Neuroanatomy of Emotion, Fear, and Anxiety

Outline

- Neuroanatomy of emotion
- 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
- Educating our patients about their brains

What is Emotion?

Key Brain Areas for Emotion

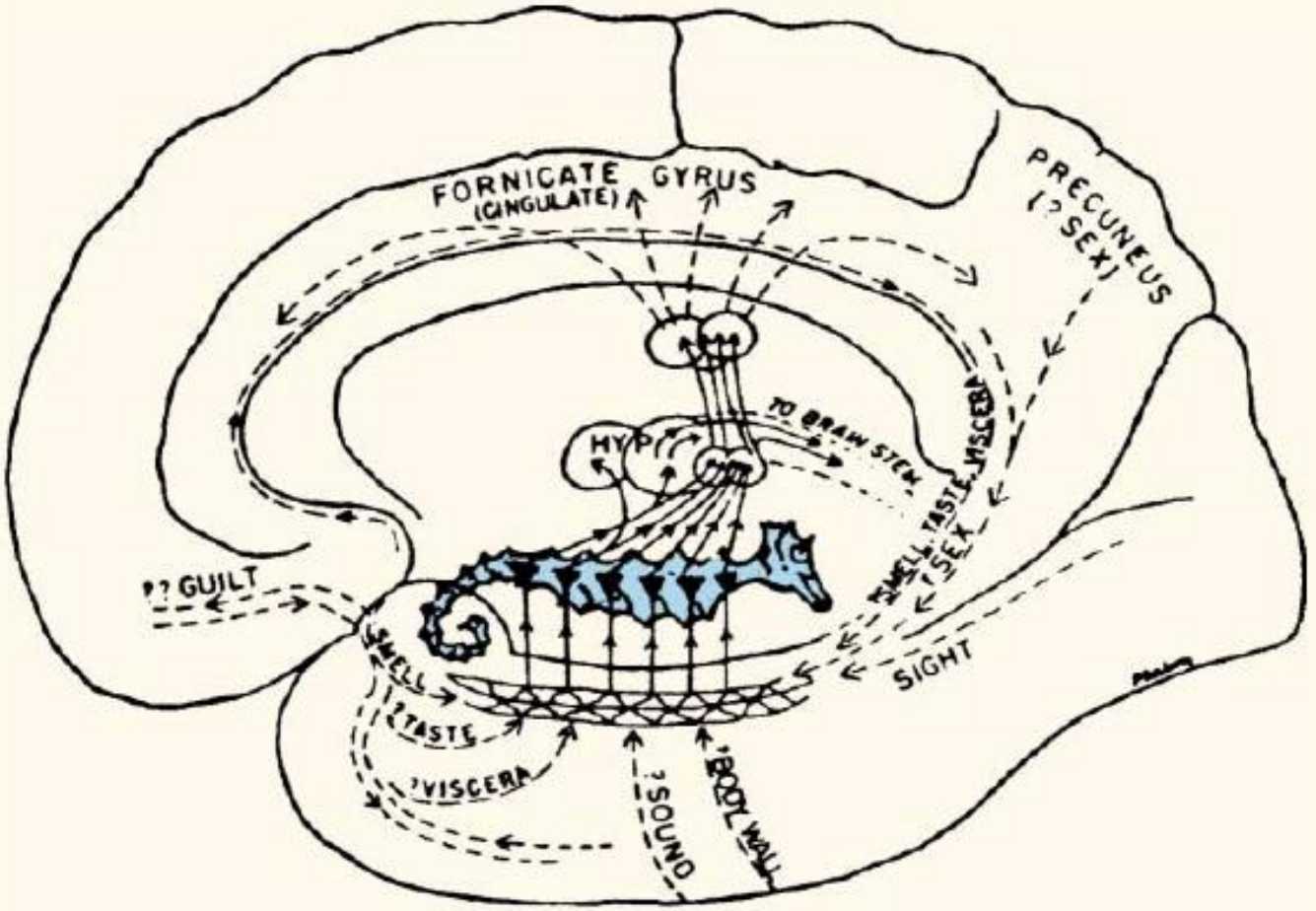


Figure 3 | **MacLean's limbic system theory of the functional neuroanatomy of emotion**. The core feature of MacLean's limbic system theory[8] was the hippocampus, illustrated here as a seahorse. According to MacLean, the hippocampus received sensory inputs from the outside world as well as information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

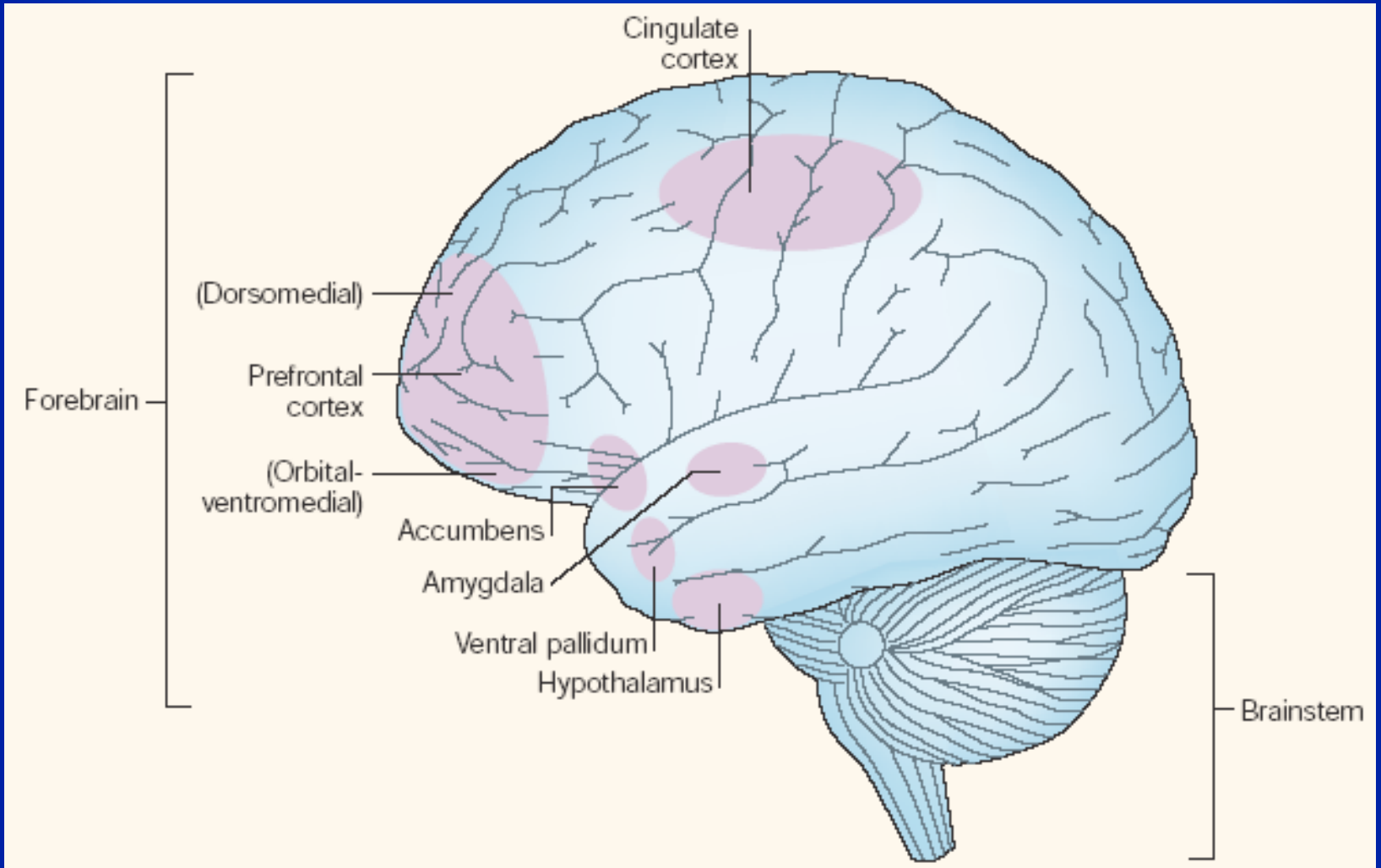


Figure 4 | **Key structures within a generalized emotional brain.** The figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen. Anatomical image adapted, with permission, from REF. 123 © (1996) Appleton & Lange.

