The Phenomenology and Treatment of Anxiety Disorders

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What is Anxiety?

Anxiety is an unpleasant, anticipatory affective state with cognitive, autonomic, neuroendocrine, behavioral, and experiential components.
What is Fear?

Fear (behavior) is the response to specific environmental stimuli that are perceived as potentially dangerous.
Anxiety vs. Fear

ANXIETY

FEAR
Anxiety and Fear

• Normal Emotions
• Purpose
Neuroanatomy of Fear
THE CIRCUITRY OF FEAR
Three Components of Anxiety

- Physical Feelings
- Cognition (Thoughts, Interpretations, Images)
- Behaviours
The Physical Component

» Increased Heart Rate
» Breathlessness
» Dizziness
» Shaking
» Sweating
» Unreality/Detachment
» Blurred Vision
» Blushing
» Numbness/Tingling
The Cognitive Component

» Anxious Thoughts
» Anxious Predictions
» Anxious Beliefs and Interpretations
» Biases in Attention and Memory
» Mental Images
The Behavioural Component

• Avoidance of Situations and Activities
• Subtle Avoidance Strategies, Safety Signals, and Overprotective Behaviours
• Alcohol, Drug, and Medication Use
Spectrum Of Anxiety Disorders

- Panic Disorder
- Social / Simple Phobias
- OCD
- PTSD
- GAD
Prevalence Of Anxiety Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Anxiety Disorder</td>
<td>24.2</td>
</tr>
<tr>
<td>Social Anxiety Disorder</td>
<td>13.6</td>
</tr>
<tr>
<td>PTSD</td>
<td>7.1</td>
</tr>
<tr>
<td>GAD</td>
<td>5.3</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>3.1</td>
</tr>
<tr>
<td>OCD</td>
<td>2.3</td>
</tr>
</tbody>
</table>
# Age of Onset

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic Disorder</td>
<td>Late-Teens / Mid-30’s</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td></td>
</tr>
<tr>
<td>• Situational</td>
<td>Childhood / Mid-20’s</td>
</tr>
<tr>
<td>• Natural Environment</td>
<td>Childhood / Early Adult</td>
</tr>
<tr>
<td>• Animal / Blood / Injection</td>
<td>Childhood</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>Mid-Teens</td>
</tr>
<tr>
<td>OCD</td>
<td>6-15 Years: M / 20-29 Years: F</td>
</tr>
<tr>
<td>PTSD</td>
<td>Any Age</td>
</tr>
<tr>
<td>GAD</td>
<td>Childhood / Adolescence</td>
</tr>
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</table>
Comorbidity of Depression and Anxiety Disorders

- 50% to 65% of panic disorder patients have depression†
- 70% of social anxiety disorder patients have depression**
- 49% of social anxiety disorder patients have panic disorder**
- 50% to 65% of panic disorder patients have depression†
- 11% of social anxiety disorder patients have OCD**
- 67% of OCD patients have depression*

Depression

Highly common

Social Anxiety Disorder

Highly comorbid

Panic Disorder

OCD
What is a Panic / Anxiety Attack?

An episode of intense fear or discomfort that peaks rapidly (within 10 minutes) and in which at least 4 of the following symptoms were experienced:

- palpitations, pounding or racing heart
- sweating
- trembling or shaking
- shortness of breath or smothering sensations
- feeling of choking
- chest pain or discomfort
- nausea or abdominal distress
- feeling dizzy, unsteady, faint or lightheaded
- feeling unreal or detached
- fear of losing control or going crazy
- fear of dying
- numbness or tingling sensations
- chills or hot flushes
Diagnostic Criteria For Panic Disorder

Criterion A: Recurrent, unexpected panic attacks followed by \( \geq 1 \) month(s) of persistent concern about another panic attack, worry about possible implications or consequences of panic attacks, or significant behavioral changes related to panic attacks

Criterion B: Diagnosis of panic disorder +/- agoraphobia*

Criterion C: Panic attacks not due to physiologic effects of a substance or medical condition

Criterion D: Panic attacks not better accounted for by another mental disorder
<table>
<thead>
<tr>
<th>Phenomenology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic Attacks</td>
<td>7.3%</td>
</tr>
<tr>
<td>Recurrent Panic Attacks</td>
<td>4.2%</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>3.5%</td>
</tr>
<tr>
<td>With Agoraphobia</td>
<td>1.5%</td>
</tr>
<tr>
<td>Without Agoraphobia</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Fearful spells corresponds to the concept of “simple panic attack.”
Agoraphobia

