The Neuroscience of Anxiety

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

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Objectives

- By the end of this brief session, you will be able to:
  - Explain how the natural fear circuitry is co-opted in anxiety disorders
  - Describe the neuroscientific concepts thought to be associated with the anxiety disorders
  - Discuss the brain regions involved in anxiety and related disorders

Stress Response

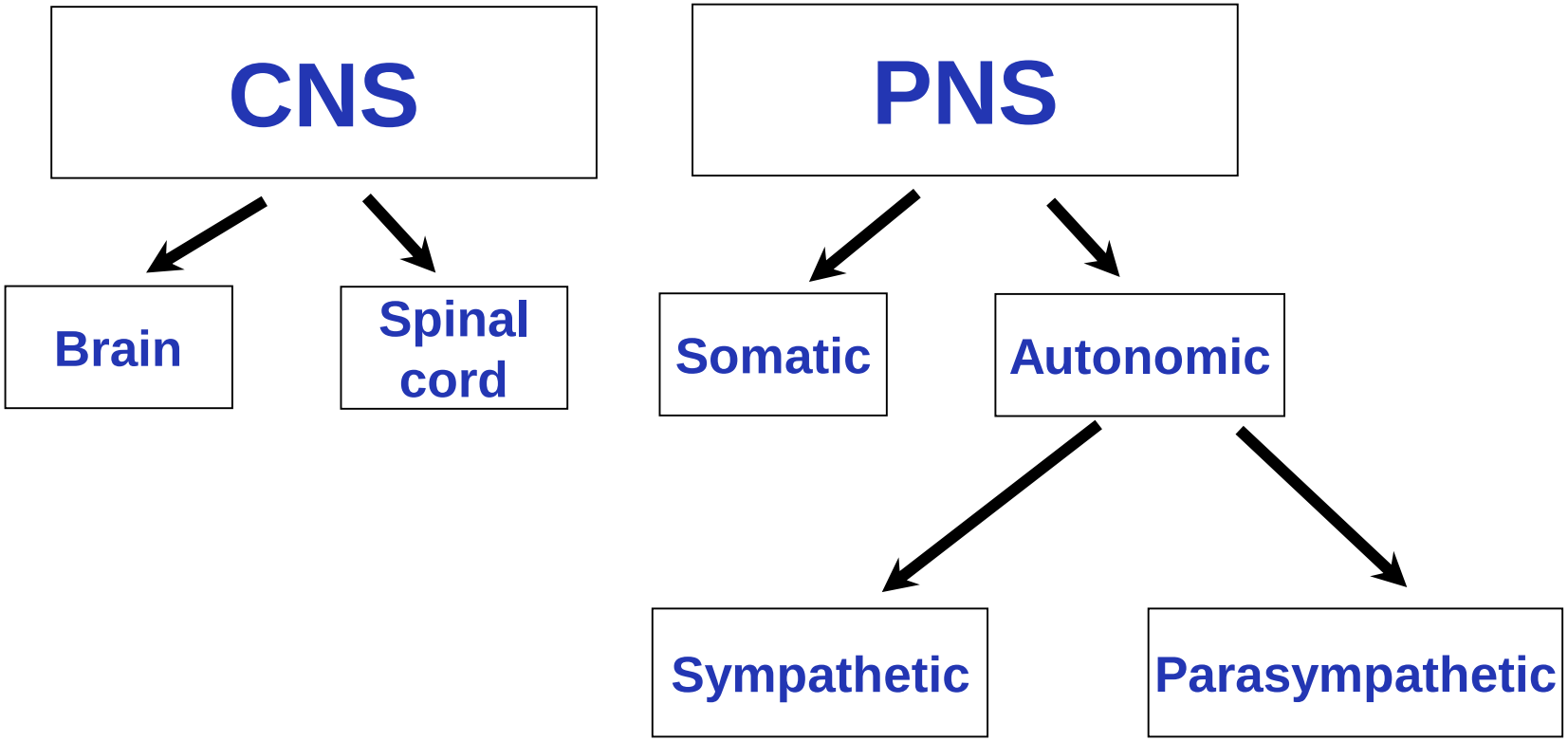
- “Men are disturbed not by things, but by the views which they take of them.” - Epictetus, Greek philosopher
- “It is not what happens to you that matters, but how you take it” - Hans Selye, father of modern endocrinology

What is the Stress Response?

