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

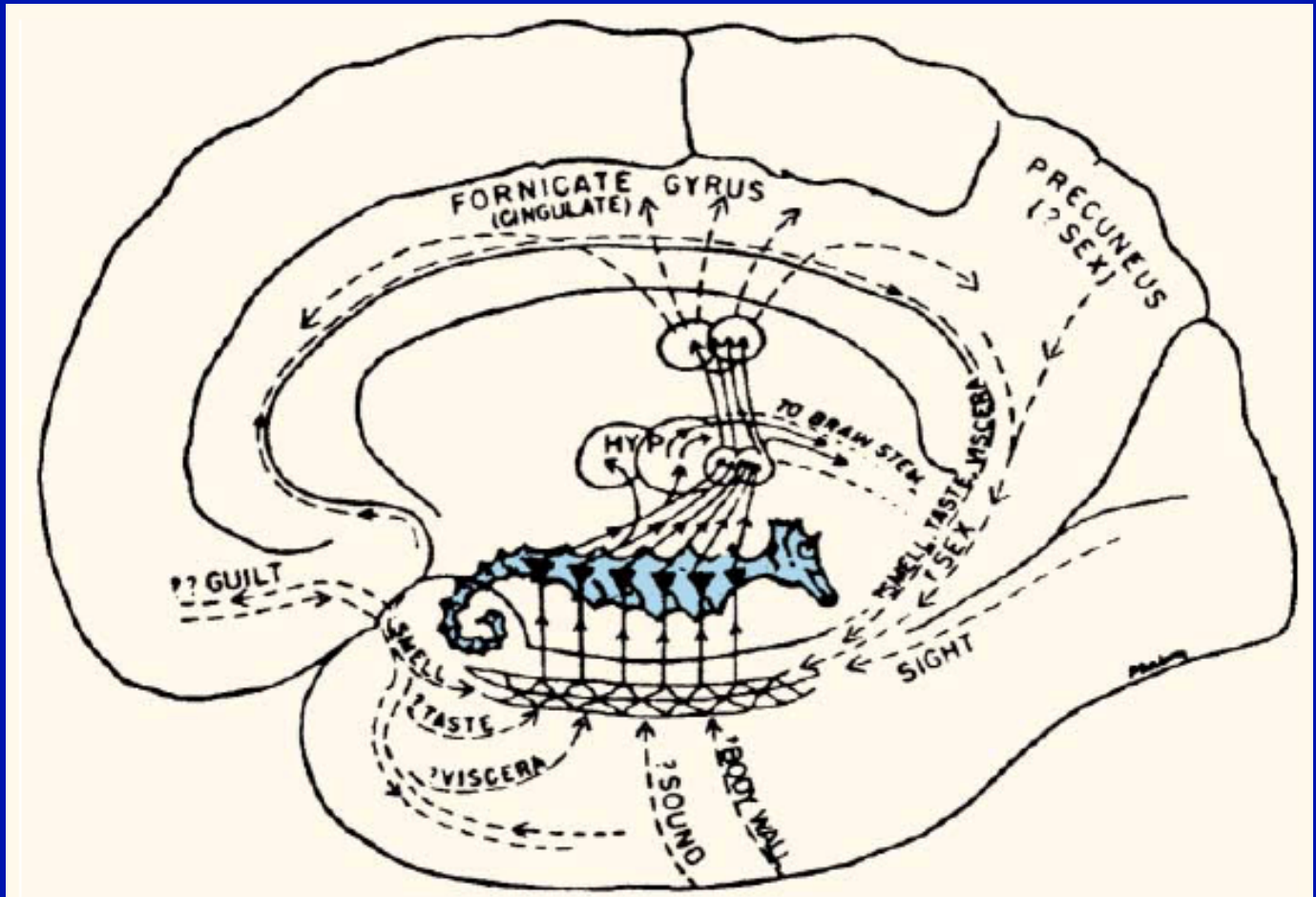


Figure 3 | **MacLean's limbic system theory of the functional neuroanatomy of emotion**. The core feature of MacLean's limbic system theory[8] was the hippocampus, illustrated here as a seahorse. According to MacLean, the hippocampus received sensory inputs from the outside world as well as information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