Anxiety about being in places or situations from which escape might be difficult or embarrassing in the event of a panic attack

Examples

Enclosed Places
Standing in Lines
Driving
Public Transportation
Being Alone
Crowds
Shopping Malls and Supermarkets
Specific Phobia

Excessive fear of a specific object or situation causing significant distress or impairment

Common Specific Phobias

- Animals and Insects
- Blood and Injections
- Heights
- Storms or Water
- Flying
- Enclosed Places
- Driving
- Choking
- Vomiting
Indiana Jones Syndrome
(Fear of Snakes)

“Snakes. Why did it have to be snakes?”
Social Anxiety Disorder
(Generalized Social Phobia)

Intense fear of social or performance situations causing significant distress or impairment

Common Feared Situations
- Parties
- Meetings
- Public Speaking
- Performing
- Eating, Drinking, or Writing in Public
- Crowded Places
- Initiating and/or Maintaining Conversations
Social Anxiety Disorder (DSM-IV)

• Fear/avoidance of social situations
• Feared situations avoided or endured with intense anxiety or distress
• Fear recognized as excessive or unreasonable
• Fear/avoidance interferes with work, social, family activities
Comorbidity In Social Anxiety Disorder

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lifetime Prevalence (%)</th>
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<tbody>
<tr>
<td>Simple Phobia</td>
<td>60</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>50</td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>15</td>
</tr>
<tr>
<td>Major Depression</td>
<td>10</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>10</td>
</tr>
<tr>
<td>Drug Abuse</td>
<td>10</td>
</tr>
<tr>
<td>OCD</td>
<td>10</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>5</td>
</tr>
</tbody>
</table>
Obsessive-Compulsive Disorder

Recurrent and persistent

**Obsessions**
intrusive thoughts, impulses, images
and/or

**Compulsions**
repetitive behaviours or mental acts

Symptoms cause marked distress or impairment
Time consuming (more than 1 hour/day)
Obsessions

Contamination Obsessions
Excessive Doubting
Need for Symmetry
Accidental Harm to Others
Aggressive Obsessions
Religious Obsessions
Compulsions

Checking
Washing and Cleaning
Need to Ask or Confess
Symmetry and Precision
Hoarding
Repeating Actions or Words
Hoarding

Fear of “Germs”
Coexisting Axis I Diagnoses In Primary OCD

- Major Depression: 67%
- Simple Phobia: 22%
- Social Anxiety Disorder: 18%
- Eating Disorder: 17%
- Alcohol Use Disorder/Dependence: 14%
- Panic Disorder: 12%
- Tourette Syndrome: 7%
- Separation Anxiety Disorder: 2%

Lifetime Prevalence (%)
Posttraumatic Stress Disorder

Exposure to a traumatic event
Reaction to the event involves extreme fear

Symptoms
Reexperiencing of the trauma
Avoidance of trauma-related cues
Numbing of emotional responsiveness
Chronic overarousal
Non-Combat-Related Trauma Associated With PTSD

- Rape
- Molestation
- Physical Attack
- Accident
- Physical Abuse

Incidence (%)

- Males
- Females
Generalized Anxiety Disorder

**Excessive Worry About**
- Work
- Family and Children
- Health
- Finances
- Minor Matters

Worry occurs most days (for at least 6 months)

Difficult to control worry

Associated with disturbed sleep, irritability, restlessness, poor concentration, fatigue, muscle tension
Diagnostic Criteria for GAD

- Excessive anxiety and worry, for more days than not for ≥6 months, about many subjects
- Worry is difficult to control
- Anxiety, worry, physical symptoms impair social, occupational, and other functioning
Diagnostic Criteria for GAD (cont’d)

• Associated with $\geq 3$ of the following
  – restlessness/keyed-up
  – easily fatigued
  – difficulty concentrating
  – irritability
  – muscle tension
  – sleep disturbances
• Cannot be confined to another Axis 1 diagnosis or the effects of a substance or medical condition
Symptom Overlap In GAD And Depression

GAD
- Agitation
- Restlessness
- Dysphoria
- Tension
- Sleep
- Irritability
- Fatigue
- Worry
- Concentration

Depression
- Interest
- Appetite
- Esteem
- Suicide
- Agitation
- Restlessness
- Dysphoria
- Tension
- Sleep
- Irritability
- Fatigue
- Worry
- Concentration
Lifetime Prevalence of Comorbid Disorders in Patients with GAD

- Any Disorder: 90.4%
- Major Depression: 62.4%
- Panic Disorder: 23.5%
- Social Anxiety Disorder: 34.4%
- Alcohol Abuse and Dependence: 37.6%
Anxiety: An Integrated Causal Model