- Stress is commonly defined as a state of real or perceived threat to homeostasis.
- Maintenance of homeostasis in the presence of aversive stimuli (stressors) requires activation of a complex range of responses involving the endocrine, nervous, and immune systems, collectively known as the stress response.

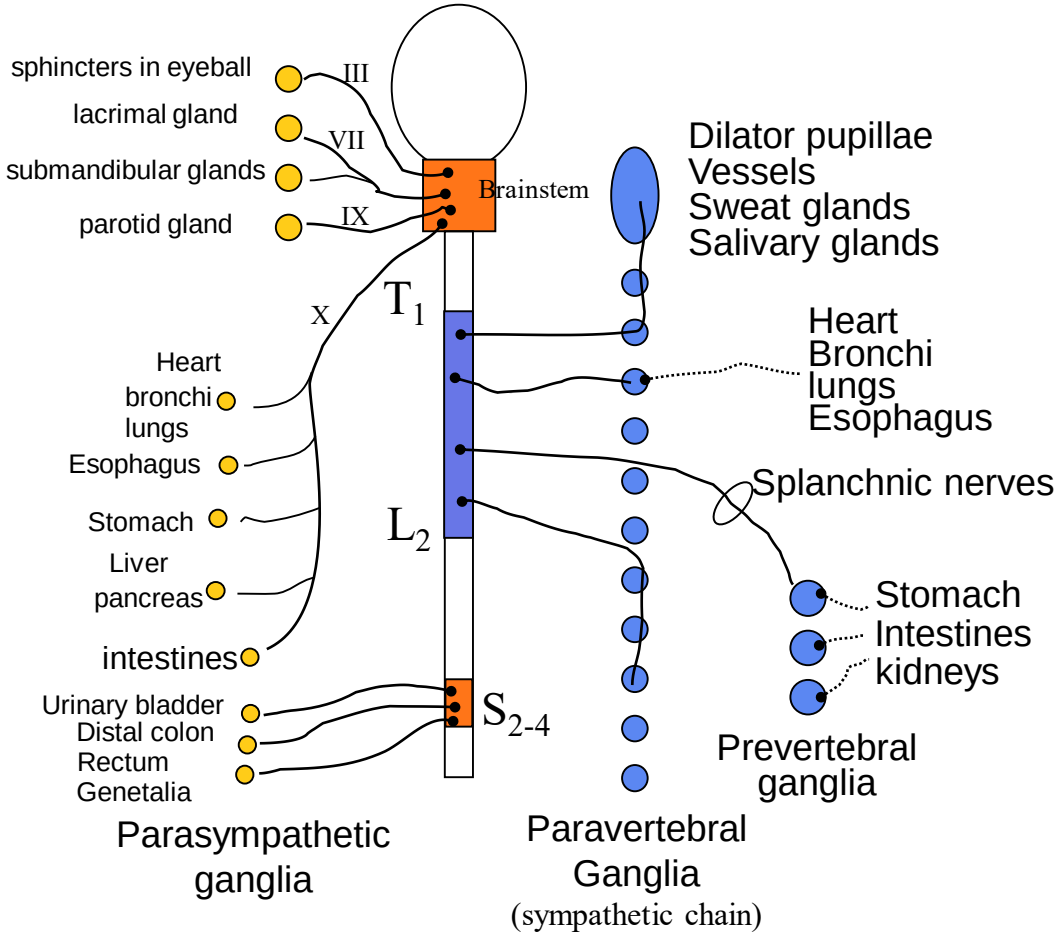
(Smith and Vale, 2006)

