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?

Key Brain Areas for Emotion

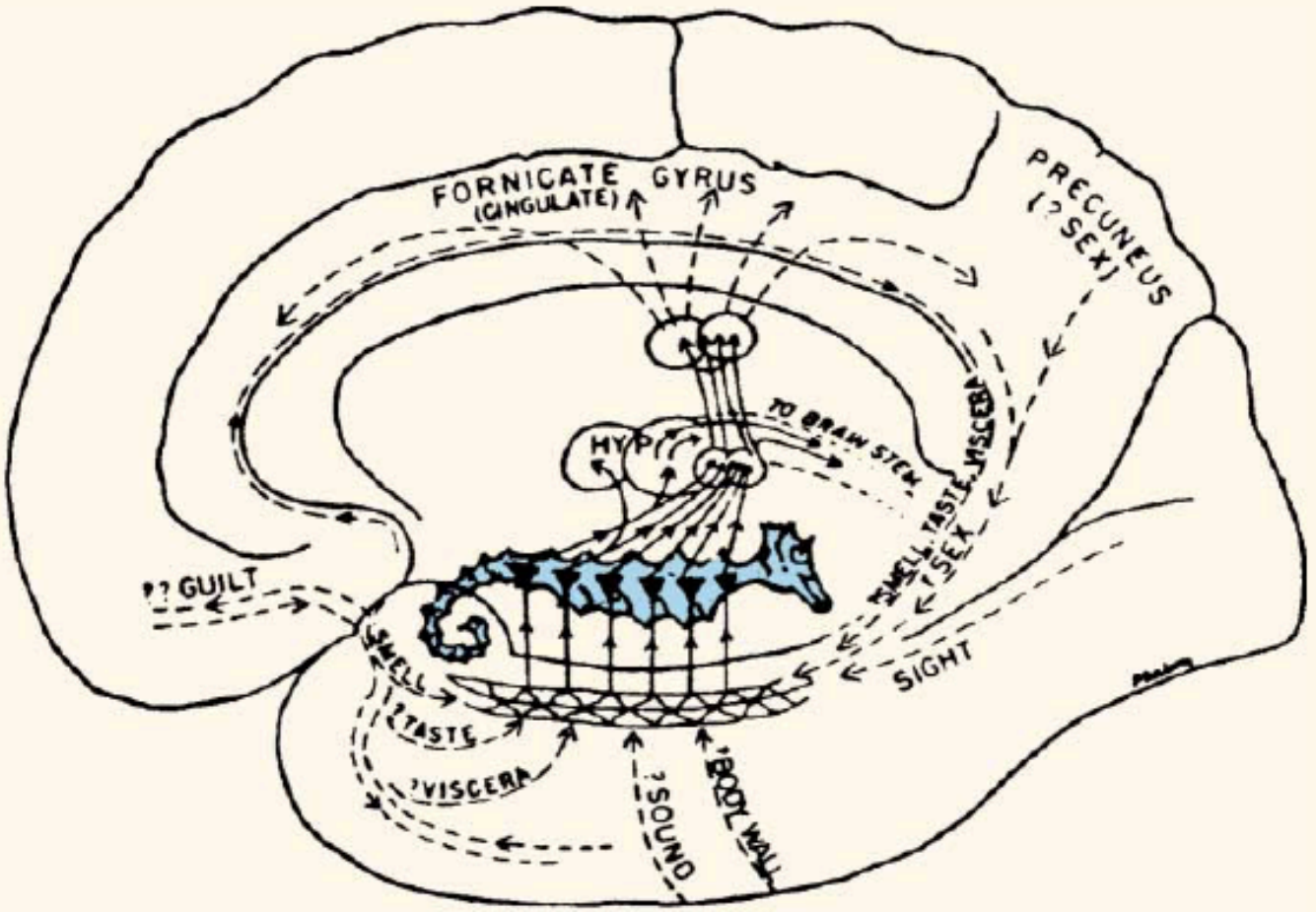


Figure 3 | **MacLean's limbic system theory of the functional neuroanatomy of emotion**. The core feature of MacLean's limbic system theory[8] was the hippocampus, illustrated here as a seahorse. According to MacLean, the hippocampus received sensory inputs from the outside world as well as information 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.

Dagleish (2004)
Nat. Rev. Neurosci.

Key Brain Areas for Emotion

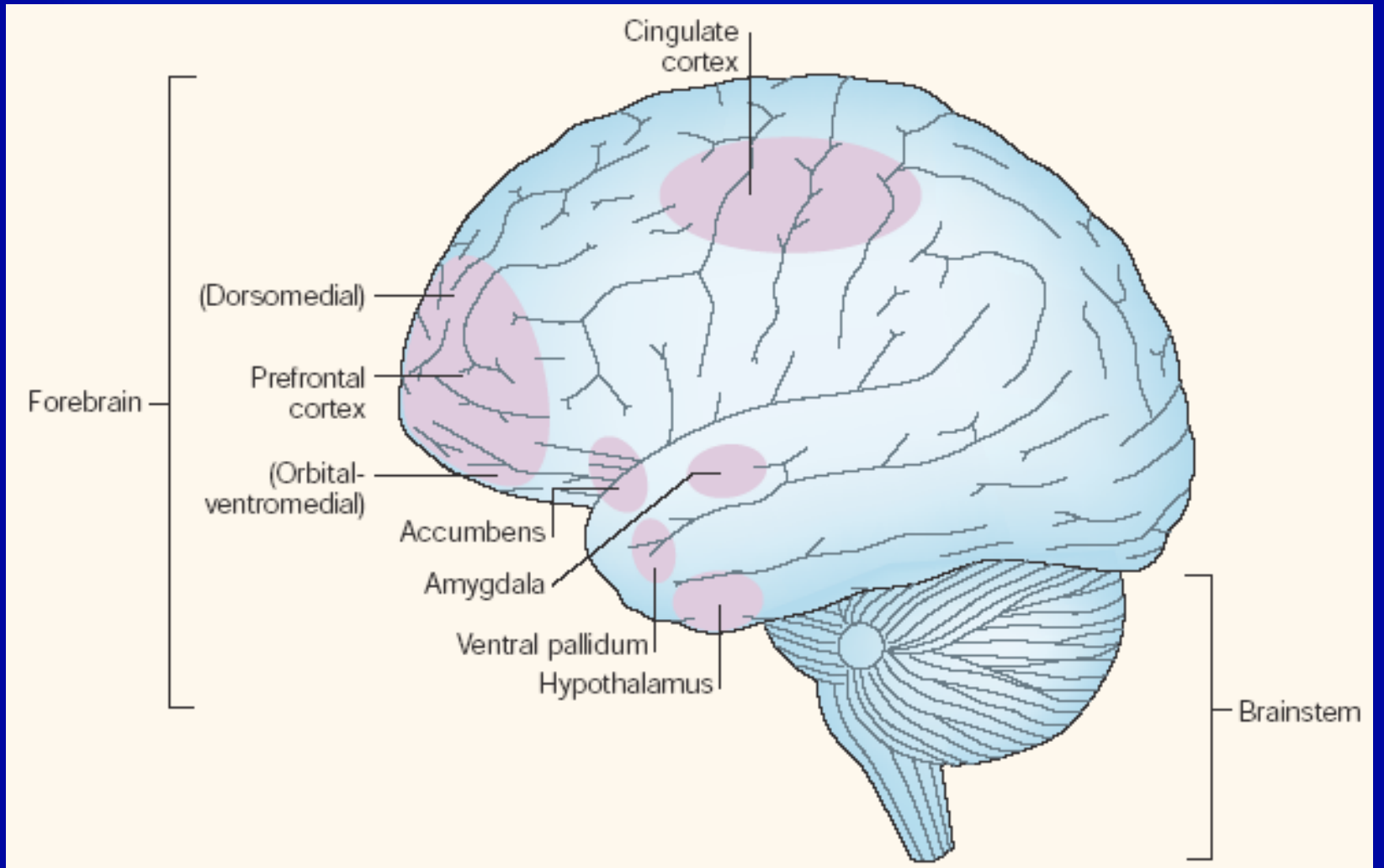
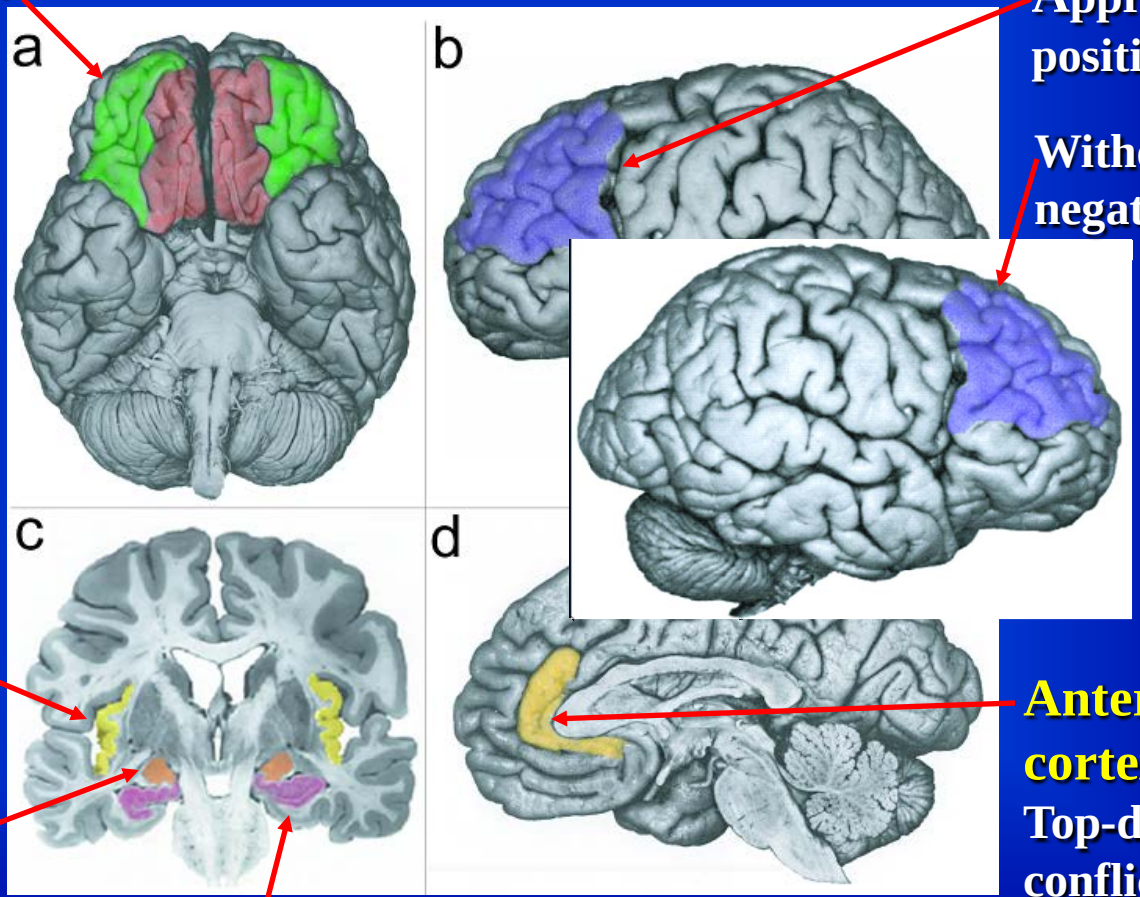