- **Biological Factors**
  - Genetics
  - Neurobiology

- **Psychological Factors**
  - Sense of Controllability
  - Conditioning (learning experiences)
  - Cognitions/Expectancies of Danger
  - Anxiety Sensitivity

- **Environmental Factors**
  - Stressful Life Events
  - Social Pressures to Succeed
Neurotransmitter Deficiency Hypotheses of Anxiety

• Serotonin (biogenic amine)

• Gamma-aminobutyric acid (GABA)
Neurotransmitter Excess Hypotheses of Anxiety

- Norepinephrine (biogenic amine)
- Glutamate
Serotonin (5HT) in Anxiety Disorders

• Role likely complex: Acute increases in 5-HT can be both anxiogenic and anxiolytic; Dorsal raphe to amygdala-HPC likely anxiogenic via 5-HT2 receptors, but medial raphe to HPC via 5-HT1A likely anxiolytic

• Selective serotonin reuptake inhibitors (SSRIs): effective anti-anxiety treatment across a number of disorders (generalized anxiety, social phobias, PTSD, OCD, panic disorder) and other serotonergic tricyclic antidepressants are effective in some anxiety disorders
GABA in Anxiety Disorders

- Benzodiazepines (BZ) which bind to the GABA-A receptor and enhance GABA activity (allosteric modulation) is a potent and acute anxiolytic, and widely effective in treating a variety of anxiety disorders.

- Other positive allosteric GABA-receptor modulators (barbiturates, alcohol) have anxiolytic effects.

- BZ-Receptor inverse agonists and antagonists (flumazenil) cause panic attacks and increase anxiety in panic disorder patients.

- Reductions in occipital cortex GABA level detected with $^1$H-magnetic resonance spectroscopy in unmedicated PD subjects.

- Some evidenced of reduced BZ receptor density and GABA in the brains of anxious individual and patients with anxiety disorders.

- Genetically-altered mice (GABA-A/BZ receptor knockouts) show enhanced anxious behaviors and are refractory to BZ treatment.
Norepinephrine (NE) in Anxiety Disorders

- Norepinephrine reuptake inhibitors (NRI) such as tricyclic antidepressants block NE are effective anti-anxiety treatments; efficacy of NRIs is associated with down-regulate β-adrenergic receptors and decreased sensitivity of 5-HT2 receptors after long term treatment.

- β-adrenergic agonists can provoke anxiety / panic, whereas β-adrenergic antagonists (β-blocker propanolol) can reduce anxiety (targets peripheral / autonomic response, but worry / anticipatory anxiety).

- α-adrenergic antagonists (yohimbine) which increase presynpatic NE output can provoke anxiety / panic, whereas α-adrenergic agonists (clonidine) which decrease presynaptic NE output can reduce anxiety. Anxiety patients (e.g., panic disorder) have enhanced anxiogenic effects to yohimbine and blunted effects to clonidine.

- Stress paradigms (e.g., learned helplessness) in animals evoke hypersecretion of NE.

- In animals, stimulation of locus ceruleus (LC) causes a release of NE and fear and anxious behaviors, whereas ablation of LC blocks fear responses.

- SSRIs, effective anxiolytics, indirectly decrease NE output via 5-HT inhibitory projections from dorsal raphe to LC.
<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Mechanism</th>
</tr>
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<tbody>
<tr>
<td>Temporal pairing of a neutral stimulus (conditioned stimulus, CS) with an aversive stimulus (the unconditioned stimulus). After one or several paired presentations, learning occurs and the CS alone can trigger the fear response</td>
<td>Sensory information from the sensory thalamus is conveyed to lateral nucleus of the amygdala. Long term potentiation in amygdalo-hippocampal pathways via NMDA receptor activation needed for memory formation of emotionally salient events</td>
</tr>
<tr>
<td>The process habituates If the CS is repeatedly presented without the paired US, the fear responses decline and cease (extinction)</td>
<td>Extinction relies on the orbitofrontal cortex, which is necessary to modulate amygdala activity</td>
</tr>
<tr>
<td>Contextual fear conditioning occurs when organisms express similar responses to the context in which the conditioning occurred. This occurs in the absence of a discrete CS.</td>
<td>The hippocampal network is crucial for this process.</td>
</tr>
<tr>
<td>Fear response triggered by the conditioned stimulus.</td>
<td>Sensory information from the sensory thalamus is conveyed to lateral nucleus of the amygdala. <em>The central nucleus projects to multiple output areas</em></td>
</tr>
</tbody>
</table>
Neuroanatomy of Anxiety Disorders

