Neuroanatomy of Emotion, Fear, and Anxiety
Outline

- Neuroanatomy of emotion
- Fear and anxiety
- Brain imaging research on anxiety
  - Brain functional activation – fMRI
  - Brain functional connectivity – fMRI
  - Brain structural connectivity – diffusion tensor imaging (DTI)
  - Brain morphometry – anatomical MRI
- Educating our patients about their brains
- Punchline
Key Brain Areas for Emotion

Figure 3 | MacLean's limbic system theory of the functional neuroanatomy of emotion. The core feature of MacLean's limbic system theory was the hippocampus, illustrated here as a seahorse. According to MacLean, the hippocampus received sensory inputs from the outside world as well as information from the internal bodily environment (viscera and body wall). Emotional experience was a function of integrating these internal and external information streams. HYP, hypothalamus. Reproduced, with permission, from REF. 8 © (1949) Lippincott Williams and Wilkins.
Figure 4 | **Key structures within a generalized emotional brain.** The figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen. Anatomical image adapted, with permission, from REF. 123 © (1996) Appleton & Lange.
**Neuroanatomy of Emotion**

**Key Brain Areas and Their Affect-related Functions**

**Orbitofrontal cortex:**
Affective evaluation; decoding punishment and reward value

**Dorsolateral PFC:**
Approach-related positive affect (left)
Withdrawal-related negative affect; threat-related vigilance (right)

**Amygdala:**
Vigilance for motivationally salient events; threat detection; emotional memory

**Anterior cingulate cortex (ACC):**
Top-down modulation; conflict detection

**Hippocampus:**
Declarative memory; spatial navigation; contextual fear

**Insula and ACC:**
Integration of sensory, affective, cognitive, and autonomic processing

**Insula:**
Representation of the body’s internal state; interoception

**Dorsolateral PFC:**
Approach-related positive affect (left)
Withdrawal-related negative affect; threat-related vigilance (right)
Nucleus Accumbens:
Reward processing; positive emotion; salience detection
What is Fear?

What is Anxiety?
What Is Anxiety?

A suite of *anticipatory* affective, cognitive, and behavioral changes in response to *uncertainty* about potential future threat

Uncertainty and Anticipation Model of Anxiety (UAMA)

A central feature of all anxiety disorders is aberrant and excessive anticipatory responding under conditions of threat uncertainty.

In anxiety, five key psychological processes involved in maladaptive responses to threat uncertainty:

1. Inflated estimates of threat cost and probability
2. Increased threat attention and hypervigilance
3. Deficient safety learning
4. Behavioral and cognitive avoidance
5. Heightened reactivity to threat uncertainty

Uncertainty and Anticipation Model of Anxiety

Five Key Psychological Processes

Five key psychological processes involved in *adaptive* responses to threat uncertainty
1. Accurate estimates of threat cost and probability
2. Appropriate threat attention and hypervigilance
3. Safety learning
4. Appropriate (and limited) behavioral and cognitive avoidance
5. Appropriate reactivity to threat uncertainty

Five key psychological processes involved in *maladaptive* responses to threat uncertainty, as seen in anxiety
1. Inflated estimates of threat cost and probability
2. Increased threat attention and hypervigilance
3. Deficient safety learning
4. Behavioral and cognitive avoidance
5. Heightened reactivity to threat uncertainty

Main Anxiety Disorders

- Separation Anxiety Disorder
- Social anxiety disorder (i.e., social phobia)
- Specific phobia
- Panic disorder
- Agoraphobia
- Generalized anxiety disorder (GAD)
- Post-traumatic stress disorder (PTSD)
- Obsessive-compulsive disorder (OCD)
Neuroanatomy of Anxiety Disorders

Key Brain Areas:

- Insula
- Amygdala
- Ventromedial prefrontal cortex (vmPFC)
- Orbitofrontal cortex (OFC)
- Dorsolateral prefrontal cortex (dIPFC)
- Anterior cingulate cortex (ACC)
- Hippocampus
What Is Anxiety?