Figure 4 | **Key structures within a generalized emotional brain.** The figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen. Anatomical 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)

Insula:
Representation of the body's internal state; interoception

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

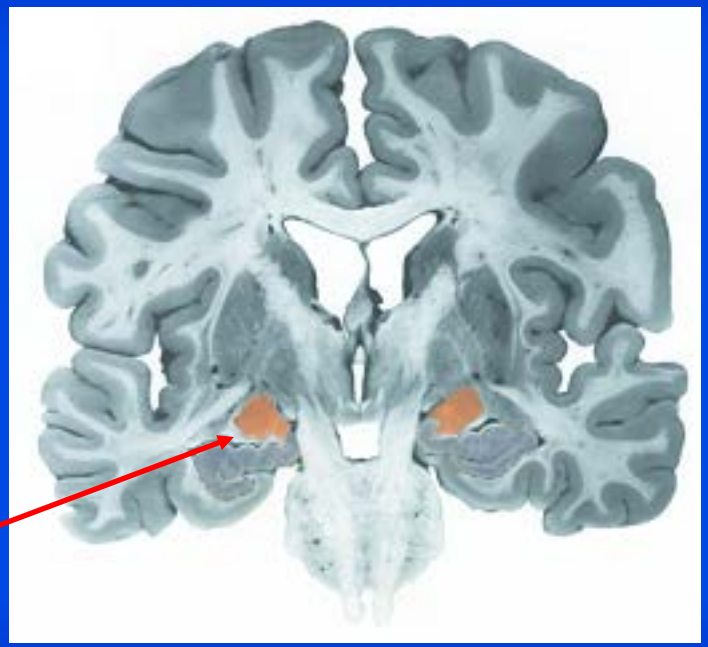
Amygdala:
Vigilance for motivationally salient events; threat detection; emotional memory

Hippocampus:
Declarative memory; spatial navigation; contextual fear

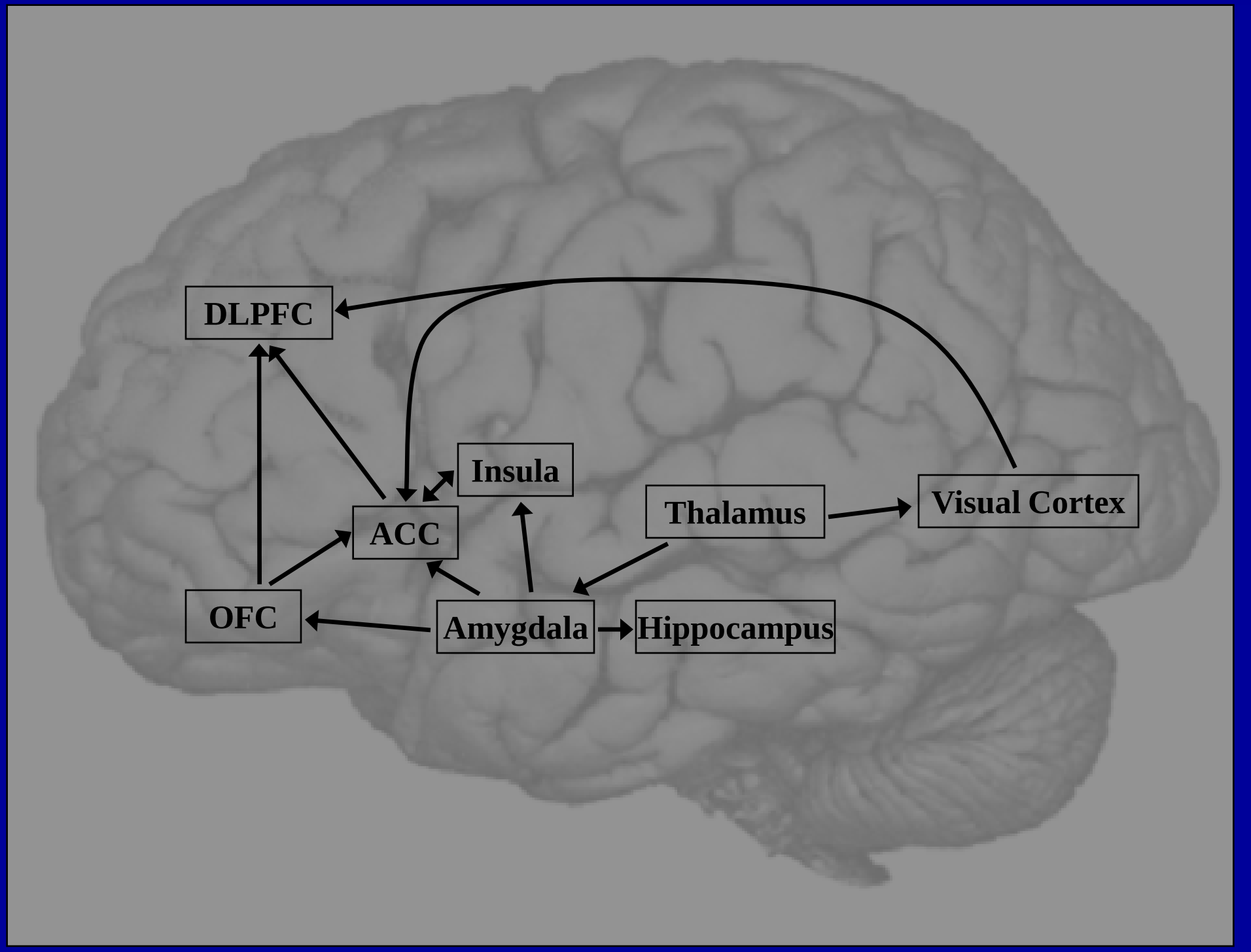
Insula and ACC:
Integration of sensory, affective, cognitive, and autonomic processing