Divisions of the Nervous System



THE AUTONOMIC NERVOUS SYSTEM

PARASYMPATHETIC **SYMPATHETIC**



General Features

Sympathetic

- Thoraco-lumbar preganglionics
- Postganglionics in sympathetic chain or prevertebral ganglia
- Involved in "Fight or flight" response
- Short preganglionics, long postganglionics
- Innervates bld vessels, sweat glands and viscera

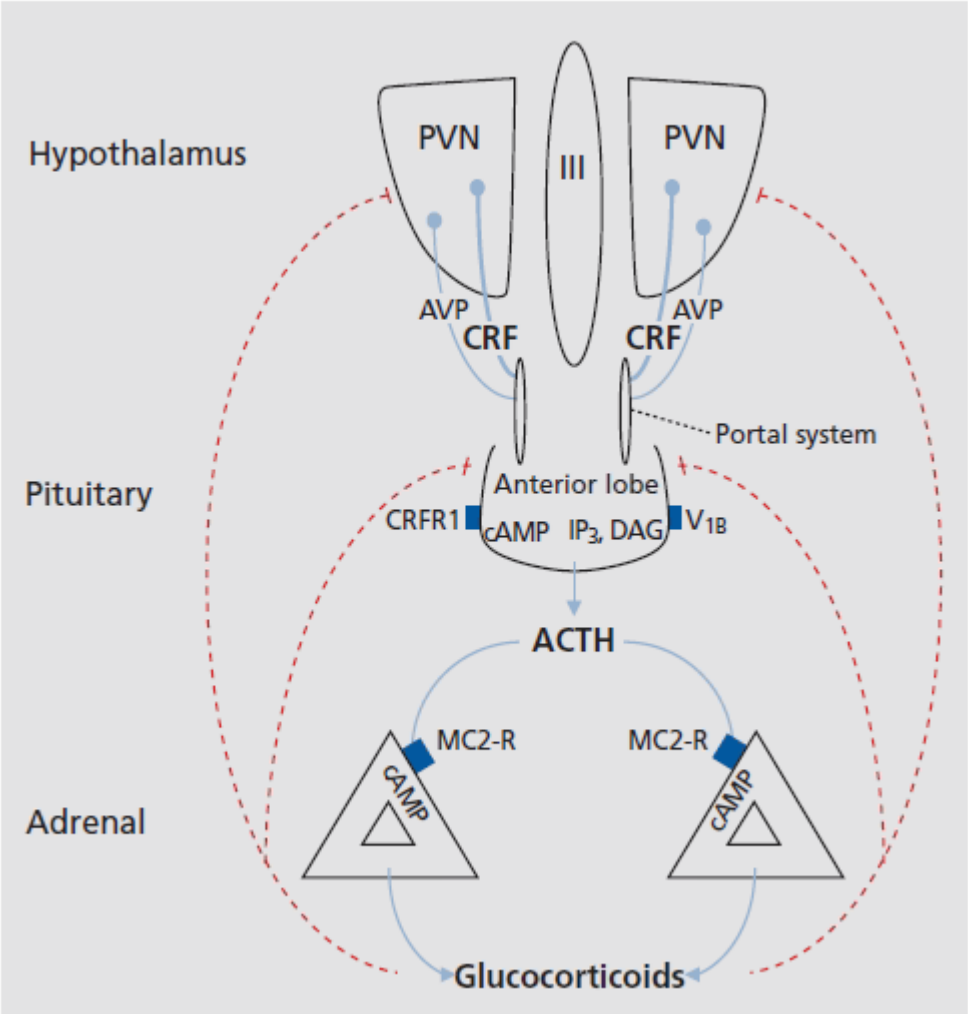
Parasympathetic

- Cranio-sacral preganglionics
- Postganglionics in small ganglia near target
- Involved in "rest and digest" response
- Long preganglionics, short postganglionics
- Innervates viscera, but not bld vessels or sweat glands

Rapid Response to Stress

- Adrenal medulla releases epinephrine and norepinephrine
- These increase heart rate, increase blood pressure, dilate pupils, increase respiratory rate, increase glucose use by the muscle, increase awareness
- Fight, Flight, or Freeze
- This occurs within seconds

