The Neurochemistry of Anxiety Disorders

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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

• Buspirone a serotonergic 1A receptor agonist is an effective anti-anxiety treatment in generalized anxiety disorder

• Serotonergic agonism (mCPP, fenfluramine, LSD, MDMA) can cause acute and chronic anxiety

• Studies of 5-HT, 5-HIAA, and 5-HT receptors levels are have revealed inconsistent findings
γ-aminobutyric acid (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 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 presynaptic 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.

- Anxious patients (panic, PTSD, phobia) have elevated levels of NE, and/or 3-methoxy-4-hydroxyphenylglycol (MHPG, an NE metabolite).

- 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.
Neurophysiologic / Neuroanatomical Theories of Anxiety Disorders
Neuroanatomy of Fear
# Fear-conditioning behavioral paradigm

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<thead>
<tr>
<th><strong>Phenomenon</strong></th>
<th><strong>Mechanism</strong></th>
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<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>
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<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>
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<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>
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<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>
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Amygdala

**Anatomical Target**
- Lateral hypothalamus
- Dorsal motor N. of vagus
- Nucleus ambiguus
- Parabrachial nucleus
- Ventral tegmental area
- Locus coeruleus
- Lateral dorsal tegmental N.
- Basal forebrain
- N. Reticularis pontis caudalis
- Central grey
- Trigeminal, Facial motor N.
- Paraventricular N. (Hypothal.) (mostly via BNST)

**Behavioral Test or Sign of Fear or Anxiety**
- Tachycardia, galvanic skin response, paleness, pupil dilation, blood pressure elevation
- Ulcers, urination, defecation, bradycardia
- Panting, respiratory distress
- Behavioral and EEG arousal, increased vigilance, increased attention
- Increased Startle
- Freezing, conflict test, CER, social interaction, hypoalgesia
- Facial expressions of tear
- Corticosteroid release ("Stress response")
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

- **Septohippocampal GABAergic system**
  - Mediates anxiety and vigilance
  - High concentration of GABAergic neurons and receptors
  - Directly connected to LC

- Translation of animal models to human clinical Anxiety Disorders have been difficult
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?
Neuroanatomy of Anxiety Disorders

• Obsessive Compulsive Disorder
  • Impaired frontal-basal ganglia loop
    • Loss of volume in caudate nucleus in OCD patients
    • Huntington’s Disease and Sydeham’s Chorea (basal ganglia lesions/degeneration) exhibit OCD symptoms
    • “Pediatric Autoimmune neuropsychiatric disorders associated with streptococcal infection” (PANDAS)
      • OCD symptoms following Group A β-hemolytic strep (URI) infection
        • toxin and/or antineuronal antibodies bind preferentially in caudate
Neuroimaging and Anxiety Disorders

- Some 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
  - Medial temporal lobe epilepsy is partly characterized by intense fear and anxiety

- Amygdala is implicated in processing threat/fear and emotional learning, and the hippocampus is important for memory
- Medial prefrontal cortex is important for extinguishing fear conditioned responses
Respiratory System and Panic

- **Panic attacks, Panic Disorder (PD):**
  - **Sodium Lactate**
    - I.V. sodium lactate produces panic in PD patients, who have an enhanced lactic response and (altered metabolism and conversion of lactate to sodium bicarbonate)
      - Panic patients respond by hyperventilation-induced hypocapnia and furthering the alkalosis
      - Non-PD (healthy) subjects respond with a typical homeostatic response to intracellular alkalosis, including slowed breathing
  - **Carbon dioxide**
    - Breathing higher levels of CO₂ (5% CO₂ - 95%O₂, CO₂-enhanced air) produces panic in PD patients, who develop hyperventilation (earlier and more, relative to controls) to compensate, causing alkalosis and reactive hypocapnea.
    - It is commonly believed that anxiety can be caused by rapid, shallow breathing (Hyperventilation Syndrome) which reduces carbon dioxide; hyperventilation is treated by having a patient in a bag normalizes (raises) CO₂ and slows breathing
    - However, hyperventilation does not cause panic attacks in PD patients. It is thought that Hypeventillation and Panic Disorder are related but different conditions.
  - Magnetic resonance spectroscopy studies have reported greater brain lactate levels in response to hyperventilation and lactate infusions
  - **Theories of Enhanced peripheral sensitivity to lactate - CO₂ in PD**
    - Enhanced activation of vagus nerve, stimulation of locus coeruleus (heighted NE activity)
    - Altered “suffocation monitor” that evokes the alarm system; hypoxia caused by severe cerebral vasoconstrictor response to hypocapnia
    - Disturbance in regulation of intracellular pH
    - Cognitive and/or brainstem misevaluation of peripheral somatic sensations
Neuroendocrine Theory of PTSD
Hypothalamic Pituitary Adrenal (HPA) Axis in Stress

STRESS

CORTISOL

NEGATIVE FEEDBACK

Fast: rate of cortisol increase
Slow: steady-state cortisol

Forebrain GR activation
- Increases acute anxiety
- Alters learning and memory

• Triggers negative feedback
• Ends stress response
• Return to homeostasis
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
Genetic Theory of Anxiety
ELEVATED PLUS-MAZE

BLAIR WITCH PROJECT
4:30 7:15 9:30

THAT WAS COOL! TOTALLY!

ULP...
I. Genetic and Other Vulnerability Factors for Anxiety

- Sex differences
- Age-specific patterns of expression
- Familial and genetic factors
  - Panic disorder is the anxiety syndrome with strongest degree of familial aggregation
Anxiety: Genetics

- **Genetics:**
  - 50% of people with panic disorder have at least one affected relative (similar, though less frequent, rates for other anxiety disorders)
  - 4% of innate anxiety within the general population is explained by the 5-HTTLPR (serotonin transporter polymorphism)
  - 2:1 MZ-DZ concordance for anxiety disorders
  - Few, inconsistent family and adoption studies
  - Temperamental / Personality traits (thought to be genetic / heritable) such as neuroticism (emotional reactivity), harm avoidance, behavioral inhibition are associated with anxiety disorders
  - Variability may be related to life events / experience

- **Environment:**
  - History of abuse elevates the risk for anxiety disorders
  - Childhood parental loss elevates risk for phobias and other anxiety disorders
Linkage studies investigating mutations in the adrenergic receptor genes, GABA$_A$ receptor genes and other genomic surveys have failed to identify specific genes for anxiety disorders.

*Underscores Complexity of Anxiety Disorders*
Targeted Mutations Leading to Anxiety-Like Endophenotypes: Studies of Transgenic Mice

• The CRH system
  • CRH-overexpressing mice display increased stress-like behaviors
  • CRH1 knockout mice: reduces anxiety
  • CRH2 knockout mice: less consistent behavioral profile

• The Serotonin (5-HT) system
  • 5-HT1A knockout mice: increased stress-like behaviors
  • 5-HT1B knockout mice: decreased anxiety

• The GABA system
  • GAD 65 knockout mice: increased anxiety-like responses