Neuroanatomy of Emotion

Key Brain Areas and Their Affect-related Functions



Nucleus Accumbens:
Reward processing; positive emotion; salience detection


DLPFC
Insula
ACC
Thalamus
Visual Cortex
OFC
Amygdala
Hippocampus

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

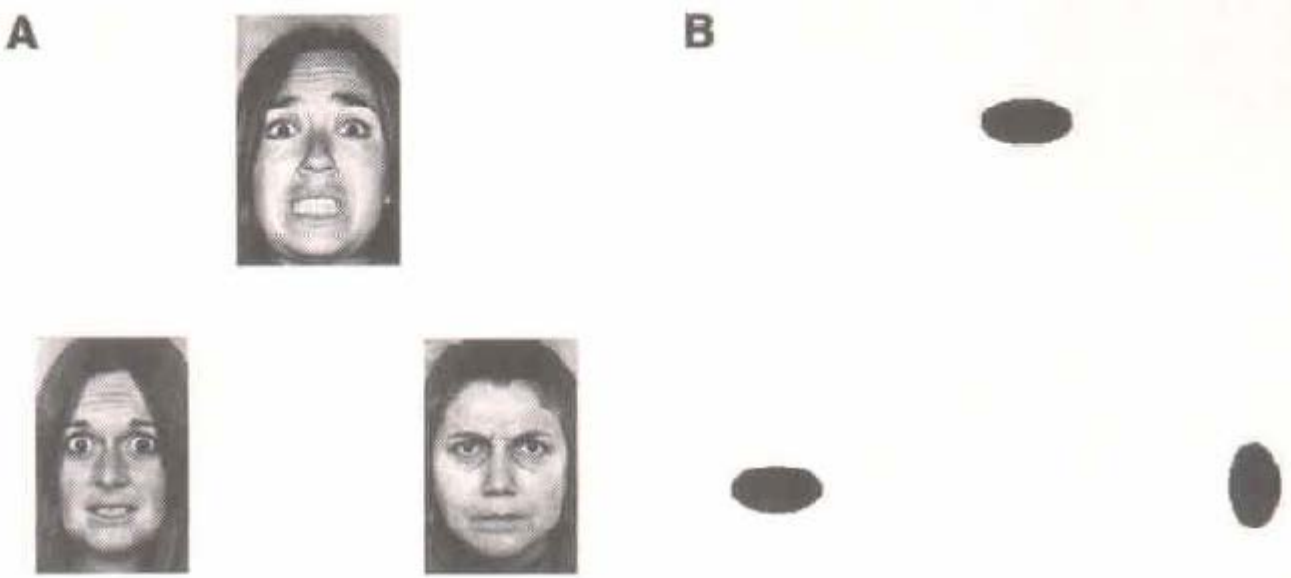


Fig. 1. fMRI paradigm. Two blocks of an emotion task were interleaved with three blocks of a sensorimotor control task. (**A**) During the emotion task, subjects viewed a trio of faces and selected one of two faces (bottom) that expressed the same emotion as the target face (top). The identity of all 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.

Hariri et al. (2002) *Science*

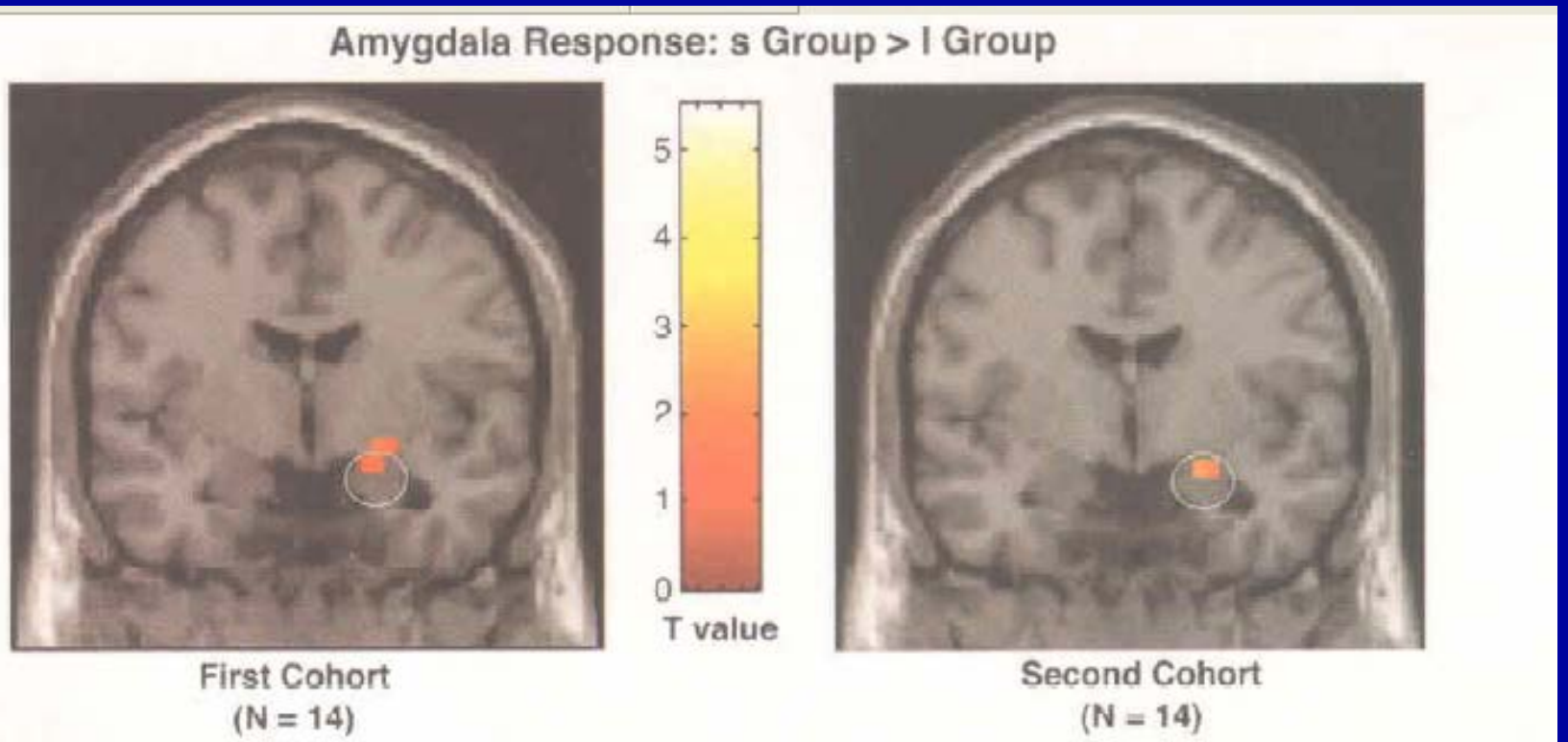
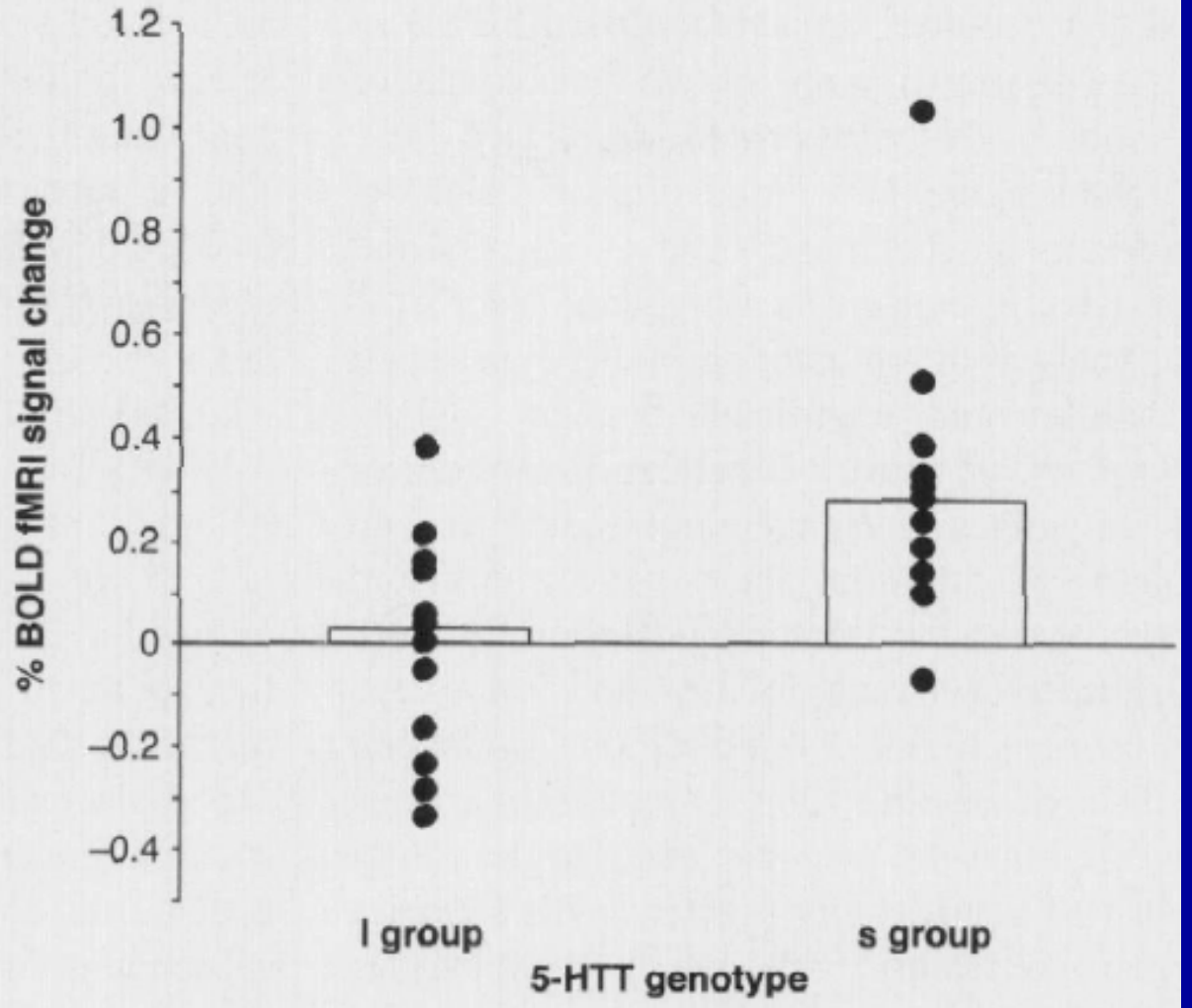