The Hypothalamic-Pituitary-Adrenal Axis (HPA)



- Paraventricular nucleus releases Corticotrophin-releasing factor (CRF)
- CRF goes to the anterior pituitary where it releases ACTH
- ACTH travels to adrenal glands where it releases cortisol
- Cortisol travels to organs where it binds to glucocorticoid receptors and mineralocorticoid receptors
- It then turns off CRF release

Regulation of the HPA axis

- High levels of circulating cortisol inhibits it's own release through a fast (poorly understood) and a delayed (gene expression) mechanism
- High levels of cortisol in the PVN reduce neural activity and, consequently, CRF secretion and ACTH release
- The *hippocampus* is a second site for negative feedback regulation. Not only does cortisol stimulate the hippocampus which send projections to shut down the PVN, cortisol is also toxic to hippocampal neurons

Neural Regulation of the HPA axis

- Connections to the PVN are from other hypothalamic nuclei, brain stem neurons, and limbic system
- Nucleus of the solitary tract receives projections from the medial prefrontal cortex and amygdala and then projects to the PVN

Effects of Cortisol in the Body

- Increase blood sugar
- Suppress the immune system
- Increase metabolism of fuels
- Decrease bone formation
- Worsens healing
- Enhances memory in short term, worsens over longer term

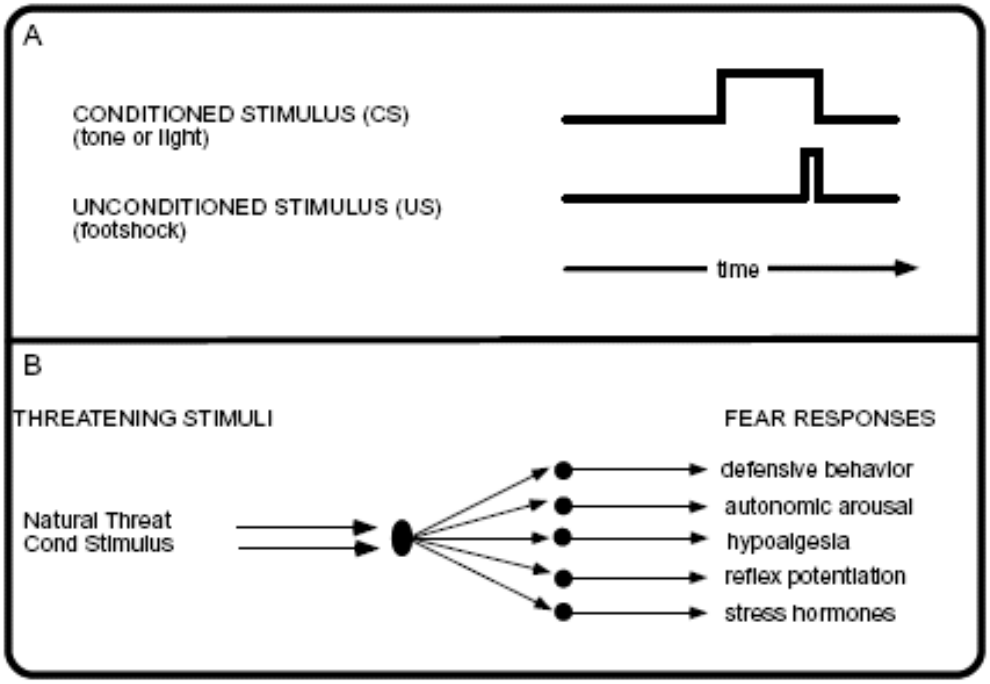
Clinical Effects of Excess Cortisol

- Depression
- Hypertension
- Fatigue
- Sleep deprivation
- Migraine headache
- Acid Reflux
- Hostility and anger
- Arthritis
- Decreased immune response – more illness
- Decreased metabolism – obesity and overweight

