoraphobia
- Generalized anxiety disorder (GAD)

- Anxiety Disorder due to a General Medical Condition
- Substance-Induced Anxiety Disorder
- Anxiety Disorder NOS
Epidemiology of anxiety disorders

Genetic Epidemiology of Anxiety Disorders

• There is significant familial aggregation for PD, GAD, OCD and phobias

• Twin studies found heritability of 0.43 for panic disorder and 0.32 for GAD.

Specific Phobia
Specific Phobia

• Marked or persistent fear (>6 months) that is excessive or unreasonable cued by the presence or anticipation of a specific object or situation
  • Anxiety must be out of proportion to the actual danger or situation
  • It interferes significantly with the persons routine or function
Specific Phobia

- Epidemiology
  - Up to 15% of general population
  - Onset early in life
  - Female: Male 2:1

- Etiology
  - Learning, contextual conditioning

- Treatment
  - Systematic desensitization
Social Anxiety Disorder (SAD)

- Marked fear of one or more social or performance situations in which the person is exposed to the possible scrutiny of others and fears he will act in a way that will be humiliating
- Exposure to the feared situation almost invariably provokes anxiety
- Anxiety is out of proportion to the actual threat posed by the situation
- The anxiety lasts more than 6 months
- The feared situation is avoided or endured with distress
- The avoidance, fear or distress significantly interferes with their routine or function
SAD epidemiology

- 7% of general population
- Age of onset teens; more common in women. Stein found half of SAD patients had onset of sx by age 13 and 90% by age 23.
- Causes significant disability
- Increased depressive disorders

What is going on in their brains??

- Study of 16 SAD patients and 16 matched controls undergoing fMRI scans while reading stories that involved neutral social events, unintentional social transgressions (choking on food then spitting it out in public) or intentional social transgressions (disliking food and spitting it out)

What is going on in their brains??

• Both groups ↑ medial prefrontal cortex activity in response to intentional relative to unintentional transgression.

• SAD patients however showed a significant response to the unintentional transgression.

• SAD subjects also had significant increase activity in the amygdala and insula bilaterally.

What is going on in their brains??

Functional imaging studies in SAD

• Several studies have found hyperactivity of the amygdala even with a weak form of symptom provocation namely presentation of human faces.
• Successful treatment with either CBT or citalopram showed reduction in activation of amygdala and hippocampus

Furmark T et al. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive behavior therapy. Arch Gen Psychiatry 2002; 59:425-433
Panic Disorder

• Recurrent unexpected panic attacks and for a one month period or more of:
  • Persistent worry about having additional attacks
  • Worry about the implications of the attacks
  • Significant change in behavior because of the attacks
A Panic Attack is:

A discrete period of intense fear in which 4 of the following Symptoms abruptly develop and peak within 10 minutes:

- Palpitations or rapid heart rate
- Sweating
- Trembling or shaking
- Shortness of breath
- Feeling of choking
- Chest pain or discomfort
- Nausea
- Chills or heat sensations
- Paresthesia
- Feeling dizzy or faint
- Derealization or depersonalization
- Fear of losing control or going crazy
- Fear of dying
Panic disorder epidemiology

- 2-3% of general population; 5-10% of primary care patients
- Onset in teens or early 20’s
- Female: male 2-3:1
Things to keep in mind

• A panic attack ≠ panic disorder
• Panic disorder often has a waxing and waning course
• 50-60% have lifetime major depression
  • One third have current depression
• 20-25% have history substance dependence
Panic Disorder Etiology

- Drug/Alcohol
- Genetics
- Social learning
- Cognitive theories
- Neurobiology/conditioned fear
- Psychosocial stressors
  - Prior separation anxiety
Agoraphobia

• Marked fear or anxiety for more than 6 months about two or more of the following 5 situations:
  • Using public transportation
  • Being in open spaces
  • Being in enclosed spaces
  • Standing in line or being in a crowd
  • Being outside of the home alone
Agoraphobia