Fig. 2. Genotype-based parametric comparisons illustrating significantly greater activity in the right amygdala of the s group versus the l group in both the first and second cohort. BOLD fMRI responses in the right amygdala (white circle) are shown overlaid onto an averaged structural MRI in the coronal 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.

Hariri et al. (2002) *Science*

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; $F(1,26) = 6.84$, $P = 0.01$].



Hariri et al. (2002) *Science*

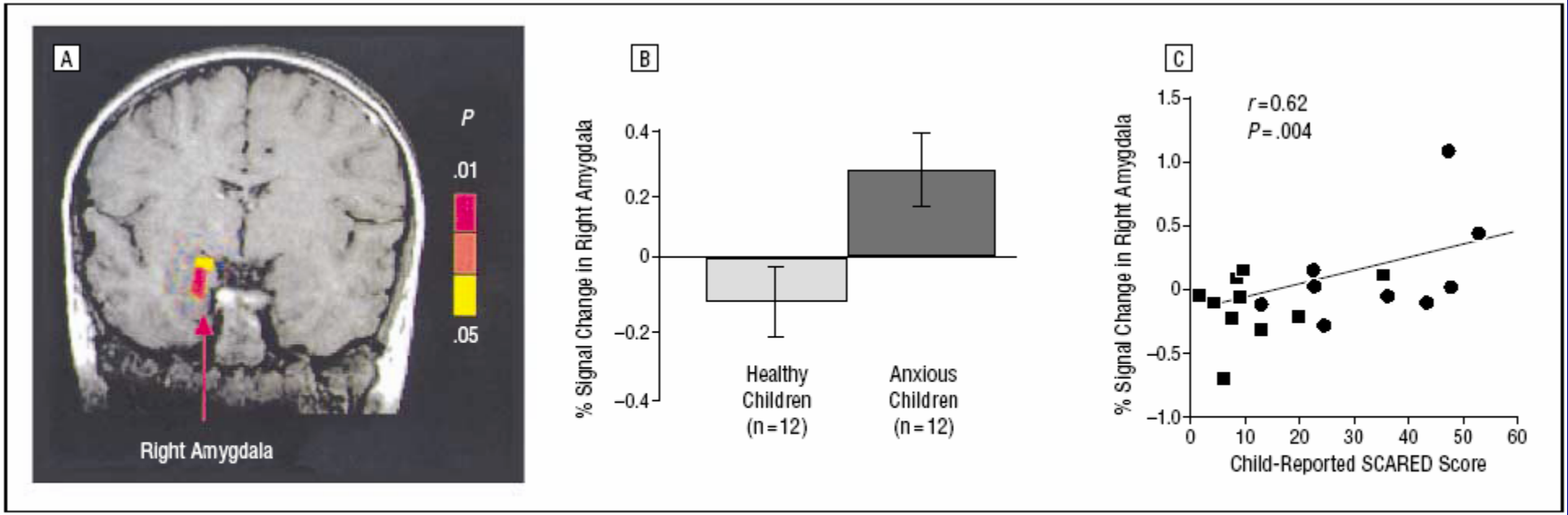


Figure 2. A, Significant region of the right amygdala (x=11, y=– 7, z=–14) observed in the diagnosis (anxious vs healthy children) × condition (fearful vs neutral faces) interaction. B, Percent change in normalized magnetic resonance signal intensity in the right amygdala for the comparison between fearful 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).

Thomas et al. (2001) ***Arch. Gen, Psychiatry***

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

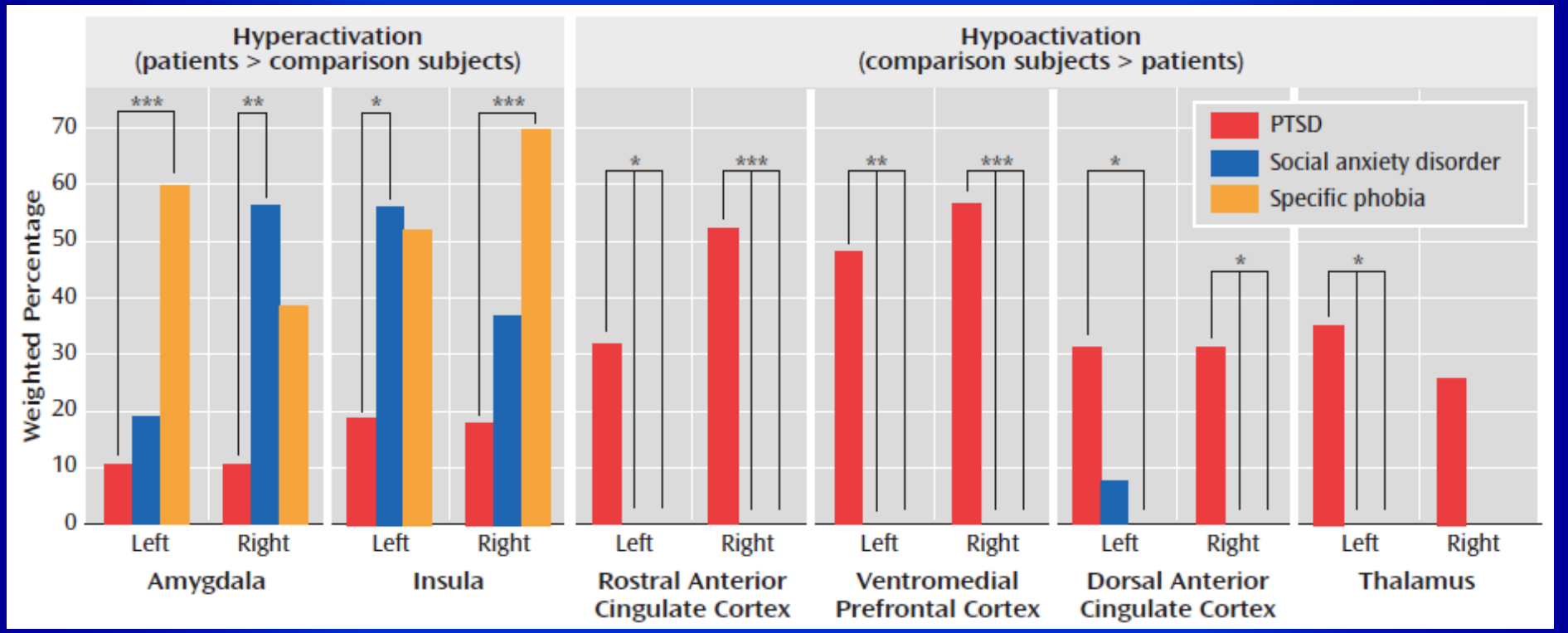
Imaging Research on Anxiety Disorders

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



Etkin & Wager (2007) *Am. J. Psychiatry*

Imaging Research on Anxiety Disorders

Summary

- Neural responses to *anxiety-provoking* stimuli (symptom provocation paradigms)
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  - Phobogenic (specific phobia)
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  - Worry (GAD)
- 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)