Features of Anxiety
Sympathetic Nervous System

- Pupil dilation
- Muscle contraction
- Increased HR
- Decreased GI mobility
- Decreased libido
- Increased vigilance
- Subjective feelings of danger, threat
- Urge to flee

Learning Theory



- Anxiety disorder theory often involves principles of learning
  - Classical conditioning: pairing of unconditioned and conditioned stimulus
  - Operant Conditioning: OCD example

Anxiety Sensitivity

- Exaggerated response to physiological alterations associated with anxiety and fear
- Initiates positive feedback loop which leads to more anxiety and fear
- Cognitive bias towards threat
- Temperamentally based
- Target of psychotherapy

Temperament, Anxiety and Brain Activity (Schwartz et al., Science, 2003)

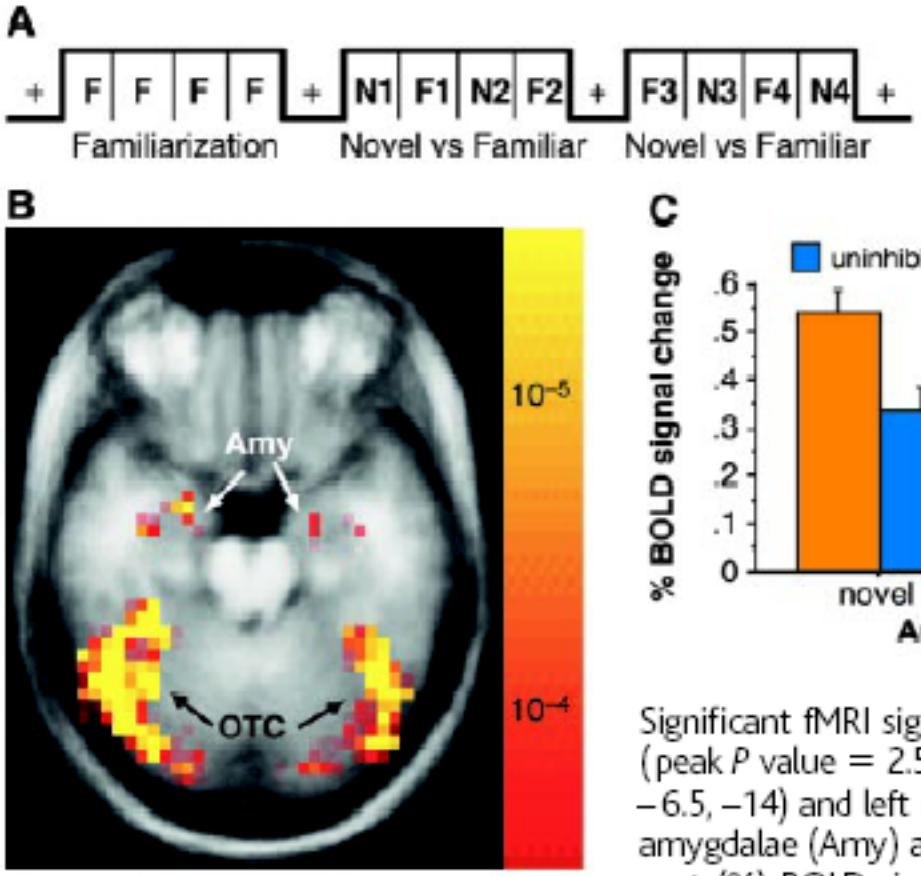
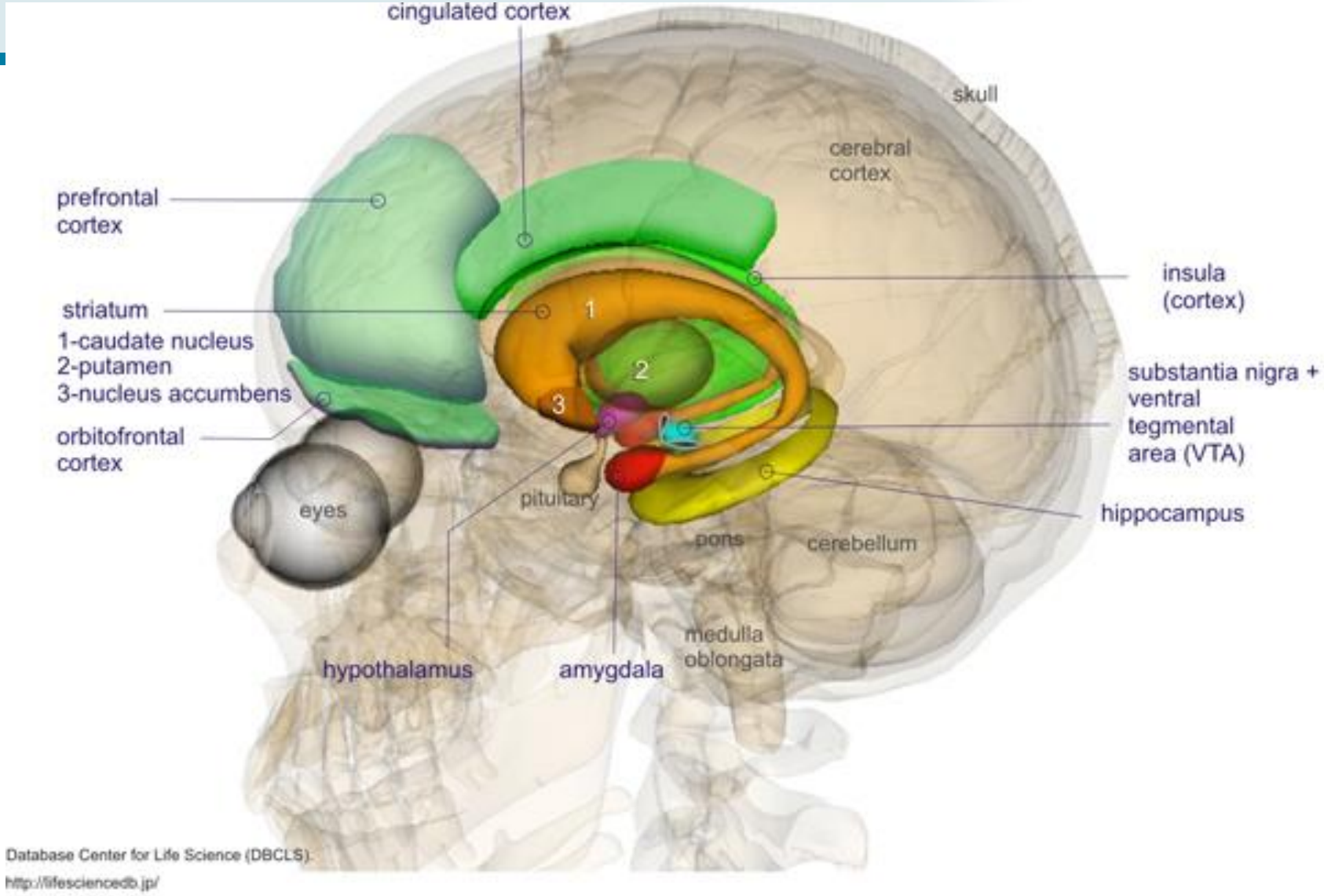


Fig. 1. (**A**) The presentation of stimuli was divided into two phases: a familiarization phase and a test phase that consisted of alternating 24-s blocks of either novel (N) or familiar (F) faces with neutral expression. Subjects viewed a fixation cross (+) during 24-s fixation blocks. (**B**) Colorized group statistical map superimposed on coronal group-averaged T1 structural image in Talairach space. Significant fMRI signal changes (arrows) are shown in the right (peak P value $= 2.5 \times 10^{-5}$; Talairach coordinates $x, y, z = 21, -6.5, -14$) and left ($P = 4.2 \times 10^{-4}$; $x, y, z = -21.5, -6.7, -18$) amygdalae (Amy) and occipito-temporal cortex (OTC). (**C**) Percent (%) BOLD signal change (versus fixation) in amygdala to novel versus familiar faces in adult subjects who were inhibited and uninhibited in the second year of life. One standard error of the mean is indicated.