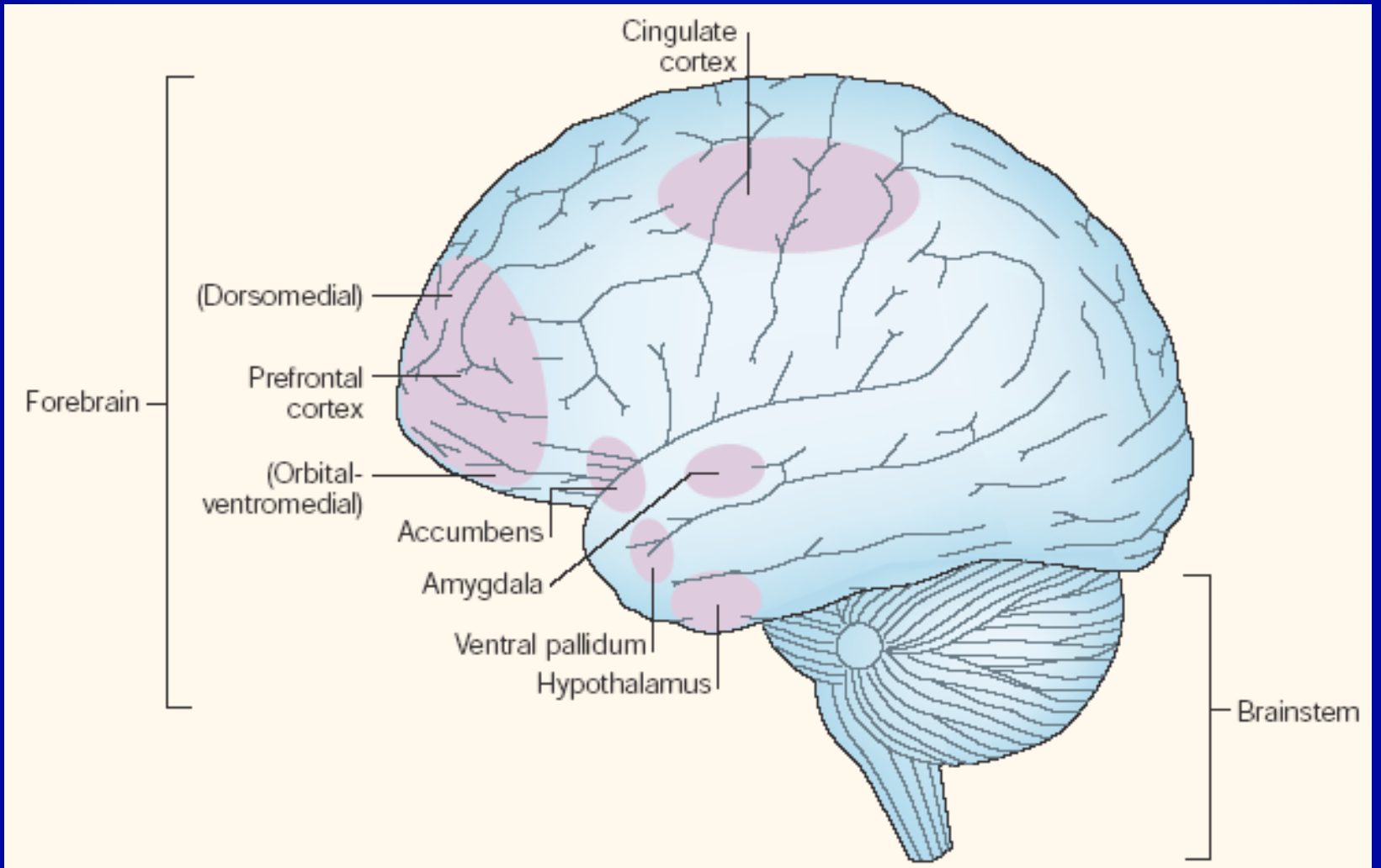
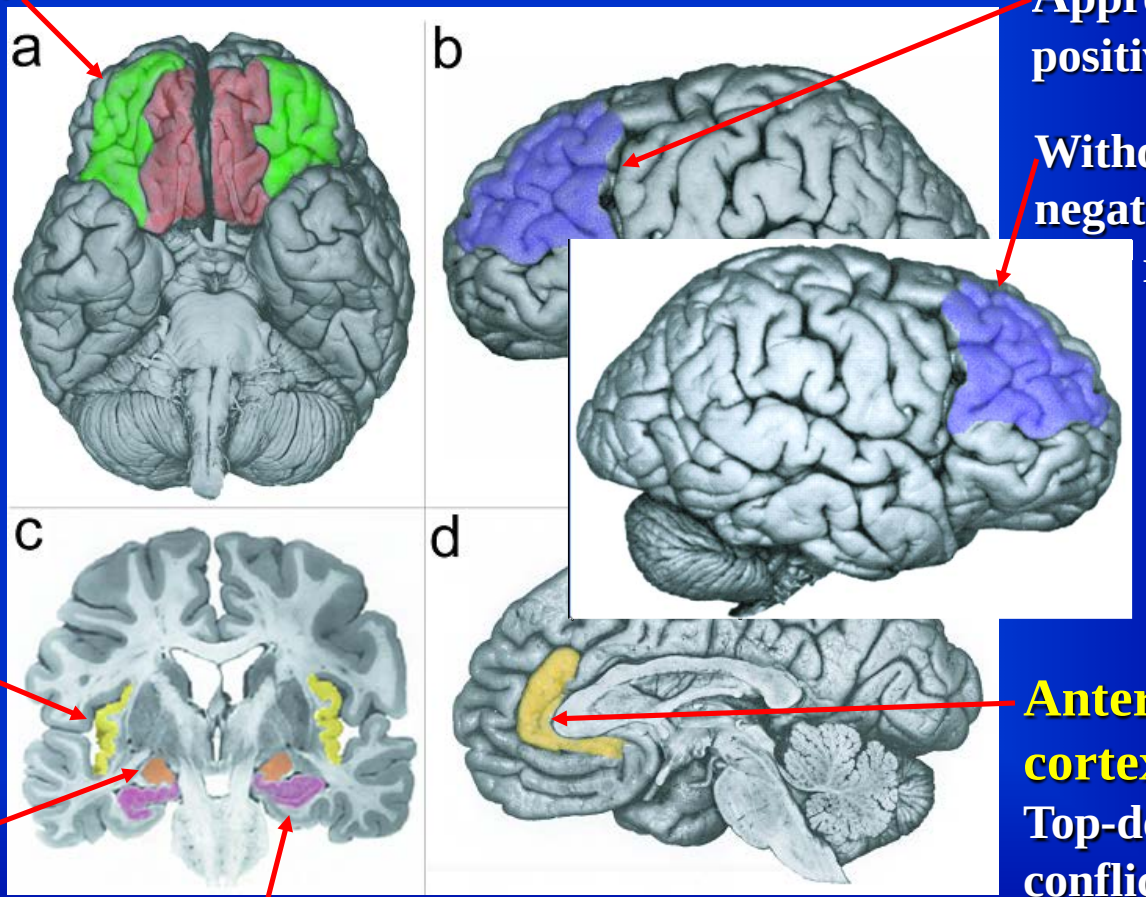


Figure 4 | **Key structures within a generalized emotional brain.** The figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen. Anatomical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