Grupe & Nitschke (2013) *Nature Rev. Neurosci*

Uncertainty and Anticipation Model of Anxiety

Five Key Psychological Processes

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

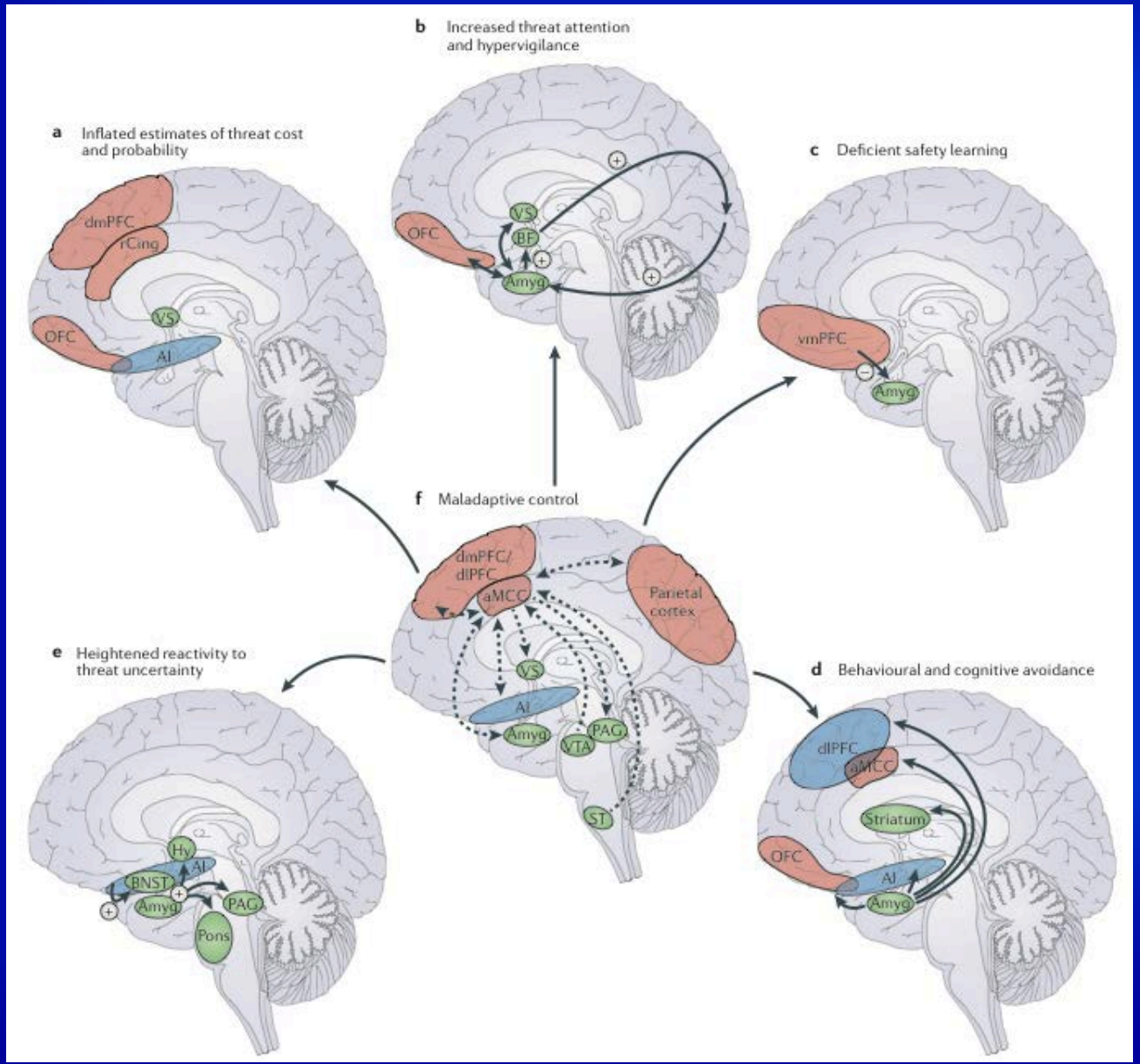
- This model identifies five processes involved in adaptive responses to threat uncertainty that function maladaptively in anxiety

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

Grupe & Nitschke (2013) *Nature Rev. Neurosci.*

Uncertainty and Anticipation Model of Anxiety

Brain Circuitry of Five Key Psychological Processes



Grupe & Nitschke (2013)
Nature Rev. Neurosci.

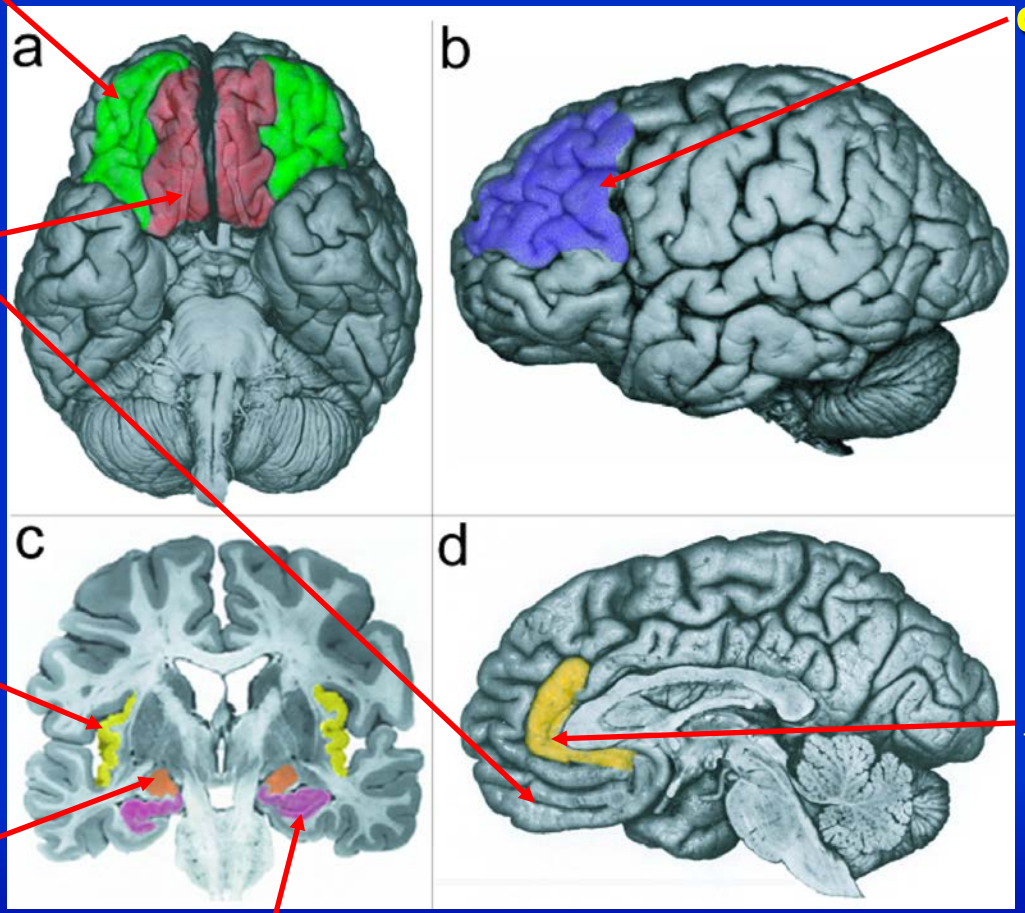
Neuroanatomy of Anxiety Disorders

Key Brain Areas

Orbitofrontal cortex (OFC)

Dorsolateral prefontal cortex (dlPFC)

Ventromedial prefrontal cortex (vmPFC)