Brain Imaging
Imaging Research on Anxiety Disorders

Summary

- Neural responses to *anxiety-provoking* stimuli (symptom provocation paradigms)
  - Social (SAD)
  - Phobogenic (specific phobia)
  - Traumatic (PTSD)
  - Obsessional (OCD)
  - Panic-inducing (panic disorder)
  - Worry (GAD)

- Neural responses to *generic emotion* stimuli
  - Emotional faces
  - IAPS slides
  - Fear conditioning
Imaging Research on Anxiety Disorders

Summary

Etkin & Wager (2007) *Am. J. Psychiatry*
Group Differences in Amygdala
GAD Patients Show *Elevated* Anticipatory Activity

Nitschke et al. (2009) *Am. J. Psychiatry*
ACC Activity and Treatment Response
Pretreatment Anticipatory ACC Activity Predicts Response to Effexor

\[ r = -0.82 \]

\[ r = -0.84 \]

Nitschke et al. (2009) *Am. J. Psychiatry*
Uncinate Fasciculus
DTI-based Tractography
Structural Connectivity
GAD Patients Show *Reductions* in Uncinate Fasciculus

*Tromp et al.* (2012) *Arch. Gen. Psychiatry*

\[ n = 88 \]
Functional Connectivity
GAD Patients Show *Reduced* ACC-Amygdala Negative Coupling

Tromp et al. (2012) *Arch. Gen. Psychiatry*

\( n = 88 \)
Functional and Structural Connectivity
Uncinate Fasciculus and Anticipatory Amygdala-ACC Function


\( n = 88 \)
Talking to Our Patients about the Brain
What will be most helpful for patients?

- Amygdala and emotional salience
- Insula and emotional experience
- Emotion regulation regions and pathways
  - VMPFC and its connections to the amygdala and insula
- Hippocampus
  - Seat of learning and memory
  - Neurogenesis
What is the punchline?
Your brain helps you get really good at whatever you spend your time doing.
The Brain and Psychopathology

- Neural connections that support bad stuff (problematic thinking and behavior patterns)
  - Anxiety, panic, worries, phobias, obsessions, avoidance
  - Depression, self-critical thoughts, suicidal thoughts
  - PTSD, self-blame, safety concerns, trust issues
  - Anger, irritability, outbursts, abusive behavior
  - Substance abuse, disorder eating, self-harm behaviors
  - Practice/repetition strengthens these neural connections
    - Same mechanisms as in learning math, chess, or piano

- The *bad news* is that these neural connections do not go away, even if they are no longer “practiced”
  - Relapses; returning to old dysfunctional patterns of thinking and behavior
Neural connections that support bad stuff (problematic thinking and behavior patterns)
- Anxiety, panic, worries, phobias, obsessions, avoidance
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The **bad news** is that these neural connections do not go away, even if they are no longer “practiced”

The **good news** is **neuroplasticity**
- Psychotherapy develops and strengthens neural connections that support accurate thinking and adaptive behavior patterns
  - Thanks to the exact same mechanisms that created the problematic thinking and behavior patterns above
Your brain helps you get really good at whatever you spend your time doing.

“I used my neuroplasticity, and things got better.”

-Anonymous patient
Anxiety cannot be reduced to abnormalities in a single brain region or system (or a “chemical imbalance”)

Understanding the neuroanatomy of anxiety disorders and their treatment will come through research simultaneously examining multiple domains

Appreciate complexity of the brain and of anxiety disorders
  ➢ Are we on the right track in our current conceptualization and labeling of anxiety pathology?

Careful not to be wowed by pretty pictures, even in Science, Nature, and JAMA
  ➢ Be good consumers of neuroimaging research by applying critical thinking

Neuroplasticity, neural connections, and pattern separation are key for understanding the development, maintenance, and treatment of mental illness
Neuroimaging of Anxiety and Depression  
Critical Conceptual, Design, and Interpretation Issues

- Emotion perception ≠ emotion experience ≠ emotion production
- Conditions and stimuli must be appropriately matched (e.g., physical characteristics)
- Asymmetries can be concluded only on basis of appropriate statistical tests
- Go beyond merely documenting which brain areas show group differences in functional activation
  - Associations with brain structural differences, brain connectivity, and behavior
- Develop a paradigm relevant to anxiety/depression symptoms
- Ground the paradigm in basic neuroscience research with healthy populations
- Replication