Anxiety Regions in the Brain



Anxiety and the Amygdala
Qin et al., Bio Psychiatry, 2014

- Study of 79 children (non-clinical) sample
- Higher anxiety related to larger amygdala (particularly left and basolateral nucleus)

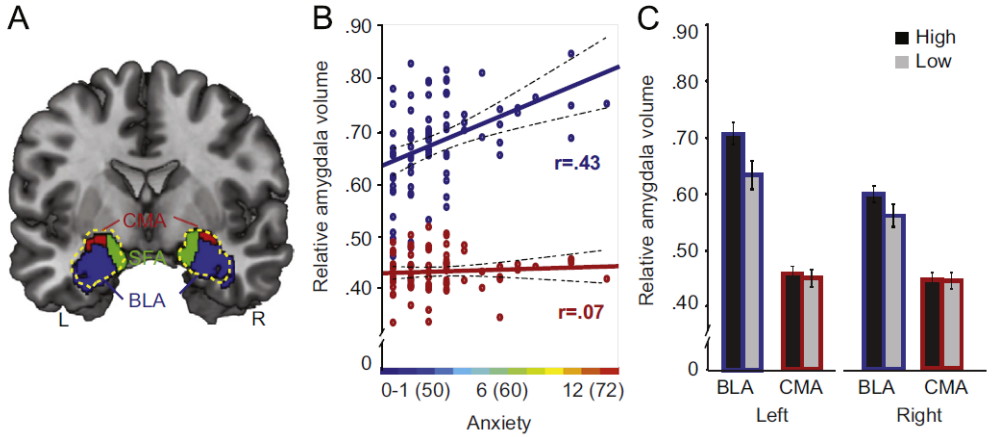


Figure 2. Relation between childhood anxiety and amygdala subregional morphometry. **(A)** Representative coronal slices of the three major subdivisions of amygdala nuclei—basolateral (BLA, blue), centromedial (CMA, red), and superficial (SFA, green) amygdala. A yellow line outlines the whole amygdala. Data regarding SFA is shown in Figure S3 in Supplement 1. **(B)** Scatter plots depicting the correlations of childhood anxiety with gray matter volume of left BLA and CMA. Prediction analyses further revealed that left BLA volume is the strongest predictor of childhood anxiety. **(C)** Histogram showing gray matter volume of the two major amygdala subdivisions in children with high compared with low levels of anxiety. Error bars represent standard error of the mean. ***$p < .001$. L, left; R, right.

Anxiety and the Amygdala

Qin et al., Bio Psychiatry, 2014

- Anxiety linked to connectivity between basolateral amygdala and other brain regions including lateral occipital cortex (LOC), superior parietal lobe (SPL) and ventromedial prefrontal cortex (vmPFC)
- Regions involved in attention and emotional regulation