Insula

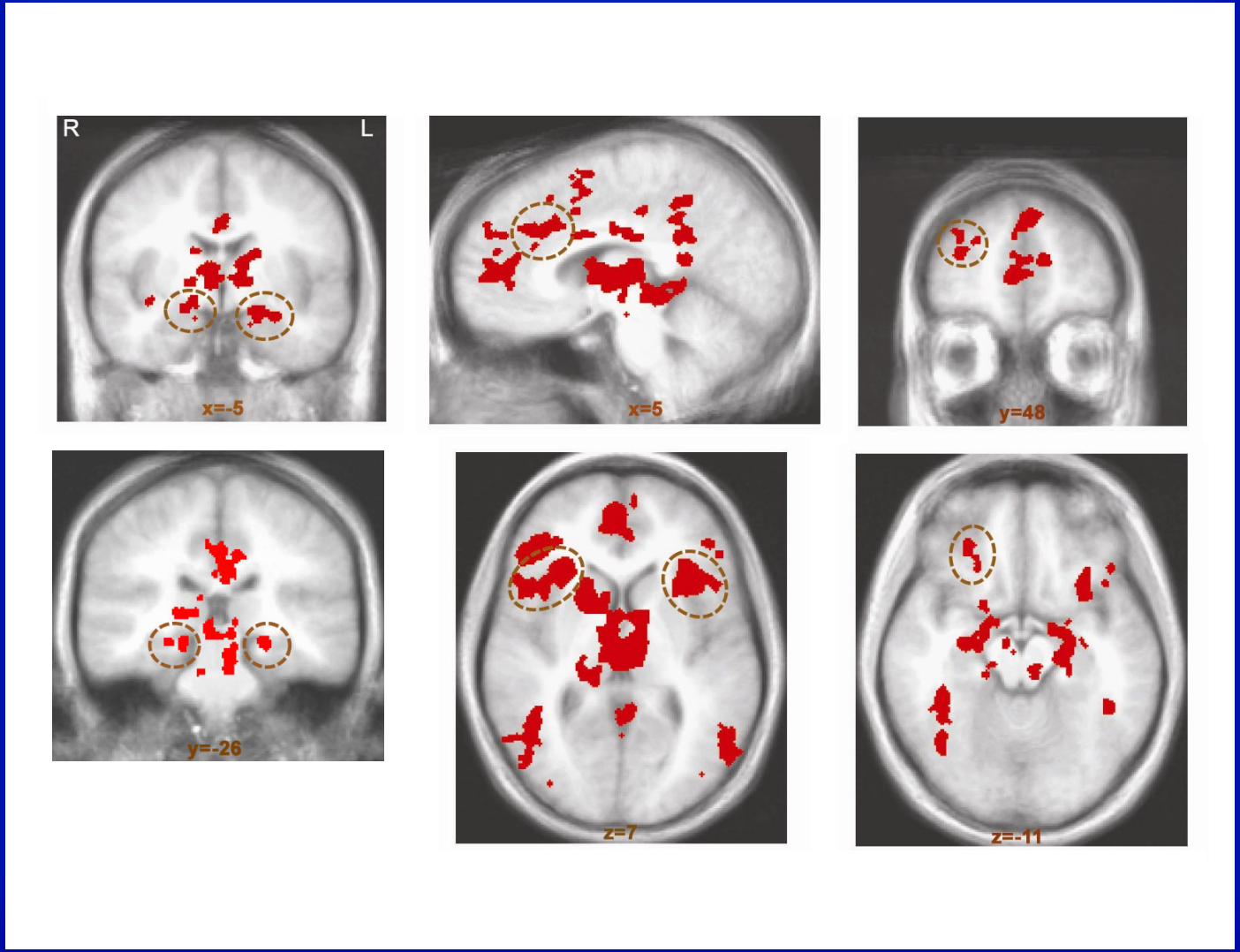
Anterior cingulate cortex (ACC)