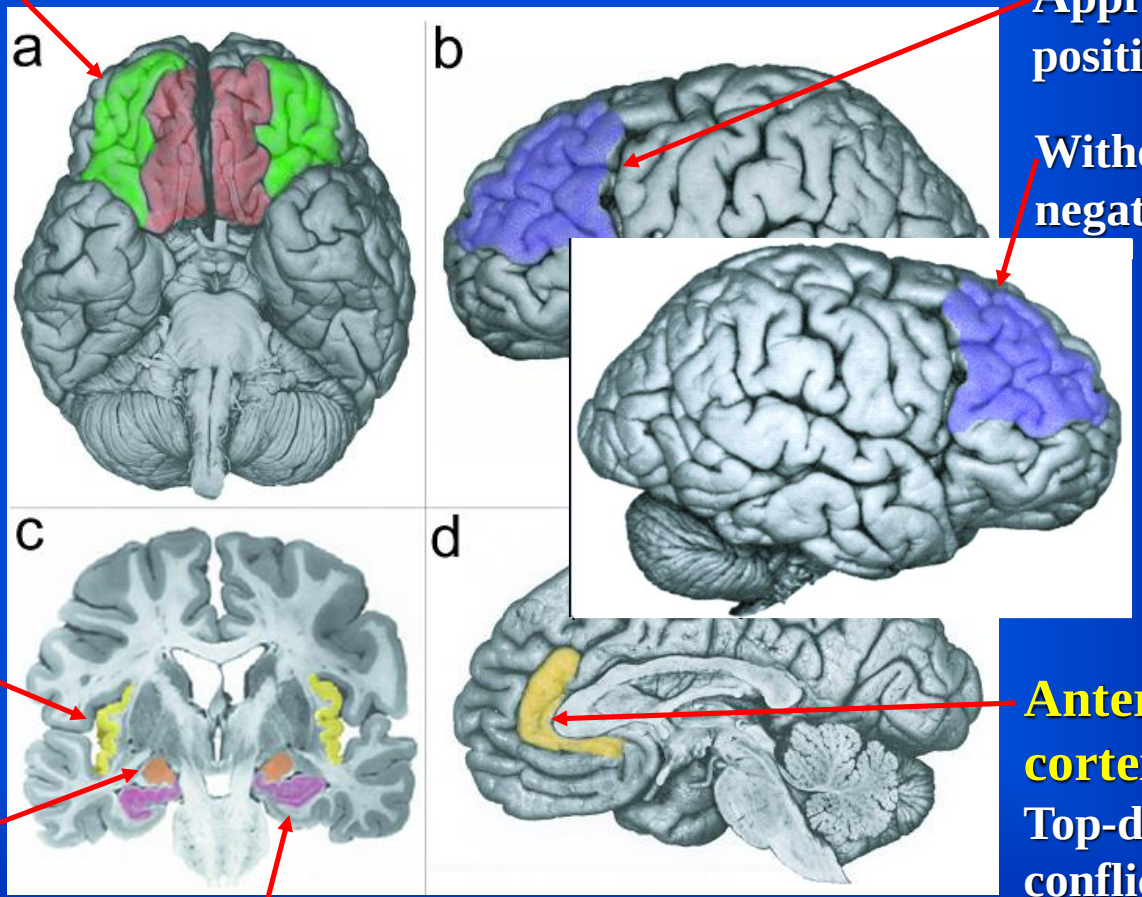
Neuroanatomy of Emotion

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

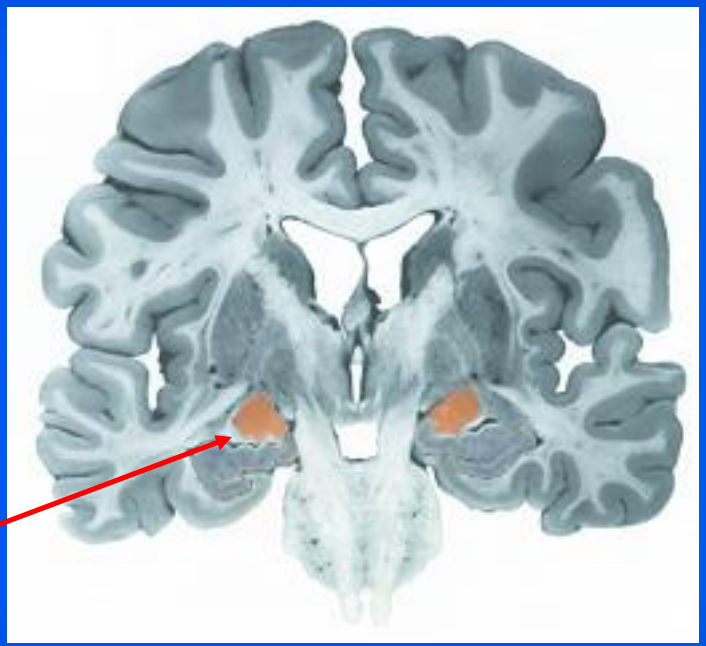
Amygdala:
Vigilance for motivationally salient events; threat detection; emotional memory

