Neuroanatomy of Emotion, Fear, and Anxiety
Outline

- Neuroanatomy of emotion
- Critical conceptual, experimental design, and interpretation issues in neuroimaging research
- Fear and anxiety
- Neuroimaging research on anxiety
  - Anxiety-related processes in healthy volunteers and patients
  - Brain functional activation – fMRI
  - Brain functional connectivity – fMRI
  - Brain structural connectivity – diffusion tensor imaging (DTI)
  - Brain morphometry – anatomical MRI
- Therapeutically communicating brain research to patients
What is 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

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

- **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
Nucleus Accumbens:
Reward processing; positive emotion; salience detection
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
Fig. 1. fMRI paradigm. Two blocks of an emotion task were interleaved with three blocks of a sensorimotor control task. (A) During the emotion task, subjects viewed a trio of faces and selected one of two faces (bottom) that expressed the same emotion as the target face (top). The identity of all three faces was always different. Each emotion block consisted of six images, three of each gender and target affect (angry or afraid) all derived from a standard set of pictures of facial affect (42), presented sequentially for 5 s. (B) During the sensorimotor control, the subjects viewed a trio of simple geometric shapes (circles, vertical and horizontal ellipses) and selected one of two shapes (bottom) identical to the target shape (top). Each control block consisted of six different images presented sequentially for 5 s. Subject performance (accuracy and reaction time) was monitored during all scans.
Fig. 2. Genotype-based parametric comparisons illustrating significantly greater activity in the right amygdala of the s group versus the l group in both the first and second cohort. BOLD fMRI responses in the right amygdala (white circle) are shown overlaid onto an averaged structural MRI in the coronal plane through the center of the amygdala. Talairach coordinates and voxel level statistics ($P < 0.05$, corrected) for the maximal voxel in the right amygdala for the first and second cohort are as follows: $x = 24$ mm, $y = -8$ mm, $z = -16$ mm; cluster size = 4 voxels; voxel level corrected $P$ value = 0.021; $T$ score = 2.89, and $x = 28$ mm, $y = -4$ mm, $z = -16$ mm; cluster size = 2 voxels; voxel level corrected $P$ value = 0.047; $T$ score = 2.03, respectively.
**Fig. 3.** Effect of 5-HTT genotype on right amygdala activity. Bar graphs represent the mean BOLD fMRI percent signal change in a region of interest (ROI) comprising the entire right amygdala in the s (n = 14) and l (n = 14) groups collapsed across both cohorts. Individual circles represent the activity for each subject in this ROI. Consistent with the statistical parametric maps (Fig. 2), which identified significant voxels within the right amygdala, analysis of variance for the entire amygdala ROI, including voxels that were not differentially activated according to statistical parametric mapping, still revealed significant group differences in the mean (±SEM) BOLD fMRI percent signal change [s group = 0.28 ± 0.08 and l group = 0.03 ± 0.05; \(F(1,26) = 6.84, \ p = 0.01\)].
Figure 2. A, Significant region of the right amygdala (x=11, y=−7, z=−14) observed in the diagnosis (anxious vs healthy children) × condition (fearful vs neutral faces) interaction. B, Percent change in normalized magnetic resonance signal intensity in the right amygdala for the comparison between fearful and neutral faces for anxious and healthy children. Bars reflect the SEM. C, Correlation between the percent change in normalized magnetic resonance signal intensity in the right amygdala and the child-reported score from the Screen for Child Anxiety Related Emotional Disorders (SCARED). Squares reflect healthy children (n=9); circles reflect children with generalized anxiety and/or panic disorder (n=10).
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
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
Imaging Research on Anxiety Disorders

Summary


![Graph showing brain regions with hyperactivation and hypoactivation in patients with anxiety disorders compared to comparison subjects.](image-url)
Neural responses to **anxiety-provoking** stimuli (symptom provocation paradigms)
- Social (SAD)
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Neural responses to **generic emotion** stimuli
- Emotional faces
- IAPS slides

Does this get at heart of anxiety and what is debilitating about it?
What is Fear?

What is Anxiety?
What is Anxiety?

An emotional state characterized by 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.

This model identifies five processes involved in adaptive responses to threat uncertainty that function maladaptively 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

Uncertainty and Anticipation Model of Anxiety
Brain Circuitry of Five Key Psychological Processes

Grupe & Nitschke (2013)
Neuroanatomy of Anxiety Disorders
Key Brain Areas

- **Orbitofrontal cortex (OFC)**
- **Dorsolateral prefrontal cortex (dIPFC)**
- **Anterior cingulate cortex (ACC)**
- **Hippocampus**
- **Insula**
- **Ventromedial prefrontal cortex (vmPFC)**
- **Amygdala**

![Brain Diagram]
Neural Circuitry of Anticipating Aversion
Anticipation of and Response to Aversive compared to Neutral Pictures

n = 21

Nitschke et al. (2006) *NeuroImage*
Group Differences in Amygdala
GAD Patients Show *Elevated* Anticipatory Activity

Nitschke et al. (2009) *Am. J. Psychiatry*

$n = 26$
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
Group Differences in Uncinate Fasciculus

GAD Patients Show *Reduced* Structural Connectivity

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

\( n = 88 \)
Uncinate Fasciculus Structural Connectivity
Associations with Anticipatory Amygdala-ACC Functional Connectivity

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

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

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

$n = 88$
Anxiety cannot be reduced to abnormalities in a single brain region or system

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

- Genes, brain anatomy and physiology (morphology, volume, activation, structural and functional connectivity, chemistry), peripheral psychophysiology, behavior, interpersonal relations, environmental factors, cultural and socioeconomic influences

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, JAMA,* and *American Journal*

- Be good consumers of neuroimaging research
Using Brain Research in Therapy
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
Neural pathways that support dysfunctional thinking and behavior patterns

- Self-critical thinking, anger outbursts, anxiety
- Fear learning
  - Classical and context conditioning, stimulus generalization
- Practice/repetition leads to strengthened neural connections
  - Same mechanisms as in learning math, chess, or piano
- These neural connections will not go away and cannot be excised
  - They are here for the rest of patient’s life
  - This is the bad news (but makes evolutionary sense)
  - Anxiety and anger co-opted these evolutionarily preserved and often beneficial mechanisms
  - But brain did provide for a way out – neuroplasticity
    (tune in 2 wks from now)

Traumatic experiences

- Neural connections supporting associations with trauma are here for the rest of patient’s life