Amygdala

Hippocampus

Neural Circuitry of Anticipating Aversion

Anticipation of and Response to Aversive compared to Neutral Pictures

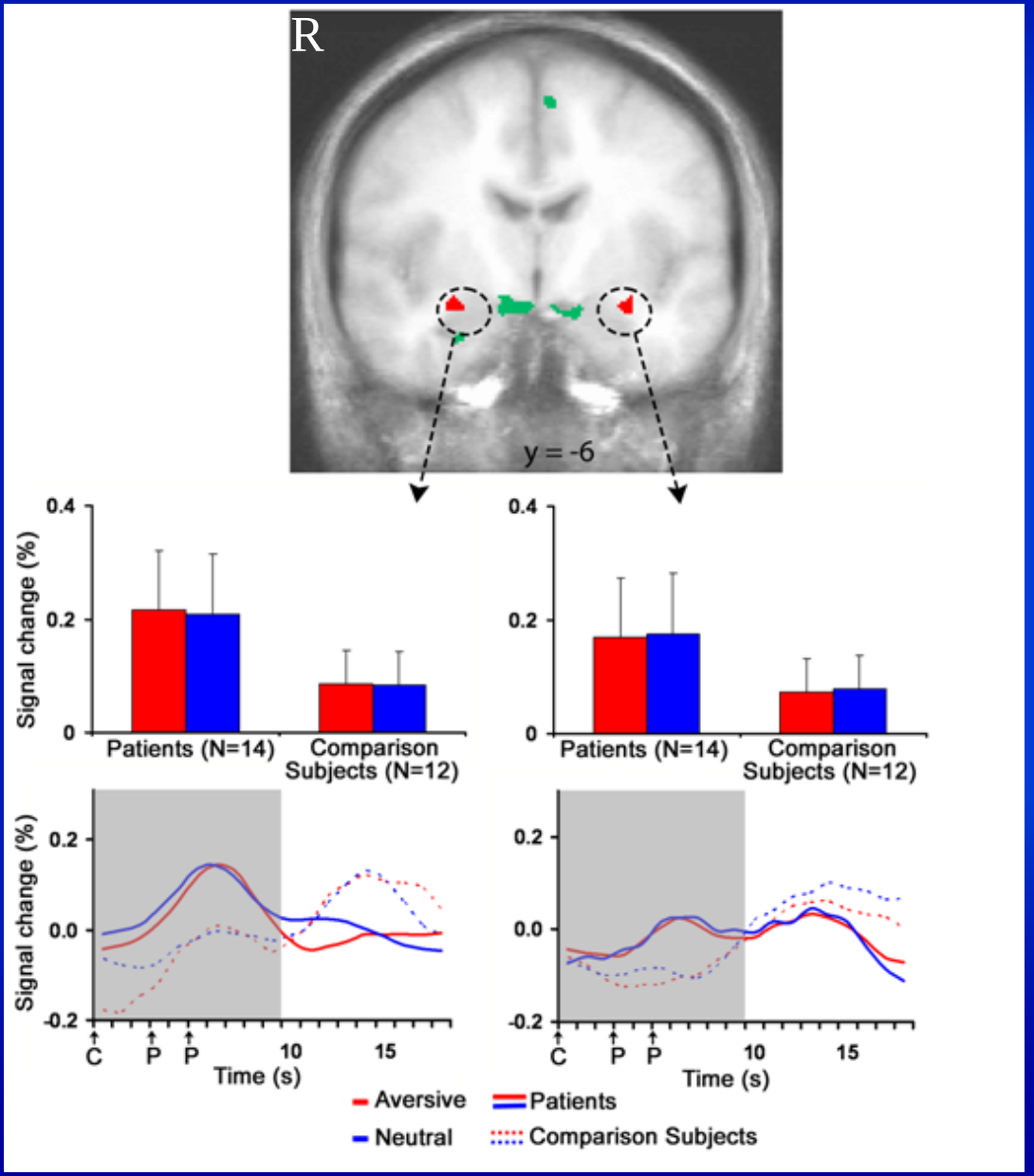


***n* = 21**

Nitschke et al. (2006) *NeuroImage*

Group Differences in Amygdala

GAD Patients Show *Elevated* Anticipatory Activity

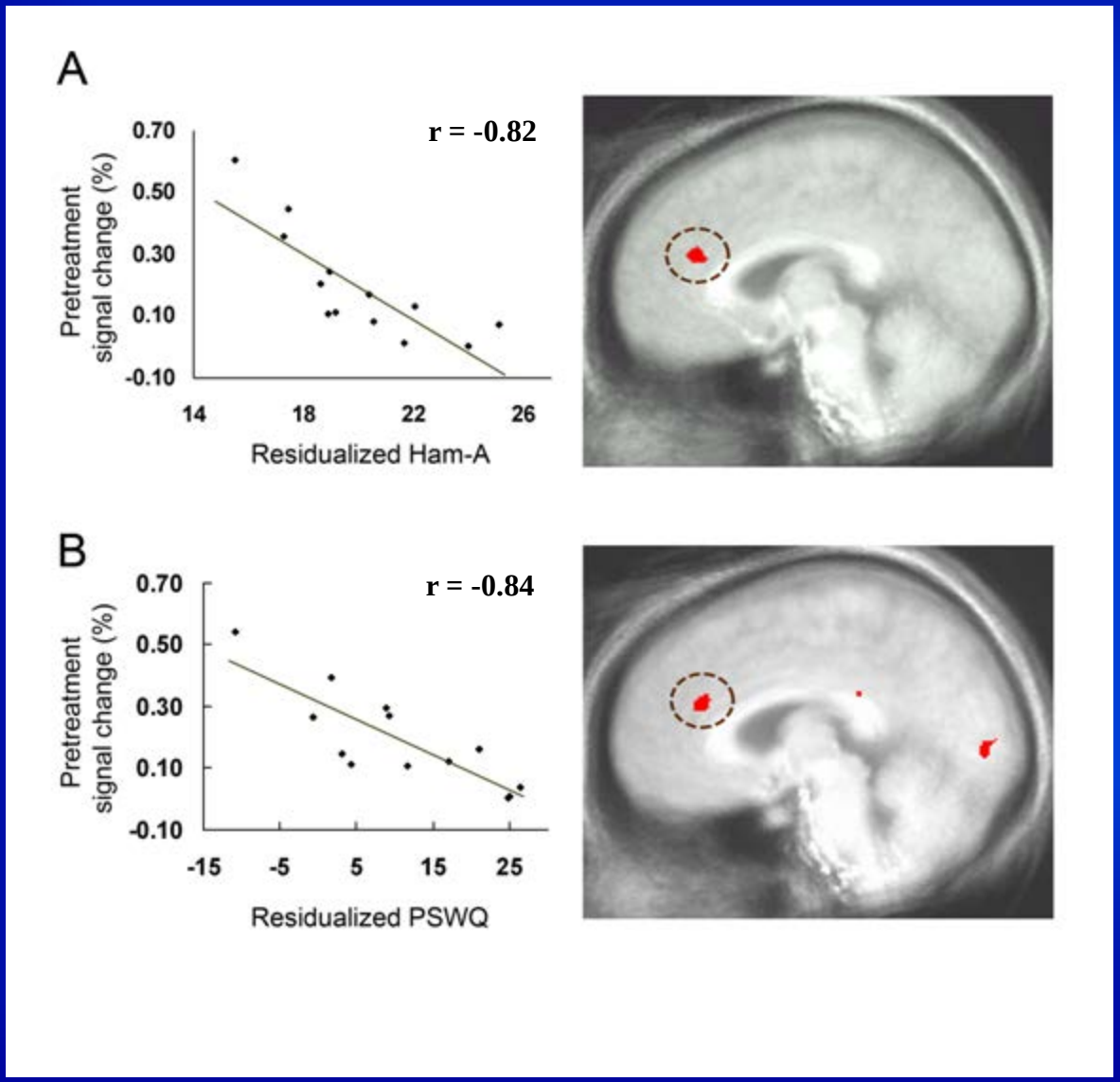


***n* = 26**

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

ACC Activity and Treatment Response

Pretreatment Anticipatory ACC Activity Predicts Response to Effexor

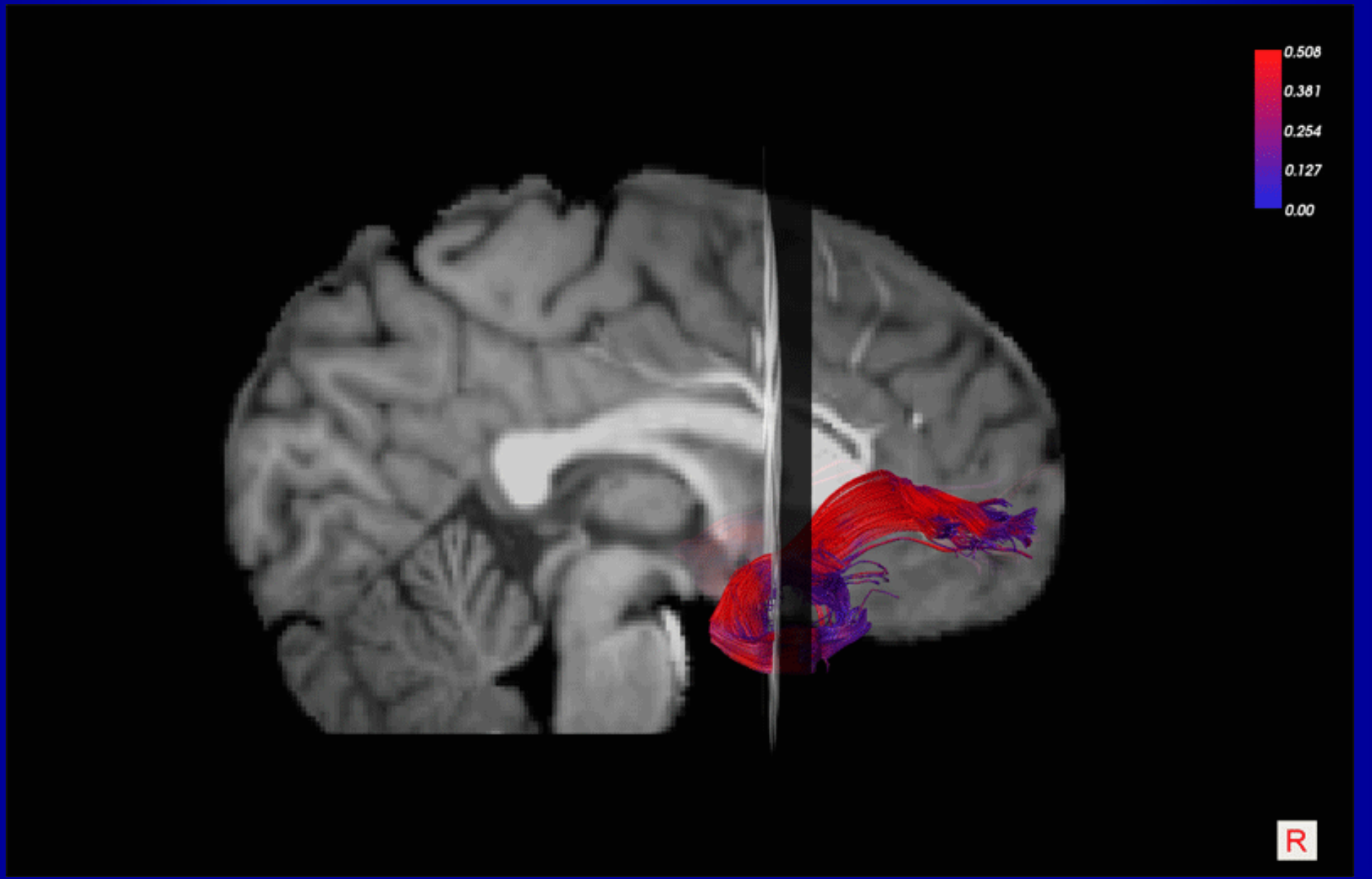


***n* = 14**

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

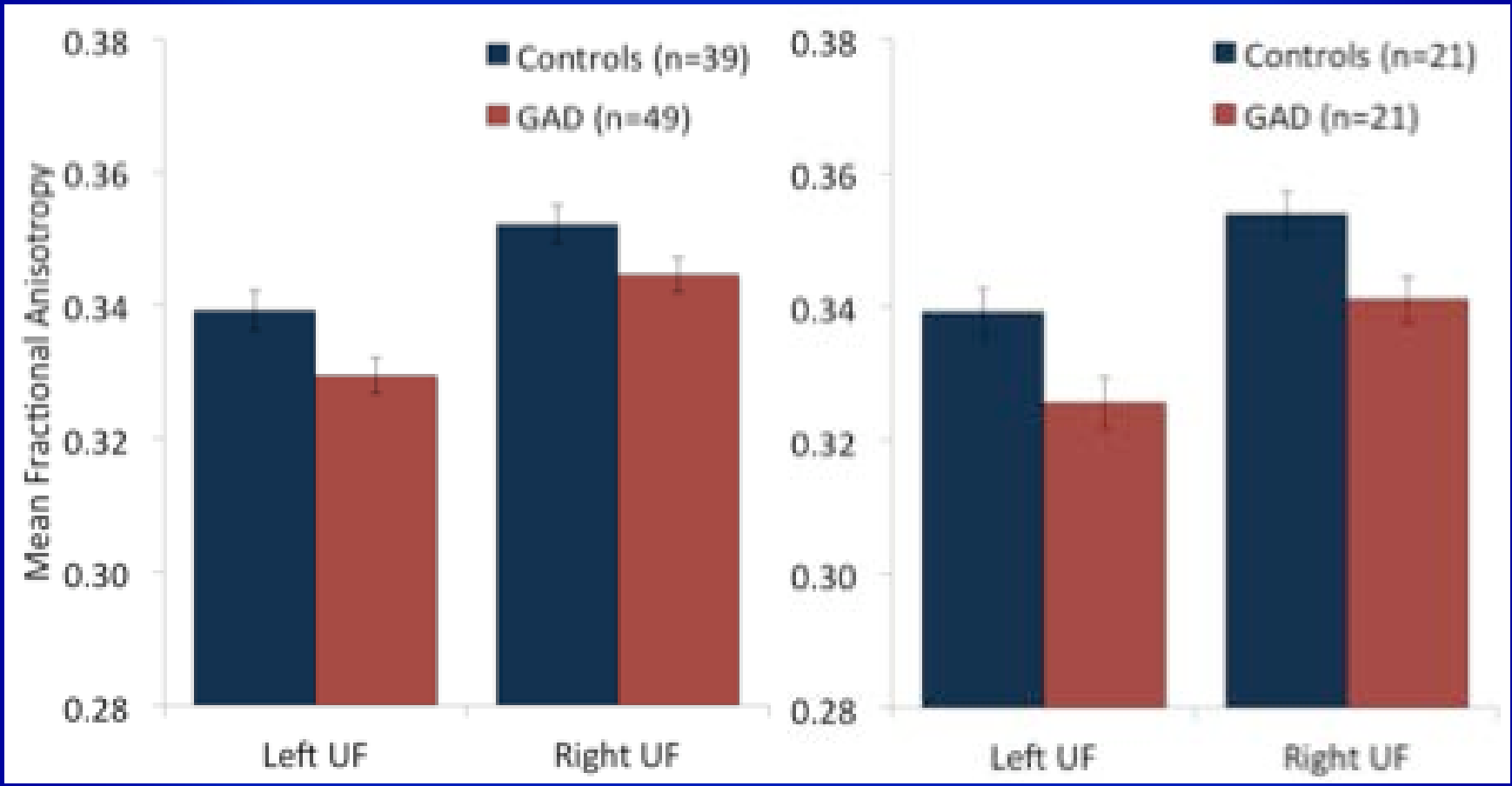
Uncinate Fasciculus

DTI-based Tractography



Group Differences in Uncinate Fasciculus