Hippocampus:
Declarative memory; spatial navigation; contextual fear

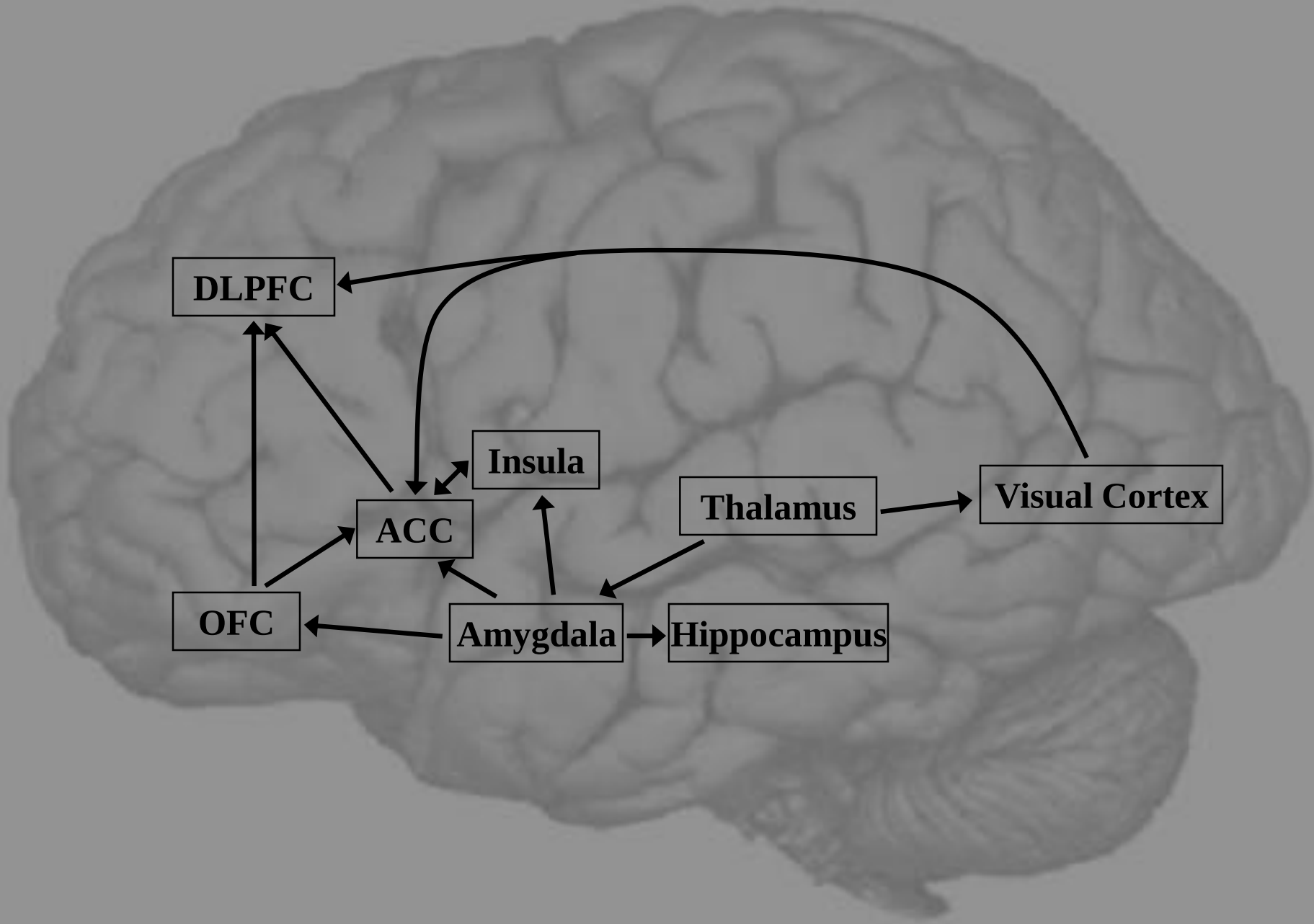
Insula and ACC:
Integration of sensory, affective, cognitive, and autonomic processing