• The individual fears or avoids these situations because escape might be difficult or help might not be available
• The agoraphobic situations almost always provoke anxiety
• Anxiety is out of proportion to the actual threat posed by the situation
• The agoraphobic situations are avoided or endured with intense anxiety
• The avoidance, fear or anxiety significantly interferes with their routine or function
Prevalence

• 2% of the population
• Females to males: 2:1
• Mean onset is 17 years
• 30% of persons with agoraphobia have panic attacks or panic disorder
• Confers higher risk of other anxiety disorders, depressive and substance-use disorders
Generalized Anxiety Disorder

• Excessive worry more days than not for at least 6 months about a number of events and they find it difficult to control the worry.
• 3 or more of the following symptoms:
  • Restlessness or feeling keyed up or on edge, easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbance
• Causes significant distress or impairment
Generalized Anxiety Disorder Epidemiology

- 4-7% of general population
- Median onset=30 years but large range
- Female: Male 2:1
GAD Comorbidity

• 90% have at least one other lifetime Axis I Disorder
• 66% have another current Axis I disorder
• Worse prognosis over 5 years than panic disorder
Obsessive-Compulsive and Related Disorders

- Obsessive-Compulsive Disorder
- Body Dysmorphic Disorder
- Hoarding Disorder
- Trichotillomania
- Excoriation Disorder
Prevalence of Obsessive-Compulsive Related Disorders

- **Body Dysmorphic Disorder-** 2.4%
  - 9-15% of dermatologic pts
  - 7% of cosmetic surgery pts
  - 10% of pts presenting for oral or maxillofacial surgery!

- **Hoarding Disorder-** est. 2-6%  
  F<M

- **Trichotillomania** 1-2%  F:M 10:1!

- **Excoriation Disorder** 1.4%  F>M
Obsessive-Compulsive Disorder (OCD)

- Obsessions defined by:
  - recurrent and persistent thoughts, impulses or images that are intrusive and unwanted that cause marked anxiety or distress
  - The person attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e. compulsion)
OCD continued

• Compulsions as defined by:
  • Repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession or according to rigidly applied rules.
  • The behaviors or acts are aimed at reducing distress or preventing some dreaded situation however these acts or behaviors are not connected in a realistic way with what they are designed to neutralize or prevent.
OCD continued

• The obsessions or compulsions cause marked distress, take > 1 hour/day or cause clinically significant distress or impairment in function

• Specify if:
  • With good or fair insight- recognizes beliefs are definitely or most likely not true
  • With poor insight- thinks are probably true
  • With absent insight- is completely convinced the OCD beliefs are true
  • Tic- related
OCD Epidemiology

- 2% of general population
- Mean onset 19.5 years, 25% start by age 14! Males have earlier onset than females
- Female: Male 1:1
OCD Comorbidities

- >70% have lifetime dx of an anxiety disorder such as PD, SAD, GAD, phobia
- >60% have lifetime dx of a mood disorder MDD being the most common
- Up to 30% have a lifetime Tic disorder
- 12% of persons with schizophrenia/ schizoaffective disorder
OCD Etiology

• Genetics
• Serotonergic dysfunction
• Cortico-striato-thalamo-cortical loop
• Autoimmune- PANDAS syndrome
  • Pediatric Autoimmune Neuropsychiatric Disorders Assoc with Streptococcal (group A beta hemolytic) infections that may produce rapid onset of OCD in subset of children
Functional imaging studies

• Increased activity in the right caudate is found in pts with OCD and Cognitive behavior therapy reduces resting state glucose metabolism or blood flow in the right caudate in treatment responders.