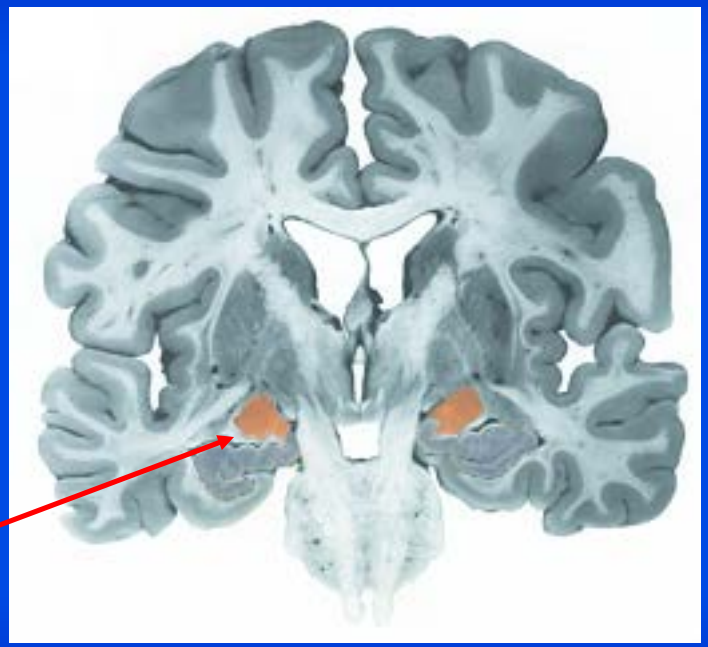
Amygdala:
Vigilance for motivationally salient events; threat detection; emotional memory

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

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)

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**

- 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

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

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**

Grupe & Nitschke (2013)
Nature Rev. Neurosci.

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)

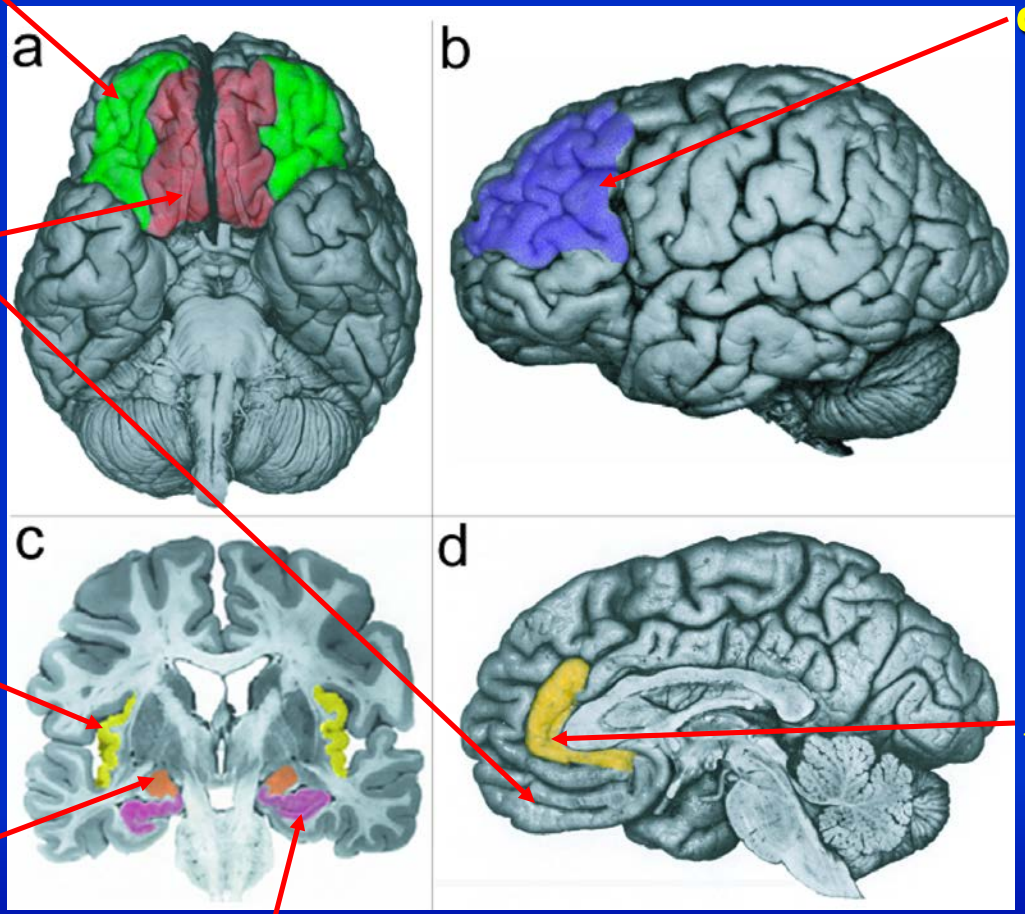
Neuroanatomy of Anxiety Disorders

Key Brain Areas

Orbitofrontal cortex (OFC)

Dorsolateral prefontal cortex (dlPFC)

Ventromedial prefrontal cortex (vmPFC)