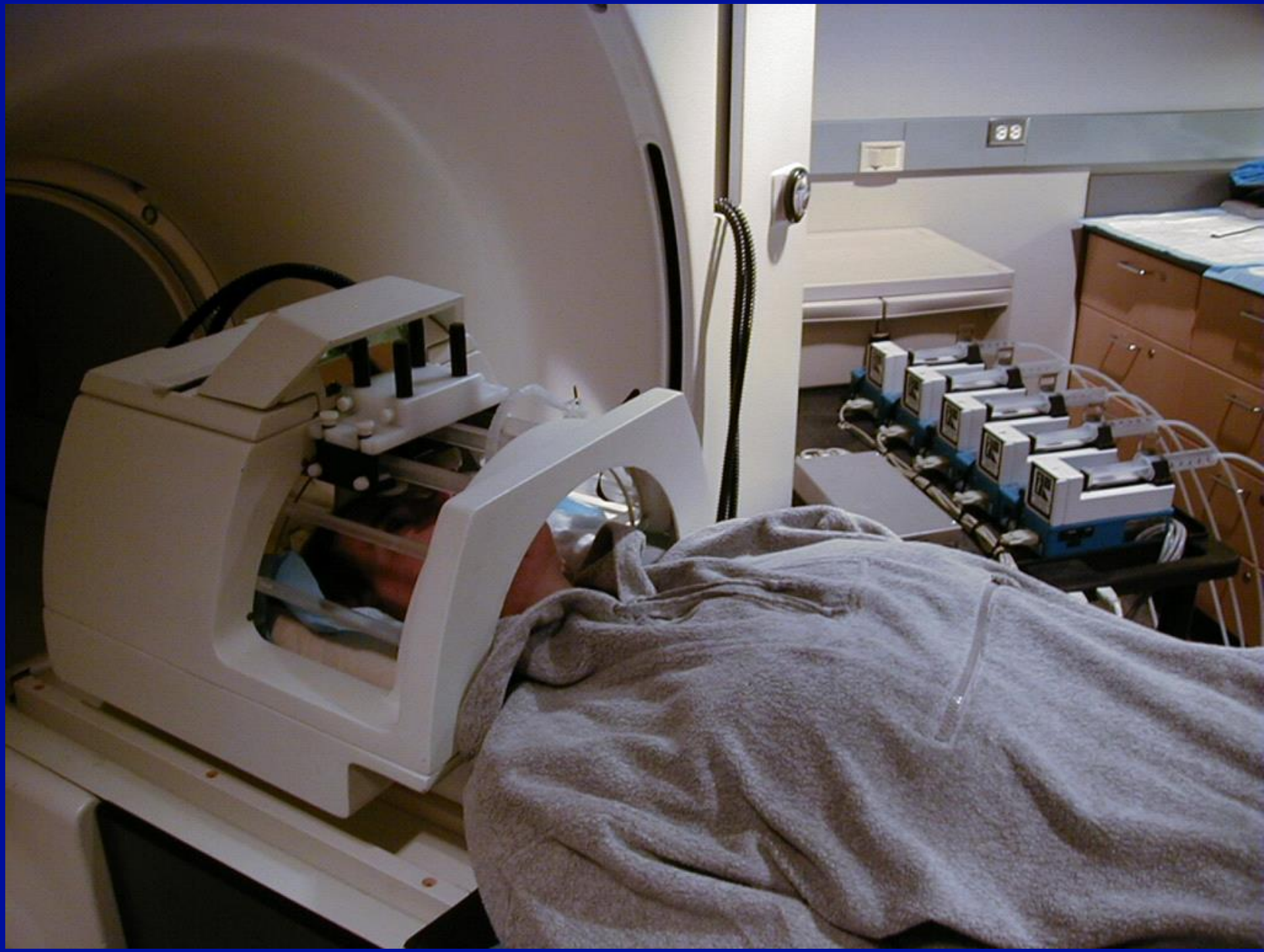
Neuroanatomy of Emotion

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



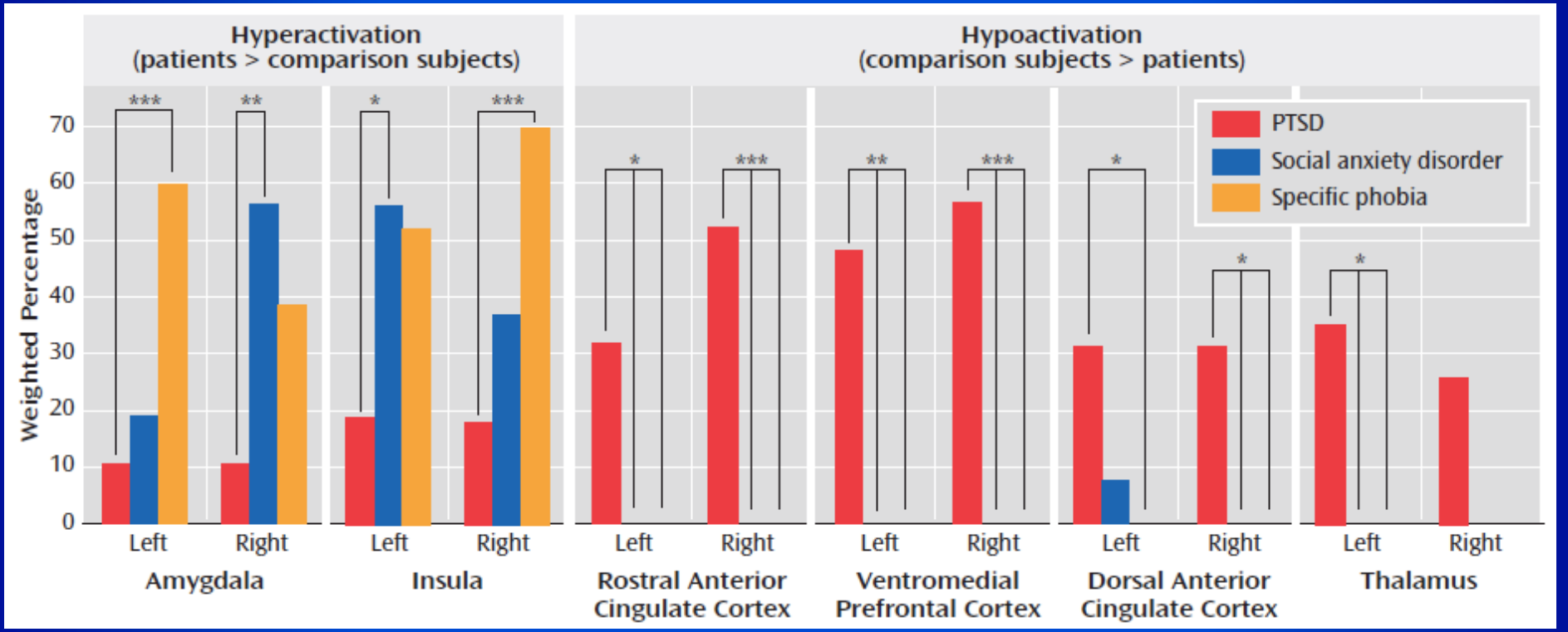
Imaging Research on Anxiety Disorders

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*

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**

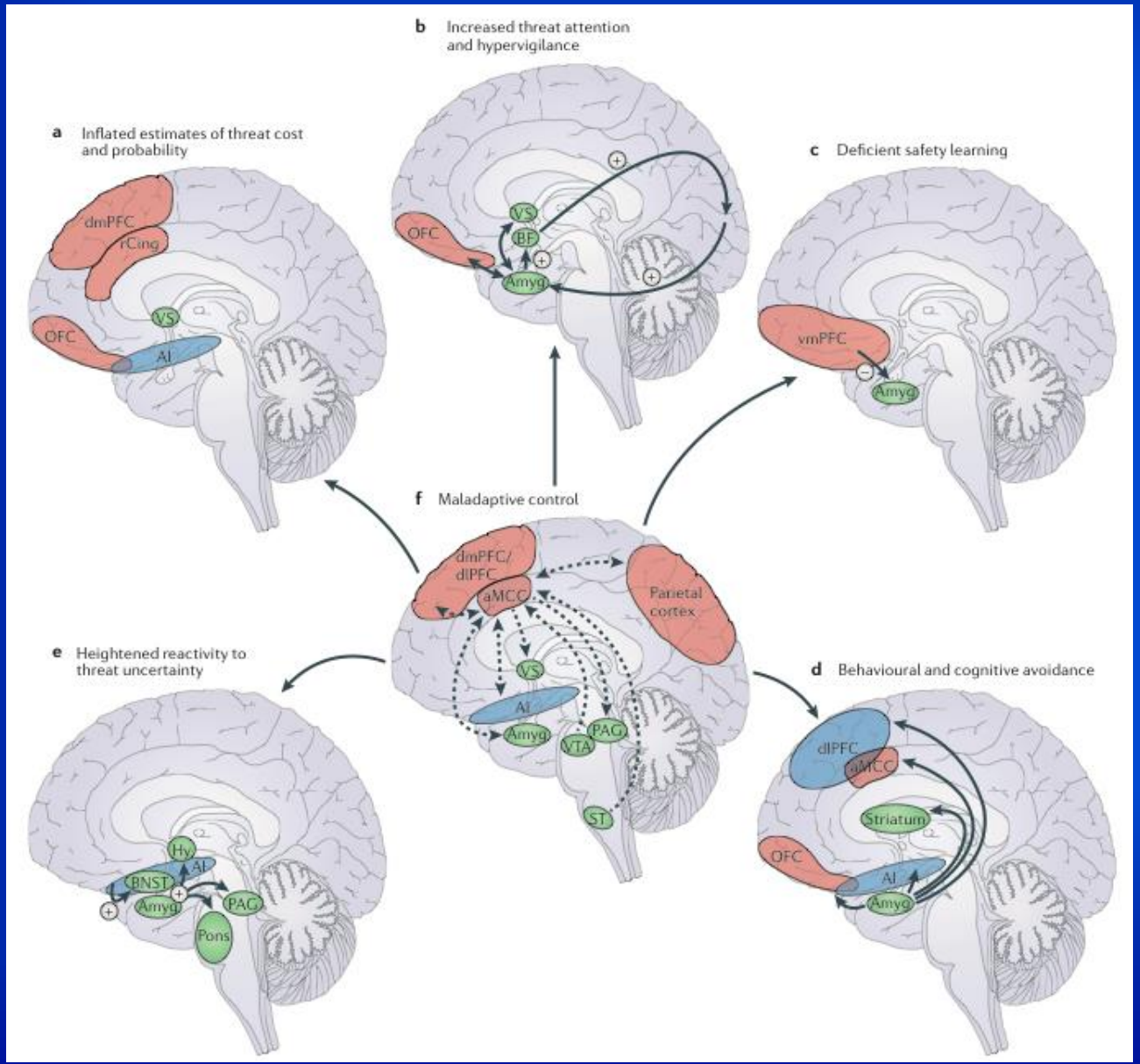
- This model identifies five processes involved in adaptive responses to threat uncertainty that function maladaptively in anxiety

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

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.