GAD Patients Show *Reduced* Structural Connectivity

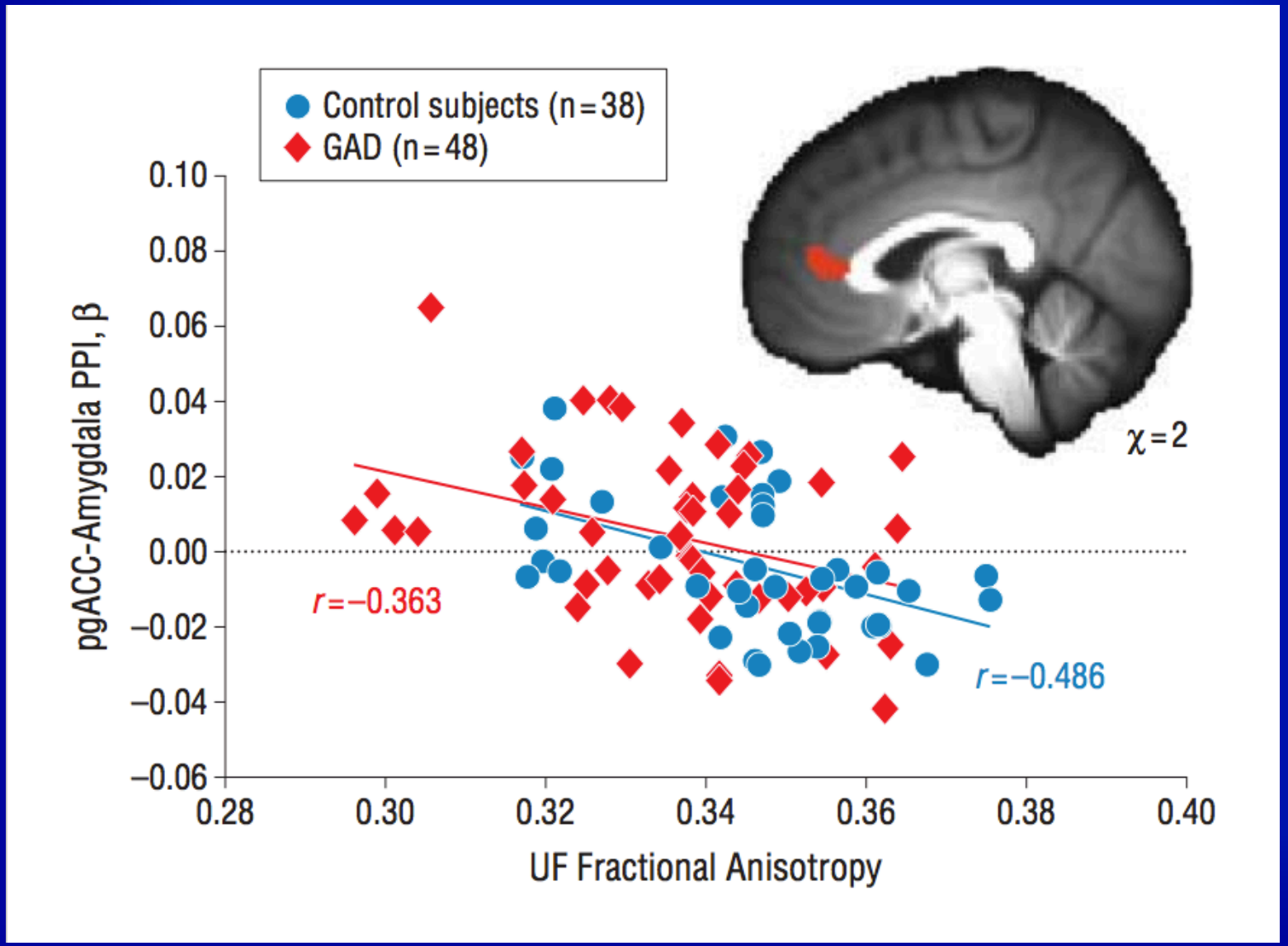


***n* = 88**

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

Uncinate Fasciculus Structural Connectivity

Associations with Anticipatory Amygdala-ACC Functional Connectivity

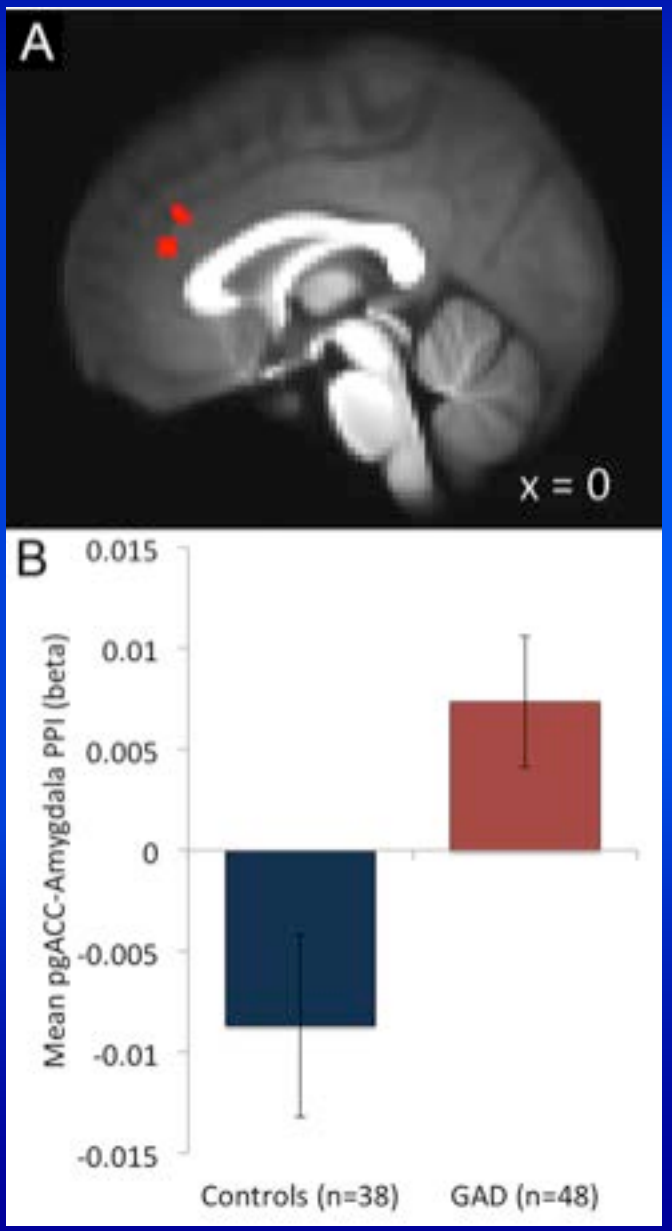


***n* = 88**

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

Group Differences in Functional Connectivity

GAD Patients Show *Reduced* ACC-Amygdala Negative Coupling



***n* = 88**

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

Neuroanatomy of Anxiety Disorders

Conclusions

- 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

Using Brain Research in Therapy

What will be most helpful for patients?

- 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