Insula

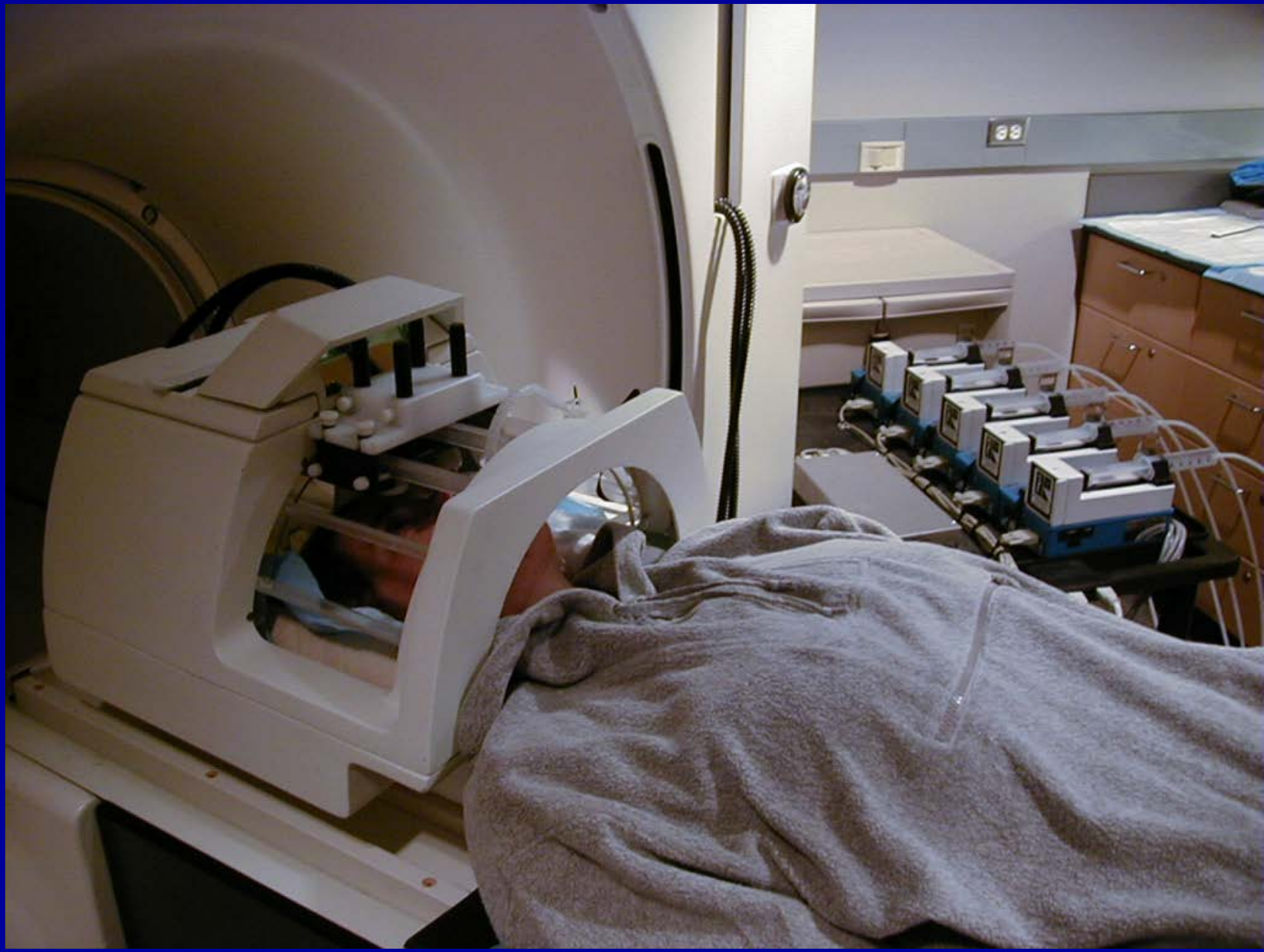
Anterior cingulate cortex (ACC)

Amygdala

Hippocampus

What Is Anxiety?