- **Amygdala**: The central “Fear Center”
  - Temporal Lobe Epilepsy related to attacks of acute fear / anxiety
  - Animal studies show that it is critical to fear conditioning / aversive learning and expression of fear responses
  - Human lesion and imaging studies show that it is important for emotional memories, and detection of fear

- **Locus Coeruleus (LC)**
  - Retropontine nucleus, major source of brain’s adrenergic innervation
  - LC stimulation generates panic attacks
  - LC blockade (by TCA, BZ) decreases panic attacks

- **Septo-Hippocampal GABAergic system**
  - Mediates anxiety and vigilance
  - High concentration of GABAergic neurons and receptors
  - Directly connected to LC
Neuroanatomy of Anxiety Disorders

**Anxiety Disorders**

Amygdala is overactive / hyperactive in response to threat-related fear-provoking stimuli in social phobia, PTSD, specific phobia

**Post-traumatic Stress Disorder**

- Hippocampal Volume Tends to be Smaller
- Correlates with Traumatic Exposure
- ? Result of Elevated Cortisol at Time of Trauma ?
- ? Do Brain Abnormalities Cause PTSD or Does PTSD Causes Abnormalities?
Neuroimaging and Anxiety Disorders

Initial findings generally implicate amygdala, medial frontal cortex, hippocampus, and basal ganglia:

- PTSD, phobic patients have increased amygdala activity to threatening stimuli, and reduced medial frontal activity
- PTSD patients have reduced hippocampal and anterior cingulate volume
- OCD patients have abnormal activity in their striatum/basal ganglia
- Neurosurgery at selected tissue (capsulotomy, cingulotomy, limbic leucotomy and subcaudate tractotomy) is effective for some patients with refractory OCD
Neuroimaging and Anxiety Disorders

- **Amygdala** is implicated in processing threat/fear and emotional learning.
- **Hippocampus** is important for memory.
- **Medial Prefrontal Cortex** is important for extinguishing fear conditioned responses.
HPA STRESS AXIS in PTSD

- Hypothalamic Pituitary Adrenal Axis (HPA) over-activity initially, but chronic trauma and/or chronic manifestations of PTSD symptoms (re-experiencing) lead to a loss of HPA function:
  - In acute stress / trauma, higher cortisol release lead to enhanced vigilance, exertion, endurance, and facilitates memory
  - Following chronic stress, cortisol levels declines overall and there is an overactive feedback system
  - Lowered cortisol present in many patients with chronic PTSD at baseline
- Hypercortisolemia during acute stress fits with overall model of hippocampal neuronal death, and damage hippocampal neurons; consistent with hippocampal atrophy in PTSD
Treatment Options

Self-Help Approaches
Support Groups
Other Mental Health Practitioners
Family Doctor
Private Psychologists
Private Psychiatrists
Specialty Clinics
Psychological Treatments

Cognitive Treatments
Exposure-Based Treatments
Relaxation-Based Treatments
Ritual Prevention

Biological Treatments

Medication
Deep Brain Stimulation in OCD
Cognitive Behavioural Therapy

COGNITIVE STRATEGIES

In anxiety, thoughts revolve around:
"probability overestimation"
"catastrophizing the consequences"

That is people overestimate that something bad will happen, and that when it happens, they will be unable to cope.
Cognitive Behavioural Therapy

BEHAVIOURAL STRATEGIES

• Controlled exposure to the feared situation.
• Anxiety responses are allowed to "habituate" or decrease without interference.
• Teaches the person that the situation is not dangerous, and that anxiety will diminish.
Medications: First Line

Selective Serotonin Re-Uptake Inhibitors (SSRIs)

- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Fluvoxamine (Luvox)
- Citalopram (Celexa)
- Escitalpram (Lexapro)
Medications: 2\textsuperscript{nd}-3\textsuperscript{rd} Line

Other Antidepressants (5-HT and NE Reuptake Inhibitors - SNRIs)
- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)
- Clomipramine (Anafranil)

Anti-Anxiety Medications (Benzodiazepines)
- Alprazolam (Xanax)
- Clonazepam (Rivotril)
- Lorazepam (Ativan)
- Diazepam (Valium)

Other Antidepressants (Monoamine Oxidase Inhibitors - MAOIs)
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
Choosing a Medication

- Research on effectiveness
- Side effect profile
- Previous response to medications
- Previous response of a family member
- Additional problems present (e.g., depression)
- Cost