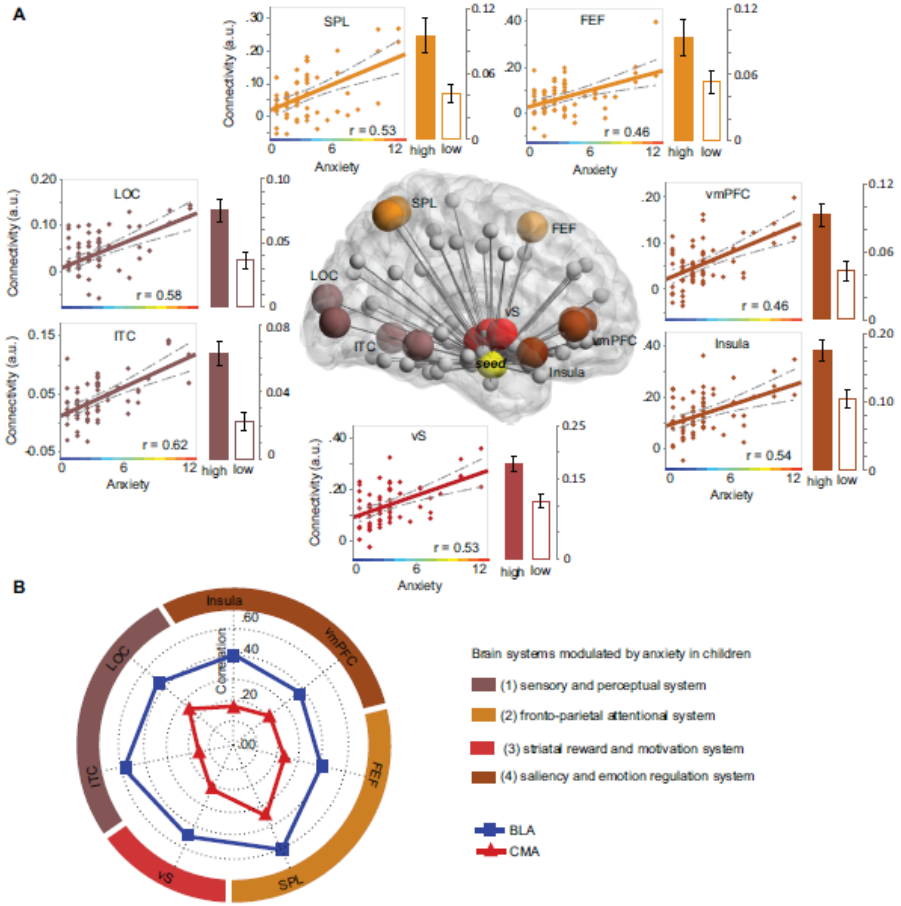


Figure 4. Schematic illustration of relation between childhood anxiety and functional connectivity of the amygdala and its subregions. **(A)** Brain regions (represented by color-coded nodes) that showed a significant correlation between childhood anxiety and functional connectivity with the left amygdala. Target regions include 1) lateral occipital cortex (LOC) and inferior temporal cortex (ITC) in sensory association cortex; 2) frontal eye field (FEF) and superior parietal lobe (SPL) that are part of dorsal fronto-parietal network; 3) ventral striatum (vS) in basal ganglia; and 4) insula and ventromedial prefrontal cortex (vmPFC) in paralimbic system. Gray nodes and lines represent the functional connectivity network of the amygdala seed (shown in yellow), with peaks of significant clusters from the intrinsic functional connectivity analysis. Scatter plots depict positive correlations between anxiety levels (x axes) and connectivity strength between the left amygdala and each target region (y axes). Bar graphs depict connectivity strength between the left amygdala and each target region in high versus low anxious groups using a median-split. The bar graphs are shown for visualization. **(B)** Polar plot illustrating the relation between childhood anxiety and amygdala subregional connectivity with multiple regions broadly classified into four functional brain systems: 1) sensory and perceptual processing (dark brown); 2) attentional control (orange); 3) motivation and reward (red); and 4) saliency detection and emotion regulation (light brown). Prediction analyses revealed that left basolateral amygdala (BLA) functional connectivity was the strongest predictor of childhood anxiety. CMA, centromedial amygdala.

A Developmental Model

- Chronic stress associated with increased dendritic arborization and abnormal pruning of neurons in amygdala
- Increased activation of HPA axis
  - Low stress, parenting can do opposite via hippocampus
- Increased anxiety state and behaviors
  - Hypervigilance (fronto-parietal)
  - Altered reward and more avoidance (ventral striatum)
  - Regulation difficulties (prefrontal cortex)

Summary

- Anxiety disorders are co-opting the typical circuitry that has evolved to respond to acute and chronic stress
- There are multiple brain regions involved, including the amygdala, HPA axis, ventral striatum, and prefrontal cortex
- Thus far, there are no reliable brain structural changes that are sensitive or specific enough to diagnose anxiety disorders

Thank you!

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