Brain Imaging



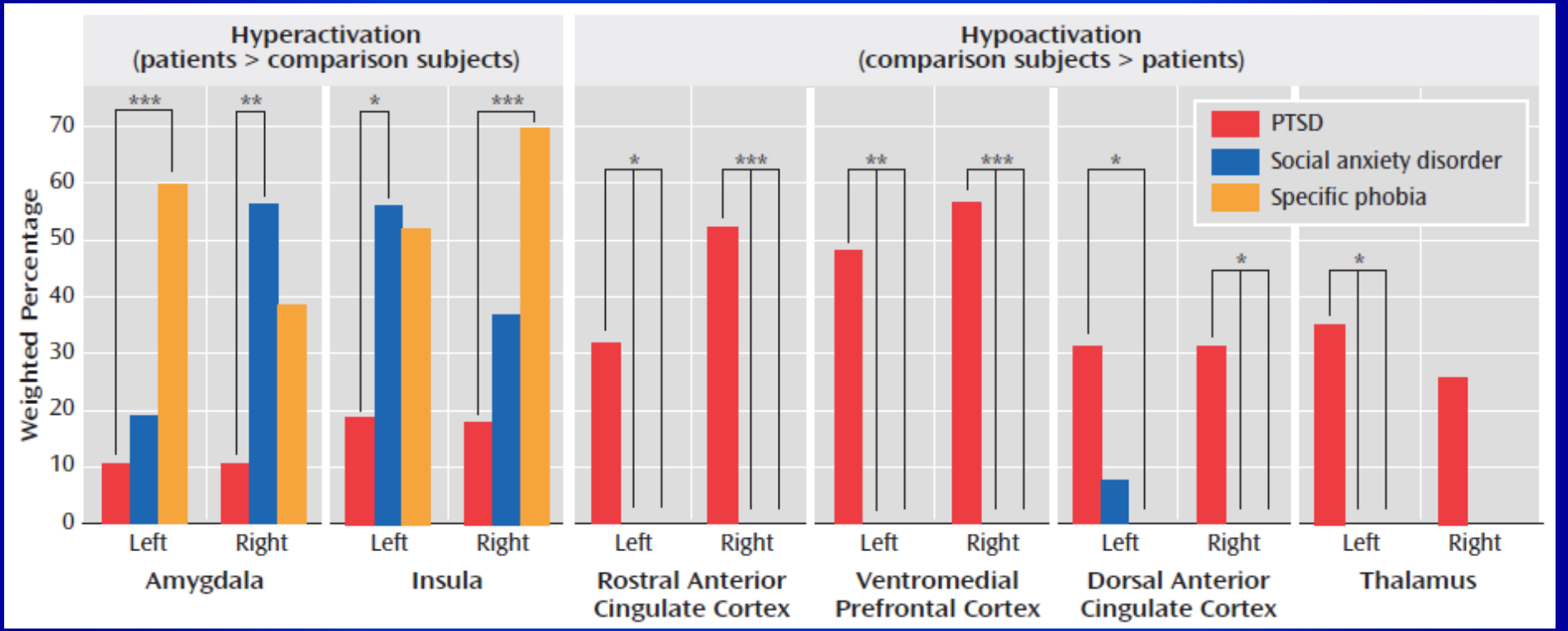
Imaging Research on Anxiety Disorders

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

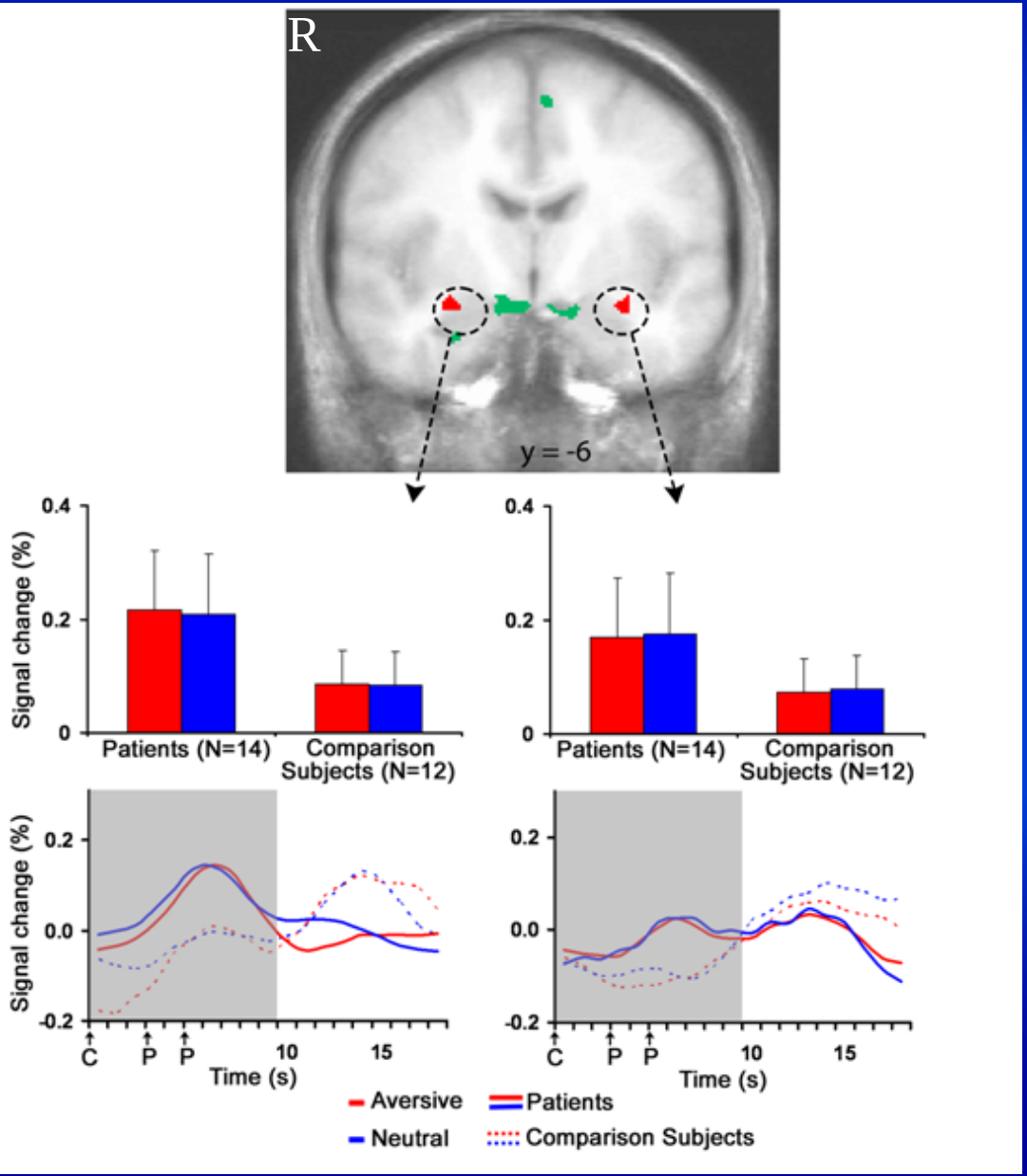
Summary



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

Group Differences in Amygdala

GAD Patients Show *Elevated* Anticipatory Activity

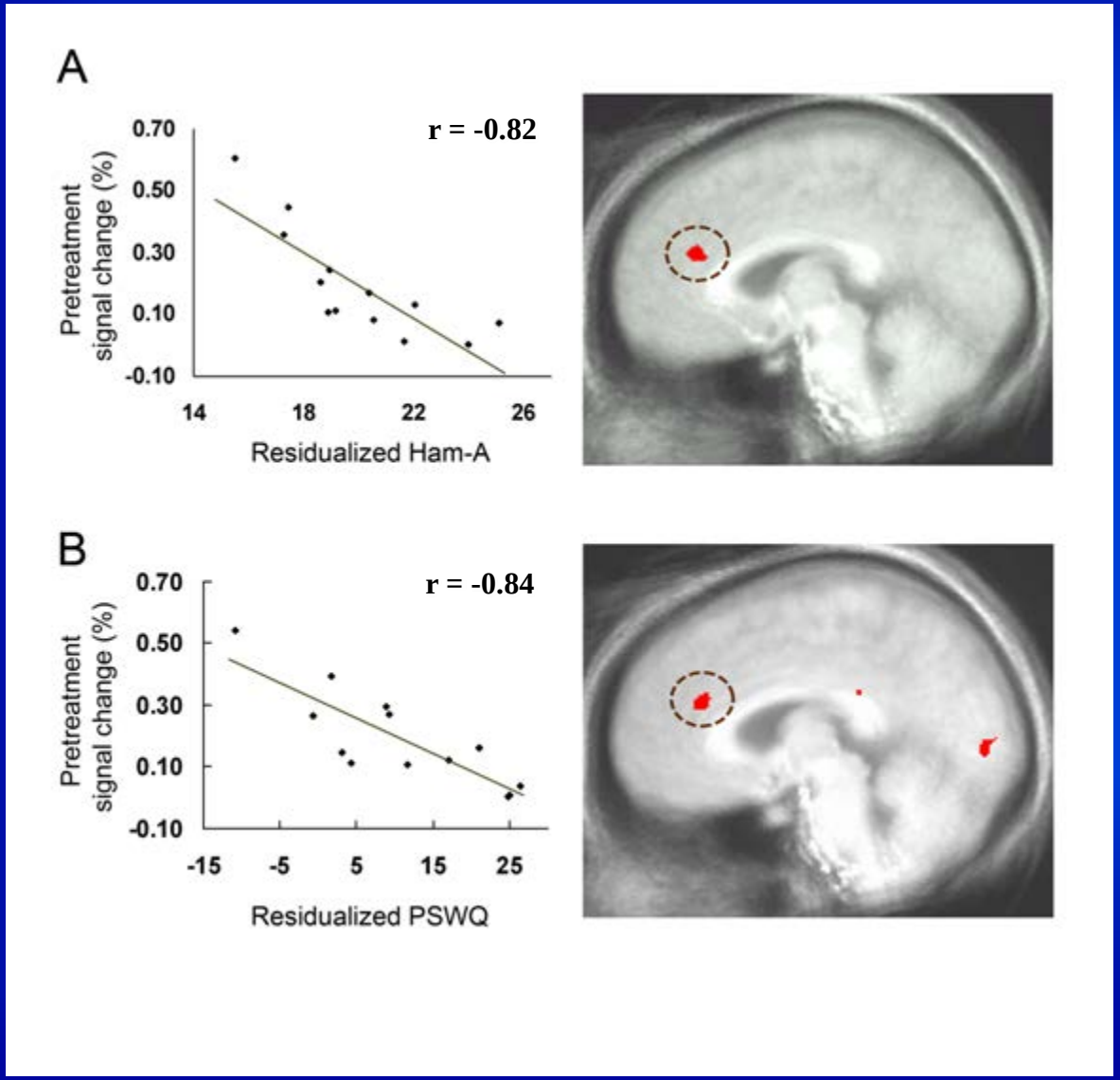