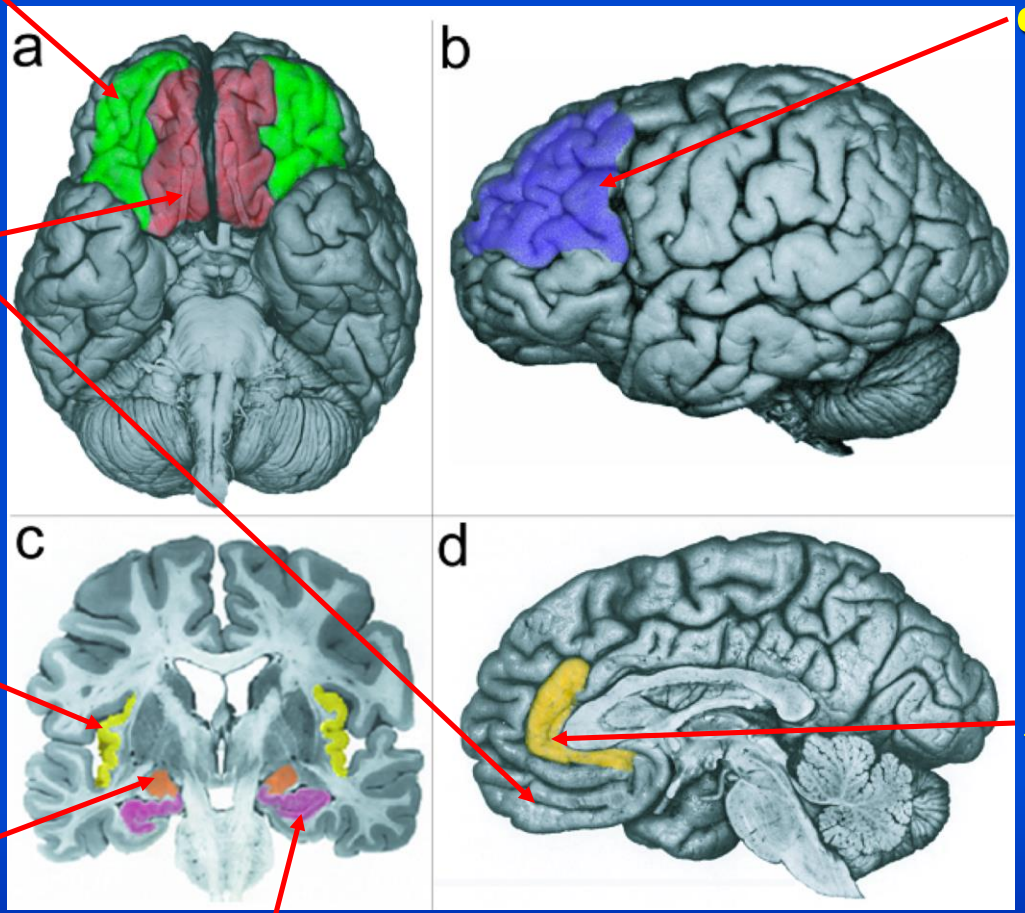
Neuroanatomy of Anxiety Disorders

Key Brain Areas

Orbitofrontal cortex (OFC)

Dorsolateral prefontal cortex (dlPFC)

Ventromedial prefrontal cortex (vmPFC)



Insula

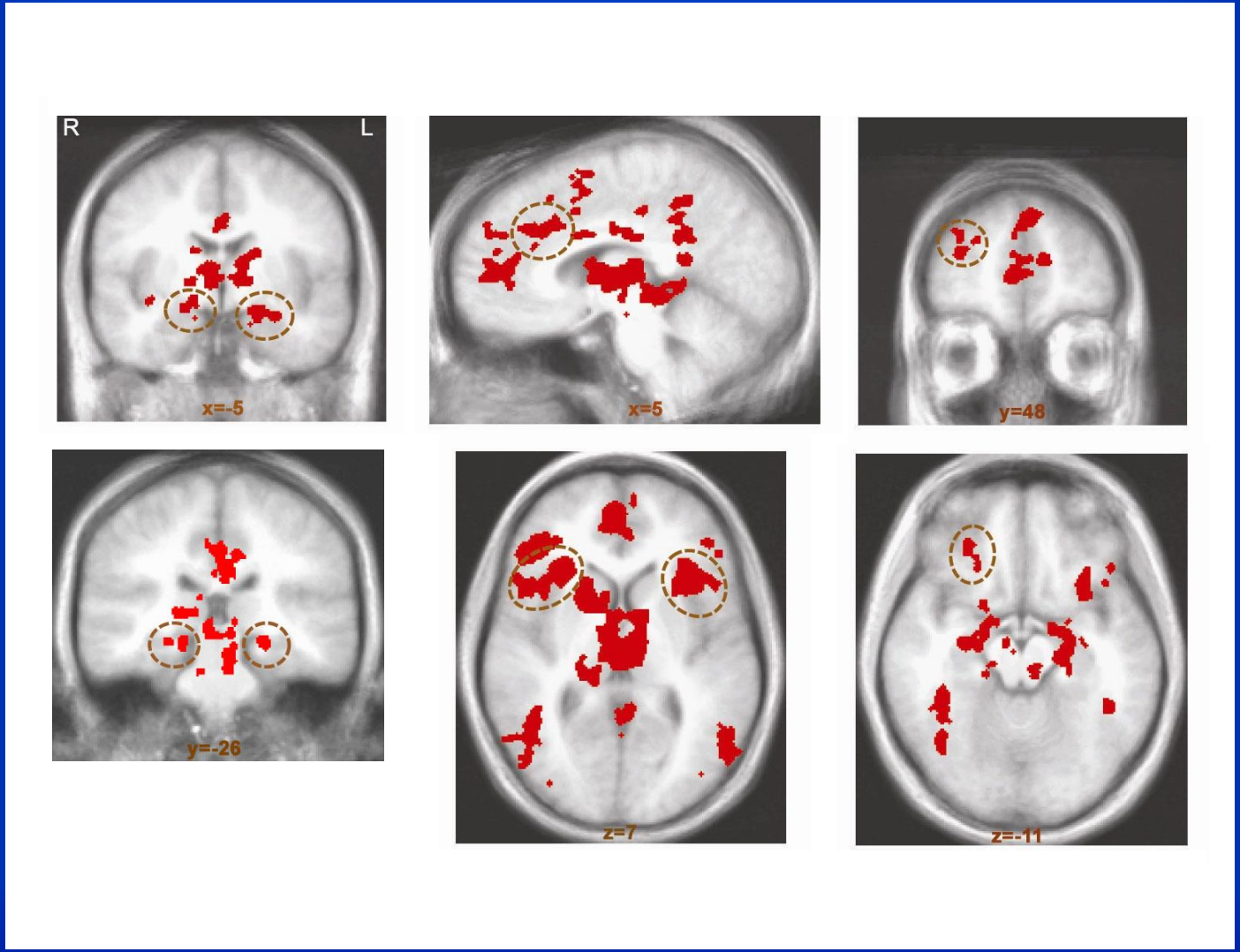
Anterior cingulate cortex (ACC)