• Similar results have been obtained with pharmacotherapy

Trauma- and Stressor-Related Disorders

- Posttraumatic Stress Disorder
- Acute Stress Disorder
- Adjustment Disorders
Posttraumatic Stress Disorder

• Exposure to actual or threatened death, serious or sexual violence in one or more of the following ways:
  • Direct experiencing of traumatic event(s)
  • Witnessed in person the events as it occurred to others
  • Learning that the traumatic events occurred to person close to them
  • Experiencing repeated or extreme exposure to aversive details of trauma
PTSD continued

Presence of 1 or more intrusive sx after the event
- Recurrent, involuntary and intrusive memories of event
- Recurrent trauma-related nightmares
- Dissociative reactions
- Intense physiologic distress at cue exposure
- Marked physiological reactivity at cue exposure

Persistent avoidance by 1 or both:
- Avoidance of distressing memories, thoughts or feelings of the event(s)
- Avoidance of external reminders of that arouse memories of event(s) e.g. people, places, activities
Negative alterations in cognitions and mood associated with the traumatic event(s) as evidenced by 2 or more of the following:

- Inability to remember an important aspect of the traumatic event(s)
- Persistent distorted cognitions about cause or consequence of event that lead to blame of self or others
- Persistent negative emotional state
- Marked diminished interest
- Feeling detached from others
- Persistent inability to experience positive emotions
Marked alterations in arousal and reactivity with 2 or more of:

- Irritable behavior and angry outbursts
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle response
- Problems with concentration
- Sleep disturbance
PTSD continued

• Duration of disturbance is more than one month AND causes significant impairment in function

• Specifiers:
  • With dissociative symptoms (derealization or depersonalization)
  • With delayed expression (criteria not met until >6 months after event)
PTSD Epidemiology

• 7-9% of general population
• 60-80% of trauma victims
• 30% of combat veterans
• 50-80% of sexual assault victims
• Increased risk in women, younger people
• Risk increases with “dose” of trauma, lack of social support, pre-existing psychiatric disorder
Comorbidities

- Depression
- Other anxiety disorders
- Substance use disorders
- Somatization
- Dissociative disorders
Post Traumatic Stress Disorder Etiology

- Conditioned fear
- Genetic/familial vulnerability
- Stress-induced release
  - Norepinephrine, CRF, Cortisol
- Autonomic arousal immediately after trauma predicts PTSD
Functional neuroimaging in PTSD

• Increased amygdala activation is seen in PTSD pts compared to controls

• Hypoactivation of the medial prefrontal cortex including the orbitofrontal cortex and anterior cingulate cortex (area implicated in affect regulation)

Acute Stress Disorder

• Similar exposure as in PTSD
• Presence of ≥9 symptoms from 5 categories of intrusion, negative mood, dissociation, avoidance, and arousal related to the trauma.
• Duration of disturbance is 3 days to 1 month after trauma
• Causes significant impairment
• In some cases may evolve into PTSD
Adjustment Disorders

• Development of Emotional or Behavioral symptoms in response to an identifiable stressor(s) within 3 months of the onset of the stressor(s)

• Clinically significant as demonstrated by marked distress out of proportion to severity of the stressor or outside range of the normal response of the individual to stressor(s) and/or

• Significant impairment in social, occupational or other area of life functioning

• Generally resolves within 6 months but may be prolonged if stressor or consequences persist (lawsuit, economic dislocation, etc)
Adjustment Disorders

- The symptoms don’t represent normal bereavement
- Adjustment disorder are specified as:
  - With Depressed Mood
  - With Anxiety
  - With Mixed Anxiety and Depressed Mood
  - With Disturbance of conduct
  - With mixed disturbance of emotions and conduct
  - Unspecified
- Prevalence is high: 5-20% in outpatient Mental Health Clinics; in hospital psychiatric consultation setting may reach 50% of all Dx
Managing Anxiety

• Medication
  • Benzodiazepines
  • Antidepressants
  • Other adjunctive medication
  • ? CBD

• Psychotherapy
  • CBT
  • Exposure
  • Biofeedback

• Meditation and Alternative Therapies

• Diet/Exercise