***n* = 26**

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

ACC Activity and Treatment Response

Pretreatment Anticipatory ACC Activity Predicts Response to Effexor

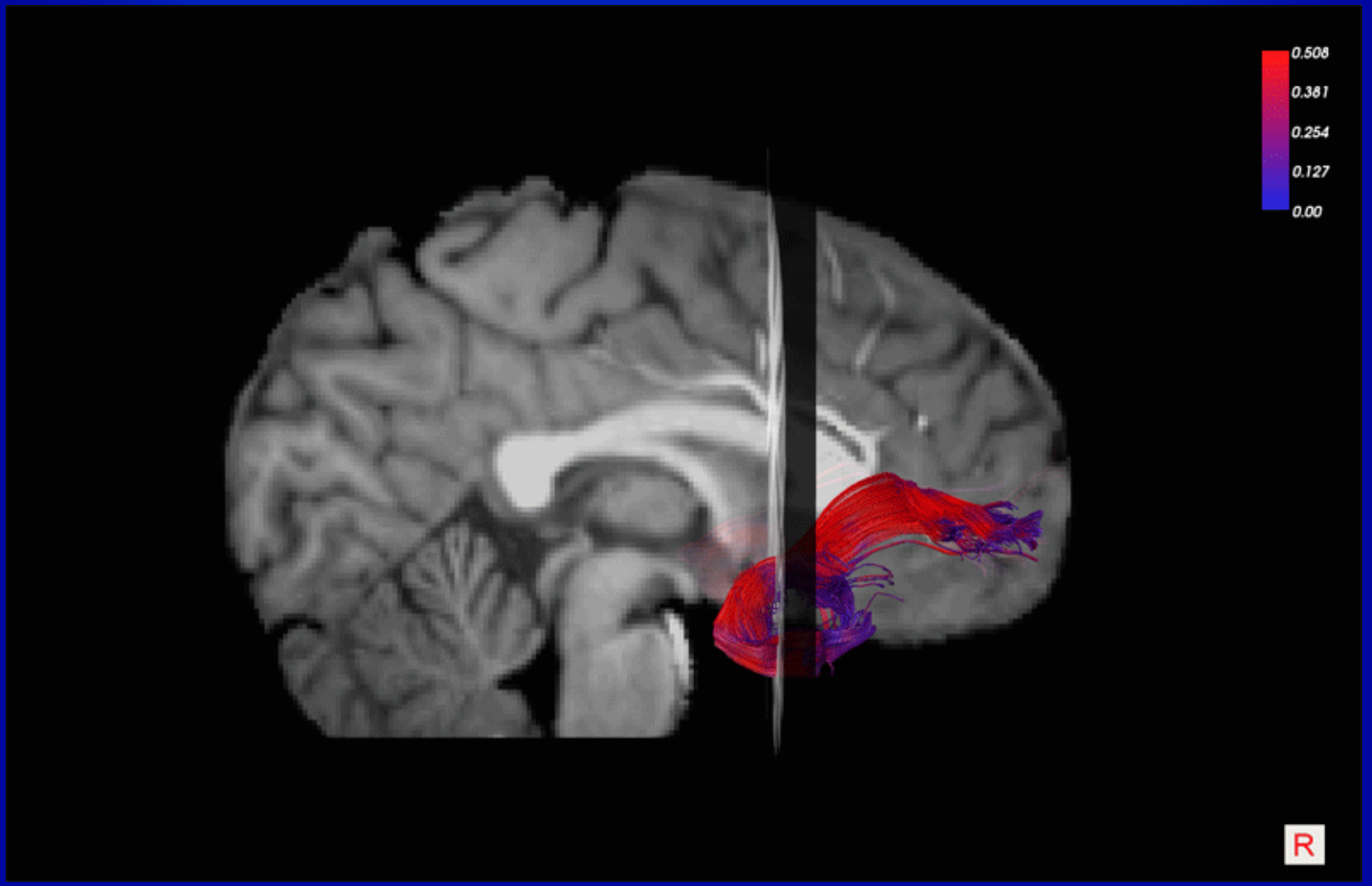


***n* = 14**

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

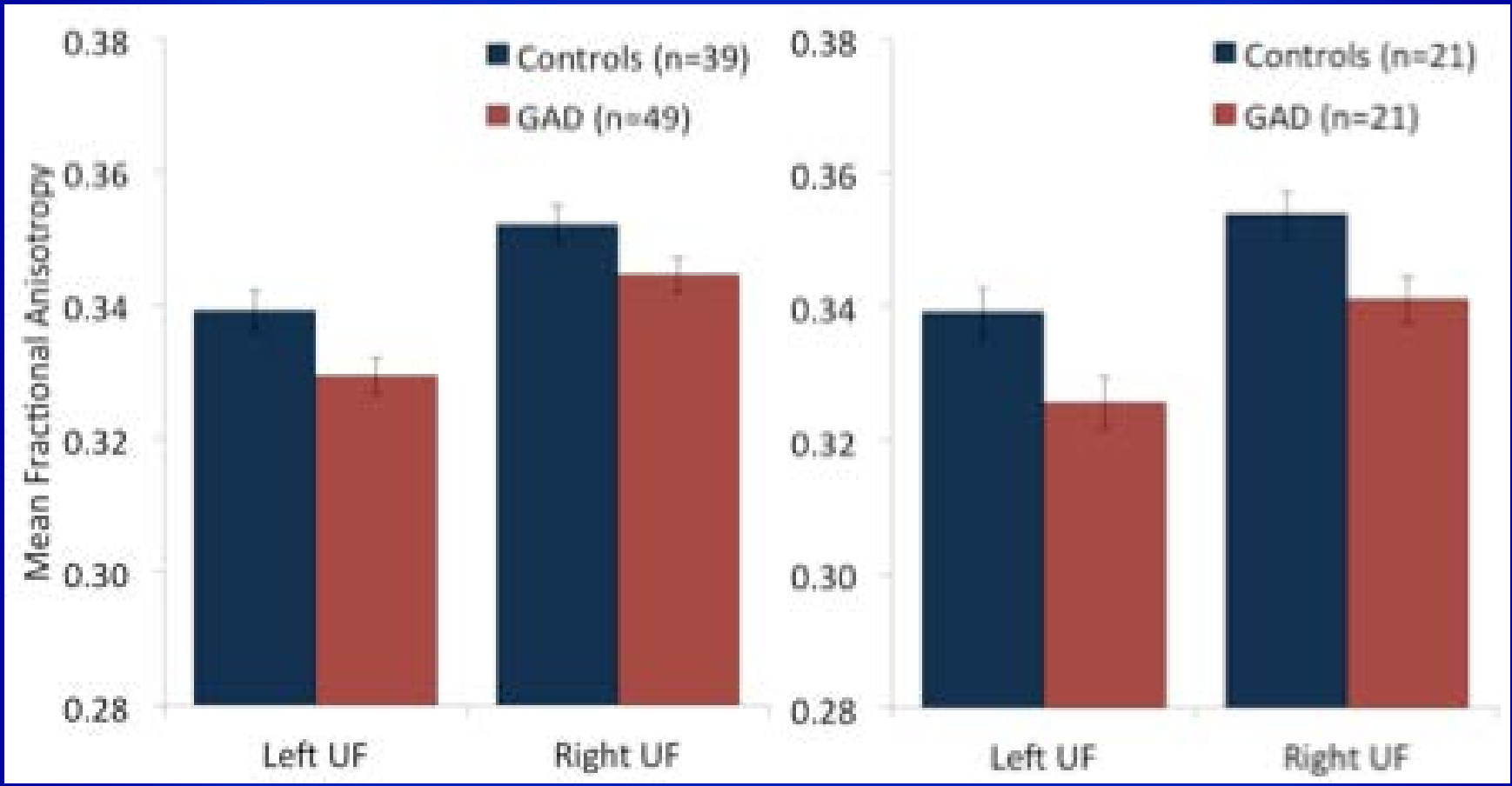
Uncinate Fasciculus