Amygdala

Hippocampus

Neural Circuitry of Anticipating Aversion

Anticipation of and Response to Aversive compared to Neutral Pictures

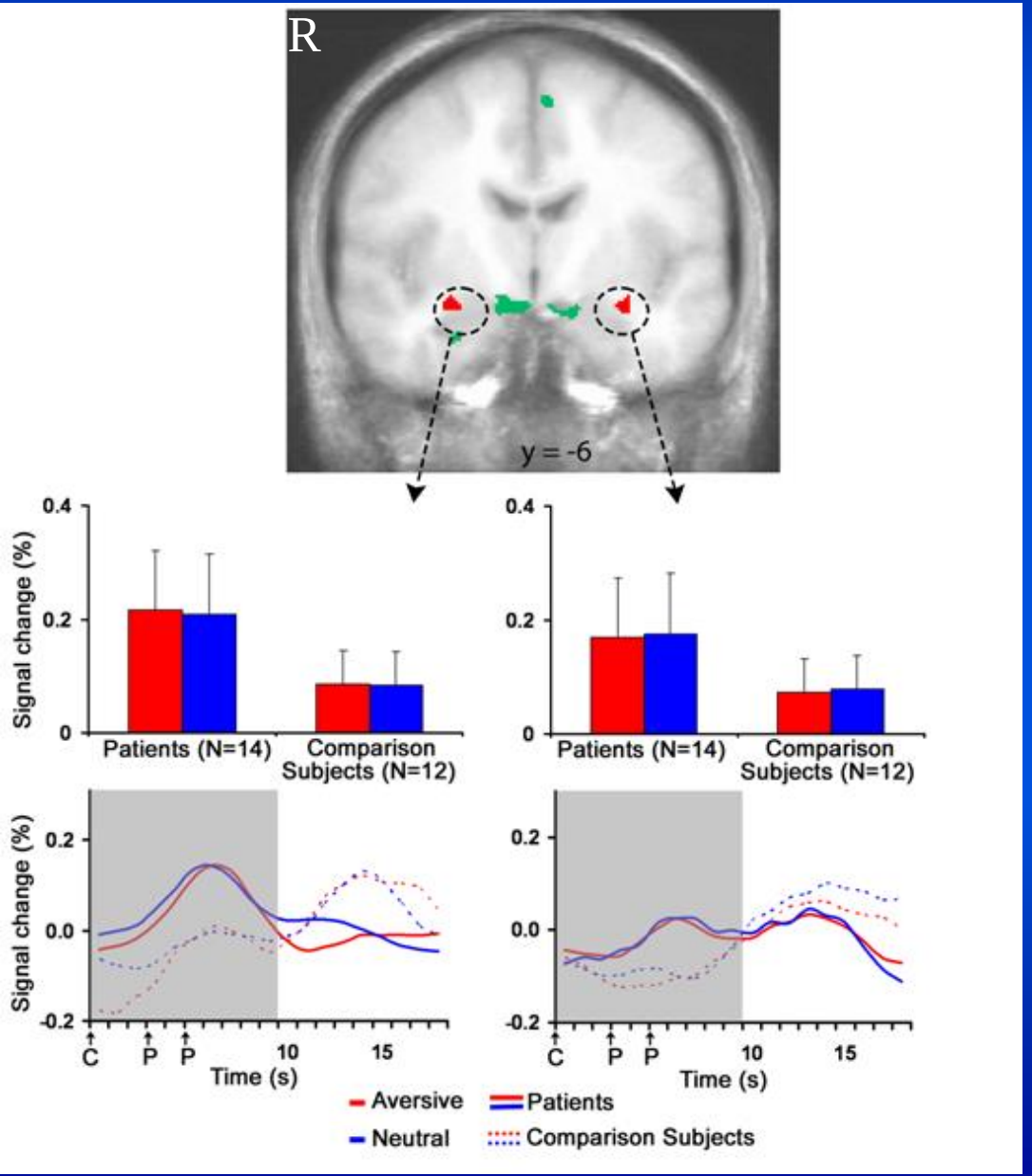


***n* = 21**

Nitschke et al. (2006) *NeuroImage*

Group Differences in Amygdala

GAD Patients Show *Elevated* Anticipatory Activity

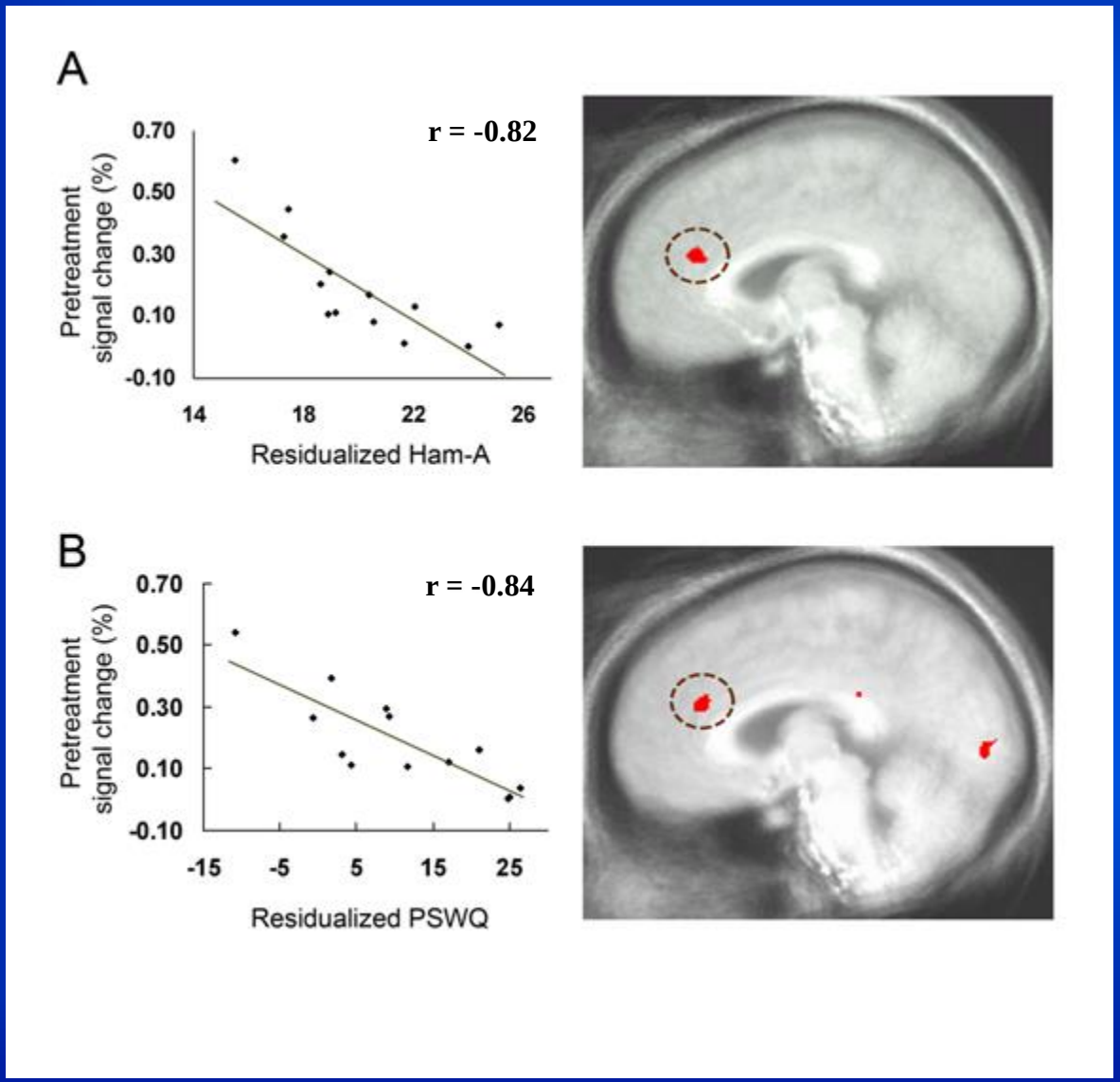


***n* = 26**

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

ACC Activity and Treatment Response

Pretreatment Anticipatory ACC Activity Predicts Response to Effexor

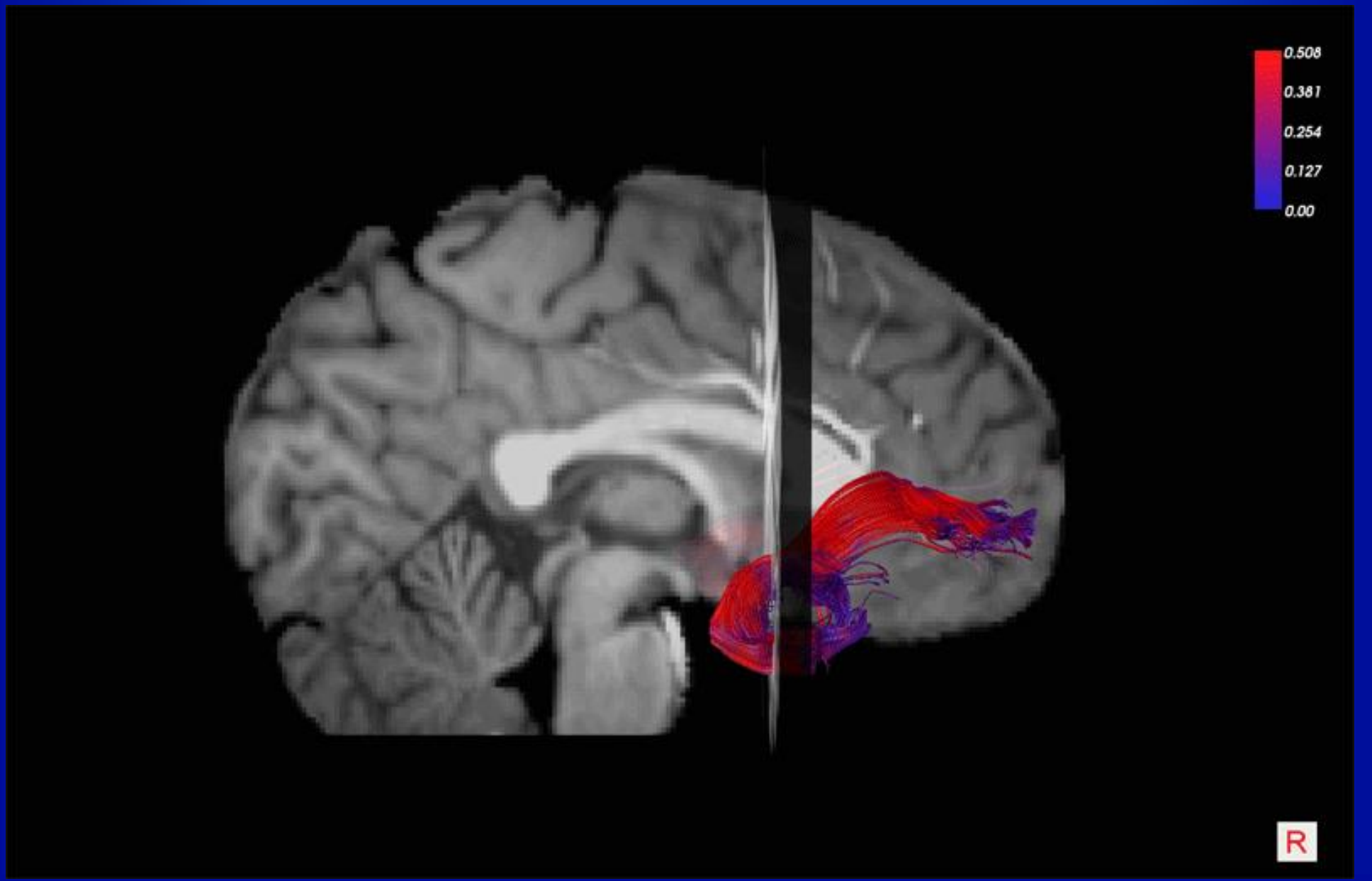


***n* = 14**

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