DTI-based Tractography



Structural Connectivity

GAD Patients Show *Reductions* in Uncinate Fasciculus

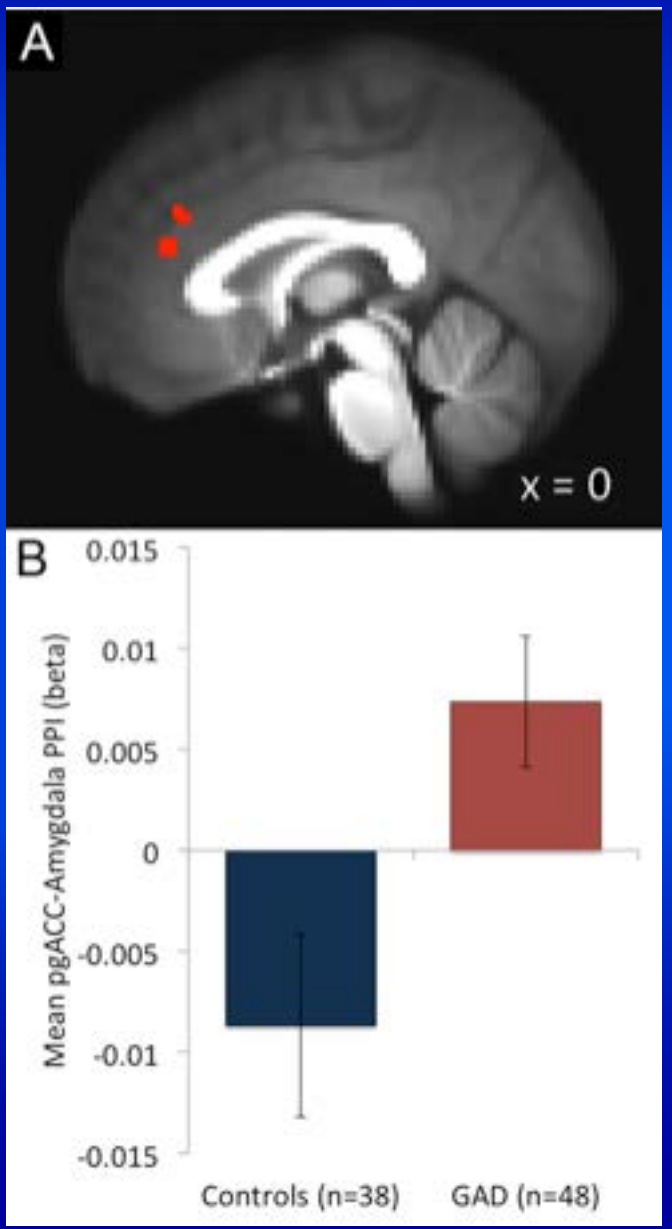


***n* = 88**

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

Functional Connectivity

GAD Patients Show *Reduced* ACC-Amygdala Negative Coupling

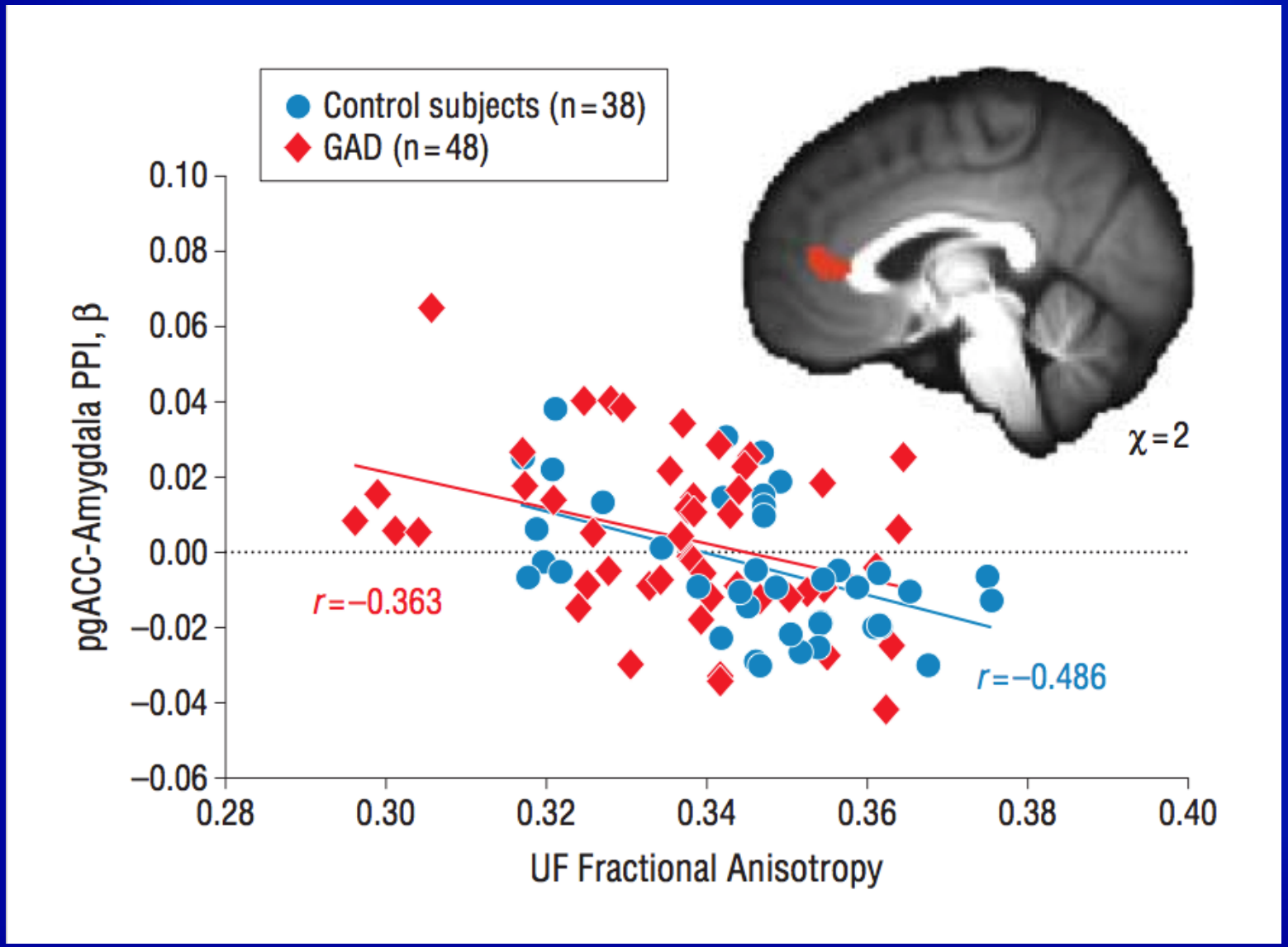


***n* = 88**

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*

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

The Brain and Psychotherapy

- 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"
- 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

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*, 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