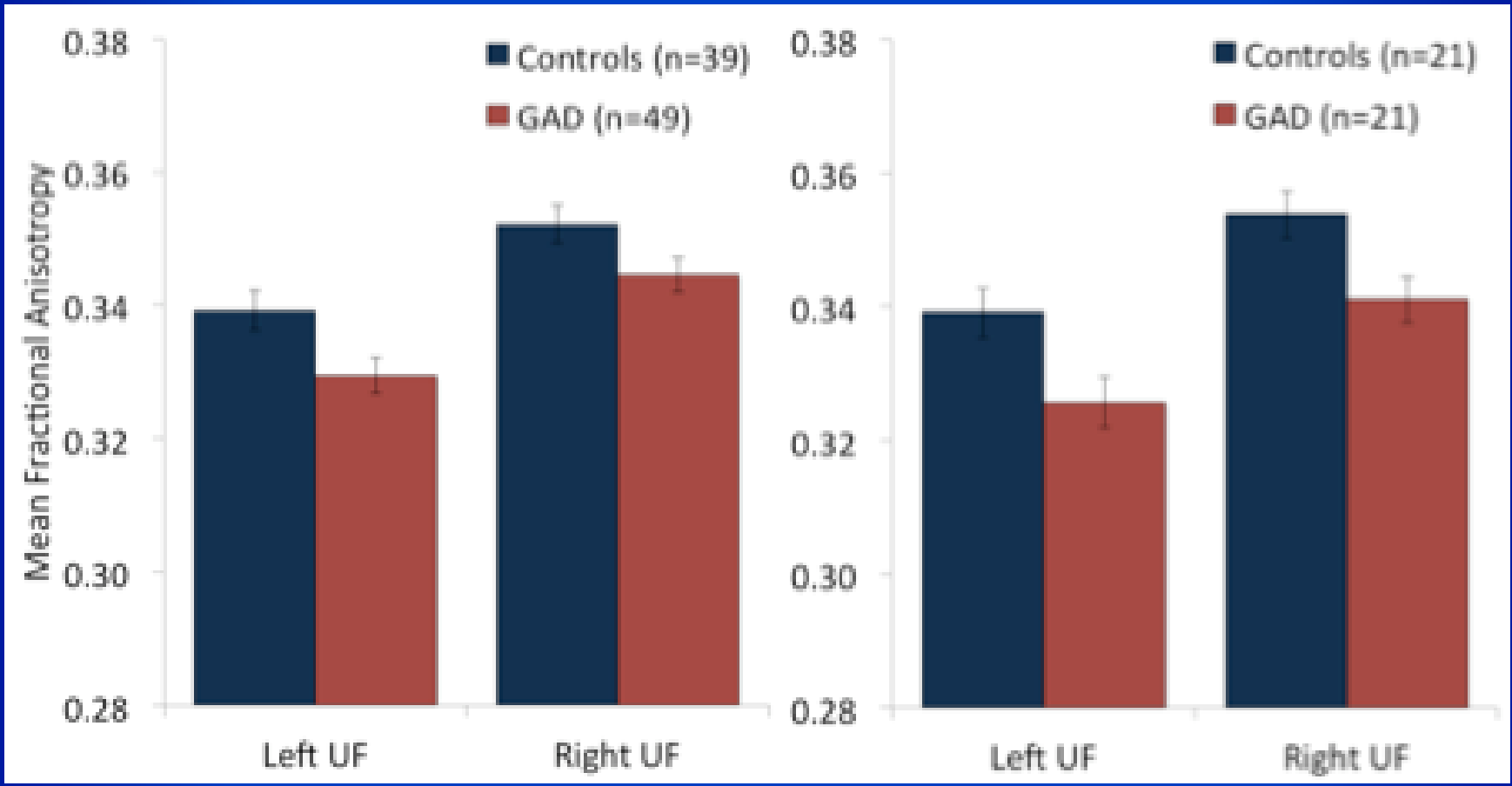
Uncinate Fasciculus

DTI-based Tractography



Structural Connectivity

GAD Patients Show *Reductions* in Uncinate Fasciculus

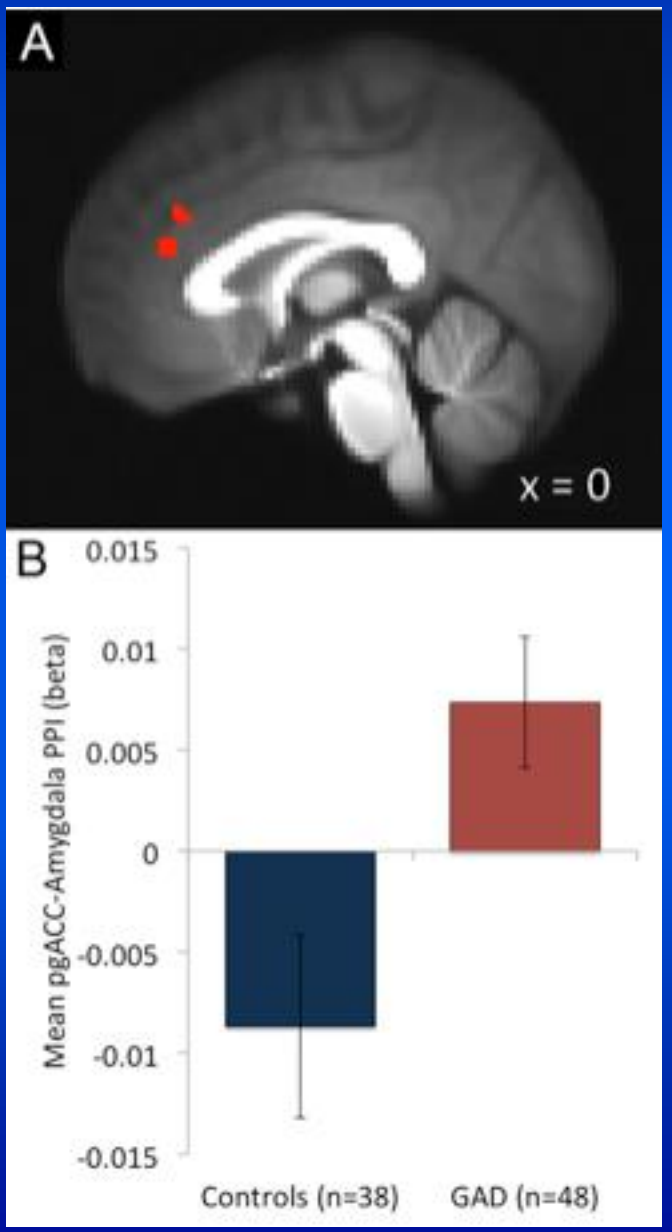


***n* = 88**

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

Functional Connectivity

GAD Patients Show *Reduced* ACC-Amygdala Negative Coupling

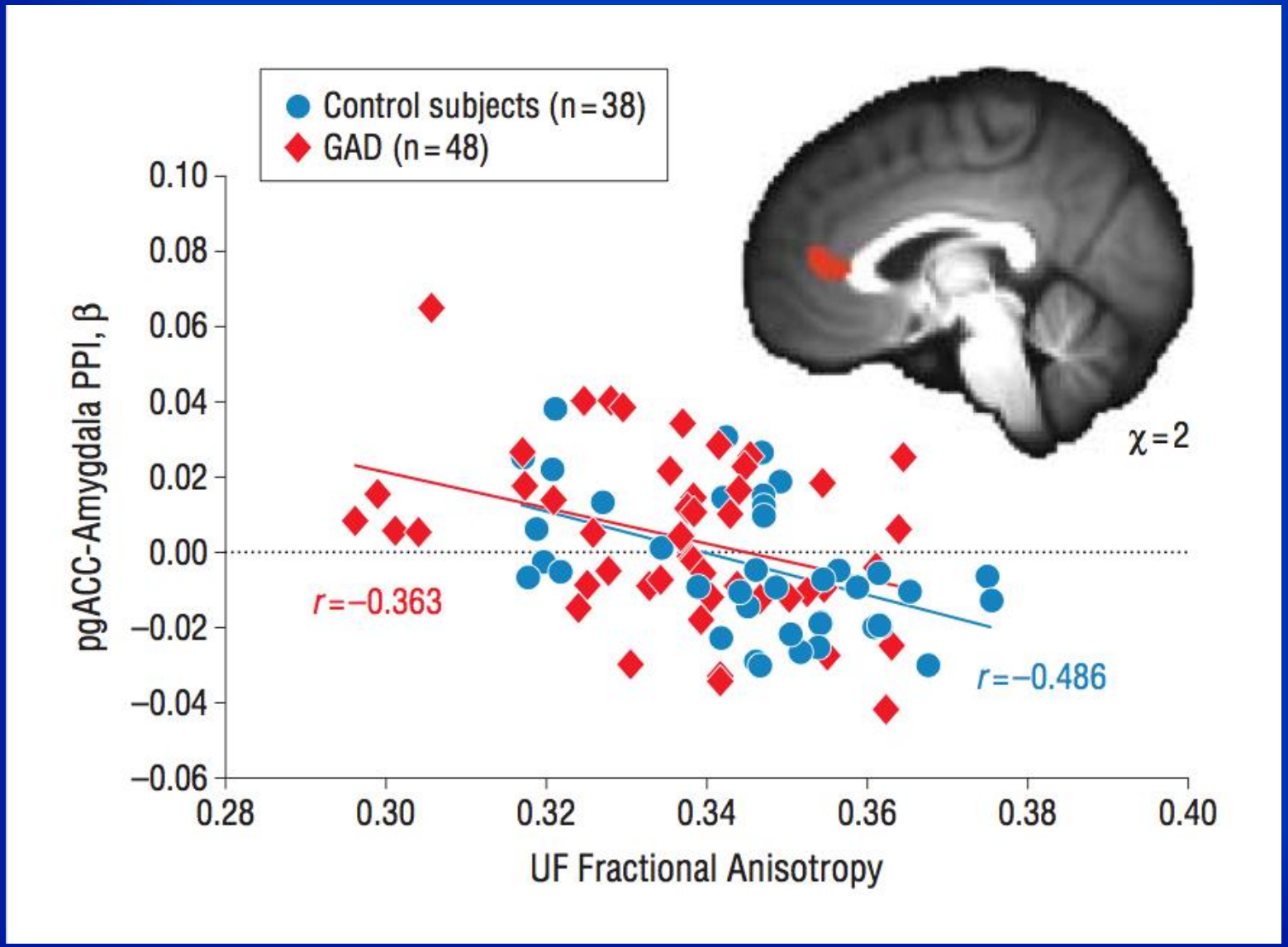


***n* = 88**

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

Functional and Structural Connectivity

Uncinate Fasciculus and Anticipatory Amygdala-ACC Function



***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 (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*, *JAMA*, and *American Journal*
  - Be good consumers of neuroimaging research by applying critical thinking

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
  - Worries, obsessions, social anxiety, self-blame, avoidance
  - Depressive thoughts, self-critical thoughts, suicidal thoughts
  - 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)
  - Traumatic experiences
    - Neural connections supporting associations with trauma are here for the rest of patient's life
- Whatever you spend your time doing, your brain will help you get really good at

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